Caspase-11 Noncanonical Inflammasome: A Novel Key Player in Murine Models of Neuroinflammation and Multiple Sclerosis

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Keywords

Caspase-11 · Inflammasome · Noncanonical · Neuroinflammation · Multiple sclerosis

Abstract

Inflammasomes are intracellular protein complexes consisting of the pattern recognition receptors and inflammatory molecules in the inflamed cells. In response to various ligands, inflammasomes play a pivotal role to execute the inflammatory responses by inducing the pyroptosis and the secretion of pro-inflammatory cytokines, interleukin (IL)-1 β , and IL-18. Unlike canonical inflammasomes, including NOD-like receptor family inflammasomes, such as NLRP1, NLRP3, NLRC4, and absence in melanoma 2 inflammasomes, noncanonical inflammasomes, such as mouse caspase-11 and human caspase-4/5 were recently discovered, and their roles in the inflammatory responses have been poorly understood. However, emerging studies have been successfully demonstrating the regulatory roles of these noncanonical inflammasomes on inflammatory responses and the pathogenesis of inflammatory/autoimmune diseases. This review summarizes and discusses the recent studies investigating the regulatory roles of the caspase-11 noncanonical inflammasome in neuroinflammation and the pathogenesis of multiple sclerosis (MS), which provides the insight for the validation of caspase-11 noncanonical inflammasome to develop novel and promising therapeutics for MS.

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Introduction

Inflammation is an innate immune response to protect the body by eliminating the invading pathogens and the intracellular danger signals [1, 2]. Inflammatory responses occur by 2 successive steps: the priming and the triggering steps. The priming is the preparatory step of inflammatory responses initiated by the molecular interaction of the extracellular pattern recognition receptors (PRRs) with the pathogen-associated molecular patterns (PAMPs) or the danger-associated molecular patterns (DAMPs), leading to the increase in the expression and production of the inflammatory molecules, such as inflammatory cytokines, enzymes, and mediators [3–5]. On the other hand, the triggering is the promoting step of inflammatory responses induced by the molecular interaction of the intracellular PRRs with various PAMPs and DAMPs, leading to the activation of inflammasomes [2, 6, 7].

Inflammasome is a protein complex consisting of an intracellular PRR and other inflammatory molecules and activated in response to a variety of stimulating ligands [8, 9]. Inflammasome activation induces the proteolytic activation of caspase-1 and gasdermin D (GSDMD), leading to the inflammatory cell death, known as pyroptosis and the proteolytic maturation and secretion of pro-inflammatory cytokines, interleukin (IL)-1 β , and IL-18 [2, 6, 7, 10]. The regulatory roles of canonical inflammasomes, including NOD-like receptor family inflammasomes,

such as NLRP1, NLRP3, NLRC4, and NLRP6 inflammasomes, absence in melanoma 2 inflammasome, and pyrin inflammasome have been intensively demonstrated in the inflammatory responses and the pathogenesis of the inflammatory/autoimmune diseases [6, 11–15]. However, noncanonical inflammasomes, such as murine caspase-11 and human caspase-4/5 inflammasomes were recently discovered [16, 17], and much effort has been made on demonstrating the regulatory roles of the noncanonical inflammasomes, especially caspase-11 noncanonical inflammasome in the inflammatory responses and the pathogenesis of the inflammatory/autoimmune diseases [2, 7, 18–21].

Multiple sclerosis (MS) is a demyelinating inflammatory and autoimmune disease in which the immune system attacks the protective myelin sheath that covers nerve fibers, resulting in communication problems between the brain and the rest of the body and the irreversible damage or deterioration of the nerves. One of the major risk factors of MS is neuroinflammation. Neuroinflammation is a chronic inflammation of the nervous tissues which may be induced by various cues, including infection, toxic metabolites, traumatic brain injury, and autoimmunity [22–25]. Neuroinflammation is characterized by the sustained activation of glial cells, such as microglia, oligodendrocytes (OLGs), and astrocytes, and the recruitment of other circulating immune cells into the central nervous system [26]. The symptoms of MS depend on the severity of nerve damage. The common symptoms of MS include sensory loss, limb weakness, gait ataxia, cognitive dysfunction, and diplopia, and MS patients with severe nerve damage lose the ability to walk independently. The average age of MS diagnosis is approximately 30 years and most of the MS patients present with periodic relapses [27]. Up to date, 15 drugs have been approved by the US Food and Drug Administration to decrease relapses and ameliorate the symptom progression [27]. However, these medications are partly efficacious, and their ability to alter the long-term period of MS still remains unclear [28]. Therefore, the identification and validation of novel targets and new therapeutic strategies to prevent and treat MS are highly demanded. This review summarizes and discusses the general aspects of caspase-11 noncanonical inflammasome and the regulatory roles of the caspase-11 noncanonical inflammasome in the inflammatory responses during MS pathogenesis, which could provide the insight of caspase-11 noncanonical inflammasome as a potential target to develop effective and safe therapeutics to prevent and treat MS.

Structure and Activation of Caspase-11 Noncanonical Inflammasome

Structure of Caspase-11 Noncanonical Inflammasome

Caspase-11 is composed of 3 main domains; an N-terminal caspase recruit domain (CARD), an intermediate p20 domain, and a C-terminal p10 domain (Fig. 1a). Caspase-11 is a mouse protein, and caspase-4 and caspase-5 (Fig. 1a) are identified as human counterparts of mouse caspase-11 [17]. Same with mouse caspase-11, human caspase-4 and caspase-5 also consist of 3 main domains; an N-terminal CARD, an p20 domain, and a C-terminal p10 domain, however, they are different in size; amino acid length of caspase-11, caspase-4, and caspase-5 are 373, 377, and 434, respectively (Fig. 1a). Caspase-11 was demonstrated as direct sensors of intracellular lipopolysaccharide (LPS) internalized from the Gram-negative bacteria through the interaction between the CARD of caspase-11 and the lipid A moiety of LPS to form LPS-caspase-11 complexes (Fig. 1b) [16, 17, 29, 30]. The LPS-caspase-11 complexes are, in turn, oligomerized to form the caspase-4/5/11 noncanonical inflammasomes (Fig. 1c), resulting in the activation of caspase-11 noncanonical inflammasomes and the subsequent caspase-11 noncanonical inflammasome-induced inflammatory responses, which will be discussed in the following chapter.

Caspase-11 Noncanonical Inflammasome-Induced Inflammatory Responses

Since caspase-11 is an intracellular PRR, extracellular LPS originated from Gram-negative bacteria needs to be internalized into the host cells to interact with and activate the caspase-11 noncanonical inflammasome. Gram-negative bacteria generate outer membrane vesicles (OMVs), LPS-containing lipid vesicles budding from the Gram-negative bacterial membrane, and the OMVs enter the host cells via direct membrane fusion or endocytosis [31, 32]. Although OMVs enter the host cells via endocytosis, different mechanisms of endocytosis have been reported. OMVs enter host cells in clathrin-coated pit-dependent or caveolin-dependent manners [32]. OMVs are also internalized into host cells via lipid raft-mediated endocytosis [32]. Extracellular LPS is also internalized via receptor-mediated endocytosis. Extracellular LPS binds with its extracellular Toll-like receptor 4 (TLR4) with help from MD2 and CD14, and the TLR4/MD2/CD14/LPS complexes enter the host cells via TLR4-mediated endocytosis [33]. Extracellular LPS also enters host cells via another type of receptor.

Fig. 1. Structure of caspase-11 noncanonical inflammasome. **a** Domain structures of human caspase-4, caspase-5, and mouse caspase-11. Caspase-4/5/11 consists of 3 main domains: an N-terminal CARD, an intermediate p20, and a C-terminal p10. The amino acid lengths of caspase-4/5/11 are 377, 434, and 373, respectively. **b** Mouse caspase-11 (also human caspase-4/5) directly interacts with iLPS through their CARD and the lipid A moiety of LPS.

c After direct interaction between caspase-4/5/11 and LPS, LPS-caspase-4/5/11 complexes are oligomerized through their CARDs to form the caspase-4/5/11 noncanonical inflammasomes, leading to the activation of the caspase-4/5/11 noncanonical inflammasomes. CARD, caspase recruitment domain; LPS, lipopolysaccharide.

Extracellular LPS binds with hepatocyte-related high-mobility group (HMGB1), followed by the interaction with the receptor for advanced glycation end-product (RAGE) to form RAGE/HMGB1/LPS complexes, and the RAGE/HMGB1/LPS complexes enter the host cells via RAGE-mediated endocytosis [19]. Regardless of the ways of LPS internalization, LPS is encapsulated in the endosomes after internalization, therefore, the biological process is required for the cytosolic release of LPS from the endosomes and the subsequent interaction with caspase-11. Interestingly, guanylate-binding proteins, GTPase family members have been demonstrated to disrupt endosomes by changing endosomal membrane integrity, resulting in the cytosolic release and access of LPS to caspase-11 [34, 35].

Once LPS is internalized, as discussed earlier, caspase-11 directly interacts with the intracellular LPS to form an active caspase-11 noncanonical inflammasome via oligomerization of LPS-caspase-11 complexes, leading to the induction of inflammatory responses in the inflamed cells, such as macrophages. Activation of caspase-11 noncanonical inflammasome cleaves the full-length

GSDMD to produce the N- and C-terminal fragments of GSDMD, and the N-terminal fragments of GSDMD move to the cell membrane and generate the pores on the cell membrane, resulting in the pyroptosis [2, 7, 18, 19]. Activation of caspase-11 noncanonical inflammasome also induces the proteolytic activation of caspase-1, a downstream effector molecule, leading to the caspase-1-mediated proteolytic maturation and secretion of pro-inflammatory cytokines, IL-1 β , and IL-18 through the GSDMD pores [2, 7, 18, 19].

Recent studies have demonstrated the functional cooperation between caspase-11 noncanonical and NLRP3 canonical inflammasomes to induce caspase-1 activation and caspase-1-mediated inflammatory responses. Caspase-11 noncanonical inflammasome induces K⁺ efflux, an essential step for NLRP3 inflammasome activation through the cell membrane damage and the membrane pores generated by bacterial pore-forming toxins, P2X₇, and GSDMD, leading to the activation of NLRP3 inflammasome [21, 36–38]. Despite these studies, the molecular mechanisms by which the caspase-11 noncanonical inflammasome activates the NLRP3 inflammasome are still

largely unknown, and further studies investigating the functional cooperation between noncanonical and canonical inflammasomes during inflammatory responses are highly required.

As described earlier, caspase-11 is only found in mice, and the research efforts have identified caspase-4 and caspase-5 are human homologs of mouse caspase-11 [17], therefore, the studies investigated whether human caspase-4 and caspase-5 form noncanonical inflammasomes in response to intracellular LPS derived from Gram-negative bacteria and activate inflammatory responses. Several studies have successfully demonstrated that caspase-4 and caspase-5 directly interact with intracellular LPS and form caspase-4/5 noncanonical inflammasomes [17, 39–41]. Similar to caspase-11 noncanonical inflammasome, caspase-4/5 inflammasomes can induce pyroptosis by generating GSDMD pores in membranes and the secretion of mature IL-1 β and IL-18 by activating caspase-1 [17, 39–42]. Interestingly, the functional cross talk between caspase-4 noncanonical and NLRP3 canonical inflammasomes was also reported. Caspase-4 noncanonical inflammasome, like caspase-11 noncanonical inflammasome, activates NLRP3 canonical inflammasome by promoting K⁺ efflux, resulting in GSDMD-mediated pyroptosis and caspase-1-mediated maturation and secretion of IL-1 β [43].

Regulatory Roles of the Caspase-11 Noncanonical Inflammasome in MS

Caspases are key players for the induction of the inflammatory responses, therefore, a large number of studies have focused on the regulatory roles of the canonical inflammasomes, especially, NLRP3 inflammasome for the pathogenesis of inflammatory and autoimmune diseases. Despite the smaller numbers of studies, the regulatory roles of caspase-11 noncanonical inflammasome on the pathogenesis of inflammatory and autoimmune diseases have been actively investigated, as well. Of the inflammatory and autoimmune diseases, MS has been focused since MS is a rare inflammatory and autoimmune disease with limited numbers of FDA-approved therapeutic drugs. Recently, anti-MS drugs are actively under development, and previous studies have demonstrated the regulatory roles of the caspase-11 noncanonical inflammasome in MS pathogenesis.

OLGs are a type of neuroglia to provide support and insulation to the axon in the central nervous system, and

the massive death of OLGs is observed during MS pathogenesis [44–47]. Miura investigated the role of caspase-11 in the tumor necrosis factor- α (TNF- α)-induced OLG deaths, and the results revealed that both caspase-11 and caspase-1 were activated in the TNF- α -induced OLG death [48]. Interestingly, TNF- α -induced OLG death was reduced by the inhibition of caspase-1 by its specific inhibitors and in the caspase-11-deficient mice [48]. A similar study was also reported by another research group. Hisahara et al. [49] reported that caspase-11 and caspase-1 are actively involved in the TNF- α -induced OLG death, and OLGs from the caspase-11-deficient mice showed the resistance to TNF- α -induced OLG death. These results indicate that caspase-11 plays a critical role in TNF- α -induced OLG death which is a major risk factor for MS pathogenesis.

The regulatory role of caspase-11 in MS pathogenesis was further investigated in OLGs and the experimental autoimmune encephalomyelitis (EAE), an animal model of MS. Hisahara et al. [50] demonstrated that caspase-11 was expressed in the OLGs of the spinal cord in the EAE lesions, and the OLGs isolated from the caspase-11-deficient mice were resistant to the cytotoxic cytokine-induced cell death. Moreover, EAE symptoms and inflammatory cytokine levels in the central nervous system were markedly decreased in the caspase-11-deficient mice [50]. Interestingly, a previous study suggested that the substrate specificity of caspase-11 is similar to that of caspase-9 [51], indicating that caspase-11 might process and activate caspase-3 and functionally cooperate with caspase-3 in pathological conditions. As expected, caspase-11 and activated caspase-3 were both expressed and co-localized in the OLGs in spinal cord EAE lesions [50], strongly suggesting that caspase-11 cooperating with caspase-3 plays a critical role in MS pathogenesis by inducing OLG death and demyelination.

Myeloid dendritic cells (DCs) are activated by cytokine-induced maturation, and the mature DCs are considered critical players to induce inflammatory responses. Hence, the regulatory role of caspase-11 in MS pathogenesis was explored in the mature DCs. Interferon- β (IFN- β) plays a pivotal role to reduce the relapse rate and the disease symptoms of MS [52]. Moreover, IFN- β administration showed a beneficial effect in EAE mice, and the EAE symptoms were significantly exacerbated in the IFN- β -deficient mice [53]. Despite the beneficial effect of IFN- β in the MS/EAE pathogenesis, the underlying molecular and cellular mechanisms have not been elucidated. Interestingly, Yen et al. [54] investigated the role of caspase-11

in MS pathogenesis in IFN- β -stimulated mature DCs. They demonstrated that IFN- β induced the apoptosis of mature, but not immature DCs by increasing the caspase-11 expression, and the increased expression of caspase-11 was mediated by the binding of NF- κ B and STAT-1 to the corresponding caspase-11 promoter regions. In addition, the expression of caspase-11 and IFN- β was significantly increased in the splenic DCs of the LPS-administered mice [54]. Moreover, the death of mature DCs induced by IFN- β or LPS was significantly inhibited in caspase-11^{-/-} mice [54]. These results strongly suggest that IFN- β -suppressed MS pathogenesis by depleting the mature and activated DCs is mediated by the increase in the caspase-11 expression in the mature DCs, and caspase-11 plays a pivotal role to ameliorate MS pathogenesis.

Microglia and astrocytes are critical players in neuroinflammation, a major risk factor for MS pathogenesis, and the regulatory role of caspase-11 in MS pathogenesis was also investigated in the lysophosphatidylcholine (LPC)-stimulated microglia and astrocytes and the cuprizone mouse model exhibiting the microglial accumulation, astrogliosis, and demyelination [55]. Freeman et al. [56] demonstrated that LPC stimulated the activation of canonical inflammasomes, such as NLRP3 and NLRC4, but not caspase-11 in microglia and astrocytes. Moreover, the cuprizone mouse model lacking both NLRP3 and NLRC4 genes, but not the caspase-11 gene showed decreased astrogliosis and microglial accumulation [56]. These results are unexpected and interesting since previous studies discussed earlier clearly showed that caspase-11 is actively involved in MS pathogenesis [48–50, 54]. The reason why caspase-11 is not activated in the LPC-stimulated microglia and astrocytes is still unclear, however, the possibilities include that molecular mechanisms of neuroinflammation might be different depending on the stimulating agents and the cell types in the central nervous system involved in MS pathogenesis. Studies in this regard need to be further investigated.

Another study also investigated the regulatory role of caspase-11 in neuroinflammation in primary astrocytes, key players for MS progression [57, 58]. Wang et al. [59] induced neuroinflammation in primary astrocytes by stimulating the cells with LPS and demonstrated the expression of caspase-11 in the LPS-stimulated primary astrocytes. Unlike the previous study [56], the level of active caspase-11 was significantly increased in the LPS-stimulated primary astrocytes, and the levels of active caspase-1 and NLRP3 were also increased in

these cells [59], indicating that both caspase-11 noncanonical and NLRP3 canonical inflammasomes are activated in primary astrocytes and induce neuroinflammation during MS pathogenesis. Interestingly, phoenixin-144), a natural pleiotropic anti-inflammatory peptide found in human and mice attenuated the inflammatory responses and reduced the level of active caspase-11, caspase-1, and NLRP3 in the LPS-stimulated primary astrocytes [59], confirming that caspase-11 noncanonical and NLRP3 canonical inflammasomes are key players in MS pathogenesis by inducing neuroinflammation in astrocytes. Although this study demonstrated the role of caspase-11 in astrocyte-mediated neuroinflammation, more direct evidence of the functional relationship between the activation of caspase-11 noncanonical and NLRP3 canonical inflammasomes and MS pathogenesis in animal models and human patients needs to be further elucidated.

The role of caspase-11 in MS pathogenesis was also investigated in the brain and spinal cord tissues of an EAE mouse model. Immunization of myelin OLG glycoprotein_{35–55} (MOG_{35–55}) peptide-induced EAE in mice, and caspase-11 expression in both brain and spinal cord tissues was increased in the EAE mice [60], suggesting that caspase-11 noncanonical inflammasome plays an inflammatory role in MS pathogenesis. Interestingly, inhibition of soluble epoxide hydrolase (sEH) by its potent inhibitor, TPPU significantly reduced the caspase-11 expression induced in EAE mice. Although sEH plays regulatory roles in multiple inflammatory diseases, and sEH inhibition could be a potential treatment of these diseases [61–63], the functional relationship between caspase-11 and sEH in MS pathogenesis is still unclear, and the studies in this regard are further required. Taken together, these studies suggest that the caspase-11 noncanonical inflammasome plays regulatory roles in neuroinflammation and MS pathogenesis as summarized in Table 1.

Conclusion

Inflammasomes are intracellular protein complexes, and their activation in response to various stimulating ligands induces inflammatory responses and pathogenesis of many human inflammatories, autoimmune, and infectious diseases. Although the regulatory roles of canonical inflammasomes, such as NLRP1, NLRP3, NLRC4, NLRP6, absence in melanoma 2, and pyrin inflammasomes have been extensively investigated in inflammatory

Table 1. Summary of studies investigating the regulatory roles of caspase-11 in MS pathogenesis

Study results	Experiment models	Ref.
Caspase-11 was activated in TNF- α -induced OLG death TNF- α -induced OLG death was reduced in caspase-11-deficient mice	TNF- α -stimulated OLGs Caspase-11-deficient mice	[48, 49]
Caspase-11 was expressed in OLGs of spinal cord in EAE lesions OLG death, EAE symptoms, and inflammatory cytokines were reduced in caspase-11-deficient mice	OLGs from caspase-11-deficient mice Caspase-11-deficient EAE mice	[50]
IFN- β induced apoptosis of mature DCs by increasing caspase-11 expression Caspase-11 and IFN- β expression was significantly increased in splenic DCs of LPS-administered mice Death of mature DCs induced by IFN- β or LPS was significantly decreased in caspase-11 ^{-/-} mice	DCs from caspase-11-deficient mice	[54]
LPC did not stimulate caspase-11 activation in microglia and astrocytes Cuprizone mouse model lacking caspase-11 gene did not show decreased astrogliosis and microglial accumulation	LPC-stimulated microglia and astrocytes Cuprizone-administered mice	[56]
Levels of active caspase-11, caspase-1, and NLRP3 were increased in LPS-stimulated primary astrocytes PNX-14 attenuated inflammatory responses and decreased the levels of active caspase-11, caspase-1, and NLRP3 in LPS-stimulated primary astrocytes	LPS-stimulated astrocytes	[59]
Caspase-11 expression was increased in both brain and spinal cord tissues of EAE mice sEH inhibition reduced caspase-11 expression in both brain and spinal cord tissues of EAE mice	Brain and spinal cord tissues from EAE mice	[60]

MS, multiple sclerosis; OLG, oligodendrocyte; LPC, lysophosphatidylcholine; PNX, phoenixin.

responses and many human diseases, noncanonical inflammasomes, including caspase-11 noncanonical inflammasome were recently discovered and have been demonstrated as critical players in inflammatory responses and the pathogenesis of human diseases. Expectedly, the regulatory roles of caspase-11 noncanonical inflammasome have been investigated to play a critical role in the neuroinflammation and MS pathogenesis with the common or unique molecular and cellular mechanisms depending on the PAMPs and DAMPs as well as the cell types, as depicted in Figure 2. Despite these previous successful studies, more efforts need to be made on demonstrating clearer evidence and the underlying molecular mechanisms that caspase-11 noncanonical inflammasome is a key player in neuroinflammation and MS pathogenesis. Further studies investigating the regulatory roles of the caspase-11 noncanonical inflammasome in other types of neuroinflammatory and neurodegenerative diseases are highly demanded, and the functional crosstalk between caspase-11 noncanonical inflammasome and other types of canonical inflammasomes in neuroinflammation and the pathogenesis of neuroinflammatory and

neurodegenerative diseases are also highly demanded. Moreover, the strategies to selectively modulate the activation of caspase-11 noncanonical inflammasome in neuroinflammation need to be investigated to treat neuroinflammatory and neurodegenerative diseases. Finally, the clinically relevant impact of the studies discussed in this review surely needs to be evaluated. Unfortunately, no study investigating the roles of human caspase-4/5 noncanonical inflammasomes in human MS patients has been reported, so far. However, given the evidence from the studies discussed in this review, the activation of human caspase-4/5 inflammasomes might also play a key role in neuroinflammation and pathogenesis of MS, therefore, developing the agents that cross the blood-brain barrier and selectively inhibit the activation of caspase-4/5 inflammasomes could be potential therapeutics of MS. Additionally, since activated caspase-4/5 inflammasomes are processed and secreted from the cells, detecting and examining the serum levels of caspase-4/5 inflammasomes could be helpful to diagnose MS as well as to evaluate the severity of neuroinflammation and MS degree in human patients. In conclusion, caspase-11 nonca-

Fig. 2. Regulatory roles of the caspase-11 noncanonical inflammasome in MS pathogenesis. Caspase-11 is activated in both OLGs and astrocytes stimulated with TNF- α and LPS, respectively. Caspase-11 expression is upregulated in the OLGs as well as brain and spinal cord tissues in EAE mice. Caspase-11 expression is also upregulated in the DCs stimulated with IFN- β or isolated from the LPS-injected mice. Activation and upregulation of caspase-11 in the TNF- α -stimulated OLGs, OLGs, brain, and spinal cord tissues

from EAE mice induce neuroinflammation and demyelination, leading to MS pathogenesis. However, IFN- β and LPS increase caspase-11 expression in mature DCs and induce DC death, leading to the inhibition of mature DC-mediated neuroinflammation and MS pathogenesis. OLG, oligodendrocyte; TNF- α , tumor necrosis factor- α ; LPS, lipopolysaccharide; EAE, experimental autoimmune encephalomyelitis; DC, dendritic cell; MS, multiple sclerosis.

noncanonical inflammasome is a critical player in neuroinflammation and a novel molecular target that has the potential for developing effective therapeutics to prevent and treat MS as well as possibly the other neuroinflammatory, neurodegenerative, and infectious diseases.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

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Author Contributions

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