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Neuroinflammation and Neuroimmunomodulation in Alzheimer's Disease

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Abstract

Purpose of Review This review provides an updated summary of our current understanding of the role of neuroinflammation in Alzheimer's disease (AD). We introduce the main cellular and molecular players in AD-related neuroinflammation, highlight the latest discovery on how inflammasome participates in the development of AD, and discuss potential neuroimmunomodulation approaches for AD prevention and therapy.

Recent Findings AD is characterized by the abnormal accumulation or aggregation of proteins such as amyloid β (Aβ) and tau, which could act as danger-associated molecular patterns that engage pattern-recognition receptors to activate inflammatory signaling pathways and promote the production and release of a variety of inflammatory mediators. While the role of neuroinflammatory response in AD is complex and poorly understood, it is generally considered that consistent neuroinflammation has detrimental effects and facilitate the progression of AD. In particular, recent evidence suggests that targeting Nod-like receptor protein 3 (NLRP3) inflammasome could slow the deposition of Aβ plaques in the brain and improve neurological outcome in AD patients.

Summary Neuroinflammation plays an important role in AD. Further elucidation of molecular mechanisms underlying AD-related neuroinflammatory response would help develop novel strategies for the prevention and treatment of AD.

Keywords Alzheimer's disease · Neuroinflammation · Inflammasome · Amyloid β

Introduction

The last decades have witnessed notable increase in our life span. Consequently, aging has become a new problem to our society. In particular, aged-related neurodegenerative disorders significantly impact the quality of life of elder people. Alzheimer's disease (AD) is the most common neurodegenerative disorder, characterized by progressive cognitive deterioration and behavioral abnormalities [1]. Therefore, AD is the most prevalent form of dementia in the elderly, contributing to their vegetative state and ultimately death [2]. The decline in the cognitive and functional abilities has been attributed to the widespread loss of synapses and neuronal cell death, which are proposed to be caused by the formation of amyloid β (Aβ) plaques and tau neurofibrillary tangles, which are two pathological hallmarks of AD [3].

Accumulating evidence has demonstrated that neuroinflammation plays an important role in the pathogenesis of AD [4•, 5]. However, it is still under debate whether neuroinflammation is a primary or secondary event in AD, and whether inflammation in the central nervous system has beneficial or deleterious effects [6, 7]. In this review, we will provide an overview of our current understanding of the role of neuroinflammation in AD. We introduce the main cellular and molecular players in AD-related neuroinflammation, highlight the latest discovery on how inflammasome participates in the development of AD,

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and discuss potential neuroimmunomodulation approaches for AD prevention and therapy.

Neuroinflammation

Inflammation is a secondary protective response caused by trauma or infections. The term "neuroinflammation" was proposed to describe inflammatory response originated in the central nervous system (CNS) after suffering an injury or infection [8]. Notably, the immune and inflammatory reactions in the CNS are different from those in the rest of the human body mainly due to the presence of the blood-brain barrier (BBB), which restricts the infiltration of the leukocytes into the brain parenchyma. In addition, the interactions of microglia and astrocytes drive most immune/inflammatory responses in the CNS [9]. Although neuroinflammation evolves as a protective reaction in response to the injury or infection in the CNS, inappropriate neuroinflammatory response could cause neurodegeneration diseases including AD [10•]. Below, we will describe the main cellular and molecular players in AD-related neuroinflammation.

Cellular Players in Neuroinflammation

Astrocytes

Astrocytes are the most numerous and diverse neuroglial cells in the CNS and play many essential functions such as neurotransmitter uptake and recycling, axon guidance and synaptic support, and the maintenance of BBB and blood flow [11]. Astrocytes can be distinguished from neurons and other glial cells by the expression of special surface markers such as glial fibrillary acidic protein (GFAP), glutamine synthetase, and calcium-binding protein S100B [12].

Astrocytes are activated and exhibit morphological changes such as hypertrophy and upregulation of GFAP expression in the brains of AD patients [13]. Impaired calcium signaling and synaptic plasticity of the astrocytes are involved in AD [14]. In addition, dysfunction of the astrocytes could promote neurodegeneration by disrupting glial-neuronal and glial-vascular interactions [15•].

Microglia

Microglia are considered as the macrophages in the CNS because they are the main innate immune cells in the CNS. Microglia are essential to healthy CNS function by remodeling the synapse, clearing the debris, and providing trophic support for the neurons. More importantly, they are the major driver of the innate immune response via the recognition of pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) [16]. In addition, microglia are phagocytic cells that ingest and clear Aβ [17]. However, there is conflicting reports on the association of the activation of microglia in vivo with Aβ plaque burden [18, 19].

Molecular Players in Neuroinflammation

PAMPs and DAMPs

PAMPs and DAMPs are important inducers and modulators of neuroinflammation [20••]. PAMPs indicate microbial molecules that are usually absent in host cells, such as bacterial flagellin, lipid A, lipoproteins, bacterial DNA, and virus double-stranded RNA. In contrast, DAMPs are molecules released by host cells upon stress as endogenous danger signals to induce and aggravate inflammatory response. Typical DAMPs include high-mobility group protein B1 (HMGB1), S100, heat-shock proteins (HSPs), and Aβ. Another class of DAMPs includes nucleic acids and derivatives, such as mitochondrial DNA, nuclear DNA, and adenosine triphosphate (ATP).

Both PAMPs and DAMPs induce neuroinflammation in AD. In particular, Aβ induces inflammatory responses via the activation of the toll-like receptors (TLRs) [21]. On the other hand, mitochondrial DNA and nuclear DNA released from the injured cells can enter the blood and act as DAMPs to induce inflammation and neurodegeneration [22].

Cytokines

Cytokines are known as the key mediators of inflammation. In the CNS, cytokines are mainly released by glia cells including astrocytes and microglia upon their activation by inflammatory challenge as described above. Up to now, three cytokines have been extensively studied due to their involvement in AD progression.

Interleukin 1β (IL-1β) serum levels are known to increase in AD patients as well as patients with mild cognitive impairment [23]. In addition, IL-1β polymorphisms have been implicated in the pathogenesis of AD [24].

IL-12 is an important cytokine that plays a role in the regulation of innate and adaptive immunity. IL-12 level increased in the cerebrospinal fluid (CSF) of AD patients, and the inhibition of IL-12 signaling could alleviate the pathology and cognitive defects associated with AD [25]. Recently, IL-12 polymorphism has been shown to be associated with AD in Han Chinese [26].

Transforming growth factor β (TGFβ) is another key regulator of inflammation. TGF-β level is high in amyloid plaques and in the CSF of AD patients. While overexpression of TGF-β promoted Aβ deposition in cerebral blood vessels, TGF-β could increase Aβ phagocytosis. Moreover, TGF-β

could regulate tau protein-associated neurofibrillary tangles. These results suggest a complex role of TGF-β in neuroinflammation [20••].

Chemokines

Chemokines function as chemoattractants to recruit immune cells from the periphery to the CNS and activate glial cells in the CNS. Therefore, chemokines are crucial inflammatory mediators and contribute to neuroinflammation [27].

CX3C chemokine ligand 1 (CX3CL1) and chemokine ligand 2 (CCL2) are two chemokines most intensively studied for their role in the pathogenesis of AD. CX3CL1 is secreted by neurons and plays an important role in modulating glial activation in the CNS because its receptor CX3CR1 is predominantly expressed on microglia. The binding of CX3CL1 and CX3CR1 activates downstream signaling cascades to induce the production of inflammatory factors such as IL-1β and nitric oxide (NO) by glial cells, leading to neuroinflammation and the progression of AD [28]. CCL2 is a β-chemokine responsible for the recruitment of myeloid-lineage such as monocyte-macrophages and microglia during inflammatory conditions. Increased CCL2 levels have been observed in the plasma, CSF, and the brain of AD patients. Aβ stimulates microglia and astrocytes to produce CCL2, which then binds its receptor CCR2 to activate CCL2/CCR2 signaling and enhance neuroinflammation [29]. However, a recent study showed that CCL2 deficiency accelerated the impairments in hippocampal neurogenesis and learning and memory dysfunction in AD mouse model [30]. Therefore, further studies are needed to reveal the precise function of CCL2 in AD pathogenesis.

Other Molecules

In addition, a variety of molecules such as interferons, tumor-necrosis factors, colony-stimulating factors, growth factors, cell adhesion molecules, complement molecules, enzymes, and other inflammatory molecules participate in neuroinflammation and play crucial role in AD progression [31]. We expect that more molecules involved in neuroinflammation will be identified and characterized in the near future, which will facilitate our understanding of complete scenario of neuroinflammatory process and provide novel biomarkers and therapeutic targets for AD.

Inflammasome and AD

The most significant breakthrough in the field of inflammation is perhaps the discovery of the inflammasome by the group of Prof. Jürg Tschopp at the University of Lausanne in 2002 [32••]. Four inflammasome complexes (NLRP1, NLRP3, IPAF, and AIM2) have been identified. The inflammasomes are multiprotein complex mainly expressed in myeloid cells and are required for the activation of inflammatory cascade, from the activation of caspase 1 protease to the downstream secretion of two of its substrates, proinflammatory cytokines IL-1β and IL-18 [33]. Inflammasome has attracted great attention of the researchers in the field of AD and it has been proposed that Aβ activates inflammasomes in neurons and microglia and induce Alzheimer's pathology [34]. A recent study confirmed that the activation of at least two different inflammasome complexes (NLRP3 and NLRP1 inflammasomes), which may explain AD-associated neuroinflammation [35].

However, AIM2 is the most dominant inflammasome sensor expressed in the brain. A recent study reported that Aim2 knockout diminished Aβ deposition and microglial activation in the mice but did not have a beneficial effect on the spatial memory or inflammatory cytokine expression of the mice, suggesting that different inflammasomes have distinct role in different physiological and pathological events [36].

Currently, NLRP3 inflammasome is the most extensively studied inflammasome among all inflammasome complexes identified so far and has been shown to be crucially involved in AD pathogenesis [37]. As shown in Fig. 1, once Aβ monomers form Aβ plaques in the brain, they are sensed by pattern-recognition receptors such as TLR on the surface of microglia. Consequently, the innate immune response is activated, leading to the activation of NF-κB. Next, the activated NF-κB is translocated into the nucleus where it drives the transcription of pro-IL-1β and NLRP3. In the cytoplasm, the newly synthesized NLRP3 protein recruits the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC) via direct interaction with the PYD domain of ASC and triggers the assembly and activation of inflammasome complex. The activated NLRP3 inflammasome could then process pro-IL-1β to mature IL-1β, which will then be released into the extracellular space to promote inflammation [38].

Notably, the activation of NLRP3 inflammasome has been documented in the brains of AD patients and transgenic AD mouse models [39•]. Moreover, genetic deficiency in NLRP3 or caspase-1 (both are components of NLRP3 inflammasome) could protect transgenic AD mice from Aβ-related pathology and spatial memory impairment as well as cognitive decline [40••]. Taken together, these results strongly suggest that the activation of NLRP3 inflammasome contributes to the progression of AD. However, while it is generally accepted that Aβ oligomers activate NLRP3 inflammasome, NLRP3 knockout mice had significantly reduced Aβ plaque burden, suggesting a reciprocal relationship between Aβ and NLRP3 [40••]. Indeed, innate immune activation can occur even before the production of Aβ. A very recent study reported a surprising discovery that the aggregation of Aβ depends on the three amino acids in the pyrin domain of

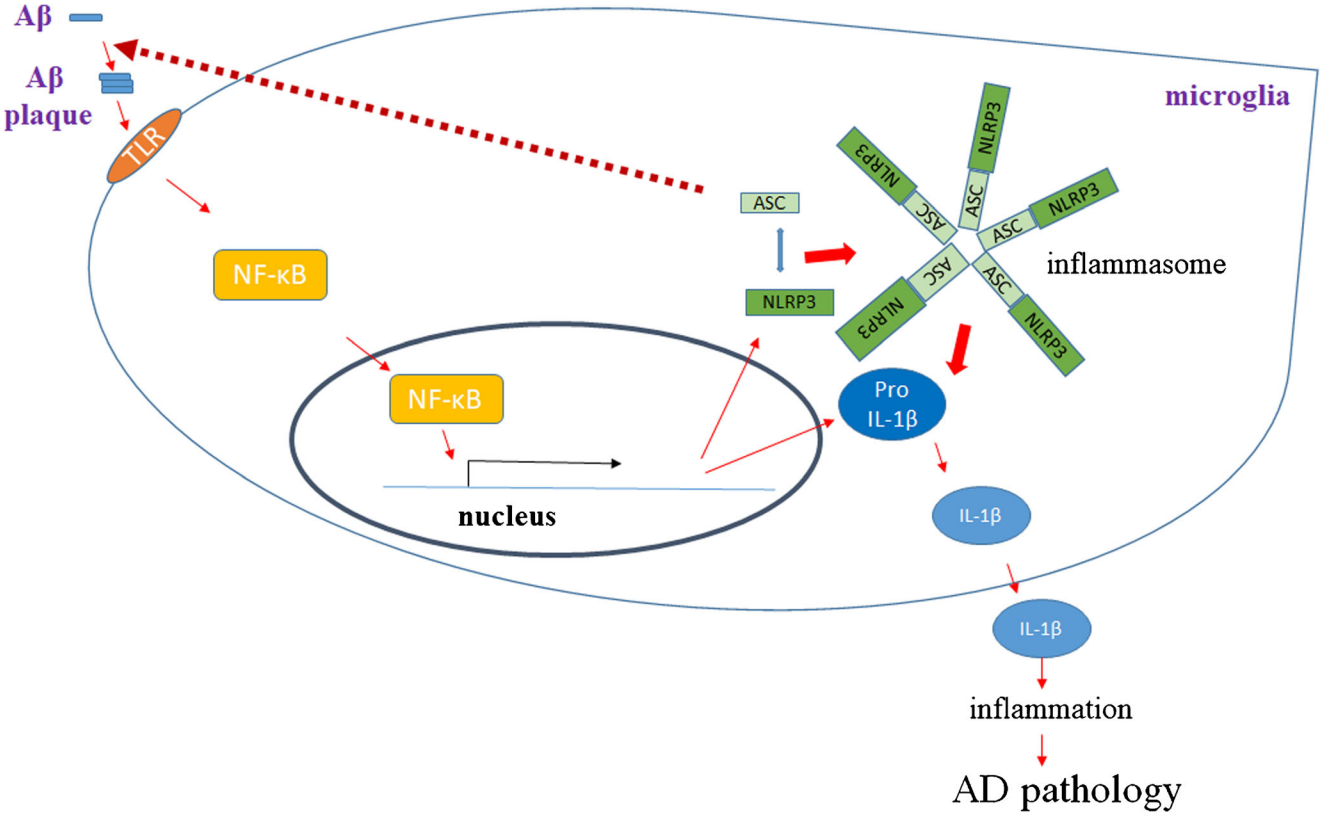

Fig. 1 A brief schematic presentation of the crucial role of NLRP3 inflammasome in AD pathogenesis. Aggregated Aβ is recognized by TLR receptor on the surface of microglia, activating the downstream inflammatory response. Among a variety of inflammatory pathways, here, we only present the activation and translocation of NF-κB into the nucleus, where it drives the transcription of NLRP3 and pro-IL-1β. In the cytoplasm, the newly synthesized NLRP3 protein recruits the adaptor protein ASC and triggers the assembly and activation of NLRP3 inflammasome. Next, the activated NLRP3 inflammasome processes pro-IL-1β to mature IL-1β, which is released into the extracellular space to promote inflammation. On the other hand, upon inflammasome activation, ASC is also released into the extracellular space to promote the seeding and aggregation of Aβ, forming a positive feedback loop and vicious cycle to accelerate AD pathology

ASC, which may mediate the direct interaction with Aβ. In vitro, purified ASC accelerated the aggregation of pathogenic forms of Aβ (Aβ1–40 and Aβ1–42). In vivo, ASC co-immunoprecipitated with Aβ in brain lysates of AD transgenic mice, but not in brain lysates of wild-type control mice. Furthermore, immunohistochemical staining confirmed the co-localization of ASC and Aβ in the brains of AD transgenic mice even before they showed AD-like symptoms. Similarly, ASC and Aβ interaction was demonstrated in the brains of AD patients including the patients at the early stage of AD, but not in the brains of patients with other neurodegenerative diseases [41••]. As expected, ASC deficiency in AD mice led to reduced Aβ plaque formation and improved spatial memory. Similarly, the injection of an anti-ASC antibody blocked Aβ plaque formation and the development of AD-like pathology in AD mice [41••]. Collectively, these striking findings suggest that upon inflammasome activation, ASC is released into the extracellular space of microglia to promote the seeding and aggregation of Aβ, which will in turn induce the activation of NLRP3 inflammasome, forming a positive feedback loop and vicious cycle to accelerate AD pathology (Fig. 1).

Neuroimmunomodulation as New Avenue for AD Therapy

Given the crucial role of neuroinflammation in AD pathogenesis, neuroimmunomodulation shows good potential to inhibit neuroinflammation and prevent and block the development of AD. In the past decades, a variety of anti-inflammatory approaches have been developed to modulate inflammation in the CNS in order to delay AD progression. These approaches include the use of non-steroidal anti-inflammatory drugs (NSAIDs), TNFα inhibitors, and other anti-inflammatory drugs such as prednisone, hydroxychloroquine, simvastatin, and atorvastatin. Although some of them showed certain efficacy in clinical trials, not all of them have produced significantly improved cognitive effects in AD patients [20••].

With recent progress in the understanding of the role of inflammasome in AD progression, inflammasome complex (in particular NLRP3 inflammasome) has become promising therapeutic targets for AD [42]. Based on the screening of

NSAIDs for the activity on NLRP3 activation in vitro, fenamate mefenamic acid was identified to selectively inhibit NLRP3 inflammasome formation and significantly reduce memory defects in several AD mouse models [43]. As discussed earlier, targeting ASC, the adaptor of NLRP3 inflammasome, by genetic knockout or antibody could reduce Aβ plaque burden and memory defects in AD mice [41••].

In addition, several cellular signaling pathways that may act as the secondary stimuli of inflammasome activation present attractive therapeutic targets for AD. Upon cell death, ATP is released into the extracellular space to activate P2X7 receptor, which will activate NLRP3 inflammasome via K^+ efflux. Aβ-mediated activation of NLRP3 inflammasome is dependent on P2X7 receptor because genetic knockout of P2X7 receptor inhibited the development of AD-like pathology in AD mice model [44]. These results suggest that pharmacological intervention with P2X7 receptor opens a new avenue for AD therapy.

Currently, several drugs have been shown to inhibit inflammasome although their mechanisms of action have not been fully understood. 3,4-methylenedioxy-β-nitrostyrene (MNS) has been shown to alter cysteines on NLRP3 protein and disrupt NLRP3-NEK7, NLRP3-NLRP3, or NLRP3-ASC interaction. MCC950 (CP-456773) is a potent inhibitor of NLRP3 activation which may act downstream of K^+ efflux but does not affect NLRP3-ASC or ASC-ASC interaction [45].

Perspective

In this review, we attempt to summarize recent advances on our understanding of the role of neuroinflammation in AD, with special focus on the NLRP3 inflammasome. It appears that Aβ and inflammasome utilize each other to amplify neuroinflammation, ultimately leading to pathological and clinical aspects of AD patients.

Although the important role of neuroinflammation in AD pathogenesis has been better appreciated by the researchers in AD field, there are still many gaps in our current knowledge of these pathological processes which hinder the development of successful therapeutics. It is necessary to further elucidate molecular mechanisms how Aβ mediates neuroinflammation and how inflammasome activation accelerates Aβ burden in AD patients. NLRP3 inflammasome is a promising pharmacological target because its inhibition would specifically abrogate pathological inflammation without affecting basal microglia function or increasing the susceptibility to infection in AD patients. By employing the state-of-art screening and structure-based molecular modeling techniques, we expect that continuous effects to develop novel inhibitors of inflammasome will bring fruit in the coming years. These inhibitors will not only provide potential immunomodulation agents for AD prevention and therapy but also equip us with a diverse set of tools to further understand the role of neuroinflammation in AD.

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Compliance with Ethical Standards

Conflict of Interest The authors received no financial support in the writing of this manuscript.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Peng D, Shi Z, Xu J, Shen L, Xiao S, Zhang N, et al. Demographic and clinical characteristics related to cognitive decline in Alzheimer disease in China: a multicenter survey from 2011 to 2014. Medicine (Baltimore). 2016;95(26):e3727.
2. Wang BR, Ou Z, Gu XH, Wei CS, Xu J, Shi JQ. Validation of the Chinese version of Addenbrooke's cognitive examination III for diagnosing dementia. Int J Geriatr Psychiatry. 2017;32(12):e173–9.
3. Gandy S. The role of cerebral amyloid beta accumulation in common forms of Alzheimer disease. J Clin Invest. 2005;115:1121–9.
4.• Bronzuoli MR, Iacomino A, Steardo L, Scuderi C. Targeting neuroinflammation in Alzheimer's disease. J Inflamm Res. 2016;9:199–208. **An excellent review on the potential of neuroinflammation as therapeutic targets of Alzheimer's disease.**
5. Shi JQ, Chen J, Wang BR, Zhu YW, Xu Y, Wang J, et al. Short amyloid-beta immunogens show strong immunogenicity and avoid stimulating pro-inflammatory pathways in bone marrow-derived dendritic cells from C57BL/6J mice in vitro. Peptides. 2011;32(8):1617–25.
6. Sastre M, Walter J, Gentleman SM. Interactions between APP secretases and inflammatory mediators. J Neuroinflammation. 2008;5:25.
7. Wyss-Coray T, Mucke L. Inflammation in neurodegenerative disease: a double-edged sword. Neuron. 2002;35:419–32.
8. Morales I, Guzmán-Martínez L, Cerda-Troncoso C, Farías GA, Maccioni RB. Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches. Front Cell Neurosci. 2014;8:112.
9. Ransohoff RM, Schafer D, Vincent A, Blachère NE, Bar-Or A. Neuroinflammation: ways in which the immune system affects the brain. Neurotherapeutics. 2015;12:896–909.
10.• Ransohoff RM. How neuroinflammation contributes to neurodegeneration. Science. 2016;353:777–83. **A nice review on the role of neuroinflammation in neurodegenerative diseases.**
11. Ben Haim L, Rowitch DH. Functional diversity of astrocytes in neural circuit regulation. Nat Rev Neurosci. 2017;18:31–41.
12. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. Acta Neuropathol. 2010;119:7–35.

13. Rodriguez-Vieitez E, Saint-Aubert L, Carter SF, Almkvist O, Farid K, Schöll M, et al. Diverging longitudinal changes in astrocytosis and amyloid PET in autosomal dominant Alzheimer's disease. Brain. 2016;139(Pt 3):922–36.
14. Vincent AJ, Gasperini R, Foa L, Small DH. Astrocytes in Alzheimer's disease: emerging roles in calcium dysregulation and synaptic plasticity. J Alzheimers Dis. 2010;22(3):699–714.
15.• Acosta C, Anderson HD, Anderson CM. Astrocyte dysfunction in Alzheimer disease. J Neurosci Res. 2017;95(12):2430–47. **An updated review on the role of astrocytes in Alzheimer disease.**
16. Baroja-Mazo A, Martín-Sánchez F, Gomez AI, Martínez CM, Amores-Iniesta J, Compan V, et al. The NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response. Nat Immunol. 2014;15(8):738–48.
17. Wilkinson K, El Khoury J. Microglial scavenger receptors and their roles in the pathogenesis of Alzheimer's disease. Int J Alzheimers Dis. 2012;2012:489456.
18. Hamelin L, Lagarde J, Dorothée G, Leroy C, Labit M, Comley RA, et al. Early and protective microglial activation in Alzheimer's disease: a prospective study using 18F-DPA-714 PET imaging. Brain J Neurol. 2016;139(Pt 4):1252–64.
19. Fan Z, Okello AA, Brooks DJ, Edison P. Longitudinal influence of microglial activation and amyloid on neuronal function in Alzheimer's disease. Brain J Neurol. 2015;138(Pt 12):3685–98.
20.•• Ardura-Fabregat A, Boddeke EWGM, Boza-Serrano A, Brioschi S, Castro-Gomez S, Ceyzériat K, et al. Targeting Neuroinflammation to treat Alzheimer's disease. CNS Drugs. 2017;31(12):1057–82. **A comprehensive review on targeting neuroinflammation as novel avenue to treat Alzheimer's Disease**.
21. Liu S, Liu Y, Hao W, Wolf L, Kiliaan AJ, Penke B, et al. TLR2 is a primary receptor for Alzheimer's amyloid β peptide to trigger neuroinflammatory activation. J Immunol. 2012;188:1098–107.
22. Thundyil J, Lim KL. DAMPs and neurodegeneration. Ageing Res Rev. 2015;24(Pt A):17–28.
23. Forlenza OV, Diniz BS, Talib LL, Mendonça VA, Ojopi EB, Gattaz WF, et al. Increased serum IL-1beta level in Alzheimer's disease and mild cognitive impairment. Dement Geriatr Cogn Disord. 2009;28(6):507–12.
24. Yuan H, Xia Q, Ge P, Wu S. Genetic polymorphism of interleukin 1β -511C/T and susceptibility to sporadic Alzheimer's disease: a meta-analysis. Mol Biol Rep. 2013;40(2):1827–34.
25. Vom Berg J, Prokop S, Miller KR, Obst J, Kälin RE, Lopategui-Cabezas I, et al. Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease-like pathology and cognitive decline. Nat Med. 2012;18(12):1812–9.
26. Zhu XC, Tan L, Jiang T, Tan MS, Zhang W, Yu JT. Association of IL-12A and IL-12B polymorphisms with Alzheimer's disease susceptibility in a Han Chinese population. J Neuroimmunol. 2014;274(1–2):180–4.
27. Le Thuc O, Blondeau N, Nahon JL, Rovère C. The complex contribution of chemokines to neuroinflammation: switching from beneficial to detrimental effects. Ann N Y Acad Sci. 2015;1351:127–40.
28. Chen P, Zhao W, Guo Y, Xu J, Yin M. CX3CL1/CX3CR1 in Alzheimer's disease: a target for neuroprotection. Biomed Res Int. 2016;2016:8090918.
29. El Khoury JB, Moore KJ, Means TK, Leung J, Terada K, Toft M, et al. CD36 mediates the innate host response to beta-amyloid. J Exp Med. 2003;197(12):1657–66.
30. Kiyota T, Morrison CM, Tu G, Dyavarshetty B, Weir RA, Zhang G, et al. Presenilin-1 familial Alzheimer's disease mutation alters hippocampal neurogenesis and memory function in CCL2 null mice. Brain Behav Immun. 2015;49:311–21.
31. Bagyinszky E, Giau VV, Shim K, Suk K, An SSA, Kim S. Role of inflammatory molecules in the Alzheimer's disease progression and diagnosis. J Neurol Sci. 2017;376:242–54.
32.•• Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell. 2002;10(2):417–26. **The first report on the discovery of inflammasome.**
33. Schroder K, Tschopp J. The inflammosomes. Cell. 2010;140(6):821–32.
34. Salminen A, Ojala J, Suuronen T, Kaarniranta K, Kauppinen A. Amyloid-beta oligomers set fire to inflammasomes and induce Alzheimer's pathology. J Cell Mol Med. 2008;12(6A):2255–62.
35. Saresella M, La Rosa F, Piancone F, Zoppis M, Marventano I, Calabrese E, et al. The NLRP3 and NLRP1 inflammasomes are activated in Alzheimer's disease. Mol Neurodegener. 2016;11:23.
36. Wu PJ, Hung YF, Liu HY, Hsueh YP. Deletion of the inflammasome sensor Aim2 mitigates Aβ deposition and microglial activation but increases inflammatory cytokine expression in an Alzheimer disease mouse model. Neuroimmunomodulation. 2017;24(1):29–39.
37. Pennisi M, Crupi R, Di Paola R, Ontario ML, Bella R, Calabrese EJ, et al. Inflammasomes, hormesis, and antioxidants in neuroinflammation: role of NRLP3 in Alzheimer disease. J Neurosci Res. 2017;95(7):1360–72.
38. Parajuli B, Sonobe Y, Horiuchi H, Takeuchi H, Mizuno T, Suzumura A. Oligomeric amyloid β induces IL-1β processing via production of ROS: implication in Alzheimer's disease. Cell Death Dis. 2013;4:e975.
39.• Heneka MT. Inflammasome activation and innate immunity in Alzheimer's disease. Brain Pathol. 2017;27(2):220–2. **An updated review on the role of inflammasome in Alzheimer's disease.**
40.•• Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature. 2013;493:674–8. **An important study to show that NLRP3 is activated and contributes to Alzheimer's disease pathology in transgenic mouse model.**
41.•• Venegas C, Kumar S, Franklin BS, Dierkes T, Brinkschulte R, Tejera D, et al. Microglia-derived ASC specks cross-seed amyloid-β in Alzheimer's disease. Nature. 2017;552(7685):355–61. **A very recent remarkable study to reveal that ASC adaptor of inflammasome seeds amyloid-β deposition in the brain of Alzheimer's disease patients or mouse models.**
42. White CS, Lawrence CB, Brough D, Rivers-Auty J. Inflammasomes as therapeutic targets for Alzheimer's disease. Brain Pathol. 2017;27:223–34.
43. Daniels MJD, Rivers-Auty J, Schilling T, Spencer NG, Watremez W, Fasolino V, et al. Fenamate NSAIDs inhibit the NLRP3 inflammasome and protect against Alzheimer's disease in rodent models. Nat Commun. 2016;7:12504.
44. Sanz JM, Chiozzi P, Ferrari D, Colaianna M, Idzko M, Falzoni S, et al. Activation of microglia by amyloid β requires P2X7 receptor expression. J Immunol. 2009;182:4378–85.
45. Coll RC, Robertson AAB, Chae JJ, Higgins SC, Muñoz-Planillo R, Inserra MC, et al. A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. Nat Med. 2015;21:248–55.