Neuronal pyroptosis

Neuronal pyroptosis refers to a form of programmed cell death specifically observed in neurons, characterized by inflammatory and lytic cell death mediated by the activation of inflammatory caspases, particularly caspase-1. Pyroptosis is distinct from other forms of cell death, such as apoptosis and necrosis, in that it involves the release of pro-inflammatory cytokines and cell swelling followed by membrane rupture, leading to the release of cellular contents and inflammatory mediators into the extracellular space. This process is often triggered by various pathogenic stimuli, including infections and neuroinflammatory conditions, and can contribute to the progression of neurodegenerative diseases like Alzheimer's, Parkinson's, and multiple sclerosis. Understanding the mechanisms and regulation of neuronal pyroptosis may offer potential therapeutic targets for treating these debilitating conditions.

A study aims to explore the molecular mechanism of Egr1 and Phlda1 in regulating hemin-induced neuronal pyroptosis, and hope to provide novel therapeutic targets for ICH treatment. Mouse hippocampal neuron cells treated with hemin were used to simulate an in-vitro ICH model. Using qRT-PCR and western blot to evaluate mRNA and protein concentrations. MTT assay was utilized to assess cell viability. LDH levels were determined by lactate Dehydrogenase Activity Assay Kit. IL-1β and IL-18 levels were examined by ELISA. The interaction of Egr1 and Phlda1 promoter was evaluated using chromatin immunoprecipitation and dual-luciferase reporter assays. Egr1 and Phlda1 were both upregulated in HT22 cells following hemin treatment. Hemin treatment caused a significant reduction in HT22 cell viability, an increase in Nlrc4 and HT22 cell pyroptosis, and heightened inflammation. However, knocking down Egr1 neutralized hemin-induced effects on HT22 cells. Egr1 bound to the promoter of Phlda1 and transcriptionally activated Phlda1. Silencing Phlda1 significantly reduced Nlrc4-dependent neuronal pyroptosis. Conversely, overexpressing Phlda1 mitigated the inhibitory effects of Egr1 knockdown on Nlrc4 and neuronal pyroptosis during ICH. Egr1 enhanced neuronal pyroptosis mediated by Nlrc4 under ICH via transcriptionally activating Phlda1 [1)].

Pyroptosis is considered a critical factor in the recovery of neurological function following traumatic brain injury. Brain injury activates a molecular signaling cascade associated with pyroptosis and inflammation, including NLRP3, inflammatory cytokines, caspase-1, gasdermin D (GSDMD), and other pyroptosis-related proteins. In this study, we explored the neuroprotective effects of LDC7559, a GSDMD inhibitor. Briefly, LDC7559, siRNA-GSDMD (si-GSDMD), or equal solvent was administrated to mice with a lipopolysaccharide + nigericin (LPS + Nig) model in vitro or with controlled cortical impact brain injury. The findings revealed that inflammation and pyroptosis levels were decreased by LDC7559 or si-GSDMD treatment both in vitro and in vivo. Immunofluorescence staining, brain water content, hematoxylin, and eosin staining, and behavioral investigations suggested that LDC7559 or si-GSDMD inhibited microglial proliferation, ameliorated cerebral edema, reduced brain tissue loss, and promoted brain function recovery. Taken together, LDC7559 may inhibit pyroptosis and reduce inflammation by inhibiting GSDMD, thereby promoting the recovery of neurological function [2)].

Previous studies reported that melanocortin-4 receptor (MC4R) activation exerted neuroprotection in several neurological diseases. The purpose of this study was to investigate the role of MC4R

activation with RO27-3225 in suppressing neuronal pyroptosis after experimental intracerebral hemorrhage (ICH) and the underlying mechanism.

EXPERIMENTAL APPROACH: One hundred and sixty-nine (169) male CD1 mice were used. ICH was induced by right side basal ganglia injection of bacterial collagenase. RO27-3225, a selective agonist of MC4R, was injected intraperitoneally at 1 h after ICH. To elucidate the underlying mechanism, we administered the specific MC4R antagonist HS024 and the specific apoptosis signaling-regulating kinase 1 (ASK1) inhibitor NQDI-1. Neurological tests, Western blot, Fluoro-Jade C (FJC), TUNEL and immunofluorescence staining were conducted.

KEY RESULTS: The expressions of MC4R and NOD-like receptor family, pyrin domain containing 1 (NLRP1) inflammasome were increased after ICH. RO27-3225 treatment decreased neuronal pyroptosis and neurobehavioral deficits at 24 and 72 h after ICH. RO27-3225 reduced the expressions of p-ASK1, p-c-Jun N-terminal kinase (JNK), p-p38 mitogen-activated protein kinase (p38 MAPK), NLRP1 inflammasome, cleaved caspase-1 and IL-1β after ICH. HS024 pretreatment prevented the effects of RO27-3225. Similar to RO27-3225, NQDI-1 alone improved neurological functions and downregulated ASK1/JNK/p38MAPK expressions after ICH.

CONCLUSIONS AND IMPLICATIONS: RO27-3225 suppressed NLRP1-dependent neuronal pyroptosis and improved neurological functions possibly medicated by MC4R activation and inhibition of ASK1/JNK/p38 MAPK signaling pathways after experimental ICH in mice. MC4R may be a promising therapeutic target for ICH management [3].

Pyroptosis in glioma

The function of pyroptosis-related genes (PRGs) in gliomas was investigated based on the Chinese Glioma Genome Atlas (CGGA), the Cancer Genome Atlas (TCGA) and the Repository of Molecular Brain Neoplasia Data (Rembrandt) databases. In this study, using the non-negative matrix factorization (NMF) clustering method, 26 PRGs from the RNA sequencing data were divided into two subgroups. The LASSO and Cox regression was used to develop a 4-gene (BAX, Caspase-4, Caspase-8, PLCG1) risk signature, and all glioma patients in the CGGA, TCGA and Rembrandt cohorts were divided into low- and high-risk groups. The results demonstrate that the gene risk signature related to clinical features can be used as an independent prognostic indicator in glioma patients. Moreover, the high-risk subtype had rich immune infiltration and high expression of immune checkpoint genes in the tumor immune microenvironment (TIME). The analysis of the Submap algorithm shows that patients in the high-risk group could benefit more from anti-PD1 treatment. The risk characteristics associated with pyroptosis proposed in this study play an essential role in TIME and can potentially predict the prognosis and immunotherapeutic response of glioma patients [4].

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