Chapter 5

Interleukin 1 Receptor and Alzheimer's Disease-Related Neuroinflammation

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Additional information is available at the end of the chapter

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Abstract

Neuroinflammation as one of the pathogenic mechanisms concerning to the development of Alzheimer's disease (AD) has aroused more attention since last decades. Amyloid beta (Aβ) peptide generation is supposed to be the initial event in AD progress, followed by neuronal impairment, neuroinflammation, and severe substantial neuronal dysfunction. Interleukin-1 receptor (IL-1R) as one of the most prevalent inflammatory mediated surface receptors, participates not only in peripheral inflammation but also in AD-related neuroinflammation. In microglia, IL-1R activation triggers the downstream signaling and the production of proinflammatory cytokines and chemokines. IL-1R signaling also participates in AD-related Aβ-induced inflammasome activation. Besides, IL-1R activation in neurons may increase APP non-amyloid pathway by modulation of APP α-secretase activity, which may prevent neurotoxic Aβ generation. Thus, the exact role of IL-1R signaling in AD development and neuronal functions is somehow tricky.

Keywords: interleukin 1 receptor, Alzheimer's disease, neuroinflammation

1. Introduction

Alzheimer's disease (AD) is kind of neurodegenerative disease, which affects elder's health and living quality. There are some hypotheses raised up for the pathogenesis of the disease, such as amyloid cascade and tau hyperphosphorylation. Besides, neuroinflammation induced by neurotoxic amyloid β (Aβ) peptide is also considered contribute to the development of AD. Inteleukin-1 receptor (IL-1R) is one of the inflammation-related surface receptors that are distributed widely in various tissues and cells in the body. Evidence has been shown that IL-1R-mediated neuroinflammation may be closely related to pathogenesis and

development of AD. In the current chapter, AD-related neuroinflammation and the participation of IL-1R in such progress would be reviewed and discussed in detail.

2. Alzheimer's disease

As a kind of chronic neurodegenerative disease, AD usually starts slowly and gets worse over comparatively longer time. The initial symptoms of AD are often mistaken with normal aging. The most common early symptom for AD is the difficulty in remembering recent events (short-term memory loss). As the disease advances, symptoms may include problems with language, disorientation (easily getting lost), mood swings, loss of motivation, not managing self-care, and behavioral issues. AD patients may suffer from the disease symptoms for years and especially at the later stage of the progress.

AD is currently supposed to be the cause of approximately 60–70% of total dementia cases. There is a large amount of data about potential risk factors for AD, including age [1], genetics [2], and injury [3]. Many treatable medical conditions are also associated with an increased risk of AD, including stroke [4], diabetes [5], midlife hypertension [6], and hypercholesterolemia [7, 8].

The early identification of molecular pathological description of AD was the functional reduction of cholinergic nerve system in the cerebral cortex, like the remarkable reduction in choline acetyltransferase (ChAT) [9]. Later, senile plaques and neurofibrillary tangles (NFTs), two typical protein depositions, were confirmed related to AD [10]. The main component of senile plaques is Aβ peptide; while NFTs are made from abnormal tau proteins [11]. A 42-amino acid long form of Aβ (Aβ42) was found as the main content in fibrillar Aβ peptides [12]. Aβ40, which is also found in the plaque, although is normally more abundantly produced by cells, contributes to the lower portion of the plaque [13]. Compared to Aβ40, Aβ42 is the more hydrophobic form that aggregates more easily and quickly [14]. NFTs are formed by hyperphosphorylated tau protein. As the raise of Aβ concentration, tau protein happens to be more easily phosphorylated, leading to an imbalance of various kinases and phosphatases [15]. Consequently, mass transport and impaired impulse occurs in neurons, followed by severe neuronal dysfunction.

Thus, the amyloid hypothesis puts Aβ accumulation at the core of AD pathogenesis. Aβ is the sequential proteolytic product of its precursor amyloid precursor protein (APP). APP is a type I transmembrane protein, consisted of a large N-terminal ectodomain, a transmembrane domain, and a short cytoplasmic domain. The Aβ peptide generation is supposed to be influenced by the pattern of cleavage from APP by α, β, and γ-secretases [16]. APP can be processed in two different pathways, the amyloid, and non-amyloid pathway. In the amyloid pathway, APP can be cleaved by β-secretase (BACE1), releasing the soluble APP β fragment (sAPPβ); and the C-terminal fragment (CTF) is still in the membrane and can be cleaved by γ-secretase (presenilin1, PS1) to release Aβ [17]. This process leads to Aβ generation, aggregation, and deposit. In the other non-amyloid pathway, APP can be cleaved by α-secretase (ADAM10/17), releasing soluble APP α fragment (sAPPα). The cleavage site of α-secretase is

between the sites of β- and γ-secretase. So the non-amyloid pathway can reduce the damage induced by Aβ on neurons.

Consider to the crucial role of Aβ in the amyloid cascade, therapeutic approaches related to APP metabolic pathways were always under careful and detail research and develop [18]. Those therapeutic approaches include inhibition of Aβ monomers developing into toxic oligomers or enhancement of clearance and disaggregation of fibrillar aggregates from cerebral cortex [19]; modulation of the fate and toxicity of Aβ using antibodies against Aβ [20]. However, the only clinical effective therapeutic approach so far is the treatment and enhancement of the functions of cholinergic neurons. Acetylcholinesterase (AChE) inhibitors, galantamine, and rivastigmine were thought to improve cognition and indirectly help function and behavior in patients with AD [21–23]. Such treatments for AD have been widely available since the mid-1990s, but these drugs do not treat the underlying mechanism, so the effects are limited.

3. AD-related neuroinflammation

As described above, the amyloid hypothesis was raised up as the most popular and acceptable pathogenesis mechanism for AD. The initial changes of the cascade happen to Aβ metabolism. The Aβ balance in favor of Aβ42 followed by the formation of diffuse plaques can induce the toxic effect to neurons to different extends. The diffuse Aβ plaques can then convert to more toxic Aβ deposit fibrillars. Aβ triggers the activation of the cellular signaling cascade, the induction of inflammatory enzyme systems in a vicious cycle and finally the expression and secretion of proinflammatory cytokines. The activation of microglial and astrocyte, together with the corresponding inflammatory reactions, is another important event in AD pathogenesis. Both aggregated amyloid fibrils and inflammatory mediators secreted by microglia contribute to neuronal dystrophy. NFTs occur under such condition, which enhances neuronal dysfunction and death. The widespread neuronal dysfunction is regarded as the immediate cause of the disease [18, 24]. On the basis of these observations, Aβ has become a major pharmacological target for the treatment of the disease. However, such trails of treatment have not reached a satisfactory outcome. Thus, the AD-related neuroinflammation starts to sneak into current research attention.

In parallel, neuroinflammation has been implicated in contributing to the etiology of AD. Epidemiological and prospective population-based studies show an association between suppression of inflammation and reduced risk for AD [25, 26]. The protective effects of nonsteroidal anti-inflammatory drugs (NSAIDs) against AD development [27] further support the neuroinflammation hypothesis. In animals, the beneficial effects of NSAIDs have also been confirmed, including behavioral improvement and reductions in glial activation, Aβ levels, and plaque size [28]. Inflammatory responses to amyloidosis have also been observed in animal models overexpressing Aβ [29, 30]. Proinflammatory cytokines, such as (interleukin-1) IL-1, IL-6, and tumor necrosis factor α (TNFα), are elevated in the plasma, brains, and cerebrospinal fluid of patients with AD or mild cognitive impairment, whereas anti-inflammatory

cytokines are decreased [31, 32]. Besides, inhibition of TNFα signaling has been shown to attenuate AD-like pathology and cognitive impairments in transgenic mouse models, as well as in AD patients [33, 34].

Inflammation is a complex cellular and molecular response to insults (stress, injury or infection), an attempt to defend against these insults. AD-associated inflammation is generally considered as a secondary response to the pathological lesions evoked by Aβ [35, 36]. AD-related inflammatory response is supposed to be driven mainly by activated microglia [37, 38].

The activation of migrolia has been reported in both AD patients and animal models [39], accompanied by increased levels of specific chemokines and cytokines [40]. Microglia surrounding plaques stain positive for activation markers and proinflammatory mediators, including cyclooxygenase-2 (Cox-2), monocyte chemotactic protein 1 (MCP-1), TNFα, transforming growth factor-β (TGFβ), IL-1α, IL-1β, and IL-6 [41–43]. Aβ and its fibrils can induce self-defense, inflammatory responses via pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) [44, 45]. Aβ aggregates interact with microglial receptors like TLR4, CD14, CD36, CD47, the receptor for advanced glycation end products (RAGE), and some integrins [46–50]. More recently, it has been reported that Aβ activates microglia through its interaction with the APP present in the membrane of these cells [51], which defines a novel function of APP in microglial regulation of the inflammatory response in AD.

Microglial activation seems to be the comparative early event in AD pathological development. Imaging study results showed that reactive microglia can be detected at the very early clinical stage of the disease [39]. In AD mouse model, microglial activation was observed before amyloid plaque formation [52]. Once activated, microglia can produce several proinflammatory signal molecules, including cytokines, growth factors, chemokines, and cell adhesion molecules. Besides, Microglia may also play a role in plaque evolution by phagocytosing and/or degrade deposited Aβ. Many different laboratories have shown that microglia, both *in vivo* and in culture, phagocytose exogenous fibrillar Aβ [53, 54].

4. Interleukin 1 receptor

IL-1R family belongs to one category of TIR domain-containing receptor superfamily. The TIR domain-containing receptors are a large family of molecules involved in the activation of innate immunity [55]. The TIR superfamily can be broadly divided into two main groups: the immunoglobulin (Ig) domain-bearing receptors and the receptors with a leucine-rich repeat (LRR) domain [56, 57]. The Ig domain subgroup of TIR receptors includes 10 members of the IL-1R family, whereas the LRR group includes the toll-like receptors (TLR). When an agonist IL-1 family cytokine binds to its specific TIR-containing receptor, the initiation of IL-1R activation signaling occurs [56]. The signaling pathway involves the recruitment of adapter molecule MyD88 and kinase IRAK, followed by interaction with TRAF6. The final step is the phosphorylation of the inhibitory molecule IκB by IκB kinase complex leading to relocalization of transcription factor NF-κB. NF-κB is translocated into the nucleus and intermediates inflammatory immune response [58]. NF-κB is a major inflammatory switch that comprises a

family of transcription factors that regulate expression of various proinflammatory cytokines (IL-1, IL-6, IL-8 and TNFα), chemokines, antiapoptotic factors and stress factors [59].

IL-1 family is the typical ligands for IL-1R and its activation. IL-1 family includes a set of cytokines, some of which have been demonstrated to play a critical role in host responses to pathogens and other noxious agents [60]. IL-1α and IL-1β are two most prevalent ligands that are supposed to trigger the activation of IL-1R. IL-1α/β are endogenous pyrogens with activities similar to lipopolysaccharides (LPS), which are the major molecular components of the outer membrane of Gram-negative bacteria [61].

One of IL-1R ligand cytokine IL-1β appears to play an important role in AD. IL-1β level was confirmed obviously in and around the area of Aβ deposit [62, 63]. The inhibition of IL-1 signaling by IL-1R knockout could significantly relief the Aβ burden in transgenic AD mice [64]. And the protective impact by IL-1R knockout was believed to be dependent on attenuated AD-related neuroinflammation [65]. Besides, the inflammation- or IL-1β-induced pathological tau development has also been well documented [66–68]. The inhibition of IL-1 signaling significantly suppressed the activation of cdk5/p25, GSK-3β, and p38-MAPK, all major kinases that phosphorylate tau in neurons. Another study demonstrated a direct effect of IL-1β secreted by microglia on neurons and subsequent activation of p38-MAPK and accumulation of tau phosphorylation [69]. NSAIDs could be repurposed as NLRP3 inflammasome inhibitors that provide neuroprotective impact against AD [70].

5. IL-1R signaling and inflammasome

Inflammasomes are responsible for the maturation of pro-inflammatory cytokines such as interleukin IL-1, IL-18, and IL-33 and activation of inflammatory cell death, pyroptosis [71]. The inflammasome is a multiprotein oligomer consisting of caspase 1, PYCARD, NALP, and sometimes caspase 5 (also known as caspase 11 or ICH-3). It is expressed in myeloid cells and is a component of the innate immune system. Analogous to the apoptosome, which activates apoptotic cascades, the inflammasome activates an inflammatory cascade. Once active, the inflammasome binds to pro-caspase-1 (the precursor molecule of caspase-1), either homotypically via its own caspase activation and recruitment domain (CARD) or via the adaptor protein ASC. Caspase-1 then assembles into its active form which obtains the peptidase activity. The metabolic process performed by caspase-1 includes the proteolytic cleavage of pro-IL-1β at Asp116 into IL-1β [72] and cleavage of pro-IL-18 into IL-18 to induce IFN-γ secretion and natural killer cell activation [73]. Thus, the inflammasome promotes the maturation of the inflammatory cytokines, interleukin 1β (IL-1β) and interleukin 18 (IL-18) [72]. Thus, IL-1R signaling is considered to play a crucial role in inflammasome activation-induced inflammation.

Nucleotide oligomerization domain (NOD)-like receptor family, pyrin domain 3 (NLRP3) containing inflammasome is an intracellular multiprotein complex, which has been verified to participate in Aβ-induced neuroinflammation [74]. Halle et al. demonstrated that the phagocytosis of fibrillar Aβ activates NALP3 inflammasomes in mouse microglia. The activation of NALP3 was dependent on lysosomal damage and cathepsin B release, as was observed earlier

in the crystal-induced NALP3 activation [75, 76]. Then, more evidence was supportive for that Aβ activate the NLRP3 inflammasome in microglial cells *in vitro* and *in vivo* [77–79]. NLRP3 inflammasome inhibitor treatment in AD mice led to decreased levels of Aβ deposition and decreased levels of soluble and insoluble Aβ42 in the brain [80]. NLRP3 or caspase-1 knockout could significantly suppress amyloidosis and neuropathology, as well as improve cognition-associated parameters in AD mice model [77].

The possible roles of the NLRP3 inflammasome in AD pathogenesis discussed above open a novel investigation of inflammasome signaling pathway for understanding AD. Designing agents for critically controlling the activation of NLRP3 inflammasome at the molecular level might offer considerable promise to tackle neuroinflammation and slow AD progression.

6. IL-1R signaling in neurons

IL-1R is widely distributed in the central nerves system (CNS). Early evidence revealed that IL-1R was detected in high density in the dentate gyrus of the hippocampus, choroid plexus, meninges, and anterior pituitary and is low expressed in the frontoparietal cortex. Both neurons and glial cells were shown to express IL-1R [81]. Later, a pile of data demonstrated that IL-1R could be activated in various cell types in CNS. In cultured human microglia, numerous proinflammatory cytokines such as IL-1, IL-6, and TNFα are produced after IL-1 stimulation. In cultured rat astrocytes, IL-1 could stimulate astrocytes to release nerve growth factor which can mediate neuroprotective effects [82]. In addition, administration of IL-1 in the cerebral ventricle induced COX-2 exclusively in endothelial cells comprising brain blood vessels [83]. As we described in the previous paragraph, IL-1R plays an important role in glial activation-induced neuroinflammation, the participation of IL-1R in neuronal function has not been carefully discussed.

IL-1β has been reported to increase the expression of APP in neuronal culture [69]. The amyloid precursor protein (APP), via stimulation of amyloidogenic processing, undergoes sequential proteolytic cleavage by β-secretase and γ-secretase to generate Aβ. Alternatively, a non-amyloidogenic pathway involving α-secretase activation could reduce Aβ generation, which competitively inhibits activation of the detrimental amyloidogenic pathway. Also, sAPPα is proven to possess neuroprotective and memory-enhancing properties, often being compared to cerebral growth stimulants. Thus, the non-amyloidogenic pathway is supposed to be a suitable therapeutic target for AD.

The identity of α-secretase of APP has been verified to be ADAM10 (a disintegrin and metalloprotease 10) constitutively and ADAM17 regulatively [84]. Different kinds of stimuli have been suggested to increase the secretion of sAPPα under certain conditions via ADAM17, including various cytokine, chemokines, adhesion molecules and growth factors [85]. The two most important ligands for IL-1R, IL-1α [86] and IL-1β [87, 88] were proved to enhance ADAM17 activity in neurons. The detail mechanism research concerning to IL-1 signaling and APP proteolysis revealed that the GC-rich APP mRNA 5′UTR-stem loop structure bears an amyloid-specific CAGA sequence, IL-1 responsive element, and an iron responsive element.

IL-1 binding to its responsive element significantly impacts the functioning of APP 5'UTR that affects APP metabolism and thus sAPPα release [89]. Besides, p38/ERK/JNK pathway and PI3K/AKT pathway are believed to participate in IL-1 signaling mediated activity regulation of APP α-secretase ADAM17 [90, 91].

Thus, IL-1R is considered play an important and distinct role in different aspects in the process of AD development. The exact relationship of IL-1R signaling activation between microglial activation-induced neuroinflammation and APP α-shedding in neurons is somehow tricky. The cytokines and growth factors from reactive microglia induced by neurotoxic Aβ may enhance ADAM17 activity in nearby neurons (paracrine), which provides a possible self-protection against Ab-induced neuronal dystrophy.

7. Conclusion

IL-1R participates in AD-related neuroinflammation by microglial activation and the secretion of various pro-inflammatory cytokines and chemokines. The anti-inflammation treatment has been raised up, including IL-1R antagonist as a potential AD therapeutic approach. However, IL-1R activation in neurons, where exactly APP proteolysis takes place, may enhance the activity of neuroprotective α-secretase. The safety of novel promising therapeutic approaches targeting IL-1R activity regulation has to be evaluated carefully to avoid unexpected side effects.

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