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).

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.

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.

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 3).

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 4).

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 5).

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.


