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REVIEW ARTICLE

Microglial NLRP3 Activity in Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD) is the major disease leading to dementia. This disease is characterized by the presence of β-Amyloid (Aβ) extracellular deposits and neurofibrillary tangles, which induce senile plaques formation. Furthermore, inflammation in AD is mainly mediated by innate immunity-related cells, especially microglia. Recent lines of evidence indicate that inflammatory parameters associated with microglia induce mechanisms of pathogenesis in AD. Although the Nucleotide-Binding Domain and Leucine-Rich Repeat Protein 3 (NLRP3) inflammasome has been reported as an important player in this disease, its activity in the Central Nervous System (CNS) during AD is still poorly understood. In this paper the role of microglial cells and the specific activity of NLRP3 in this cell type during AD are highlighted.

Keywords

Alzheimer's disease, NLRP3, Microglia, Neuroinflammation

Introduction

Alzheimer's Disease (AD) is a disorder leading to dementia, and is one of the greatest public health problems in the 21st century. AD affects more than 25 million individuals worldwide and projections indicate that AD incidence will significantly increase in coming years due to factors such as longer life expectancy and obesity [1]. AD presents multifactorial etiology resulting in progressive cognitive impairment and memory loss [2]. Extracellular deposits of β-Amyloid (Aβ) protein and intracellular neurofibrillary tangles of hyperphosphorylated tau proteins are in the core of AD pathogenesis and induce senile plaque formation [2].

Inflammatory responses are another important aspect associated with AD and it is mainly related to myeloid lineage cells [3]. Unlike other neuroinflammatory diseases, such as Multiple Sclerosis (MS), in which infiltrating T lymphocytes are key players in the Central Nervous System (CNS) inflammation, innate immune response-associated resident cells, including astrocytes and especially microglia, are crucial for the establishment of AD neuroinflammatory parameters [4]. Moreover, inflammasomes are potent innate-associated sensors producing proinflammatory mediators involved in many physiological and pathological events [5-7].

This review outlines the role of microglial cells in the CNS homeostasis as well as in AD pathogenesis. Moreover, this paper reviews aspects associated with inflammatory responses related to NLRP3 inflammasome activity, specifically in microglial cells during AD.

Microglia

Microglia is hematopoietic derived cell related to innate immunity, which are phenotypically defined as CNS resident macrophages [8]. Among various microglial functions, they play a crucial role in CNS surveillance, monitoring brain environment and eliminating undesired substances, such as cell debris, through phagocytosis, and maintaining CNS integrity [8]. Microglial cells are highly sensitive to changes in the CNS homeostasis [8]. Another important role associated with this cell type is antigen presentation through Major Histocompatibility Complex (MHC) class I and II molecules, activating T lymphocytes and influencing adaptive immune response [9]. Additionally, microglia have a role in modulating synaptic activities through bidirectional communication with neurons via distinct receptor types, in-

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Table 1: Findings in animal models and clinical studies concerning NLRP3 activity in AD.

Type of study	Reference	Findings
Animal model	Heneka, et al. [37]	NLRP3$^{-/-}$ and Caspase-1$^{-/-}$ mice are resistant to experimentally developed AD
	Griffin, et al. [28]	IL-1β induces tau protein hyperphosphorylation
	Gustin, et al. [42]	Aβ stimuli activate NLRP3 specifically in microglia
	Wu, et al. [45]	Aβ protofibrils induce NLRP3 activation and IL-1β accumulation in microglia
	Couturier, et al. [38]	ASC$^{-/-}$ mice are resistant to experimentally developed AD
Clinical study	Ojala, et al. [27]	Increase of IL-18 in AD brain
	Heneka, et al. [37]	Increase of Caspase-1 in AD brain
	Griffin, et al. [29]	IL-1β is involved in neuronal damage
	Saresella, et al. [30]	NLRP3 is upregulated in monocytes of severe AD patients
	Dursun, et al. [31]	IL-1β is significantly increased in serum of early-onset AD patients
	Chen, et al. [32]	IL-18 is increased in serum of AD patients

cluding neurotransmitter, adrenergic and dopaminergic receptors [10]. Resting microglia express low levels of CD45, CD40, CD80, MHC I and II, among others. However, after inflammatory stimulus, these cells significantly increase expression of these molecules, as well as their phagocytic capacity and may stimulate lymphocyte proliferation [11]. Importantly, activated microglia also secrete several cytokines and chemokines, immunomodulating other cell types [12,13].

NLRP3 Inflammasome

Microglial and other myeloid lineage cells express innate immune response-related receptors [14-16]. Antigen recognition in innate immune response is mediated by pattern recognition receptors, such as NOD-Like Receptor Family Receptors (NLRs), which recognize Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs) [17]. Inserted in NLR family, inflammasomes are multi-protein complexes formed in the cytosolic compartment of immune cells after stimulation by both PAMPs and DAMPs. The formation of these protein platforms results in caspase-1 activation and cleavage, as well as subsequent activation of proinflammatory cytokines, such as IL-18 and IL-1β [18,19].

Among inflammasomes, Nucleotide-binding domain and Leucine-Rich repeat Protein 3 (NLRP3) is the most well-studied component. While other inflammasome types recognize a limited number of DAMPs or PAMPs, a great variety of signals is able to activate NLRP3, highlighting its importance in the immune response against both endogenous and exogenous stimuli, and increasing its clinical relevance [20]. The microbial stimuli that activate NLRP3 include bacterial RNA, hemozoin crystals derived from *Plasmodium ssp*, viral products, and many others. Endogenous stimuli such as ATP, urate, silica, amyloid protein and cholesterol are some examples of NLRP3 activators [21,22].

Activation of NLRP3 complex is thought to occur in two steps. In the first one, cognate ligands are recognized by innate receptors, such as Toll Like Receptors (TLRs), resulting in translocation of nuclear factor κB (NF-κB) to the nucleus and subsequent induction of *nlrp3*, *pro-il-1β* and *pro-il-18* gene expression. In the second step, different PAMPs and DAMPs may induce NLRP3 machinery oligomerization and activation with recruitment and interaction of Apoptosis-associated Speck-like protein containing a CARD (ASC) and procaspase-1, inducing caspase autocleavage and finally cytokine processing [23]. Some pathways have been described as possible mechanisms for the second step. For example, potassium (K^+) efflux is necessary during inflammasome assembly process. Studies have shown that blocking K^+ efflux in cell culture inhibits NLRP3 activation after stimulation with several agonists [24]. NLRP3 inflammasome activity is a potent inflammatory mechanism involved in the immune response against various microorganisms, such as *Plasmodium spp* and *Toxoplasma gondii* [25,26]. However, deregulated inflammasome activity may result in severe pathological processes due to strong inflammatory response.

Microglia, NLRP3 and Alzheimer

NLRP3 has been linked to pathogenic mechanisms in AD. Table 1 summarizes some important findings in animal models and clinical studies. For example, there is an increased IL-18 level in AD brain patients [27]. Moreover, high levels of IL-1β in the brain induce tau protein hyperphosphorylation in animals [28]. In addition, IL-1β plays an important role in neuronal damage, since this cytokine induces the production of inflammatory factors such as NO (Nitric Oxide) and TNF-α (Tumor Necrosis Factor α) and these molecules promote the transformation of diffuse amyloid plaques into inflammatory plaques, resulting in cortical neuron damage and cerebral atrophy [29].

Studies have shown that NLRP3 activation may also play a role in the periphery during AD. Monocytes from patients with severe AD have significantly greater NLRP3 activation compared to control groups [30]. Moreover, IL-1β levels are significantly increased in patients with early-onset AD [31]. In another study, Chen and coworkers demonstrated that IL-18, IL-23 and IL-17 are increased in the serum of patients with AD compared to age-matched healthy controls [32].

Polymorphisms in *nlrp3* and associated genes have been implicated in AD. Tan and coworkers demonstrate

that 5'-flanking rs2027432 polymorphism is strongly associated with late-onset AD in Chinese population [33]. In a meta-analysis study, Di Bona and coworkers show that the IL1B +3953 TT genotype is associated with increased AD risk, while IL1B -511 TT genotype only increases AD risk in Caucasians [34]. Furthermore, studies demonstrate that mutations in the IL-18 gene are also associated with the development of AD. For example, individuals carrying the CC genotype are at increased risk of developing AD [35]. Additionally, -607 C allele and -137 G allele were implicated in the risk of late-onset AD [36].

Heneka and coworkers recently reported significant increased caspase-1, both in AD human brain and animals that experimentally developed AD [37]. In this study, APP/PS1/NLRP3$^{-/-}$ and APP/PS1/caspase-1$^{-/-}$ mice were highly protected from experimental development of AD, showing reduced neuroinflammation and decreased amyloid burden [37]. Furthermore, ASC$^{-/-}$ mice with AD model reduced amyloid aggregation, increased astrocyte phagocytosis and reduced memory deficits [38]. Together, these findings strongly suggest a role of NLRP3 inflammasomes in AD pathogenesis.

Regarding specific NLRP3 activity in CNS, recent lines of evidence suggest that inflammasome activities in the nervous tissue are important for the pathogenesis of neurodegenerative diseases, such as MS [39-41]. In AD, little is known about NLRP3 activation mechanisms in the CNS during the course of the disease. In experiments using Aβ as NLRP3 stimulus as well as known inflammasome agonists such as ATP and nigericin, Gustin and coworkers indicated that NLRP3 machinery is only present in microglia, at least in some circumstances, and not in astrocytes, reinforcing the crucial role of microglial NLRP3 activity in CNS [42]. However, other studies disagree with these findings and suggest NLRP3 activation in astrocytes after CNS injury. Therefore, further studies are needed to address these issues [43,44].

In primary cultures of microglia, Aβ (1-42) protofibrils induce NLRP3 activation and finally IL-1β accumulation downstream TLR/MyD88 pathway [45]. Additionally, activated microglia surrounding senile plaques in AD brain present high IL-1β production in a Cathepsin B-dependent manner [46].

Autophagy is also an important mechanism for Aβ fibrils degradation and a disability in the autophagy machinery may result in ineffective clearance of misfold proteins, leading to formation of Aβ plaques or neurofibrillary tangles [47]. In microglial cells, Aβ induces autophagy through AMP-Activated Protein Kinase catalytic subunit Alpha 1 (PRKAA1) pathway, inducing autophagy deregulation and NLRP3 inflammasome activation, which suggests that impaired autophagy activity in microglia from AD human brains induces NLRP3-mediated inflammation [48].

Oxidative damage has also been observed in AD patient samples. For example, in postmortem AD brain, there is an increased oxidative damage to DNA compared with age-matched controls [49]. Oxidative damage may modulate NLRP3 inflammasome activation. NLRP3 microglial neurotoxicity mediated by Aβ is associated with Reactive Oxygen Species (ROS) and induces NADPH oxidase-induced ROS production [50]. Aβ peptides induce NADPH oxidase complex activation and stimulate ROS production [51].

NLRP3 Pathway as a Target for AD Treatment

Because of the key role of NLRP3 pathway in AD, the development of therapeutic strategies targeting its cascade molecules, such as NLRP3, IL-1β, IL-18 and Caspase-1 seems highly attractive. Recently, Daniels and coworkers demonstrated that fenamate subclass of Nonsteroidal Anti-Inflammatory Drugs (NSAID) selectively inhibit NLRP3 inflammasome formation in peripheral macrophages. In addition, this treatment prevents memory deficit and neuroinflammation, besides decreasing NLRP3 activation in microglia from treated animals [52]. In another study, the treatment with mefenamic acid, another NSAID drug, reduced neural cell toxicity and protected rats from memory deficits [53]. Furthermore, ibuprofen specifically reduced pro-amyloidogenic α1 antichymotrypsin *in vitro* and *in vivo* by suppressing IL-1β [54]. These findings indicate that NSAID targeting NLRP3 pathway may be promising drug candidates for the treatment of patients with AD.

Considering that NLRP3 complex formation can be activated by signals recognized by TLRs, receptor signaling pathways may be promising targets for AD treatment. However, the activation of these receptors may have positive or negative effects during AD. For example, Jin and coworkers reported that TLR4 up regulates proinflammatory cytokines, including IL-1β, and is involved in AD animal model progression [55]. On the other hand, another study demonstrated that TLR4, TLR 2 and 9 have an important role in the clearance of Aβ deposits in animal brains [56].

Myd88 is a downstream intracellular adaptor of TLR2, 4 and IL-1R signaling, and activates NF-κb transcription factor to activate proinflammatory cytokine genes. MyD88 deficiency may reduce Aβ load by enhancing the phagocytic capability of microglia [57]. In this line, blocking this molecule could be an interesting target for the inhibition of inflammatory and toxic mechanisms in cells during AD. However, MyD88 seems a controversial target for AD. For example, Michaud and coworkers showed that MyD88-deficient mice present accelerated AD pathology and memory deficits [58]. It is noteworthy that this adapter is central in the signaling of several innate receptors and participates in the activation of many important inflammatory genes against pathogens. Thus, a therapeutic approach targeting

MyD88 might not be beneficial, inducing susceptibility to infections.

In vitro studies demonstrate that caspase-1 inhibitor Z-YVAD-FMK inhibits the processing of IL-1β via NLRP3 pathway, and attenuates microglial neurotoxicity. This finding suggests that caspase 1 inhibition or IL-1β neutralization can improve the inflammatory process by microglia activation upon Aβ stimuli [50].

The role of IL-1β in AD appears to be more complex than previously thought. Shaftel, et al. demonstrated that IL-1β overexpression lead to robust neuroinflammation in hippocampus of mice, characterized by activation of astrocytes and microfibers as well as secretion of proinflammatory cytokines. Surprisingly, in a mouse model of AD, 4 weeks of IL-1β overexpression for 4 weeks protected animals to Aβ pathology [59].

Conclusion

Neuroinflammatory events have recently been reported as additional parameters to the protein deposition involved in the etiology and pathogenesis of AD. Innate immune molecules in microglia are important to outcome AD and may play a crucial role in the establishment of severe inflammation in CNS. Recent studies have indicated the NLRP3 activation pathway as a key immune component for the development of AD. Consequently, NLRP3 could be an important target in therapies for AD as well as other neurodegenerative and neuroinflammatory diseases. To date, no drugs have been developed to directly bind and inhibit NLRP3 activity. Because NLRP3 pathway may influence other important pathways in the immune system, the challenge is to establish a specific strategy to inhibit the activation of this inflammasome and consequently decrease the pathological effects of inflammation in the CNS without altering the functionality of resident cells, such as microglia, or leading the patient to greater vulnerability to infections due to immune deficiency.

Conflict of Interest

Not existent.

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