Inflammasomes in neurological diseases: emerging pathogenic and therapeutic concepts

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Inflammasome activation in the central nervous system occurs in both health and disease. Inflammasomes are cytosolic protein complexes that sense specific infectious or host stimuli and initiate inflammatory responses through caspase activation. Assembly of inflammasomes results in caspase-1-mediated proteolytic cleavage and release of the pro-inflammatory cytokines, interleukin-1β and interleukin-18, with initiation of pyroptosis, an inflammatory programmed cell death. Recent developments in the inflammasome field have uncovered novel molecular mechanisms that contribute to a broad range of neurological disorders including those associated with specific mutations in inflammasome genes as well as diseases modulated by inflammasome activation. This update focuses on recent developments in the field of inflammasome biology highlighting different inflammasome activators and pathways discovered in the nervous system. We also discuss targeted therapies that regulate inflammasomes and improve neurological outcomes.

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Abbreviations: DAMP = danger-associated molecular patterns; EAE = experimental autoimmune encephalomyelitis; PAMP = pathogen-associated molecular patterns; ROS = reactive oxygen species

Introduction

Inflammasomes were first described in 2002 as cytosolic caspase-activating protein complexes in macrophage lineage cells, responsible for the proteolytic cleavage and release of the cytokines IL-1β and IL-18 as well as a distinct type of programmed cell death, termed pyroptosis (Martinon et al., 2002) (Fig. 1). It was soon recognized that inflammasome machinery is present in numerous cell types and contributes to innate immune activation in multiple organs including the CNS (Bergsbaken et al., 2009). Innate immunity is an integral component of neuroinflammation and is recognized as both a causative and consequent aspect of many neurological diseases (Heneka et al., 2014). Innate immune responses including inflammasome activation are initiated by host recognition of pathogen-associated molecular patterns (PAMPs) expressed on microbial pathogens (e.g. bacteria, viruses, parasites) or by danger-associated molecular patterns (DAMPs) produced by host cells [e.g. ATP, DNA, reactive oxygen species (ROS)] (Kanneganti et al., 2006; Martinon and Tschopp, 2007). These molecules serve as ligands for pattern-recognition receptors expressed on cells of the innate immune system, including microglia, macrophages and astrocytes in the CNS (Bryant and Fitzgerald, 2009). Binding of PAMPs or DAMPs to pattern-recognition receptors induces
inflammasome gene transcription and assembly providing platforms for proteolytic cleavage and subsequent release of IL-1β and IL-18 (Fig. 2). Both cytokines are present in cells as inactive precursors (pro-IL-1β and IL-18) and require caspase-1-mediated cleavage for conversion into active forms. Pro-caspase-1 undergoes autocatalysis during inflammasome activation to yield active caspase-1 (Martinon et al., 2002; Dagenais et al., 2012). Caspases-4 and 5 were shown to mediate IL-1β release via one-step non-canonical inflammasome activation (Vigano et al., 2015). Recent reviews have enhanced our understanding of the role of inflammasomes in CNS disease (Freeman and Ting, 2016; Kong et al., 2016). In this comprehensive update, we highlight the major new developments in CNS inflammasome research encompassing a broader spectrum of neurological diseases in the context of both pathogenesis and therapy.

**Figure 1 Inflammasome components and actions.** Inflammasomes are activated by one or more signals resulting in assembly of individual inflammasomes that provide a platform for caspase-1 autocatalysis and activation. Activated caspase-1 mediates proteolytic cleavage and release of IL-1β and IL-18. Additionally, caspase-1 also cleaves gasdermin D, which forms pores in the membrane, contributing to pyroptosis.

**Inflammasomes: biology and mechanisms of activation**

Inflammasomes contain different structural domains that mediate individual functions (Fig. 1). Nucleotide-binding domain (NB) and leucine-rich repeat (LRR) containing receptors (NLR), also called NOD-like receptors, are cytosolic pattern-recognition receptors found chiefly in macrophage-like cells. More than 20 NLR proteins have been identified to date. NLRs contain an N-terminal effector binding domain (e.g. PYD, CARD), a nucleotide-binding oligomerization domain (NACHT), and a C-terminal LRR receptor domain, which binds to ligands and leads to activation of inflammasomes (Kita et al., 2009). Most inflammasomes have ASC (apoptosis-associated speck-like protein, encoded by PYCARD) as an adaptor molecule, which translocates to
the cytoplasm in response to stimuli to form specks and recruit caspase-1. Caspase-1 activation also cleaves gasdermin D (GSDMD) to active N-terminal GSDMD causing it to form cytotoxic pores in cell membrane, driving the cell towards pyroptosis (Shi et al., 2017) (Fig. 1).

**Inflammasomes in the nervous system**

Microglia, neurons, oligodendrocytes, astrocytes and Schwann cells can exert immune actions depending on the circumstances although neurons and oligodendrocytes are not usually regarded as immune effector cells. Basal levels of IL-1β and IL-18 are essential for physiological functions of the nervous system and cytokine deficiencies can result in adverse outcomes (Dinarello, 2007; Blok et al., 2014). These cytokines participate in molecular and cellular mechanisms linked to learning, memory and sensory functions (Netea et al., 2006; McAfoose and Baune, 2009). There is cell-specific expression of inflammasome components in the nervous system with NLRP1, NLRP3, NLRC4 found primarily in microglia (Cho et al., 2014; Denes et al., 2015), NLRP2 and NLRP3 in astrocytes (Minkiewicz et al., 2013; Lu et al., 2014) and AIM2 and NLRP1 in neurons (Adamczak et al., 2014; Tan et al., 2014) (Supplementary Fig. 1). The NLRP3 inflammasome is the most abundant inflammasome in the CNS and one of the key contributors to neuroinflammation in a broad spectrum of nervous system disorders and, therefore, the most extensively investigated inflammasome (Song et al., 2017). Expression of specific inflammasome proteins awaits further analyses for oligodendrocytes and Schwann cells.

Primary microglia respond to similar stimuli as haematopoietic macrophages but microglial responses are more sustained due to lack of negative regulation of pro-IL-1β expression (Burm et al., 2015). Microglia are the primary producers of IL-1β, following NLRP3 upregulation, in a depression model in rats (Pan et al., 2014). Human astrocytes express a novel NLRP2 inflammasome, activated by ATP. NLRP2 assembly and activation is mediated by the P2X7 receptor and the pannexin 1 channel leading to downstream activation of caspase-1 and ensuing IL-1β production (Minkiewicz et al., 2013). Neurons sense danger stimuli of mechanical, thermal or chemical nature. They are known to express several inflammasome proteins including NLRP1, NLRP3 and AIM2 (Kummer et al., 2007; Kaushal et al., 2015). However, the consequences of inflammasome activation in neurons awaits further investigation (Santoni et al., 2015).

**Endogenous regulation of inflammasomes**

While PAMPs and DAMPs drive inflammasome activation, individual inflammasomes can be modulated by endogenous and exogenous mechanisms (Fig. 2). For example, the cyclopentenone prostaglandin 15d-PGJ2 inhibits NLRP1 and NLRP3 inflammasomes (Maier et al., 2015). Prostaglandin E2 restricts activation of the NLRP3 inflammasome through intracellular cyclic AMP in human macrophages (Sokolowska et al., 2015). The NLRP3 inflammasome is also regulated by multiple microRNAs at different stages of protein assembly and activation; an inverse relationship between miR-223 and NLRP3 activation was reported, suggesting that miR-223 offered a novel therapeutic approach following intracerebral haemorrhage (Yang et al., 2015). In another study, miR-133a-1 suppressed inflammasome activation by downregulating uncoupling protein 2 (UCP2). miR-133A-1 prevented inflammasome activation without affecting the basal expression of NLRP3, ASC, pro-IL-1β or pro-caspase-1 (Bandyopadhyay et al., 2013). miR-7 repressed NLRP3 activation in microglia with important implications for Parkinson’s disease (Zhou et al., 2016).

Other endogenous inhibitors of inflammasomes include IL-37 and type 1 interferons (IFNs). IL-37 is a 30kDa member of the IL-1 family of ligands and shares amino acid sequences with IL-18. It binds to the IL-18 receptor in a non-competitive manner and exerts anti-inflammatory effects by translocating to the nucleus and also inhibiting expression of IL-1β (Bulau et al., 2014). The inhibitory effects of IL-37 have been confirmed in bone marrow-derived macrophages and neutrophils (Moretti et al., 2014). The type 1 IFNs including IFNα and -β exert anti-proliferative and antimicrobial actions while also contributing to neuropsychiatric disorders (depression, psychosis, neurocognitive impairments) (Robaesys et al., 2007; Capuron and Miller, 2011).

Inflammasome activation in the CNS has important implications for neurological disease involving neuroinflammation. Below we review acute and chronic neurological diseases, for which there is detailed fundamental and clinical evidence of inflammasome involvement. In addition, other neurological diseases for which mechanisms of inflammasome activation are under investigation are summarized in Table 1.

**Inflammasome activation in acute neurological diseases**

**Stroke**

Stroke causes 10% of deaths worldwide and results in long-term disability in survivors. Inflammation during stroke begins with secretion of pro-inflammatory cytokines (e.g. IL-1β and IL-18) by activated glial cells (Fann et al., 2013b). This primary response is followed by secondary infiltration of neutrophils and monocytes from the vascular circulation, which secrete cytokines and other cytotoxic agents including ROS and matrix metalloproteinas (MMPs) (Jin et al., 2010). Both NLRP1 and NLRP3 are major sensors of reduced intracellular ATP (Liao and
Mogridge, 2013; Nomura et al., 2015). Diminished ATP activates AMPK (AMP-activated protein kinase), which in turn activates NLRP1. Interestingly, AMPK activation is insufficient to induce NLRP1 inflammasome activation but lower ATP concentrations are a co-requirement, suggesting that ATP in physiological circumstances might inhibit NLRP1 (Liao and Mogridge, 2013).

High cytosolic Ca$^{2+}$ with reduced K$^+$ concentrations activates NLRP3 during stroke. Lower ATP results in aberrant function of the Na$^+$/K$^+$-ATPase pump that causes an imbalance in ionic concentrations and eventual NLRP1 and NLRP3 inflammasome activation (Munoz-Planillo et al., 2013; Rajamaki et al., 2013).

**Meningitis**

Bacterial meningitis, caused by *Streptococcus pneumoniae*, carries a mortality rate of 16–37%, with approximately half of the survivors suffering neurological disability (Hoogman et al., 2007). CSF from patients with pneumococcal meningitis shows upregulation of caspase-1 activity as well as IL-1β and IL-18 (Hoegen et al., 2011). Correlation of elevated IL-1β and IL-18 levels with meningitis severity and associated complications has been reported (Zwijnenburg et al., 2001). Interestingly, ASC and NLRP3 knockout mice exhibited decreased bacterial loads but NLRP3 expression was neuroprotective in this infection model. NLRP3 knockout mice showed increased leucocyte infiltration and cerebral haemorrhage following bacterial infection with worsened outcomes (Geldhoff et al., 2013). In fact, IL-1 receptor knockout mice were more susceptible to developing meningitis. Increased mortality and enhanced growth of pneumococci in IL-1R$^+/−$ mice was observed compared with wild-type mice (Zwijnenburg et al., 2003). These studies emphasize the beneficial effects of IL-1 signalling in bacterial clearance.
Zika infection

Zika virus (ZIKV) is a mosquito-borne flavivirus, widespread in North Africa, Southeast Asia and South America, and is associated with meningoencephalitis in human foetuses and Guillain-Barré Syndrome in adults (Munoz et al., 2016). ZIKV infection of skin fibroblasts activates AIM2 and IL-1β at the transcript level (Hamel et al., 2015). Recent studies suggest that astrocytes are the principal reservoir for ZIKV (Nowakowski et al., 2016). Increased expression of IL-18, IL-6 and TNFα were observed in sera from ZIKV-infected mice (Zmurko et al., 2016). ZIKV infection increased IL-1β, NLRP3 and caspase-1 transcripts in glial cell line, leading to cell death (Tricarico et al., 2017). Thus, activation of inflammasomes and pyroptotic cell death during ZIKV infection might be a potential host defence strategy to amplify the immune response.

Traumatic nervous system injuries

Traumatic neurological injuries lead to a wide range of long-term disabilities and/or death, associated with
neuroinflammation (Woodcock and Morganti-Kossmann, 2013). Caspase-1 is activated after both traumatic brain injury (TBI) (de Rivero Vaccari et al., 2009) and spinal cord injury (de Rivero Vaccari et al., 2008). The expression levels of NLRP1 were unchanged but ASC and caspase-1 protein levels were elevated in CSF of patients with TBI (Adamczak et al., 2012). NLRP3 inflammasome expression was observed in cerebral cortex in a rat TBI model (Liu et al., 2008). Neurons respond to injury by activation of AIM2 inflammasome and oligomerization of ASC. This cascade resulted in formation of discrete pores in plasma membrane, neuronal pyroptosis and release of IL-1\(\beta\) (Adamczak et al., 2014). Hyperbaric oxygen therapy inhibited inflammasome signalling and alleviated symptoms in mouse models of TBI (Geng et al., 2016).

### Inflammasome involvement in chronic neurological diseases

Prolonged activation of inflammasomes in the brain can promote neuroinflammation, which is pathogenic in many chronic neurological disorders.

### NeuroAIDS

Human immunodeficiency virus (HIV) enters the brain early during the infection. IL-1\(\beta\) and TNF\(\alpha\) are the most consistently induced cytokines in the CNS during HIV infection (Tyor et al., 1993; Wesselingh et al., 1997; Xing et al., 2009). We showed that IL-1\(\beta\), IL-18 and caspase-1 are induced in brains of patients with HIV/AIDS, specifically in microglia and that pro-IL-1\(\beta\) was induced within 4 h of microglial infection with HIV, by a NLRP3-dependent mechanism (Walsh et al., 2014). Similarly, HIV infection of human dorsal root ganglia induced the expression of IL-1\(\beta\) in conjunction with distal symmetric polyneuropathy (Jones et al., 2005). Recently, we reported that the HIV-encoded protein, Vpr, was responsible for activating the NLRP3 inflammasome in microglia, resulting in depressive behaviours (Mamik et al., 2017). These studies suggest that targeting inflammasome activation might represent a therapeutic intervention in HIV-associated neurological diseases (Walsh et al., 2014).

### Glioblastoma multiforme

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumour in adults. The cellular and molecular composition of GBMs is highly variable but immune activation is a consistent feature involving both infiltrating macrophages and lymphocytes. Glioblastomas produce IL-1\(\beta\) in an NLRP3-dependent mechanism resembling macrophages or microglia. IL-1\(\beta\) activates STAT3, a transcription factor implicated in glioma progression (Tarassishin et al., 2009). The consequence of inflammasome activation on GBM progression remains uncertain at present.

### Epilepsy

Temporal lobe epilepsy is characterized by refractory seizures and neuronal loss in the hippocampus. NLRP1 and caspase-1 signalling has been implicated in epileptogenesis,

### Table 2 Pharmacological inhibition of inflammasomes

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accompanied by neuronal pyroptosis in an animal model of temporal lobe epilepsy (Tan et al., 2015). In a rat model of prolonged epileptic seizures, upregulated IL-1β, NLRP3 and caspase-1 expression was observed suggesting NLRP3 as a therapeutic target for epilepsy (Meng et al., 2014).

**Alzheimer’s disease**

Alzheimer’s disease is characterized by extracellular accumulation of amyloid-β in senile plaques together with phosphorylated neurofilaments (tangles) comprised of the tau protein (MAPT). The accumulation of amyloid-β activates NLRP3 inflammasome in microglia leading to IL-1β expression in brain and CSF from Alzheimer’s disease patients (Tan et al., 2013). Elevated levels of IL-1β have been detected in astrocytes in Alzheimer’s disease (Liu and Chan, 2014). The mechanism by which NLRP3 activation occurs during Alzheimer’s disease likely involves: (i) increased amyloid-β phagocytosis by microglia; (ii) lysosomal breakdown in microglia; (iii) release of cathepsin B; and (iv) NLRP3 activation followed by caspase-1 activation and ensuing IL-1β release (Guo et al., 2015). NLRP3 activation is positively correlated with neuropathology in transgenic mice expressing amyloid-β. Decreased amyloid-β deposition and better spatial memory was reported in NLRP3 knockout mice (Heneka et al., 2013). IL-1β-mediated neuronal cell death in Alzheimer’s disease is mediated by mitogen-activated protein kinase (MAPK) pathway and by inducible nitric oxide synthase (iNOS) production in hippocampal neurons (Barone et al., 2001).

**Multiple sclerosis**

Although the cause of multiple sclerosis is unknown it is defined by progressive neurological disability associated with inflammatory demyelination within the CNS. Caspase-1 was upregulated in peripheral blood mononuclear cells (PBMCs) (Furlan et al., 1999) and acute and chronic demyelinating lesions (Ming et al., 2002) in patients with multiple sclerosis. Elevated IL-18, IL-1β and caspase-1 have been found in PBMCs, serum and CSF from patients with multiple sclerosis (Hauser et al., 1990; Huang et al., 2004; Heidary et al., 2014). Of interest, the cryopyrin-associated periodic syndromes (CAPS) are a group of hereditary inflammatory disorders, with associated neurological manifestations (Kitley et al., 2010), caused by gain of function mutations in NLRP3 gene, and often present with multiple sclerosis-like lesions (Claxton et al., 2015). In the murine model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), several reports indicate that knock-out of key inflammasome components (Nlrp3−/−, Asc−/−, and Casp1−/−) causes an attenuated form of EAE. Pharmacological inhibition of caspase-1 and P2X7 attenuates disease severity in the EAE model (Matute et al., 2007). IFNβ, a first-line therapy for relapsing-remitting multiple sclerosis (Kappos et al., 2006), had no effect on NLRP3-independent EAE but reduced disease severity in NLRP3-dependent EAE, demonstrating a direct relationship between IFNβ and NLRP3 suppression via reducing the production of mitochondrial ROS (Inoue et al., 2012). Peptidoglycan and bacterial genomes are reported in macrophages and dendritic cells in demyelinating lesions in multiple sclerosis patients’ brain tissue (Schrijver et al., 2001; Branton et al., 2016), highlighting their role as PAMPs and signalling through Toll-like receptors (TLRs) (Bsibsi et al., 2002) with the capacity to activate inflammasomes. Transcriptional regulator high mobility group box protein 1 (HMGB1), poly(ADP-ribose) polymerase 1 (PARP1) and 15-HC (a derivative of cholesterol) are elevated in patients with multiple sclerosis (Farez et al., 2009; Malhotra et al., 2015), which could be the potential DAMPs contributing to inflammasome activation in multiple sclerosis. Uncertainty regarding the impact of inflammasomes on multiple sclerosis is derived from the dichotomy of effects mediated by inflammasome activation within the CNS versus inflammasomes’ effects on circulating (and infiltrating) leucocytes implicated in multiple sclerosis pathogenesis.

**Neuropathic pain**

Neuropathic pain is an increasingly understood syndrome in terms of its molecular determinants and is caused by injury to the CNS or peripheral nervous system. Microglial activation within the spinal cord participates in the pathogenesis of neuropathic pain, usually in association with cytokine production (Ellis and Bennett, 2013). NLRP1 and caspase-1 activation are also features of neuropathic pain but as an analgesic effect, directly mediated by NLRP1 suppression (Li et al., 2013). A mouse model of neuropathic pain displayed elevated IL-18 and inflammasome activation in sciatic nerve tissue at the site of injury (Vasudeva et al., 2015). Interestingly, NLRP3 inflammasome was not involved in the neuropathic pain phenotype as pain-related behaviours were unaffected in NLRP3 deficient mice (Curto-Reyes et al., 2015).

**Neuropsychiatric disorders**

Mood disorders including depression, chronic stress and post-traumatic stress disorder are associated with increased inflammatory markers including IL-1β (Stepteo et al., 2007; Gola et al., 2013). Chronic stress releases DAMPs (Hsp72, uric acid etc.), which activate inflammasomes in the CNS. Patients with major depression exhibited increased NLRP3 and caspase-1 transcripts in PBMCs and IL-1β and IL-18 in serum (Alcocer-Gomez et al., 2014). Caspase-1 deficiency led to reduced stress and abrogated depressive behaviour in mice (Wong et al., 2016). HMGB1 is implicated in stress-induced priming of NLRP3 through TLR signalling (Frank et al., 2015). Elevated ASC transcript expression in PBMCs has been suggested as a marker for depression and a link to neuropsychiatric disorders (Momeni et al., 2016).
Pharmacological modulation of inflammasomes

Existing therapies available clinically are predicated on inhibiting the products of inflammasome activation, for example, inhibiting IL-1β using anti-IL-1β antibodies or recombinant IL-1 receptor antagonists. Effective anti-IL-18 therapies are currently unavailable (Neta et al., 2015). Anakinra is a recombinant IL-1 receptor antagonist that blocks the activity of both IL-1α and IL-1β, with both peripheral and CNS efficacy (Dinarello et al., 2012), and was approved by the U.S. Food and Drug Administration (FDA) in 2001. Improved neuroinflammatory responses to TBI were reported in a phase II clinical trial using anakinra (Helmy et al., 2014). Anakinra has been shown to be safe with limited adverse effects and effective in controlling peripheral inflammation (Galea et al., 2017). Canakinumab, a human monoclonal antibody directed against IL-1β, was approved by the FDA in 2009 and is currently in clinical trials for arthritis (Chakraborty et al., 2013), type 1 diabetes (Howard et al., 2014) and chronic obstructive pulmonary disease (Rogliani et al., 2015). Several small molecules have been identified as inhibitors of inflammasome assembly and activation, thus constituting candidates for clinical testing.

Glyburide

Glyburide is a commonly used drug for treatment of type 2 diabetes. In addition, it was the first compound reported to act upstream of NLRP3, resulting in inhibition of caspase-1 activation, IL-1β secretion and subsequent cell death. However, the inhibitory effect of glyburide on NLRP3 is independent of its action on KATP channels (Lamkanfi et al., 2009). It also inhibits NLRP3 downstream of the P2X7 receptor. Of note, P2X7 receptor signalling leads to ROS-dependent inflammasome activation (Bartlett et al., 2013).

Although glyburide is an oral medication used in the treatment of type 2 diabetes, there is also an intravenous formulation, RP-1127, being tested against TBI and ischaemic stroke for safety and efficacy in preventing haemorrhage and malignant oedema (https://clinicaltrials.gov ID#NCT01794182, NCT01454154, NCT01268683). An intermediate substrate (5-chloro-2-methoxy-N-[2-(4-sulfoamoylphenyl) ethyl] benzamide), free of the cyclohexylurea, was developed (Marchetti et al., 2014). Since cyclohexylurea is indispensable for insulin release, absence of this moiety results in a compound possessing the inhibitory activity against NLRP3 but without effects on insulin release.

VX-765

The pro-drug VX-765 (Vertex Pharmaceuticals) is an orally absorbed compound that is converted to an active metabolite, VRT-043198, by plasma and liver esterases, and is a selective caspase-1 inhibitor. It reduces the production of IL-1β and IL-18 both in vitro and in vivo (Wannamaker et al., 2007), with no adverse effects on cell survival or proliferation when tested in human neuroblastoma cells. In addition, it also reduces peripheral inflammation and disease severity in models of rheumatoid arthritis and skin inflammation (Wannamaker et al., 2007). VX-765 is currently in clinical trials to assess its effects in patients with epilepsy (https://clinicaltrials.gov ID#NCT01501383), which is based on studies showing reduction of seizures in animals by VX-765 (Maroso et al., 2011).

Parthenolide

Parthenolide is a plant lactone extract and acts by directly inhibiting both the protease activity of caspase-1 and ATPase activity of NLRP3. The NF-κB inhibitor, BAY 11-7082, selectively inhibits NLRP3 in a non-NF-κB mediated pathway, whereas parthenolide can inhibit multiple inflammasomes including NLRC4 (Juliana et al., 2010). In a rat model of stroke, parthenolide treatment reduced blood–brain barrier permeability and infarct size along with suppression of caspase-1 expression (Dong et al., 2013).

Cytokine release inhibitory drugs

Cytokine release inhibitory drugs (CRIDs) are a class of sulphonylurea-containing compounds that inhibit post-translational processing of IL-1β. CRID3, a small molecule inhibitor of NLRP3 inhibits caspase-1 activation and IL-1β secretion in response to stimulation of NLRP3 but not AIM2 and NLRC4. CRID3 exerts its effect by inhibiting the formation of ASC complexes, in response to NLRP3 activation (Coll et al., 2011).

Other inflammasome inhibitors

Other inflammasome inhibitors include MCC950, which is a potent and selective inhibitor of NLRP3, but not AIM2, NLRC4 or NLRP1 inflammasomes. It suppresses IL-1β production in vivo, in conjunction with reduction in severity of EAE (Coll et al., 2015). It might be effective in multiple sclerosis and other neuroinflammatory disorders because it is readily absorbed from the gut and can potentially cross the blood–brain barrier. In addition, several inflammasomes (e.g. NLRP1, NLRP3 and NLRC4) can be inhibited by arsenical compounds including sodium arsenite and arsenic trioxide. These compounds modulate the cellular environment, which indirectly inactivates caspase 1 (Maier et al., 2014).

Conclusions and future perspectives

With the growing appreciation of the molecular mechanisms underlying inflammasome activation, multiple drug-susceptible processes have emerged permitting therapeutic interventions, especially at early stages of disease to prevent
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or delay neurological disease progression. Inflammasome activation is essential for host defence against PAMPs and DAMPs; however, prolonged and excessive inflammasome activation can lead to inflammation. Thus, a balanced approach is essential in studying modulation of inflammasomes (Song et al., 2017). Targeting the inflammasome products (IL-1ß and IL-18) is a limited approach and can cause general immune suppression (Jesus and Goldbach-Mansky, 2014). Future investigations are required to develop therapeutic approaches targeting tissue specific inflammasome subtypes compared to the universal inhibition of inflammasome products. Indeed, recently recognized inflammasome-associated caspases (caspases 4 and 5) represent potential therapeutic targets. Novel DAMPs including HMGB1 (Festoff et al., 2016) and defensins (Biragyn et al., 2008) might serve as future neurological biomarkers and therapeutic targets. As new therapies appear targeting the sensor, adaptor and effector components of inflammasomes, the prospect of modulating inflammasome activation at multiple stages is a clinical reality, compared to targeting only the inflammasome products, thus enabling improved outcomes for inflammasome-associated neurological diseases.

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Supplementary material

Supplementary material is available at Brain online.

References


