NLRP3

NLRP3, or NOD-like receptor family, pyrin domain-containing 3, is a protein that plays a key role in the innate immune system. It is a member of the NOD-like receptor (NLR) family, specifically associated with the formation of inflammasomes.

Points

Structure and Function:

NLRP3 consists of three main domains: a central nucleotide-binding and oligomerization domain (NACHT), an N-terminal pyrin domain, and C-terminal leucine-rich repeats (LRRs). These structural features enable NLRP3 to interact with other proteins and form the inflammasome complex.

Inflammasome Activation:

NLRP3 is a critical component of the NLRP3 inflammasome. When the NLRP3 sensor recognizes specific signals associated with danger, such as pathogens or cellular damage, it triggers the assembly of the inflammasome. This, in turn, leads to the activation of caspase-1, an enzyme that cleaves pro-inflammatory cytokines like pro-IL-1β and pro-IL-18 into their active forms (IL-1β and IL-18).

Proinflammatory Response:

The activation of the NLRP3 inflammasome and subsequent release of IL-1β and IL-18 contribute to the initiation and regulation of proinflammatory responses. These responses are important for host defense against infections and for coordinating tissue repair and healing. Implications in Diseases:

Dysregulation of the NLRP3 inflammasome has been implicated in various inflammatory and autoimmune diseases. Conditions such as cryopyrin-associated periodic syndromes (CAPS), gout, atherosclerosis, and neurodegenerative diseases have been associated with aberrant NLRP3 inflammasome activation. Therapeutic Target:

Due to its involvement in inflammatory diseases, NLRP3 has been explored as a potential therapeutic target. Researchers are investigating ways to modulate the activity of NLRP3 or the inflammasome as a strategy for treating conditions with dysregulated inflammation. Understanding the molecular mechanisms involving NLRP3 and the inflammasome is crucial for unraveling the complexities of the immune response and developing targeted therapies for diseases associated with inflammation. Ongoing research continues to shed light on the specific roles and regulatory pathways involving NLRP3 in health and disease.

NLRP3 inflammasome plays an important role in the development of neuroinflammation after SAH, but the mechanism of NLRP3 inflammasome activation after SAH is still unclear. TRPV1 is a non-selective calcium channel that is involved in the pathology of neuroinflammation, but its role in SAH has not been revealed. Our study showed that TRPV1 was significantly upregulated after SAH and was predominantly expressed in microglia/macrophages. Antagonism of TRPV1 was effective in

ameliorating neurological impairment, brain edema, and neuronal damage, and reducing the inflammatory response (evidenced by reducing the number of CD16/32 positive microglia/macrophages, inhibiting the expression of CD16, CD32, CD86, IL-1b, TNF-a and blocking NLRP3 inflammasome activation). However, this effect can be abolished by NLRP3 inflammasome antagonist MCC950. In vitro experiments confirmed that TRPV1 activated NLRP3 inflammasome by increasing intracellular calcium levels. In conclusion, TRPV1 mediates EBI after SAH via calcium/NLRP3, and TRPV1 is a potential therapeutic target after SAH [1].

NLR family pyrin domain containing 3, is a protein that in humans is encoded by the NLRP3 gene located on the long arm of chromosome 1. NLRP3 is expressed predominantly in macrophages and as a component of the inflammasome, detects products of damaged cells such as extracellular ATP and crystalline uric acid.

It plays a critical role in Alzheimer's disease pathogenesis. Microglial autophagic degradation not only decreases the deposits of extracellular Aβ fibrils but also inhibits the activation of NRLP3 inflammasome. Here, we aimed to identify the potent autophagy enhancers from Penthorum chinense Pursh (PCP) that alleviate the pathology of AD via inhibiting the NLRP3 inflammasome.

Methods: At first, autophagic activity-guided isolation was performed to identify the autophagy enhancers in PCP. Secondly, the autophagy effect was monitored by detecting LC3 protein expression using Western blotting and the average number of GFP-LC3 puncta per microglial cell using confocal microscopy. Then, the activation of NLRP3 inflammasome was measured by detecting the protein expression and transfected fluorescence intensity of NLRP3, ASC, and caspase-1, as well as the secretion of proinflammatory cytokines. Finally, the behavioral performance was evaluated by measuring the paralysis in C. elegans, and the cognitive function was tested by Morris water maze (MWM) in APP/PS1 mice.

Four ellagitannin flavonoids, including pinocembrin-7-O-[4″,6″-hexahydroxydiphenoyl]-glucoside (PHG), pinocembrin-7-O-[3″-O-galloyl-4″,6″-hexahydroxydiphenoyl]-glucoside (PGHG), thonningianin A (TA), and thonningianin B (TB), were identified to be autophagy enhancers in PCP. Among these, TA exhibited the strongest autophagy induction effect, and the mechanistic study demonstrated that TA activated autophagy via the AMPK/ULK1 and Raf/MEK/ERK signaling pathways. In addition, TA effectively promoted the autophagic degradation of NLRP3 inflammasome in Aβ(1-42)-induced microglial cells and ameliorated neuronal damage via autophagy induction. In vivo, TA activated autophagy and improved behavioral symptoms in C. elegans. Furthermore, TA might penetrate the blood-brain barrier and could improve cognitive function and ameliorate the Aβ pathology and the NLRP3 inflammasome-mediated neuroinflammation via the AMPK/ULK1 and Raf/MEK/ERK signaling pathways in APP/PS1 mice.

They identified TA as a potent microglial autophagy enhancer in PCP that promotes the autophagic degradation of the NLRP3 inflammasome to alleviate the pathology of AD via the AMPK/ULK1 and Raf/MEK/ERK signaling pathways, which provides novel insights for TA in the treatment of AD [2].

The nucleotide binding oligomerization domain-like receptor (NOD)-like receptor family pyrin domain containing 3 (NLRP3) inflammasome-mediated inflammatory response has emerged as a prominent contributor to the pathophysiological processes of traumatic brain injury (TBI).

NOX2-induced ROS production is a double-edged sword that exacerbates brain injury in the acute phase but promotes functional recovery. This effect appears to be achieved by inhibiting NLRP3 inflammasome activation and promoting angiogenesis via autophagy activation [3].

Rashad et al., from Sendai, Japan showed the intense activation of immune cells, particularly the microglia, along with the increase in macrophage activity and NLRP3 inflammasome activation that is indicated by NLRP3, Interleukin 1 beta (IL-1β), and Interleukin 18 gene and caspase 1 upregulation and cleavage as well as pyroptosis.

Leukocytes were observed in the brain parenchyma, indicating a role in cerebral venous thrombosis (CVT)-induced inflammation. In addition, astrocytes were activated, and they induced glial scar leading to parenchymal contraction during the subacute stage and tissue loss. MMP9 was responsible primarily for the BBB breakdown after CVT and it is mainly produced by pericytes. MMP9 activation was observed before inflammatory changes, indicating that BBB breakdown is the initial driver of the pathology of CVT. These results show an inflammation driven pathophysiology of CVT that follows MMP9-mediated BBB breakdown, and identified several targets that can be targeted by pharmaceutical agents to improve the neuroinflammation that follows CVT, such as MMP9, NLRP3, and IL-1β. Some of these pharmaceutical agents are already in clinical practice or under clinical trials indicating a good potential for translating this work into patient care [4].

A potent, selective, small-molecule NLRP3 inflammasome inhibitor, MCC950, was described. Here, we investigated the effect of MCC950 on inflammatory brain injury and long-term neurological outcomes in a mouse model of TBI. Male C57/BL6 mice were subjected to TBI using the controlled cortical impact injury (CCI) system. Western blotting, flow cytometry, and immunofluorescence assays were utilized to analyze post-traumatic NLRP3 inflammasome expression and determine its cellular source. We found that NLRP3 inflammasome expression was significantly increased in the peri-contusional cortex and that microglia were the primary source of this expression. The effects of MCC950 on mice with TBI were then determined using post-assessments including analyses of neurological deficits, brain water content, traumatic lesion volume, neuroinflammation, blood-brain barrier (BBB) integrity, and cell death. MCC950 treatment resulted in a better neurological outcome after TBI by alleviating brain edema, reducing lesion volume, and improving long-term motor and cognitive functions. The therapeutic window for MCC950 against TBI was as long as 6 h. Furthermore, the neuroprotective effect of MCC950 was associated with reduced microglial activation, leukocyte recruitment, and pro-inflammatory cytokine production. In addition, MCC950 preserved BBB integrity, alleviated TBI-induced loss of tight junction proteins, and attenuated cell death. Notably, the efficacy of MCC950 was abolished in microglia-depleted mice. These results indicate that microglia-derived NLRP3 inflammasome may be primarily involved in the inflammatory response to TBI, and specific NLRP3 inflammasome inhibition using MCC950 may be a promising therapeutic approach for patients with TBI [5].

The NLR family pyrin domain containing 3 (NLRP3) inflammasome is necessary for initiating inflammation and is involved in various central nervous system disorders.

The aim of a study was to investigate the neuroprotective effect of resveratrol and elucidate the underlying mechanisms of resveratrol associated regulation of the NLRP3 inflammasome in TBI. The results demonstrated that the activation of NLRP3, caspase-1 and sirtuin 1 (SIRT1), enhanced the production of inflammatory cytokines and reactive oxygen species (ROS) following TBI. Administration of resveratrol alleviated the degree of TBI, as evidenced by the reduced neuron-specific enolase (NSE) and brain water content (WBC). Resveratrol pretreatment also inhibited the activation of NLRP3 and caspase-1, and reduced the production of inflammatory cytokines and ROS. In addition, resveratrol further promoted SIRT1 activation. Furthermore, the suppressing effect of resveratrol on the NLRP3 inflammasome and ROS was blocked by the SIRT1 inhibitor, sirtinol. The results revealed that the activation of the NLRP3 inflammasome and the subsequent inflammatory responses in the cerebral cortex were involved in the process of TBI. Resveratrol may attenuate the inflammatory response and relieve TBI by reducing ROS production and inhibiting NLRP3 activation. The effect of resveratrol on NLRP3 inflammasome and ROS may also be SIRT1 dependent [6)].

Zhou et al., review described mechanisms that are involved in the activation and regulation of NLRP3 inflammasome. In addition, they summarize the recent researches on the role of NLRP3 inflammasome in central nervous system (CNS) diseases, including traumatic brain injury, ischemic stroke and hemorrhagic stroke, brain tumor, neurodegenerative diseases, and other CNS diseases. In conclusion, the NLRP3 inflammasome may be a promising therapeutic target for these CNS diseases [7)].

SAH was induced by the filament perforation model of SAH in male Sprague Dawley rats. Minocycline or vehicle was given via an intraperitoneal injection 1 h after SAH induction. Minocycline treatment markedly attenuated brain edema secondary to blood-brain barrier (BBB) dysfunction by inhibiting NLRP3 inflammasome activation, which controls the maturation and release of pro-inflammatory cytokines, especially interleukin-1β (IL-1β). Minocycline treatment also markedly reduced the number of terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL)-positive cells. To further identify the potential mechanisms, we demonstrated that minocycline increased Bcl2 expression and reduced the protein expression of P53, Bax, and cleaved caspase-3. In addition, minocycline reduced the cortical levels of reactive oxygen species (ROS), which are closely related to both NLRP3 inflammasome and P53 expression. Minocycline protects against NLRP3 inflammasome-induced inflammation and P53-associated apoptosis in early brain injury following SAH. Minocycline's anti-inflammatory and anti-apoptotic effect may involve the reduction of ROS. Minocycline treatment may exhibit important clinical potentials in the management of SAH [8)].

NLRP3 inflammasome is a novel therapeutic target for inflammatory bowel disease (IBD). The aim of this study was to investigate the anti-inflammatory effect of a bioactive flavonoid-oroxylin A on the treatment of dextran sulfate sodium (DSS)-induced murine colitis via targeting NLRP3 inflammasome. In this study, we found that oroxylin A attenuated experimental colitis in mice, including loss of body weights, shortening of the colon lengths and infiltration of inflammatory cells. The production of IL-1β, IL-6 and TNF-α in colon was also markedly reduced by oroxylin A. Moreover, oroxylin A significantly decreased the expression of NLRP3 in intestinal mucosal tissue. In addition, NLRP3-/- mice were observably protected from DSS-induced acute colitis, and oroxylin A treatment had no effects on attenuating inflammation in NLRP3-/- mice. Further study found that the activation of NLRP3

inflammasome was dose-dependently inhibited by oroxylin A in both THP-Ms and BMDMs, followed by decrease in the cleavage of caspase-1 and secretion of IL-1β. This inhibitory effect of oroxylin A was due to restraint of the NLRP3 protein expression and the inflammasome formation in macrophages. Furthermore, the reduction of NLRP3 protein expression by oroxylin A was dependent on the inhibition of NF-κB p65 expression and nuclear translocation. Besides, oroxylin A directly suppressed the ASC speck formation and the inflammasome assembly which in turn restrained the activation of NLRP3 inflammasome. Our findings demonstrated that oroxylin A inhibited NLRP3 inflammasome activation and could potentially be used for the treatment of IBD [9].

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