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Review Article

NLRP3 Inflammasome and Alzheimer's Disease

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Abstract

NLRP3 inflammasome is an important part of the innate immune system and mediates inflammatory responses and pyroptosis. A two-signal model of NLRP3 inflammasome activation has been proposed. Ionic flux, lysosomal damage, reactive oxygen species and mitochondrial dysfunction have been shown to activate the NLRP3 inflammasome. The regulating mechanism of the NLRP3 inflammasome include post-translational modifications of NLRP3 and interacting partners. Recently, Nek7 has been identified as a critical NLRP3 regulator. NLRP3 inflammasome is closely related to the occurrence and development of neuroinflammation in Alzheimer's disease. NLRP3 inflammasome is closely related to the occurrence and development of Alzheimer's disease neuroinflammation and is considered as a new target for the treatment of Alzheimer's disease.

Keywords: NLRP3 inflammasome; Alzheimer's disease

Abbreviations

PRRs: Pattern-recognition receptors
PAMP: Pathogen-associated molecular pattern
DAMP: Damage-associated molecular pattern
NLRNOD: Like receptor
ASC: Apoptosis-associated speck-like protein contain a CARD
AIM2: Absent-in-melanoma 2
GSDMD: Gasdermin-D
TLRs: Toll-like receptors
ROS: Reactive oxygen species
P2X7P2X: Ligand-gated ion channel 7
TXNIP: Thioredoxin-interacting protein
TRX: Thioredoxin
NOX2: NADPH oxidase 2
NOX4: NADPH oxidase 4
CPT1: Acarnitine palmitoyltransferase 1A
MAM: Mitochondrial binding endoplasmic reticulum membrane
MAVS: Mitochondrial antiviral-signaling protein
PKR: Double-stranded RNA dependent protein kinase
GBP5: Guanylate binding protein 5
AP2: Aminopurine
NIMA: Never-in-mitosis A
shRNA: Short hairpin RNA
DAPPDN: N′-diacetyl-p-phenylenediamine

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Introduction

Alzheimer's Disease (AD) is the main cause of dementia and constitutes a major public health problem as the world's population is aging. At present, the etiology and pathogenesis of AD are still not very clear, and there is no specific treatment for AD. Recent studies have shown that persistent inflammation plays an important role in the pathophysiological mechanism of AD. NLRP3 Inflammasome plays a critical role in the inflammatory response in AD. In this article, we reviewed the mechanisms of NLRP3 inflammasome activation and regulation, and progress in targeting NLRP3 in the AD therapy.

NLRP3 Inflammasome

Pattern-recognition receptors (PRRs) is a specific protein in innate immune system that recognizes foreign stimuli and feels damage from the internal body [1]. PRRs recognize specific microbial components which is named pathogen-associated molecular pattern (PAMP) or damage associated molecular pattern (DAMP). NOD-like receptor (NLR) is an intracellular PRR which can recruit pro-caspase-1, the precursor of caspase-1, directly or through apoptosis-associated speck-like protein contain a CARD (ASC), and then forms a protein complex called the inflammasome. NLR family members NLRP1, NLRP3 and NLRC4 have been confirmed to form inflammasomes as well as absent-in-melanoma 2 (AIM2) and pyrin [2,3]. The NLRP3 inflammasome has been the most intensively investigated inflammasome in the past decade. The assembly of inflammasome can activate pro-caspase-1 and produce caspase-1 with enzymatic activity, which further processes the precursors of the inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL -18) into mature IL-1β and IL -18. These cytokines are secreted extracellularly, and finally play a proinflammatory role. NLRP3 inflammasome also mediates a caspase-1 dependent cell death which is called pyroptosis. Gasdermin-D (GSDMD) protein is the executor of pyroptosis. Activated Caspase-1 specifically cleaved GSDMD into the N-terminal domain and the C-terminal domain. The lipophilic GSDMD-N-terminal domain forms oligomers and result in the occurrence of cell pyrolysis [4].

Activation of NLRP3 Inflammasome

It has been suggested that NLRP3 inflammasome activation requires two signals: priming and activation. Priming signal conferred

by stimulation such as ligands for toll-like receptors (TLRs) activates NF-κB pathway which then upregulates the expression of NLRP3 and pro-IL-1β [5,6]. Following the priming step, a lot of stimuli including ATP, K^+ ionophores [7], particulate matter [8,9], pathogen-associated RNA [10] can active NLRP3. Activation of NLRP3 induces multiple molecular and cellular signaling events including ionic flux, mitochondrial dysfunction and the production of reactive oxygen species (ROS), and lysosomal damage, which have been shown to activate the NLRP3 inflammasome.

NLRP3 stimuli induce ionic flux events including K^+ efflux, Ca^{2+} mobilization, Na^+ influx and Cl^- efflux. High concentration of ATP released during cell injury or necrosis can bind to purine receptor P2X ligand-gated ion channel 7(P2X7), leading to rapid outflow of potassium (K^+) and activation of NLRP3 inflammasome [11]. Recent studies have found that several small chemical compounds, including imiquimod, GB111-NH2, and CL097 were able to activate NLRP3 independently of potassium efflux [12,13]. Some studies suggest Ca^{2+} mobilization were involved in NLRP3 inflammasome activation, but how the increase in cytosolic Ca^{2+} promotes NLRP3 inflammasome activation remains unclear [14,15]. One study suggests that increase of Ca^{2+} can promote interaction between NLRP3 and ASC in cell lysates of macrophages thereby directly regulates NLRP3 inflammasome activation [16]. Most studie suggest Ca^{2+} mobilization might not be essential for NLRP3 inflammasome activation [17]. Na^+ influx and Cl^- efflux play a regulatory role in NLRP3 inflammasome activation related to the potassium ion flow. Some PAMPs, such as larger particles, crystals or living pathogens, can destabilize the phagocytes and disrupt lysosomal membranes, leading to the release of cathepsin B into the cytoplasm and the activation of NLRP3 inflammasomes [18]. However, after inhibiting acid-dependent lysosomal proteases with proton pump inhibitors, the activation of NLRP3 inflammatome induced by crystallization was almost completely inhibited, confirming the important role of lysosomal injury in the activation of NLRP3 inflammatome. Lysosomal rupture leads to release of several components such as cathepsin G, cathepsin B and then activates the NLRP3 inflammasome [19].

ROS is considered to be a common signal of activation of NLRP3 inflammosome. Thioredoxin-interacting protein (TXNIP) is a ligand for NLRP3 and is sensitive to ROS. Under normal physiological conditions, the oxidoreductase thioredoxin (TRX) binds to TXNIP and inhibits its activity; when the intracellular ROS concentration increases, the complex dissociates, TXNIP and NLRP3 (mainly LRRs domains) combined to activate NLRP3 [20]. Recently, a study showed that the deletion of superoxide generating NADPH oxidase 2 (NOX2) reduces the expression of NLRP3 in a model of traumatic brain injury, which disrupts NLRP3-TXNIP interaction in the cerebral cortex of mice after ischemic stroke, but not in umbilical vein endothelial cells, suggesting that role of ROS in activation of NLRP3 inflammasome have tissue specificity [21]. Another reseach found that NADPH oxidase 4 (NOX4) could regulate carnitine palmitoyltransferase 1A (CPT1A) and cause increased fatty acid oxidation, which contributes to NLRP3 inflammasome activation [22]. Lysosomal NADPH oxidase was originally thought to be the source of ROS production. But In human peripheral blood monocytes and mouse macrophages that lack NADPH oxidase activity, NLRP3 inflammatory bodies can still be activated normally [23]. Mitochondria are thought to be involved in inflammasome activation as an important source of ROS and interaction with the components of the NLRP3 inflammasome. Research suggests mitochondrial dysfunction and mtROS production are dispensable in NLRP3 inflammasome activation [24]. NLRP3 inflammasome mediated IL-1β secretion is affected by cytoplasmic and mitochondrial ROS levels and mitochondrial function [25]. A reaserch fiound that mtROS can stimulate the relocation of NLRP3 from the endoplasmic reticulum to the mitochondrial binding endoplasmic reticulum membrane (MAM). At the same time, ASC is also recruited from the cytoplasm to the MAM, and it is sequentially combined with NLRP3 and pro-caspase-1 to assemble the NLRP3 Inflammasome [26]. Some research found oxidized mtDNA is required for NLRP3 inflammasome activation [27]. Besides the generation of mtROS and mtDNA, some mitochondrial molecules are associated with NLRP3, such as mitochondrial antiviral-signaling protein (MAVS),mitofusin 2 and cardiolipin [28,29]. Taken together, mitochondrial function plays an important role in the activation of NLRP3 inflammasome.

Regulation of NLRP3 Inflammasome

NLRP3 inflammasome activation is regulated by several mechanisms. Post-translational modifications of NLRP3 have been identified in regulating NLRP3 such as ubiquitination and phosphorylation. Some NLRP3 Interacting partners, have been reported to regulate the NLRP3 inflammasome, including double-stranded RNA dependent protein kinase (PKR), guanylate binding protein 5 (GBP5), and Nek7.

PKR regulates the activation of all known inflammasome, including NLRP3. It has been evidenced that the activation of Caspase-1 and the secretion of IL-1β and IL-18 were significantly inhibited in in macrophages extracted from PKR-deficient mice; and PKR inhibitor 2-aminopurine (2-AP) could inhibit the activation of Caspase-1 and the production of IL-1β in macrophages derived from wild-type mice [30]. However, the results were not consistent as another study suggested that PKR was not necessary for the activation of inflammasomes, the activation of Caspase-1, the lysis of pro-IL-1β, and the secretion of IL-1β [31]. The role of GBP5 in the activation of NLRP3 inflammasomes is also controversial. When stimulated by ATP, nigericin and bacteria, GBP5 promotes the activation of NLRP3 inflammasome but this effect had not been observed when NLRP3 stimulated by insoluble particulate matter such as MSU or alum [32]. Unlike PKR and GBK5, three research groups have independently found that Nek7 was a critical regulator for NLRP3 inflammasome activation. Nek7 belongs to the NIMA (never-in-mitosis A)-related kinase family and is mainly involved in regulating the mitotic process and DNA damage response. Studies have shown that mice with defects in Nek7 died later in their embryonic development and their growth was blocked, indicating that Nek7 might play a pivotal role in embryo growth and survival [33]. Related studies have suggested that Nek7 was dispensable for NLRP3 inflamasome activation by all kinds of stimuli (including ATP, nigericin, MSU crystals, and alum), while it was not a necessity in the activation of NLRP4 and AIM2 inflammasome [34-36]. The catalytic region of Nek7 binds to the LRR domain of NLRP3 to form a NLRP3-NEK7 macromolecular complex, which is enhanced by NLRP3 agonists. Nek7 can regulate the oligomerization of NLRP3, ASC Speck formation and caspase-1 activation downstream of K^+ outflow. Compared with wild-type mice, Nek7-deficient mice have reduced IL-1β secretion, weakened immune cell aggregation, and reduced disease severity, suggesting the important role of Nek7 in NLRP3 activation in in vivo models [34,35]. However, more researches are needed to determine the mechanism by which Nek7 regulates NLRP3 inflammasome activation.

NLRP3 Inflammasome and Alzheimer's Disease

Microglia play an important role in Aβ clearance and neuroinflammatory response, and microglia-mediated inflammation has been a focus of AD researches. Recent studies have found that microglia can express NLRP3, ASC and Caspase-1 [37]. Researchers first reported in 2008 that NLRP3 inflammasomes were activated after incubating primary microglia in mice with Aβ, and microglia phagocytosis of fibrotic Aβ resulted in lysosome rupture to promote the secretion of inflammatory cytokines including IL-1 [38], which could has been proved to activate NLRP3 inflammasome [39]. NLRP3 inflammasome activation can promote Aβ deposition and the pathological process of AD in the brains of APP/PS1 transgenic mice, while NLRP3 or Caspase-1 gene knockout can regulate the microglia phenotype of APP/PS1 transgenic mice, enhance their phagocytic ability, and improve Aβ deposition and behavioral abnormalities; Specifically knockdown of NLRP3 or Caspase-1 in microglia transformed microglia into the M2 phenotype, presenting as an increased clearance and spatial memory [40]. Systemic inflammation reduced microglial clearance of Aβ in APP/PS1 mice through NLRP3 inflammasome and NLRP3 inflammasome knockout blocked microglial changes upon lipopolysaccharide, including alterations in microglial morphology and amyloid pathology [41]. Intrahippocampal injection of ASC specks resulted in spreading of Aβ pathology in transgenic double-mutant APP/PS1 mice, supporting the concept that inflammasome activation is connected to seeding and spreading of Aβ pathology in patients with Alzheimer's disease [42]. NLRP3 inflammasome can be activated not only by fibrillar Aβ aggregates, but also by lower molecular weight Aβ oligomers and protofibrils. Besides Aβ pathology, tau protein has been shown to activate the NLRP3 inflammasome in microglia and its oligomerization was exacerbated by ASC similar to Aβ plaques [43]. Another study showed that loss of NLRP3 inflammasome function reduced tau hyperphosphorylation and aggregation by regulating tau kinases and phosphatases. Tau activated the NLRP3 inflammasome and intracerebral injection of fibrillar amyloid-beta-containing brain homogenates induced tau pathology in an NLRP3-dependent manner [44].

Further studies have shown that Aβ can induce cortical neuron pyrolysis, and Caspase-1 short hairpin RNA (shRNA) has the effect of reducing neuropyrolysis in brain tissue of APP/PS1 transgenic mice and improving behavioral abnormalities [45]. NLRP3 inflammasome Inhibitor can reduce the microglia pyrolysis of APP/PS-1 transgenic mouse and promote Aβ clearance. A recently study found that $A\beta_{1-42}$ could induce pyrolysis by GSDMD protein, and NLRP3-caspase-1 signaling pathway was important to initiate GSDMD cleavage, which plays an important role in $A\beta_{1-42}$-induced pyrolysis in neurons [46]. These studies suggested that the pyrolysis mediated by inflammasome may be involved in the pathogenesis of AD.

Due to the important role of NLRP3 inflammasome in AD, progresses have been made in the development of therapeutics that target the NLRP3 inflammasome and its associated pathways. So far, several specific NLRP3 inflammasome inhibitors have been confirmed, including MCC950, JC-124, CY-09, OLT1177, Tranilast and Oridonin, some of which been found to help ameliorate AD pathology in animal experiments. MCC950 was proved to reduce the accumulation of Aβ in the brain tissue of APP/PS1 transgenic mice and improve their behavioral abnormalities [47]. JC-124 was found to ameliorate Aβ deposition and reduce the level of $A\beta_{1-42}$ in the brain of CRND8 mice which was accompanied by reduced β-cleavage of APP, reduced activation of microglia but enhanced astrocytosis [48]. Oridonin can inhibit glial activation, decrease the release of inflammatory cytokines, inhibit NF-κB pathway and $A\beta_{1-42}$-induced apoptosis in the hippocampus of AD mice model [49]. A study found that a small synthetic molecule N,N′-diacetyl-p-phenylenediamine(DAPPD) , was able to promote the phagocytic aptitude of microglia and subsequently ameliorate cognitive defects by suppressing the expression of NLRP3 inflammasome- associated proteins through its impact on the NF-κB pathway [50].

Some drugs, which have been shown to inhibit the NLRP3 inflammasome, are found to play a protective role in AD. Edaravone, a commonly used drug ischemic cerebrovascular disease, has been proved to attenuates the proinflammatory response in Aβ-treated microglia by inhibiting NLRP3 Inflammasome-mediated IL-1β secretion [51]. Another drug used for ischemic cerebrovascular disease, Dl-3-n-butylphthalideis, has also been found to exert protective effect in APP/PS1 transgenic mice by inhibiting the activation of NLRP3 inflammasome [52]. Progesterone, a neuroactive steroids, can significantly inhibit Aβ-induced NLRP3-Caspase-1 inflammasome activation and play a protective role in AD [53]. Choline supplementation could improve behavioral deficits and pathology in APP/PS1 mice through inhibition of NLRP3 inflammasome activation and restoration of synapse membrane formation [54]. Artemisinin inhibits the activation of NF-κB and NLRP3 inflammasome and reduces Aβ deposition in the brain tissue and neuroinflammation of APP/PS1 transgenic mice [55]. A recently study found gut microbiota in AD patients could induce the activation of NLRP3 inflammasome in the intestinal tract of mice, which could causing the subsequently release of inflammatory factors. The inflammatory factors could further aggravate the inflammation in the nervous tissue and activation of microglia through the intestinal tract. This study suggested a novel idea of AD treatment by improving the composition of gut microbiota [56].

Concluding Remarks

NLRP3 inflammasome plays an important role in the neuroinflammatory response associated with AD. Although the NLRP3 inflammasome has been the most intensively investigated inflammasome in the past decade, a unified mechanism for NLRP3 inflammasome activation has not been determined. Recently, Nek7 is identified as a critical NLRP3 regulator. Regardless of the complexity of the pathway, many molecules and drugs targeting the NLRP3 inflammasome have been discovered, providing a new direction for the treatment of AD. The activation/inhibition mechanism of NLRP3 inflammasome and its regulation of the functional state of brain microglia and the pathophysiological process of Alzheimer's disease remain to be further studied. Further clinical trials are necessary to confirm the role of NLRP3 inhibitors in AD.Research on the neuroinflammation mechanism in AD is beneficial to the prevention, treatment and management of AD patients [57].

Author Contributions

Xie Zhaohong and Xu Feng conceived the review; Li Fan and Jin Suqin discussed and contributed to the writing of this review.

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