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Review

Activation mechanism of NLRP3 inflammasome and its role in the pathogenesis of Alzheimer's disease

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ABSTRACT

Nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) is an important pattern recognition receptor in human innate immunity. The inflammasome with NLRP3 as its main component plays an important role in the course of Alzheimer's disease (AD). The theory for explaining activation of NLRP3 inflammasome has reactive oxygen species theory, lysosomal damage theory and mitochondrial DNA theory. Activation of NLRP3 contributes to the pathogenesis of AD by producing IL-1β, IL-18 and other cytokines, and maybe affecting the deposition of Aβ and tau proteins. It may provide new clues for the prevention and treatment of AD by clarifying the molecular mechanism of NLRP3 inflammasome activation and exploring how these changes promote the pathological formation of AD.

KEYWORDS: Alzheimer's disease; Inflammasome; Activation; Pathogenesis; Nucleotide-binding oligomerization domain-like receptor protein 3.

ABBREVIATIONS: NLRP3: Nucleotide-binding oligomerization domain-like receptor protein 3; AD: Alzheimer's disease; Aβ: β-amyloid; IL-1β: Interleukin-1 beta; ROS: Reactive Oxygen Species; NADPH: Nicotinamide Adenine Dinucleotide Phosphate Oxidase; TXNIP: Thioredoxin interacting Protein; GPCRs: G-protein Coupled Receptors; CASRs: Calcium Sensitive Receptors; STAT: Signal Transducers and Activators of Transcription; GMF: Glial Maturation Factor; LTP: Long-Term Potentiation.

INTRODUCTION

Alzheimer's disease (AD) is a common chronic progressive neurodegenerative disease and is one of the most common dementia diseases in the elderly. Patients may have memory loss and cognitive dysfunction in the early stage. Late, they often have difficulties in daily life and occur some mental symptoms.[1] With the increase of the elderly population, the number of AD patients is increasing year by year. According to WHO report, the current treatment and care of AD cost all over the world is more than 81.8 billion U.S. dollars annually.[2] In order to reduce the burden of society and family, it is urgent to explore the pathogenesis of AD and find new ways to treat AD. The pathogenesis of AD is mainly related to the deposition of β-amyloid (Aβ), neurofibrillary tangles caused by microtubule-associated protein phosphorylation and the loss of neurons. In addition, more and more studies have found that the above pathological changes are associated with the innate immune abnormalities in the brain, among them; cerebrovascular injury and neuroinflammatory response play a larger role.[3] Nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) is an important pattern recognition receptor in human innate immunity. The role of the NLRP3-based inflammasome in the pathogenesis of AD has been recently emphasized.

NLRP3 Inflammasome Composition and Structure

Inflammatory bodies, also known as inflammasomes, are a class of multi-protein complexes in-

volved in the assembly of intracytoplasmic pattern recognition receptors that not only recognize foreign pathogenic molecules and the host's own danger signals, but also are capable of recruiting and activating proinflammatory proteasome caspase-1. The activated caspase-1 can enzymolyze and cut the precursor of interleukin-1 beta (IL-1β) and interleukin-18 (IL-18), and produce corresponding mature cytokines.[4] The cell apoptosis dependent on caspase-1 is called pyroptosis and its occurrence is mainly regulated by the inflammasome. There are certainly many inflammasomes involved in the host's defense response against pathogens, and the pathogens have evolved mechanisms to inhibit the activation of the inflammasome.[5] There are four main inflammasome: NLRP3 inflammasome, NLRP1 inflammasome, IPAF inflammasome and AIM2 inflammasome.

NLRP3 inflammasome is a complex composed of NLRP3, ASC and caspase-1 protein, in which NLRP3 plays a dominant role.[6] The NLRP3 protein is a pattern-recognizing NOD-like receptor protein that has a carboxyl-terminal leucine-rich repeat domain but lacks the CARD domain and therefore does not bind directly to the caspase-1 precursor protein but requires heat. The pyrin domain, in combination with ASC, recruits the caspase-1 precursor protein and activates caspase-1. NLRP3 protein and caspase-1 precursor protein binding manner PYD-PYD connection and CARD-CARD bridge way. The caspase-1 precursor protein to form a tetramer self-activation, followed by the formation of enzyme activity of heterodimers. The caspase-1 as an inflammasome effector is capable of cleaving inactive IL-1β precursor protein and IL-18 precursor protein into mature IL-1β and IL-18, respectively, thereby exerting various nonspecific inflammatory reaction.[7]

ASC is an adapter protein for this particular inflammasome with a PYD domain at the amino terminus and a CARD domain at the carboxy terminus; the CARD domain functions as a recruitment effector that matches the CARD domain in the caspase-1 precursor protein Cohesion. NLRP3 protein is widely expressed in immune-related cells such as monocyte-macrophage, neuronal dendritic cells and certain myeloid cells. The abnormality of NLRP3 inflammasome and many refractory diseases, such as diabetes, coronary heart disease, Gout, AD, etc.) have a closer relationship,[8] so to study the activation and function of NLRP3 inflammasome has important clinical significance.

NLRP3 Inflammasome Activation and Regulation

Activation of the NLRP3 inflammasome typically requires two steps: the first is to elicit an inflammatory response and the second is the oligomerization of NLRP3 and the assembly of ASC and caspase-1 precursor proteins.[9] The inflammatory response is usually the result of the deregulation and nuclear translocation of the nuclear transcription factor-kappa B (NF-κB), which leads to the transcription of NLRP3 itself and IL-1β. Many hormone-induced signaling pathways are reduced in the activation of NF-κB. As an early transcription factor, the activation of NF-κB does not require the regulation of new proteins. Yet the stimulation of lipopolysaccharide (LPS) needs to be carried out by toll-like receptor 4/ leukocyte differentiation antigen 14 (TLR4/CD14).

De-ubiquitination of NLRP3 is thought to be dependent on the activity of mitochondrial reactive oxygen species (ROS).[10]

External signal activation NLRP3 inflammasome involves a complex pathophysiology and pharmacological biochemical processes, there are three main theories to explain this activation mechanism.[11] The first theory is that reactive oxygen species theory: the doctrine that ROS is the key mediator of NLRP3 inflammasome regulation of this concentration and catalase or reduced nicotinamide adenine dinucleotide phosphate oxidase (NADPH) high concentration or high expression. The normal body thioredoxin interacting protein (TXNIP) and thioredoxin (TRX) are bound to each other, when certain cell stress to increase ROS, TRX in order to clear the ROS itself Oxidation, TXNIP will be separated from TRX, and then induced TXNIP and NLRP3 binding, which rely on ASC to raise caspase-1 precursor protein, and finally completed the assembly and activation of NLRP3 inflammasome; activators of crystal, high glucose, ATP (Activation signals) usually take this approach to activate the NLRP3 inflammasome.[12] The second theory is lysosomal damage theory: This theory that the phagocytosis of foreign pathogens (PAMP) by macrophages, the phagosome will lose stability, leading to acidosis and rupture of lysosomes, and then cathepsin B Will is released from the lysosome to the cytoplasm. As cathepsin B degrades the NLRP3 inhibitory protein, it activates the NLRP3 inflammasome.[13] The third theory is the theory of mitochondrial DNA: This doctrine that a variety of PAMP and injury-related molecules (DAMP) under certain conditions are likely to attack or destroy mitochondria within the body cells, damaged mitochondria often release mitochondrial deoxy (MtDNA), and mtDNA activates NLRP3 inflammasome by potassium ion outflow or influx of calcium ions, cytotoxins destroy membrane, ATP-binding purinergic receptor P2X7R and microbial toxin intervene mitochondrial micropore structure may promote potassium efflux. Calcium influx may need to be assisted by G-protein coupled receptors (GPCRs), calcium sensitive receptors (CASRs) and pannexin-1 channels.[14]

The activation signal that activates the NLRP3 inflammasome is one or more internal and external activators, including various PAMPs and DAMPs. PAMP that can be perceived by the NLRP3 inflammasome is silica, calcium pyrophosphate, sodium urate, palmitate, cholesterol, Aβ and some viruses, etc. Currently, known to be able to be perceived by the NLRP3 inflammasome DAMP hypokalemia, High calcium, and high glucose, LPS, cathepsin B, ATP and ROS.[15]

Activation of the NLRP3 inflammasome may, to a limited extent, be beneficial to the body; however, over-activation of the inflammasome often compromises the health of the cells and the body. At present, it is also found that there are various mechanisms in the body of cells for the negative regulation of NLRP3 inflammasome activation. This negative regulation may be through receptor binding block mechanism, autophagy mechanism, cytokine mechanism, related gene expression mechanism and play a

role.[16] For example, miR-223 negatively regulates the activation of the NLRP3 inflammasome by inhibiting the expression of the NLRP3 gene at the transcriptional level. T-cells and interferons, through downregulation of P2X7R expression and activation of the signal transducers and activators of transcription (STAT) signaling pathway But inhibits the activation of NLRP3 inflammasome. The increase of autophagy LC3B leads to the decrease of ROS level and thus the activation of NLRP3 inflammasome.[17] The viral hot protein interferes with the binding of ASC and NRLP3 through PYD-PYD mode, Thereby negatively regulating the assembly and activation of the NLRP3 inflammasome. Caspase-12 competes with ASC in the CARD-CARD fashion to negatively regulate the activation of the NLRP3 inflammasome.[18]

The Relationship between the Incidence of AD and NLRP3 Inflammasome

As early as 1989, it has been reported that elevated levels of IL-1β are present in the brains of AD patients and may be the result of some inflammasome activation.[19] Halle et al[20] treated microglia with Aβ and found that the expression of IL-1β was significantly reduced in the treatment group treated with lysosomal inhibitor cytochalasin D or cathepsin B inhibitor, suggesting that Aβ is reduced by lysosomal enzymes. The body rupture pathway activates the NLRP3 inflammasome to induce the high expression of IL-1β, thereby promoting the development and progression of AD. Relaxin D, which inhibits phagocytes, abolishes inflammatory body activation of Aβ fibrils; after their phagocytosis, Aβ fibrils are localized in intracellular lysosomes, impairing the membranes of these lysosomes will result in the release of cathepsin B into the cytosol. Sheedy et al[21] showed intracellular formation and lysosome location of Aβ fibrils after 3 hours of treatment with soluble Aβ, but were unable to determine lysosomal integrity or cathepsin B levels.

NLRP3 activation can promote the pathogenesis of AD through two processes. First, it can regulate the production of IL-1 and neurotoxins which may lead to degeneration of neurons. Second, it reduces the gap between Aβ leading to increased deposition,[22] inducing a self-sustained positive feedback loop that eventually leads to AD progression. Some scholars[23] found in the study that due to the high expression of NLRP3 and caspase-1 genes in the brain of AD patients, it is helpful to the formation of aging lesions in the brain of APP/PS-1 transgenic mice by reducing the expression of Caspase-1 and IL-1β, contribute to the clearance of Aβ. In NLRP3 knockout mice, Aβ deposition decreased and spatial memory was improved; on the other hand, activation of NLRP3 inflammasome could reduce the phagocytosis of Aβ by microglia and increase the deposition of Aβ and promote the progression of AD Occurrence and development.[24] Ahmed ME et al[25] studied the brains of AD patients with age-matched non-AD brains in human autopsy using immunohistochemical techniques to analyze the NLRP3 inflammasome and autophagy-lysosomally labeled A0205 protein, p-tau protein, and glial maturation factor (GMF) and other related components and found that NLRP3 inflammasome-promoted neuroinflammation can be enlarged and regulated by GMF, and further reduce protein aggregates mediated by autophagy pathway Clear. Saresella M et al found[26] evidence of activation of both NLRP3 inflammasomes and NLRP1 inflammasomes in peripheral blood mononuclear cells of patients diagnosed with AD using either LPS or Aβ stimulation, suggesting that peripheral mononuclear cells migration of cells in the blood-brain barrier is likely to be an important factor in the neurogenic inflammation of the AD, and the nucleoside reverse transcriptase inhibitors can inhibit the activation of these inflammatory factors.

The high expression of IL-1β in microglia around Aβ plaques is present in both AD patients and AD animal models. Several studies have found that neuritic plaques secrete neurotoxic factors in AD and recruits microglia to phagocytose Aβ aggregates. The secrete chemical and proinflammatory molecules that further affect the surrounding tissues and amplify the neurotoxic effects of Aβ.[27] Maybe Aβ deposition and inflammasome activation can each other cause and result. Activation of intracellular NLRP3 inflammasome can induce M1-like activation of microglia and lead to increase A [beta] deposition and cognitive impairment in AD mouse models; conversely, in the absence of specific functional disruption of the NLRP3 inflammasome In glia, these cells favor the M2 phenotype, thereby reducing the deposition of extracellular A [beta], protecting neurons from synaptic dysfunction, and reducing brain cognitive decline.[28]

Heneka MT et al[29] found that there is activation of NLRP3 protein in AD patients or AD animal models. This activation helps AD-like pathological changes in APP/PS1 transgenic mice. In order to assess the role of NLRP3 inflammasome in the pathogenesis of AD, the authors used NLRP3 knockout mice to cross with APP/PS1 transgenic mice and found that the hybrid mice lack the cleavage of caspases in their brains whereas Total IL-1β levels were similar to total IL-1β levels in the brains of wild-type mice. Apoptosis-associated speck-like proteins, which are components of the inflammatory corpuscles, were detected by immunohistochemistry in the microglia positive for Iba1 factor-activated microglia from APP/PS1 transgenic mice. This change is consistent with the activation of inflammasomes. The water maze test was used to detect the spatial memory retention capacity of wild-type mice, NLRP3 knockout mice, AD mice and APP/PS1/NLRP3 hybrid knockout mice, and compared with each other. It was found that APP/PS1 mice exhibited out of serious spatial memory formation defects, and APP/PS1/NLRP3 hybrid knockout mice to a large extent prevented the damage of spatial and memory functions significantly reduced. The authors also analyzed the plasticity of synapses in the hippocampus of mice by detecting long-term potentiation (LTP) and found that mice deficient in NLRP3 or caspase-1 completely blocked LTP inhibition. Bai et al found[30] that H_2O_2-induced microglial IL-1β release is dependent on NLRP3 activation. Genetic and pharmacological inhibition of cathepsin B dramatically impaired H^2O^2-induced NLRP3 activation, the processing of pro-caspase-1to caspase 1, IL-1β release and subsequent cell death. Importantly, cathepsin B activity is positively correlated with oxidative stresses and IL-1β levels in plasma of AD patients.

CONCLUSION

In summary, activation of NLRP3 inflammasome may play an important role in promoting the pathogenesis of AD. Aβ and other activation signals activate NLRP3 inflammasome by different ways, which promote neuroinflammation and senile plaque formation. By elucidating the molecular mechanism of NLRP3 inflammasome activation and gaining a deeper understanding of how these changes contribute to pathological abnormalities in AD, we can provide more clues to the therapeutic strategies of AD. Blocking the aggregation of Aβ is still of great value in the prevention and treatment of AD. It is worth exploring a new approach to prevent AD from inhibiting the activation of NLRP3 inflammasome.

COMPETING INTERESTS

The authors declare no competing interests.

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