The NLRP3 inflammasome: a potential therapeutic target for traumatic brain injury

Introduction

Traumatic brain injury (TBI) is one of the leading causes of mortality and disability across the globe, associated with life-threatening public health problems in people of all ages (Ghajar, 2000; Levin and Diaz-Arrastia, 2015). An estimated 2 million people suffer from TBI each year in the US, and, of those, 50,000 die and 80,000 sustain permanent disabilities (Lin et al., 2017). Additionally, there are over 60,000 children hospitalized because of TBI per year in the USA alone (Moreau et al., 2013). Many of those suffer from mild to moderate neurological deficits, which impair their lives irrespective of age or gender (Finnie, 2013). Based on the severity of injury, TBI can be mild, moderate or severe. The current management of TBI focuses on detection and treatment of associated secondary injury, since the damage due to the primary injury is considered to be irreversible (Seule et al., 2015). Primary injury results from the mechanical damage to neuronal tissue that occurs at the time of TBI, including contusion and hemorrhage as a result of shearing, tearing or stretching. Secondary injury then occurs over minutes to days and even months after the initial insult and is characterized by neurochemical, metabolic and behavioral alterations (Kumar and Loane, 2012). The consequences of brain injury can induce behavioral, emotional and cognitive deficiencies, and thus unfavorably affect the quality of life. Rapid and effective treatment is necessary to prevent undesirable complications and promote better recovery. Standard therapy is supportive in nature and focuses on the prevention of secondary complications. New research is ongoing in an effort to elucidate therapeutic strategies for attenuating the devastating consequences of TBI.

The pathomechanisms of TBI stem from mechanical damage that trigger multifactorial secondary cellular responses including disturbances in ionic homeostasis, glutamate excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid degradation, diffused axonal injury, initiation of inflammatory and immune responses, and cellular apoptosis (Nizamutdinov and Shapiro, 2017). The initial insult triggers the invasion and migration of immune cells such as macrophages and neutrophils to the injured area, thereby inducing inflammation and edema. These neurochemical events induce the generation of pro-inflammatory mediators such as cytokines, chemokines and prostaglandins, ultimately resulting in blood-brain barrier (BBB) leakage and the development cerebral edema (Kumar

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and Loane, 2012). More than thirty prospective clinical trials for treating TBI have not shown significant promise, as these trials focused on single mechanisms of secondary injury while the mechanisms involved in TBI are clearly multifactorial in nature (Maas et al., 2010).

Although, the exact mechanisms triggering secondary brain injury remain ambiguous, it is suggested that inflammatory responses contribute to the pathophysiology. Post-traumatic neuroinflammation is a central response to the secondary injury that leads to continuous neurodegeneration and neurological impairment. It is characterized by microglial activation, leukocyte recruitment and secretion of inflammatory mediators (Morganti-Kossmann et al., 2007). Gene expression profile analyses in animal models of TBI demonstrated that genes related to inflammation and transcriptional regulators are strongly elevated in the acute phase of injury (Kobori et al., 2002; Natale et al., 2003). Rapid elevation of pro-inflammatory cytokines such as interleukin (IL)-1β, are observed within hours of TBI in both rodents and humans (Li et al., 2011; Lin et al., 2017). The secreted IL-1β can activate other pro-inflammatory cytokines, including tumor necrosis factor-a (TNF-a) which will further exacerbate the secondary tissue damage (Lu et al., 2005). IL-1β maturation (cleavage of proform) and its release to the systemic circulation is predominantly regulated by the NLRP3 inflammasome, via a newly described mechanism that governs inflammatory responses during secondary tissue injury (Henao-Mejia et al., 2012; Karmakar et al., 2015). Mainly localized in immune cells, the nucleotide oligomerization-like receptor protein 3 (NLRP3) inflammasome is composed of NLRP3, oligomers apoptosis-associated speck-like (ASC) adapter protein and pro-caspase-1, serving as a platform for cleavage of caspase-1 and subsequent IL-1β maturation. According to recent findings, TBI appears to coincide with NLRP3 and ASC oligomerization, inducing the activation of caspase-1 and subsequent IL-1β and IL-18 maturation (Figure 1) (Liu et al., 2013; Fan et al., 2017). This finding may be highly significant since NLRP3 has been suggested as a cerebrospinal fluid (CSF) biomarker in TBI patients with poor prognosis (Wallisch et al., 2017). Despite all these evolving research, little has been evaluated with regards to the potential benefit of NLRP3 inhibitors in TBI. Notably, recent studies from our groups and others indicated that pharmacological inhibition of NLRP3 improves neurological outcomes in animal models of TBI. The present review focuses on the mechanism of the inflammatory responses, mediated by the NLRP3 inflammasome and its possible therapeutic potential in the management of TBI.

Search Strategy and Selection Criteria
The most relevant publications included in this article were identified in the PubMed database: https://www.ncbi.nlm.nih.gov/pubmed/. 1) Keywords used for searching (selection criteria): traumatic brain injury, NLRP3 inflammasome, brain, inhibitors, inflammation; neurodegeneration. 2) Dates of searching: 2000–2019.

The Nucleotide Oligomerization-Like Receptor Protein 3 Inflammasome
The innate immune response to cellular stress, infection and tissue injury occurs via pattern-recognition receptors (PRRs) expressed mainly by inflammatory cells such as monocytes, macrophages, neutrophils, and “inflammatory” dendritic cells. PRRs are components of innate immune system, which recognize pathogen-associated molecular patterns (PAMPs), of pathogens, and damage-associated molecular patterns (DAMPs), components of host cells that are released during cellular damage (Schroder and Tschopp, 2010). Toll-like receptors prime the signaling cascade that leads to cellular activation and production of inflammatory mediators, such as TNF, IL-6, IL-8 and type I interferons (IFNs), in response to extracellular signals. Nod-like receptors (NLRs), a group of PRRs, function in the response to danger signals introduced into the host cell cytoplasm. There are more than 20 NLR genes in humans and more than 30 in mice (Ting et al., 2008). These NLRs include NLRP1, NLRP3, NLRC4, NLRCS5, NLRP6, NLRP7, NLRP12, as well as the non-NLR inflammasome receptor known as AIM2. Among these, NLRP3 is the most studied inflammasome.

The NLRP3 inflammasome was first described in the Muckle-Wells autoinflammatory disorder, which is associated with spontaneous release of IL-1β (Agostini et al., 2004). The NLRP3 inflammasome is activated by various stimuli and stimulates the activation of caspase-1 (the effector molecule), which sequentially leads to the maturation and release of IL-1β and IL-18, and ultimately potentiates inflammatory responses (Agostini et al., 2004; Sutterwala et al., 2006). NLRP3 contains an amino-terminal-terminal pyrin-only domain (PYD), a conserved central nucleotide binding and oligomerization domain (nucleotide oligomerization or NACHT) and a carboxy-terminal leucine-rich repeat (LRR) domain (Jo et al., 2016). The LRR domain senses PAMPs and other endogenous ligands, the NLRP3 in active state, and facilitates protein-protein interactions. The NACHT domain binds with nucleotides, and is vital for protein oligomerization of NLRP3 inflammasome assembly process (Duncan et al., 2007). The PYD domain supports the binding between NLRP and the bipartite adapter ASC via homophilic interactions resulting in the large speck-like structure (Liepinsh et al., 2003). ASC consists of an N-terminal PYD and a C-terminal caspase activation and recruitment domain (CARD). ASC communicate with procaspase-1 through the CARD domain (Srinivasula et al., 2002). Under resting state caspase-1 exists as a catalytically dormant precursor, pro-caspase-1. Induction of pro-caspase-1, contributes to the proteolytic maturation of the proenzym into its active form (Agostini et al., 2004). The activated caspase-1 further induces the maturation and release of pro-inflammatory cytokines IL-1β and IL-18, which belong to the IL-1 family and mediate succeeding immune responses (Keller et al., 2008).

The role of mature caspase-1 is not restricted to secretion of proinflammatory mediators, in fact activated caspase-1 induces inherent inflammatory cell death, known as pyroptosis, which is characterized by cellular swelling, rapid release of intra cellular contents and DNA fragmentation (Bergsbaken et al., 2009; Liu et al., 2018a). Additionally, rupture of the plasma membrane is followed by excessive secretion of pro-inflammatory mediators such as TNF-a, IL-1β, IL-6 and CX3C-chemokine ligand 3, which may exacerbate pyroptosis as is observed during the acute phase of TBI (Fink et al., 2008; Liu et al., 2018a). Pyroptosis is also known as caspase-1 dependent cell death, and is morphologically and mechanistically distinct from apoptosis and other forms of cell death (Bergsbaken et al., 2009).

Regulation of Nucleotide Oligomerization-Like Receptor Protein 3 InflammasomeActivation
The NLRP3 inflammasome plays a crucial role in priming inflammatory responses. NLRP3 is induced by a variety of stimuli including pore-forming toxins, extracellular ATP in the presence of various pathogen-associated molecules, uric acid crystals, virus-associated DNA, RNA, asbestos and ultraviolet-B irradiation (Gurcel et al., 2006; Kanneganti et al., 2006; Mariathasan et al., 2006; Martinon et al., 2006; Koo et al., 2008; Munve et al., 2008). However, the mechanism by which NLRP3 responds to multiple stimuli is elusive. ATP acts as an extra cellular NLRP3 agonist, inducing activation and oligomerization of the inflammasome by inducing K⁺ efflux through a P2X purinergic receptor 7 (P2X7)-dependent pore consisting of a pannexin-1 hemichannel. Additionally, NLRP3...
can be induced by changes in cellular ionic homeostasis such as low K⁺ concentration, Ca²⁺ flux, redox imbalance or mitochondrial dysfunction (Pétrilli et al., 2007; Zhou et al., 2010, 2011; Lee et al., 2012). Several PAMPs and DAMPs induce the activation of the NLRP3 inflammasome, mediated via the thioredoxin-interacting protein (TXNIP) (van Bruggen et al., 2010). Mitochondrial reactive oxygen radicals are the primary stimuli for activation of TXNIP (Kim et al., 2012), and interactions between TXNIP and NLRP3 stimulate the secretion of inflammatory mediators (Zhang et al., 2015). Cytosolic NADPH oxidase 2 (NOX2) also contributes to the activation of the NLRP3 inflammasome through production of reactive oxygen species (Abais et al., 2015). NLRP3 is negatively regulated by nuclear factor erythroid-2 related factor 2 (Nrf2), a redox sensitive transcription factor that regulates expression of cellular antioxidant system. Activators of Nrf2 stimulate the transcription of cellular redox responses that scavenge oxidative damage and results in reduced priming of NF-κB (Jhang and Yen, 2017; Hou et al., 2018). Reduced Nrf2 activity is associated elevated intracellular reactive oxygen species (ROS) level eventually leads to dissociation of TXNIP from thioredoxin and increases the binding of latter to NLRP3 (Jhang and Yen, 2017). Additionally, lysosome destabilization stimulates the activation of NLRP3 by the release of cathepsin B from its contents (Bruchard et al., 2013). Conversely, autophagy acts as negative controller of NLRP3 inflammasome activation (Figure 1) (Nakahira et al., 2011).

The intrinsic activity of NLRP3 is modulated by distinct mechanisms. BRCA1-BRCA2-containing complex-3 (deubiquitinating enzyme), double-stranded RNA-dependent protein kinase, death-associated protein kinase 1 and Bruton’s tyrosine kinase function as positive regulators of NLRP3 inflammasome activity (Song et al., 2017). A member of the NIMA-related kinase (NEK) family, NEK7 has been proven to directly interact to the LRR domain of NLRP3 and act downstream of K⁺ efflux and ROS generation to stimulate the oligomerization of NLRP3 inflammasome (He et al., 2016). K⁺ efflux triggers NEK7-NLRP3 assembly which leads to activation of NLRP3 inflammasome, cleavage of pro-caspase-1, and subsequent neuronal injury. NEK7 knockdown in in vivo experiments reduces NEK7-NLRP3 binding and attenuates NLRP3 inflammasome activity, pro-caspase recruitment, and pyroptosis in nerve injuries status-post TBI. Additionally, autophagy, microRNAs, CARD-only proteins, pyrin-only proteins and nitric oxide (NO) act as endogenous negative regulators of NLRP3 (Saitho et al., 2008; Hernandez-Cuellar et al., 2012; Yang et al., 2015; de Almeida et al., 2015).

Role of the Nucleotide Oligomerization-Like Receptor Protein 3 Inflammasome in Traumatic Brain Injury

The main mechanism of secondary brain injury following TBI is known as perilesional edema and is characterized by increased secretion of pro-inflammatory markers, recruitment of innate immune cells into the brain, and activation of local brain astrocytes and microglia (Yi et al., 2019). Accumulating evidence indicates that activation of the NLRP3 inflammasome occurs during the secondary injury of TBI, this has shed a new light on understanding the pathophysiology and development of new strategies for the management of TBI. A temporal relationship between the expression of the NLRP3 inflammasome components and TBI has been reported (Liu et al., 2013). Injury initiated elevated expression of components of the NLRP3-inflammasome, up-regulation of the ASC and caspase-1, and led to maturation and cleavage of IL-1β and IL-18. At the cellular level, NLRP3-inflammasome was identified in neurons, astrocytes, and microglia in the pericontusional cortex. There was a drastic increase in the IL-1β secretion in the pericontusional area at 6 hours post-injury, with a rapid decrease beginning at 24 hours. Conversely, IL-18 protein expression was elevated gradually from 6 hours to 7 days suggesting a role in delayed injury. Supporting data reported a delayed secretion of IL-18 following TBI occurred, which gradually increased over a period of 7 days (Qian et al., 2017). Moreover, protein expression of NLRP3, ASC and caspase-1 continued to increase from 6 hours to 7 days. Acute stimulation of NLRP3 inflammasome components were also observed in a rodent model of penetrating ballistic-like brain injury, which simulates cranial gunshot injury and is associated with progressive tissue loss (Lee et al., 2018). NLRP3 inflammasome activation reached peak at 48 hours after injury followed by the induction of pyroptosis. Initially the inflammasome activation was localized predominantly in neurons and later switched to microglia between 24 and 48 hours after injury. This could be explained by the pyroptotic response of neurons, later stimulate inflammasome activation in neighboring microglia, whereas astrocytes showed delayed inflammasome activation (Lee et al., 2018). At 48 hours after penetrating ballistic-like brain injury, there was a significant rise in the population of primed and ameboid-type microglia expressing inflammasome proteins. These microglia persisted in the injured brain for up to 12 weeks post-injury with continuous neurodegeneration. The possible reason for the discrepancy in the temporal profile of inflammasome expression may be due to variability in extent of brain jury and difference in animal model. The temporal expression pattern of NLRP3 inflammasome components implies that, initial cell death induced by mechanical injury stimulate innate immune response by rapid elevation of NLRP3 and later it is down regulated by activation of protective mechanisms of the body. One study demonstrated the activation of NLRP3 inflammasome in mediating inflammatory responses in rodent model of blast induced TBI (Ma et al., 2016). They demonstrated that there was increased expression of thioredoxin-interacting protein (TXNIP), a redox sensitive critical regulator of NLRP3 activity, with elevated expression of NLRP3 and activation of caspase-1.
Additionally, there was a higher expression of proinflammatory cytokines including IL-1β and TNF-α in response to blast injury. Administration of propofol (2,6-disopropyl phenol), a well-known lipid-soluble intravenous anesthetic, was accompanied by attenuation of NLRP3 expression, IL-1β maturation and oxidative stress. Similarly, hyperbaric oxygen treatment attenuated neuroinflammation and brain edema, with accompanied improvements in motor function (Qian et al., 2017). However, the beneficial effect of hyperbaric oxygen treatment on NLRP3 is elusive as it can induce oxidative stress which is known to induce NLRP3 inflammasome (Tsopp and Schmider, 2019). Additionally, hyperbaric oxygen therapy associated IL-1β secretion in traumatic cerebral edema has been demonstrated (Erdi et al., 2016). Moreover, treatment with telmisartan, an angiotensin receptor blocker, ameliorated cerebral edema, and subsequently improved neurological outcome which was associated with decreased NLRP3 inflammasome assembly after TBI. The beneficial effect of telmisartan is mediated by inhibition of NLRP3 dependent IL-1β and IL-1β release (Wei et al., 2016). Elevated NLRP3 concentration was found in CSF of children with severe TBI. Elevated expression of NLRP1 was detected in only 11% of children with severe TBI in compared with uninjured controls (Wallisch et al., 2017).

Blast induced TBI is a form of brain trauma due to the use of explosives, for example those associated with war zones and terrorist activities. The resulting secondary damage induces free radical induced TXNIP expression and its downstream NLRP3 inflammasome activation (Fan et al., 2017). Treatment with mangiferin (1,3,6,7-tetrahydroxyxanthone-C2-β-D-glucoside), a component of traditional Chinese medicine alleviated brain damage by inhibition of ROS-TXNIP-NLRP3 inflammasome pathway. Supporting this, the contribution of oxidative stress in mediating NLRP3 inflammasome stimulation was recently confirmed. The deletion of NOX-2, a component of NAPDH oxidase, a major ROS inducer, attenuated NLRP3 inflammasome activation following TBI and was correlated with reduced interaction between TXNIP and NLRP3. NOX is a family of enzymes particularly devoted to the production ROS. Clinical (autopsy) and experimental studies have confirmed the elevated expression of NOX isoforms following TBI (Zhang et al., 2017). This was localized cortex and hippocampus in animal models (Zhang et al., 2012). Additionally, pharmacological inhibition of NOX is associated with attenuation of apoptosis, inflammation and reduced TXNIP expression (Lucke-Wold et al., 2015). Enhanced oxidative stress, brain water contents (edema) and inflammatory markers that are associated with TBI were attenuated by treatment with resveratrol (Zou et al., 2018). TBI induces down regulation of Nrf2 and subsequent elevation of oxidative and nitrosative stress, which activates neuroinflammation and cellular apoptosis. Deletion Nrf2 function in mice resulted in exacerbated brain damage and inflammatory response in TBI model of fluid percussion injury (Bhowmick et al., 2019). These observations collectively demonstrated that modulation of oxidative stress may attenuate the TXNIP-NLRP3 inflammasome mediated secondary injury after TBI.

Recently, activation of NLRP3 inflammasome was also reported in a rodent model of controlled cortical impact injury (CCI). In this study, treatment with ω-3 fatty acids, alleviated inflammation and behavioral deficits. This response was mediated by the elevated expression of anti-inflammatory β-Arrestin-2 scaffold protein, a downstream molecule of GPR40, which negatively modulates NLRP3 inflammasome activation. The role of NLRP3 has been further confirmed by both genetic and pharmacological approaches. NLRP3 knock out mice demonstrated a preserved cognitive function, less severe damage and less inflammatory response compared to wild-type mice in response to TBI (Irrera et al., 2017).

Additionally, pharmacological inhibition of NLRP3 with BAY 11-7082 revealed more preserved brain structure and reduced edema following TBI. Recently, we have reported that the inhibition of NLRP3 inflammasome components protected mice from TBI induced brain damage in a murine model of CCI (Ismael et al., 2018a). Pharmacological inhibition with highly specific small molecular inhibitor MCC950 protected mice from edema, and resulted in improved neurological function. The study validated both the acute (24 hours) and subacute (72 hours) phases after TBI. Treatment with MCC950 reduced the level of apoptotic markers such as cleaved caspase-3 and cleaved poly(ADP-ribose) polymerase (PARP), while causing an upregulation of cell survival molecule protein kinase B. MCC950 also attenuated NLRP3 inflammasome priming by modulation of NFkB p65 expression. However, the study was unable to validate the long term beneficial effect on neurological outcome and structural integrity of the damaged brain. Similar studies were later conducted by another group over an extended period and found elevated NLRP3 inflammasome expression in the peri-contusional cortex and microglia to be the primary source of NLRP3 expression (Xu et al., 2018). Inhibition of NLRP3 inflammasome activation is associated with an improved long term neurological outcome, preserved blood brain barrier integrity, reduced microglial activation, and leukocyte infiltration following TBI. However, MCC950 administration started 12 hours post-TBI did not result in any significant progress. The beneficial effects were evident up to 6 hours post TBI, suggesting that the therapeutic window for MCC950 may be 6 hours. Additionally, it was reported that α2-adrenergic receptor agonist that has been used as sedative hypnotic, analgesic (Fang et al., 2015) has beneficial effects in TBI via NFk-B-mediated inhibition of NLRP3 inflammasome, and can attenuate neurological dysfunction (Wang et al., 2018). Dexmedetomidine, a novel α2-adrenergic receptor agonist, has been shown to alleviate post traumatic inflammation through inhibition of the NLRP3 inflammasome. Dexmedetomidine reduced BBB disruption and cellular apoptosis, and improved neurobehavioral outcomes in the acute phase of TBI (Wang et al., 2018). A recent study evaluated the potential role of receptor-interacting protein 3 (RIP3) in the pathogenesis of TBI (Liu et al., 2018b). RIP3 was found to be upregulated following TBI in parallel with neuroinflammation, impaired neurological and behavioral function. RIP3 ablation improved neurological function and alleviated NLRP3 inflammasome activation, suggesting it may have a regulatory role on the NLRP3 inflammasome. More recently it was demonstrated that NIMA-related kinase 7 (NEK7) mediated NLRP3 inflammasome activation and silencing of NEK7 attenuates NLRP3 inflammasome activation, neurological deficit and pyroptosis following TBI in mouse model of CCI. NEK7 shows a low level of activity under normal circumstances and increased in response to TBI, suggesting its role as the upstream instigator (He et al., 2016). The mechanism of activation of NLRP3 inflammasome in TBI is depicted in Figure 2.

TBI is a heterogeneous condition and may result from many different types of insults leading to variable inflammatory responses. There were differences in the temporal profiles of inflammasome activation between the various TBI models, these are likely corresponding to model-specific responses and tissue vulnerability patterns produced by the different models. This makes the comparison more difficult to interpret and limits its translation into clinical trials. Most of the preclinical studies for TBI are well monitored rapid studies, and none of the models simulate the exact clinical condition. Although several pharmacological agents have been validated in experimental studies, none of them have Food and Drug Administration approval for the treatment of TBI. There is an urgent need of specific therapeutic approach targeting multiple mechanism of disease progression in TBI.
including pneumococcal meningitis, Staphylococcus aureus in a broad spectrum of microbial infections of the CNS and pathology of a wide range of neurological diseases. Clinical of NLRP3 inflammasome signaling has been reported in the central nervous system (CNS). However aberrant activation signaling pathway in the innate immune system of the NLRP3 mediated inflammasome activation is a pivotal Neurological Diseases and Conditions Receptor Protein 3 Inflammasome in Other Role of Nucleotide Oligomerization-Like receptor protein 3; PAMP: pathogen-associated molecular patterns; P2RX7: adenosine dinucleotide phosphate; NLRP3: nucleotide oligomerization-like patterns; IL-1β: interleukin-1 beta; IL-18: interleukin-18; NADPH: nicotinamide protein; ATP: adenosine triphosphate; DAMP: damage-associated molecular and proapoptotic signaling caused by TBI. ASC: Apoptosis-associated speck-like oligomerization, eventually alleviating the NLRP3-induced neuroinflammation the subsequent release of IL-1β and inflammatory mediators. Prolonged NLRP3 activation induces proapoptotic molecular complexes such as cleaved PARP and cleaved caspase-3. The specific inhibitor MCC950 blocks NLRP3-induced ASC oligomerization, eventually alleviating the NLRP3-induced neuroinflammation and proapoptotic signaling caused by TBI. ASC: Apoptosis-associated speck-like protein; ATP: adenosine triphosphate; DAMP: damage-associated molecular patterns; IL-1β: interleukin-1 beta; IL-18: interleukin-18; NADPH: nicotinamide adenine dinucleotide phosphate; NLRP3: nucleotide oligomerization-like receptor protein 3; PAMP: pathogen-associated molecular patterns; P2RX7: P2X purinoreceptor 7; TXNIP: thioredoxin interacting protein.

Role of Nucleotide Oligomerization-Like Receptor Protein 3 Inflammasome in Other Neurological Diseases and Conditions

NLRP3 mediated inflammasome activation is a pivotal signaling pathway in the innate immune system of the central nervous system (CNS). However aberrant activation of NLRP3 inflammasome signaling has been reported in the pathology of a wide range of neurological diseases. Clinical and in vivo studies reported the role of NLRP3 inflammasome in a broad spectrum of microbial infections of the CNS including pneumococcal meningitis, Staphylococcus aureus infection (Hanamsagar et al., 2011; Hoegen et al., 2011). Moreover, aberrant expression of NLRP3 inflammasome has been described in viral infections with Japanese Encephalitis virus, influenza virus and human immunodeficiency virus (Hanamsagar et al., 2011; Hoegen et al., 2011; Kaushik et al., 2012; Walsh et al., 2014).

Several studies have validated the pathogenic role of the inflammasome in neurovascular diseases such as Alzheimer’s disease (AD), amyotrophic lateral sclerosis, multiple sclerosis, ischemic stroke, traumatic injury and microbial infections (Kaushik et al., 2012; Inoue et al., 2012; Geldhoff et al., 2013; Liu et al., 2013; Zhao et al., 2015; Lammerding et al., 2016; Saresella et al., 2016). Inflammatory responses are essential for eliminating invading agents, clearing injured cells and promoting tissue repair. However, prolonged neuroinflammation may lead to further tissue damage and neurovascular dysfunction. The aberrant NLRP3 inflammasome activation is involved in many chronic inflammatory diseases including Alzheimer’s disease and aging, which is different from acute neuro inflammation. Chronic inflammation is a low-grade, controlled, chronic systemic inflammatory state and usually asymptomatic, where NLRP3 inflammasome is triggered by metabolic end by products such as urate and cholesterol crystals (Ozaki et al., 2015). In Alzheimer’s disease, the increase in Ab plaques leads to release of DAMPS from neurons. These DAMPs are sensed by NLRP3 inflammasome complex leading to a cascade of events ending in prolonged neuroinflammation (Katsumoto et al., 2018). However, in the case acute brain injury such as TBI and stroke, DAMPS released from injured and necrotic cells and trigger the NF-kB and MAPK signaling pathway through PRRs. These activated pathway contribute to the expression and activation of NLRP3 inflammasome (Alishahi et al., 2019).

Recently we have demonstrated TXNIP mediated enhanced NLRP3 inflammasome activation in cerebral cortex of human AD brain (Li et al., 2019). Increased activation of NLRP3 was reported in intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), characterized by enhanced production of inflammatory cytokines mediated by reactive oxygen free radicals and the P2X7R pathway (Wang and Doré, 2007; Keep et al., 2012; Feng et al., 2015). Our in vivo studies showed that NLRP3 protein expression was found to be increased after experimental ischemic stroke, which was concomitant with an elevated expression of inflammatory mediators IL-1β and IL-18. Pharmacological inhibition of NLRP3 inflammasome improved cerebral ischemia outcomes, as demonstrated by reduced infarction volumes, alleviated neurovascular damage, and the attenuation of inflammatory markers (Ismael et al., 2018b). The significant contribution of NLRP3 in ischemic stroke and spinaward injury were extensively reviewed (Mortezaaee et al., 2018; Alishahi et al., 2019).

Nucleotide Oligomerization-Like Receptor Protein 3 Inhibitors in Traumatic Brain Injury

A large number of investigations are warranted for developing a specific NLRP3 inhibitor for the treatment of TBI. Propofol and mangiferin were shown to provide significant inhibition of NLRP3 which is claimed to be responsible for their therapeutic activities in TBI (Fan et al., 2017). Telmisartan, an angiotensin receptor blocker, has also been reported to have NLRP3 antagonistic activity in the state of TBI (Erđi et al., 2016). One recent in vivo study demonstrated that BAY 11-7082 can attenuate NLRP3 action in the treatment of TBI (Irrera et al., 2017). Treatment with BAY 11-7082 led to a decrease in edema and preserved brain structure in a mouse model of TBI, even though BAY 11-7082 is not a direct inhibitor of NLRP3.

Hyperbaric oxygen treatment inhibited the production of inflammatory markers via inhibition of the NLRP3 inflammasome, but the exact mechanism still needs to be elucidated (Qian et al., 2017). Resveratrol, a nutraceutical and also alleviated brain damage following TBI by modifying the expression of NLRP3 inflammasome components, ROS and edema (Zou et al., 2018). The beneficial effect of resveratrol is mediated by NLRP3 attenuation via sirtuin 1 and ROS dependent mechanism. Previously, we have reported that resveratrol inhibits NLRP3 expression through a TXNIP mediated mechanism (Ishrat et al., 2015).

Ketone metabolite β-hydroxybutyrate is known to inhibit inflammatory mediators via NLRP3-specific inhibition, it also inhibits NLRP3-induced ASC oligomerization (Youn et al., 2015). Supplementation with a ketogenic diet specifically inhibits NLRP3 inflammasome activity, without affecting the activation of NLR4 or AIM2 inflammasomes. β-hydroxybutyrate is bioavailable for vital tissues like the brain and heart under conditions of starvation. Finally, type I IFNs, including IFN-α and IFN-β, are NLRP3-specific inflammasome inhibitors that have been used to inhibit NLRP3 and other inflammasomes in various auto-immune and auto-inflammatory diseases (Shao et al., 2015); however they have not been validated in the setting of TBI. Artesunate, a derivative of the traditional Chinese phytochemical artemisinin that has been shown to
have multiple pharmacological actions including anti-neuroinflammatory activity, administration of artesunate decreased the degree of brain injury and lesion volume by inhibiting NLRP3 inflammasome activation and NFKB nuclear translocation in mouse model of CCI (Gugliandolo et al., 2018). Additionally, artesunate protected against apoptosis, microglial activation, neuroinflammation and modulated the release of neurotrophic factors. Dexmedetomidine is an alpha 2 adrenergic receptor agonist whose administration in rats following TBI significantly reduced perilesional cerebral edema through attenuation of NLRP3 activity and subsequent downstream cytokines and in reducing activation of astrocytes and microglia (Yi et al., 2019). Table 1 summarizes the studies on modulation of NLRP3 inflammasome in animal models of TBI.

**Table 1** Summary of studies on the modulation of the NLRP3 inflammasome in TBI

| TBI model | NLRP3 modulation | Inference | Reference |
|-----------|------------------|-----------|-----------|
| Rat model of blast-induced TBI | Propofol, 50 mg/kg, 1 h after explosion | Suppression of enhanced NLRP3 expression with the decreased oxidative stress, cytokine production, and the amelioration of cerebral cortex damage | Ma et al. (2016) |
| Rat model of blast-induced TBI | Mangiferin 100 mg/kg i.p. 20 min after explosion | Inhibition of TXNIP-NLRP3 inflammasome activation, with accompanied inhibition of oxidative stress and inflammation | Fan et al. (2017) |
| Mouse model of CCI | NOX2 knockout mice | Attenuation of the expression, assembly, and activity of the NLRP3 inflammasome via modulation of TXNIP | Ma et al. (2017) |
| Rat model of CCI | Omega-3 fatty acids (100 mg/kg, twice a week for 6 wk before surgery) | Ameliorated TBI-induced inflammation and behavior deficits by inhibition of NLRP3 inflammasome activation by inducing ARRB2, a negative regulator | Lin et al. (2017) |
| Mouse model of impact acceleration model of diffused TBI | NLRP3−/− or BAY 11-7082 (20 mg/kg, i.p.), 10 min after injury | Preserved cognitive function, less severe brain damage and attenuation of inflammatory mediators | Irrera et al. (2017) |
| Mouse model of CCI | MCCC950, 50 mg/kg/d | Attenuated inflammasome activation, cerebral edema, and improved neurological function. Modulation of apoptotic signaling and inflammasome priming | Ismael et al. (2018a) |
| Mouse model of CCI | MCCC950 (10 mg/kg body weight, i.p.) daily for the first 3 d and then every other day up to 21 d | Attenuated microglia-derived NLRP3 inflammasome activation and subsequent reduction in brain edema, tissue loss, microglia activation, leukocyte infiltration, BBB disruption, and cell death, and improved long-term neurological function | Xu et al. (2018) |
| Mouse model of CCI | After injury, animals received 3 d of consecutive dexametomidine therapy (25 μg/kg/d) | Inhibited NLRP3 inflammasome pathways by down regulation of NF-κB expression | Wang et al. (2018) |
| Mouse model of CCI | Hyperbaric oxygen treatment was given for 1 h at 2 ATA once daily for 7 d | Attenuated neurological dysfunction and brain edema, BBB damage and apoptosis | Qian et al. (2017) |
| Mouse model of CCI | RIP3 knockout | Improved motor function and reduced brain edema, with the attenuation of NLRP3 inflammasome activation in microglia | Liu et al. (2018b) |
| Mouse model of CCI | Artesunate (30 mg/kg) at 1 h after craniotomy | Inhibited NLRP3 inflammasome complex and nuclear factor kappa-B, and modulated the release of neurotrophic factors | Chen et al. (2019) |
| Rat model of CCI | Dexmedetomidine (20 μg/kg, i.p.) for 4 d | Inhibited NLRP3 inflammasome activation, improved neuronal survival and expression of NLRP3 inflammasome components, decreased cortical lesion volume and improved neuronal survival | Zheng et al. (2018) |
| Rat model of CCI | JC124 (100 mg/kg, i.p.), 4 doses | Inhibited the expression of NLRP3 inflammasome components, decreased cortical lesion volume and improved neuronal survival | Kuwar et al. (2019) |
| Mouse model of weight drop | Pioglitazone (20 mg/kg, i.p.), daily | Reduced cerebral edema and inflammation by down regulating NLRP3 inflammasome activation. Reduced microglial and astrocyte activation | Yi et al. (2019) |
| Mouse model of CCI | NIMA-related kinase 7 shRNA, icv following TBI | Down regulation of NLRP3 inflammasome and inflammatory mediators | Chen et al. (2019a) |
| Rat model of CCI | JC124 (100 mg/kg, i.p.), 4 doses | Inhibited the expression of NLRP3 inflammasome components, decreased cortical lesion volume and improved neuronal survival | Kuwar et al. (2019) |

ATA: Atmospheres absolute; BBB: blood-brain barrier; CCI: controlled cortical impact; NIMA related kinase: never in mitosis gene A-related kinase; NLRP3: nucleotide oligomerization-like receptor protein 3; NOX: NADPH oxidase; RIP3: receptor-interacting protein kinase 3; TBI: traumatic brain injury; TXNIP: thioredoxin interacting protein.

**MCC950, a Novel Selective Nucleotide Oligomerization-Like Receptor Protein 3 Inhibitor**

MCC950 is a selective small molecule inhibitor of the NLRP3 inflammasome, and a promising candidate for the treatment of inflammatory diseases (Salla et al., 2016). It is a diarylsulphonylurea-containing compound, specific for NLRP3, but not for AIM2, NLRC4 or NLRP1 inflammasomes, and it blocks NLRP3-induced ASC oligomerization (Coll et al., 2015). Because of its specificity, MCC950 is less immunosuppressive than other inflammasome inhibitors (Ren et al., 2018) and is orally bioavailable. The beneficial effects of MCC950 have been shown in experimental autoimmune encephalomyelitis and AD, where its ability to cross BBB was verified (Coll et al., 2015; Dempsey et al., 2017). Recently we demonstrated that inhibition of NLRP3 with MCC950 protect mice against TBI. This is the first report validating efficacy of MCC950 in a mouse model of TBI induced by controlled cortical impact (Ismael et al., 2018a). TBI induced activation of...
mediated by modulating oxidative stress and the consequent NLRP3 inflammasome in TBI. These beneficial effects are via inhibition of NLRP3 inflammasome activation. However, it should be noted that none of the available antioxidants have proven efficacy in clinical trials. Moreover, there is no specific inhibitor for TXNIP. MCC950, specific small molecular NLRP3 inflammasome inhibitor, can cross the BBB and thereby by modulate inflammatory response. Although these studies have clinical implications, limited number of studies validated the beneficial effect of MCC950 in the setting of TBI. Further long-term functional investigation is required to suggest MCC950 as a promising new therapeutic candidate for patients with TBI.

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Conclusion
The NLRP3 inflammasome, is a multiprotein complex activated in response to brain injury in a time dependent manner. Accumulating evidence demonstrated that the beneficial effects of various non-specific inhibitors in attenuating inflammatory responses is via inhibition of NLRP3 inflammasome in TBI. These beneficial effects are mediated by modulating oxidative stress and the consequent TXNIP inhibition signify the potential of targeting TXNIP as a possible therapeutic option for the attenuation of NLRP3 inflammasome activation. However, it should be noted that none of the available antioxidants have proven efficacy in clinical trials. Moreover, there is no specific inhibitor for TXNIP. MCC950, specific small molecular NLRP3 inflammasome inhibitor, can cross the BBB and thereby by modulate inflammatory response. Although these studies have clinical implications, limited number of studies validated the beneficial effect of MCC950 in the setting of TBI. Further long-term functional investigation is required to suggest MCC950 as a promising new therapeutic candidate for patients with TBI.
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