COL, A Biased Activator of FPR2, Enhances Phagocytic Activity and Attenuates Inflammation in Macrophages

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Phagocytosis by professional phagocytes is an important mechanism for maintaining tissue homeostasis. However, pharmacological approaches to enhance phagocytosis remain scarce. Formyl peptide receptor 2 (FPR2), a promising target for promoting phagocytosis, is highly expressed in various phagocytes as a member of G protein-coupled receptors (GPCRs). Natural compound libraries are effective sources for lead compounds discovery. Here, using a fluorescent system for engulfing apoptotic cells by macrophages (a specialized phagocytosis termed efferocytosis) and high-throughput screening, we reported the identification of columbamine (COL), a natural enhancer of phagocytosis. Our results showed that COL promoted macrophage-mediated efferocytosis and attenuated intestinal inflammation in a DSS-induced inflammatory bowel disease (IBD) mouse model. Mechanistically, we associated the potentiation of efferocytosis by COL with the promotion of LC3-associated phagocytosis (LAP, a non-canonical form of autophagy). Through transcriptome and pharmacology analysis, we found that COL is a biased agonist of FPR2. Knockout of FPR2 or FPR2 antagonist can inhibit COL-induced efferocytosis and LAP and alleviate intestinal inflammation in vitro and in IBD mouse models.

Microglia are macrophages in the central nervous system that highly express FPR2. Our results in an Alzheimer's disease (AD) mouse model showed that COL can promote the phagocytosis of abnormally aggregated Aβ (the main pathological hallmark of AD) by microglia and improve the behavioral performance of AD mice.

Taken together, our study confirms the great potential of macrophage FPR2 as a therapeutic target for IBD and AD. The natural biased agonist COL of FPR2 is a potential therapeutic strategy to promote inflammation relief and degradation of abnormally aggregated proteins.

Key words: FPR2, columbamine, phagocytosis, macrophage, inflammatory bowel disease, Alzheimer's disease

Figure 1

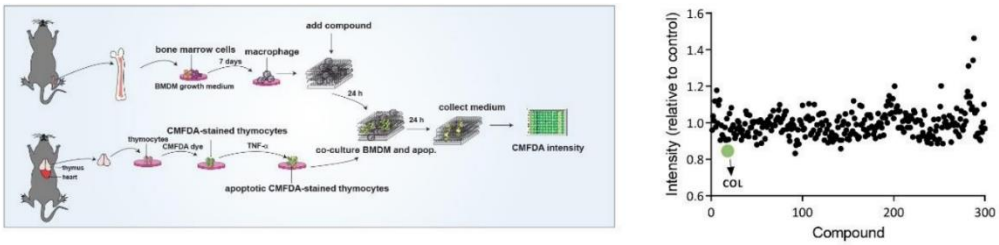

Figure 2

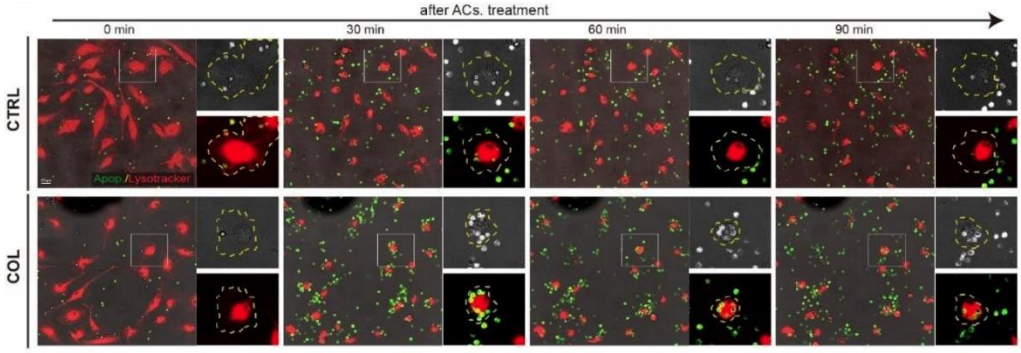

Figure 3

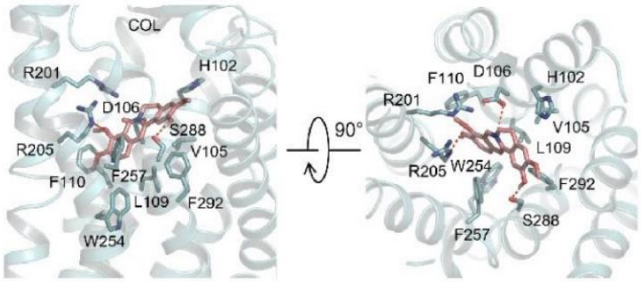

Figure 4

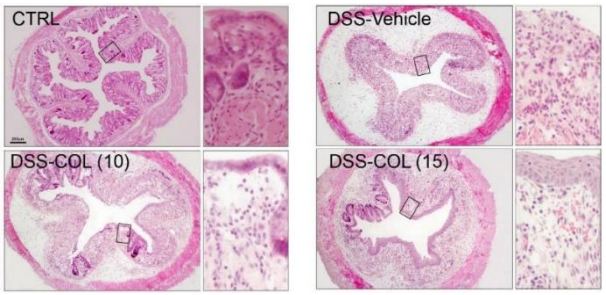

Figure 5

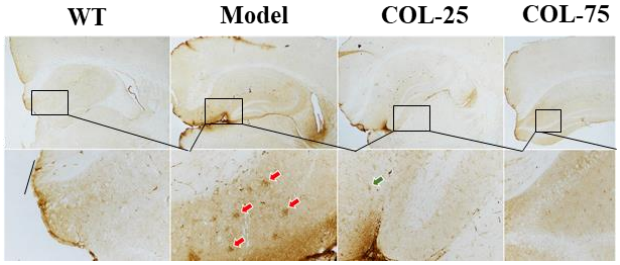

Figure 6

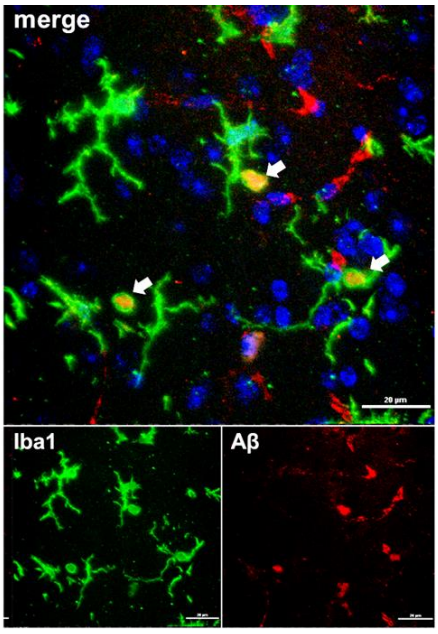

Figure 1: Screening of COL with phagocytic activity from natural compound library.
Figure 2: COL promotes phagocytosis of apoptotic cells by BMDMs.
Figure 3: Detailed interactions between COL and amino acids in the FPR2 binding pocket.
Figure 4: COL alleviates intestinal inflammation in IBD mice model.
Figure 5: COL reduces the accumulation of Aβ in the brain of AD mice model.
Figure 6: COL promotes the phagocytosis of Aβ by microglia in the brain of AD mice model.

Acknowledgment:

This study was supported by Shenzhen Fundamental Research Program (No. SGDX20210823103804030), The Science and Technology Development Fund, Macau SAR (File no. 0025/2022/A1, 0128/2019/A3), National Natural Science Foundation of China (No. 82271455; 32070950), The Guangdong Basic and Applied Basic Research Foundation (No. 2022A1515012416) The 2020 Guangdong Provincial Science and Technology Innovation Strategy Special Fund (Guangdong-Hong Kong-Macau Joint Lab, No: 2020B1212030006), The University of Macau grants (No. MYRG2022-00094-ICMS) awarded to Jia-Hong Lu.