**Role of the inflammasome in brain pathogenesis: a potential therapeutic target?**

Guest editorial

Delphine Boche and David Brough

The term “inflammasome” was introduced in 2002 by Prof Jurg Tschopp to describe a large multiprotein complex involved in innate immunity and cell death. The inflammasome complex is considered to contribute to the initial host defense against infection by eliminating and exposing the pathogens to the immune system. Several inflammasomes have been identified that all have in common involvement of a sensor, an adaptor and members of the caspase family leading to activation of the pro-inflammatory cytokine interleukins (IL)-1β and IL18 with possible pyroptosis, a lytic mode of cell death observed upon infection with intracellular pathogens.

The host innate immune response to pathogens is triggered via sensors called pattern recognition receptors (PRRs) that sense conserved microbial motifs such as the pathogen-associated molecular patterns (PAMPs), and endogenous danger molecules called damage-associated molecular patterns (DAMPs). PRRs can also be activated by DAMPs in the absence of microbial signals, and the sterile inflammation that ensues either resolves the initial insult or leads to disease.

Since its identification, the inflammasome complex has triggered intense investigation with nearly 5,000 publications available on the subject in the PubMed database to date. Despite this extensive literature, significant questions remain regarding the expression of the inflammasome complex in the brain in physiology and pathological conditions where cell death is associated with inflammation-related processes.

In this mini-symposium for Brain Pathology, we are privileged to have reviews written by international leaders in the field of the inflammasome to provide an update and new insights into its role in varied types of brain pathologies and on the possibilities of manipulating the inflammasome for therapeutic purposes.

In the first review, Delphine Boche and colleagues set the scene in describing the molecular structure and mechanism of activation of the different inflammasomes with a particular focus on inflammasome complexes expressed in humans, highlighting differences in some of the components between humans and mice. Then they describe the location of the inflammasome components identified in human peripheral and brain tissues, and the inflammasome complex



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associated with genetic and acquired inflammatory disorders. Finally, the authors discuss the strengths and weaknesses of the information available on the inflammasome with an emphasis on the importance of studying human tissue.

In the second review, the group led by Stuart Allan discuss the involvement of the inflammasome in stroke, the second leading cause of death worldwide. Focusing on the latest advances in inflammasome research, they describe the time–course of the events that leads to an acute sterile inflammation with a key role for the cytokine IL1. Recent animal studies reported by the authors indicate that inflammasome components are expressed in the hours following the initiation of stroke, highlighting NRLP3 as the most cited sensor molecule in preclinical stroke research. They emphasize the importance of identifying the inflammasome complex formation to analyse its activity and the need for functional readouts. Finally, they suggest a role for self-propagating inflammasomes with the presence of extracellular complexes in the brain following a stroke, potentially driving an acute injury towards a chronic inflammation.

Autoinflammatory diseases are the consequences of immune-mediated inflammation against the self, through innate and adaptive immunity. Excessive inflammasome activation can cause autoinflammatory disorders, such as hereditary periodic fevers. In this review, William Barclay and Mari Shinohara consider in detail the role of the inflammasome in experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis (MS). The authors summarise recent literature and emphasize the role of the NLRP3 inflammasome in the development and progression of EAE. Interestingly, they report inflammasome activation as a contributor to the generation of the pathological $T_H17$ cells, providing a link between the innate and adaptive immunity. They discuss the recent literature on IL1β in EAE and MS before finishing with the effects of interferon (IFN)-β treatment on the inflammasome, supporting components of the complex as potential drug targets in MS.

Alzheimer's disease (AD) is the most common dementia in the elderly population. Recent genetic studies have identified risk factors with innate immunity promoting a role for the brain myeloid cell, the microglia, in the development and progression of the disease.

In his review, Michael Heneka reviews evidence of an inflammasome expression and activation by the peptide Aβ describing experiments in *in vitro* and *in vivo* models of AD. Finally the author report evidence of the role of inflammasome activity in the human disease.

In the final contribution to the mini-symposium, David Brough and colleagues review the role of inflammation in relation with AD pathogenesis, including our knowledge of the inflammasome in AD, with the NRLP3 complex being the most strongly implicated in AD. They discuss the role of IL1β and IL18 in AD pathogenesis and focus the last part of their review on the possibilities of

using the rapidly developing knowledge of the role of the inflammasome in Alzheimer's disease for therapeutic purposes, describing their successful pharmacological manipulation of the NRLP3 inflammasome in an animal model.

One of the points in common between these reviews is the NRLP3 inflammasome being the most studied inflammasome complex in the brain, perhaps due to its broad sensitivity to endogenous stimuli. New information is clearly awaited to better understand the function of inflammasome activation in human brain physiology and pathology, and its potential to be manipulated for therapeutic purposes.



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