The translational study of target therapy for CNS neurodegeneration

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According to World Health Organization report, stroke is among the top ten causes of death in the world in 2021. Intracerebral hemorrhage (ICH) is due to a rupture of blood vessels in the brain and has a high morbidity and mortality rate for about 50% worldwide. With limited therapeutic treatments, such as antihypertensive agents and supportive cares, it is urge to search potential neuroprotective agents for ICH. In the present study, we established an ICH *in vitro* model using primary cultured cortical neurons which was subjected to hemin, a degraded product of hemoglobin. Hemin concentration-dependently induced cytotoxicity in primary cultured cortical neurons with IC_{50} at 30 μM. Incubation of Zorifertinib, a blood brain barrier-permeable epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), concentration-dependently attenuated hemin-induced neuronal death. Furthermore, Zorifertinib attenuated phosphorylation EGFR and its down-stream signaling, AKT in primary cultured cortical neurons. At the same, Zorifertinib inhibited hemin-induced morphological neurite damages, elevation in FDP-lysine (an acrolein-lysine adduct) and heme oxygenase-1 (a redox-regulated biomarker) as well as elevation in RIP1/3 (a necroptotic biomarker), cleaved caspase 3 (an apoptotic biomarker), and GPX-4 (a ferroptotic biomarker). The *in vivo* study is undergoing. Due to its adverse effect, Zorifertinib may be of translational significance in "ACUTE" ICH therapy. Conclusively, in addition to our previous study which showed that afatinib is neuroprotective against oxygen-glucose deprivation-induced neuroinflammation in astrocytes, the present study demonstrated that Zorifertinib is neuroprotective against hemin-induced neurotoxicity, suggesting that the EGFR-TK pathway be a druggable target for the CNS neurodegenerative diseases.