REVIEW ARTICLE

Therapeutics targeting the inflammasome after central nervous system injury

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Innate immunity is part of the early response of the body to deal with tissue damage and infections. Because of the early nature of the innate immune inflammatory response, this inflammatory reaction represents an attractive option as a therapeutic target. The inflammasome is a component of the innate immune response involved in the activation of caspase 1 and the processing of pro–interleukin 1β. In this article, we discuss the therapeutic potential of the inflammasome after central nervous system (CNS) injury and stroke, as well as the basic knowledge we have gained so far regarding inflammasome activation in the CNS. In addition, we discuss some of the therapies available or under investigation for the treatment of brain injury, spinal cord injury, and stroke. (Translational Research 2015;■:1–11)

Q2 **Abbreviations:** ■■■ = ■■■

INTRODUCTION

Inflammation is a critical response of the immune system to infection and disruption of tissue homeostasis. Generally, the inflammatory response diminishes after removal of the infectious pathogens or after tissue damage has been repaired. However, persistent inflammation may result if the inflammatory inducers are not eliminated, leading to tissue damage and chronic inflammatory disease. Emerging studies have revealed that inflammasome complexes comprising large molecular platforms for caspase 1 activation and downstream inflammatory cytokine production play a critical role in innate immune inflammatory responses and contribute to various pathologies and metabolic dysfunctions. Therefore, an understanding of the mechanisms of inflammasome activation and regulation will aid in the development of novel therapeutics for treating diverse inflammatory diseases associated with persistent inflammasome hyperactivation.

Recent knowledge regarding the inflammasome, its structure, and the different mechanisms of inflammasome activation offer a variety of therapeutic targets to modulate this innate immune complex. In the present review, we cover a brief introduction on the inflammasome and its mechanisms of activation in the central nervous system (CNS). We also discuss current therapies available for the treatment of brain injury, spinal cord injury (SCI), and stroke and describe different therapies that may be used to inhibit inflammasome activation in the CNS after injury.

WHAT IS THE INFLAMMASOME?

The inflammasome is a multiprotein complex involved in the activation of the inflammatory cysteine

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aspartase caspase 1. Once activated, caspase 1 processes the proinflammatory cytokines interleukin (IL)-1β and IL-18.[1] IL-1β and IL-18 belong to the family of IL-1 cytokines and have been shown to play a detrimental role after CNS injury.[2-9]

The inflammasome was first described by Tschopp et al in THP1 cells as a multiprotein complex comprising caspase 1, the adaptor protein apoptosis–associated speck-like protein containing a caspase activating recruitment domain (ASC) and a NOD-like receptor (NLR) such as NLRP1 or NLRP3.[1] Other inflammasome components initially described include caspase 5 in humans and caspase 11 in rodents.[1] However, recent evidence indicates that caspase 11 forms a caspase 1–independent inflammasome, which is referred to as the noncanonical inflammasome.[10] This noncanonical inflammasome is yet to be thoroughly studied in the CNS.

Overall, NLRP3 is the most studied inflammasome. In the CNS the NLRP1, NLR2, and AIM2 inflammasomes have been well characterized after injury to the brain and the spinal cord.[11-14] The NLRP1 inflammasome in the CNS comprises NLRP1, caspase 1, caspase 11, ASC, and the inhibitor of apoptosis protein XIAP.[13] In addition to XIAP, other inhibitor of apoptosis proteins has been described to inhibit inflammasome activation such as cIAP-1 and cIAP-2,[15] but their involvement in CNS inflammasomes is yet to be determined. The NLRP1 inflammasome is present in motor neurons of the spinal cord and in brain cortical neurons.[11-13,16] The NLRP2 inflammasome is present in astrocytes[14] and comprises NLRP2, caspase 1, and ASC.[14] Neurons also express the AIM2 inflammasome, containing AIM2, ASC, and caspase 1. The AIM2 inflammasome is involved in the activation of caspase 1 and the program cell death process of pyroptosis.[11]

Recently, inflammasome activation has been associated with downregulation of TH_2 responses and IL-33 production in a model of house dust mite–induced experimental allergic airway inflammation.[17] In the CNS, IL-33 is present in oligodendrocytes and when secreted it acts on microglia and astrocytes to induce recruitment of monocytes.[18] After injury, IL-33 is responsible for the recruitment of M_2 macrophages.[18] Taken together, it could be hypothesized that after injury there is activation of the inflammasome, which inhibits IL-33 production, resulting in the downregulation of a TH_2 response and decreased recruitment of M_2 macrophages into the tissue, resulting in impaired recovery after CNS injury.

WHAT IS THE MECHANISM OF INFLAMMASOME ACTIVATION IN THE CNS?

There are several mechanisms that have been described regarding inflammasome activation. In general, the innate immune response is activated by danger/damage-associated molecular patterns (DAMPs) or by pathogen-associated molecular patterns (PAMPs) that stimulate pattern recognition receptors (PRRs).[19] PAMPs are proteins derived from pathogens such as bacteria (lipopolysaccharide, flagellin, or muramyl dipeptide) or viruses (double-stranded RNA).[20] In contrast, DAMPs are endogenous proteins that when sensed by PRRs trigger an innate immune response.[19] PRRs include toll-like receptors, rig-like receptors, C-type lectin receptors,[21] or NLRs. NLRs such as NLRP1 or NLRP2 inflammasome components have recently been reviewed elsewhere.[22]

In general, PRRs sense a DAMP or PAMP, resulting in the activation of a PRR, which results in the production of inflammatory cytokines. In the case of the inflammasome, the PRR is an NLR that forms protein-protein interactions with the proinflammatory caspase caspase 1 and with the adaptor protein ASC. Once these proteins associate as a holoenzyme, caspase 1 is cleaved. Once cleaved, caspase 1 has the catalytic activity necessary to process the proinflammatory cytokines pro–IL-1β and pro–IL-18 into their respective active forms.[1]

There are several unanswered questions regarding the activation of the inflammasome. For instance, how does the inflammasome sense DAMPs or PAMPs? Do DAMPs/PAMPs directly bind to NLRs? If there is no direct contact between an NLR and a DAMP/PAMP, what is the upstream signaling event that triggers the oligomerization of the different inflammasome components? How does the upstream activating signal communicate with the inflammasome?

Evidence indicates that inflammasomes composition may vary in different tissues. For instance, the NLRP1 inflammasome in the CNS is a preassembled multiprotein complex.[12,13] However, that is not the case in cells outside the CNS where inflammasome components assemble into a complex on activation.[23] This diversity in inflammasome-activating signaling is consistent with different activating mechanisms that have been described. These mechanisms include potassium efflux[23] and reactive oxygen species,[24] but whether these play a role in the CNS has not been clearly determined. The current accepted mechanism of inflammasome activation in the CNS involves signaling through purinergic receptors and the pannexin 1 channel.[25]

The series of events leading to inflammasome activation in the CNS is as follows (Fig 1): (1) the purinergic receptor P2X4 is activated by ATP that is released from dying cells.[26] (2) Once P2X4 is activated, it causes an efflux in potassium that results in increased extracellular potassium concentration in the vicinity of pannexin 1.[25] (3) The increase in extracellular potassium results in