CZFC 2025

第9届全国斑马鱼研究大会

The 9th Chinese Zebrafish Conference

助力生物医药发展，斑马鱼研究的创新与突破

会议摘要集

2025年8月15-18日　甘肃国际会议中心





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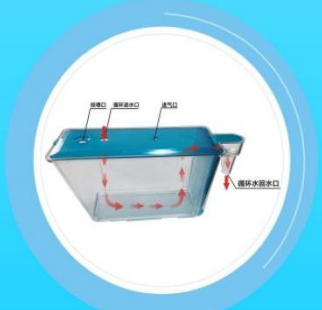
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青年论坛

Youth Forum

BLOC-3 complex and Hermansky-Pudlak syndrome

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摘要：Hermansky-Pudlak 综合征（HPS) 是一种由溶酶体相关细胞器（LROs）生物发生缺陷引起的常染色体隐性遗传病，临床表现为眼皮肤白化、出血倾向及肺纤维化等。BLOC-3 复合物（由 HPS1 和 HPS4 蛋白组成）是调控 LROs 生物发生的关键因子，其功能异常与 HPS 发病密切相关。本研究首次通过冷冻电镜解析了人源 BLOC-3 复合物的高分辨率结构，阐明了 HPS1 与 HPS4 形成异源二聚体的组装模式，并阐明其兼具 RAB32/RAB38-GEF 及 RAB9A 效应因子双重功能。为深入解析 BLOC-3 功能异常在 HPS 中的致病机制，本研究构建了斑马鱼基因敲除模型（*hps1*/*hps4* crispants）。敲除 *hps1* 或 *hps4* 基因均导致黑色素生成缺陷，回补野生型人源 HPS1/HPS4 可有效挽救斑马鱼的黑色素减少表型。相反，破坏 BLOC-3 复合物组装的突变体（如 HPS1-L588P）或特异性阻断与 RAB9A 相互作用的突变体（HPS4-KR）均丧失了挽救黑色素生成的能力。这些结果明确证实：BLOC-3 复合物的正确组装及其与 RAB9A 的互作对于体内黑色素生成至关重要，其功能破坏是导致 HPS 相关白化表型的核心机制。综上，本研究阐明了 BLOC-3 复合物的结构及其双重调控功能，并通过斑马鱼模型直接解析了其在 HPS 色素异常中的致病机理，为深入理解 HPS 发病机制及探索潜在治疗策略奠定了基础。

关键词：BLOC-3，Hermansky-Pudlak 综合征，LROs，RAB9A，斑马鱼

Jund orchestrates cis-regulatory element dynamics to facilitate endothelial-to- hematopoietic transition

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The tightly controlled spatiotemporal expression of developmental genes depends on the concerted action of cis-regulatory elements and transcription factors to ensure cell fate decisions. Endothelial-to-hematopoietic transition is a cell fate transition process by which endothelial cells acquire hematopoietic identity and become hemogenic endothelial cells and then hematopoietic stem and progenitor cells, but the underlying cis-regulatory element network dynamics and its regulation by transcription factors remain unclear. In this study, we characterized the dynamics of cis-regulatory element activation and transcription factor occupancy during zebrafish endothelial-to-hematopoietic transition, and found that the enhancer–promoter collaboration forms the basis for endothelial-to-hematopoietic transition. Moreover, a ubiquitously expressed transcription factor AP-1 collaborates with diverse lineage-specific transcrition factors to remodel enhancer landscape. Deletion of AP-1 family member Jund impaired hematopoietic specification, resulting from the enhanced endothelial identity in the hemogenic endothelial cells. Mechanistically, Jund and hematopoietic transcription factor Hoxa9a collectively repress the activity of an endothelial-related dll4 enhancer through tight control of the active histone modification H3K27ac. Our study provides insights into the cooperative function among ubiquitous transcription factors and cell type–specific transcription factors in orchestrating cell fate transition, not only deepening the understanding of HSPC generation in vivo, but also holding a great promise for its application in producing HSPCs in vitro.

Key Words： hematopoietic stem and progenitor cells, endothelial-to- hematopoietic transition, cis-regulatory elements, AP-1, Jund

Nap1L4a cooperates with Scl/Klf1 to recruit H2A.Z in mediating interactions among cis-regulatory elements and transcription essential for primitive erythropoiesis

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The chromatin remodeler nucleosome assembly protein 1 like 4 (Nap1L4) is highly expressed in megakaryocyte/erythroid progenitor cells (MEPs) and erythroid cells. Mutations, deletions, and abnormal expressions have been observed in diseases such as acute myeloid leukemia (AML). However, the roles of Nap1l4 in erythropoiesis and the related diseases, as well as the underlying mechanisms remain unknown. Here, we demonstrate that *nap1l4a* homozygous mutants (*nap1l4a*$^{-/-}$) are more sensitive to hypoxia stress during early embryonic stage and exhibited impaired primitive erythropoiesis.. Mechanistically, Nap1l4a interacted with erythropoiesis transcriptional factors (TFs) Scl and Klf1, and recruited histone variant H2A.Z. This remodels cis-regulatory element landscape (CREs) and the consequent nascent RNA transcription of erythropoiesis genes. Meanwhile, Nap1l4a deficiency impaired the chromatin accessibility of epigenetic genes *kdm6b* and *kmt2c.* This leads to expanded H3K27me3 and diminished H3K4me1 in erythrocytes, resulting in altered histone epigenomics at erythropoiesis TF loci and reduced TF expression. Moreover, Nap1l4a regulates primitive erythropoiesis by transcriptionally and epigenetically modulating the canonical WNT/β-Catenin pathway. Together, our findings reveal a lineage-selective transcription, with histone epigenomics dependent role of nap1l4a in vertebrate primitive erythropoiesis. This highlights potential therapeutic targets for human blood disorders involving Nap1l4 deficiency.

Key Words： Nap1l4a, primary erythropoiesis, Scl/Klf1, Kdm6b/Kmt2c, histone epigenomics, WNT/β-Catenin

Mechanistic study on the brain colonization of VDA-derived slec+ microglia

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Microglia, serving as the resident macrophages of the central nervous system (CNS), are instrumental in its development and homeostasis. Their functional abnormalities have been associated with the onset and progression of neurological diseases. Previous research has demonstrated that microglia in the adult zebrafish brain display a significant heterogeneity. However, the molecular mechanisms underlying the developmental origins and brain colonization of distinct microglial subpopulations remain elusive. In this study, we employed scRNA-seq to construct a transcriptional heterogeneity map for adult zebrafish microglia. By the screening of characteristic genes and their promoter sequences across various microglial subpopulations, we successfully engineered a transgenic zebrafish line specifically tracing the slec+ microglial subpopulation. Cell lineage tracing reveals that slec+ microglia arises from definitive hematopoiesis initiated in the ventral wall of the dorsal aorta (VDA) region, which subsequently migrates and colonizes the parenchyma regions of the adult brains. We further discovered that the brain-derived slecl and its receptor (slec) facilitate the colonization of slec+ microglial progenitors in the brain parenchymal regions of adult zebrafish. Notably, in both slecl- and slec-deficient zebrafish, there is a remarkable reduction in the number of slec+ microglia in adult parenchyma, accompanied by an increase in the number of slec+ cells in peripheral tissues. Moreover, supplementation of slecl can preemptively induce the brain colonization of slec+ microglial progenitors. Overall, our study reveals the crucial role of slecl-slec signaling in regulating the adult parenchyma colonization of VDA-derived microglia during the late-stage zebrafish development.

Key Words： Zebrafish, Microglia, VDA, Definitive hematopoiesis, Slecl-Slec signal pathway

DNA nanostructure-mediated enhancement of CRISPR-Cas9 knock-in efficiency in zebrafish

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Incorporating large DNA fragments into zebrafish is notably difficult, as traditional Knock-in donors, including plasmids, double-stranded DNA (dsDNA), and single-stranded DNA (ssDNA), have limited efficacy in delivering donor components into the target cells. We propose an approach utilizing DNA nanostructures as programmable nanomaterials created by folding lengthy single-stranded DNA (ssDNA) into compact, structured frameworks as templates for CRISPR-mediated homology-directed repair (HDR) to facilitate successful knock-in. Notwithstanding their potential, the efficient intracellular delivery of DNA nanostructures, especially nuclear translocation, continues to pose a considerable challenge in zebrafish. Hence, we also describe that 12 HB DNA nanostructures can successfully enter the cell nucleus and perform gene editing in zebrafish embryos. These nanostructures were designed to co-encode an intact endogenous zebrafish gene (prospero homeobox 1a (prox1a), tyrosine hydroxylase (th), or cell division cycle 6 (cdc6) in conjunction with an enhanced green fluorescent protein (EGFP). We assessed HDR efficiency at these genomic loci using microinjection as a delivery method. Our findings indicated effective transport and genomic integration of DNA nanostructures in zebrafish embryos, with a measurable EGFP signal validating successful knock-in. DNA nanostructures demonstrated better insertion efficiency relative to conventional HDR donors in F0 zebrafish embryos, underscoring their enhanced capability for precise genome editing. These findings establish DNA nanostructures as viable knock-in (KI) donor templates for precise gene editing in difficult-to-reach cell types, such as brain cells, where traditional donor molecules often face obstacles to effective delivery or internalization.

Key Words： DNA nanostructure, CRISPR, HDR, Zebrafish, Knock-in (KI), Genomic integration

fgfr1a 突变诱发斑马鱼颅内软骨发育缺陷的机制研究

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摘要：成纤维细胞生长因子受体 1（FGFR1）是 FGFR 基因家族的一员。FGFR 基因家族由四个高度相关的基因 FGFR1-4 组成，参与几乎所有器官的发育。FGFR1 的功能增强型点突变可引起颅面骨发育不良（osteoglophonic dysplasia, OD）综合征。研究表明敲除 fgfr1a 会引起同源基因补偿效应，因此在本研究中，我们针对 fgfr1a 的关键功能结构域，利用单碱基编辑工具构建了一系列点突变，筛选出具有人类疾病相似表型的点突变品系（fgfr1a-/-）。通过阿利新蓝染色、茜红素染色、原位杂交等方法进行表型分析，发现该突变体第一至第四角鳃弓缺失、舌骨畸形、胸鳍缺失、体长和鱼鳔面积显著下降。但是其硬骨、体节没有显著变化。摄食实验表明 fgfr1a-/-幼鱼无法正常开口进食。行为学分析发现 fgfr1a-/-与 sibling 在相同时间内的运动时间无显著差异，但运动速度有显著差异，表明该突变体的缺陷可能仅存在于身体，智力没有明显缺陷。为进一步探究颅内软骨缺陷的分子机制，从 fgfr1a-/-转录组中筛选出关键基因 dlx2a，通过原位杂交发现 24 hpf 和 30 hpf 的突变体中神经嵴细胞的形成与迁移存在明显异常。综上所述，fgfr1a 点突变诱发的斑马鱼颅内软骨缺陷可能是由于其介导了神经嵴细胞的形成与迁移而导致的，研究成果有望为人类相关疾病的治疗和药物研发提供了重要的理论依据。

关键词：斑马鱼，fgfr1a，颅内软骨，OD 综合征，神经嵴细胞

Light intensity and opsin sensitivity shape the morphology of cone photoreceptor outer segments

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The regulation of neural cell morphology remains a fundamental question in neuroscience. Photoreceptor cells, a specialized class of neurons capable of initiating the phototransduction cascade, exhibit quite distinct structural and morphological characteristics. While the structural and morphological differences between rod and cone photoreceptors have been extensively studied, the variability in the morphology of cone outer segments (OS) remains largely unexplored. Zebrafish possess four distinct cone types, each displaying unique OS morphologies. By modulating opsin expression across cone types, we reveal that the morphology of the cone OS correlates directly with the wavelength sensitivity of the expressed opsins, with cones expressing longer wavelength-sensitive opsins exhibiting elongated OS. This regulatory mechanism is conserved across diverse various vertebrates. Furthermore, we show that alterations in light intensity—induced by ectopic lipid droplet formation in the light path or by changing the environment light intensity—can also modulate OS morphology. Notably, this morphological plasticity is not transient, but rather dependent on long-term neural activity. Based on these findings, we propose a model for the regulation of cone OS length. Our data suggest that both opsin sensitivity and light intensity shape cone OS morphology through long-term neural activity, providing critical insights into neural plasticity in these light-sensitive neurons.

Key Words： Zebrafish, Cone Cells, Outer Segment, Opsin

高糖诱导微血管病变的机制研究：基于斑马鱼的新发现

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摘要：微血管作为机体氧合与营养交换的核心枢纽，其功能障碍是糖尿病并发症、高血压及心脑血管疾病的共同病理基础。微血管病变具有隐匿性强、早期诊断困难等特点，而斑马鱼胚胎凭借其光学透明和体外发育特性，为实时活体观察血管动态提供了理想模型。

本研究通过高浓度葡萄糖浸泡，首次成功构建了能高度模拟糖尿病患者微血管病变特征的斑马鱼模型，并对表型进行了机制探讨：

微血管过度新生的调控机制：单细胞测序数据显示，高糖下调内皮细胞中 *foxo1a 表达*，进而解除其对下游靶基因 *marcksl1a* 的转录抑制，促进尖端细胞驱动的微血管过度新生。

血管管腔狭窄的分子基础：高糖处理可下调水通道蛋白（AQP）家族基因表达，*aqp1a.1* 与 *aqp8a.1* 功能缺失导致斑马鱼血管管径减小，而 *aqp1a.1* 过表达可逆转高糖引发的血管狭窄。机制上，高糖下调 AQP 表达，减少内皮细胞内空泡生成，进而引发血管狭窄与灌注缺陷。

微血管内皮细胞核聚集的机制阐释：实时动态成像显示，高糖处理后斑马鱼节间血管内皮细胞核迁移活性显著增强，迁移距离约为对照组 3 倍。机制研究表明，该表型由 *foxo1a-klf2a* 信号轴介导。

本研究建立的斑马鱼模型为糖尿病微血管病变提供了可重复的活体研究体系，首次在单细胞水平揭示了高糖诱导微血管病变的多维度调控网络，不仅深化了对糖尿病微血管并发症病理机制的认知，更为靶向微血管病变的药物研发提供了全新的干预靶点与动物模型基础。

关键词：斑马鱼，微血管功能障碍，疾病模型

Mcm5 突变通过抑制 Stat1-Bcl2 通路促进 DNA 损伤诱导的未成熟 T 细胞凋亡

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摘要：DNA 复制相关基因的突变会持续破坏复制过程，导致基因组不稳定性，这是肿瘤发生的关键驱动力之一。为了防止白血病的发生，发育中的未成熟 T 淋巴细胞在发生基因组不稳定时通常会迅速凋亡。然而，这一过程中所涉及的分子机制仍不明确。本研究发现，在斑马鱼模型中，*mcm5* 基因突变导致未成熟 T 淋巴细胞出现 DNA 损伤，并诱导其发生快速凋亡。机制研究表明，在 *mcm5* 突变体中，*tp53* 上调，同时抗凋亡基因 *bcl2a* 的转录显著下调。进一步研究发现，Mcm5 蛋白可直接与 Stat1a 结合并促进其磷酸化，增强 *bcl2a* 的表达，从而在 DNA 复制压力条件下保护 T 细胞存活。在 *mcm5* 突变体中，Mcm5-Stat1 复合体缺失使 Stat1 的磷酸化受阻，bcl2a 表达下降，导致未成熟 T 细胞更容易因基因组不稳定而凋亡。此外，我们的研究还发现 Mcm5 在 T 细胞发育中的作用在小鼠中也具有保守性。综上所述，本研究不仅揭示了 Mcm5 在 T 细胞发育中的新功能，还发现其通过调控 Stat1-Bcl2 信号轴，在 DNA 复制压力下维持未成熟 T 细胞的生存，从而在基因突变导致的 DNA 损伤情况下促进异常 T 细胞的清除。这一发现为深入理解 T 细胞发育过程中的基因组稳定性维持机制及其与白血病发生的关系提供了重要理论依据。

关键词：Mcm5，T 细胞发育，DNA 损伤，细胞凋亡，斑马鱼

E3 泛素连接酶 ubr5 在斑马鱼胚胎发育中的功能探索

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摘要：UBR5 是一种重要的 E3 泛素连接酶，在蛋白质调节、信号转导调控等过程中发挥作用。然而 ubr5 在动物体内的调控作用并不清楚，其在小鼠以及果蝇中均为纯合致死。所以我们运用斑马鱼这一模式动物来探究 ubr5 在动物胚胎早期发育中的作用。首先利用 CRISPR/Cas9 基因编辑技术构建了 ubr5 敲除斑马鱼，发现纯合突变体在 9-14 天内死亡。并且通过原位杂交技术探索 ubr5 在斑马鱼中的表达模式，观察到其在骨骼、肠道、肝脏等器官中高表达，并对高表达器官组织进行观察。

关键词：ubr5，斑马鱼，肠道

Cellular Activation and Dynamics of Cardiomyocytes During Zebrafish Heart Regeneration

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Adult zebrafish possess a remarkable capacity for heart regeneration through a complex orchestration of molecular and cellular activities. Following cardiac injury, wound-edge cardiomyocytes (CMs) are sequentially triggered to undergo dedifferentiation, proliferation, and redifferentiation, ultimately regenerating the amputated heart muscle. However, this remarkable process, which is largely non-existent in humans, remains incompletely understood. Here, we utilize integrated spatial transcriptomics (Stereo-seq) and single cell RNA sequencing (scRNA-seq) to generate a spatially resolved molecular and cellular atlas of regenerating zebrafish heart across eight stages. We characterized the cascade of cardiomyocyte cell states responsible for producing regenerated myocardium. Five injury-induced ventricular myocardium-enriched domains were identified, which were localized to the wound edge spatially and appeared temporal-specifically. Especially, at 6 hpa, the emergence of activated cardiomyocytes along the wound edge was observed, which is characterized by upregulation of specific genes *tnfrsf11b*, *nppa*, and *nppb*. This indicates that the CM population marked by *tnfrsf11b* at 6 hpa represents an early CM reactivation for cardiac regenerating initiation. Furthermore, the role for *tpm4a* in cardiomyocyte redifferentiation was explored. Our comprehensive atlas serves as a valuable resource to the cardiovascular and regeneration scientific communities and their ongoing efforts to understand the molecular and cellular mechanisms underlying vertebrate heart regeneration.

Key Words：Zebrafish, Heart Regeneration, Cardiomyocytes

How granulocytes interact and function in the zebrafish inflammatory bowel disease model

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Inflammatory bowel disease (IBD) is featured by the infiltration of various types of immune cells, while their functions, crosstalk, and underlying mechanisms remain to be further elucidated. In our previous research, we utilized zebrafish colitis model to study the regulation and function of neutrophils. We found that the elevated intestinal IL-22 was responsible for the enriched neutrophils during colitis. Further, the TGF-β pathway was activated in neutrophils, triggering Mmp9 expression to exacerbate the colitis. Therefore, we highlighted the role of IL-22/TGF-β/Mmp9 axis of neutrophils in IBD pathogenesis. Our next question is whether other granulocytes crosstalk with neutrophils and their potential roles of in IBD. Our results show that during colitis, neutrophils promote the enrichment of eosinophils in the intestine. Further analysis reveals that eosinophils induce intestinal cell proliferation and extracellular matrix formation, thus contributing to intestinal wound healing during colitis. We further identify that the Aryl Hydrocarbon Receptor (AHR) pathway is specifically activated in intestinal eosinophils, and the AHR-Complement axis is responsible for the wound healing function of intestinal eosinophils during colitis. In summary, our study reveals a novel crosstalk between neutrophils and eosinophils, and elucidates the regulation, function, and underlying mechanisms of eosinophils in IBD, providing new insights into IBD biology with potential therapeutic implications.

Key Words： Zebrafish, Inflammatory Bowel Disease, Neutrophil, Eosinophil

Super-fast generation of knock-in alleles by trunk xenograft into immunodeficient zebrafish

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Microhomology-mediated end joining (MMEJ) is a major mechanism responsible for the repair of DNA double-strand breaks (DSBs) in zebrafish embryos. The distance between the DSB end and the microhomology sequence critically determines the frequency of MMEJ repair. Previous MMEJ-mediated knock-in approaches used universal gRNA(s) in donor vectors to induce DSBs for MMEJ repair, and this generally resulted in a 6-bp sequence between the DSB end and the homology sequence, which might severely compromise knock-in efficiency. To develop a more efficient KI strategy leveraging spacer-free MMEJ, we utilized the reverse complement of the genomic gRNA target as the vector gRNA target. incorporating a 3-bp sequence followed by the PAM site after the target sequence. This configuration aligns the cleavage sites in both the genome and the vector, creating two spacer-free microhomologous sequences, thereby enhancing KI efficiency. Using this method, we could visualize the knock-in events in the injected F0 embryos with high efficiency and successfully generate precise knock-in alleles. In some cases, the F0 knock-in embryos showing tissue-specific EGFP expression failed to survive. We dissected trunks with gonadal ridge from the F0 KI embryos and grafted it into immunodeficient host at 2 months post-fertilization. Within one month, the grafted tissues underwent rapid gonadal development and gametogenesis. Functional spermatozoa were obtained from the grafted gonads, which produced heterozygous F1 embryos with a precise knock-in allele. In this way, we have developed a high-efficient and super-fast method to generate knock-in alleles, which could be easily adapted in a wide range of applications.

Key Words： Zebrafish, MMEJ, Knock-in, Surrogate Reproduction

腺苷激活的 per2 通过上调 TGF-β 信号促进斑马鱼嗅觉上皮球形基底细胞(GBCs)的再生

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摘要：生物钟在维持组织稳态和促进神经发生中起着至关重要的作用。嗅觉上皮（OE）的神经发生和再生能力与水平基底细胞（HBCs）和球形基底细胞（GBCs）密切相关。然而，生物钟在 GBC 介导的再生中的作用机制尚不清楚。在这里，我们观察到 OE 和嗅觉球（OB）显示出强大的昼夜节律振荡，关键的昼夜节律基因主要在 OE 和嗅觉神经层（ONL）、OB 的颗粒层（GL）中节律性表达。对斑马鱼、小鼠和狒狒嗅觉球的转录组时间序列分析都揭示了再生和嘌呤主要在 CT20-CT22 左右达到峰值，这表明嗅觉再生可能与嘌呤代谢紧密相关。有趣的是，外源性腺苷处理增强了嗅觉球的昼夜节律振荡，提前了 GBC 介导的再生节律，通过化学遗传学消融嗅觉感觉神经元（OSNs）后恢复了行为节律，并上调了 p-Creb/Creb 和 *per2*。此外，对 *adora2aa*$^{-/-}$斑马鱼的 RNA-seq 和 OSNs 消融的 *Tg(ompb:DenNTR;CG2)*斑马鱼的 scRNA-seq 分析都揭示了 TGF-β信号传导可能有助于 GBCs 介导的再生。特别是，*per2* 的缺失上调了 TGF-β信号抑制剂 *tgif1* 和 *six3b*，并抑制了 GBCs 介导的再生。总的来说，我们的研究结果表明，腺苷激活的 *per2* 通过下调 *tgif1* 和 *six3b* 促进 TGF-β信号传导，识别了腺苷-CREB-Per2-TGF-β信号轴在 OE 的 GBCs 再生中的作用，并为 OE 神经发生缺陷提供了一种有前景的治疗策略。

关键词：the olfactory epithelium, p-CREB/CREB, per2, GBC regeneration rhythm, TGF-β signaling pathway

S1. 早期发育与形态发生

Early development and morphogenesis

Transcriptional Reactivation of Huluwa Reveals Maternal Mechanisms of Genetic Robustness

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Genetic robustness refers to the ability of an organism to maintain viability and adaptability under environmental perturbations or genetic mutations, which can be achieved through compensatory mechanisms such as gene redundancy, alternative splicing, transcriptional adaptation, and epigenetic regulation. Huluwa, a maternally inherited factor that mediates β-catenin signaling to specify the dorsal organizer and initiate body axis formation, exhibits a distinct maternal-specific transcriptional activation pattern, the underlying mechanism of which remains unclear. In this study, we generated a rescued zebrafish mutant (*huluwa*$^{tsu01sm/tsu01sm;rev/rev}$) from a maternal mutant background (*huluwa*$^{tsu01sm/tsu01sm}$), in which body axis development and huluwa expression were restored, and found that the *tsu01sm* and *rev* mutation sites were genetically linked. Transcriptome profiling and RLM-RACE analysis revealed that the rescued mutant may employ alternative transcription start sites to restore *huluwa* transcriptional activity. Furthermore, integrated analysis of whole-genome sequencing and histone modification mapping identified a mutation-dense region approximately 0.5 Mb downstream of the *huluwa* locus enriched in H3K27me3 specifically in the *tsu01sm* mutant, as revealed by Cut&Tag analysis of stage I oocytes, suggesting that mutations in this region may influence chromatin state or higher-order architecture and consequently affect *huluwa* transcription. These findings uncover a compensatory mechanism underlying maternal-specific gene regulation and provide new insight into how early embryonic systems preserve developmental stability in response to transcriptional loss, advancing our understanding of epigenetic robustness and regulatory plasticity of the maternal inheritance.

Key Words：zebrafish; Genetic robustness; huluwa; Maternal regulation

Maternal Erk1/2 regulate dorsal development and axis body formation

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The dorsal development and the establishment of basic embryonic body axis provide the foundation for the formation of body plan. In many vertebrates, determination of dorsal-ventral axis requires proteins of Wnt signaling, which have been asymmetrically located in oocytes and maternal Huluwa is an essential determinant of the dorsal organizer and body axis in early embryonic development. Despite these intriguing findings, whether there exist other maternal genes regulating dorsal development and what the co-regulatory factors of maternal Hwa remain enigmatic.

Here we found that maternal extracellular signal-regulated kinase 1 (Erk1) and Erk2, the downstream effectors of mitogen-activated protein kinase (MAPK) signaling, are essential for dorsal-ventral patterning in zebrafish. Phosphorylated Erk1/2 (p-Erk1/2), indicating Erk activation, colocalize with β-catenin in nucleus at the 1k-cell stage and predict the dorsal organizer. Notably, maternal Erk1/2 activation can rescue body axis formation of maternal *huluwa* mutant and maternal-zygotic *β-catenin2* mutant, and has strong secondary axis-inducing activities whose induction efficiency is better than caβ-catenin. Mechanistically, Hwa binds to and promotes GSK3β degradation, resulting in Erk1/2 phosphorylation and p-Erk further induce organizer and axis body through *jun/fos* activation. In turn, maternal Erk1/2 activation can promote *hwa* transcription by *jun/fos* in oocytes.

Therefore, maternal Erk1/2 play a critical role in dorsal-ventral patterning and it is the first time to focus on and plan to systematically elaborate the molecular mechanism of maternal MAPK/Erk signaling pathway regulating dorsal-ventral fate at oocyte stage and blastocyst stage,as well as the new mechanism about Hwa in dorsal determination and body axis formation.

Key Words： Maternal-effect gene, Erk1/2, Hwa, Dorsal development, Axis body formation

巨指的疾病模型构建

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摘要：巨指症（Macrodactyly）源自希腊语“makros”，是一种罕见的先天性手部和/或足部异常，表现为一个或多个手指或脚趾的过度生长。这种增大可能涉及所有组织，包括骨骼、肌肉、脂肪和神经，会显着改变肢体的外观并损害其功能。目前暂未有针对巨指症的局部增殖性的稳定模型的相关报道，在我们的研究中，选用 ZRS 增强子，构建了稳定的 PIK3CA（H1047R）的斑马鱼模型；此外，我们还选用了 sZRS、hZRS（正常及点突变）、800bp（我们实验室此前发现的与 ZRS 具有类似功能的增强子）进行了模型的构建，可用于后续对巨指症的药物筛选和靶向治疗探究。鉴于斑马鱼和人类的基因相似度虽然高达 87%，但在生理和病理状态上仍然存在显著差异，我们还探索了使用人来源的 IPS 建立肢芽类器官的方案，目前已经得到并验证了稳定的肢芽间充质细胞。

关键词：巨指，斑马鱼，iPSC

视黄酸通过 Rcan2 调控钾离子通道控制发育和再生中的斑马鱼附肢尺寸

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摘要：所有器官都需要多种细胞的协调生长，以达到与身体的正确比例。我们发现了一种电生理机制，即钾离子通道调控发育分子机制来控制整个解剖结构的尺寸比例。以斑马鱼胸鳍鳍芽作为早期脊椎动物鳍/肢发育的模型，我们观察到在鳍芽生长过程中，所有胚胎组织的内源性细胞内钾离子水平协调性地降低，并发现钾离子通道 Kcnk5b 在发育中鳍芽的间充质组织中表达。过表达 Kcnk5b 能够通过降低细胞内钾离子水平，增强形态发生素的转录，进而增大解剖结构的尺寸。由于这些形态发生素是脊椎动物胚胎鳍/肢芽发育程序的一部分，而该发育程序在脊椎动物中是保守的，故这些结果表明这一电生理调控尺寸的机制在所有脊椎动物中都保守。视黄酸是一种能够增加肢体尺寸的激素类形态发生素，我们发现其能降低鳍芽所有组织的细胞内钾离子水平。随后我们发现，RA 上调了鳍芽中 rcan2 的表达，而 rcan2 是钙调磷酸酶 calcineurin 的调节因子，我们后续发现 rcan2 的过表达不仅可以降低细胞内钾离子水平，还能促进整个鳍芽的生长。相反，敲除 rcan2 会导致鳍芽细胞内钾离子水平升高，并抑制协调生长。此外，我们还发现 rcan2 的这一尺寸调控能力依赖于 Kcnk5b，因为 Kcnk5b 敲除会阻断 rcan2 诱导的细胞内钾离子水平降低和增强生长。我们在成年鱼鳍的再生中也观察到了类似现象。这些结果揭示了视黄酸可以通过 rcan2 调控 kcnk5b 进而调节鳍芽和再生尾鳍大小。

关键词：协调生长，kcnk5b，rcan2

斑马鱼卵黄囊消失的机制研究

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摘要：斑马鱼卵黄囊是胚胎早期的关键营养与代谢器官：其内富含卵黄颗粒，外层由≈300 个细胞核构成的卵黄核包层（YSL）包裹。0–5 dpf 期间，卵黄颗粒经大规模降解，为胚胎提供主要能量；当卵黄储备在 5–6 dpf 耗尽后，卵黄囊本身会悄然退化并最终消失，但其具体清除机制尚未阐明。

本研究在斑马鱼活体系统中解析卵黄囊的程序性自我消除。我们提出卵黄囊衰退可能遵循“自噬活化→局部凋亡→免疫细胞静默吞噬”三级协同路径，并正系统评估各环节的重要性。同时，我们探索卵黄囊退化对肠-肝等外源营养器官接管功能的影响，借此构建“代谢器官交班”整体模型。该工作有望揭示发育过程中大型多核同步体的低炎症清除逻辑，提供触发组织退化的新型分子开关，为再生医学与溶酶体-代谢疾病研究开拓思路。

关键词：斑马鱼，卵黄囊，程序性自我消除

Systems Identification of Otolith Formation Regulators via Single-Cell Omics Profiling of Otic Vesicle Development

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The molecular mechanisms governing otolith biomineralization remain incompletely resolved due to limitations in spatiotemporal resolution of traditional approaches. To address this, we present an integrated single-cell atlas of zebrafish inner ear development, combining public datasets with newly generated 96753 single-cell transcriptomes from our laboratory. After rigorous quality control and batch effect correction using Seurat v4 and Harmony integration, 58,835 high-confidence cells were retained, capturing the complete trajectory of otic vesicle morphogenesis from placode induction (14hpf) to functional maturation (120hpf).Our analysis leveraged multi-modal dynamic profiling: Pseudotemporal reconstruction revealed bifurcation points in otic vesicle and otolith lineages at 14–120 hpf; Cellular interaction networks (CellChat) predicted the pathway crosstalk between dorsolateral epithelium and differentiating otolith-forming cells (OFCs). Three pivotal biological events govern otolith formation:

Establishment of the polarity center defining the spatial axis for biomineralization; Specification and enrichment of otolith precursors (OFCs lineage) through chemoattractant-guided aggregation; Emergence of tether hair cells anchoring otoliths to the sensory epithelium via kinocilial coupling.

Focusing on OFC as a novel subcluster we performed multi-method regulator screening:Cis-regulatory analysis prioritized 23 TFs (e.g., nr4a2b， dacha);Weighted gene co-expression networks (WGCNA) uncovered mineral transport modules (slc26a, ca2+ paralogs).

Cross-validation confirmed functional convergence:In situ hybridization localized mb to OFC1 during crystal nucleation (48 hpf);knockdown of slc26a10 disrupted otolith calcification (Alizarin red quantification, *$p<0.01$);

Critically, our computational model (multi-omics neural network) predicted stage-specific expression of otolith regulators , This resource establishes a systems-level framework for otolith regulation, with implications for vestibular dysfunction therapies.

Key Words： zebrafish, development, otic vesicle, otolith

敲降 snx9a 对斑马鱼早期发育影响的表型鉴定

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摘要：分选连接蛋白（Sorting nexins，SNXs）是一个高度保守且多样化的膜相关蛋白家族，在蛋白质运输的调节及内吞途径中都起着关键作用，SNXs 家族通过参与蛋白质降解、细胞内信号传导、损害跨膜蛋白的表达或功能来间接调节下游信号传导等途径参与内吞转运作用。目前已有多项研究结果表明 SNXs 与心脑血管疾病发生发展有关，其中发现斑马鱼 snx9 基因存在早期内体膜中，在周皮、尾芽、血管和腹侧中胚层中均有表达，参与早期内体到高尔基体的转运和细胞内蛋白质，提示 snx9 基因可能对斑马鱼早期发育有影响。Snx9 基因在斑马鱼中存在等位基因 *snx9a* 和 *snx9b* 两种亚型，通过生物信息分析发现 *snx9a* 比 *snx9b* 与人类同源性更高，因此本实验通过常用的基因敲除技术之一的吗啉代寡核苷酸技术下调斑马鱼 *snx9a* 基因的表达，构建 *snx9a* 基因敲降模型，初步鉴定 *snx9a* 基因表达降低后对斑马鱼形态发育的影响，以期为后续探索 *snx9a* 基因缺陷在斑马鱼异常发育过程中可能发挥的作用奠定研究基础。使用吗啉代寡核苷酸技术下调斑马鱼 *snx9a* 基因的表达后，在体式显微镜下观察实验组与对照组斑马鱼形态发育情况，初步发现 *snx9a* 基因表达降低后，斑马鱼的形态发育出现一定程度的缺陷。

关键词：斑马鱼，吗啉代寡核苷酸技术，snx9a 基因，发育；

高时间特异性分析母源 Rbm24a 在生殖颗粒组装中的功能

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摘要：生殖颗粒是一类核糖核蛋白（RNP）生物分子凝聚体，决定原始生殖细胞（PGCs）的命运，并被广泛用作研究 RNP 颗粒组装的模型体系。在本研究中，我们发现母源 RNA 结合蛋白 Rbm24a 是控制 mRNA 特异性进入生殖颗粒的关键因子。Rbm24a 与生殖质组分 Buc 相互作用，驱动生殖质 mRNA 被招募到相分离的凝聚体中。缺少 Rbm24a 及其绑定 mRNA 的生殖颗粒无法朝卵裂沟定向移动并在该处将多个小颗粒融合为大型生殖颗粒。结果，母源 Rbm24a 的缺失导致生殖颗粒降解并造成 PGCs 不能分化。为了分析 Rbm24a 的“组装后”功能，我们将秀丽隐杆线虫的 AID 系统改造并应用于斑马鱼。实验证明，在 4-细胞期之后去除 Rbm24a 会破坏生殖质 mRNA 和蛋白质在颗粒内的亚区分布，进而导致颗粒解离和衰亡。综上，Rbm24a 充当了维持生殖颗粒所必需的“成核支架”，揭示了 RNA 结合蛋白如何招募 RNA 并维系颗粒亚结构的全新机制。

关键词：Germ granule, Targeted protein degradation, AID, zGrad, Rbm24a

孤独症相关基因 TMLHE 在斑马鱼神经发育和行为中的作用研究

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摘要：孤独症谱系障碍（ASD）是以社交沟通缺陷、重复刻板行为为核心特征的神经发育障碍，其遗传基础尚待深入解析。TMLHE 基因编码三甲基赖氨酸羟化酶，参与肉碱生物合成，其功能异常与 ASD 发病风险显著相关，但其在神经发育中的具体作用机制尚未明确。整胚原位杂交显示，TMLHE 在斑马鱼胚胎期呈时空特异性表达，于中后脑边界、后脑及耳泡等区域高表达，提示其可能调控神经系统发育。吗啉代寡核苷酸（MO）构建的 TMLHE 敲降模型（*tmlh*e-MO）早期体长较短且躯干卷曲；结合 Tg（*elavl3*：EGFP）转基因斑马鱼（标记 GABA 能神经元）观察，发现 *tmlhe*-MO 胚胎荧光强度显著降低，提示 GABA 能神经元发育受损。行为学分析显示，5 dpf tmlhe-MO 幼鱼游泳能力下降且趋触行为明显，呈典型焦虑样表型，与 ASD 核心行为特征高度吻合。*tmlhe*-MO 胚胎中相关神经标记基因（*adgrb1*、*gad1b*、*zic1*、*sox2*）表达显著下调，提示 TMLHE 缺失可能通过抑制 GABA 能神经元分化及突触形成，干扰早期神经系统及后脑发育。本研究揭示，*tmlhe* 敲降可诱导早期 GABA 能神经元发育异常、神经标记基因下调及 ASD 相关焦虑样行为，表明 *tmlhe* 通过调控 GABA 能神经环路发育参与 ASD 病理过程，为进一步探究其在斑马鱼神经发育中的作用机制提供重要线索。

关键词：斑马鱼，孤独症谱系障碍，易感基因，TMLHE

Distinct contributions of Nanog, Pou5f3 and Sox19b to zebrafish oogenesis and early embryogenesis revealed by systematic gene knock-in

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Pioneer factors Nanog, Pou5f3, and Sox19b (collectively referred to as NPS), activate zygotic genome activation (ZGA) and facilitate the maternal-zygotic transition (MZT). However, the functions of NPS during oogenesis remain unknown, and the mechanisms underlying the phenotypic differences in early embryonic development caused by individual loss of Nanog, Pou5f3, or Sox19b are still unclear. Here, we characterized the distinct contributions of Nanog, Pou5f3 and Sox19b to zebrafish oogenesis and early embryogenesis through systematic gene knock-in. We demonstrate that maternal depletion of *nanog*, *pou5f3*, or *sox19b* individually causes defects of varying severity in egg activation, including impaired chorionic elevation and blocked cortical granule (CG) exocytosis, revealing critical and distinct functions for each NPS factor in oogenesis. Furthermore, the KI lines revealed unique localization and expression dynamics for each NPS factor during oogenesis. Critically, CUT&RUN analysis using the nanog KI line identified maternal Nanog specifically bound to promoter regions of egg activation genes *larp6b* and *slc39a9*. The egg activation defect in maternal Nanog-deficient embryos is primarily attributed to failed transcriptional activation of the two genes. Finally, we delineate the distinct maternal and zygotic expression profiles of NPS throughout embryonic development, demonstrating their close association with the specific mutant phenotypes. Thus, this study establishes essential maternal roles for NPS factors during zebrafish oogenesis and early embryonic development, defines their dynamic expression profiles, and links Nanog's maternal function to direct transcriptional regulation of key effector genes, providing a mechanistic basis for their divergent developmental contributions.

Key Words： Zebrafish, Knock-In, MZT, CUT&RUN, Pioneer Factors

S2. 血液发生和疾病

Blood production,diseases

ATF7IP/SETDB1-mediated epigenetic programming regulates thymic homing and T lymphopoiesis of hematopoietic progenitors during embryogenesis

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T lymphocytes, which are essential for cell-mediated immunity in vertebrates, rely on the successful thymic seeding of lymphoid progenitors for lineage commitment, stepwise differentiation, and full maturation into functional T cells. However, the underlying epigenetic mechanisms that regulate the migration and developmental programming of lymphoid-primed progenitors remain incompletely understood. Here, we demonstrate that zebrafish embryos deficient in either the epigenetic modulator Atf7ip or the histone H3K9 methyltransferase Setdb1 exhibit decreased thymic homing and differentiation of lymphoid progenitor cells. Mechanistically, we reveal that Atf7ip regulates T cell progenitor homing and differentiation via Setdb1- triggered H3K9 trimethylation. Specifically, Atf7ip interacts with Setdb1 to catalyze H3K9me3 modification of the key immune regulator *bach2b* to derepress the expression of *ccr9a* and *irf4a*, thereby promoting lymphoid progenitor homing and intrathymic differentiation. In the absence of Atf7ip or Setdb1, replenishing *irf4a* or diminishing *bach2b* restores the thymic trafficking and differentiation of lymphoid progenitor cells. Notably, depletion of ATF7IP by two complementary cre-recombinase alleles in mice (*CAG-CreERT2* and *Mx1-iCre*) impedes the migration of hematopoietic progenitors to the thymus, resulting in declined T lymphopoiesis. Together, these findings establish the role of ATF7IP/SETDB1-mediated epigenetic programming in governing T lymphoid progenitor trafficking and differentiation, with implications for understanding the pathogenesis of human T lymphoid diseases.

Key Words： ATF7IP, SETDB1, histone modification, T cell progenitor, thymic homing

Prdm15 cooperate with Scl/Klf1/Nap1l4a to mediate interactions among cis-regulatory elements and transcription essential for primitive erythropoiesis

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Prdm15 shows high expression in hematopoietic tissues, with mutations, deletions, and abnormal expression in diseases such as acute myeloid leukemia (AML). However, the roles of Prdm15 in the development of erythropoiesis and the related diseases remain known. Here, using genetically engineered zebrafish embryos and larvae, we demonstrate that prdm15 homozygous mutants (prdm15-/-) were more sensitive to hypoxia stress and exhibited impaired primitive erythropoiesis. Mechanistically, proteins Prdm15 cooperates with erythrocyte-specific transcriptional factors (TFs) Scl and Klf1, and cooperating with Nap1l4a for the following recruitment of histone variant H2A.Z, to remodel cis-regulatory elements (CREs) landscape and the consequent nascent RNA transcription of erythropoiesis genes. Meanwhile, Prdm15 deficiency impaired the chromatin accessibility of epigenetic genes kmt2ca and kmt2cb, led to diminished H3K4me1 in erythrocytes and the associated epigenomics and led to abnormal erythropoiesis. Prdm15 deficiency diminished PolII binding on chromatin of erythrocyte-specific transcriptional factors (TFs) and erythropoiesis genes, and led to their impaired transcriptional initiation and elongation and the resulted in abnormal erythropoiesis. Moreover, Prdm15 functioned as potential lysine methyltransferase in regulating protein stabilities of PolII and Klf1, to regulate erythropoiesis. Together, the results demonstrate a novel, cell-type-specific function for Prdm15 in which it may serve to facilitate the precise transcriptional complex deposition in CREs, and serve to maintain the protein stabilities of TFs as a novel identified lysine methyltransferase.

Key Words： Prdm15; cis-regulatory elements; erythropoiesis; lysine methyltransferase

CREG1 调控斑马鱼红细胞发育研究

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摘要：CREG1 是一种在物种进化过程中高度保守的小分子糖基化修饰蛋白，涉及细胞增殖、分化、衰老以及自噬等多种生理过程。然而，现阶段 CREG1 在造血发育，特别是在红细胞发育中的生物学功能尚不明确。本研究发现，CREG1 的表达水平随着红系细胞的分化成熟进程而逐渐升高。在斑马鱼胚胎期，敲除 CREG1 基因导致红系祖细胞分化成熟障碍以及过度细胞凋亡，从而引起红细胞生成减少。在分子机制层面，CREG1 缺失导致 TGF-β/Smad2 信号通路减弱，采用 Smad2 激动剂（IDE2）处理后，贫血表型在 *creg1*$^{-/-}$突变体中得到显著缓解。此外，Klf1 作为 TGF-β/Smad2 信号通路的下游关键靶基因，参与了 CREG1 调控的红细胞发育过程。在斑马鱼成体期，单细胞转录组测序（scRNA-seq）进一步揭示 CREG1 缺失导致的贫血现象持续存在。值得关注的是，我们还鉴定出一类具有免疫特征的红细胞亚群。CREG1 缺失抑制红系祖细胞向经典红细胞分化，同时促进其向具有免疫特征的红细胞分化。这些发现揭示了 CREG1 作为红细胞生成的关键调节因子的新角色，有望为理解正常红细胞发育及相关红系疾病的发生机制提供新的见解。

关键词：CREG1，红细胞，TGF-β/Smad2 信号通路，免疫调控

TRMT10C 介导的线粒体 tRNA 修饰通过 ROS/mTOR 通路调控造血谱系分化

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摘要：造血干细胞（HSC）是干细胞研究的重要模型。在造血发育过程中，代谢方式从糖酵解向氧化磷酸化的转变对于谱系分化至关重要。然而，线粒体功能如何影响这一过程仍不清楚。为探讨这一问题，我们聚焦于 tRNA 修饰，这一机制可以快速调控线粒体转录本的翻译效率，从而迅速改变细胞的能量代谢状态。我们研究了线粒体 tRNA 修饰酶 TRMT10C，该酶能修饰作用于线粒体 tRNA 第 9 位的嘌呤碱基。Trmt10c 在造血干/祖细胞中高表达，因此成为研究线粒体 RNA 修饰对造血谱系分化影响的理想靶点。

为了探究 TRMT10C 在造血发育中的作用，我们构建了 Vav1-iCre; Trmt10cfl/fl 小鼠。由于 Trmt10c 缺失导致胚胎致死，我们分析了胚胎第 14.5 天（E14.5）的胎肝。流式分析显示，LSK 和 LK 细胞群体显著扩增，但红系发育受阻。

我们对胎肝细胞进行了 RNA-seq 和 Ribo-seq。RNA-seq 结果显示，氧化磷酸化相关基因下调，凝血相关基因上调，提示代谢转换失败及谱系偏向巨核细胞方向。联合分析发现， ROS 引起的 AKT/mTOR 通路的多种上游因子均上调，表明翻译调控通路异常激活。

最后，我们进行了雷帕霉素（mTOR 通路抑制剂）拯救实验。在竞争性移植实验中，Trmt10c 缺失细胞的受体小鼠在雷帕霉素处理后，其红系发育明显改善，进一步支持 mTOR 通路异常激活在 Trmt10c 缺失引起的发育障碍中的关键作用。

关键词：线粒体，tRNA 修饰，TRMT10C，造血干细胞，mTOR

Nanopore Direct RNA Sequencing Reveals mettl3-dependent m6A Regulation of Vascular Development

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N^6-methyladenosine (m6A) modifications play important roles in vascular development, but the underlying mechanisms remain unclear. Oxford Nanopore direct RNA sequencing (DRS) profiles isoforms, RNA modifications and poly(A) tails at the single-molecule, single-nucleotide resolution. Vascular defects have been observed in *mettl3*$^{-/-}$ knockout (KO) zebrafish, therefore we performed direct RNA sequencing on 24 hours post-fertilization (hpf) WT and KO embryos, generating 9.8 M and 8.9 M reads that revealed 17,728 and 18,378 expressed genes, of which 1,530 and 1,896 were novel, respectively. The m6A sites were enriched near stop codons and preferentially located in long exons that fall outside of exon-junction–complex protection. In KO embryos, the total number of m6A sites (probability >= 0.9) was increased by ~3.9%, while the number of highly methylated (>80%) sites was decreased by ~4.2%, suggesting the presence of functional *mettl3* splice isoforms or other compensatory mechanisms. There were no significant differences in the distribution of alternative-splicing types, whereas transcripts with long poly(A) tail length (>150 bps) in KO embryos was increased by ~9.3%. Differential m6A methylated genes were enriched in fundamental RNA functions, such as transcription, RNA binding, and transcription factor binding. Correspondingly, these genes were also enriched in angiogenesis related signaling pathways, including the VEGF, Wnt, Hippo, and Notch pathways. By integrating m6A profiling with analysis of gene expression data, we identified candidate genes *wnt8a* and *pfkla* that appear to influence vascular development through the Wnt and mTOR signaling pathways.

Key Words： Vascular development; RNA m6A methylation; Nanopore direct RNA sequencing; Zebrafish model

Function and Regulatory Mechanism of Tfpia in Hematopoiesis in Zebrafish

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The tissue factor pathway inhibitor (TFPI), a Kunitz-type serine protease inhibitor, regulates the tissue factor (TF)-dependent coagulation pathway, however, its role in hematopoiesis remains to be systematically investigated. In this study, we established tfpia-knockout (KO) or knockdown (KD) zebrafish using CRISPR-Cas9 gene editing and morpholino technologies to explore tfpia's functions in hematopoiesis. We found that tfpia-deficient embryos exhibited reduced expression of hemangioblast markers etsrp, scl, and fli, indicating tfpia's role in early hemangioblast differentiation. During primitive hematopoiesis, tfpia KO or KD decreased expression of myeloid markers mpo for granulocytes and l-plastin for monocytes/macrophages, while erythroid markers gata1 and hbae1 remained unaffected, suggesting a role tfpia in primitive myelopoiesis. In definitive hematopoiesis, tfpia KO or KD led to downregulation of myeloid markers mpo, l-plastin and lymphoid marker rag1, reduced hemoglobin levels, decreased expression of HSC differentiation markers runx1 and c-myb, diminished fluorescent signals marking HSCs, and lowered c-myb expression in caudal hematopoietic tissue. The results collectively demonstrate tfpia's role in definitive hematopoiesis by regulating HSC production, migration and homing. Increased apoptosis in HSCs following tfpia KD may contribute to reduction of HSC numbers. Mechanistically, tfpia KO decreased Wnt signaling, while LiCl-mediated Wnt activation rescued the HSC deficiency caused by tfpia KD, suggesting that tfpia regulates HSC development through Wnt signaling. This study provides the first in vivo systematic analysis of tfpia's critical roles in zebrafish hematopoiesis, which reveals its novel functions in hemangioblast differentiation, primitive myelopoiesis and definitive hematopoiesis. The results also identify a new molecular mechanism whereby tfpia modulates Wnt signaling to influence HSC production, migration and homing, potentially offering new therapeutic strategies for blood and vascular disorders.

Key Words： Zebrafish, hematopoiesis, tfpia

chd2 Mediates crosstalk between Neural Development and Hematopoietic stem and progenitor cell Expansion via Inflammation in Zebrafish Embryos

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Hematopoietic stem and progenitor cells (HSPCs) require a tightly regulated developmental microenvironment for normal functions. While neural signals are known to be critical for HSPC emergence, their role in regulating rapid HSPC expansion remains poorly understood. Chromodomain helicase DNA binding protein 2 (Chd2) is a chromatin remodeling factor previously associated with congenital epilepsy and intellectual disability. Here, we reveal that *chd2* regulates HSPC development in the caudal hematopoietic tissue (CHT) through a neuro-immune pathway, wherein *chd2* controls glutamate release from glutamatergic neurons, leading to macrophage activation and inflammatory remodeling of the hematopoietic niche. First, we generated a *chd2* mutant zebrafish, which exhibited defective HSPC development in CHT, attributable to alterations in the hematopoietic niche rather than impaired HSPC emergence. Given that *chd2* is a known causative gene for neurological disorders, we then examined neural development in mutant embryos and found aberrant development of glutamatergic neurons. Exploring the potential connection between developing glutamatergic neurons and HSPCs, we found that HSPC development in the CHT requires glutamate released from glutamatergic neurons. Finally, we discovered that macrophages mediate the effect of glutamatergic neurons on HSPCs. Specifically, macrophages sense extracellular glutamate through the NMDA receptor, thereby modulating their inflammatory response and ultimately shaping HSPC development within the CHT. Heightened inflammatory stress in *chd2* mutant embryos may contribute to the ferroptotic death of HSPCs. These findings reveal a novel role for the nervous system in regulating HSPC development, providing new insights into the co-occurrence of neurodevelopmental disorders and immune deficiencies.

Key Words： HSPC expansion; Neuron development; Inflammation; Chd2; Ferroptosis

Wdr5-mediated H3K4 methylation facilitates HSPC development via maintenance of genomic stability in zebrafish

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Abstract: During fetal stage, hematopoietic stem and progenitor cells (HSPCs) undergo rapid proliferation with a tight control of genomic stability. Although histone H3 lysine 4 (H3K4) methylation has been reported to stabilize the genome in proliferating cells, its specific role in HSPC development remains elusive. In this study, we demonstrated that *wdr5*-mediated H3K4 methylation is crucial for maintaining genomic stability of proliferating HSPCs in zebrafish embryos. Loss of *wdr5* led to a severe reduction of HSPC pool in the caudal hematopoietic tissue (CHT), accompanied with attenuated H3K4 methylation level and evident *p53*-dependent apoptosis in the HSPCs. Mechanistically, Wdr5-mediated H3K4 methylation maintains genomic stability by inhibiting the formation of abnormal R-loops in the HSPCs, whereas accumulation of R-loops exacerbates DNA damage. Moreover, the absence of H3K4 trimethylation leads to an inactivated DNA damage response pathway, which is deleterious to DNA damage repair and genomic stability. Subsequently, we found that DNA damage response-associated genes, *mlh1* and *brip1*, are important to ensure HSPC survival, likely by stabilizing their genome. In summary, these findings reveal that Wdr5-mediated H3K4 methylation is essential for HSPC development through tight control of R-loop accumulation and DNA damage response-associated program to ensure genomic stability and survival of proliferating HSPCs.

Key Words： Hematopoietic Stem and Progenitor Cell, H3K4 Methylation, Genome Stability, R-loops

四物汤及白芍改善造血功能障碍的药效作用及机制研究

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摘要：造血障碍的有效治疗仍是重要临床挑战。以四物汤为代表的补血类中药在治疗造血障碍相关疾病中经验丰富，临床疗效确切，运用现代研究手段挖掘其药效物质基础具有重要意义。本工作通过敲降 Diamond-Blackfan 贫血常见致病位点核糖体蛋白 Rps19 编码基因构建造血障碍斑马鱼模型，并对四物汤及其成分的造血调控作用进行评价。发现四物汤能显著增加 rps19KD 中循环红细胞数量与血红蛋白含量，在对四物汤中四种药材进行药效评价后，发现白芍具有显著促红系造血作用，可能是在该疾病模型中介导四物汤药效的关键药材。组学分析揭示白芍能够缓解疾病模型所引起的蛋白应激，铁死亡及过氧化物酶体损伤。继而通过 CX-5461 构建小鼠红系造血障碍模型，发现白芍也能挽救小鼠外周血与骨髓中幼红细胞数量。为挖掘白芍中活性药效物质，进而结合液相质谱分析与斑马鱼药效物质筛选，定位若干具有造血调控潜力的活性单体化合物，并在细胞与小鼠模型中探索其作用机制。本工作为进一步诠释中药补血养血理论科学内涵提供了生物学证据。

关键词：斑马鱼、模式动物、造血障碍、中医药。

RNA 解旋酶 DDX10 通过 MDM4-p53 轴调控造血干细胞发育的机制研究

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摘要：造血干细胞（Hematopoietic Stem Cells, HSCs）在血液系统疾病的发生与治疗中发挥着至关重要的作用。然而，HSCs 在体内的发育机制仍未被完全阐明。我们的前期研究在斑马鱼中发现，RNA 解旋酶 Ddx10 在尾部造血组织中高表达，其功能对于 HSCs 的形成至关重要。敲除 *ddx10* 显著减少胚胎 HSCs 的数目。机制研究表明，*ddx10* 突变导致 *mdm4* 的可变剪接模式发生改变，并伴随 p53 信号通路的异常激活。进一步功能实验显示，过表达野生型 *mdm4* 或敲降 *p53* 均可在一定程度上恢复 HSCs 的生成缺陷。此外，在小鼠模型中，条件性敲除 *Ddx10* 会导致外周血中淋巴细胞和红细胞数量显著减少，而中性粒细胞数量则无明显变化，提示 *Ddx10* 在脊椎动物中发挥保守的造血调控功能。综上，本研究揭示了 *ddx10* 在造血干细胞发育过程中的关键作用，并通过其调控 *mdm4* 剪接与 p53 信号轴影响 HSCs 形成。这不仅拓展了我们对 HSCs 发育调控网络的理解，也为 p53 信号通路的调控机制研究提供了新思路，未来有望为造血干细胞的体外扩增与相关血液疾病的治疗提供理论基础。

关键词：斑马鱼，造血干细胞，mdm4，可变剪接，p53

Prpf4 以不同的机制顺序性调控了红细胞增殖和成熟

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摘要：早期红细胞的增殖及其后续的成熟是红细胞生成过程中的关键事件，而这两个独立但又相互关联的过程如何在红细胞生成过程中被高效协调，在很大程度上是未知的。Prpf4 基因的表达从红系前集落形成单位（PreCFU-E）到有核红细胞阶段显著富集，尤其在 CFU-E 细胞中，这暗示 Prpf4 在红细胞生成中扮演着关键角色。本文中，我们证明 prpf4 在斑马鱼终末造血过程中依次调控红细胞的增殖和成熟。数据显示，prpf4 突变导致严重的红细胞生成缺陷，其特征是红系细胞数量大幅减少以及红细胞成熟受损。进一步分析表明，prpf4 突变导致红细胞在 S 期和 G2/M 期发生细胞周期阻滞，并显著增加红细胞凋亡。从机制上讲，prpf4 突变导致 DNA 损伤，继而激活 DNA 损伤应答（DDR），触发 ATM/CHK2-p53 信号通路。这一过程抑制了早期红细胞的增殖并诱导红细胞凋亡。另一方面， prpf4 突变导致前体 mRNA 剪接过程中发生显著的外显子跳跃缺陷，同时伴随 slc25a39 前体 mRNA 的严重剪接缺陷。这导致 slc25a39mRNA 显著下调，最终损害红细胞生成晚期的红细胞成熟。总之，我们证实 prpf4 依次调控早期红细胞增殖和后续的红细胞成熟。prpf4 的这种双重功能，部分解释了在红细胞生成过程中，早期红细胞增殖与晚期红细胞成熟是如何被高效协调的。

关键词：Prpf4; erythrocyte proliferation；DNA damage response;RNA splicing; erythrocyte maturation.

Minoxidil Ameliorates Myelodysplastic Syndrome by Targeting Wnt4 While Sparing Normal Hematopoiesis

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Hematopoietic development is a fundamental biological process that governs the formation and maturation of blood cells through tightly regulated multilineage differentiation. Despite extensive research, many regulatory mechanisms remain elusive. Hematopoietic stem cells, the source of all blood cell types, are central to maintaining hematopoietic homeostasis and represent key targets in the treatment of hematologic diseases. Through a small-molecule screen in zebrafish, we identified a well-known antihypertensive and hair growth-promoting agent, minoxidil, as a compound that significantly reduces the number of hematopoietic stem and progenitor cells. Functional assays confirmed that wnt4 regulates hematopoietic stem and progenitor cell numbers, with overexpression significantly increasing and knockout markedly reducing their levels, highlighting wnt4 as a critical regulator of their abundance. Furthermore, minoxidil treatment alleviates myeloid malignancies in the c-mybhyper zebrafish model of myelodysplastic syndrome, potentially via modulation of wnt4 signaling. Minoxidil also demonstrated a dose-dependent safety profile. Lower or intermittent dosing regimens preserved peripheral blood cell counts in mice, while sustained high-dose administration induced hematopoietic suppression. These findings demonstrate that minoxidil alleviates myelodysplastic syndrome-like myeloid expansion via Wnt4 signaling modulation. This reveals a dual role for minoxidil, suppressing normal hematopoiesis while offering therapeutic potential against malignancy at appropriate doses. Our work identifies Wnt4 as a novel regulatory factor and a promising therapeutic target for myelodysplastic syndrome.

Key Words：Hematopoiesis，Minoxidil，Wnt4

S3. 心血管发生和疾病

Cardiovascular occurrence and diseases

Zebrafish cardiomyocyte reorient polarity during involution

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During early zebrafish heart development, cardiomyocyte precursor cells (CPCs) differentiate from the lateral plate mesoderm, migrate toward the midline, involute, and directionally extend to form the heart tube. While cellular polarity is essential for these processes, the dynamic changes in polarity, its establishment, and regulatory mechanisms have remained poorly understood. Using fluorescence in situ hybridization, immunofluorescence staining, and live imaging, we systematically reveal for the first time that CPCs undergo significant polarity remodeling during involution, accompanied by altered distributions of adhesion molecules (ZO-1, Cdh2), polarity transport protein Rab11, and apical complexes. Functional disruption of Pard6gb and Rab11 leads to polarity remodeling defects, resulting in heart tube elongation anomalies and cardiac developmental defects, confirming the necessity of polarity remodeling for heart development. Further investigations identify the asymmetric distribution of extracellular matrix (ECM) as a key trigger for polarity remodeling. ECM asymmetry drives the enrichment of Podocalyxin (Podxl) on the inner membrane of bilayered CPCs, promoting degradation of adhesion molecules to ensure proper cell separation. Generation of afdna mutant zebrafish reveals that loss of Afdna (the zebrafish homolog of Afadin) disrupts CPC polarity remodeling, leading to ectopic interlayer adhesions, heart tube elongation failure, and severe cardiac developmental defects. Mechanistically, Afdna collaborates with ECM to restrict active Rap1 to the outer membrane of CPCs, enabling correct activation of Rho on the inner membrane. This spatial regulation of small GTPases guides precise trafficking of Podxl to the inner membrane, eliminating cell adhesions and completing polarity remodeling. Our study systematically maps the molecular changes during CPC polarity remodeling in involution, confirms the critical role of polarity remodeling in heart development, and uncovers an ECM-Afdna-small GTPase-Podxl regulatory network. These findings provide novel theoretical insights into the mechanisms governing vertebrate heart development.

Key Words： Zebrafish, Heart Morphogenesis, Polarity Reorientation, Afadin

Transcriptional Dynamics of Brain Pericytes During Development

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Pericytes are critical components of the neurovascular unit, essential for blood-brain barrier formation and neurovascular coupling. However, transcriptional changes in brain pericytes across developmental stages, particularly during postnatal development and adulthood, remain to be characterized. In this study, we employ single-cell RNA sequencing (scRNA-seq) to profile brain pericytes from embryonic to adult stages, unveiling distinct developmental stage-specific transcriptional signatures. In the adult zebrafish brain, pericytes exhibit reduced intercellular communication and increased levels of metabolic activity. This shift suggests that as pericytes mature, their role transitions from actively interacting with surrounding cells to supporting tissue homeostasis through enhanced metabolic functions. Such changes may reflect adaptation to the stable vascular environment of the adult brain, in contrast to the dynamic developmental phase. Understanding these alterations provides valuable insights into pericyte function during brain maturation, aging, and their potential involvement in regenerative processes. Through integrative bioinformatics analysis, complemented by in vivo imaging and advanced tissue-clearing techniques, we identify a transient cell state of brain pericytes marked by a unique transcriptional program. This state emerges during cerebrovascular development, contributing to the expansion of the brain pericyte population. These findings provide a comprehensive transcriptional atlas of brain pericytes and mechanistic insights into their developmental dynamics.

Key Words： Brain; development; pericyte; single-cell RNA sequencing; zebrafish

DDX24 Spatiotemporally Orchestrates Vascular Development in Zebrafish

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Vascular development is a highly coordinated and tightly regulated process that ensures the proper formation and function of the circulatory system. However, the molecular mechanisms governing its spatiotemporal dynamics, especially across different tissue environments, remain incompletely understood. Our previous studies identified the DEAD-box RNA helicase 24 (DDX24) as a pathogenic gene associated with multi-organ vascular anomalies, yet its developmental role remains to be fully elucidated. In this study, we investigate the function of DDX24 during zebrafish embryogenesis. We find that DDX24 is dynamically and robustly expressed in endothelial cells during key stages of embryonic angiogenesis. Loss-of-function experiments reveal spatially distinct vascular phenotypes: hyperbranching of intersegmental vessels (ISVs) in the trunk and defective central artery (CtA) sprouting in the brain, indicating a context-dependent role of DDX24. Mechanistically, DDX24 deficiency leads to upregulation of VEGFR2 signaling in non-brain endothelial cells via direct binding to KDR mRNA, whereas in brain endothelial cells, it impairs GPR124/RECK-mediated Wnt signaling essential for cerebrovascular patterning. Spatial transcriptomics further uncovers that DDX24 orchestrates endothelial interactions with surrounding cell types, modulating angiocrine signaling landscapes. These findings establish DDX24 as a critical and multifaceted regulator of vascular development, providing novel mechanistic insights and potential therapeutic targets for treating vascular malformations.

Key Words： DDX24, developmental angiogenesis, VEGFR2, Wnt signaling, zebrafish

Spatiotemporal Regulation of DDX24 in Meningeal and Trunk Lymphatic Development in Zebrafish

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The lymphatic vascular system plays a pivotal role in maintaining fluid homeostasisand, immune regulation, and brain interstitial balance. Its development is tightly governed by spatiotemporal mechanisms, yet the organ-specific regulatory pathways involved in lymphangiogenesisremain incompletely understood. This study focuses on the function of the DEAD-box RNA helicase DDX24 in zebrafish lymphatic development. Our preliminary data revealed that DDX24 is highly expressed in endothelial cells of the brain and trunk regions in zebrafish embryos.Using morpholino antisense oligonucleotide (MO)-mediated knockdown of ddx24, we observed pronounced lymphatic defects during late embryogenesis (3–5 days post-fertilization), including progressive loss of meningeal lymphatic endothelial cells [HHH1] (muLECs) and thoracic duct (TD) structures.Transcriptome analysis These results suggest that DDX24 is a critical regulator of lymphatic morphogenesis.Building upon previous studies (Li Hanjie et al., Sun Yat-sen University, 2021),inhumanlymphatic endothelial cellsxxx (HLEC)with DDX24 knockdown, weidentifiedy significant downregulation of lymphangiogenesis-related pathways, particularly VEGFCsignalingthatyyy.Further mechanistic studydemonstratesthat DDX24 has been shown tointeracts with the long non-coding RNA PVT1 andtomodulate the VEGFC/VEGFR3/PROX1 signaling axis, thereby promoting lymphatic endothelial cell proliferation and differentiation. We hypothesize that ddx24 may regulate muLEC and TD formation in zebrafish through a similar mechanism. Follow-up experiments including qPCR andtranscriptome analysiswill be conducted to assess changes in signaling pathway activity and further delineate the underlying regulatory mechanisms. In summary, our findings provide initial evidencesuggestthat ddx24 plays a key role in the development of both cranial and trunk lymphatic vessels in zebrafish. This study, which advances our understanding of the region-specific regulation of lymphangiogenesis and lays the groundwork for future investigations into DDX24-associated lymphatic developmental disorders.

Key Words： DDX24; lymphatic development; meningeal lymphatic vessel, VEGFR3; spatiotemporal regulation

rps20 调节斑马鱼后脑血管发育

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摘要：衰老过程中，脑血管会显著退化，表现为动脉迂曲度增加、血脑屏障功能障碍及脑血流减少——这些变化会共同导致多种神经疾病的发生。然而，衰老相关基因在脑血管发育中的具体作用尚不明确。本研究发现核糖体蛋白 S20（rps20）在衰老脑血管内皮细胞中显著下调表达，是后脑血管发育的关键调控因子。通过分析中老年脑血管内皮细胞的单细胞 RNA 测序数据及 qPCR 验证，我们发现 rps20 在斑马鱼胚胎中高表达，而在成年及老年斑马鱼脑中下调表达。利用 CRISPR/Cas9 介导的 rps20 敲除，我们观察到斑马鱼后脑中央动脉生长受损，颅内出血率升高。进一步的 qPCR 分析显示，参与后脑血管发育的关键信号通路（包括 vegf、cxcl12b 和 cxcr4a）显著下调。我们的研究证明，rps20 对斑马鱼脑血管发育及血管稳态维持至关重要，揭示了一种衰老相关基因调控脑血管发育的新机制。该研究亦为理解衰老相关血管畸形和病变提供了新的视角。

关键词：脑血管、rps20、血管通透性、衰老、斑马鱼

MRAS promotes atherosclerosis by regulating ISG15 activation

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Abstract:Genome-wide association studies (GWAS) have shown that several noncoding single nucleotide variants in the MRAS gene significantly increase the risk of coronary artery disease (CAD). The MRAS gene is an oncogene that encodes a membrane-bound small GTPase. MRAS is involved in a variety of signaling pathways, including regulation of cell differentiation and cell survival as well as acute phase response signaling. However, the role of MRAS in atherosclerosis remains unknown. To study whether MRAS affects the manifestation of atherosclerosis, we established a knockout (KO) line of zebrafish using CRISPR/Cas9 editing, and fed these zebrafish with a high-cholesterol diet for 10 days. In parallel, we evaluated the severity of atherosclerosis in mras-/- KO zebrafish by examining vascular cholesterol deposition, Nile red staining, ROS, and neutrophil and macrophage aggregation. Preliminary data demonstrate a reduction of atherosclerosis in mras-/- KO zebrafish after feeding with a high-cholesterol diet for 10 days as the intravascular cholesterol accumulation, vascular inflammation, systemic lipid levels and oxidative stress were reduced as compared with wide type (WT) zebrafish. Mechanistically, MRAS upregulates ISG15 expression by upregulating p-STAT1tyr701 expression. In conclusion, we show that MRAS regulates the development of atherosclerosis by regulating ISG15, which provides a potential therapeutic target for treatment of atherosclerosis.

Key Words：Zebrafish, atherosclerosis, MRAS

Single-Cell Sequencing Reveals the Mechanism of AGGF1 in Regulating Hemangioblast Developmental Abnormalities

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Hemangioblasts are a type of multipotent progenitor cell derived from the mesoderm, possessing the dual potential to differentiate into hematopoietic cells and vascular endothelial cells. Abnormalities in their differentiation and developmental processes are a major cause of diseases associated with defects in the development of the hematopoietic or vascular systems. Therefore, in-depth investigation of the molecular regulatory network governing hemangioblast differentiation and identification of novel specific marker genes during their differentiation process are crucial for elucidating the pathogenesis of related diseases and identifying novel effective therapeutic targets. Previous studies by our research group have shown that the aggf1 gene is the most upstream key factor regulating hemangioblast differentiation. In aggf1-/- embryos, the expression of npas4l/cloche, the earliest marker for vascular progenitor cells, was significantly reduced; overexpression of aggf1 in embryos increased the expression of npas41/cloche; and overexpression of npas4l reversed the aggf1-/- embryo phenotype. To further investigate the molecular mechanisms underlying these findings, we employed high-throughput single-cell RNA sequencing (scRNA-seq) technology to conduct a systematic analysis of wild-type and aggf1-/- embryo samples. Data analysis revealed that in the abnormally developing cell subpopulations, two previously unreported genes, Gene U and Gene B, which are directly associated with vascular and hematopoietic system development, were significantly and specifically upregulated, suggesting that abnormal expression of Gene U and Gene B may be associated with developmental abnormalities in vascular and hematopoietic progenitor cells. This study provides important clues for elucidating the molecular mechanisms underlying the development and differentiation of vascular and hematopoietic progenitor cells.

Key Words： Zebrafish, Hemangioblast, single-cell RNA sequencing

Dynamic Visualization of the Glomeruloid Vessel Formation in Brain Metastasis

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Brain metastasis (BM) is the most common type of tumor in the central nervous system, leading to high morbidity and mortality in cancer patients. It frequently occurs in patients with lung cancer, breast cancer, and melanoma. After metastasizing to the brain, cancer cells closely interact with and extensively remodel the brain vasculature through mechanisms, such as sprouting angiogenesis and vessel co-option, to sustain their invasion and growth. However, the precise mechanisms underlying the brain vascular remodeling remain poorly understood. Leveraging the in vivo optical imaging in zebrafish larvae, we developed a zebrafish brain metastasis model to study brain vascular dynamics during metastasis. Our findings reveal that the brain metastatic cancer cells remodel brain vessels, resulting in the formation of glomeruloid vessels, which is correlated with the formation of brain micrometastases. Time-lapse imaging further showed that the glomeruloid vessels are formed through the aggregation of neighboring vessels pulled together by cancer cells, instead of sprouting angiogenesis. Mechanistically, we found inhibition of the VEGF signaling pathway significantly decreased the glomeruloid vessel formation. Thus, our study found the formation of glomeruloid vessels during brain metastasis. Further mechanistic insights gained from this model could provide novel therapeutic targets for the prevention and treatment of brain metastasis.

Key Words： Brain metastasis, Vascular remodeling, Glomeruloid vessel, Zebrafish

血管内皮细胞炎症的血流动力学调控机制研究

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摘要：心脑血管疾病是致死率最高的疾病，其主要病理基础是动脉粥样硬化，而动脉粥样硬化和其早期血管内皮细胞炎症事件一般发生在血流动力学异常和紊乱（低/振荡剪切应力）的区域，但是相关机制仍不清楚。血管内皮细胞特异转基因斑马鱼是血流动力学研究的重要模型，课题组研究显示调控斑马鱼血流切应力的改变影响血管内皮细胞炎症和功能。进一步研究发现振荡剪切应力通过改变细胞染色质分布调控细胞炎症。为了研究内皮染色质改变的力学机制，我们开发了细胞核力学定量探针，拟在斑马鱼早期胚胎中开展血管内皮细胞在不同发育阶段，不同切应力大小的情况下的细胞核力学和表观遗传调控。揭示血管内皮细胞炎症发生的血流动力学机制有往为动脉粥样硬化的预防、诊疗提供新靶点。

关键词：斑马鱼、血管内皮细胞、炎症、血流动力学、切应力

Zic3 通过不同机制协同调控 CNS 血管新生与屏障形成

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重庆大学

摘要：协调的血管新生及血脑屏障成熟对中枢神经系统（CNS）血管发育至关重要，但其分子机制尚未明确。本研究发现转录因子 Zic3 是调控上述过程的关键因子。通过构建内皮特异性 Zic3 敲除小鼠模型及斑马鱼 zic3 突变体，我们发现 Zic3 缺失导致 CNS 血管新生受损、血管畸形及出血性渗漏。这些病理表型在携带 ZIC3 突变的先天性心脏病患者胚胎脑血管中重现，证实了 Zic3 在维持跨物种神经血管稳态中的关键作用。在机制上，Zic3 通过双重调控发挥作用：它转录抑制 Braf 和 Jun，阻遏 MAPK 通路驱动的异常血管出芽；同时抑制 Plvap 介导的转胞吞作用，促进内皮屏障成熟。功能挽救实验表明：MEK 抑制剂可逆转血管新生缺陷，而内皮特异性 Plvap 缺失则能恢复 Zic3 敲除小鼠的血脑屏障功能。综上所述，Zic3 通过抑制 MAPK 介导的异常血管出芽和阻断 PLVAP 依赖的转胞吞作用，协同调控 CNS 血管新生与屏障成熟。该发现确立了 Zic3 在神经血管发育中的关键作用，为相关疾病机制研究提供了新靶点。

关键词：Zic3、脑血管新生、血脑屏障、MAPK、转胞吞。

polr2i 基因敲低对斑马鱼胚胎心血管系统发育的影响

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摘要：先天性心脏病（CHD）是指出生时心脏和大血管存在结构和功能异常。在我们之前的研究中，RNA 聚合酶 II 亚基 I（POLR2I）被确定为 CHD 的潜在遗传因素。然而，其功能作用在很大程度上仍未被探索。在本研究中，我们首先利用生物信息学分析了 POLR2I 在不同物种中的保守性。POLR2I 在多种脊椎动物中的氨基酸序列相似性超过 90%，表明其具有共同的进化起源。我们采用吗啉代寡核苷酸（MO）基因编辑技术，靶向下调斑马鱼中的 polr2i，同时使用 polr2i 基因的加帽 mRNA 进行拯救实验。结果显示，MO 介导的 polr2i 敲低显著改变了发育轨迹，表现为体型减小、弯曲度增加以及卵黄囊增大，同时畸形率和死亡率增加。拯救实验证实了这些表型对 polr2i 缺失的特异性。受影响的胚胎表现出心管延长、心腔间重叠减少以及显著的心包水肿，表明存在严重的心脏畸形或功能损害。每搏输出量、射血分数和心输出量的测量值均显著降低。此外，关键心血管标志物的表达水平也显著降低。血管生成过程也受到干扰，表现为节段间血管和尾静脉丛的形成减少。敲低后观察到心肌细胞线粒体质量受损，同时心脏、肝脏和胰腺的左右不对称性出现显著缺陷。结论是，POLR2I 的敲低不仅损害了心脏的结构和功能，还破坏了多个器官的正常发育不对称性。 这些发现加深了我们对 POLR2I 在先天性心脏病（CHD）中作用的理解，并凸显了其作为治疗干预靶点的潜力。

关键词：先天性心脏病，polr2i，斑马鱼

丙戊酸对斑马鱼心血管发育的危害

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摘要：丙戊酸（VPA）主要用于治疗癫痫、惊厥和其他精神疾病。作为一种表观遗传调节剂，它也被用于治疗各种癌症。该药物的临床需求可能会对环境造成危害。有证据表明，VPA 显著的治疗价值是以可能的毒副作用为代价的，因为在动物实验中使用 VPA 已证实会导致出生缺陷症状。然而，VPA 在循环系统发育过程中的影响尚不清楚。在本研究中，斑马鱼胚胎在受精后三小时（hpf）至受精后五天（dpf）期间暴露于一系列浓度的 VPA。结果显示，斑马鱼的发育存在时间和剂量依赖性的延迟，包括心血管畸形以及运动和反应时间减少。与体内实验结果一致，暴露于 VPA 会通过心脏线粒体代谢紊乱增加心肌活性氧（ROS）水平和细胞凋亡。与心血管发育和抗氧化反应相关的基因表达水平下调，而与凋亡途径相关的基因表达水平上调。总体而言，我们对 VPA 暴露的毒理学研究揭示了其对心血管发育的损害，引发了人们对早孕期暴露于 VPA 危害的担忧。本研究为 VPA 的潜在环境风险提供了新的见解。

关键词：心血管疾病，环境暴露，氧化应激，丙戊酸，斑马鱼

Cardiovascular developmental hazards of valproic acid in zebrafish

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Valproic acid (VPA) is predominantly prescribed for epilepsy, convulsions, and other psychiatric disorders. As an epigenetic regulator, it is also used to treat various forms of cancer. The clinical demand for the drug may pose an environmental hazard. Evidence indicates that VPA's significant therapeutic value comes at the cost of possible side toxic effects, as symptoms of birth defects have been confirmed in animal experiments using VPA. However, the effects of VPA during the development of the circulatory system remain unclear. In this study, zebrafish embryos were exposed to a series of concentrations of VPA between three hours post fertilization (hpf) and five days post fertilization (dpf). The results demonstrated time- and dose-dependent developmental delays in the zebrafish, including cardiovascular malformation and decreased movement and reaction time. Consistent with the in vivo results, exposure to VPA increased the levels of myocardial reactive oxygen species (ROS) and cell apoptosis through cardiac mitochondrial turnover disorders. The expression levels of genes related to cardiovascular development and antioxidant response were downregulated, while genes related to apoptosis pathways were upregulated. Overall, our toxicological studies of VPA exposure illustrate the damage to cardiovascular development, raising concerns about the hazard of VPA exposure in early pregnancy. Our study provides novel insights into the potential environmental risks of VPA.

Key Words： Cardiovascular disorders; Environmental exposure; Oxidative stress; Valproic acid; Zebrafish.

The adverse effects of paromomycin on early cardiovascular system development in zebrafish

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This study exposed zebrafish embryos to paromomycin at concentrations of 0, 0.3, 3, 30, and 300 μg/mL for 5 days to investigate its cardiovascular toxicity through morphological, cardiovascular phenotypic, and behavioral assessments. Paromomycin exposure was found to induce significant early embryonic toxicity, including adverse effects on growth and developmental morphological indices such as mortality, hatching rate, and malformation. Furthermore, paromomycin exposure caused abnormalities in cardiac function and vascular development in zebrafish larvae, manifesting as decreased heart rate, cardiac morphological deformities, reduced vascular number, and formation of abnormal collateral circulation. Molecular level analysis further confirmed these observations: elevated levels of ROS and antioxidant enzymes, aggregation of apoptotic bodies in the pericardial region, and dysregulation of pro-/anti-apoptotic gene expression collectively demonstrated paromomycin-induced early developmental toxicity in zebrafish larvae. Our research provides preliminary evidence that paromomycin triggers cardiovascular developmental abnormalities in zebrafish by inducing oxidative stress-mediated apoptosis. This study offers novel insights for the safe use and management strategies of paromomycin.

Key Words： paromomycin, Zebrafish, cardiovascular system.

polr2i is required for zebrafish early cardiac development

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Congenital heart disease (CHD) involves structural and functional anomalies of the heart and great vessels present from birth. It is recognized as the most common congenital defect. Epidemiological studies underscore the substantial contribution of genetic factors to CHD. In our preceding research, RNA polymerase II subunit I (POLR2I) was identified as a potential genetic contributor to CHD. However, its functional role remains largely unexplored. In the study, we firstly employed bioinformatics to analyze the conservation of POLR2I across various species. POLR2I exhibits over 90% amino acid sequence similarity across diverse vertebrates, suggesting a common evolutionary origin. Quantitative PCR (qPCR) measured gene expression levels, and POLR2I expression was notably high in early embryonic stages and in adult zebrafish organs such as the heart, eyes, and brain. Morpholino (MO) gene editing technology was employed and targeted the downregulation of polr2i in zebrafish, while the rescue experiments were conducted using capped mRNA of the polr2i gene. Transgenic zebrafish labeled with specific fluorescent protein facilitated detailed studies of cardiac and vascular development, myocardial mitochondrial quality, and embryonic asymmetry, respectively. Hemoglobin staining with o-Dianisidine assessed red blood cell accumulation. Results showed that MO mediated knockdown of polr2i significantly altered developmental trajectories, evidenced by reduced body size, curvature, and enlarged yolk sacs, alongside increased malformation and mortality rates. Rescue experiments confirmed the specificity of these phenotypes to polr2i loss. Affected embryos displayed elongated heart tubes with reduced overlap between chambers and significant pericardial edema, indicating severe cardiac malformations or functional impairments. Measurements of stroke volume, ejection fraction, and cardiac output were substantially decreased. Furthermore, expression levels of critical cardiovascular markers were markedly reduced. Angiogenic processes were also disrupted, as seen in the reduced formation of intersegmental vessels and caudal vein plexus. Impaired mitochondrial quality in myocardial cells was observed post-knockdown, along with notable defects in the left-right asymmetry of the heart, liver, and pancreas. It was concluded that knockdown of POLR2I not only impairs cardiac structure and function but also disrupts the normal developmental asymmetry of multiple organs. These findings enhance our understanding of POLR2I's role in CHD and underscore its potential as a target for therapeutic intervention.

Key Words： RNA polymerase II subunit I, cardiac development, embryonic development, zebrafish, morpholino.

Effects of water fluoridation on early embryonic development of zebrafish

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Fluoride exhibits potent biological activity and significant bioavailability, being readily absorbed by the yolk sac during critical organogenesis stages in zebrafish. This absorption profoundly disrupts embryonic development across multiple organ systems through two primary mechanisms: compromised nutrient utilization efficiency and pronounced induction of lipid peroxidation cascades. These interconnected processes collectively drive pathological superoxide radical accumulation within vital embryonic structures—specifically the yolk sac, developing hepatic tissue, and intestinal tract. Concurrently, fluoride-induced pericardial edema generates persistent mechanical compression on adjacent cephalic and axial structures, directly impairing brain and eye morphogenesis. This mechanical stress subsequently manifests as spinal curvature defects and significantly reduced somatic growth (body length). Critically, acute fluoride exposure demonstrates clear concentration-dependent teratogenicity: environmentally relevant low-dose aqueous exposure preferentially disrupts embryonic yolk sac development and function, while distinct vascular malformations, including aberrant angiogenesis, are prevalent across all treatment groups. Fluoride's deleterious impact on cardiovascular function and hemodynamics is remarkably extensive, demonstrably affecting even morphologically normal larvae lacking overt terata. Furthermore, exposure to sub-teratogenic fluoride concentrations alters fundamental neurobehavioral responses, as rigorously evidenced by significantly diminished spontaneous larval locomotor activity and delayed startle stimulus reactivity following aqueous fluoride exposure in standardized behavioral assays.

Key Words： zebrafish,embryonic development

Identifying Novel Regulators in Vascular Development

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In patients with diabetic microvascular complications, a decrease in vascular diameter leads to reduced perfusion and potential vascular occlusion, resulting in insufficient blood supply, yet the underlying regulatory mechanisms and effective treatments are not well understood. Our study found that human AQP1 expression was significantly reduced in diabetic retina samples and high-glucose-treated retinal endothelial cells, and this was associated with a decrease in vascular diameter and compromised perfusion in zebrafish embryos exposed to high glucose levels. The downregulation of aquaporins aqp1a.1 and aqp8a.1, which are highly enriched in endothelial cells (ECs) and responsive to hyperglycemic conditions, was also observed. The loss of function of these aquaporins in zebrafish resulted in reduced intersegmental vessel diameters, mimicking the hyperglycemic phenotype. Overexpression of aqp1a.1and aqp8a.1 in zebrafish ECs enlarged microvascular diameters and rescued the reduced vessel diameters caused by high-glucose treatment. These aquaporins were found in intracellular vacuoles, which are essential for lumen formation, and their loss reduced vacuole numbers. Although AQP1 loss did not affect EC differentiation from human stem cells, it significantly inhibited vascular formation in differentiated ECs. Our findings indicate that EC enriched aquaporins regulate blood vessel diameter through an intracellular vacuole-mediated process under hyperglycemic conditions, suggesting their potential as targets for gene therapy to address vascular perfusion defects in diabetes. This insight into the role of AQPs in blood vessel regulation under hyperglycemia could be pivotal for treating diabetes-related microvascular complications, as hyperglycemia-induced issues such as hemorrhages, microaneurysms, capillary non-perfusion, and neovascularization are major contributors to morbidity and mortality in diabetes.

Key Words： Aquaporin, vascular diameter, hyperglycemia, single-cell transcriptomics

S4. 神经发育、功能和疾病

Neurodevelopment, function and disease

熊果酸衍生物 UA312 通过靶向 chrna3 和 grik5 改善斑马鱼电离辐射诱发的心脏毒性和神经发育毒性

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摘要：电离辐射 (IR) 造成的生物损伤不仅取决于组织成分暴露的时间和剂量，还取决于细胞的发育状态。目前，氨磷汀是唯一用于放射治疗相关临床适应症的放射防护剂，但该化合物具有多种缺点，包括毒性高、半衰期短以及对神经系统没有保护作用。熊果酸（UA）是一种天然的五环三萜类化合物，具有多种保护作用，包括抗炎、抗致癌和抗氧化作用。由于其溶解性和生物利用度较差。在本研究中，我们研究了 UA 的优化衍生物 UA312 对斑马鱼胚胎和幼虫辐射诱导的发育毒性的影响。在 4、24、48 和 72 hpf 时观察了胚胎和幼虫的存活率。UA312 在受精后 3 hpf 时给药，而胚胎在受精后 4 hpf 时接受 6 Gy γ射线照射。我们确定 40 μM UA312 对斑马鱼胚胎和幼体是安全的。用 UA312（40 μM）治疗可以修复红外线诱导的斑马鱼胚胎和幼体早期发育不良。转录组分析显示，红外线照射抑制了斑马鱼神经发育和心肌细胞功能相关的多条通路，这通过评估心脏形态异常、神经递质水平变化和运动行为改变得到了验证；并且 UA312 治疗可以改善这些改变。我们证明 UA312 治疗通过靶向 chrna3 和 grik5 显著逆转了相关的信号通路。总而言之，本研究发现了一种有前景的放射保护药物 UA312，它通过靶向 chrna3 和 grik5 来减轻斑马鱼电离辐射诱导的心脏毒性和神经发育毒性。UA312 有望开发为一种新型的放射保护剂，用于对抗人类急性电离辐射损伤。

关键词：电离辐射，UA312，放射保护剂，心肌活性，神经毒性，斑马鱼

组氨酰 tRNA 合成酶通过调节线粒体稳态促进斑马鱼胚胎视网膜分层

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摘要：人类组氨酰 tRNA 合成酶（HARS）突变导致多种神经系统疾病，部分伴随视网膜发育异常，但 HARS 调控视网膜发育的功能和机制仍不清楚。人类基因组中同时存在 HARS1 和 HARS2 两个同源基因，分别编码细胞质和线粒体 HARS 蛋白。斑马鱼中仅有一个 hars 同源基因，通过可变剪接形成 2 个分别编码细胞质和线粒体 Hars 蛋白的转录本。有研究表明，特异性敲除细胞质 hars 转录本导致视网膜发育缺陷，但是对于线粒体 Hars 转录本在视网膜发育中的功能仍不清楚。通过构建同时缺失细胞质和线粒体 Hars 转录本的斑马鱼模型，我们发现 Hars 完全缺失导致斑马鱼胚胎视网膜分层结构出现紊乱，提示线粒体 Hars 可能参与调控斑马鱼胚胎的视网膜分层（Lamination）。透射电镜结果显示，Hars 突变体视网膜细胞减少，且细胞中线粒体变小、线粒体嵴肿胀、线粒体自噬增多，提示 Hars 缺失破坏了斑马鱼胚胎视网膜细胞的线粒体稳态。转录组结果显示，细胞色素 C、Apaf-1、Diablo 和促凋亡因子 Bax 在 Hars 突变体中的表达均显著上调，提示 Hars 缺失诱导的线粒体稳态失衡激活了凋亡途径。我们的研究结果表明，斑马鱼线粒体 Hars 可能通过维持视网膜细胞的线粒体稳态，减少异常凋亡的发生，促进视网膜分层的顺利进行。

关键词：视网膜发育，视网膜分层，组氨酰 tRNA 合成酶，HARS

敲除 p53 上游新启动子对斑马鱼低温耐受能力的影响

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摘要：P53 是一种经典的抑癌蛋白，在多种细胞应激反应中发挥关键调控作用。我们课题组此前在低温驯化的斑马鱼细胞中鉴定到一个新的上游 p53 启动子区域，但该启动子在斑马鱼低温胁迫中的具体功能尚不清楚。

本研究利用 CRISPR/Cas9 基因编辑技术构建了新型 p53 上游启动子缺失斑马鱼（novel p53 promoter-/-），并系统评估其在不同温度条件下的生理反应。在常规培养温度（28°C）下，该突变品系与野生型斑马鱼相比在发育、体长增长及运动能力方面均未表现出显著差异。然而，在低温胁迫条件（8°C）下，其低温耐受能力显著下降。鳃组织的转录组测序（RNA-seq）结果显示，在 8°C 低温下，novel p53 promoter-/- 斑马鱼中与氧化应激相关的多个关键基因表达水平显著下调。进一步生理生化实验证实，与野生型相比，突变斑马鱼在冷胁迫下活性氧（ROS）水平显著升高，而超氧化物歧化酶（SOD）及谷胱甘肽过氧化物酶（GSH-PX）等抗氧化相关酶的表达明显降低，表明其抗氧化防御能力受损。

本研究首次从功能层面证实了 p53 上游新型启动子在斑马鱼低温适应过程中的重要作用。该启动子可通过调控抗氧化防御系统，维持斑马鱼在极端低温条件下的生理稳态。我们的研究不仅丰富了鱼类环境适应机制的理论基础，也为进一步探索 p53 在寒冷胁迫中的调控网络提供了实验依据和参考价值。

关键词：p53、上游启动子、斑马鱼、低温耐受、氧化应激

抗阿尔茨海默病靶标组合及双靶点药物研究

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唐都医院

摘要：阿尔茨海默病（Alzheimer's Disease, AD）是最常见的神经退行性疾病，临床表现为记忆力衰退和认知功能障碍，并伴随行为和情绪障碍等问题。AD 发病机制复杂，开发靶向疾病不同病理环节的多靶点药物成为 AD 治疗的重点方向。协同靶标组合是多靶点药物设计的关键，但目前尚无系统的靶点组合研究。迄今为止，有效的抗 AD 靶点组合较少，多是由临床经验和表型筛选而来，耗时耗力，大大限制了多靶点抗 AD 药物的研发空间。因此，本研究首先利用收集的相关疾病治疗靶点组合对、蛋白序列、蛋白-蛋白互作以及疾病信号通路等信息，结合知识图谱和图卷积神经网络创新性地构建了一个系统的抗 AD 协同双靶点组合预测模型—长距离图卷积神经网络（LDGCN）。该模型在测试集中的准确率和召回率均为 73%，具有较好的预测性能，并可泛化至其他病理复杂疾病中进行研究；其次利用本实验室构建的斑马鱼 AD 模型，通过 CRISPR/Cas9 基因敲除以及双靶点特异性调节剂联合给药，证明所选靶点组合均能协同改善 AD 斑马鱼的认知障碍，证实 LDGCN 在抗 AD 靶点组合预测中的应用潜力；最后针对协同性最好的 ACHE + NLRP3 组合，利用计算机虚拟筛选、分子对接、亲和力检测以及活性验证，获得了一个新型双靶点化合物 6，其能抑制 AChE 活性、炎症反应、β-淀粉样蛋白沉积和神经细胞凋亡，显著改善 AD 斑马鱼和小鼠的认知障碍，可作为候选抗 AD 化合物深入研究。

关键词：阿尔茨海默病、人工智能、斑马鱼模型、双靶点药物

UPF0258 蛋白家族在神经系统发育与疾病中的作用

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摘要：UPF0258 蛋白家族包括 Minar1/Ubtor/Kiaa104 和 Minar2/Kiaa1014L 这两个成员，其蛋白序列在羧基端跨膜区及近跨膜区保守；除了这个跨膜区附近的保守区段，其蛋白序列与其他所有已知蛋白均缺乏序列保守性。我们之前的研究发现 Minar1/Ubtor 是 mTOR 信号通路的负调控因子，在包括神经元轴突生长及动物感觉运动行为中发挥作用，并参与调节大脑的兴奋-抑制平衡与癫痫样行为。我们还发现此家族另一成员 Minar2/Kiaa1024L 在听觉毛细胞中通过调控胆固醇在纤毛束中分布与稳态，从而在毛细胞发育及听觉中发挥关键作用。同期研究显示 MINAR2 是一个新的人类退行性非综合征耳聋致病基因。近期我们与临床医学和人类遗传学课题组合作继续考察了 UPF0258 蛋白家族与相关人类神经系统疾病。研究发现 Minar1/Ubtor 的缺失，与在斑马鱼中类似，在小鼠模型中也导致大脑兴奋-抑制失调及癫痫。研究开展了对中国癫痫人群中新候选基因的功能研究，发现在其中多个基因的斑马鱼突变模型中出现脑电、行为学等癫痫样表型，初步验证这些基因在人类癫痫发病中的作用。此外，我们建立了深度学习模型 ZEN-former (禅定)，以期明确神经元亚类发育的内在逻辑，以及在关键基因的表达调控序列中的单碱基突变在癫痫等人类疾病中的作用。

关键词：神经发育、神经系统疾病、耳聋、发育与癫痫性脑病、深度学习模型

跨物种单细胞组学分析脑内皮细胞的分子特征 揭示 bsg 在大脑血管形成中的作用

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摘要：血管的结构和功能完整是器官正常运作的关键；脑血管异常发育会导致多种神经功能障碍与疾病。因此系统的鉴定参与脑血管发育与功能的调控因子并阐释其调控机制意义重大。前期研究中，我们整合分析了人、猪、鼠、鸡和斑马鱼的单细胞转录组数据集；通过对脑内皮细胞(endothelial cell, EC)与其它组织器官的 EC 相比，以及大脑 EC 与脑内其它不同类型细胞相比进行差异表达基因分析，发现 Bsg 在脑 EC 中特异表达且高度保守。此外相比其他脑 EC 亚群，BSG 在血脑屏障(BBB)内皮细胞中显著高表达。斑马鱼模型的功能验证证实，保守基因 BSG 的缺失会导致血脑屏障破坏和脑血管发育异常，其机制可能与内皮细胞凋亡通路激活相关。 本研究阐明了脑内皮细胞在屏障功能维持中的核心作用，强调了 bsg 基因在血管发育以及血脑屏障生成中的重要作用， 为相关神经系统疾病的治疗供了新的分子靶点和理论依据。

关键词：单细胞测序，跨物种，脑内皮细胞，bsg

溶酶体蛋白 SLC38A9 通过 mTOR 信号通路调控斑马鱼焦虑样行为

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摘要：mTOR 是一种极为关键的细胞内信号分子，除了在细胞水平上的多种功能外，mTOR 还与生物体的行为密切相关。mTOR 信号通路受到众多营养感知因子的调控。近年来，发现了一种名为 SLC38A9 的新型营养感知因子，其在调节细胞内氨基酸感应和激活 mTORC1 信号通路中发挥着关键作用。然而，目前对于 SLC38A9 在体内（in vivo）的完整功能和作用机制仍然知之甚少。为了深入探究 SLC38A9 在体内的功能，首先我们通过社会互动行为测试发现，在饥饿状态下 slc38a9−/−突变体社交频率显著下降，通过捞网刺激测试发现，slc38a9−/−突变体在饥饿状态下表现出更高的焦虑水平。在突变体里，多巴胺能神经元荧光更强。通过 Lysotracker 染色，发现 slc38a9−/−突变体的溶酶体荧光信号显著增强，然后通过透射电镜分析发现 slc38a9−/−突变体的溶酶体比野生型体积更大。重新导入全长 slc38a9 或仅具有激活 mTOR 信号通路突变体能够恢复溶酶体水平和抑制焦虑样行为，但缺失 mTOR 激活功能的 slc38a9 突变体蛋白却无此效果。DiSignAtlas 数据库分析发现 SLC38A9 在多种神经性疾病中的表达量显著降低。这些发现揭示了 SLC38A9 通过 mTOR 信号通路调控溶酶体功能和焦虑样行为的分子机制，为深入研究 SLC38A9 在神经性疾病中的作用机制提供了重要基础。

关键词：SLC38A9，溶酶体，mTOR 信号通路，行为

ATF4 介导的综合应激通路调控斑马鱼对纳米塑料的行为与代谢响应

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摘要：纳米塑料已成为威胁水生生物健康的重要因素，其在水生动物体内的富集会引发一系列细胞应激反应。综合应激反应（Integrated Stress Response, ISR）是一条关键的细胞保护信号通路，能在多种胁迫条件下维持细胞稳态，但其是否参与调控纳米塑料诱导的应激响应尚不明确。本研究利用荧光标记纳米塑料和 ISR 缺陷型斑马鱼模型，探讨纳米塑料对水生动物的影响及其应对机制。研究发现，经 25 nm 聚苯乙烯纳米塑料处理 3 小时后，斑马鱼脑组织中可检测到明显的荧光信号。代谢组学分析显示，48 小时处理后糖酵解和三羧酸循环中间代谢物含量显著下降，表明能量代谢受损。纳米塑料处理能够诱导 eIF2α磷酸化和 ATF4 蛋白表达升高，提示 ISR 通路被纳米塑料激活。通过敲除 Atf4a 基因构建的 ISR 缺陷型斑马鱼在高浓度纳米塑料处理下存活率显著降低。行为分析发现，Atf4a 突变体对光刺激反应增强，在暗环境中运动距离显著增加，该异常行为可被奥氮平抑制。此外，野生型斑马鱼在纳米塑料处理后 P62 蛋白水平升高，而该效应在 Atf4a 突变体中受限，表明其自噬功能存在缺陷。综上，综合应激反应在纳米塑料诱导的细胞代谢紊乱、行为异常和自噬中发挥关键调控作用，为深入理解水生动物对环境纳米污染物的适应机制提供了新的视角。

关键词：纳米塑料，代谢，Atf4a，综合应激反应，行为

Huang-Qi-Long-Dan Granule alleviates ischemic stroke injury by regulating the crosstalk between Nrf2 and NF-κB signaling

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Huang-Qi-Long-Dan Granule (HQLDG) is an herbal formula commonly used to treat ischemic stroke (IS) in clinical. Understanding the underlying mechanism is conductive to our better understanding and use of the formula. Zebrafish cerebral thrombosis model and mouse transient middle cerebral artery occlusion (tMCAO) model were used in our study to explore the anti-IS effect and the underlying mechanism of HQLDG. We found that HQLDG significantly decreased brain thrombosis, increased blood vessel diameter and blood flow velocity, ameliorated motor activity and regulated the coagulation cascade in zebrafish model. The ameliorated motor activity and improved brain pathology were also observed in tMCAO mice. Furthermore, we found that HQLDG decreased oxidative stress, inflammation and apoptosis related indicators in zebrafish. And these results were also confirmed in tMCAO mice. Moreover, it could increase the translocation of Nrf2 into the nucleus in brain tissue. However, the protective effect of HQLDG on brain thrombosis, motor activity, blood vessel diameter and blood flow velocity were decreased after the inhibition of Nrf2 with ML385 or CRISPR/Cas9 gene-editing technology in zebrafish. Meanwhile, the inhibition of Nrf2 could significantly attenuate the effect of HQLDG on NF-κB. The protective effect of HQLDG on motor activity was significantly decreased in NF-κB inhibition gene-editing zebrafish. These findings underscore the potential of HQLDG as a promising therapeutic agent for treating IS, while further confirming the reliability of zebrafish as a IS model, and expanding the visual detect index of zebrafish for IS evaluation.

Key Words： Ischemic stroke; Huang-Qi-Long-Dan Granule; nuclear factor erythroid 2-related factor 2; nuclear factor kappa-B, CRISPR/Cas9

Separate brainstem circuits for fast steering and slow exploratory turns

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Locomotion requires precise tuning of descending commands to scale turning movements, such as rapid steering during prey pursuit or shallow turns during exploration. We show that these two turn types are governed by distinct brainstem circuits. The rapid steering circuit involves excitatory V2a and inhibitory commissural V0d neurons, distributed across different brainstem nuclei. These neurons are coupled via gap junctions and activated simultaneously, ensuring rapid steering through asymmetrical activation of spinal motor neurons. The recruitment of this circuit correlates more with the degree of direction change than with locomotor frequency. Steering neurons are, in turn, controlled by a subset of V2a neurons in the pretectum, activated by salient visual input. In contrast , slow exploratory turns are governed by a separate set of V2a neurons confined to fewer brainstem nuclei. These findings reveal a modular organization of brainstem circuits that selectively control rapid steering and slow exploratory turning during locomotion.

Key Words： brainstem circuits, fast steering turns, slow exploratory turns, V2a neurons, descending commands, V0d neurons

Visuomotor transformation and behavioral state transitions in the zebrafish brain

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The visual system can process diverse stimuli and flexibly execute appropriate behaviors depending on the animal's state, but it remains unclear where and how this transformation takes place. Here, we developed a novel visually-evoked freezing paradigm in larval zebrafish and showed that presenting a moving dark disk could trigger immobility, as well as bradycardia, a transient decrease in heart rate which is another hallmark of freezing. We then combined this assay with escape and hunting paradigms and large-scale imaging to investigate how these stimuli are transformed into behavior. We imaged the zebrafish visual system while larvae responded with hunting, freezing, and escape behaviors, and systematically identified visually driven neurons and behaviorally correlated sensorimotor neurons. Our analyses indicate that within the optic tectum, broadly tuned sensory neurons are functionally connected to sensorimotor neurons which respond specifically during one behavior. We also identified sensorimotor neurons in four other areas downstream of the tectum, and these neurons are also specific for one behavior, indicating that once the decision to behave has been made, the segregation of the pathways continues in later areas.

Finally, we have begun to study how visuomotor circuits are influenced by behavioral state. We identified persistent internal states that modulate locomotion in zebrafish larvae, and found that larvae show state-dependent changes in visual behaviors. Overall, our findings shed light on how visual inputs may be flexibly converted into different behaviors and the key brain areas involved.

Key Words：zebrafish, visuomotor, behavior

BMP–Smad1/9 signaling is required for PGC proliferation in zebrafish

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The specification and maintenance of germ cell lineage are vital for reproductive development and heredity. In mammals, bone morphogenetic protein (BMP) signaling induces the germ cell fate in the epiblast cells. However, whether BMP signaling is necessary for zebrafish germ cell development remains unknown. Here, we demonstrated that, in zebrafish, BMP-Smad1/9 signaling is required for primordial germ cell (PGC) maintenance but not for PGC fate determination or migration. BMP inhibitor treatment or whole-embryo smad1/9 knockdown reduce the number of PGCs. Furthermore, to distinguish cell-autonomous roles of BMP-Smad1/9 in PGCs from secondary effects caused by global BMP disruption, we generated PGC-specific smad1/9 knockout mutants using a double-transgenic approach with PGC-specific Cas9 and ubiquitous gRNA expression. Loss of Smad1/9 in PGC leads to impaired PGC proliferation and increased cell apoptosis, causing PGC loss and adult male-biased sex determination. Moreover, transcriptome analysis of smad1-deficient PGCs revealed no significant changes in PGC-specific gene expression but demonstrated a marked upregulation of genes involved in cell cycle checkpoints and DNA damage repair. Notably, ectopic ATR-pChk1 activation in smad1-cKO PGCs validated cell cycle defects and DNA replication stress. ATR inhibition restored PGC reduction in mutant embryos. Collectively, these findings underscore a critical role for BMP-Smad1/9 signaling in zebrafish PGC population maintenance, while revealing that it is dispensable for PGC cell fate determination and migration.

Key Words：BMP-Smad1/9, PGC, Conditional knockout, Zebrafish

S5. 生殖与生理

Reproduction and Physiology

GDF9 和 BMP15：协奏斑马鱼卵泡发生的交响乐

葛伟

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摘要：卵母细胞源性生长因子在卵泡生成过程中发挥关键作用。生长分化因子 9（GDF9）和骨形态发生蛋白 15（BMP15）均是卵母细胞特异生长因子。通过基因敲除技术，我们在斑马鱼模型中发现：缺失 GDF9 或 BMP15 均会导致卵泡发育严重紊乱，表现为生长停滞和退化。GDF9 对激活初级生长卵泡向次级生长阶段转化至关重要。其缺失将导致卵泡停滞在 PG 阶段，伴随卵泡退化及雌性向雄性的性逆转。这种性逆转可通过敲除雄性促进基因 dmrt1 来阻断。有趣的是，同时突变抑制素α（inha）基因可部分挽救 gdf9 缺陷表型，但雌二醇（E2）处理则无效，这提示 GDF9 通过激活素-抑制素系统（而非 E2）发挥作用。BMP15 缺失同样造成卵泡停滞，但发生在卵黄生成前期（PV）至卵黄生成期，并同样引发性逆转。在 bmp15-/-;inha-/-双突变体中，该表型同样得到部分挽救，卵泡可发育至卵黄生成中期（MV）并积累卵黄。与 gdf9 突变体不同，bmp15 突变体表型可通过 E2 治疗恢复。这些发现表明 BMP15 通过激活素-抑制素系统与 E2 信号协同调控卵泡发育。综上，本研究揭示 GDF9 与 BMP15 虽共同参与调控斑马鱼早期卵泡生成，但分别作用于不同阶段且机制有别：GDF9 依赖激活素-抑制素系统，而 BMP15 同时涉及 E2 与激活素-抑制素信号通路。该发现凸显了卵泡发生过程的精准调控，以及卵母细胞因子与体细胞信号通路在调控卵泡发育中的复杂互作机制。

关键词：卵泡发生，卵母细胞生长因子，GDF9，BMP15，斑马鱼

Enhanced Reproductive Toxicity of Photodegraded Polylactic Acid Microplastics in Zebrafish

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Microplastics are widely used due to their numerous advantages. However, they can have detrimental effects on marine ecosystems. When microplastics enter the ocean, they can be absorbed by marine organisms, leading to toxic effects. Additionally, the transformation of microplastics during natural degradation can alter their toxicity, necessitating further investigation. Polylactic acid (PLA) biodegradable plastics are commonly used, yet research on their toxicity, particularly their reproductive effects on aquatic organisms, remains limited. In this study, we conducted photodegradation of PLA using potassium persulfate as a catalyst to simulate natural degradation conditions. Our objective was to assess the reproductive toxicity of photodegraded PLA microplastics on zebrafish. The results revealed that photodegraded PLA exhibited elevated reproductive toxicity, resulting in abnormal oocyte differentiation, disruption of sexual hormone levels, and alterations in ovarian tissue metabolism. Metabolomics analysis indicated that both unphotodegraded PLA (UPLA) and photodegraded PLA (DPLA) disrupted oxidative stress homeostasis in zebrafish ovarian tissue by influencing pathways such as purine metabolism, phenylalanine metabolism, glutathione metabolism, and riboflavin metabolism. Furthermore, the DPLA treatment induced abnormal biosynthesis of taurocholic acid, which was not observed in the UPLA treatment group. Importantly, the DPLA treatment group exhibited more pronounced effects on offspring development compared to the UPLA treatment group, characterized by higher mortality rates, inhibition of embryo hatching, accelerated heart rates, and reduced larval body length. These findings underscore the varying levels of toxicity to zebrafish ovaries before and after PLA photodegradation, along with evidence of intergenerational toxicity.

Key Words： Microplastics, Polylactic acid, Photodegradation, Reproductive toxicity, Zebrafish

促性腺激素和性激素对斑马鱼性腺分化的调控研究

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摘要：促性腺激素(gonadotropin)和性激素(sex steroid hormone)是下丘脑-垂体-性腺（hypothalamic-pituitary-gonadal，HPG）构成的动物繁殖内分泌调控轴中激素级联信号系列的重要组成。近年来借助基因编辑技术的采用，利用多种敲除模型的构建与观察，对于促性腺激素和性激素在斑马鱼性腺分化过程的调节，取得了可喜的进展。我们发现促黄体酮生成素β(lhβ）敲除、促卵泡激素β(Fshβ)敲除、促卵泡激素受体(Fshr)敲除等单基因敲除于至 4mpf 时期，雌性个体依然约占敲除群体的42%、40%、30%，而 lhβ-/-;fshβ-/-、lhβ-/-;fshr-/-双敲群体中，雌性个体比例则下降至 10%、8%；我们也发现 Lhβ和 Fshβ的共同α亚基分子 Cgα与 Fshβ信号的共敲除模型 cga-/-;fshβ-/-、cga-/-;fshr-/-群体中，雌性个体比例分别为 10%和 0%，观察也显示 Fshr 分子自身具有一定的持续激活功能。然而敲除雄激素合成酶 Cyp17a1、雌激素合成酶 Cyp191a，则均可导致其单敲群体均使性腺 100%发育为精巢的表型，且其性腺的精巢化不可为 Tp53 的缺失所挽救，表明性激素对性腺分化的调控具有早期的、非促性腺激素依赖的作用。由此，更多深入研究正在进一步开展。

关键词：斑马鱼，促性腺激素，性激素，性腺分化

Reproductive toxicity and transgenerational effects of co-exposure to polystyrene microplastics and arsenic in zebrafish

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Microplastics (MPs) are ubiquitous environmental pollutants that have garnered significant attention due to their small particle size, resistance to degradation and large specific surface area, which makes it easy to adsorb various pollutants, particularly heavy metals. Arsenic (As), a common metal poisons, poses significant risks due to its widespread industrial use. When MPs and As co-exist in the environment, they can exert combined toxic effects on organisms, affecting various systems, including the nervous system. However, research on the reproductive damage caused by the co-exposure to MPs and As is limited, and the toxic effects and mechanisms remain unclear. In this study, we investigated the co-exposure of polystyrene microplastics (PSMP) and As on female zebrafish to evaluate the reproductive toxicity and transgenerational effects. The results revealed that the combined exposure exhibited elevated reproductive toxicity, resulting in reduced gonadal indices, abnormal oocyte maturation, and disrupted sex hormone levels, as evidenced by an increased E2/T ratio. Metabolomics analyses revealed that the co-exposure to PSMP and As primarily affected pathways involved in aminoacyl-tRNA biosynthesis, sphingolipid metabolism, linoleic acid metabolism, galactose metabolism, and amino sugar and nucleotide sugar metabolism. These pathways are associated with oxidative stress, lipid synthesis, and sex hormone synthesis. Importantly, the combined exposure group exhibited more pronounced effects on offspring development compared to the alone treatment group, characterized by increased mortality rate, decreased hatching rate, and reduced heart rate. These findings provide evidence that co-exposure to MPs and As damages the reproductive system and adversely affects offspring growth and development.

Key Words： Microplastics, Arsenic, Reproductive toxicity, Zebrafish

Somatostatin regulation of the pancreatic β-cell proliferation

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Understanding the regulation of pancreatic β-cell proliferation is crucial for comprehending the pathogenesis and treatment of diabetes. In a previous study, we found that somatostatin 1.2 (sst1.2) deficient mutants displayed both a germ cell and pancreatic β-cell over-proliferation phenotype, suggesting a possible regulator of energy allocation during reproduction. Analysis of the sst1.2 promoter revealed enrichment with binding sites for Hoxb8a, with expression of hoxb8a transcripts located to β and δ cells in 5-dpf zebrafish. Both knockdown and knockout of hoxb8a showed a β-cell over-proliferation phenotype analogous to that of the sst1.2 mutant. A thymidine incorporation assay confirmed that both sst1.2 and hoxb8a regulate β-cell mass via cell proliferation. The sst1.2/hoxb8a double mutant also had an increase in β-cell mass. In the hoxb8a knockout, sst1.2 was downregulated compared to the wild-type, and Hoxb8a promoted the transcription of sst1.2 in a luciferase assay.

To further elucidate the downstream gene regulation mediated by sst1.2 and hoxb8a, we analysed Nrf2, which has been found to regulate β-cell mass in mice. We localised nrf2a mRNA in β cells in 5-dpf zebrafish and found upregulation of nrf2a mRNA and nrf2/pnrf2 protein in both sst1.2 and hoxb8a mutants. The zebrafish nrf2a gene knockout also showed reduced β-cell mass.

To investigate the crosstalk between β and δ cells, we analysed the protein kinases Akt and AMPK, which are important, respectively, for cell growth and survival, as well as an energy sensor. We found a decrease in the protein levels of Akt and pAkt in both sst1.2 and hoxb8a mutants, including in β-cells. In parallel, AMPK and pAMPK protein levels were upregulated in both sst1.2 and hoxb8 mutants, including the pancreatic β cells. In conclusion, hoxb8a regulates sst1.2, which targets nrf2a to limit β-cell proliferation via protein kinases pAKt and pAMPK.

In conclusion, our study offers novel insights into the regulation of somatostatin-mediated β-cell proliferation.

Key Words： sst1.2, hoxb8, β-cell proliferation,zebrafish

The role of melatonin signaling in fish spermatogenesis in vitro

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In vitro production of functional gametes revolutionizes reproduction by reducing generation intervals and accelerating genetic breeding in aquaculture, especially for the fish having long mature period. In this study, we isolated premeiotic spermatogonial stem cell (SSC) from marine four-eyed sleepers (Bostrychus sinensis) and induced the differentiation of SSC into flagellated sperm by using two kinds of three-dimensional (3D) culture materials the 3D- transwell and the spherical microplate. We found that the spherical microplate could more efficiently promote SSC formation to the testis-like structure and differentiation into functional sperms. Moreover, we found that melatonin plays an important role in regulation SSC proliferation and meiosis via different melatonin receptors (Mtnrs). Furthermore, we found that Mtnrs can regulated different downstream signalings including the CREB, ERK1/2 and CAMKII in SSC development in vitro. Supplementation with different signaling agonist and antagonist with the melatonin can significantly increase the production of functional sperms in vitro. The 3D culture system and resulting functional sperm hold great promise for improving the genetic breeding of aquaculture fish.

Key Words： melatonin, spermatogenesis in vitro, melatonin, 3D culture

从氨基酸吸收到微生物稳态：Ace2 介导的斑马鱼生长调控研究

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摘要：血管紧张素转换酶 2（Ace2）在哺乳动物中具有重要生理功能，但其在非哺乳脊椎动物中的作用尚不明确。本研究利用 CRISPR/Cas9 技术构建了 ace2 敲除（ace2-/-）斑马鱼模型，系统评估了 Ace2 在鱼类中的生物学功能。ace2-/-突变体表现出显著的生长迟缓，体长和体重均明显下降。组织表达分析显示，ace2 在肠道中高表达，提示其在肠道中可能发挥重要作用。Ace2 缺失后，突变体血浆及肌肉中的阳离子和中性氨基酸（如 L-(+)-精氨酸、L-(+)-赖氨酸、亮氨酸和缬氨酸）含量显著降低，表明氨基酸摄取受损；与此同时，ace2-/-突变斑马鱼的肠道微生物多样性下降，群落结构发生重塑，菌群中碳水化合物代谢相关基因表达上调，而氨基酸生物合成通路基因表达下调。这些微生物学改变与突变体肝脏碳水化合物代谢增强及肌肉氨基酸减少的表型一致。综上，本研究首次揭示了 Ace2 在斑马鱼生长发育、氨基酸代谢和肠道微生态稳态中的核心作用，为其在脊椎动物中的保守功能提供了新视角。

关键词：关键词：Ace2；生长；斑马鱼；肠道微生物；代谢

Maternal epigenetic factors regulate the inviability of inter-species hybrids in Xenopus

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Reproductive isolation is a key factor in speciation, often resulting in hybrid lethality or sterility; however, the mechanisms underlying chromatin incompatibility during interspecific hybridization remain unclear. The *Xenopus* genus, including allotetraploid *Xenopus laevis* (*X. laevis*) and diploid *Xenopus tropicalis* (*X. tropicalis*), provides a model for studying these phenomena. In crosses where *X. tropicalis* eggs are fertilized with *X. laevis* sperm (te×ls), embryos exhibit early developmental arrest and paternal chromosome loss, while the reciprocal cross (le×ts) develops normally. Here, we investigated chromatin dynamics in *Xenopus* hybrids and found widespread DNA reduction at multiple chromosomal sites in both hybrid types. Most transcript loss was compensated by increased expression from homologous genes of the S and *X. tropicalis* subgenomes. Hyperactivation of the cell cycle pathway after hybridization may underlie abnormal hybrid morphology. Notably, the epigenetic marker H3K4me3 was nearly absent before gastrulation in lethal te×ls hybrids, resembling *X. tropicalis* embryos, while surviving le×ts hybrids maintained high H3K4me3 levels, similar to *X. laevis* embryos. Gene expression in le×ts hybrids showed hyperactivation of the L chromosome, whereas te×ls hybrids had a more active S subgenome, potentially linked to H3K4me3 deficiency. These findings suggest that subgenome imbalance and loss of H3K4me3 contribute to chromatin loss and developmental failure in te×ls hybrids. Our study provides new insights into reproductive isolation and highlights the crucial roles of maternal epigenetic factors in maintaining chromatin compatibility during embryonic development.

Key Words： Inter-species hybridization, reproductive isolation, maternal factors, H3K4me3, epigenetics, mitochondria, Xenopus laevis, Xenopus tropicalis

营养代谢通过胆囊收缩素介导调节鱼类性腺发育的作用

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摘要：性腺发育需要消耗大量的能量，因此性腺的成熟与生物体的营养代谢状态紧密相关。然而，目前尚不清楚营养代谢与性腺发育之间是如何联系在一起的。胆囊收缩素（CCK）是一种饱感神经肽，本研究发现摄食能够通过升高血糖显著诱导草鱼下丘脑 CCK 的表达。此外，CCK 及其受体在鱼类下丘脑-垂体-性腺（HPG）轴中高表达，表明 CCK 可能通过 HPG 轴参与鱼类生殖调控。进一步研究发现，CCK 能显著刺激下丘脑中促性腺激素释放激素（GnRH3）的表达。此外，草鱼垂体单细胞转录组分析显示，CCK 受体（cckbr）在垂体卵泡刺激素（FSH）细胞中高度富集；在体和离体实验证明 CCK 是草鱼垂体 FSH 合成与分泌的主效调节因子。此外，以原代培养的卵巢细胞为模型，离体实验发现 CCK 能直接诱导卵巢中 lhr、fshr 和 cyp19a1a mRNA 的表达。为了验证 cck 突变后的表型，我们近期以斑马鱼为研究对象，构建了 cck1，cck2 单突变和 cck1;cck2 双突变模型，表型验证发现 cck1-/-;cck2-/-斑马鱼全部为雄性并且不育。此外，虽然 cck1-/-;cck2-/-斑马鱼摄食量增加，但其性腺仍然败育；这进一步证明摄食是通过 CCK 的介导促进鱼类性腺发育。基于上述信息，我们证实 CCK 是一种关键的性腺发育调节因子，它能在鱼类营养代谢与性成熟调节之间建立直接的神经内分泌联系。

关键词：营养代谢、胆囊收缩素、性腺发育、斑马鱼、草鱼

Efficient Recovery of Maternal Zygotic Mutant Embryos from Cryopreserved Spermatogonial Stem Cells

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Sperm cryopreservation preserves haploid genetic information but is often time-consuming and costly for homozygous strain reconstruction. Combining spermatogonial stem cell (SSC) cryopreservation with surrogate reproduction offers a promising alternative for long-term genetic resource conservation. However, this technique faces two main challenges: 1) low SSC yields following cryopreservation and thawing, resulting in low transplantation success; and 2) a lack of suitable recipients for efficient donor-derived oocyte production. In this study, cyp11a2-/- were used to expand SSCs in vivo, and a cryopreservation protocol was optimized. SSCs isolated from thawed cyp11a2-/- recipients were several hundred times more abundant than those from controls (148.75 ± 62.33 times), significantly improving transplantation efficiency. The number of transplantable recipients increased from 105 ± 7 to 670 ± 60, with the success rate rising from 0.95 ± 0.06% to 74.80 ± 4.98%. Using nanos2-/- mutants as recipients, both donor-derived sperm and oocytes were generated. Notably, 100% maternal zygote nanog mutant (MZnanog) zebrafish were successfully recovered in F1 offspring within 3 months, outperforming traditional sperm cryopreservation (6 months). In conclusion, this novel approach combining SSC expansion, cryopreservation, and transplantation enables rapid recovery of zygote/maternal zygote lethal mutants and multi-gene mutation systems, offering significant advantages for genetic research and conservation.

Key Words：Zebrafish, Genetic resource conservation, Spermatogonial stem cell, Surrogate reproduction, Recovery of maternal zygotic mutants

Identification of fish spermatogenic cells through high-throughput immunofluorescence against testis with an antibody set

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Image-based identification and quan ntification of different types of spermatogenic cells is important, not only for reproductive studies but also for genetic breeding.Here,we have developed antibodies against spermatogenesis-related proteins in zebrafish(Danio rerio),including Ddx4, Piwil1, Sycp3, and Pcna,and a high-throughput method for immunofluorescence analysis of zebrafish testicular sections.By immunofluorescence analysis of zebrafish testes,our results demonstrate that the expression of Ddx4 decreases progressively during spermatogenesis,Piwil1 is strongly expressed in type A spermatogonia and moderately expressed in type B spermatogonia,and Sycp3 has distinct expression patterns in different subtypes of spermatocytes.Additionally,we observed polar expression of Sycp3 and Pcna in primary spermatocytes at the leptotene stage.By a triple staining of Ddx4,Sycp3,and Pcna, different types/subtypes of spermatogenic cells were easily characterized.We further demonstrated the practicality of our antibodies in other fish species,including Chinese rare minnow(Gobiocypris rarus),common carp(Cyprinus carpio), blunt snout bream (Megalobrama amblycephala),rice field eel(Monopterus albus) and grass carp(Ctenopharyngodon idella).Finally,we proposed an integrated criterion for identifying different types/subtypes of spermatogenic cells in zebrafish and other fishes using this high-throughput immunofluorescence approach based on these antibodies.Therefore, our study provides a simple, practical, and efficient tool for the study of spermatogenesis in fish species

Key Words： Ddx4, Sycp3, Piwil1, PCNA, spermatogonia

S6. 代谢与组织器官发生

Metabolism and tissue and organ occurrence

组成型活性 GCGR：鸟类维持高血糖和瘦体重的关键因素

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血糖是人体能量的主要来源，维持血糖对整体健康和代谢稳态是不可或缺的。而人类肥胖是一个普遍存在的健康问题，是全球第五大死亡原因。脂肪量的减少和维持是肥胖管理的核心挑战。血糖主要由胰高血糖素受体家族调节，该家族在脊椎动物中高度保守。与其他脊椎动物相比，鸟类的血糖水平相对较高，且利用有限的脂肪积累用作飞行燃料。但鸟类的血糖调节和脂肪利用的生理机制尚不清楚。本研究表明，禽类胰高血糖素受体(GCGR)在肝脏中的高表达与组成型活性胰高血糖素信号传导有关，这取决于不同结构域的相互作用。体内实验表明，在鱼类、爬行动物、鸟类和哺乳动物中，肝细胞中组成型活性 GCGR 的表达通过激活下游信号通路导致相应的高血糖、肝脂质快速利用和高代谢率。单细胞测序分析显示高 GCGR 在禽类脂肪细胞中表达水平，而在其他动物脂肪组织中表达水平极低脊椎动物。禽类 GCGR 具有独特的脂肪快速利用机制保持轻盈的身体。此外，我们在鸡的 GCGR 基因区域附近发现了一个点突变，导致 GCGR mRNA 表达减少，体重增加。在小鼠中过表达具有适度构成活性的天然人 GCGR 变体 HSGCGR (H339R)可增加血糖浓度并降低体重。综上所述，我们发现 GCGR 的高表达和组成活性可能对鸟类祖先的飞行进化做出了贡献也在脂肪利用和能量利用方面具有重要作用，可被用于治疗人类肥胖的治疗方法。

关键词：胰高血糖素受体（GCGR），血糖调节，脂肪利用，能量利用

High-throughput screening reveals paeoniflorin's efficacy against Apoc2-deficient hypertriglyceridemia via HNF4A/PPARA/LDLR

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Hypertriglyceridemia (HTG) is a significant risk factor for cardiovascular disease, fatty liver, and acute pancreatitis, yet remains a therapeutic challenge due to limitations of current treatment options. To address this unmet clinical need, we screened a natural small-molecule library to identify effective HTG therapeutic candidates using a CRISPR/Cas9-generated apolipoprotein C2 (apoc2) knockout zebrafish model that resembles human lipid metabolism disorders. Phenotype-based screening identified paeoniflorin (PAE) from 351 compounds as a potent triglyceride-lowering agent. Lipidomics analysis revealed PAE promoted triglyceride lipolysis by β-oxidation and lipophagy. Mechanistic studies demonstrated PAE upregulates peroxisome proliferator-activated receptor α (ppara) and lipoprotein receptor (ldlr) in apoc2 mutants. In oleic acid-induced Huh7 human hepatocytes, PAE reduces intracellular lipid droplet accumulation and significantly upregulated PPARA and LDLR expression, indicating enhanced hepatocellular uptake and oxidative catabolism of triglyceride-rich lipoproteins. Further investigation revealed that PAE upregulates the expression of hepatocyte nuclear factor 4 α (HNF4A), a key upstream transcription factor of PPARA. The HNF4A inhibitor BI-6015 completely abolished PAE's triglyceride-lowering effects, suggesting mediation through the HNF4A-PPARA-LDLR axis. These findings establish PAE as a promising therapeutic candidate for HTG through a novel mechanism targeting the HNF4A-PPARA-LDLR pathway. Our work not only identifies a potential lead compound for HTG treatment but also supports the zebrafish model as an effective platform for discovering drugs targeting hepatic lipid metabolic pathways.

Key Words： hypertriglyceridemia; zebrafish; phenotypic screening; paeoniflorin; HNF4A; PPARA

组织蛋白酶在斑马鱼早期胚胎发育中的作用机制研究

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摘要：卵黄为卵生动物胚胎发育提供关键的营养物质，在斑马鱼中卵黄营养主要由卵黄蛋白原（Vtgs）组成。尽管已有研究表明组织蛋白酶在卵母细胞成熟期对 Vtgs 的降解发挥关键作用，但这些酶在胚胎发育期间对卵黄颗粒的降解及其对胚胎发育的影响仍不完全明确。本研究首先通过 RNA-seq 分析发现，多个组织蛋白酶（如 Ctsba、Ctsc、Ctsh 等）在卵黄中具有特异性表达，并且大部分定位于卵黄颗粒中。抑制组织蛋白酶活性后，Vtgs 蛋白的降解受到显著抑制；此外，抑制组织蛋白酶活性导致斑马鱼胚胎身体发育延缓，神经和肌肉的发育受到显著影响；同时，卵黄颗粒的形态发生变化，最小颗粒消失并伴随颗粒形态出现明显变化。这些结果进一步验证了组织蛋白酶在斑马鱼胚胎发育中的重要作用，特别是在营养物质降解和卵黄颗粒代谢中的关键功能。未来的研究将进一步探讨组织蛋白酶在溶酶体调控中的作用及其与卵黄颗粒降解之间的关系。

关键词：斑马鱼、溶酶体、组织蛋白酶、卵黄蛋白原

人类与长寿动物衰老与寿命的共性机制研究

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摘要：随着全球人口老龄化的加剧，中国已成为世界上老龄人口最多的国家，也是老龄化速度最快的国家之一。围绕应对人口老龄化的重大需求，延长健康寿命成为当今社会面临的重大挑战之一。衰老是一个复杂的生理过程，表现为机体功能随年龄增长逐渐衰退，这一过程受遗传基因、环境因素以及生活方式等多维度因素的共同作用和调控。长寿动物因其具有独特的进化和发育机制，其寿命延长的机制与人类共享多种机制，涉及基因组稳定性、端粒缩短、表观遗传、代谢、炎症、干细胞等多个机制，这些机制共同构成了长寿动物维持长寿和再生能力的关键因素，为人类衰老和长寿机制的研究提供了天然的模型。本研究从进化生物学的独特视角出发，探讨了衰老与寿命的内在联系及其演替规律，并通过比较人类和多种长寿动物的基因组，结合遗传发育学、比较基因组学、代谢组学等多学科手段，揭示人类和多种动物衰老和长寿过程中共有的保守核心通路和保守机制，致力于找到导致衰老和长寿的最底层和基础的机制，为延缓衰老进程、延长健康寿命提供理论支撑和创新性解决方案。

关键词：衰老，长寿，进化发育机制，长寿动物，洞穴鱼

Increased Yolk Lipid Mobilization Powers Post-Segmentation Growth via an Hnf4–Lipoprotein Axis

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Embryogenesis is a period of explosive growth that imposes ever-increasing nutritional demands, yet the timing and control of maternal-store utilization remain poorly resolved. In oviparous vertebrates, all maternal reserves are sequestered in the yolk, creating a self-contained system that allows nutrient flux to be monitored in vivo. Here, using live imaging, biochemical assays and transcriptomics in zebrafish, we chart the fate of the two principal yolk constituents—proteins and lipids—across the first two days of development. Vitellogenin-derived proteins are degraded continuously from cleavage through hatching by maternally deposited and zygotically maintained cathepsins, fueling early cell divisions and gastrulation. In contrast, bulk lipid mobilization is postponed until after segmentation. This second wave is triggered by zygotic expression of the transcription factors Hnf4a and Hnf4b in the yolk-syncytial layer (YSL). Hnf4 induces the lysosomal phospholipase Pla2g15, which liberates phospholipids and neutral lipids from yolk granules. Released fatty acids are transferred to the YSL endoplasmic reticulum, assembled into nascent lipoproteins by Mttp, and delivered through the newly established circulation to the embryo. Blockade of protein degradation arrests development at all stages, whereas disrupting Pla2g15 or Mttp leaves early embryos unaffected yet severely retards post-segmentation growth, particularly of muscle and neural tissues. Cross-species transcriptomic analyses reveal an HNF4-lipoprotein signature in the mouse and human yolk sac, indicating evolutionary conservation. Together, our data define a two-phase, transcriptionally gated program in which continuous protein catabolism is supplemented by a later, Hnf4-dependent burst of lipid export, ensuring that maternal reserves are redeployed in step with the embryo's escalating energetic and biosynthetic needs.

Key Words： Maternal nutrient, Yolk-syncytial layer, Extra-embryonic metabolism, Lipid mobilization

斑马鱼卵黄磷脂代谢障碍阻碍视网膜发育

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摘要：本研究探讨了脂质代谢在斑马鱼胚胎发育中的作用，重点分析不同脂质（如磷脂、甘油三酯、胆固醇）在器官发育中的依赖性，特别是磷脂代谢对视网膜发育的影响。通过构建多个脂质代谢基因突变体（mttp, pla2g15, lipf, pla2g12b, npc2, npc1, spns1 等），我们发现不同器官对脂质类型有特异性需求，其中视网膜发育对磷脂依赖性最强。进一步分析表明，pla2g15 缺失导致磷脂降解受阻，造成视网膜细胞对 DHA 等多不饱和脂肪酸的供应不足，进而影响视网膜的正常发育。脂质组学分析和 RNA-seq 揭示了卵黄磷脂代谢缺陷如何通过改变视网膜相关基因和代谢通路，从而导致功能障碍。该研究为理解脂质在胚胎器官发育中的作用提供了新视角，并为孕期膳食脂质优化提供理论依据。

关键词：斑马鱼，脂质代谢，视网膜发育

Hdac11 在斑马鱼低温适应和糖原代谢中的作用研究

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摘要：生物如何适应环境变化一直是生物学的研究热点。温度是影响鱼类生长、繁育、分布的重要因子，低温冷害常导致鱼类疾病、死亡，带来巨大经济损失。有报道表观遗传调控和肝糖原累积在鱼类抵抗寒冷中发挥重要作用，但其详细调控机制仍不清楚。我们前期研究发现南极鱼类和低温驯化斑马鱼中组蛋白去乙酰化酶 11（Hdac11）表达显著降低。相比较与野生型（Wild Type, WT）斑马鱼，CRISPR-Cas9 敲除斑马鱼 hdac11 后，低温耐受力增强，肝糖原含量显著增多，糖原代谢关键基因 ppp1r3b 表达上调。Ppp1r3b 过表达可以提高斑马鱼肝糖原含量和低温耐受力。结合肝脏 RNA-seq、ChIP-seq 数据，发现 Hdac11、H3K27ac 结合在 ppp1r3b 基因的启动子区和上游 60kb 位点。双荧光素酶报告系统和染色体构象捕获技术（Chromatin Conformation Capture，3C）进一步证实 ppp1r3b 基因-60k 区域具有增强子活性，并与 ppp1r3b 启动子有相互作用，互作频率在 hdac11 敲除后增强，并伴随有 ppp1r3b mRNA 转录显著增加。进一步研究发现人肝细胞内也存在有类似的调控机制。本研究揭示斑马鱼 Hdac11 调控肝糖原代谢和低温适应的表观遗传调控机制，对全面解析鱼类低温适应机制具有重要意义，同时可揭示生物在极端环境下普适的生存策略和调控机制。

关键词：Hdac11，斑马鱼，表观遗传学，环境适应，糖原合成

揭示超长链多不饱和脂肪酸（VLC-PUFA）生物合成中的关键酶机制：肝脏与视网膜系统性研究

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摘要：超长链多不饱和脂肪酸（Very long chain polyunsaturated fatty acids，VLC-PUFAs，C≥22）在多种生物过程中发挥关键作用，对生命健康具有益处。在斑马鱼中 VLC-PUFAs 的合成依赖于 Elovl2、Elovl4 和 Elovl5 等延长酶，以及 Fads2 介导的不饱和酶的协同作用。为了系统解析 VLC-PUFAs 合成机制，我们利用 CRISPR/Cas9 技术构建了关键酶的内源蛋白标签与荧光标记的斑马鱼基因敲入品系。通过对基因敲入模型系统分析，发现这些酶在多个组织中具有差异性分布，尤其在视网膜中表现出特异性的表达。为了进一步探究内源性 VLC-PUFAs 的功能，我们构建了 elovl2、elovl4b、elovl5 和 fads2 突变体，从而破坏了 VLC-PUFAs 的内源性合成通路。通过对这些基因敲除模型的全面分析，我们发现 VLC-PUFAs 在维持肝脏和视网膜健康中具有关键作用。我们的研究不仅建立了一套可视化 VLC-PUFAs 生物合成的完整工具，还深入揭示了 VLC-PUFAs 在脊椎动物器官发生过程中的组织特异性代谢功能，尤其是在视网膜系统中发挥的关键生理作用。

关键词：超长链多不饱和脂肪酸，基因敲入，肝脏，视网膜，斑马鱼

新合成的 DHA 积累是心脏再生的关键因素

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摘要：成年斑马鱼和新生小鼠能够通过已存在的心肌细胞的增殖实现心脏部分切除后的完全再生。然而，成年哺乳动物心脏在损伤后再生能力极其有限，这一现象的机制尚未阐明。本研究发现，二十二碳六烯酸（DHA）仅在斑马鱼和新生小鼠的心脏损伤部位特异积累，伴随着损伤区心肌细胞、成纤维细胞和巨噬细胞中 DHA 合成基因的上调，而在成年小鼠中未见此现象。抑制 DHA 合成酶 Fads2 会显著损害斑马鱼和新生小鼠的心脏再生能力。注射 DHA 可诱导成年小鼠心肌梗死后转录组模式从损伤应答向再生应答转变，并改善心脏功能。值得注意的是，DHA 既能促进心肌细胞增殖，又能抑制纤维化和炎症反应。机制研究表明，DHA（而非油酸 OA）通过特异性激活过氧化物酶体增殖物激活受体δ（PPARD），使其与心脏再生相关基因（如 Mef2d、Phlda3 和 Txndc5）的启动子区域结合并调控其表达。分子对接、分子动力学模拟及点突变实验揭示，DHA 与 PPARD 的结合模式不同于 OA，这可能是二者调控心脏再生基因能力差异的结构基础。本研究揭示了 DHA 信号在心脏再生中具有进化保守的重要作用，为心肌梗死治疗提供了新策略。

关键词：心脏再生、斑马鱼、小鼠、DHA、PPARD

Identification of a biphasic RA-Notch regulatory cascade governing islet development and differentiation

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Understanding pancreatic islet development is crucial for advancing diabetes treatment. Zebrafish (Danio rerio) endocrine pancreas consists of primary and secondary islets, and development is regulated by key signaling pathways including retinoic acid (RA) andNotch. RA promotes ectopic islet formation during early development (8–10 hpf), while RA inhibition is required for secondary islet differentiation (3–5 dpf). Similarly, Notch signaling maintains pancreatic duct cells but must be inhibited for their differentiation into secondary islets. However, the precise crosstalk between RA and Notch pathways remains unclear. Expression of Notch target genes was downregulated in RA-deficient mutant fish, suggesting that Notch signaling functions downstream of RA. Further, transient activation of Notch during early pancreatic development induced ectopic islet formation, mimicking RA treatment. Furthermore, inhibition of either RA or Notch at later stages enhanced this effect, demonstrating the biphasic nature of their regulation. Through analysis of transcriptomic data, 48 RA-regulated genes associated with Notch signaling were identified, and analyzed by knockout mutation. ndrg1a mutant showed reduced primary islet size, increased secondary islet numbers, and decreased number of duct cells. RA was found to regulate ndrg1a via conserved enhancer elements, while Ndrg1a modulated Notch signaling by interacting with GSK-3β. Chemical genetics confirmed the RA-Ndrg1a/GSK-3β-Notch cascade's role in islet formation is conserved across zebrafish and human pancreas. These findings provide novel insights into pancreatic islet development with use for novel therapies.

Key Words： Pancreas; Pancreatic islet cell; ndrg1a; RA pathway; Notch pathway; Pathway crosstalk; Retinoic acid; Notch

Arunsylester A 通过抑制 TNF-α 保护多巴胺能神经元治疗帕金森病的研究

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摘要：帕金森病（PD）是一种以多巴胺能神经元退化和运动功能障碍为特征的进行性神经退行性疾病。目前的治疗手段虽可延缓病情进展，但无法根治且常伴随副作用。本研究探讨了从 Aruncus sylvester Kostel 根部提取的生物活性化合物 Arunsylester A（ASE-8） 在 MPTP 诱导的帕金森病斑马鱼和小鼠模型中的治疗潜力。研究结果显示，ASE-8 在多种动物模型中均能有效减少神经炎症、保护多巴胺能神经元并改善运动功能。在斑马鱼模型中，ASE-8 显著抑制了早期受 PD 影响的嗅球区域的细胞凋亡。通过网络药理学和生物信息学分析，我们识别出 肿瘤坏死因子-α（TNF-α）、半胱氨酸蛋白酶-3（CASP3） 和 前列腺素-内过氧化合酶合成酶 2（PTGS2） 为 ASE-8 在 PD 中可能作用的潜在靶点。随后的功能缺失与功能获得实验进一步验证了 TNF-α 在其神经保护机制中的关键作用。

RNA 测序（RNA-seq）表明，ASE-8 显著抑制了胞葬（efferocytosis）相关基因 及其信号通路的表达。这种调控作用可能通过抑制过度吞噬活动，减轻神经炎症反应，维持中枢神经系统的免疫稳态，从而发挥神经保护作用。综上，本研究提示 ASE-8 作为一种天然产物，具有成为未来 PD 治疗候选药物的潜力，为神经退行性疾病的治疗提供了新的思路和机制。

关键词：帕金森病、多巴胺能神经元、天然药物

血小板来源的 Hb-egfb 调控斑马鱼心脏再生的机制研究

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摘要：斑马鱼的心脏再生涉及来自不同类型心脏细胞间信号传导的协同作用。然而，关于血小板及其相关信号如何调控心脏再生的机制仍知之甚少。本研究发现，血小板来源的配体 Hb-egfb 对斑马鱼心脏再生至关重要。通过使用全身性的 hbegfb 基因敲除突变体（hbegfb KO），我们发现 hbegfb 缺失会干扰心外膜向梗死区域的迁入，减少损伤诱导的心肌细胞分裂，增加心脏纤维化和胶原沉积，而 hbegfb 的同源基因 hbegfa 的缺失对心室切除后的心肌细胞增殖和心脏再生影响甚微。有趣的是，本研究发现损伤后心脏中的 Hb-egfb 在血小板中高度富集，并且在血小板中进行条件性 hbegfb 敲除（hbegfb cKO）会导致与 hbegfb KO 突变体相似的心脏再生缺陷，这表明血小板中的 Hb-egfb 在心脏再生过程中发挥着关键作用。正在进行的研究关注于血小板中的 Hb-egfb 如何与心外膜中的受体相互作用，以协调心脏再生。因此，本研究揭示了 Hb-egfb 在斑马鱼心脏再生过程中所发挥的关键作用，提示其是一种新型的血小板衍生因子。

关键词：斑马鱼、hbegfb、血小板

Platelet-derived Hb-egfb regulates zebrafish heart regeneration

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Zebrafish heart regeneration is involved in an orchestra of intercellular signaling from different heart cell types. However, it remains poorly understood how platelets and related signaling participate in heart regeneration. Here, we report that platelet-derived ligand Hb-egfb is critical for zebrafish heart regeneration. By using global hbegfb knockout mutants (hbegfb KO), we found that hbegfb deficiency interfered with epicardial invasion into the infarct area, decreased injury-induced cycling cardiomyocytes, and increased cardiac fibrosis and collagen deposition, while the deficiency of hbegfb paralogue gene, hbegfa, had minimal impact on cardiomyocyte proliferation and heart regeneration after ventricular resection. Interestingly, we found that Hb-egfb was highly enriched in platelets in the heart after injury, and conditional hbegfb knock-out in platelets (hbegfb cKO) had heart regeneration defects that were similar to hbegfb KO mutants, suggesting that Hb-egfb in platelets play essential function during cardiac regeneration. Ongoing studies focus on how Hb-egfb in platelets interacts with its receptors in the epicardium to coordinate heart regeneration. Therefore, this work presents the critical role of Hb-egfb as a novel platelet-derived factor during zebrafish heart regeneration.

Key Words：Zebrafish, hbegfb, Platelet

Pdia3 介导维生素 D3 信号调控胰岛素表达

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摘要：1,25(OH)D3 信号通路调控斑马鱼脂肪分解和葡萄糖稳态，维生素 D3 缺乏导致斑马鱼肥胖和胰岛素功能紊乱，但是其结合下游受体调节胰岛素的机制仍不清楚，我们通过对 vdra、vdrb 以及 pdia3 基因的敲除，建立了 1,25(OH)D3 受体缺失的斑马鱼模型，vdra 和 vdrb 双敲除胰岛素表达升高，表现为餐后血糖下降速度加快，脂肪合成升高，脂肪分解降低，血液 1,25(OH)D3 水平升高，预测可能高 1,25(OH)D3 激活了下游非经典受体；PDIA3 作为潜在的 1,25(OH)D3 受体，其敲除斑马鱼 1,25(OH)D3 水平升高，但是胰岛素降低，血糖升高；三基因纯合突变杂交斑马鱼损坏了 vdra/vdrb 双敲除的高胰岛素表达，和 pdia3-/-突变体表达水平相当；同时，三基因突变斑马鱼也显著降低了 vdra/vdrb-/-导致的脂肪肝症状。结论：pdia3 和 vdrs 敲除均可以反馈促进 1,25(OH)D3 的生成，vdra/vdrb 双敲除提升 1,25(OH)D3 水平从而促进胰岛素高表达，PDIA3 介导 1,25(OH)D3 信号，促进胰岛素表达。

关键词：斑马鱼，双羟 VD3，胰岛素，PDIA3

S7. 组织器官衰老

Aging of tissues and organs

胰腺肿瘤的衰老细胞起源与衰老逃逸机制探讨

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摘要：肿瘤细胞衰老及逃逸是癌症发生发展中的关键生物学过程，但其在消化道肿瘤起源中的作用及分子机制尚未完全明确。本研究通过斑马鱼转基因肝癌模型发现，KRAS 癌基因激活可诱导肝细胞发生癌基因诱导的衰老（OIS），表现为 β- 半乳糖苷酶（SA-β-gal）活性升高等。然而，当 KRAS 与 MYC 基因共表达时，上述衰老表型显著减弱，细胞获得持续增殖能力并形成侵袭性肿瘤，提示 MYC 可通过调控 p53/p16 信号通路介导衰老逃逸。进一步利用 Cdkn2a-CreERT2 小鼠构建衰老细胞追踪模型，通过雨蛙素诱导小鼠胰腺细胞衰老和癌基因表达，发现胰腺细胞化生可以起源于 Cdkn2a+衰老前体细胞。单细胞 RNA 测序（scRNA-seq）分析显示，衰老胰腺细胞高表达衰老相关分泌表型（SASP）因子，其分泌的微囊泡（SVs）可招募巨噬细胞聚集于肿瘤微环境，而巨噬细胞通过吞噬衰老细胞来源的 SVs，释放促增殖细胞因子，通过旁分泌机制激活邻近细胞的 β-catenin/Myc 信号，最终导致衰老逃逸及肿瘤转化。本研究为靶向衰老细胞及其微环境互作的肿瘤防治策略提供了新的理论依据。

关键词：胰腺癌，衰老，KRAS，MYC，巨噬细胞

跨物种血管衰老的特征

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摘要：血管根据结构可分为弹性血管、肌性血管和毛细血管，其中弹性血管和肌性血管对血液运输和器官灌注发挥重要作用。其功能或结构异常与多种老年心脑血管疾病相关。血管衰老增加心脑血管疾病的易感性，研究血管衰老的机制对延缓心脑血管疾病的发生和发展有重要意义。目前研究血管衰老的模型包括非人灵长类、大小鼠、鸡、斑马鱼等。但这些模型的血管与人类血管在衰老过程中的变化规律是否一致，尚缺乏系统比较。本研究比较这些血管的转录组随衰老变化的规律，确定血管衰老的指纹图谱已经这些改变对血管功能和疾病的影响，探讨延缓血管衰老的可能性。

关键词：血管，衰老，弹性血管，肌性血管

转录因子在消化器官发育中的协同作用研究

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摘要：动物消化系统的形成源于内胚层细胞。目前对于不同区域的内胚层细胞如何特化发育为特定的消化器官已有一定的研究，但针对不同区域的内胚层细胞如何协调区域性有序特化并最终形成功能性的消化系统的科学问题仍缺乏系统深入研究。利用斑马鱼作为模式动物，我们发现 hhex，prox1a，sox9b，pdx1 和 cdx1b 形成一个遗传调控网络协调肝脏，胰腺和肝胰导管与肠道的协同发育。我们的研究结果显示，hhex 突变导致肝外导管肠样化，cdx1b 突变导致肠道肝样化，hhex 和 prox1a 双基因突变导致肝前体细胞无法分化为肝脏细胞。基于此，我们认为 hhex 和 prox1a 的协同作用是肝向分化的主控因子，cdx1b 是抑制内胚层细胞肝向分化的主控因子，hhex 是肝外导管发育的主控因子，由此绘画出一个协调肝脏和肝胰导管与特定肠道区域协同发育的遗传调控网络。下一步，我们的主要目标是揭示 Hhex 和 Prox1a 决定内胚层细胞向肝脏细胞分化的分子机制。

关键词：hhex,prox1a,sox9b,pdx1,cdx1b

S8. 感染与免疫

Infection and Immunity

Notch3 orchestrates microglial lysosomal degradation via the Rheb-mTORC1 signaling axis

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Microglia, the primary phagocytes of the central nervous system, are essential for neural development and neurological disease progression, largely by tightly regulating lysosomal activity to clear apoptotic neurons. However, the precise intracellular degradation mechanisms of engulfed cells remain incompletely understood. Here, we dissect the specific roles of individual Notch receptors in early microglia development and reveal that Notch1 primarily governs early microglial differentiation, while Notch3 is critical for lysosomal degradation. Although *notch3*$^{-/-}$ zebrafish embryonic microglia retain the ability to recognize and engulf apoptotic neurons, they exhibit enlarged lysosomal compartments filled with undigested lipids and membranes, suggesting impaired degradative processing. Notably, the fluorescence intensity of DQ-BSA, a protease-sensitive reporter, is markedly reduced in *notch3*$^{-/-}$ microglia compared to controls, reflecting a severe defect in lysosomal proteolytic activity. Colocalization and rescue experiments further demonstrate that Notch3 regulates lysosomal function in a cell-autonomous manner. Integrated transcriptomic analyses, genetic perturbations, and cellular assays reveal that Notch3 sustains lysosomal degradation by modulating *rheb* expression, thereby activating the mTORC1–TFEB signaling pathway. Consistently, the deletion of Notch3 in BV2 murine microglial cells suppresses the Rheb-mTORC1 signaling pathway, leading to lysosomal accumulation and a compromised degradative capacity. Collectively, our findings demonstrate that the conserved Notch3–Rheb–mTORC1 signaling axis serves as a key regulator of lysosomal degradation in microglia, providing mechanistic insights into phagosome processing and identifying potential therapeutic targets for neuronal disorders.

Key Words： Microglia, Lysosomal degradation, Notch3, Rheb, mTORC1

斑马鱼视角：肠道菌群/外泌体与 VKH 致病机制新探索

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目的：本文旨在探讨 VKH 综合征的病因与发病机制的最新进展，尤其是肠道微生物及外泌体的新角度，并进一步探讨斑马鱼模型筛选 VKH 综合征致病靶点的可能。

方法：通过文献综述，总结了 VKH 综合征发病机制的相关研究成果，详细梳理了从肠道微生物及外泌体的角度探讨临床及基础研究的新进展。其次，还探讨了斑马鱼模型在 VKH 相关研究中的潜在应用前景。

结果：肠道微生物及外泌体在 VKH 的发病机制中扮演着重要角色，如 miR-410-3p，假单胞菌噬菌体。其中，血液外泌体中 miR-410-3p 通过靶向 CXCL5 抑制自体 CD4T 细胞；紊乱的假单胞菌噬菌体通过影响肠道细菌的叶酸合成，从而促进色素脱失。此外，油酸通过上调 ODC1 蛋白和腐胺水平，抑制 STAT5A 蛋白的磷酸化，导致 Th1/Th17 和 Treg 细胞失衡促进全身免疫紊乱。斑马鱼在眼科研究中应用广泛，如药毒物筛选、基因敲除等领域。lrpap1 缺陷可通过 TGF-β诱导的细胞凋亡信号传导导致近视； 500nm 聚苯乙烯导致 TGF-β-晶体蛋白轴紊乱，使视觉感知和晶状体发育失调，从而可能导致斑马鱼的视力障碍。斑马鱼葡萄膜炎模型的建立预示着其在葡萄膜炎领域的巨大研究潜力。

结论：肠道菌群及外泌体是探讨 VKH 发病机制的重要途径，未来的研究应该基于斑马鱼黑色素细胞分布于体表可直接观察色素脱失动态的特性进一步深入探讨 VKH 致病靶点，以期为治疗 VKH 治疗提供新方向。

关键词：VKH 综合征，斑马鱼，肠道菌群，外泌体

Extracellular β-glucan induces hematopoietic bias towards neutrophils to engage trained immunity in zebrafish larvae

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β-Glucans are the naturally occurring polysaccharides in fungi, yeast, and grains and stand out as a paradigmatic stimulus of trained immunity – a form of innate immune memory. However, the bioactivity of β-glucans is frequently constrained by structural heterogeneity and low production efficiency. Given the emerging demand for effective trained immunity inducers that can develop the approaches to fight against infectious diseases, we engineered an Aureobasidium melanogenum strain to secrete extracellular β-glucan (eBG) with higher branching degree and molecular weight than cell wall-derived β-glucan (cBG). Taken the advantage of utilizing zebrafish larvae as the in vivo trained immunity model, we demonstrated that eBG training provides robust protection against Edwardsiella piscicida infection by promoting neutrophil differentiation. Mechanistically, we found that eBG training could trigger hematopoietic skewing towards neutrophil through the conserved C-type lectin receptor in zebrafish, resulting in emergency granulopoiesis and accelerating the neutrophil replenishment to combat bacterial infection. Taken together, our results establish an efficient microbial platform for high-quality β-glucan production and provide crucial mechanistic insights into its efficiency as an inductor of trained immunity, which paves the way for better understanding the mechanisms underlying innate immune memories, as well as developing potential innovative products to improve human and animal health.

Key Words： Zebrafish, Trained Immunity, Hematopoietic Bias, Neutrophils

CLDC1 mediates β-glucan-induced trained immunity in zebrafish via Syk-MAPK signaling

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β-Glucan, a widely used immunostimulant in aquaculture, enhances host resistance to infections by activating the innate immune system. Recent studies have demonstrated that β-glucan can induce innate immune memory (termed "trained immunity") in both mammals and teleost fish, thereby conferring long-term protection against nonspecific pathogens. However, the receptor responsible for β-glucan recognition in teleosts and its downstream regulatory mechanisms remain elusive, impeding the development of effective and targeted immune strategies. In this study, we identified C-type lectin domain-containing 1 (CLDC1) as a putative β-glucan receptor in zebrafish and confirmed its direct, dose-dependent binding to β-glucan. Using a zebrafish larval trained immunity model, we demonstrated that CLDC1 is indispensable for β-glucan-induced trained immunity. Mechanistically, β-glucan priming triggers CLDC1-mediated enrichment of H3K4me3 at the promoter regions of Syk/MAPK signaling pathway genes, leading to epigenetic reprogramming. Upon secondary infection, this epigenetic memory facilitates rapid transcriptional activation of inflammatory cytokines (IL-1β, TNFα), thereby enhancing broad-spectrum antimicrobial defenses. In summary, our study identifies CLDC1 as the key receptor for β-glucan recognition in zebrafish and elucidates the molecular mechanism by which the β-glucan-CLDC1 signaling axis mediates trained immunity through regulation of the Syk-Akt-mTOR and MAPK pathways. These findings provide novel insights for developing β-glucan-based precision immunostrategies.

Key Words：Zebrafish, Trained immunity, CLDC1, β-Glucan, Epigenetic

槐尺蛾中抗菌肽 MorA 的序列鉴定及基于斑马鱼模型的体内抗菌活性验证

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目的：抗生素耐药问题日益严峻，抗菌肽（AMPs）因其广谱活性和不易诱导耐药性的特点成为潜在替代药物。槐尺蛾（*Semiothisa cinerearia*）作为一种常暴露于复杂的微生物环境的鳞翅目物种，抗菌肽在其免疫应答机制中或发挥核心作用。本研究拟通过转录组测序鉴定槐尺蛾中的新型抗菌肽，并以斑马鱼为模型评估其体内抗菌活性。

方法：转录组测序比对筛选候选抗菌肽序列。结合 moricin 家族保守结构域特征预测成熟肽序列，合成抗菌肽 MorA。体外测定其对金黄色葡萄球菌和大肠杆菌的 MIC/MBC。使用 CM-DiI 对细菌进行标记，以显微注射的方式移植到 3 dpf 野生型 AB 品系斑马鱼卵黄囊内，评估 MorA 的体内抗菌效果。

结果：经生物信息学分析，获得 1 条 moricin 家族抗菌肽序列。经信号肽预测与剪切位点分析获得成熟肽序列。体外实验表明，MorA 对金葡菌的 MIC/MBC 为 1 μmol/L，对大肠杆菌为 2 μmol/L。斑马鱼模型中，2.5 μmol/L MorA 使金葡菌感染载量下降 27.2%，优于阳性对照组 200 μg/mL 氨苄西林（21.2%）； 5 μmol/L 浓度下对大肠杆菌的抑制率为 16.8%，略低于氨苄西林（25.5%）。

结论：本研究首次从槐尺蛾中鉴定出广谱抗菌的抗菌肽，尤其对革兰阳性菌效果显著。其广谱性与低毒性特点为解决病原体耐药问题提供了新思路，为开发新型抗菌药物提供了有前景的候选分子。

关键词：槐尺蛾，抗菌肽，moricin，斑马鱼

新型巨噬细胞亚群在结核性肉芽肿中抑制过度炎症维持免疫稳态

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摘要：肉芽肿在结核病的发病机制中发挥着关键作用，但调控其形成的免疫环境仍不清楚。为探究结核性肉芽肿形成过程中免疫微环境的动态变化，我们用海洋分枝杆菌感染成年斑马鱼，并分析了未感染与感染状态下的肾脏组织，以及肾脏中的大小肉芽肿。通过单细胞 RNA 测序技术，我们在未感染的斑马鱼造血组织（肾脏）中鉴定出两大类主要的巨噬细胞亚群：单核细胞来源的巨噬细胞和组织驻留型巨噬细胞。有趣的是，感染诱导了上皮样细胞及一种此前未被描述的 *grna.2*$^{+}$巨噬细胞亚群的出现。利用硝基还原酶-甲硝唑系统特异性消除 *grna.2*$^{+}$巨噬细胞后，斑马鱼感染后的存活时间明显缩短，体内细菌负荷升高，肉芽肿数量增多，尤其是坏死性肉芽肿显著增加。此类去除还导致肉芽肿结构更致密，T 细胞浸润减少。RNA 测序和流式细胞术分析显示，*grna.2*$^{+}$巨噬细胞的缺失会增强炎症信号通路的激活（如 *tnfα*和 *il1β*），并加剧巨噬细胞的裂解性死亡。类似地，在结核病患者样本中，我们也观察到表达 GRN 的巨噬细胞，它们具有与上述 *grna.2*$^{+}$巨噬细胞相似的抗炎功能。这一新发现的 *grna.2*$^{+}$巨噬细胞亚群存在于发育中的肉芽肿中，能够抑制过度的炎症反应，缓解巨噬细胞裂解性死亡，减少组织损伤，促进 T 细胞浸润，最终有助于在体内控制分枝杆菌的生长。

关键词：分枝杆菌，肉芽肿，巨噬细胞，免疫微环境，Granulin

鱼类肝细胞核因子 HNF4 抗多病因共感染的作用机理研究

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摘要：肝细胞核因子 HNF4 是调控肝脏基因特异性表达的一类转录因子，目前哺乳动物 HNF4 的研究主要集中在 HNF4α，发现其参与调控脂肪肝等多种肝脏代谢性疾病。鱼类 HNF4 的相关研究比较少，主要集中在 HNF4α对代谢基因的转录调控上。我们围绕鱼类 HNF4 在免疫代谢中的功能及其调控机制开展了相关研究。在斑马鱼中，建立了肝胆综合症并发 GCRV-II 感染的模型。利用此模型，研究发现抑制自噬和 HSP90 活性可缓解肝胆综合征和（或）GCRV-II 感染引起的肝脏脂质沉积和 ROS 积累，从而提高肝胆综合征、GCRV-II 感染或肝胆综合征并发 GCRV-II 感染斑马鱼幼鱼的存活。在斑马鱼和草鱼中，阐明了 Hnf4α介导的双依赖凋亡通路及其结构域特异性识别机制。Hnf4α 通过与凋亡诱导因子（AIF）及 caspase 3/9 形成核内信号复合物，驱动两条并行的凋亡路径：通过 DNA 结合结构域（DBD）与 AIF 互作，介导不依赖 caspase 的凋亡；通过配体结合结构域（LBD）激活 caspase 3/9 介导的凋亡。这种 “双路径协同” 机制首次揭示了核受体通过结构域分工协调细胞死亡。证实了鱼类 Hnf4α对细菌 - 病毒共感染具有显著保护作用。此外，研究结果还揭示了斑马鱼 Hnf4α靶向抑制 VDR 抵制肝胆综合症并发 GCRV-II 感染的作用机制。

关键词：斑马鱼，肝细胞核因子 HNF4，肝胆综合症，GCRV-II 感染，细菌-病毒共感染

Ace2 通过抑制 Nlrp3 介导的细胞焦亡以保护胚胎造血干祖细胞产生

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摘要：在脊椎动物胚胎发育过程中，造血干祖细胞（HSPCs）通过内皮-造血转化起源于背主动脉的生血内皮（HE）。适度的基础炎症对此过程至关重要，但过度的免疫激活则会破坏 HSPC 的产生。本研究发现肾素-血管紧张素系统的关键组分血管紧张素转换酶 2（Ace2）是斑马鱼和小鼠胚胎造血过程的重要抗炎调节因子。Ace2 缺失会损害 HE 特化并减少新生 HSPC 的产生。转录组分析揭示 Ace2 缺失导致血管内皮细胞中 NLR 家族 Pyrin 域蛋白 3（ Nlrp3）信号通路的异常激活和细胞焦亡的发生。重要的是，药物抑制 Nlrp3 或 Caspase-1 能够回救 Ace2 缺失情况下 HSPC 的产生，这与使用 Ace2 的下游产物，外源性血管紧张素-(1-7)（Ang-(1-7)）处理的效果一致。此外，在小鼠胚胎中敲低 Ace2 可重现斑马鱼中的缺陷，证明了 ACE2 在哺乳动物发育造血过程中的进化保守性。综上所述，我们的研究结果揭示了 ACE2 在维持 HSPC 发育所需的适度炎症环境中的关键作用，并暗示靶向 ACE2/Ang-(1-7)/Nlrp3-细胞焦亡轴在炎症性造血疾病中具有治疗潜力。

关键词：造血干祖细胞，Nlrp3 信号通路，细胞焦亡，Ace2，炎症

Prkra 二聚体感知 dsRNA 调控整体翻译效率

陆通、邵明

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摘要：双链 RNA（dsRNA）是一种进化上保守的病原体相关分子模式，能够被细胞内的模式识别受体感知，进而引发抗病毒先天免疫应答。在分化细胞中，dsRNA 能够激活 PKR，触发整合应激反应。该反应通过磷酸化翻译起始因子 eIF2α，导致细胞内整体翻译抑制。然而，在干细胞中，dsRNA 刺激并不会引发 IFN 的高表达，dsRNA 的感知及感知后翻译调控机制长期未被阐明。

本研究以斑马鱼早期胚胎为多能干细胞模型，首次揭示了干细胞在不依赖 PKR 的情况下，是如何有效地实现 dsRNA 介导的细胞内翻译抑制。研究发现，Prkra 是干细胞中识别 dsRNA 的关键感受器。在干细胞中，Prkra 通过 dsRBD1 和 dsRBD2 结合 dsRNA，并通过 dsRBD3 以二聚化形式存在。当结合 dsRNA 后，Prkra 二聚体能够阻止 eIF2 组装到 40S 核糖体亚基上，来减少 43S 翻译起始前复合物的形成，并最终实现翻译抑制。这种应激反应机制能够有效地限制 RNA 病毒在斑马鱼胚胎中的复制。同时，我们在哺乳动物体系中验证了 PRKRA 的功能，发现在小鼠胚胎干细胞中 PRKRA 所介导的翻译调控是高度保守的。而且，在小鼠分化细胞中，这种调控机制可能协同 PKR 所介导的 eIF2α磷酸化来共同实现翻译抑制。总之，Prkra 介导的 dsRNA 感知与翻译调控机制在不同物种和细胞中均发挥关键作用，这种独特的应激反应机制可能是细胞为了适应环境压力而进化出的应对策略。

关键词：dsRNA；Prkra；dsRNA 感受器；翻译抑制；胚胎干细胞

Pu.1/Spi1 dosage controls the turnover and maintenance of microglia in zebrafish and mammals

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Microglia are brain-resident macrophages playing pivotal roles in central nervous system (CNS) development and homeostasis. Yet, the cellular and molecular basis governing microglia maintenance remains largely unknown. Here, by utilizing a visible conditional knockout allele of *pu.1/spi1b* gene (the master regulator for microglia/macrophage lineage development) to generate mosaic microglia populations in adult zebrafish, we show that while *pu.1*-deficient microglia are immediate viable, they are less competitive and chronically eliminated through Tp53-mediated cell competition. Interestingly, when conditionally inactivating Pu.1 in adult *spi-b* (the orthologue of mouse *Spi-b*) null mutants, microglia are rapidly depleted via apoptosis, suggesting that Pu.1 and Spi-b regulate microglia maintenance in a dosage-dependent manner. The dosage-dependent regulation of microglia maintenance by PU.1/SPI1 is evolutionarily conserved in mice, as shown by conditionally inactivating single and both *Spi1* alleles in microglia, respectively. Collectively, our study reveals the conserved cellular and molecular mechanisms controlling microglia turnover and maintenance in teleosts and mammals.

Key Words：Pu.1 Dosage, Microglia, Turnover, Maintenance, Cell Competition

The positive domino effect of host-microbe cross-talk along the gut-liver axis in alleviating hepatic steatosis in zebrafish

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Studies on the gut-liver axis interaction mechanisms have been mainly focused on the microbial metabolites and/or host metabolites. However, the importance of these microbial metabolites further metabolized by the host cells on this axis is poorly understood. Herein, using fatty liver zebrafish model, we identified that mannose did not have a direct effect on mitigating hepatic steatosis induced by high-fat diet, but promote the growth of gut Cetobacterium somerae. Further, C. somerae can utilize Arginine to produce agmatine, which was further metabolized into putrescine, but the bacterium cannot metabolize putrescine to spermidine. Conversely, the host cells can absorb microbial putrescine and further metabolized into spermidine in the liver and spermidine is the effector molecule in liver lipid lowering. Collectively, these findings uncover a new mechanism whereby gut microbiota and host collaboratively complete the Arginine-putrescine-spermidine cascade metabolic pathway to ameliorate hepatic steatosis, providing important insights into the host liver-gut microbiome axis driven regulatory mechanisms.

Key Words： Gut-liver axis, Hepatic steatosis, Mannose, Putrescine, Spermidine

S9. 再生生物学

Regenerative biology

肝细胞胶质成熟因子β对急慢性肝损伤的影响

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目的：利用斑马鱼构建急慢性肝损伤模型，探究肝细胞中胶质成熟因子β(gmfb)（hep-Gmfb）在肝再生修复作用。

方法：构建肝细胞靶向 gmfb 过表达（HepGOE）斑马鱼。HepGOE 和野生型（WT）的斑马鱼行部分肝切除术（PHX）模拟急性肝损伤，构建代谢相关脂肪性肝病（MASLD）模型模拟慢性肝损伤。观察斑马鱼的外观、生存率。组织病理染色观察肝脏病理变化。IHC 观察增殖指标在肝组织分布表达；F-actin 染色观察肌丝蛋白分布；检测增殖和炎症因子、il6/stat3 通路分子的表达。

结果：对照组中 HepGOE 组和 WT 组的生存率、外观和肝脏组织学无差异。PHX 后，HepGOE 组脂肪变性较 WT 组轻，IHC 和 RT-qPCR 显示 WT 组的肝脏 gmfb 水平与细胞增殖和促炎因子水平呈正相关，HepGOE 组增殖因子水平更高。在 MASLD 中，WT 组肝脏的 gmfb 水平随疾病发展增加，组织染色显示 HepGOE 组改善肝细胞肿胀、脂肪变性。IHC 和 RT-qPCR 显示 HepGOE 组肝细胞增殖率较高，MASLD 各组中促炎因子水平均升高，但 HepGOE 组水平较低。F-actin 染色显示 HepGOE 组的肌丝蛋白分布高于 WT 组。RT-qPCR 和 WB 显示 stat3 在 HepGOE 组中高度激活。

结论：Hep-Gmfb 通过增强肝细胞增殖、缓解肝脂肪变性、调节 Il6/Stat3 信号通路及重塑肝细胞的肌动蛋白丝网络促进再生。

关键词：肝细胞胶质成熟因子β，斑马鱼，肝再生，部分肝切除，代谢相关脂肪性肝病。

Identification of Renal Stem Cells in Zebrafish

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Renal stem cells (RSC) hold great promise as kidney disease regenerative therapies. However, RSCs capable of regenerating de novo nephrons remain unidentified in vertebrates. Therefore, this study aimed to identify RSCs in zebrafish. Single-cell RNA sequencing revealed eya2, pax2a and six2a as primary markers of zebrafish RSCs. Real-time imaging demonstrated that RSCs originated from eya2-positive mesenchymal cells. Notably, photoconversion-based lineage tracing and serial transplantation assays revealed a unique RSC renewal process, characterized by a differentiation-proliferation-dedifferentiation mode. This process generates nephrons and nascent RSCs concurrently. Additionally, precise Wnt signaling is key for RSC renewal and differentiation balance and directly activates eya2 expression to initiate renewal. This discovery establishes a foundation for the advancement of stem cell therapies for kidney diseases.

Key Words： Renal stem cells;zebrafish;kidny

Mongolian medicine Eerdun-Wurile promotes myocardial regeneration by regulating MVDA in zebrafish

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Myocardial infarction (MI) is a leading cause of death and disability worldwide. The promotion of myocardial regeneration is a promising therapeutic strategy for acute MI. Using a zebrafish ventricular ablation system, we found that the Mongolian traditional medicine Eerdun-Wurile (EW) promotes myocardial regeneration in zebrafish. EW treatment significantly accelerated proliferation of myocardial cells and improved cardiac function. EW effectively restored heart function and relieved arrhythmia. The EW treatment group exhibited a gradual increase of EF and FS, suggesting the great progression in heart contractibility. The locomotor activity of the embryos also recovered significantly following EW treatment. Transcriptome sequencing revealed a significant decrease in mevalonate diphosphate decarboxylase a (mvda) expression in the metronidazole-induced ventricular ablation group, whereas mvda expression was restored in the EW group. mvda knockdown using morpholino oligonucleotides reversed the EW-mediated myocardial regeneration. Whereas mvda overexpression enhanced the regenerative ability, the locomotor activity and the heart beat fluctuation frequency markedly. The proliferation of cardiomyocytes was significantly enhanced after overexpression of mvda. When overexpression mvda by Tol2 system in cardiomyocytes, heart regeneration could also be recovered efficiently after ventricular ablation. In conclusion, EW may promote zebrafish myocardial regeneration, accelerate myocardial cell proliferation, and improve cardiac function by upregulating mvda expression. Our data partially revealed the molecular mechanism by which EW promotes myocardial regeneration and repair, and provides experimental data and novel insights for advancing MI treatment.

Key Words： Key Words：: Cardiomyocytes; Regeneration and repair; MVDA; Proliferation

Cloche/Npas4l is a pro-regenerative platelet factor during zebrafish heart regeneration

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Organ regeneration remains a century-old question in spite of tremendous efforts to explore the replenishment of lost cells and tissues. In mammals, heart regeneration is restricted to before postnatal day 7, whereas some lower vertebrates like zebrafish keep this regenerative capacity over a lifetime. Because of a lack of adult cardiac stem cells, it is generally believed that injury-induced de-differentiation and proliferation of CMs contributes to new myocyte regeneration. In addition, the synchronized regeneration of coronary vessels, along with the precise modulation of cardiac fibrosis and inflammation, create a permissive environment with essential oxygen and nutrient supplies, thereby facilitating a regenerative niche for the proliferation of new myocytes.

Zebrafish has full capacity of heart regeneration, but little is known about how blood cells, especially platelets, are involved in this regenerative process. Here we report cloche/npas4l is a pro-regenerative platelet factor for heart regeneration. We found that haploinsufficiency of npas4l disrupted cardiomyocyte (CM) and endothelial cell (EC) proliferation and heart regeneration after injury. A single-cell transcriptomic atlas identified npas4l was dynamically expressed in platelets after heart injury and controlled robust interactions between platelets-CMs or -ECs. Decreasing platelets impaired CM/EC proliferation, and over-expression of npas4l in platelets sufficiently induced CM/EC proliferation in uninjured hearts, as well as rescued CM/EC proliferation defects
in cloche mutants. Mechanistically, Npas4l positively controlled a panel of ligands expression including bmp6 in platelets to fine-tune CM proliferation and heart regeneration. Therefore, this work demonstrates a platelet Npas4l signaling and presents mechanisms on how platelets modulate CM/EC proliferation via ligand-receptor network during zebrafish heart regeneration.

Key Words： cloche; npas4l; platelets; heart regeneration; zebrafish

力学刺激扰乱尾鳍再生过程中上皮细胞与巨噬细胞互作的分子机制研究

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背景：再生医学旨在探索器官与组织缺损的修复及功能重建机制。近年来，力学刺激与细胞应答之间的动态互作被认为在再生过程中发挥关键作用。然而，力学刺激如何调控组织再生与修复的具体机制仍有待深入研究。因此，系统探究力学刺激如何精细调控细胞间信号传导及其对再生能力的长期影响，对于推动再生医学的临床转化具有重要意义。

方法：本研究建立了基于游泳水槽系统的实验模型，通过持续游泳干预在尾鳍再生过程中施加机械载荷。分别在再生不同时期收集每组 6 条斑马鱼的再生尾鳍，制备冰冻切片后进行免疫组织化学染色。每个样本再生区域使用原子力显微镜（AFM）测定其力学性能。同时，采用实时荧光定量 PCR 检测相应时间点尾鳍组织的基因表达水平。

结果：力学刺激显著抑制尾鳍的再生形态学进程，主要表现为再生结构减慢及细胞增殖能力下降。与对照组相比，力学刺激组中调控炎症反应的相关基因表达呈显著下调趋势。免疫染色结果显示，力学刺激降低了上皮细胞的集体迁移能力，进而抑制了再生潜能。AFM 测试结果表明，再生区域的弹性模量与硬度在对照组中显著高于力学刺激组。

讨论：持续的力学刺激通过干扰上皮细胞的迁移及炎症反应，破坏了尾鳍的稳健再生过程。本研究提示，上皮细胞与免疫细胞之间的生物力学耦合机制对再生具有重要调控作用，其受机械微环境影响显著。

关键词：尾鳍再生，力学刺激，上皮细胞，巨噬细胞

Spontaneous regeneration of sensory hair cells in zebrafish semicircular canals

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Sensory hair cells (HCs) are highly susceptible to damage from environmental noise, ototoxic medications, aging, and genetic factors. Injury to HCs in mammals typically leads to permanent hearing or balance deficits due to their limited regenerative capacity. In contrast, zebrafish exhibit a remarkable ability to regenerate HCs, with nearly all studies focusing on neuromast HCs due to their simple structure and easy accessibility. However, the HCs in the zebrafish inner ear are more anatomically and functionally similar to those of mammals; their regeneration remains poorly understood. Here, we established a novel injury model of hair cells in zebrafish semicircular canals and described the regeneration process and functional recovery after injury, based on live imaging analysis. Using two lineage-tracing approaches, we demonstrated that the regenerated hair cells were derived from supporting cells and supporting cell progenitors in the ampulla. ScRNA-seq analysis reveals dynamic gene expression in each cell type during the regeneration process after injury. Notably, we described the cell-cell interaction during the regeneration process and found the key interaction. Additionally, we identified a crucial transcription factor essential for crista hair cell regeneration.

Key Words： Spontaneous regeneration; hair cell; supporting cell; cell chat; transcription factor

Knockout of thyroid hormone receptor alpha a (thraa) enhances cardiac regeneration in zebrafish through metabolic and hypoxic regulation

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Thyroid hormone (TH) signaling drives cardiomyocyte (CM) maturation in endothermic animals. Elevated TH levels, coupled with increased basal metabolism, promote CM cell cycle exit and polyploidization, thus limiting heart regenerative potential. However, a comprehensive understanding of TH and its receptors, thyroid hormone receptors (TRs), orchestrating with other regulatory processes for heart regeneration, such as the hypoxia signaling pathway and post-injury metabolic switches, remains elusive. Here, we investigated the molecular mechanisms of TH signaling in heart regeneration using a time-course sequencing experiment. We assessed heart regeneration capacity in *hormone receptor alpha a* (*thraa*) mutant zebrafish, which carry an 8-bp insertion that leads to truncation of the Thraa protein and impaired TH signaling. The *thraa* +8 bp mutant zebrafish exhibited an enhanced heart regenerative response. Our study showed that, in *thraa*+/– mutants, a transiently augmented inflammatory response and an extended CM proliferative window are associated with metabolic switches across different phases. Moreover, we found that thraa transcriptionally regulates *hypoxia-inducible factor 3 subunit alpha* (*hif3a*), and its knockout in zebrafish impairs heart regeneration. In conclusion, our study highlights the role of TH signaling via thraa in modulating zebrafish heart regeneration through metabolic regulation, inflammation, cardiac tissue regeneration, and its interplay with *hif3a*.

Key Words： Thyroid hormone; metabolism; hypoxia; heart regeneration; inflammation; cardiomyocytes; zebrafish

Functional study of DNA methylation in zebrafish heart regeneration

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The zebrafish, renowned for its remarkable ability to fully regenerate the heart after injury, has emerged as an ideal model organism for studying cardiac regeneration. DNA methylation, a key epigenetic modification, has been shown to play a crucial role in regulating the regeneration of tail fins and retina in zebrafish. However, its specific contribution to cardiac regeneration remains underexplored.

Our study systematically characterized the genomic distribution patterns of organ-wide DNA methylation (5-methylcytosine, 5mC; N6-methyladenine, 6mA) in adult zebrafish heart and their dynamic alterations upon cardiac injury by combining whole-genome methylation sequencing with immunofluorescence staining. Particularly focusing on the role of 5mC modification for cardiac regeneration, we pharmacologically intervened in this modification using the inhibitor 5-azacytidine (5-AzaC) and observed an impairment in the cardiac regeneration process, including defective nerve regeneration, reduced cardiomyocyte proliferation, and failure of cardiomyocyte differentiation. To further investigate the molecular mechanisms underlying these effects, we analyzed the gene locus with significant changes in 5mC modifications following cardiac injury and found sema3e as a potential regulator of cardiac regeneration. The subsequent study of its transgenic fish revealed a regulation mechanism mediated by Sema3a-Wnt signaling for zebrafish heart regeneration.

In conclusion, our study highlights the crucial role of 5mC modification in promoting successful cardiac regeneration in zebrafish. Further studies will focus on elucidating the intricate relationships between epigenetic modifications and signaling pathways during cardiac regeneration, with the ultimate goal of advancing the development of innovative cardiac regenerative therapies.

Key Words： Zebrafish, heart regeneration, DNA methylation

建立基于硝基还原酶的靶向细胞消融系统揭示室管膜胶质细胞在墨西哥钝口螈大脑皮层再生中的关键作用

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摘要：墨西哥钝口螈（以下简称蝾螈）是研究组织器官再生的重要模式生物，在蝾螈中建立精确的靶向细胞消融技术，对于阐明特定细胞类型在再生过程中的作用以及构建疾病模型具有重要意义。本研究在蝾螈中成功建立了基于硝基还原酶（Nitroreductase，NTR）的靶向细胞消融系统。通过构建 Sox2:Cherry-NTR 基因敲入蝾螈品系，我们实现了对中枢神经系统室管膜神经胶质细胞（ependymoglial cells，EGCs）的特异性消融。结合脊髓和脑的移植及损伤模型研究发现，EGCs 的消融会导致蝾螈脊髓和脑的再生失败，这提示 EGCs 是中枢神经系统再生的主要甚至唯一细胞来源。进一步，为模拟神经退行性疾病并探究大规模神经元消融后的脑再生过程，我们构建了用于消融皮层神经元的 NeuroD6:Cherry-NTR 和 NeuroD6:Cherry-NTR2.0 基因敲入蝾螈品系。实验结果显示，在蝾螈中，NTR 难以有效消融神经元，而 NTR2.0 则能够高效消融超过 95%的皮层神经元。值得注意的是，在几乎所有皮层神经元被消融后，蝾螈能够按照与发育模式一致的时间顺序（先外后内）再生丢失的神经元，并分化形成相应的神经元亚型。这一现象提示，脑再生可能是发育过程的重现。此外，我们利用组成型 CAGGs 启动子构建了基于 Cre-LoxP 系统的条件性 NTR2.0 转基因蝾螈品系，该品系与已有的蝾螈 Cre 品系结合使用时，可实现特定靶细胞的消融。综上所述，本研究在蝾螈中建立了高效的靶向细胞消融系统，为深度解析蝾螈组织器官再生机制提供了重要的技术工具。

关键词：再生、墨西哥钝口螈、细胞消融、皮层、室管膜胶质细胞

S10. 发育与演化

Development and Evolution

Detection of Newly Synthesized RNA During Zebrafish Embryogenesis via Improved Metabolic Labeling and Time-Resolved scRNA-seq

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Metabolic RNA labeling with high-throughput single-cell RNA sequencing (scRNA-seq) enables precise measurement of gene expression dynamics in complex biological processes, such as cell state transitions and embryogenesis. This technique, which tags newly synthesized RNA for detection through induced base conversions, relies on the conversion efficiency, RNA integrity, and transcript recovery. These factors are influenced by the chosen chemical conversion method and platform compatibility. Despite its potential, a comprehensive comparison of chemical methods and platform compatibility has been lacking. Here, we benchmark ten chemical conversion methods using the Drop-seq scRNA-seq platform, analyzing 52,529 ZF4 fibroblast cell line derived from zebrafish embryos. We find that on-beads methods, particularly the meta-chloroperoxy-benzoic acid/2,2,2-trifluoroethylamine (mCPBA/TFEA) combination, outperform in-situ approaches. To assess in vivo applications, we apply these optimized methods to 9,883 zebrafish embryonic cells (approximately 5.5 hours post-fertilization) during the maternal-to-zygotic transition (MZT), identifying and experimentally validating zygotically activated transcripts, which enhanced zygotic gene detection capabilities. Additionally, we evaluate two commercial platforms (10x Genomics and MGI C4) with higher capture efficiency and find that on-beads iodoacetamide (IAA) chemistry is the most effective. Our results provide critical guidance for selecting optimal chemical methods and scRNA-seq platforms, advancing the study of RNA dynamics in complex biological systems.

Key Words： Metabolic RNA labeling, scRNA-seq, Zebrafish Embryo, Maternal-to-Zygotic Transition

Mechanisms of Depigmentation in Cavefish Triplophysa rosa

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Trait regression, such as pigmentation loss in cave-dwelling species, offers valuable insights into evolutionary dynamics under extreme environments. In this study, we found that, compared with its surface-dwelling relative *Triplophysa stenura*, significant down-regulation of melanogenesis-related genes is the primary cause of disrupted melanin synthesis in the cavefish *T. rosa*. Further analysis revealed that a 63-nt deletion in *mitfa* (*melanocyte inducing transcription factor a*), caused by a novel splicing site, may be an important contributor to pigmentation loss, likely through its regulatory control of downstream melanogenesis-related genes. Functional assays confirmed that the loss of 21 amino acids in the activation domain of Mitfa severely compromises melanin synthesis. Additionally, a premature stop codon in *tyrp1a* (*tyrosinase-related protein 1a*) was detected, which may also contribute to the depigmented phenotype. Comparative protein sequence analysis further revealed multiple amino acid substitutions in pigmentation genes, which may affect pigment pathways. Evolutionary analyses indicated relaxed purifying selection on pigmentation-specific genes in *T. rosa*, consistent with reduced functional constraints in cave environments. Together, our findings demonstrate the central role of splicing alteration in mitfa in the regression of pigmentation and provide new insights into how cave-adapted fishes evolve regressive traits through both genetic and regulatory changes under relaxed selection.

Key Words： Cavefish, Triplophysa rosa, Pigmentation, mitfa, Alternative Splicing

极地鱼类耐寒性状的遗传基础和趋同演化

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摘要：地球两极的海洋常年或季节性地处于冰冻状态，但各自仍有 200 多种鱼类在此生存繁衍。过去数十年的研究已深入阐述了这些鱼类如何通过特殊的抗冻蛋白，在低于冰点的温度下保持体液处于液态这一趋同进化现象，并对各类抗冻蛋白基因的起源与演化规律进行了全面分析，极大地丰富了新基因起源的理论与实例。然而，目前对于极地鱼类如何在低温下维持正常细胞生理功能的机制，以及关键基因和调控序列的演化规律，仍知之甚少。本研究通过对极地鱼类及其近缘种基因组进行大规模多重比较分析，在全基因组水平鉴定出大量保守非编码序列(CNEs)。在此基础上，结合耐低温表型特征及是否含有抗冻蛋白基因等信息进行关联分析，筛选出极地鱼类各支系中快速进化及趋同进化的基因和 CNEs。为进一步解析其功能，我们利用基因编辑技术构建了斑马鱼、罗非鱼等物种的基因敲除品系，评估其耐寒能力变化并探究相关分子机制，同时通过野外池塘实验验证其在育种中的应用潜力。本研究将为揭示耐寒性状的遗传基础及其与细胞基本生命过程之间的联系开辟新视角。

关键词：耐寒，趋同演化，鱼类

基因拷贝数变异驱动南极鱼类对极端环境适应性演化

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摘要：南极地区呈现极度低温与高氧的环境特征。南极鱼亚目（Notothenioidei）鱼类在南极海洋逐渐变冷的过程中发生了快速适应性进化，成为研究鱼类适应性进化的理想模型。以往基于基因芯片的比较基因组杂交研究揭示了大量在南极鱼中特异性扩增的关键基因，对其适应南极环境至关重要。随着高通量技术的发展，越来越多的南极鱼基因组被成功组装。本研究通过比较基因组学分析及公共数据库挖掘，鉴定出 55 个在南极鱼类中特异性扩增的基因及 30 个丢失的基因。特别值得注意的是，我们发现一个在心血管生成与血细胞发生中起重要作用的基因，在南极鱼类中通过串联重复方式显著扩增。转录组分析显示，由于拷贝数增加，该基因在南极鱼心脏中的表达量显著上调，推测其在高氧环境适应中发挥关键作用。然而，在南极鱼亚目的鳄冰鱼科（Channichthyidae）物种中，该基因表达量却显著降低；这种低表达状态与其特殊的表型特征——血红蛋白缺失、血管增粗、心脏体积增大至其他南极鱼类的三倍——相关联。本研究拟利用已构建的心血管特异性荧光标记的转基因斑马鱼品系，对该基因进行功能探究。综上，本研究揭示了基因扩增与南极鱼类极端环境适应的潜在关联，为深入解析其分子机制提供了重要线索。

关键词：南极鱼类，基因扩增，极端环境适应，斑马鱼

可变剪接在葛氏鲈塘鳢（Perccottus glenii）寒冷耐受中的作用

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摘要：极端的温度波动对鱼类的生存与繁殖成功构成了巨大挑战。葛氏鲈塘鳢（*Perccottus glenii*）是一种耐寒的淡水鱼类，可作为解析寒冷适应分子机制的重要模式物种。尽管可变剪接（Alternative Splicing, AS）已被认为是关键的转录后调控机制，其在寒冷耐受中的具体作用仍未被充分揭示。本研究对 *P. glenii* 在三种生理状态（活跃期、冰冻期和恢复期）下脑、肝、肌肉三种组织中的 AS 事件进行了系统的转录组可变剪接分析。结果识别出大量可变剪接基因，后续的 Gene Ontology（GO）和 Kyoto Encyclopedia of Genes and Genomes（KEGG）富集分析的基因功能显示出显著的组织特异性：脑组织中的 AS 事件主要富集于信号转导与代谢调控通路，肝脏中则主要涉及葡萄糖与脂质代谢以及细胞稳态维持等过程。值得注意的是，例如 *adgrb1a* 与 *baxa* 等基因的剪切变体被认为可能参与了寒冷耐受机制。这些发现共同表明可变剪接在 *P. glenii* 寒冷适应过程中可能发挥着关键作用，并为水产养殖和低温保存中提升耐寒能力提供了理论基础。

关键词：葛氏鲈塘鳢、可变剪接、耐寒性、适应

海龙科鱼类雄性育儿的遗传基础与环境适应机制

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摘要：海洋生命的性状形成与演化机制是当前国际学术界的重要命题。作为已知动物界中独树一帜的类群，海龙科鱼类的“雄性育儿”被学界视为奇特的极端进化事件，也是当前国际学术界在鱼类演化领域所关注的焦点问题。而作为“雄性怀孕”重要器官的育儿袋在进化过程中展现出了多种形式，并与哺乳动物的子宫呈现结构与基因的趋同进化现象。本研究通过单细胞多组学和基因组学的比较分析，系统解析了海龙科鱼类进化过程中胎生转变的细胞基础，并比较了特殊“雄性怀孕”与哺乳动物“雌性怀孕”趋同进化的遗传及细胞学机制。作为脊椎动物适应性进化的重大创新，“雌性怀孕”已经独立进化了 150 多次，亲本在妊娠期间的免疫耐受与免疫保护平衡是这一进化创新的关键。然而，“雄性怀孕”繁殖系统作为在脊椎动物中的一个全新研究体系，其雄性怀孕与免疫系统的协同进化机理仍是未知。基于前期研究基础，本研究进一步利用 3 个 CRISPR/Cas9 基因敲除系统精确证实了海龙科基因 tlx1 特异性点突变（tlx1A208T）调控其“脾脏丢失”的遗传机制；基于海洋鱼类比较全基因组学分析，揭示了海龙科鱼类关键免疫基因（C4、MHC 等）数目显著减少是对繁殖适应的重要进化策略，拓展了对海洋生命繁殖系统多样化的认知。

关键词：海龙科，雄性怀孕，类胎盘，免疫耐受

S11. 时间生物学

Chronobiology

Automated microinjection for zebrafish xenograft models

Yi Ding

Life Science Methods

Zebrafish xenograft models are increasingly recognized for predicting patient responses to cancer therapeutics, suggesting their potential as clinical diagnostic tools. However, precise microinjection of cancer cells into numerous small and fragile zebrafish larvae is laborious, requires extensive training for new operators, and often yields variable results, limiting their clinical and drug discovery applications. To address these challenges, we have designed, built, and validated an automated microinjection robot. Using machine learning, zebrafish larvae are recognized, and the injection site is determined using a 10× telecentric lens and camera that can visualize the injection process from above. To adjust the needle direction to the sample orientation, a needle holder is developed that can rotate quickly around this lens. Using coaxial lighting through the bottom lens, the depth of view of the top camera is increased to observe the blood flow for vasculature injections. The robot performs injections into the duct of Cuvier, perivitelline space, and hindbrain ventricle in both fully automated and semi-automated modes. Combined results by four independent laboratories demonstrate an average injection success rate of approximately 60% and larvae survival exceeding 70%, comparable to manual methods, with the fully automated mode being twice as fast. This automation reduces the need for extensive personnel training while enhancing reproducibility, efficiency, and accuracy, paving the way for more extensive use of zebrafish xenograft models in drug discovery and patient diagnostics.

Key Words： Zebrafish larvae, Automated microinjection, Zebrafish xenografts

Comparing robotic and manual injection methods in zebrafish embryos for high-throughput RNA silencing using CRISPR-RfxCas13d

Yi Ding

Life Science Methods

Microinjection into one-cell stage zebrafish embryos is a widely used technique for genetic manipulation, including CRISPR/Cas9 genome editing. However, manual injection is labor-intensive, low-throughput, and constrained by the narrow developmental window of one cell stage embryos within approximately 45 minutes. To overcome these limitations, we developed a user-friendly automated zebrafish egg injector equipped with a touchscreen interface for seamless control of needle calibration, droplet calibration, injection, and killing of non-injected embryos. Zebrafish embryos were positioned using an agarose grid mold containing either 9 × 100 or 1024 wells. We then compared the performance of automated versus manual microinjection using the CRISPR-RfxCas13d (CasRx) system for RNA knockdown and Cas9 for DNA targeting. As a proof of principle, both systems targeted the no tail (TBXTA) gene, and phenotypic outcomes were evaluated. Our results showed that both Cas9 and CasRx induced loss-of-function phenotypes in TBXTA. Cas9 protein induced a higher frequency of severe phenotypes compared to Cas9 mRNA, while CasRx protein and mRNA performed similarly. Notably, robotic and manual injection methods yielded comparable phenotype penetrance and embryo survival rates. This study demonstrates the effectiveness of RNA-targeting CRISPR effectors for precise gene knockdown in zebrafish and validates automated microinjection—operating at a speed of 1.0 second per embryo—as a scalable, high-throughput alternative to manual injection.

Key Words：Zebrafish embryos, Robotic microinjection, CRISPR/Cas9, CRISPR-RfxCas13d

解析光照响应 microRNA 在斑马鱼与洞穴鱼昼夜节律与 DNA 修复系统中的作用机制

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摘要：昼夜节律系统与 DNA 修复系统是生物体中两项至关重要的生理过程，在功能和进化历程中高度关联，并深受环境光照的调控。然而，环境线索如何调节这些系统并推动其进化的机制，仍未被完全揭示。斑马鱼（Danio rerio）因其对可见光和紫外线的高度敏感性，成为研究光照调控昼夜节律与 DNA 修复机制的理想模式生物。相比之下，索马里洞穴鱼（Phreatichthys andruzzii）长期生活在完全黑暗的环境中，进化出了独特的生理适应性，为解析光照响应分子机制提供了有力的比较研究模型。

我们近期的研究发现，洞穴鱼中光照响应增强子功能的丧失，是其昼夜节律严重紊乱和光复活修复能力受损的部分原因。这种对永久黑暗环境的适应不仅使光诱导的昼夜节律和 DNA 修复基因的转录激活失效，还可能重塑了基因特异性的转录后调控途径。

在本研究中，我们通过高通量测序分析，在斑马鱼和洞穴鱼细胞中鉴定出一系列的光照响应性 microRNA（miRNA）。功能分析显示，这些光照响应 miRNA 在调控昼夜节律、代谢、氧化应激及 DNA 修复系统中发挥各自独特的作用。研究结果揭示了非编码 RNA 介导的光依赖性基因调控机制，并强调了恒暗环境中发生的适应性调控重构。

本研究为理解脊椎动物对光环境的分子适应性进化提供了全新的视角和机制启示。

关键词：光照，生物钟，DNA 修复，比较分析，微小 RNA

Photolyase Evolution, Regulation and Function

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摘要：DNA 修复通路、生物节律以及氧化损伤等环境应激之间存在复杂的相互作用。此外，在暴露于多种环境应激因子的情况下，会产生具有动态变化特征的 DNA 损伤谱。因此，在进化过程中，DNA 修复系统必须适应不断变化的环境以维持基因组的完整性。

光裂合酶是一类高度保守的黄素蛋白，能够通过可见光驱动的“光复活”过程修复紫外线诱导的 DNA 损伤，特别是相邻嘧啶碱基之间的共价交联（包括 CPD 和 6-4 光产物）。与此一致，光复活酶基因的表达受光照和生物钟调控。

在完全隔绝紫外线和可见光达数百万年的盲穴鱼（*Phreatichthys andruzzii*）中，我们发现其 6-4phr 和 DASHphr 光复活酶基因发生了多种多态性变异和功能丧失性突变，而 CPDphr 基因却异常地保持高度保守。为了探究 CPDphr 是否具有光照非依赖性的功能，我们构建了光复活酶功能缺失的青鳉突变品系以及光复活酶功能获得的哺乳动物细胞系。

通过对这些体内外模型的系统研究与比较，我们发现 CPDphr（而非 6-4phr 或 DASHphr）能够在无紫外线照射条件下修复 CPD 及 8-OHdG（氧化损伤的鸟苷形式），这两类 DNA 损伤均可在氧化应激下产生。因此，我们利用这种比较研究策略揭示了盲穴鱼中光照非依赖性光复活酶功能的选择性保守性，使其能够修复在极端地下环境中遇到的 DNA 损伤。

关键词：盲穴鱼，青鳉，斑马鱼，DNA 损伤，光复活

Sleep Deprivation Activates a Conserved Lactate-H3K18la–RORα Axis Driving Neutrophilic Inflammation Across Species

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Abstract: Sleep deprivation critically disrupts physiological homeostasis, impairing development, metabolic balance, and immune regulation, with excessive neutrophil activation being a hallmark consequence. However, the molecular mechanisms underlying sleep deprivation-induced neutrophilic inflammation remain elusive. Here, we show that acute sleep deprivation in mice triggers neutrophil hyperactivation, resulting in aberrant peripheral accumulation and a systemic cytokine storm. Mechanistically, this pathology is driven by metabolic dysregulation—specifically, heightened glycolytic flux that elevates tissue lactate levels and enhances histone H3K18 lactylation. Through H3K18 lactylation-specific CUT&Tag profiling, we identified pronounced lactylation enrichment at the promoter of the Rorα gene, directly activating its transcription. Genetic ablation of Rorα or pharmacological inhibition of glycolysis normalized neutrophil recruitment and mitigated inflammation in sleep-deprived mice. Strikingly, this metabolic-epigenetic axis is evolutionarily conserved, as demonstrated by recapitulating key findings in diurnal zebrafish and pigs. Our study uncovers a lactate-H3K18 lactylation-Rorα signaling cascade that links sleep deprivation to immune dysregulation, offering actionable targets for combating sleep-related inflammatory disorders.

Key Words： Sleep deprivation, Lactylation, Neutrophil, Rorα, Zebrafish

Impact of Circadian Rhythm Disruption on Early Neurodevelopment in Zebrafish: Mechanisms and Functional Consequences

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Circadian rhythm disruption has emerged as a critical public health concern, driven by modern lifestyle factors such as increasing life stressors, shift work, and transmeridian travel. Extensive studies have associated circadian misalignment with adverse neurological effects and neurodevelopmental disorders, yet the underlying mechanisms remain incompletely understood. The zebrafish (Danio rerio), a diurnal vertebrate model organism with robust circadian rhythmicity, high genomic synteny, neurodevelopmental, and functional conservation with humans. In this study, we used zebrafish to elucidate the impact and mechanisms of circadian rhythm disruption on early neurodevelopment through multiple approaches, including neurobehavioral analysis, two-photon in vivo imaging, RNA-sequencing and metabolomics, and molecular biological assays. Our findings demonstrate that circadian disruption does not affect other developmental indices except frequency of spontaneous movement, suggesting that circadian rhythm disruption may affect early neurodevelopment. Behavioral assays under three distinct perturbation paradigms—locomotion activity, light-dark stimulation, and vibration stimulation paradigms—revealed suppressed locomotor activity and diminished responsiveness in larval zebrafish, indicative of neuronal dysfunction. Subsequent two-photon imaging in transgenic zebrafish lines with labeled neurons and microglia revealed that circadian disruption adversely impacts zebrafish neurodevelopment, and triggered neuroinflammatory responses. Multi-omics integration found dysregulated pathways in DNA replication, DNA repair, redox balance, and energy metabolism associated with circadian misalignment. These findings elucidate key mechanisms by which circadian disturbances impair neurodevelopment, providing a foundation for therapeutic strategies in circadian-related neurological disorders.

Key Words： zebrafish (Danio rerio), circadian rhythm disruption, neurodevelopment

Photoperiod Mediates Cognitive Changes in Medaka (Oryzias latipes): Roles of Neuroplasticity and Neurotransmitter Dynamics

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Photoperiodism drives seasonal adaptations in vertebrates, yet its neural and molecular mechanisms in teleosts remain elusive. Using medaka *(Oryzias latipes)* as a model, we investigated photoperiodic effects on cognition and neuroplasticity. Adult fish were exposed to long (LP: 14h-light/10h-dark) or short photoperiod (SP: 10h-light/14h-dark) for 30 days and analyzed through behavioral tests, transcriptomics, histology, and metabolomics. Male medaka under LP showed significantly impaired spatial learning and memory capabilities. However, these cognitive functions were restored to levels comparable to females when exposed to short photoperiod (SP). Notably, photoperiod alterations did not affect female cognitive performance. These behavioral changes were associated with corresponding variations in neuronal density within the optic tectum region. Male-specific responses included upregulation of ribosomal genes (*rpl29/rpl37/rpl34*) and elevated cell proliferation in visual processing regions, while females showed steroidogenesis pathway activation. Neurochemical analyses revealed SP-induced increases in acetylcholine in males and GABA in females, contrasting with LP-driven rises in testosterone and gonadotropins. Crucially, α-GPC supplementation rescued LP-induced cognitive deficits in males, demonstrating cholinergic modulation of photoperiodic adaptation. These findings establish medaka as a powerful model for studying seasonal neuroplasticity and reveal sexually dimorphic mechanisms underlying photoperiodic cognitive regulation in teleosts.

Key Words： Photoperiodism, Seasonal plasticity, Neurobehavior and cognition, Neuroendocrine

Zebrafish Behavioral Fingerprints Identify WAY-296818 as a Key Circadian Clock Modulator

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Circadian misalignment has long been implicated in a variety of human diseases. Hence, the discovery of compounds that can interfere with the circadian clock should aid in treating these arrhythmia-derived diseases. Previous cell line-based studies have identified dozens of small molecules targeting core circadian clock genes. However, it remains unknown whether these small molecules exert similar effects on diurnal vertebrate zebrafish. Here, we select 29 known compounds targeting the circadian clock, including CRY, ROR, REV-ERB, CK1, CK2, and GSK3 inhibitors or activators, and generate behavioral fingerprints, sleep fingerprints, *Tg(per3:luc)* expression fingerprints, and circadian clock gene expression fingerprints in zebrafish larvae. Most compound treatments result in reduced amplitudes, and in particular, CK1 inhibitors lead to period lengthening, while ROR agonists or inhibitors have a minimal effect on zebrafish circadian rhythms. Using these fingerprints, we found that WAY-296818 significantly lengthens the period of the circadian clock in zebrafish in a dose-dependent manner, and that WAY-296818 affects the expression of per by inhibiting the activity of CK1δ. Taken together, these fingerprint approaches not only identify WAY-296818 as a key modulator of the circadian clock but also establish zebrafish as a suitable in vivo model for screening compounds targeting circadian clocks.

Key Words： Circadian Clock Targeting Compounds, Zebrafish, Fingerprint, Behavior, Sleep, WAY-296818

Searching for circadian cell populations – a time-series single-cell RNA-sequencing analysis of zebrafish adult brains

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The circadian clock orchestrates rhythmic functions and activities in the nervous system of the brain. However, the circadian fingerprints in various brain regions and cell types, as well as their functional roles, remain unclear. We have conducted time-series single-cell RNA-sequencing and bulk RNA-sequencing analyses of the zebrafish adult brain to identify brain cell types and characterized their circadian patterns and cellular functions. 11 brain regions and 18 major cell types are revealed to display distinct patterns of circadian gene expression. Compared to approximately 10% circadianly expressed genes identified by the time-series bulk RNA-sequencing analysis, approximately 67% genes are revealed to be circadianly expressed by the time-series scRNA-sequencing analysis. Furthermore, heterogeneous circadian gene expression patterns are observed across brain regions, including the habenula, pineal gland, and hypothalamus. Together, these findings shed light on uncharted circadian roles of a considerable portion of uncharacterized circadian cell populations in the zebrafish brain.

Key Words： Circadian cell populations, time-series scRNA-seq, time-series bulk RNA-seq, brains, zebrafish

Anti-Müllerian hormone signalling sustains circadian homeostasis in zebrafish

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摘要：生物钟是生物体在长期进化过程中，为适应地球昼夜交替的环境变化而形成的一种内在计时机制。它几乎存在于每一个器官和每一类细胞中，精准地掌控着生物体 24 小时的生理和行为昼夜节律，使其能与外界环境的周期性变化同步。尽管构成生物钟的核心分子已逐步被发现，但复杂的生物钟系统如何在机体中维持稳态，仍是尚未解开的谜团。本研究首次揭示了一种内分泌因子 Amh（Anti-Müllerian hormone）在生物钟稳态调控中的关键作用。结果表明，Amh 功能缺失，会抑制分子时钟振荡，扰乱内分泌和行为昼夜节律，并影响多个外周组织的节律。Amh 在垂体中主要作用于生长激素分泌细胞和促性腺激素分泌细胞。单细胞测序进一步揭示了 Amh 对各个垂体细胞类群中生物钟的具体影响。进一步结合体内体外实验，证实了 Bmpr2a 蛋白是 Amh 的二型受体，敲除 bmpr2a 基因会导致斑马鱼的内分泌和行为昼夜节律紊乱，这与 amh 突变体的表型相似。我们发现在野生型垂体中，磷酸化的 Smad1/5/9 与大多数生物钟基因结合，而在 amh 和 bmpr2a 突变体中，这种结合明显减少。并通过体内实验证实了 Amh-Bmpr2a 通过介导 Smad1/5/9 蛋白磷酸化调节生物钟基因表达。在机制上，Amh 与其受体 Bmpr2a/Bmpr1bb 结合，并招募 Smad1/5/9 蛋白；这些蛋白经磷酸化后转移至细胞核，通过结合多个生物钟调控元件（E/E’-boxes、RREs、CREs），维持分子时钟振荡和内分泌节律，精确控制昼夜节律信息的输出，从而在组织和系统水平维持节律的一致性和生物钟稳态。研究结果揭示了一种新的内分泌与时钟相互作用机制，对于深入理解脊椎动物昼夜节律的神经内分泌调节和长期稳态具有重要意义。

关键词：生物钟、稳态、抗缪勒管激素（Amh）、斑马鱼

S12. 疾病模型与转化医学

Disease models and Translational Medicine

异槲皮苷通过靶向 SAPS2 调节心肌细胞中 PPP6C 介导的 NF-κB 抑制作用来改善心肌病

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蛋白磷酸酶 6（PP6）是一种三聚体全酶，主要由调节亚基（SAPS2）和催化亚基（PPP6C）组成，在人体心脏中高度分布。然而，SAPS2 和 PPP6C 的心脏功能仍不明确。本研究通过代谢组学和蛋白质组学分析，鉴定了异槲皮苷（IQ）处理氧化诱导型心肌病（OIC）时抑制作用的靶蛋白。通过 SAPS2 和 PPP6C 敲低（KD）的 H9c2 细胞，以及规律成簇间隔短回文重复序列（CRISPR）/Cas9 敲低 saps2a 和 saps2b 的斑马鱼模型，证实了 SAPS2 在 IQ 调控 OIC 进展中的关键作用。为优化 IQ 水溶性不足的问题，开发了可注射的 IQ@凝胶，以提高 IQ 的生物利用度和 OIC 治疗效果，并在小鼠模型中进行了验证。本研究提出了一条靶向 OIC 中 SAPS2/PPP6C/NF-κB 轴的新进展通路，且靶向氧化应激和炎症的 SAPS2 激活剂 IQ 为 OIC 治疗提供了新途径。

关键词：Oxidant-induced cardiomyopathy, Isoquercitrin, Phosphatase 6 Regulatory Subunit 2

P301S 突变型 tau 驱动的斑马鱼疾病模型的建立和在药物筛选中的应用

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摘要：编码 tau（MAPT）基因的突变是导致阿尔茨海默病和额颞叶痴呆的主要原因。其病理特征主要表现为 tau 蛋白的过度磷酸化，神经原纤维缠结的形成和聚集，以及神经元的死亡。由于受 Tau 在 AD 早期阶段介导疾病发生分子机制研究的局限性,导致目前各种治疗方案都难以达到理想的效果。本研究中,我们成功建立了 Tau-P301S 转基因斑马鱼模型，利用斑马鱼神经元特异性启动子 huc 驱动人源 TAU P301S 突变蛋白的表达，该突变蛋白被 eGFP 绿色荧光蛋白标记。该模型概括了 tau 病早期发展的关键病理特征，包括人 tau 蛋白的磷酸化和构象改变、神经原纤维缠结形成、神经元功能障碍、行为异常和细胞死亡，表现出与 tau 病患者非常相似的病理表型。此外，我们将计算机分子对接与斑马鱼模型相结合，对 tau 激酶糖原合成酶 3β (GSK3β)进行了高通量筛选，从而鉴定出一种新的高效 GSK3β抑制剂 CDK4/6-IN-2。该化合物在 tau 转基因斑马鱼和小鼠中有效降低 tau 磷酸化并改善认知功能。这种转基因斑马鱼模型可能为进一步研究痴呆的神经病理学提供有价值的工具。

关键词：神经退行性疾病, 斑马鱼模型, tau 病理, 药物筛选, CDK4/6-IN-2

Dysfunction of brsk2, related to autism, interferes with retinal structure and visual function

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Early development depends heavily on the proper visual function. Patients diagnosed with autism spectrum disorder (ASD) often display atypical visual perception. Our previous work developed a novel brsk2ab deficient zebrafish model exhibiting distinct ASD-like behaviors. To investigate visual function in brsk2ab$^{-/-}$ zebrafish, we employed a combination of behavioral and molecular techniques. Visual function was assessed using the light/dark test and body color pigmentation detection, which allowed us to quantify light perception and pigmentation changes. The structural integrity of retinal cell layers was analyzed using Hematoxylin-Eosin (HE) staining, while opsin expression was examined via RT-qPCR and immunostaining techniques. Further, transcriptome analysis was performed to explore alterations in the signaling pathways involved in phototransduction, aiming to uncover the molecular mechanisms underlying the visual dysfunction in brsk2ab$^{-/-}$ zebrafish. brsk2ab$^{-/-}$ zebrafish larvae exhibited significantly heightened light perception function compared to wild-type controls, as demonstrated by their enhanced visual motor response. Structural analysis of the retina revealed disruptions in the layered organization, alongside an up-regulation of rhodopsin expression in retinal cells. Additionally, transcriptome analysis indicated that key opsins and genes involved in visual development and phototransduction pathways were markedly up-regulated following brsk2ab deletion. This study provides the first evidence that brsk2 deficiency affects not only retinal structure but also the molecular pathways critical for normal visual function.

Key Words：zebrafish; BRSK2 gene; autism spectrum disorder; vision function

基于斑马鱼模型的藏药二十五味珊瑚丸抗脑血栓药效评价研究

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目的：脑血栓形成是导致缺血性脑卒中的主要病理机制，其早期预防和干预对于降低致残率和病死率具有重要意义。传统藏药方剂二十五味珊瑚丸长期用于治疗脑血管相关疾病，但其抗脑血栓作用缺乏系统实验验证。本研究旨在基于斑马鱼脑血栓模型，评估二十五味珊瑚丸在血栓预防、脑部血流改善及运动功能恢复方面的药效。

方法：采用 2 dpf 的 Albino 品系斑马鱼，通过水溶性酪氨酸激酶抑制剂诱导构建脑血栓模型。实验动物分为正常对照组、模型对照组、阳性对照组（银杏叶片提取物）及二十五味珊瑚丸组（250 mg/L）。通过邻联茴香胺染色观察血栓形成情况，利用血流分析系统评估脑部血流变化，并通过行为分析平台监测斑马鱼总运动距离。数据采用 R 语言 dplyr 包进行数据清洗与分组统计，以 $p < 0.05$ 为差异具有统计学意义的判断标准。

结果：经干预处理后，与模型对照组相比，二十五味珊瑚丸显著降低斑马鱼脑血栓发生率（40%），改善脑部血流状态（32.65%），并有效提升其运动能力(26.36%)。与阳性对照组相比，二十五味珊瑚丸在表现出相近优越的干预效果，提示其具备良好的抗血栓潜力和神经保护作用。

结论：二十五味珊瑚丸在斑马鱼脑血栓模型中具备明确的抗血栓作用。本研究不仅为该方剂的药效机制研究提供了动物实验依据，也验证了斑马鱼作为传统药物复方制剂药效评价模型的可靠性与适用性，并为后续开展分子机制及临床转化研究奠定了基础。

关键词：藏药、二十五味珊瑚丸、脑血栓、神经保护、斑马鱼。

基于斑马鱼模型的冬虫夏草复方胶囊对化疗诱导免疫损伤的保护作用

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目的：探讨冬虫夏草复方胶囊对化疗所致免疫损伤的保护作用。

方法：以斑马鱼为实验动物模型，采用长春瑞滨药物处理建立斑马鱼免疫损伤模型；采用静脉注射荧光微球法建立斑马鱼巨噬细胞吞噬功能评价模型。通过耐受性考察及免疫低下模型确定给药剂量，观察不同浓度冬虫夏草复方胶囊对长春瑞滨造成的免疫损伤斑马鱼体内巨噬细胞、T 细胞和中性粒细胞的影响，探究冬虫夏草复方胶囊的对化疗药物导致的免疫损伤的相关作用。采用实时荧光定量 PCR 方法检测免疫相关细胞因子重组激活基因 Rag1、Rag2、IL-12、肿瘤坏死因子（TNF-α）、γ干扰素（IFN-γ）基因 mRNA 水平的变化。

结果：500μg/mL、250μg/mL、125μg/mL 冬虫夏草复方胶囊提升了斑马鱼巨噬细胞的吞噬能力（$P<0.001$），逆转了长春瑞滨导致的斑马鱼 T 细胞荧光强度的降低（$P<0.05$），同时，显著逆转了长春瑞滨导致的斑马鱼中性粒细胞数量的减少（$P<0.001$）。与造模组比较，冬虫夏草复方胶囊组中 Rag1、Rag2、IL-12、IFN-γ mRNA 表达水平显著升高（$P<0.01$），TNF-α mRNA 表达水平显著降低（$P<0.01$）。

结论：冬虫夏草复方胶囊对化疗药物导致的免疫损伤具有一定的保护作用，其机制可能与促进免疫细胞增殖和增强巨噬细胞吞噬功能有关。

关键词：斑马鱼；冬虫夏草；免疫损伤；实时荧光定量 PCR

Protective Effects of Cordyceps sinensis Compound Capsules on Chemotherapy-Induced ImmuneInjury based on the Zebrafish Model

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Objective: To explore the protective effect of Cordyceps sinensis compound Capsules(CSCC) on chemotherapy-induced immune injury. Methods: Using zebrafish as the experimental animal model, vinorelbine was used to establish a zebrafish immune injury model. The zebrafish macrophage phagocytosis evaluation model was created by intravenous microinjection of fluorescent microspheres. The T-cell deficiency model was created by transgenic zebrafish (Tg(rag2:DsRed)) and the neutrophil deficiency model was established by transgenic zebrafish (Tg(mpx:EGFP)). The drug dosage of Cordyceps sinensis compound Capsules and the optimal modeling dose of vinorelbine were determined by tolerance test. To observe the effect of different concentrations of CSC on the immune injury of macrophages, T cells, and neutrophils by vinorelbine-induced immunocompromised zebrafish.The mRNA levels of Rag1, Rag2, IL-12, TNF-α and IFN-γ genes were detected by qPCR. Results: At the concentration of 500μg/mL, 250μg/mL, 125μg/mL CSCC significantly promoted the phagocytosis of zebrafish macrophages ($P<0.001$), reduced the injury of vinorelbine to zebrafish T-cells ($P<0.05$) and neutrophils ($P<0.001$). Compared with vinorelbine group, the mRNA expression of Rag1, Rag2, IL-12 and IFN-γ gene in CSCC group was significantly higher ($P<0.01$), and TNF-α mRNA expression in CSCC group decreased ($P<0.01$). Conclusion: CSCC has protective effect on immune injury induced by chemotherapy, and its mechanism potentially mediated by promoting immune cell proliferation and enhancing the phagocytic function of macrophages.

Key Words：Zebrafish, Cordyceps sinensis, Immune Injury, qPCR

Mediator 复合物亚基 Med14 缺失与 VACTERL 联合征

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摘要：MED14 是 Mediator 复合体中最大的亚基，在调控 RNA 聚合酶 II 介导的转录过程中起关键作用，但其在发育中的功能尚不明确。通过构建 med14-/-突变体斑马鱼，本研究发现 med14 基因对心脏、胸鳍、脊椎、泄殖腔和前肾等多器官的正常发育具有重要作用。这些器官主要源自中胚层，且均为 VACTERL 综合征的常见受累部位。通过构建的 med14-/-突变体模型，我们进一步揭示 med14-/-突变体的多器官畸形源于器官发生过程中细胞命运决定的异常，而非早期中胚层形成缺陷。重要的是，我们在一位患者及其家系中发现 X 染色体上 MED14 基因的新型错义突变（p.Ile550Val），而携带对应突变的新生小鼠表现出 VACTERL 综合征的特征性表型。深入的研究表明该突变通过破坏 MED14 的结构功能，影响特定亚基（如 MED7 和 MED17）向 Mediator 复合体的募集，进而损害 Mediator 复合体与 RNA 聚合酶 II 的相互作用，最终导致 VACTERL 综合征相关器官发生所需的下游基因表达下调。通过染色质免疫共沉淀测序（ChIP-seq）结合深度 RNA 测序分析，我们鉴定了 MED14 下游可能参与 VACTERL 综合征相关生物学过程的关键基因。本研究不仅揭示了 MED14 在器官发生中的关键作用，还为阐明 VACTERL 综合征与 Mediator 复合体的关联提供了新的解释。

关键词：疾病模型, 基因转录, MED14, Mediator 复合体, VACTERL 综合征

HMGCS2 缓解三氯生诱发的线粒体功能紊乱及肾纤维化

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摘要：肾纤维化以肾脏结缔组织异常增殖和沉积为特征，是慢性肾脏病进展至终末期肾衰竭的关键病理环节，最终导致正常肾单位被瘢痕组织替代。现有研究表明肾纤维化进程受多种环境污染物及遗传因素共同驱动。三氯生（TCS）作为常用抗菌剂，广泛存在于个人护理及日用消费品中。既往研究表面 TCS 暴露可诱发肾脏脂质蓄积并破坏脂肪酸代谢，这些改变可能参与肾纤维化发生。但上述研究尚未阐明 TCS 诱导肾纤维化的下游确切机制，因此本研究拟通过系统研究揭示 TCS 导致肾纤维化的关键作用机制。通过 RNA 深度测序，我们发现三氯生暴露后肾脏 PPARα表达显著降低。进一步研究表明，PPARα激动剂处理可部分逆转三氯生诱导的肾纤维化。脂质蓄积和线粒体结构在三氯生暴露后同样出现紊乱，但可被 PPARα激动剂改善。脂质组学测序证实了三氯生处理后的脂质堆积现象。研究发现三氯生处理组肾脏中酮生成限速酶 Hmgcs2 表达下降，伴随β-羟基丁酸（BHB）水平降低，与 Hmgcs2 表达减少相一致。Hmgcs2 过表达可部分修复线粒体结构异常并改善脂质蓄积，也能减轻三氯生诱导的纤维化。通过 Hmgcs2 siRNA 敲降实验，我们发现纤维化相关蛋白水平随 Hmgcs2 表达下调而升高。本研究不仅证实了 Hmgcs2 在三氯生致肾纤维化中的关键作用，更揭示了三氯生肾毒性的分子机制。该研究为脂质代谢研究提供了新见解，并表明激活酮体生成可能成为对抗肾纤维化的潜在治疗策略。

关键词：疾病模型，基因转录，MED14，Mediator 复合体，VACTERL 综合征。

动态监测脑转移瘤细胞诱导的肾小球样血管形成

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摘要：脑转移瘤是多种恶性肿瘤致死的主要原因之一，大约 10-40%的实体肿瘤患者会发生肿瘤细胞脑转移。为了模拟肿瘤细胞通过血管进行脑转移，并深入研究肿瘤细胞脑转移及脑微血管结构的动态变化过程，我们将肿瘤细胞注射入斑马鱼的循环系统，建立了斑马鱼的脑转移瘤模型。我们发现，脑转移的乳腺癌细胞 MDA-MB-231 显著重构了脑血管，形成了肾小球样血管（Glomeruloid Vessels，GVs），并且脑内微转移瘤的形成总是伴随着该肾小球样血管。为了进一步研究该 GVs 形成的细胞机制，我们利用多种转基因斑马鱼，结合血管造影和长时程在体成像追踪 MDA-MB-231 的脑转移过程，结果显示：1）GVs 是由脑转移瘤细胞介导的周边脑血管聚集形成，而不是通过出芽血管新生方式；2）GVs 形成过程中，脑血管内皮细胞增殖没有发生变化；3）GVs 的形成没有影响脑血管的通透性和血液流动；4）GVs 形成没有影响周细胞在脑血管上的分布。进一步，我们发现抑制 VEGF 信号通路在不影响肿瘤细胞脑转移概率的情况下，显著降低了 GVs 的形成，表明其在 GVs 形成中的关键作用。综上，我们构建了斑马鱼的脑转移瘤模型，并发现脑转移瘤细胞导致了脑血管重构，形成肾小球样血管，促进脑微转移瘤的形成，并初步阐明了其细胞机制，对其形成机制的进一步研究将为脑转移瘤的干预和治疗提供新的理论依据和靶点。

关键词：斑马鱼，脑转移瘤，肾小球样血管，VEGF

应用鸡尾酒疗法和可编程学习记忆自动化训练系统对 Nomo1 相关社交障碍和智力障碍的研究

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摘要：Nomo1 变异与孤独症、智力障碍等多种神经精神疾病相关，研究者前期发现可改善重复刻板行为和过度自发运动，为探索 Nomo1 缺失对智力的影响和社交障碍的改善，进一步开展了研究。.孤独症发病率高，且无治疗社交缺陷核心症状的药物可用，因此亟需从 nomo1 缺陷的机制出发，对其干预进行深入研究。

基于 nomo1 敲除斑马鱼模型，发现全脑散在的神经元功能异常，表现神经炎症反应。这与研究者提出的脑损伤累积放大机制脑损伤累积放大机制 c 相符合，提示多种小分子药物鸡尾酒疗法优于单一小分子。结果证实该疗法不仅能改善过度自发运动，也改善其社交缺陷与重复刻板行为。

为客观高效准确地检测斑马鱼的学习记忆能力，目前斑马鱼模型的学习记忆行为多基于奖励学习，实现较为困难。研究者创新性地应用可编程自动化设计了基于惩罚学习的自动训练斑马鱼学习记忆训练硬件系统，结合对训练视频进行数据分析的软件系统，分析 nomo1 缺失对学习记忆能力的影响。学习检测系统，结果表明经过经过 5 天自动化训练学习，缺陷斑马鱼的导致其学习记忆能力显著低于野生型。

结论：对于 nomo1 纯合缺失突变导致的多种神经精神疾病表型，鸡尾酒疗法比单一小分子干预效果好；可编程学习记忆自动化训练系统的应用结果表明 nomo1 纯合缺失对斑马鱼智力有显著影响基于惩罚学习的自动训练学习检测系统能够反映基因缺陷斑马鱼模型的学习记忆能力。

关键词：社交障碍, 可编程学习记忆自动化训练系统, 脑损伤, 鸡尾酒疗法

Establishment of a Zebrafish Mutant Model of the Autism Risk Gene cc2d1a-2 Using CRISPR/Cas9 Technology

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Autism Spectrum Disorder (ASD), characterized by abnormal language ability, abnormal social skills, narrow interests, and stubborn behavior patterns. The incidence of autism in the world shows a significant growth trend. Among children aged 0-6 years in China, the incidence rate of autism has reached 1‰. *Cc2d1a* (Coiled-coil and C2 domain-containing 1A-2) has recently been identified as a high-risk gene closely associated with autism spectrum disorder (ASD), playing a role in regulating neurodevelopment, synaptic plasticity, and behavioral functions. Previous studies have shown that *cc2d1a* deficient mice develop normally during the uterine stage but die shortly after birth due to swallowing and respiratory defects, suggesting that the gene is critical for early central nervous system function. However, the mechanisms underlying its role in early development remain poorly understood, and ideal model organisms are lacking. In this study, we successfully generated a *cc2d1a-2* mutant zebrafish model using CRISPR/Cas9 technology. Target-specific gRNAs were designed and co-injected with Cas9 mRNA into one-cell-stage embryos of the AB wild-type zebrafish line. Mutants were screened using Sanger sequencing to obtain heterozygous *cc2d1a-2* mutants, which were subsequently in-crossed to establish a homozygous mutant line. Phenotypic analysis revealed that homozygous mutants exhibited distinct developmental abnormalities, such as body curvature. Behavioral analysis showed a significant reduction in swimming speed and overall activity, indicating impaired neural regulatory function.

Key Words： utism Spectrum Disorder (ASD), Cc2d1a-2, CRISPR/Cas9, Behavioral phenotype

Mongolian medicine Eerdun Wurile improves the zebrafish Parkinson's disease model by promoting the regeneration of meningeal lymphatic vessels

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Parkinson's disease (PD) is a common neurodegenerative disease with an age-dependent incidence, which is higher in the middle-aged and elderly population. Currently, the pathogenesis of PD remains largely unknown, and there is a lack of effective treatment measures. Long-term use of dopamine-based medications for the treatment of Parkinson's disease can lead to a decline in efficacy and the occurrence of severe side effects. It is currently necessary to explore effective, long-term and safe treatment methods to improve patients' quality of life. Mongolian medicine Eerdun Wurile (EW) has significant effect in cardiovascular and cerebrovascular diseases, however, its neural repair mechanism is still unclear. In the study, the Mongolian drug Eerdun Wurile was used to treat MPTP-induced zebrafish PD model. Mongolian medicine Eerdun Wurile could significantly alleviate MPTP-induced Parkinson's disease through imaging observation, behavioral testing, and pathological examination. The study found that EW can significantly enhance the motor ability of zebrafish and improve the symptoms of motor dysfunction in zebrafish. In addition, EW can restore the TH expression and the reduction of dopaminergic neurons in the zebrafish model of Parkinson's disease,and the number of meningeal lymphatics increased significantly after treatment. And the therapeutic effect of EW is related to promoting the regeneration of meningeal lymphatic vessels, enhancing lymphatic drainage function, and promoting the clearance of harmful substances in the brain.

Key Words： Parkinson's disease; Eerdun Wurile; MPTP; meningeal lymphatic vessels

Construction of BPAN Model in Zebrafish and Research on Pathological mechanisms

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Neuropathy with brain iron deposition (NBIA) is a neurodegenerative disease characterised by imaging features of brain iron overload. Recent clinical statistics and genetic studies have revealed that β-propeller protein-associated neurodegeneration (BPAN), which is caused by mutations in the WDR45 gene, has developed into the current major subtype. Autophagy, a known cellular function of WDR45, has remained undefined in studies of its specific pathogenic mechanisms. Recent studies have found that WDR45 mutations trigger ferroptosis and phase-separation-mediated impairment of stress granule depolymerisation. In order to further clarify the main molecular mechanisms of BPAN pathogenesis, WDR45 mutants were constructed using zebrafish as a model material, and the complex symptoms of BPAN patients were more comprehensively replicated at the individual level, including behavioural and pathohistological histology. Dynamic in vivo monitoring of the effect of mutations on autophagy by autophagy-tagged transgenic lines was also achieved. The mutant neurodevelopmental abnormalities were observed at different developmental periods using the neural marker lines, and the main neuronal cell subtypes and regions of the lesions were explored. Finally, combined with multi-omics analysis, we screened for more relevant targets of WDR45 pathogenicity and validated them at the individual level. In conclusion, the present study has initially constructed a more suitable animal disease model, which on the one hand can be used as a diagnostic basis for early pathological features and facilitate early intervention; more importantly, it can facilitate the discovery of the pathogenic mechanism and causative factors of neurodegenerative diseases such as BPAN, which can provide clues and bases for clinical treatments.

Key Words： Zebrafish, Neurodegenerative Diseases, WDR45, BPAN, Autophagy

成纤维细胞通过 Cxcl12a-Cxcr4a 信号通路驱动黑色素细胞定向迁移并诱导炎症后色素沉着

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摘要：炎症后色素沉着（post-inflammatory hyperpigmentation, PIH）作为临床高发皮肤疾病，因发病易、消退难的特点导致患者显著容貌焦虑与心理负担。传统理论认为 PIH 源于炎症诱导的黑色素细胞过度活化，但黑色素细胞在 PIH 过程中的响应机制及生物学意义尚未明确。本研究首先采用乙酸腐蚀斑马鱼皮肤的方法，诱导构建了斑马鱼 PIH 疾病模型。随后结合黑色素细胞特异性转基因斑马鱼品系与实时荧光成像技术，揭示色素沉着过程中伴随黑色素细胞向炎症部位的定向迁移。进一步研究发现该迁移过程独立于巨噬细胞/中性粒细胞，而依赖于炎症区活化的成纤维细胞。在分子机制层面，转录组测序揭示活化后的成纤维细胞通过损伤应答特异性分泌 Cxcl12a 趋化因子，经 Cxcl12a-Cxcr4a 信号轴介导黑色素细胞募集。在功能研究方面，我们发现迁移至炎症部位的黑色素细胞具有双重屏障功能：通过覆盖损伤区域减少增殖细胞受到的紫外线诱导 DNA 损伤，同时形成物理屏障阻断病原体入侵。本项研究为 PIH 病理机制提供新的理论框架，并阐明黑色素细胞在皮肤炎症应答与组织稳态维持中的生物学功能。

关键词：斑马鱼,炎症后色素沉着,黑色素细胞,成纤维细胞,Cxcl12-Cxcr4

Loss of the adaptor protein Sh3bgrl initiates ovarian fibrosis in zebrafish

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Ovarian fibrosis is a reproduction obstacle leading to female infertility in vertebrates, but the cause underlying the cellular events is unclear. Here, we found that the small adaptor protein SH3-domain-binding glutamate-rich protein like (Sh3bgrl) plays an important role in female reproduction in zebrafish. Depletion of Sh3bgrl protein caused by two distinct sh3bgrl mutant alleles impairs female spawning in zebrafish, as evidenced by both the reduced ratio of spawning females within the population and the decreased number of eggs laid per female. Comparative transcriptome analysis revealed that sh3bgrl knockout mechanistically causes the upregulation of genes associated with extracellular matrix (ECM) and fiber generation in the zebrafish ovary. Consequently, extra ECM or fibers accumulate and are deposited in the ovary, resulting in eventual spawning inability. Increased collagen deposition, indicative of tissue fibrosis has been associated with declined ovulation and reproductive failure. This fiber deposition in ovary led to the reduction of the fertility of sh3bgrl knockout female zebrafish, indicating that Sh3bgrl is a crucial molecule in maintaining fiber homeostasis in females to impede ovarian fibrosis. Our findings thus provide insights into understanding the underlying mechanism of infertility by ovarian fibrosis and provide a novel and valuable model to study female reproduction abnormality.

Key Words： sh3bgrl; ECM; POI; ovarian fibrosis; zebrafish

颅缝早闭综合征致病机制研究及治疗药物筛选

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摘要：罕见病发病率极低、病因复杂，其中约 80%为先天性疾病，由基因突变遗传导致。由于罕见病种类繁多，临床表现多样，使当前的临床诊断面临重重困难。同样，因为对其发病机制了解不足，当前医学尚缺乏快速有效的诊疗手段。颅缝早闭（Craniosynostosis，CS）指由一条或多条颅缝提前闭合所导致的颅面发育畸形，其发病率居颅面畸形疾病第二位（在新生儿中约占 1/1400-1/2500，仅次于唇腭裂）。基于我国的人口基数，每年新生儿中的病患数量巨大。颅缝的骨性提早闭合可致颅腔狭小,致使病人形成舟状头、斜头等,同时可致颅内压升高、视力障碍,严重者影响智力发育,或危及生命。本团队在多年罕见遗传病患者样本收集过程中，追踪到隐性遗传 CS 综合征患者家系，其中多名病人均表现矢状缝闭合伴随先天性心脏病表型。本团队利用高通量测序技术筛选致病基因，深入研究该突变蛋白结构与功能变化，揭示基因突变导致疾病发生的分子机制，为临床诊断提供理论依据。同时利用斑马鱼及小鼠等模式动物探索潜在的治疗靶点，为临床靶向治疗提供新的思路和方向。

遗传型颅缝早闭综合征是众多颅颌面遗传疾病中的一个缩影，也是颅颌面遗传性疾病诊疗前进过程中的重要组成部分，精准的分子诊断是探索精准医学过程中不可或缺的一步，同时配合生物模型进行致病机制的探究，可为将来靶向治疗提供理论基础，为出生缺陷防治和优生优育提供保障。

关键词：遗传疾病，模式动物，转化医学

Tetraspanin is a conserved receptor for rhabdoviruses across genera and nitazoxanide as a potent broad-spectrum rhabdoviruses inhibitor targeting tetraspanin -glycoprotein G interaction

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Fish rhabdoviruses are among the most widespread fish pathogens, causing fatal diseases in both wild and cultured fish worldwide. The envelope glycoproteins (G) of fish rhabdoviruses are responsible for binding to host cells, but the viral receptor(s) involved in this process have remained unknown. Here, we identified Lateolabrax japonicus tetraspanin, a member of the tetraspanin family, as an entry receptor for viral hemorrhagic septicemia virus (VHSV), the type species within the Rhabdoviridae family. Overexpression of tetraspanin facilitates VHSV entry, whereas knockdown of tetraspanin had the opposite effects. We also demonstrated a direct interaction between tetraspanin and VHSV G (KD approximately 10-10 M), with the G protein domain IV and the tetraspanin EC2 domain being responsible for this interaction. Blocking tetraspanin with antibodies or purified proteins notably reduced VHSV entry into cultured cells. Exogenous expression of tetraspanin independently facilitated the internalization of VHSV into VHSV-negative cells. Additionally, we successfully identified nitazoxanide as a potent inhibitor of VHSV entry by disrupting the VHSV G-tetraspanin interaction. Furthermore, tetraspanin interacted with another fish rhabdovirus, SCRV (Siniperca chuatsi Rhabdovirus), G protein and facilitated SCRV entry into HEK293T cells, indicating that tetraspanin acts as a cross-genus functional receptor for fish Rhabdoviruses. Finally, we found that tetraspanin mediated VHSV entry via clathrin- and caveolae-mediated endocytosis. In summary, our findings identified a novel receptor responsible for facilitating the entry of Rhabdoviruses into host cells via clathrin- and caveolae-mediated endocytosis in fish and revealed tetraspanin as a potential therapeutic target for Rhabdoviruses in fish.

Key Words： Rhabdoviruses; tetraspanin; VHSV; SCRV; receptor; nitazoxanide

癌症组织构筑：肿瘤细胞特性解析

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摘要：肿瘤组织成分由肿瘤细胞、基质细胞、血管及胞外基质等构成。肿瘤细胞是核心驱动者：具有持续增殖、抵抗凋亡/自噬、自我更新与转移等特性，直接决定肿瘤组织的特性及肿瘤治疗效果。对肝癌和结直肠癌病人组织样本及基因表达数据库人急性淋巴细胞白血病、葡萄膜黑色素瘤、骨肉瘤、前列腺癌、胰腺导管腺癌、乳腺癌及非小细胞肺癌原发肿瘤样本；人 ETV6-RUNX1 融合基因阳性急性淋巴细胞白血病、EGFR 突变型肺腺癌、MYCN 转基因小鼠神经母细胞瘤及 MYC 驱动型小鼠前列腺癌具有明确驱动基因的肿瘤样本；并收集人慢性淋巴细胞白血病的单细胞染色质可及性测序数据进行分析，利用斑马鱼胚胎等细胞进行对比分析。结果显示肿瘤细胞与胚胎细胞不同 mRNA 表达量完全依赖基因表达数，基因表达谱与染色质变异无关。肿瘤细胞携带其起源细胞分化特征，三羧酸循环和 ATP 产生能力相对恒定；并具有组织构筑能力；肿瘤细胞均具有增殖倾向，都有可能发生凋亡、自噬、衰老。肿瘤细胞内存在两类预设的导向型基因表达网络，一类是维持细胞存活及能量代谢相关基因表达网络，另一类为分化程序相关网络。无论基因表达活性高低，肿瘤细胞始终保留遵循起源细胞的分化路径，但肿瘤细胞中同时存在不确定性基因表达网络，这类不确定性基因表达网络可通过调控细胞行为干扰既定的分化通路，最终导致细胞停滞于去分化、分化阻滞或转分化状态。

关键词：人肿瘤组织、斑马鱼胚胎、肿瘤细胞特性、细胞分化

GFPT1 as a cross-ancestry validated target for degenerative spinal disease: genetic association in Chinese cohort and functional characterization in zebrafish

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Degenerative spinal disease (DSD), encompassing conditions like spinal stenosis and spondylosis, lacks effective pharmacological treatment. To identify druggable targets and simultaneously evaluate their cross-ancestry applicability, we integrated multi-omics discovery using Summary-data-based Mendelian Randomization (SMR) and colocalization of European blood/CSF eQTL/pQTL data with genetic validation through whole-genome sequencing (WGS) in Chinese cohorts. Initial analyses identified 7 genes/proteins associated with spinal stenosis and 5 with spondylosis, of which GFPT1, GPX1, and SERPINA1 were shared by spinal stenosis and spondylosis. Phenome-wide MR prioritization based on safety profiles selected GFPT1 and GPX1, which were found to have no potential side effects, while exert beneficial effects on both hypertension and essential hypertension. Subsequent WGS uncovered 4 GFPT1 cis-eQTL loci (rs13016371, rs35392088, rs12997521, and rs13019789) associated with the risk of Lumbar spinal stenosis (LSS) in the Chinese cohort. In addition, drug prediction using DGIdb database screened IOX1 as candidate drugs for GFPT1, confirmed by molecular docking showing robust interaction (binding energy: -6.31 kcal/mol), indicating promising druggability. Pharmacological validation in zebrafish demonstrated that IOX1-mediated GFPT1 inhibition significantly ameliorated key degenerative phenotypes. These findings establish GFPT1 as a cross-ancestry validated therapeutic target for DSD, with IOX1 emerging as a promising disease-modifying compound, which deserve further clinical research and experimental validation.

Key Words： Degenerative spine disease, GFPT1, Cross-ancestry validation, Zebrafish model, Therapeutic target, Mendelian randomization

一种类囊性纤维化伴随骨骼发育畸形的新型综合征的分子机制研究

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摘要：囊性纤维化（cystic fibrosis，CF）是一种常见的常染色体隐性遗传病，主要由 CFTR 基因突变导致。本研究发现一罕见隐性遗传病家系，其先证者表现为囊性纤维化、佝偻、脊柱弯曲及手足中节指（趾）骨缩短。经对已知相关囊性纤维化和短指症致病基因的筛查，未发现致病突变。通过家系分析及全外显子组测序，识别出 MKU1 基因 点突变 R→S ，经 Sanger 验证和群体排查明确其致病性。

蛋白热稳定性实验及生信预测显示 点突变 R→S 显著降低 MKU1 蛋白稳定性，提示功能丧失为主要致病机制。敲低斑马鱼模型出现胰肠发育不全、胸鳍缩短及骨发育障碍；同源突变小鼠表现出生长迟缓、轻度肺炎、回肠黏液增多及骨骼异常；体外稳转细胞系中 MKU1 缺失导致 pH 失衡、活性氧增高、炎症因子上调。这表明 MKU1 功能缺失可能会导致类囊性纤维化和骨骼发育障碍。

机制上，Pull-down 结合质谱鉴定出 MKU1 蛋白与 VCP 直接相互作用，VCP 可调控 CFTR 和 IHH，影响器官发育稳态。VCP 抑制剂处理后，斑马鱼、小鼠及细胞系的病理表型缓解，支持 “MKU1–VCP–CFTR/IHH” 调控轴的作用。

综上所述，本研究首次明确了 MKU1 基因 R→S 点突变在“类囊性纤维化伴骨骼发育畸形”综合征中的致病性，系统揭示了其通过破坏“MKU1–VCP–CFTR/IHH”信号轴引发多器官发育异常的机制。

关键词：囊性纤维化、基因 MKU1、斑马鱼模型、骨骼发育

High-throughput screening identifies MEZ as a heart failure therapeutic via biased GPER signaling pathway

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Heart failure (HF) remains a major global health challenge due to its high prevalence and mortality, necessitating the discovery of novel therapeutic agents. Here, we employed a zebrafish-based high-throughput screening system and identified MEZ, an estrogen analogue, from the Connectivity Map (CMap) as a potent cardioprotective compound. Contrary to the conventional nuclear estrogen receptors (ERs), we discovered that the estrogen analogue MEZ mitigates HF disorders via the G protein-coupled estrogen receptor (GPER). Compared with 17β-Estradiol and the GPER agonist G1, MEZ exhibits superior effects in alleviating cardiac pathological malfunctions. Moreover, we found that MEZ well alleviates cardiomyocyte apoptosis and reactive oxygen species accumulation in zebrafish and rat cardiomyocyte H9C2 cells. Mechanically, MEZ mitigates HF by activating GPER signaling, suppressing the expression of HF marker genes, and alleviating calcium transient disorder. Our study elucidates the molecular mechanisms underlying the cardioprotective effect of MEZ, offering valuable insights for the development of novel heart failure treatments.

Key Words： MEZ, heart failure, GPER, cardiomyocyte apoptosis, calcium transient disorder

Assessing the Efficacy and Safety of Chemotherapy-Induced Hematotoxicity and Thrombocytopenia Interventions in Zebrafish

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Hematotoxicity is a major side effect of intravenous chemotherapy drugs. However, current treatments of chemotherapy-induced hematotoxicity (CIH) are limited and insufficient to meet the clinical needs. There is an urgent need to develop a rapid, accurate, and cost-effective model for CIH to assess the efficacy of potential treatments. In this study, we established a zebrafish model of CIH using gemcitabine (GEM). The model mainly exhibited thrombocytopenia and neutropenia, which are consistent with the toxicities observed in patients receiving GEM therapy. Our results suggest thrombopoietin receptor agonists (TPO-RAs) appear more promising than recombinant human thrombopoietin (rhTPO) for chemotherapy-induced thrombocytopenia (CIT). Additionally, considering the widespread use of combination chemotherapy, we assessed the antagonistic and synergistic toxicities of gemcitabine-based combination treatments. We found that the combination of gemcitabine and carboplatin was less likely to cause thrombocytopenia, whereas the combination of gemcitabine and oxaliplatin was more likely to result in this condition. In conclusion, we have developed a GEM induced CIH zebrafish model that closely mimics the hematotoxic responses seen in humans. This model serves as a valuable tool for screening drugs designed to mitigate the effects of CIH, with a particular emphasis on CIT. Furthermore, it provides new insights into the hematotoxicity of combination chemotherapy, which is essential for developing safe and effective treatment regimens.

Key Words： Zebrafish; Chemotherapy-induced hematotoxicity; Gemcitabine; Thrombocytopenia

比较医学视角下的罕见病多组学研究

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摘要：罕见病由于病例稀少、病因复杂，传统诊疗模式面临巨大挑战。近年来，多组学技术（基因组学、转录组学、蛋白质组学、代谢组学等）的快速发展为罕见病研究提供了新的突破口。本讲座从比较医学的视角出发，探讨多组学整合分析在罕见病机制解析、精准诊断及治疗策略开发中的应用价值。通过跨物种比较（如人类与斑马鱼、小鼠等模式动物），结合患者来源类器官，多组学数据可揭示罕见病保守的致病通路及物种特异性差异，为机制研究提供新线索。报告人曾发现四个新的致病基因，以自己姓氏命名了“郭-坎波型脊椎骨骺发育不良”等四个新疾病。完成了世界首例“3 型脊椎肋骨发育不良”的产前诊断。本讲座以报告人自身临床和研究经历为主线，结合基因组、单细胞转录组、空间组学数据在罕见病领域的实际应用成果，阐述比较医学在罕见病研究中的特征，强调跨物种比较思维对当前罕见病研究的重要推动作用。

关键词：罕见病，多组学，比较医学，斑马鱼，类器官

DNAJB6 介导肌质网应激反应在扩张型心肌病中的机制研究

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目的：扩张型心肌病 (Dilated cardiomyopathy，DCM)，简称扩心病，是一种进行性加重的难治性心血管疾病，全球发病率呈逐年上升趋势，是我国心衰患者中排名第三位的病因。扩心病发病机制复杂，30-40% 病例与遗传因素有关。目前，临床治疗以抗心力衰竭的对症治疗为主。现有证据表明蛋白质稳态机制的破坏，与心肌病的进展密切相关。*DNAJB6* 作为一种分子伴侣蛋白编码基因，参与人体蛋白质转运等过程，明确其在扩心病中的功能与作用机制，有利于开展靶向药物的测试。

方法：利用 TALEN、CRISPR 技术，在斑马鱼活体模型中,构建同源基因 *dnajb6* 过表达突变体 (Tg[cmlc2:*dnajb6b*-EGFP]) 、功能缺失突变体 (*dnajb6*-KO)，结合生物化学、遗传学、影像学等实验方法，探究 *DNAJB6* 在心肌病和心力衰竭中的特异性作用，通过灌胃在斑马鱼活体模型中测试 4-苯基丁酸 (4-PBA) 的治疗效果。

结果：DNAJB6 的功能增益突变通过提升肌浆网应激 (SRS) 以及破坏蛋白停滞，导致心肌病和心力衰竭。SRS 抑制剂 4-PBA 能够显著改善斑马鱼扩心病模型的心功能，并显著提升生存率，具有一定治疗效果。

关键词：扩张型心肌病，DNAJB6，斑马鱼，肌质网应激，4-苯甲丁酸

Molecular mechanism of β-glucan in repairing diabetic vasculopathy through the Cd36/Ppar axis

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Vascular complications account for most of the excess mortality in patients with diabetes, search for drugs that can effectively control blood sugar and repair vascular complications becomes an imperative requirement in diabetes therapy. Carbohydrates are an important source of new drug development, but its intervention role in vascular complications of diabetes is still unclear. In this study, β- glucan with high yield and novel structure were obtained from Agaricus bisporus . In our preliminary work we successfully used zebrafish to develop diabetic models through high glucose stress and MTZ/NTR cell ablation system. In these models, β-glucan can effectively reduce the high tissue（blood）glucose concentration in larvae and adult, and can significantly repair the vascular lesions induced by high-glucose stress and MTZ, and can repair vascular development abnormalities caused by high glucose. The receptor blockade experiment confirmed that the scavenger receptor Cd36 mediates this process. Further analysis of intracellular targets revealed that β-glucan ameliorates diabetic vascular lesions through the CD36/Pparγ signaling. Our experimental findings provide a scientific basis for the development of β-glucan as a naturally derived therapeutic agent for diabetic vascular complications.

Key Words：Zebrafish diabetic models, MTZ/NTR system, β-glucan, Cd36 receptor

Cr3 deficiency affects zebrafish hematopoietic function

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Complement receptor 3 (Cr3, also known as Mac-1 or αMβ2 integrin), which consists of the Cd11b (Itgam) and Cd18 (Itgb2) subunits, is a crucial effector receptor of the complement system, playing key roles in innate immunity and hematopoietic regulation. In the complement system, CR3 mediates phagocytic clearance of immune complexes and pathogens by binding to the complement fragment iC3b, as well as mediating inflammatory responses and immune cell migration.

Cr3 may also influence the proliferation and differentiation (myeloid-biased differentiation) of hematopoietic stem/progenitor cells (HSPCs), indicating a non-classical role in hematopoietic regulation. Zebrafish (Danio rerio) serve as an ideal model organism for studying haematopoietic development. The effect of Cr3 on haematopoiesis in zebrafish was observed after knockdown of cr3 through cr3 MO (Morpholino) injection, which resulted in the blockage of vascular development and down-regulated the mRNA expression of the myeloid marker genes, cmyb and runx1. Platelet production was also disrupted, leading to a significant proliferation of neutrophils migrating towards the head. Further construction of the cr3 mutants revealed severe cerebral haemorrhage, cardiac oedema, and scoliosis phenotypes. These data suggests that Cr3 may be involved in the regulation of the differentiation of HSPCs, as well as their generation and maturation. The role of complement receptors in haematopoietic homeostasis and immune-hematopoietic interactions provides new perspectives. Since CR3 is aberrantly expressed in human haematopoietic diseases, the zebrafish cr3 mutation model provides a potential platform for the study of related pathomechanisms and drug screening, which is of great value.

Key Words：Zebrafish, Cr3, Haematopoiesis

西洋参细胞外囊泡样纳米颗粒靶向心脏抑制铁死亡缓解 DOX 诱导的心肌病的作用及机制

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摘要：以阿霉素（Dox）为代表的蒽环类药物的心脏毒性（Doxorubicin-induced cardiomyopathy，DIC）限制了其在癌症化疗中的广泛应用。因此寻找新的有效活性物质干预 DIC 仍然迫在眉睫。西洋参（American gensing，AG）是全球最为著名的传统草药和膳食补充剂。传统医学认为 AG 归心经，其单用或方剂对阿霉素化疗后的“热毒”具有明显的缓解作用，但是其抗 DIC 的关键活性物质尚不清楚。本研究采用超速结合密度梯度离心法结合提取、分离和制备了 AG-EVLP。采用 Dox 诱导的斑马鱼模型用于快速评估 AG-EVLP 的对 DIC 的保护活性。结果显示 AG-EVLP 可显著改善斑马鱼 DIC 模型中的心脏形态、分数缩短和每搏输出量等心脏功能指标。经标记后的 AG-EVLP 可以显著富集在斑马鱼的心脏，显示一定的组织靶向性。在 H9C2 心肌细胞实验中，也能观察到 AG-EVLP 能被心肌细胞内化。AG-EVLP 中的皂苷类成分显示了明显的抗 DIC 活性，提示可能为 AG-EVLP 中的主要活性成分。AG-EVLP 可以抑制 Dox 诱导的线粒体膜电位变化，下调细胞内 Fe^{2+} 积累，并可通过激活 Nrf2/HO-1/GPX4 通路抑制 H9C2 细胞中 Dox 诱导的铁死亡，从而保护心脏功能。本研究首次证明 AG-EVLP 能够靶向心脏干预 DIC，同时其抗 DIC 作用可能与 Nrf2/HO-1/GPX4 途径介导的细胞凋亡密切相关。

关键词：斑马鱼 DIC 模型；西洋参；西洋参囊泡；阿霉素；铁死亡

遗传性牙病选择性表型的临床和基础研究

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摘要：遗传性牙病表现为牙齿数目、外形、结构、萌出和排列等异常，其种类多、占比大，可单独发生，或作为综合征的局部特征表现。本研究通过家系和大量临床病例研究发现，先天缺牙和牙萌出异常存在牙位选择性，即缺失和萌出的牙齿只累及特定位置的牙，而不是所有牙，并且这些选择性先天缺牙和选择性牙萌出失败与特定基因相关，其中选择性先天缺牙相关基因包括 MSX1 和 PAX9 等 10 种以上基因，而选择性牙萌出失败与 PTH1R 等 6 种以上基因密切相关；这些基因的选择性存在差异，其中部分基因对牙位的选择性在动物模型中得到了验证。

关键词：牙；先天缺牙；牙萌出；选择性

斑马鱼碱基编辑器的开发和优化

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摘要：碱基编辑技术能够在动物模型中实现精确的单核苷酸突变（SNV），有助于模拟人类遗传疾病。胞嘧啶碱基编辑器（CBEs）可将 C•G 碱基对转化为 T•A 碱基对，这涵盖了近一半的人类致病 SNV。然而，传统的 CBEs 在斑马鱼中对 GC 和 CC 基序的编辑存在困难，限制了其应用。为解决此问题，我们团队开发了两种适用于斑马鱼的优化 CBE 系统：zTadA-CBEs 和 zevoCDA1。这些工具克服了序列偏好性，显著增强了对 GC 和 CC 基序的编辑能力。利用这些工具，我们成功建立了几个先前极具挑战性的疾病模型，包括赫曼斯基-普德拉克综合征（Hermansky-Pudlak syndrome）和阿克森费尔德-里格尔综合征（Axenfeld-Rieger syndrome），并将斑马鱼 FMS 受体基因突变体中的一个错义突变（T>C）纠正回野生型，恢复了巨噬细胞数量。总而言之，这两套胞嘧啶碱基编辑器工具包显著增强了斑马鱼作为人类遗传疾病模型的能力，为解析意义未明变异的致病意义、探索疾病发病机制以及开发个体化治疗策略提供了更多可能性。

关键词：碱基编辑器，斑马鱼，精准疾病模型

S13. 毒理与健康

Toxicology and Health

纳米氧化钕和氟化钕暴露的神经毒性机制研究

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摘要：本研究旨在探究纳米氧化钕（NPs-Nd_2O_3）和氟化钕（NdF_3）单一及联合暴露对斑马鱼和神经母细胞瘤细胞的神经毒性效应及机制。通过建立斑马鱼急慢性暴露模型，发现 NPs-Nd_2O_3/NdF_3 单/联合暴露显著阻碍胚胎生长发育（表现为孵化异常、体长缩短、死亡率升高），并诱导脑部萎缩（脑区面积缩小 42-100 dpf）和神经元损伤（尼氏体减少、结构松散）。行为学测试显示暴露组运动能力减弱并出现焦虑样行为（自发摆尾增加、游泳速度下降）。分子机制研究表明：急性暴露通过干扰视黄醇代谢（rdh1/raldh2/cyp26a1 下调）和谷氨酸兴奋性毒性（gria3b/grin3bb 上调）诱发神经损伤；慢性暴露激活神经-免疫互作，RNA-Seq 和 PPI 分析揭示 EGR1-c-Fos/JunB 转录调控轴失衡是关键机制。体外实验证实联合暴露对 SK-N-BE(2)C/SK-N-AS 细胞具有协同毒性（抑制细胞活力与增殖），Western blot 验证 NPs-Nd_2O_3/NdF_3可显著下调 EGR1/c-Fos/JunB 蛋白表达。上述研究成果为评估稀土复合污染的环境与健康风险提供了重要理论依据。

关键词：纳米氧化钕，氟化钕，单/联合暴露，视黄醇代谢，神经毒性

长期低浓度全氟丁酸暴露通过细胞间连接失调破坏斑马鱼精巢发育的分子机制

袁明哲

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摘要：全氟丁酸（PFBA）作为一种持久性环境污染物，因其对水生生物潜在的内分泌干扰效应而备受关注。然而，其对精巢发育的影响机制仍不明确。本研究通过将雄性成年斑马鱼长期（9 周）暴露于环境相关浓度的 PFBA（1000ng/L），探究其在性腺关键发育阶段的作用。组织病理学分析表明，PFBA 可引起睾丸组织结构紊乱和精子损伤，表现为精小叶数量减少，精巢结构异常和精子出现大量 DNA 损伤。转录组分析筛选出细胞间连接相关基因（如 *cldn5*、*zo1*、*cx43*）的显著下调，并通过 qPCR 进一步验证。投射电镜和 WB 实验结果证实，PFBA 通过破坏间隙连接和紧密连接完整性，干扰支持细胞-生殖细胞通讯，导致凋亡生殖细胞积累。机制研究表明，PFBA 可能激活 PPARγ/NF-κB 信号通路，诱发氧化应激和炎症反应，加剧细胞间连接功能障碍。本研究发现 PFBA 通过双重作用机制——干扰细胞间连接动态平衡与氧化-炎症级联互作——损害精巢发育，为全氟化合物对生殖健康的生态毒理学风险提供了新见解。

关键词：全氟丁酸；斑马鱼；细胞间连接；精巢发育

DBP 及新型替代物 ATEC 对斑马鱼黏膜免疫系统的毒性效应

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摘要：增塑剂广泛应用于塑料工业，以邻苯二甲酸二丁酯（DBP）为代表的传统增塑剂因易释放至环境中并富集于水体，已被证实对水生生态系统及人类健康构成潜在威胁。近年来，乙酰柠檬酸三乙酯（ATEC）等新型替代物逐渐推广，然而其安全性，特别是对水生动物免疫系统的毒性尚缺乏系统评估。本研究以斑马鱼（Danio rerio）为模式生物，采用 1.5 μM 浓度暴露 7 天，综合应用组织学观察、抗氧化指标检测、转录组测序和肠道微生物 16S rRNA 测序，系统评估 DBP 与 ATEC 对斑马鱼黏膜免疫系统的影响。结果表明，两种化合物均引发斑马鱼肝脏抗氧化能力下降，ATEC 毒性更为显著。组织病理学分析显示，两者均可损伤肠道及鳃等黏膜器官结构，引发炎症反应，肠道对暴露更敏感。转录组数据揭示免疫相关通路被激活，细胞膜功能与屏障完整性受损，表明其对黏膜免疫屏障具有潜在危害。此外，微生物组分析发现 DBP 显著改变放线菌门和厚壁菌门的丰度，ATEC 与变形菌门变化密切相关。多种潜在益生菌（如 Romboutsia、Dialister、Cetobacterium）在暴露组显著变化，与紧密连接蛋白表达呈相关性，提示其可能调控肠道屏障功能。综上，DBP 及 ATEC 均对斑马鱼黏膜免疫系统具有明显毒性，可能通过扰乱菌群结构、激活免疫通路并引发氧化应激，导致免疫功能紊乱。本研究为新型增塑剂的生态毒理学评估及益生干预策略提供重要理论依据。

关键词：邻苯二甲酸二丁酯，乙酰柠檬酸三乙酯，黏膜免疫系统，斑马鱼。

非成像视觉损伤介导下溴代阻燃剂致斑马鱼仔鱼睡眠障碍

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摘要：睡眠障碍是全球普遍的健康问题。视觉输入对睡眠调节至关重要。非成像视觉以表达黑视蛋白的自感光视网膜神经节细胞为核心，介导昼夜节律系统的光感知，并调节情绪、警觉性、睡眠/觉醒和学习等功能。

基于 Tg(elavl3:EGFP)转基因斑马鱼的结果表明，HBCD 暴露显著提升了视觉相关脑区的神经元活性。两栖动物同源的黑视蛋白基因 opn4x 相对表达量受 HBCD 影响显著上调，但哺乳动物同源基因 opn4 并未受显著影响。研究还利用转基因品系 Tg (th-P2A-EGFP)考察了 HBCD 暴露对仔鱼体内多巴胺能神经元的影响，发现 25 μg/L HBCD 暴露下仔鱼视前区、中间下丘脑和后结节三个脑区的多巴胺阳性细胞量均显著增加。在睡眠方面，HBCD 暴露下仔鱼睡眠/觉醒行为紊乱，具体表现为“失眠样”的睡眠障碍和对昼夜转换的敏感性增强。HBCD 暴露下仔鱼的睡眠结构被破坏，睡眠潜伏期较对照组显著延长 10 min。在分子水平上，HBCD 暴露致褪黑素主要合成基因 aanat2 表达显著下降，且钟基因 cry1a 表达水平显著上升。

总结来说，本研究发现环境浓度的 HBCD 暴露同时激活了成像和非成像视觉通路，增强了斑马鱼仔鱼的光敏感性，并进一步影响了广泛的神经行为和生理功能，尤其是干扰了仔鱼的睡眠/觉醒行为。同时，本研究发现 HBCD 对两栖动物同源黑视蛋白基因存在特异性干扰，表明 HBCD 在水生生态系统中具有较高环境风险。

关键词：睡眠障碍、斑马鱼、溴代阻燃剂、非成像视觉、节律紊乱

结构相似的有机磷酸酯阻燃剂 TPHP 与 CDP 引起斑马鱼幼鱼相反的视觉损伤研究

宋怡群、徐挺、尹大强

同济大学

摘要：视觉不仅是许多动物至关重要的感官系统，也是一类对环境污染物高度敏感的毒性靶标。近年来，毒理学信息相对有限的新型有机磷酸酯阻燃剂（emerging organophosphate flame retardants, eOPFRs）正迅速取代传统阻燃剂，引发了对其生态与健康安全性的广泛关注。本研究以斑马鱼为模型，探究了传统型有机磷酸酯阻燃剂磷酸三苯酯（triphenyl phosphate，TPHP）和新型有机磷酸酯阻燃剂甲苯磷酸二苯酯（cresyl diphenyl phosphate，CDP）在环境相关浓度（3 和 30 nM）下的视觉毒性效应。结果显示，经过 5 天的暴露后，两种 OPFRs 在光感知行为和视蛋白基因表达上呈现出相反的毒性趋势：CDP 暴露显著抑制视蛋白基因表达（表达量下降至原始水平的 0.7–0.8 倍）并削弱幼鱼的光反应，而 TPHP 则增强了这些反应（表达量提升至 1.2–2.4 倍）。此外，我们还发现了一个关键转录因子 tbx2a，在两种 OPFRs 暴露下均发生了显著的表达变化，其与两种 OPFRs 结合方式的差异可能是导致相反视觉损伤效应的潜在原因。这些发现为有机磷酸酯阻燃剂的毒理学机制提供了新线索，并重新审视了这些新污染物安全替代的相关问题。

关键词：有机磷酸酯阻燃剂，斑马鱼，视觉毒性，光感受细胞，tbx2a

苯并噻唑类物质致斑马鱼仔鱼视觉毒性效应

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摘要：苯并噻唑（BTHs）是一类由 1,3-噻唑环和苯环组合而成的杂环芳香族化合物，常被用作轮胎硫化促进剂。近期研究发现 BTHs 暴露可诱导斑马鱼仔鱼眼损伤，影响其视觉系统功能，但 BTHs 致仔鱼视觉毒性的作用机制尚未明晰。因此，本研究选定三种代表性 BTHs，包括 2-巯基苯并噻唑（MBT）、2-羟基苯并噻唑（2-OH-BTH）和 2-氨基苯并噻唑（2-ABTH），旨在探讨 BTHs 致视觉毒性的作用机制。将 4 hpf 斑马鱼胚胎分别暴露于 5 和 500 μg/L 浓度的三种 BTHs 中，并设置对照。每日更换一半体积的暴露液，5 d 后进行行为学和分子测试。行为学结果显示，2-OH-BTH 组仔鱼游泳距离呈浓度依赖性下降，而 MBT 组与之相反，呈浓度依赖性升高，2-ABTH 组虽同样呈升高趋势，但没有浓度依赖性。游泳距离的变化表明 BTHs 影响了仔鱼的视觉系统，并且三者之间不同乃至相反的结果表明取代基的不同显著影响了其视觉毒性效应。qPCR 结果显示，暴露于三者均上调了 ahrra 基因，其中 2-OH-BTH 组上调最明显，达 10 倍。AHR 通路是生物体内重要解毒机制之一，被证明与青光眼等眼病有关。作为通路中的一环，ahrra 具有负反馈调节作用，其上调表明该通路参与了 BTHs 对仔鱼的视觉毒性。此外，500 μg/L 2-ABTH 还下调了 rho 基因，表明视杆细胞是其潜在作用对象。本研究为 BTHs 引起的视觉毒性的机制研究提供了新思路。

关键词：苯并噻唑，视觉毒性，AHR 通路，斑马鱼

The developmental toxicity of Bisphenol F exposure on the zebrafish larvae

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As a major substitute for the bisphenol A (BPA), the use of the bisphenol F (BPF) has increased dramatically in recent years. Growing evidence suggest that BPF shares numerous toxicological properties with BPA, raising the concerns about its potential impact on the health of organisms. However, the developmental toxicity of BPF remains poorly understood. In this study, we conducted a 5-day BPF exposure experiment on zebrafish (*Danio rerio*) from blastula stage at concentrations of 2, 20, 200, and 2000 μg/L. Our results demonstrated a significant increase in hatching rates across all treatment groups at 2 days post-fertilization (dpf). The *esr1* was significantly upregulated at 2000 μg/L by 5 dpf, while no significant change was observed in *ar*. The frequency of operculum loss significantly increased at exposure concentrations of 20, 200, and 2000 μg/L, and a notable increase in notochord loss was observed at 2000 μg/L. To explore the underlying mechanisms, transcriptomic analysis was performed to identify differentially expressed genes (DEGs). GO and KEGG pathway enrichment analysis revealed that the toxic effects of BPF were closely associated with osteoclast differentiation, the FoxO signaling pathway, and the MAPK signaling pathway. These pathways influenced critical biological processes, including response to stimuli, animal organ morphogenesis, detoxification, and biomineralization. This study provides evidence that BPF exposure at environmentally relevant concentrations (2 μg/L) is harmful to hatching, concentrations above 20 μg/L exhibit estrogenic-disrupting activity and exert toxicological effects on the development of the head skeleton in zebrafish. These effects are particularly linked to disruptions in osteoclast differentiation.

Key Words： bisphenol F; early hatching; head skeleton; toxicity mechanism; zebrafish

Mongolian medicine Eerdun-Wurile alleviates alcohol-induced nerve injury by upregulating asb12a gene in zebrafish

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The central nervous system (CNS) is one of the primary targets of alcohol-induced damage. Chronic alcohol consumption leads to cognitive deficits, motor impairments, anxiety-like behaviors, and even irreversible neuronal degeneration and death. However, therapeutic strategies for alcohol-related neurotoxicity remain limited, posing a significant public health concern. Using an ethanol-induced nervous injury model in zebrafish (Danio rerio), this study demonstrates that the traditional compound Eerdun Wurile (EW) significantly accelerates spinal motor neuron proliferation and improves zebrafish locomotor recovery. Furthermore, EW substantially alleviated ethanol-induced oxidative stress, as evidenced by reduced Reactive oxygen species (ROS) levels, and attenuated inflammation caused by ethanol, as shown by Enzyme Linked Immunosorbent Assay (Elisa) detection. Transcriptomic analysis revealed that EW promotes recovery from alcohol-induced spinal cord injury through multiple potential pathways, and EW treatment robustly upregulates the expression of the ubiquitin ligase gene asb12a, which is significantly downregulated following ethanol-induced neurotoxicity. Critically, asb12a knockdown by morpholino oligonucleotides abolished the pro-regenerative effects of EW, while asb12a overexpression phenocopied EW's therapeutic benefits by rescuing motor neuron regeneration and functional recovery. These findings suggested that EW promotes spinal cord repair primarily through asb12a upregulation, identifying the EW-asb12a axis as a key regulator of neuronal regeneration and a promising therapeutic target for SCI.

Key Words： Alcohol, Spinal cord injury (SCI); Eerdun Wurile (EW); asb12a

The combined toxic effects of polystyrene microplastics and different forms of arsenic on the zebrafish embryos (Danio rerio)

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Microplastics have been widely studied for their ability to adsorb heavy metals. In the natural environment, arsenic exists in different forms and its toxicity depends mainly on its form and concentration. However, different forms of arsenic combined with microplastics have yet to be explored for their biological hazards. This study was conducted to reveal the adsorption mechanism of different forms of arsenic onto PSMP and to study the effects of PSMP on the tissue accumulation and developmental toxicity of different forms of arsenic in zebrafish larvae. As a result, the absorbing ability of PSMP for As(III) was 35 times higher than that of DMAs, in which hydrogen bonding plays an important role in the adsorption process. In addition, the adsorption kinetics of As(III) and DMAs on PSMP were in good agreement with the pseudo-second-order kinetic model. Furthermore, PSMP reduced the accumulation of As(III) early in zebrafish larvae development, thereby increasing hatching rates compared with the As(III)-treated group, whereas PSMP had no significant effect on DMAs accumulation in zebrafish larvae, but decreased hatching rates compared with the DMAs-treated group. In addition, except for the microplastic exposure group, the other treatment groups could lead to a decrease in the heart rate of zebrafish larvae. Both PSMP+As(III) and PSMP+DMAs exhibited aggravated oxidative stress compared with PSMP-treated group, but PSMP+As(III) caused more severe oxidative stress at later stages of zebrafish larvae development. Moreover, specific metabolic differences(e.g., AMP, IMP, and guanosine) were produced in the PSMP+As(III) exposure group, which would mainly affect purine metabolism and promoted.

Key Words： Polystyrene microplastic, Arsenic, Combined toxicity, Metabolism disorder, Zebrafish larvae

6PPD 暴露导致斑马鱼肝脏发育缺陷的毒性研究

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摘要：N-(1,3-二甲基丁基)-N'-苯基-对苯二胺（6PPD），主要用作轮胎和其他橡胶制品的抗氧化剂，可防止轮胎裂纹和老化，6PPD 已证实在发育、神经、心脏、脑血管方面的毒性。肝脏是重要的消化及免疫器官，然而 6PPD 在肝脏发育过程中的毒性作用尚未可知。将斑马鱼胚胎暴露于高浓度 6PPD，我们在特异性标记肝脏的斑马鱼转基因系 *Tg（lfabp:eGFP）*可以观察到肝脏发育缺陷（图 1A、1B），并且使用原位杂交技术检测了成熟肝细胞标记基因 *gc* 和 *cp*，发现其表达量显著降低（图 2A、2B），表明 6PPD 对于肝脏发育有毒性影响。本研究通过将斑马鱼胚胎暴露于环境污染物 6PPD 中，发现其影响胚胎的正常发育，出现了器官畸形，具体表现为肝脏体积减小，虽具体机制有待阐明，但我们的研究结果为该环境污染物 6PPD 的毒理学特征提供了新的科学认知，尤其揭示了其对肝脏发育的不良影响。

关键词：斑马鱼、6PPD、肝脏、原位杂交

BPA 暴露下斑马鱼心脏毒性和恢复机制的初步研究

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摘要：双酚 A（Bisphenol A，BPA）作为一种常见的环境内分泌干扰物，广泛存在于塑料制品和工业副产物中，其对心血管系统的潜在毒性日益受到关注，但缺乏深层次的心脏毒性机制探讨。本研究以斑马鱼为模式动物，系统评估 BPA 暴露对心脏结构与功能的影响，并观察其在清水环境中的自我恢复能力。通过组织学染色、心率监测、电镜观察以及转录组与代谢组联合分析的手段，我们对暴露前后斑马鱼心脏状态进行了多层次分析。结果显示，BPA 暴露可导致斑马鱼心率下降、心脏组织结构紊乱及肥大现象，且呈剂量依赖性。在清水恢复阶段，部分心肌损伤得到缓解，心率亦有回升，提示 BPA 心脏毒性可能在一定程度上具有可逆性。组学分析进一步揭示，BPA 可能通过干扰能量代谢和细胞结构相关通路介导心脏功能损伤。本研究初步揭示了 BPA 对斑马鱼心脏发育与功能的不良影响，并观察到在一定条件下的恢复趋势，为理解环境污染物的心脏毒性风险及其干预策略提供了理论基础和研究方向。后续研究中将进一步聚焦关键信号通路及分子修复机制，以期为环境毒物所致心脏损伤的干预提供实验依据与理论支持。

关键词：BPA，心脏毒性，心脏恢复，组学联合

基于斑马鱼模型的α和β-硫丹农药造血毒性效应及机制研究

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摘要：大量流行病学研究表明农药暴露与血液疾病发生相关。农药种类繁多，且大部分农药对造血系统的毒理学信息未知。因此，对农药开展造血毒性筛查成为环境污染风险监管的迫切需求。硫丹是具有环境持久性的有机氯农药，市售硫丹中包含α-硫丹和β-硫丹两种异构体。目前，硫丹的两种同分异构体是否具有造血毒性尚不明晰。本研究利用透明血细胞标记斑马鱼模型和高通量识别方法对α-硫丹和β-硫丹两种农药开展造血毒性筛查，发现环境剂量的α-硫丹（0.5 μg/L）具有造血毒性效应，而β-硫丹（0.6-60 μg/L）对造血功能无明显影响。进一步研究发现α-硫丹暴露促使胚胎的淋巴细胞和血红细胞数目减少，中性粒细胞及巨噬细胞数目增加，血小板细胞数目没有变化；暴露胚胎的造血干细胞数目增加。另外，α-硫丹暴露促使淋系前体细胞和红系前体细胞减少，髓系前体细胞增加。这提示α-硫丹暴露导致斑马鱼胚胎造血干细胞异常增加，并且抑制造血干细胞向淋系和红系分化，促进分化偏向髓系发生。本文还研究了α-硫丹造血毒性的细胞学机制。

总之，α-硫丹可能通过抑制细胞凋亡诱导造血干细胞异常增加；α-硫丹抑制造血干细胞向红系和淋系的分化，促进其偏向髓系分化，进而导致成熟中性粒细胞和巨噬细胞生成增加，而血红细胞和淋巴细胞生成受抑制，最终产生造血毒性作用。本研究揭示了α-硫丹暴露具有致血液疾病发生的风险，为具有造血毒性的环境污染物的识别和研究提供了新思路。

关键词：硫丹、异构体、斑马鱼、造血毒性、高通量评价、造血干细胞

多组学联合分析依托咪酯暴露诱导斑马鱼神经毒性及代际效应机制

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摘要：依托咪酯（ETO）作为一种常用于临床麻醉诱导的催眠剂，近年来其滥用情况日益严重，甚至成为一种新型毒品。前期研究表明，ETO 暴露可能对神经行为产生影响，但其潜在的神经毒性及代际效应机制尚未明确。多组学联合分析技术结合了转录组、蛋白组和代谢组等多种组学方法，可以从“因”和“果”两个层面深入研究生物系统的复杂性和动态变化，并相互验证，从而全面揭示生物过程的机制和规律。本报告基于液相色谱-质谱联用技术（LC-MS/MS）揭示 ETO 在斑马鱼不同组织中的积累和分布；通过多组学联合分析，阐明 ETO 暴露对斑马鱼神经毒性及代际效应的分子机制。研究结果显示，ETO 在斑马鱼的脑部、卵巢及胚胎中积聚，并引起斑马鱼亲代与子代的行为异常。ETO 暴露导致 MAPK 信号通路紊乱和肌钙蛋白水平的变化。此外，ETO 暴露还引起脑部新陈代谢失调、神经递质水平改变、活性氧（ROS）过量和大脑神经炎症。进一步研究发现，ETO 暴露导致母代斑马鱼卵巢病变，诱导卵巢氧化应激和性激素紊乱，通过调控 TORC1 信号通路引起母代的生殖毒性，从而导致子代出现行为异常和畸形。该工作从机制上揭示了 ETO 诱导的神经毒性及代际效应，为探究其他新型毒品的神经毒性机制提供了新思路

关键词：斑马鱼、依托咪酯、多组学联合分析、神经毒性、生殖毒性。

基于斑马鱼模型的哈巴苷对放射性造血损伤防护作用研究

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摘要：核技术的广泛应用为人类带来了巨大的经济和社会效益，但其潜在的危险也不容忽视。意外核泄露可对水生生物的健康、生存和繁衍造成严重危害。目前针对水生生物辐射损伤的防治手段仍十分有限。本研究以中药玄参的主要生物活性成分哈巴苷（harpagide，HPG）为研究对象，探索其对受辐射斑马鱼的潜在辐射保护作用及机制。生存率和畸形率统计表明，HPG 对斑马鱼胚胎的安全浓度范围为 0~0.2 mM。0.1 mM HPG 可缓解电离辐射诱导的胚胎发育相关因 *sox-19a*、*p53* 和 *Wnt* 的表达失调；抑制氧化应激标志物 ROS 及丙二醛 MDA、促炎因子 TNF-α及 IL-1β和凋亡水平的升高；并减缓氧化保护因子 SOD 和 CAT 的降低。在转基因斑马鱼模型 *Tg(mpx:EGFP)*中，其绿色荧光强度随电离辐射剂量升高而减弱，而 HPG 可使电离辐射抑制的荧光信号强度得以回升。邻联茴香胺和苏丹黑 B 染色实验显示 HPG 可促进电离辐射诱导的红系和髓系造血细胞恢复。通过 RNA-seq 分析筛选并验证了造血相关基因（*kitb*、*hbae3* 和 *s100s*）的表达水平。应用 *kitb* 的抑制剂处理可逆转 HPG 的防护作用及改变重要造血干细胞标志物 *c-myb* 的表达水平。本研究表明，HPG 具有显著的辐射防护潜力，或可开发为有效的辐射防护剂。同时，血液系统荧光标记的转基因斑马鱼 *Tg(mpx:EGFP)*作为一种敏感的辐射监测模型，为环境辐射监测提供了新的思路。

关键词：电离辐射，斑马鱼，发育毒性，造血损伤，哈巴苷

Long-term Exposure to Areca Alkaloids at Environmental Concentrations induces Psychoactive Effect in Zebrafish through Microbiota-gut-Brain Axis

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Arecoline and arecaidine, the primary alkaloids derived from Areca catechu, are emerging neuroactive environmental pollutants. This study investigates the effects of chronic exposure to environmental concentrations (0.1 ppm) of arecoline and arecaidine on adult zebrafish, with a focus on behavior and the microbiota-gut-brain axis. After 90 days of exposure, zebrafish exhibited significant impairments in locomotor activity, social interaction, and aggression. Histological analysis revealed villus atrophy, reduced goblet cell density, and elevated intestinal inflammation, accompanied by increased expression of CX3CR1 and MLCK1. 16S rRNA sequencing indicated dysbiosis characterized by altered beta diversity and shifts in microbial composition, with arecoline exposure increasing Kosakonia and arecaidine exposure significantly elevating Acinetobacter. In the brain, areca alkaloids induced pathological alterations and apoptosis, as evidenced by disrupted neural structures and elevated expression of p53 and BAX. LC-MS/MS-based metabolomics revealed significant changes in lipid, organic acid, and aromatic compound metabolism, with more pronounced metabolic disruptions observed in the arecaidine group. Correlation analysis indicated that DL-vanillylmandelic acid in the arecoline group was associated with microbiota shifts and behavioral deficits, while argininosuccinic acid and DL-serine were key contributors in the arecaidine group. Together, these findings demonstrate that chronic exposure to environmental levels of areca alkaloids compromises intestinal integrity, alters gut microbiota, and induces neurochemical and behavioral toxicity, highlighting the ecological risks of these compounds and the critical role of the microbiota-gut-brain axis in environmental neurotoxicology.

Key Words： Areca alkaloids, Zebrafish, Gut-brain axis, Neurotoxicity, Gut microbiota.

纳米材料 ZIF-67 暴露下斑马鱼的铁死亡效应研究

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摘要：类沸石咪唑酯骨架材料（ZIFs）是一类重要的金属有机骨架材料。其中，ZIF-67 因其独特的性能，在催化合成、生物传感及食品检测等领域发挥重要的作用。但目前有关 ZIF-67 生物安全性的研究相对较少。因此，本研究通过 ZIF-67 暴露实验，检测斑马鱼胚胎的生理指标、行为学指标及铁死亡相关指标，以揭示 ZIF-67 诱导的生物学效应。结果显示：不同浓度（50、100、200 mg/L）的 ZIF-67 暴露 120 h 时，斑马鱼胚胎的死亡率和畸形率均极显著升高（P＜0.01），体长均小于对照组水平（P＜0.05），200 mg/L 组孵化率显著上升（P＜0.05）；暴露 24 h 时各浓度组的自主运动频率极显著降低（P＜0.01），暴露至 72 h 时机械触碰逃避次数也明显降低（P＜0.01）。暴露至 120 h 时，Fe2+含量随 ZIF-67 暴露浓度的升高呈剂量依赖性上升，还原型谷胱甘肽（GSH）的含量则随暴露浓度的升高而降低；50 mg/L 和 100 mg/L 组丙二醛（MDA）含量显著升高（P＜0.05），100 mg/L 和 200 mg/L 组谷胱甘肽过氧化物酶（GPx）活性显著降低（P＜0.05）。各浓度组的铁死亡关键基因 fth1a 的表达量显著下调（P＜0.05），而 tfr 表达量在 200 mg/L 组显著上调（P＜0.05）。

关键词：纳米材料，斑马鱼，铁死亡，生物学效应

S14. 前沿技术与新方法

Frontier technologies and new methods

Low-input CUT&Tag for efficient epigenomic profiling of zebrafish stage I oocytes

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Histone modification signatures serve as pivotal biomarkers for identifying transcriptional regulatory elements and demarcating genomic domains associated with gene activation and repression. These epigenetic landscapes exhibit substantial heterogeneity across diverse cell types and display dynamic alterations throughout developmental processes and disease pathogenesis. In oocytes, the production of maternal factors critical for early embryogenesis is rigorously governed by epigenetic modifications. However, comprehensive profiling of epigenetic states during oogenesis has been impeded by technical constraints, primarily attributable to the intricate association with tightly adherent granulosa cells that compromise sample purity.To address this challenge, we developed an optimized low-input CUT&Tag (Cleavage Under Targets and Tagmentation) methodology specifically adapted for zebrafish stage I oocytes. This innovative platform facilitates high-resolution genome-wide mapping of histone post-translational modifications and DNA-binding protein occupancy, thereby enabling unprecedented interrogation of chromatin dynamics in oocyte development. Our integrated workflow encompasses: (1) enzymatic dissociation for isolation of somatic cell-free stage I oocytes, (2) streamlined library construction requiring <500 cells, and (3) rigorous quality control metrics.Validation experiments confirmed the technique's efficacy through distinct histone modification profiling and differential gene expression analysis comparing intact versus granulosa-depleted oocytes. Furthermore, we successfully delineated divergent histone modification patterns between wild-type and huluwa mutant oocytes. These methodological breakthroughs resolve longstanding technical barriers in zebrafish oocyte epigenomics, establishing a robust framework for deciphering maternal epigenetic contributions to embryonic programming.

Key Words： zebrafish, oocyte, CUT&Tag, histone modifications, epigenetic

Zebrafish Gene Knock-in and Tissue-specific Gene Knockout Techniques

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The zebrafish (Danio rerio) is a prominent vertebrate model in genetics, developmental biology, and neurobiology. However, significant technical bottlenecks hinder its full potential: the lack of efficient methods for inserting large exogenous DNA sequences compromises gene integrity in knockin (KI) approaches, while the low efficiency of homologous recombination (HR) poses a major challenge for generating conditional gene knockout (CKO) models essential for tissue-specific studies. To address the first limitation, we developed a novel intron-targeted, high-efficiency KI strategy. This method uniquely combines HR principles for donor design with non-HR mechanisms for integration, preserving endogenous coding sequences and cis-regulatory elements. Co-injection of Cas9 protein, synthesized sgRNA, and a donor plasmid into one-cell embryos enabled efficient multicistronic or fused integration of reporters (EGFP, Gal4) into diverse cell type-specific genes (e.g., tyrosine hydroxylase, tryptophan hydroxylase, gfap, flk1, cdh5, pdgfrb), achieving germline transmission rates up to 18% while maintaining targeted gene function. Concurrently, to overcome CKO limitations, we created a non-HR-based zebrafish Conditional Knockout and Knockin Switch (zCKOIS) system. This strategy couples dual-color fluorescent reporters (EGFP, TagRFP) with a Cre-inducible genetic switch. It generates functional KI reporter alleles that, upon tissue-specific Cre recombinase expression, seamlessly switch to non-functional CKO alleles, enabling direct visualization of allele status and knockout events within specific cell populations. Together, these advances – offering high efficiency, preserved gene integrity, visible conditional allele switching, and germline transmission – provide robust and versatile solutions for precise tissue-specific genome engineering in zebrafish research.

Key Words： Genome editig, Knockin, Conditional knockout

Inheritance of epigenetic signature and phenotype acquired via DNA methylation editing in the zebrafish

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Epigenetic modifications are changes in genetic material other than DNA sequence that play critical roles in gene expression and phenotype formation. In our previous studies, we have established a DNA methylation editing method in the zebrafish (*Epigenetics*, 2023, 18(1): 2192326), and proposed the epigenome editing technique as a potential approach for aquaculture breeding (*Reviews in Aquaculture*, 2024, 16(4): 1463-1466). Building on this work, we used intermuscular bones (IBs) as a model system to demonstrate that the acquired epigenetic signatures and resulting phenotypes could be stably inherited by offspring. While the development and application of genome editing technology has produced intermuscular bone-free fish through knocking out key genes responsible for IBs, particularly the *runx2b* gene, this study employed CRISPR/dCas9-mediated epigenome editing to target the *runx2b* promoter region in zebrafish and alter its DNA methylation status. Our results showed that elevated methylation level in the *runx2b* promoter significantly inhibited *runx2b* expression. The *runx2b* mRNA expression in the F0 generation significantly decreased, and the intermuscular bone length in the 11th to 16th muscle segments of adult F0 fish was significantly shorter than that in the control group. After self-crossing the F0 founders to produce F1 and F2 generations, high methylation levels were maintained in the offspring. This heritable hypermethylation was accompanied by persistent inhibition of *runx2b* expression and reduced intermuscular bone development, demonstrating the feasibility of epigenome editing for aquaculture breeding.

Key Words： CRISPR/dCas9, Zebrafish, DNA Methylation; Intermuscular Bone; runx2b

完整动物中整合单神经元多模态信息的新型光遗传学工具的开发和应用

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摘要：在体整合单个神经元的形态、功能及分子信息对于分类神经元细胞类型和解析脑功能相关神经环路机制至关重要。尽管已通过随机稀疏标记技术建立了大量单神经元形态数据集，但在体内精准标记任意选定神经元的完整形态仍面临挑战，尤其是结合其功能与分子特征进行联合表征。在此，我们报道了一种基因编码的光诱导单细胞标记系统（Photo-inducible single-cell labeling system, Pisces），该系统可实现幼年斑马鱼活体中任意神经元全形态的简单、快速、长期标记。Pisces 系统可在同一完整动物个体内顺序追踪多个神经元形态，从而便于全脑投射组（projectome）图谱的构建。更重要的是，结合钙成像、单细胞转录组测序技术和单分子荧光原位杂交技术，Pisces 系统不仅支持单个神经元形态与功能的整合表征，还可实现对目标神经元的转录组靶向分析和 mRNA 分子的原位检测。这一创新策略为构建单神经元多模态图谱提供了新方法，并将加速脑功能相关神经环路机制的解析。

关键词：斑马鱼，神经科学，多模态整合，神经元形态，全脑投射组

AI-Driven Imaging for Blood Lineage Classification

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摘要：组织损伤修复过程中，多种免疫细胞的时空动态行为与微环境互作是决定修复效率的关键因素。传统方法难以实现活体内多细胞类型的同步动态观测与量化分析。为此，我们建立了一套人工智能驱动的活体成像分析平台，通过结合高分辨率活体显微成像与深度神经网络分类算法，突破活体环境下细胞识别瓶颈。我们以转基因斑马鱼为模型，利用活体荧光成像采集中性粒细胞、巨噬细胞等免疫细胞的三维动态影像数据，并设计时空双通路架构，分别提取细胞运动轨迹与形态学特征，实现对免疫细胞的自动分类，并对细胞关键行为参数进行量化，解析不同细胞类型间相互作用的时空分布规律。该系统为揭示多细胞协同修复机制提供了新型研究方法，可用于肿瘤免疫、感染炎症、再生修复等动态过程研究。

关键词：斑马鱼，活体成像，人工智能，细胞分类，细胞互作

建立斑马鱼基因组安全港位点

杨博雅、王家胜、邵明

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摘要：在模式动物中实现外源基因的稳定表达需要将外源基因整合到基因组上，但并非任何区域的基因组都适合外源基因的插入。在小鼠、线虫和人细胞系中，存在所谓的基因组安全港位点。在这些位点中，外源 DNA 片段的插入对动物健康无害，并且能高效表达。斑马鱼的转基因目前主要依赖随机整合，缺乏可以支持高效敲入的安全港位点。为此，本研究构建了用于筛选安全港位点的转基因质粒，该质粒含强终止子、荧光蛋白、loxP 序列、高效外源 sgRNA 等元件，利用 Tol2 转座子随机转座插入斑马鱼基因组。经过静水加压获得纯合二倍体鱼，筛选其中健康可育、荧光表达量高的品系，然后提取基因组进行 SC-PCR 确定插入拷贝数，inverse PCR 确定插入位点。筛选标准为先确定位点安全性，确保该位点不影响内源基因的表达、不受内源增强子的影响，其次选择高荧光表达量位点。目前共筛选 99 条转基因鱼，得到其中 28 个纯合二倍品系，在其中得到了 1 个可用品系。该品系中的插入片段拥有外源高效 sgRNA 靶点，并可支持可视化的 KI，有助于提升建立 KI 品系的效率。该工具品系的建立为实现外源基因在斑马鱼中稳定高效表达奠定了基础。

关键词：斑马鱼，安全港位点，可视化基因敲入

基于编码的 Cas9 RNP 液滴实现高通量母源因子功能筛选

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摘要：母源产物是驱动早期胚胎发育的关键因子。然而对于母源因子的功能分析需要克服纯和突变引发的合子致死。目前最前沿的斑马鱼母源基因敲除策略仅仅针对单个或少数基因，缺少大范围筛选的潜力。为了克服这一问题，我们提供了一种经济的基于液滴的高通量筛选平台。本系统将含有基因特异的 Cas9 RNP 的且含有编码的液滴递送进受精卵中，产生数十个基因的 CRISPants 库。为了绕开合子致死，这一研究母源因子功能的主要障碍，我们从筛选库中识别出这些合子必需基因，并通过降低 sgRNA 剂量实现半致死剂量编辑。使用九个母源功能缺失表型已被充分表征的基因进行验证，结果证实了该策略的稳健性。我们这一高效省时的筛选平台为在基因组范围内对模式动物中母源因子的反向遗传筛选奠定基础。

关键词：母源突变体、液滴、高通量筛选

斑马鱼实验动物福利讨论

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摘要：实验动物在生命科学领域起着重要的基础性支撑作用，其巨大贡献往往与以承受痛苦和死亡为代价。斑马鱼作为重要的模式生物，近年来成为应用最广泛的实验动物之一。如何在保护实验结果科学可靠的前提下保障斑马鱼福利，是本领域科研人员面对的重要问题。国家斑马鱼资源中心对斑马鱼研究中实验动物福利的关键点进行了系统地讨论，关键点涵盖痛苦感知、水环境、饲育、实验操作、运输及安乐死等方面，为提升实验室斑马鱼生存质量，推动实验鱼标准化进程提供理论支撑与实践参考。

关键词：斑马鱼，实验动物，实验鱼，动物福利

斑马鱼微生物与寄生虫等级及监测团体标准的研究和制定

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摘要：斑马鱼是应用最为广泛的实验鱼类。作为一种极具价值且科研需求极大的实验动物资源，标准化质量控制已经成为斑马鱼研究发展的必然趋势。国家斑马鱼资源中心牵头编制了首个《实验动物 斑马鱼微生物与寄生虫等级及监测》团体标准。该标准适用于实验用普通级斑马鱼和无特定病原体级斑马鱼的病原等级及监测。同时，规定了普通级斑马鱼和无特定病原体级斑马鱼的病原等级、监测指标、程序、方法、结果判定和报告等。该标准的制定将为无特定病原级斑马鱼资源的标准化繁育提供参考，提高斑马鱼的质量控制水平，进一步提升实验鱼资源服务和科技创新的能力。

关键词：实验动物，斑马鱼，微生物，寄生虫，无特定病原，团体标准

发光分子探针的体内原位构建及其在炎症检测中的应用

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摘要：π-共轭有机自由基具有独特的光电磁性质，在生物医学领域具有广泛的应用潜力。在前期研究中，我们制备了红至近红外发光的吡咯阳离子自由基，其发光量子效率高达 40%，不仅可以用于胃肠道动态荧光成像，还可选择性杀灭突变 p53 癌细胞。鉴于炎症与许多疾病密切相关，活性氧（ROS）的高表达是炎症的一个重要标志，为了实现炎症的原位检测，我们近期制备了一系列富电子的氮杂环，可以在活性氧作用下，原位氧化生成具有近红外发光性质的氮杂环阳离子自由基，基于线粒体膜电位高的结构特点，选择性富集于线粒体，进而高灵敏检测斑马鱼、小鼠等模型的体内炎症病灶，具有操作简便、成像信噪比高等优势。

关键词：炎症，活性氧，荧光，分子探针

发育与稳态中的生物力学调控：从亚细胞动态到组织结构

尹建民

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摘要：力学互作在生命体结构构建与功能维持中发挥核心作用，然而体内环境的复杂性与动态变化为相关研究带来重大挑战。我们通过整合力学传感、活体成像、操控干预与建模模拟等技术，建立了面向发育与稳态研究的体内力学解析平台，系统探索组织－细胞－亚细胞间的多尺度力学互作机制。在斑马鱼模型中，结合高分辨率活体成像、多种荧光标记、遗传学操控与定量分析，我们深入研究了血管内皮细胞如何感应并修复因内在或外在应激导致的细胞连接破裂。首先，通过构建一系列内源性标记系统，我们发现血管内皮细胞在迁移与形态重塑过程中，受骨架动力学与血流剪切力与压力影响，细胞连接处常形成微小裂隙（Junctional gaps）。内皮细胞通过定向激活局部肌动-肌球蛋白收缩，牵引连接分子快速重定位至裂隙，促进裂隙闭合。机制上，我们鉴定出血管内皮钙黏蛋白（VE-cadherin，Cdh5）可通过 PI3K–Akt 通路抑制正常细胞连接处的收缩力，从而精确引导裂隙处的收缩修复。进一步研究表明，Cdh5 依赖的 PI3K 信号可动态调控细胞连接处的细胞膜脂质组成，通过调节 PIP2/PIP3 比例精确控制局部肌动蛋白活性。这种空间受限的局部收缩既确保连接修复的时效性，又保留了形态重塑所需的结构可塑性。综上，我们揭示了一条脂质介导的信号轴，将细胞连接感应与局部修复机制紧密耦合，为理解内皮细胞如何在持续的组织动态重构中维持血管屏障功能提供了新的分子基础。

关键词：生物力学，血管内皮细胞，细胞连接，细胞骨架，PI3K 信号

一步法产生携带确定基因编辑的半克隆斑马鱼

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摘要：半克隆技术与 CRISPR/Cas9 介导的基因组编辑技术相结合，能够以孤雄单倍体胚胎干细胞为供体高效构建具有复杂基因修饰的小鼠。然而，这种方法在斑马鱼中尚未实现，本研究利用斑马鱼单倍体囊胚细胞为供体进行了半克隆斑马鱼的构建。将单倍体囊胚细胞注射入卵母细胞，我们成功获得了具有生育能力的半克隆斑马鱼。通过优化供体细胞的细胞周期和显微注射操作过程中的温度参数，重构胚胎发育到成年的效率从 0.2%显著提高至 32.8%。将基因编辑技术与半克隆技术相结合，我们成功构建了携带多重基因突变和靶向基因敲入的 F0 代半克隆斑马鱼。为了构建携带确定基因编辑类型的半克隆斑马鱼，我们通过将单倍体细胞注射到核失活卵母细胞，建立了单倍体细胞的克隆扩增方法，并基于预先测序鉴定供体细胞的基因型，成功构建了携带 capn12 突变的半克隆斑马鱼。总之，本研究证实了通过单倍体囊胚细胞胞间内注射生成具有特定遗传修饰的半克隆斑马鱼的可行性，使半克隆技术成为斑马鱼基因改造模型建立的有效新工具。（未发表工作）

关键词：单倍体细胞，核移植，半克隆技术，基因编辑，动物模型

斑马鱼全脑神经观测无麻醉实时捕捉药物动态

张召

广东芯选检验检测有限公司

摘要：在神经科学研究中，构建全脑活动图谱对于解析脑功能及药物机制具有重要意义。斑马鱼作为目前唯一可实现全脑单细胞分辨率成像的脊椎动物模型，已广泛应用于神经研究与药物筛选。然而，传统固定方法（如甲基纤维素、麻醉剂）存在操作繁琐、生理信号失真及无法实时记录动态反应等问题，严重制约了成像效率与数据质量。针对上述问题，我们开发了一种基于流体力学原理的斑马鱼自动化微流控固定芯片，无需凝胶或麻醉也可实现幼鱼的定向固定、连续监测和无干扰检测。该芯片采用独特的通道结构，可精准利用液流力量自动捕获并稳定定位单尾未麻醉斑马鱼幼鱼，避免了物理挤压或化学麻醉带来的干扰与偏差。实验验证：固定成功率高达94.80%，单条处理时间为 23.17±2.09 秒，兼具高通量与高精度，显著提升了实验效率。

将转基因斑马鱼 Tg(elavl3:GCaMP5G)与微流控芯片系统联用，可通过荧光显微镜监测钙动态变化记录神经元锋电位，实现单像素分辨率的全脑神经活动记录。集成实时给药模块可动态捕捉给药前后脑活动动态：全脑活动密度图直观呈现药物诱导的神经激活或抑制区域，单个神经元荧光变化轨迹可揭示药物作用的时空动态。该平台为解析全脑神经元的时空活动特征及药物作用机制提供了有力的技术支撑。该微流控平台不仅革新了斑马鱼神经药理研究，其无干扰、高精度、自动化的特性在心血管、骨骼、免疫等多个研究领域亦展现出广泛应用潜力。

关键词：斑马鱼；微流控芯片；全脑神经元活动；无麻醉活体成像；药物动态响应

S15. 非斑马鱼模式生物

Non-zebrafish model organism

ScRNA-sequencing of cholesterol crystal embolism reveals CCR5 and CD74 as potential therapeutic targets for necroinflammation

Chongxu Shi

Nantong University

Atherosclerosis is a leading cause of global morbidity and mortality. In advanced atherosclerosis, cholesterol crystal (CC) embolism injures various organs, including causing acute kidney injury with ischemic cortical necrosis. However, the cellular and molecular architecture of the CC embolism kidney at the single-cell level remains uncovered. In this study, we identified 17 cell types in the kidneys of the control and CC embolism mice model. CC embolism induced transcriptomic changes in all cell types. However, the differentially expressed genes varied dramatically, with 1659 in the ascending loop of Henle and 1505 in the proximal tubular, while only 7 in the dendritic cell. Cell-cell interaction analyses predict substantial endothelial-to-immune cell ligand-receptor cross-talk and immune-related pathways, revealing a central role of CCL and MIF pathways within CC embolism formation and related outcomes. Further analysis found that the CCL3/CCL4-CCR5 and MIF-CD74 axes promoted the development of necroinflammation during arterial thrombosis formation and related tissue injury. A human kidney biopsy also detected CD74 positive staining inside the obstructed artery with CC cleft left. Importantly, inhibition of CCR5 and/or CD74 potently prevented and relieved CC embolism-induced vascular thrombosis, tissue necroinflammation, and their consequences. Delayed inhibition of CCR5 and CD74 3 hours after CC embolism attenuated CC-induced thrombotic angiopathy, AKI without increasing the risk of prolonged bleeding complications. Our single-cell atlas of the CC embolism reveals CCR5 and CD74 as potential therapeutic targets for its related necroinflammation, also serves as a powerful reference for studies in this field.

Key Words： Atheroembolism, immunothrombosis, endothelial cell, CCR5, CD74

半滑舌鳎性别生长异形的脑单细胞多组学机制

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摘要：性别异形特别是性别生长异形普遍存在于两性动物。近年来证据表明性染色体基因或环境因子等首先会引起脑和垂体等的性别差异，进而导致性别异形。为了研究脑调控半滑舌鳎性别生长异形的分子机制，我们利用 Chromium 单细胞多组学 ATAC +基因表达测序技术，绘制了半滑舌鳎雌、雄及伪雄鱼脑组织的单细胞水平基因表达及染色质可及性图谱，在水产动物中首次实现了对同一细胞的基因表达及染色质开放状态的联合分析。发现半滑舌鳎脑组织包括神经元细胞、星形胶质细胞、少突胶质细胞、免疫细胞和红细胞五种细胞类群，其中放射性胶质细胞被鉴定为神经元及胶质细胞分化的祖细胞。不同性别的表达趋势分析表明雄性脑细胞具有更快的神经传导速度和更强的细胞通讯概率，而雌性脑细胞则分泌更多的神经肽；这表明雄性可能耗费更多能量用于脑神经传导，导致用于个体生长的能量减少，而相反的，雌性则可能通过刺激垂体产生更多生长激素来实现个体快速生长。进一步结合细胞通讯分析，发现不同于哺乳类的 ghrh 基因，半滑舌鳎的 adcyap1b 基因是刺激垂体激素特别是生长激素分泌的关键神经肽，同时，来源于放射性胶质细胞的雌激素也参与这一过程。最后，基因表达和染色质可及性的联合分析揭示上游重要转录因子 SOXs、Neurod1 等可以通过影响特定基因的染色质开放状态调控脑不同细胞类型的分化和发育，其中 SOX5 可调控 adcyap1b 等神经肽的性别差异分泌过程。

关键词：半滑舌鳎，性别生长异形，脑，单细胞多组学 ATAC +基因表达，adcyap1b

双酚类化合物对青鳉早期发育的隔代遗传效应

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摘要： 双酚 A（BPA）是一种典型的内分泌干扰物，可诱导表观遗传改变，对未暴露的世代造成不利的健康影响。双酚 F（BPF）和双酚 S（BPS）是 BPA 的常见替代品，其化学结构与 BPA 的相似性可能使其具有类似的毒性效应，影响水生生物健康。目前关于环境浓度 BPF 和 BPS 对青鳉隔代遗传效应的研究较少，因此，本研究以青鳉（Oryzias latipes）为模式动物，开展 21 d 亚急性暴露实验，探究 2 μg/L 环境浓度的双酚类物质（BPs）包括 BPA、BPF 和 BPS 暴露对青鳉早期发育的隔代遗传效应。亲本青鳉接受 BPs 暴露后，对其 F2-F3 代青鳉胚胎的发育情况进行分析，发现孵化率存在显著下降，孵化时间明显延长，胚胎存活率普遍降低。对 F2 代青鳉胚胎进行转录组分析，发现有 2060 个差异表达基因，富集到蛋白代谢过程等 GO 功能。BPs 暴露的隔代遗传效应造成了 F2-F3 代青鳉仔鱼心脏功能受损和骨骼畸形，出现心率显著异常和脊柱弯曲等现象，心脏发育相关基因（gata4 和 tbx2b）和骨骼发育相关基因（bmp2 和 bmp4）表达水平显著改变。行为分析表明，亲本青鳉的暴露史还影响了 F2-F3 代青鳉仔鱼的运动能力，表现为运动距离减少和速度减慢等。综上，本研究为深入探究 BPs 对青鳉早期发育的隔代遗传效应机制提供了有价值的实验证据，为新污染物特别是 BPF 和 BPS 等 BPA 替代品，对水生生物影响的早期预警提供一定依据。

关键词：双酚类物质，隔代遗传，青鳉，早期发育

KAG2 deficiency causes a developmental disorder with growth retardation and craniofacial malformations

Yi Ding

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KAG2 is a transmembrane protein and potential drug target in cancer. In contrast to the well-studied oncogenic effects of KAG2 hyperactivation, the biological consequences of its deficiency remain poorly defined. Here, we identify recurrent germline loss-of-function KAG2 variants in patients with growth retardation, orofacial clefts, and other manifestations. These variants disrupt KAG2 protein stability, membrane localization, or site-specific phosphorylation. Kag2 loss leads to embryonic lethality in mice, precluding further analysis of its role in late developmental stages. Strikingly, knock-in mice expressing a patient-derived KAG2 variant and mice maternally exposed to an KAG2 small-molecule inhibitor recapitulate patient phenotypes: retarded growth and diverse craniofacial anomalies, including ocular defects, short jaws, and cleft palate. Collectively, our findings define a novel developmental disorder that we designate GRACE syndrome (Growth Retardation and Craniofacial Malformations Caused by KAG2 Deficiency), establish KAG2's essential role in human growth and craniofacial morphogenesis, and reveal potential teratogenic effects of anti-KAG2 agents that are being developed for cancer treatment.

Key Words： Developmental disorder; exome sequencing; genetic variants.

细胞周期偶联的心咽祖细胞转录水平成熟与多谱系潜能建立

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摘要：在心脏早期发育进程中，多能心前体细胞经历精确调控下的谱系特异性状态转变，最终分化为具有特定功能的心脏细胞。这一发育过程的分子本质在于包括特征性基因表达谱在内的细胞生物分子组成的程序性变化，从而导致细胞多能性逐渐受限和谱系特异性特征的获得。本研究利用海洋模式生物海鞘的独特优势，深入探究了心咽祖细胞获得多谱系分化能力的分子机制。研究发现，心咽祖细胞在第二心区前体细胞命运决定前需经历关键的"转录水平成熟"过程，表现为转录组特征和信号通路激活状态的特异性转变，这一成熟过程对后续细胞命运的正确决定至关重要。通过创新性地结合转基因样本条形码技术和单细胞转录组测序，我们首次系统描绘了迁移中的心咽祖细胞在细胞周期各阶段（G1、S 和 G2 期）的全转录组动态变化规律。研究鉴定出 Depdc1b 等关键成熟态标志基因，还通过系统的功能验证阐明了这些基因的作用机制及其调控网络。此外，我们还揭示了由 FoxF1/2 介导的 FGF 对 BMP 信号通路的双向调控在"转录水平成熟"过程中的核心作用，进一步拓展了对心前体细胞命运决定分子机制的深入理解。

关键词：心咽祖细胞、细胞周期、转录水平成熟、多谱系潜能、海鞘。

鲤生长性别二态性的调控机制研究

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摘要：生长性别二态性是同一物种个体雌雄在生长存在显著差异的现象，是自然选择和性别选择在漫长演化过程中共同作用的结果。鲤是我国最重要的淡水养殖鱼类之一，养殖历史悠久，其在生长上具有明显的性别二态性。利用 CRISPR/Cas9 技术，我们在黄河鲤敲除性类固醇激素合成通路关键基因 cyp17a1，成功构建了伪雄鲤（cyp17a1-/- XX），并通过人工授精的方式，将其与野生型雌鲤（cyp17a1+/+ XX）进行杂交，从而获得全雌鲤群体（cyp17a1+/- XX）。通过同塘养殖试验，我们发现 1 龄全雌鲤体重较野生型显著提升 22.58%，肌肉粗蛋白、总蛋白含量显著提高，肌纤维增殖加快；这与雌鲤肌肉中具有较高的氨基酸和 EPA 含量密切相关；同时发现，全雌鲤具有较高的饲料转化率和摄食能力。为进一步研究影响鲤生长性别二态性的潜在机制，我们从 8 周饲料营养调控入手，发现雌鱼增重率、特定生长率和饲料效率显著高于雄鱼；雌鱼肠道对葡萄糖、脂肪和氨基酸的消化吸收能力显著高于雄性，这与雌鱼较丰富的肠绒毛密切相关。同时发现，雌鱼肌肉蛋白合成和肌肉增殖分化相关基因水平显著高于雄鱼。综上所述，肠道吸收功能以及肌肉蛋白沉积差异可能是导致鲤生长性别二态性的重要因素。

关键词：性别二态性、生长、消化吸收、蛋白沉积、黄河鲤

运动、代谢与寿命的关联机制--以枝角类为例

刘香江、徐雪盈、曾芷丹、陈文凯、李珂欣、胡钰韬、孙晓萌

华中农业大学

摘要：寿命与能量代谢的普遍关联性已获广泛证实，然而调控寿命的具体代谢过程仍需深入探索。本研究聚焦于一个独特现象：与中华溞（Daphnia sinensis）等常见高活跃度游泳型枝角类相比，附着型角类——老年低额溞（Simocephalus vetulus）虽然代谢率较低，却表现出更长的寿命。通过代谢组学分析和药物验证实验，我们首次证实：较低的丙酮酸脱氢酶（PDH）活性是老年低额溞运动能力减弱的关键因素，并首次确立 PDH 活性为调控水蚤寿命的决定性因子。使用特异性抑制剂 CPI-613 抑制 PDH 活性后，枝角类的 ATP 供给与运动能力均下降，但其寿命却显著延长。研究进一步发现，无脊椎动物神经递质章鱼胺（octopamine）和温度均能显著影响 PDH 活性，进而调控枝角类寿命；当使用抑制剂或激动剂分别抵消温度或章鱼胺对 PDH 活性的作用时，它们对寿命的影响随即消失。这些结果深入阐明了 PDH 在枝角类寿命调控和运动能力中的核心作用，为理解寿命的代谢调控机制提供了重要新见解。

关键词：丙酮酸脱氢酶、中华溞、老年低额溞、能量代谢、寿命

Genome-wide Identification of ZSWIM family members and Functional Characterization of Zswim6 in Xenopus

Hassan ltiaz ul

THE CHINESE UNIVERSITY OF HONG KONG

Abstract: The Zinc-finger SWIM domain-containing protein family (Zswim) is a novel and functionally uncharacterized group of proteins with unclear biological roles in embryonic development. We conducted a genome-wide analysis of Zswim members across four model organisms: human, mice, zebrafish, and Xenopus. Using BLAST, we identified nine zswim genes in humans and mice, eight in Xenopus, and three in zebrafish. Bioinformatics analyses revealed conserved evolutionary members and motifs in Zswim4, Zswim5, Zswim6, and Zswim8. Transcriptome analysis confirmed tissue-specific expression patterns for each member; for instance, zswim2 was primarily expressed in the testis, while zswim6 was notably expressed in the spinal cord and various brain regions. Special expression analysis in Xenopus demonstrated that zswim1 and zswim3 were expressed only from stages 2 to 10, whereas zswim5 and zswim6 were localized to the brain, eyes, somites, and bronchial arches during later stages. Zswim8 exhibited dynamic expression throughout development, while zswim9 showed low-level expression across all stages. Based on our comprehensive genome-wide and transcriptome-wide analyses, along with examinations of temporal and spatial expression patterns, we focused on the functional characterization of Zswim6. Overexpression of Zswim6 severely impaired gastrulation. The Zswim6 overexpressed embryos continued to develop, but the yolk plug remained exposed even at tailbud stages. In an attempt towards understanding the molecular mechanism by which Zswim6 regulates development, we first analyzed its role in the Hedgehog signaling pathway. Luciferase assays indicate that overexpression of Zswim6 significantly upregulates the Hedgehog signaling pathway in a dose-dependent manner. Further work is needed to elucidate Zswim6 function during development, especially in the Hedgehog signaling pathway.

Key Words： ZSWIM gene family, Xenopus, Gene expression, Phylogenetic analysis, Bioinformatics

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	心衰		高尿酸		抗癌药药效评价		糖尿病视网膜病变
	心肌损伤		脂肪代谢				
	脑出血						
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	渐冻症		淋巴管		伤口愈合		紫外敏感性遗传疾病
	抑郁	肝脏/肾脏疾病	肝损伤		骨骼发育		
	失眠		脂肪肝		骨质疏松		皮肤感染及修复
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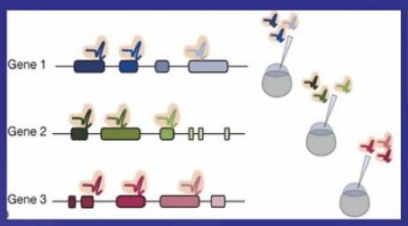
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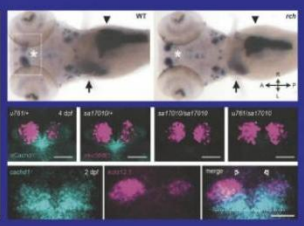
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高通量工作站


行为分析系统


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斑马鱼智能投喂系统

斑马鱼智能投喂系统，专为现代化、规模化斑马鱼养殖设计，提供全自动、高精度的饲喂解决方案，显著提升实验室运行效率与动物福利。

1.智能定量，精准投喂：

系统依据用户预设的单鱼投喂量（如5毫克/条/餐），自动计算每个鱼缸所需饲料总量，确保每条斑马鱼获得恰到好处的营养，彻底杜绝过量投喂导致的**饲料浪费与水质污染**。

2.全自动运行，省时省力：

灵活设定每日喂食时间点与次数，系统将严格按计划自动执行整个喂食流程，无需专人值守，**极大解放科研人员生产力**。

3.便捷管理，掌控随心：

支持本地触控屏直观设置，更可通过**手机APP远程监控与控制**（支持WIFI/4G），随时随地管理喂食任务。

4.智能联动水循环：

与养殖水系统无缝协同。喂食启动时自动暂停循环泵，防止饲料流失；喂食完成后自动重启循环泵并**开启管路自清洁**，杜绝残留，保障水质纯净与系统卫生。

5.高效匀浆输送：

系统智能完成饲料称量、注水、磁力搅拌匀浆，并通过蠕动泵将均匀的饲料悬浮液精准输送至每个指定鱼缸，确保每条鱼都能获得饵料。

6.强大扩展，规模无忧：

单台控制系统即可高效管理**多组鱼架（N组）**，轻松应对大型实验室海量鱼缸（数百至上千缸）的喂食需求，是规模化斑马鱼研究的理想伙伴。

斑马鱼智能投喂系统——以精准自动化，赋能高效科研，守护斑马鱼健康，降低实验室运行成本。

上海海圣生物实验设备有限公司
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IWAKI AQUATIC
SYSTEMS AND SERVICES

LAbREED

IWAKI（易威奇）公司成立于 1956 年，主要致力于研发、生产、销售流体设备，如泵及控制器等。在日本本土拥有 13 家分公司及 140 多家分销商，除日本外全球总计 23 家公司，包括美国，中国，德国等直营子公司。产品覆盖水处理、半导体、化工、医疗设备（人工心脏耐久性测试装置 Laboheart）、新能源等各个领域。

IWAKI AQUATIC 是易威奇股份有限公司的全球品牌，专注于水生生物的维护和管理。

LAbREED 是由日本和美国的专业团队联合开发的科研设备产品系列。

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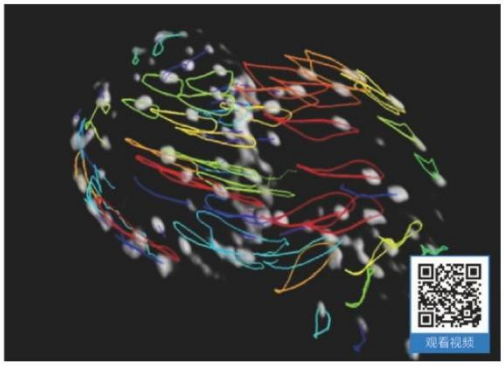
新一代共聚焦即将在
蔡司苏州工厂下线并交付给用户



一次拍摄 一个体积

同时获取空间信息和快速动态过程，无需妥协

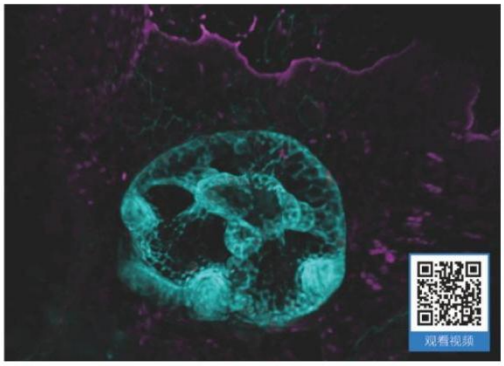
斑马鱼心脏的形态和心壁运动的研究。1.2 秒内记录斑马鱼幼体整个心脏三次跳动。使用 arivas Pro 分割并追踪单细胞的三维轨迹。拍摄体积：723 x 723 x 430 µm³



最小曝光 更多信息

不影响生命过程，随心所欲地长时间观察整个生物体

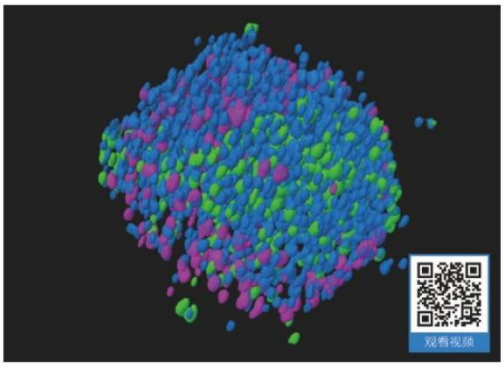
斑马鱼胚胎受精后 2-3 日耳囊发育的长时间观察。在 16 个小时内，每隔 2 分钟对 4 个不同斑马鱼胚胎耳囊发育进行成像。



快速采集 提高通量

通过瞬时体成像加速采集多标大样品和多个位置的检测

HCT-116-GFP（结肠癌）/NIH-3T3-RFP（成纤维细胞）共培养细胞的透明化细胞团，使用 arivis Pro 对数据集进行分割。



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Seeing beyond

瑞德生物

甘肃瑞德生物科技有限公司

公司介绍

甘肃瑞德生物科技有限公司成立于2013年，是一家专注于生命科学领域，集研发、生产、销售于一体的综合性企业。公司业务广泛覆盖实验室仪器、试剂、耗材销售，并向科研和医药工作者提供全面的生物技术服务，包括基因检测，蛋白质工程，细胞培养，分子诊断等，助力客户加速研发进度，提升科研效率。

秉承“精品服务科研”的宗旨

瑞德生物坚持“诚信为首，客户至上，质量为本，合作共赢”的经营理念，致力于为客户创造价值，为员工提供发展平台，为社会贡献积极力量。

经过十年的发展，瑞德生物已拥有一支经验丰富的销售、技术支持和售后服务团队，确保客户在各环节都能获得高质量的服务、最佳的体验！

公司在发展中亦不断整合国内外优质实验试剂、耗材和仪器设备资源，已与多个知名品牌建立区域经销、代理合作，可满足不同客户的需求。如今，瑞德生物已成为西北地区备受认可的一站式实验室解决方案提供商。

试剂耗材

（科研实验室试剂耗材推广、销售、文献提供，让您用的放心、安心）

Raybiotech(瑞博奥)	抗体芯片；流式多因子检测；多组学联合分析等；
森贝伽(生航生物)	胎牛血清和细胞培养全套基础培养基、缓冲液、抗菌剂、消化液、冻存液等系列产品；动物血液制品；细胞系及原代细胞等
BIOFIL(洁特)	细胞培养类耗材；液体处理和保存系列；过滤系列；分子检测类；
OMEGA(欧米伽)	质粒/基因组DNA提取；DNA/RNA纯化；RNA提取；
BIOSS(博奥森)	一抗、一抗标记;二抗，二抗标记;纯化试剂;蛋白质与多肽;正常动物血清及免疫球蛋白;试剂盒、实验室常用试剂;
菲恩生物	ELISA试剂盒;一抗、二抗，信号增强系列;蛋白重组、天然蛋白、标记蛋白；细胞功能检测试剂盒、FC辅助试剂、IHC试剂盒、其它科研试剂;
abm	永生化细胞；细胞系；病毒类产品；

仪器设备

（科研实验室仪器的推广、销售、租赁、试用服务，多种合作模式可选，帮您选到好用、放心的产品）

细胞产品线产品	Halo Counter 全自动智能细胞技术仪、CUY21EDITII超级多模式活体/细胞电转化仪； CytoFLEX S流式细胞仪、CytoFLEX LX 流式细胞仪、CytOFLEXSRT桌面型流式分选仪； CFB16-HB多功能细胞融合仪、BioS pherix高低氧、激光全息细胞成像及分析系统； ZCZY-CSES组合式超大容量二氧化碳震荡培养箱、二氧化碳培养箱等；
WB产品线产品	eBlot@ 电子压片成像仪； M-Blot快速转膜仪 ； M-Blot梯度制胶仪； M-Blot全自动WB孵育工作站； 化学发光仪、高通量微量样品分离制备系统、全自动蛋白印迹仪、超纯外泌体分离制备系统等；
通用产品线产品	超纯水机、生物安全柜、超净工作台，生物显微镜，倒置荧光显微镜、振荡培养箱、PCR仪、核酸提取仪、冷冻研磨仪、酶标仪、生物反应器、压力蒸汽灭菌器、离心机、凝胶成像仪等，例如： L4-5K/L4-5KR自动脱帽离心机、H6-10KR 高速冷冻离心机、GDR421A大容量高速冷冻离心机； Ultra-100F超微量分光光度计、双槽基因扩增仪、智能酶标分析仪、高通量组织研磨仪； DS-11超微量紫外/可见分光光度计、三气培养箱、二级生物安全柜； 实验室器皿清洗机CTLW-220、实验室冷冻干燥机CTFD-10S-U、大型器具清洗机等；

技术服务

（公司有专业实验室，已配备行业先进仪器，可提供多种科研技术服务、实验共享服务）

服务内容	涵盖分子生物学、细胞生物学、免疫学、病理学、稳转株构建、动物模型等；
主要项目	**病理实验** 包埋、石蜡/冰冻切片、免疫荧光、HE染色、免疫组化、特殊染色、电镜、共聚焦、全景扫描成像等； **细胞实验** 细胞培养、细胞增殖、缺氧造模、细胞流式实验、细胞瞬时/稳定转染、细胞划痕、Transwell实验、克隆形成实验等； **分子生物** 基因分型鉴定、WB、Co-IP、Q-PCR/RT-PCR、SNP、生化/Elisa检测等； **动物实验** 动物饲养/成瘤/疾病模型构建、毒理/药代/药效评测； **组学测序** 转录组、蛋白组、代谢组的高通量测序及分析； **课题设计**
服务流程	方案设计—建模实施—结果检测的一站式服务；

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MOLECULAR DEVICES

WPI WORLD PRECISION INSTRUMENTS

百迈客生物科技 BIOMARKER TECHNOLOGIES

百创智造

RWD 瑞德生物

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中国动物学会

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