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Reprint of: Microglial toll-like receptors and Alzheimer's disease ☆

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ABSTRACT

Microglial activation represents an important pathological hallmark of Alzheimer's disease (AD), and emerging data highlight the involvement of microglial toll-like receptors (TLRs) in the course of AD. TLRs have been observed to exert both beneficial and detrimental effects on AD-related pathologies, and transgenic animal models have provided direct and credible evidence for an association between TLRs and AD. Moreover, analyses of genetic polymorphisms have suggested interactions between genetic polymorphisms in TLRs and AD risk, further supporting the hypothesis that TLRs are involved in AD. In this review, we summarize the key evidence in this field. Future studies should focus on exploring the mechanisms underlying the potential roles of TLRs in AD.

Contents

Abbreviations: AD, Alzheimer's disease; TLRs, toll-like receptors; AβPP, amyloid-β protein precursor; NSAIDs, non-steroidal anti-inflammatory drugs; CNS, central nervous system; TNF-α, tumor necrosis factor-α; IL-1β, interleukin 1-β; IL-6, interleukin-6; NO, nitric oxide; ROS, reactive oxygen-nitrogen species; DAMPs, danger-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; NF-κB, nuclear factor κB; MAPK, mitogen-activated protein kinase; Aβ, amyloid-β; PET, positron emission tomography; PS1, presenilin 1; iNOS, inducible nitric oxide synthase; PGN, peptidoglycan; PI3K, phosphatidylinositide 3-kinases; IKK, IκB kinase; MyD88, myeloid differentiation factor; FPRL1, formyl peptide receptor-like 1; MMP-9, matrix metalloproteinase-9; SIGIRR, single-Ig-interleukin-1 related receptor; PPARγ, peroxisome proliferator-activated receptor γ; LPS, lipopolysaccharide; MPL, Monophosphoryl lipid A; IFN, interferon; TRIF, Toll/interleukin-1 receptor domain-containing adaptor inducing IFNβ; ISGs, IFN-stimulated genes; TRAF6, TNF receptor associated factor 6; TIRAP, Toll-IL-1R domain-containing adapter protein; IRAK, IL-1R-associated kinase family; TRAM, TRIF-related adaptor molecule; FoxO1, forkhead box O1; IRF3, interferon regulatory factor 3; ICV, intracerebroventricular; CpG, cytosine–guanosine-containing oligodeoxynucleotides; NFT, neurofibrillary tangles; HO-1, heme oxygenase-1; CCR1, C–C chemokine receptor type 1; CX3CR1, CX3C chemokine receptor 1; mFPR2, mouse homologue formyl peptide receptor 2; HSP70, heat shock protein 70; AIF, apoptosis-inducing factor; GT repeat, Guanine–thymine repeat; LOAD, late-onset Alzheimer's disease; SNPs, single nucleotide polymorphisms; JNK, c-Jun N-terminal kinas.

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1. Introduction

Alzheimer's disease (AD), a neurodegenerative disease that is characterized by a progressive decline in cognitive and functional abilities, is one of the leading causes of disability among the elderly, and the number of people affected by AD is expected to increase in the coming years unless effective methods are found to cure the disease or to halt the associated declines in cognitive functions (Brookmeyer et al., 2007). Substantial effort has been made to explore the exact mechanisms underlying AD, and emerging evidence has suggested that inflammation may exacerbate or even cause AD. This concept is not new; approximately two decades ago, the demonstration of the activation of both the complement system and the innate immune system in AD patients implied an association between AD and neuroinflammation (Retz et al., 1998; Yasojima et al., 1999). Moreover, increased levels of inflammatory cytokines and chemokines have been detected in the postmortem brains of both AD patients and amyloid-β protein precursor (AβPP) transgenic animals (Cacabelos et al., 1991; Grammas and Ovase, 2001; Perry et al., 2001; Xia and Hyman, 1999; Xia et al., 1998). Although with some controversies (Arvanitakis et al., 2008; Breitner et al., 2009), epidemiological investigations have provided further support for this concept by showing that the long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the risk of developing AD, especially in individuals who are treated in middle ages (Landi et al., 2003; Vlad et al., 2008). In some experiments, the explanation for why NSAIDs failed to show protective effects may be that the drugs were provided for elderly individuals, whose AD pathology had already developed prior to treatment with anti-inflammatory medications (Arvanitakis et al., 2008; Breitner et al., 2009).

Dysfunctions in microglia, which are brain-specific macrophages and the most important immune cells in the central nervous system (CNS), are receiving an increasing amount of attention in the context of the neuroinflammatory process in AD. In healthy brains, microglia are in a 'resting' state, and they perform immune surveillance (Nimmerjahn et al., 2005). Under pathological conditions, microglia can be activated by various stimuli, and different types of stimulation induce microglial activation toward a 'classical (M1)' or 'alternative (M2)' state (Colton and Wilcock, 2010). The M1 activated microglia secrete various pro-inflammatory cytokines [such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin 1-β (IL-1β)] and cytotoxic factors [such as nitric oxide (NO) and reactive oxygen species (ROS)] (Aloisi, 2001) to promote the destruction of pathogens (Kettenmann et al., 2011). However, the non-specific immune responses can simultaneously induce neurotoxicity in the healthy tissue (Colton and Wilcock, 2010). Hence, M2-activated microglia play key roles in maintaining homeostasis by secreting anti-inflammatory cytokines [for example, IL-10 and transforming growth factor-β] to down-regulate the pro-inflammatory processes and promote tissue reconstruction (Colton and Wilcock, 2010). The activation of microglia has been demonstrated in AD tissue, especially in surrounding amyloid plaques (Cagnin et al., 2001; Higuchi, 2009), and the pro-inflammatory factors released from activated microglia appear to contribute to detrimental effects (Galasko and Montine, 2010; Zaheer et al., 2008). However, the beneficial effects of microglial activation also deserve substantial attention. In particular, activated microglia clear amyloid plaques (Hickman et al., 2008; Maier et al., 2008; Tahara et al., 2006), which are believed to be not only the core hallmark of AD but also the initiator of downstream responses that exacerbate neurodegeneration. The complexity of microglial activation makes it difficult to completely understand the role of microglia in AD, but it has been suggested that microglial dysfunction augments their neurotoxic effects and suppresses their neuroprotective functions, thus contributing to the process of the disease. If this hypothesis is true, the modulation of microglial activation may be a promising target for AD therapy.

Toll-like receptors (TLRs) are important members of the family of pattern recognition receptors (PRRs). In mammals 12 types of TLRs have been detected in various cell types and human microglia express TLRs 1–9. TLRs are transmembrane proteins that are composed of highly conserved structural domains, containing the binding sites for both their ligands and their coreceptors. They recognize specific ligands to initiate the inflammatory process, activating signaling molecules such as the transcription factor nuclear factor κB (NF-κB) and the mitogen-activated protein kinase (MAPK) to promote microglial phagocytosis, cytokine release and the expression of the co-stimulatory molecules needed for adaptive immune responses (Hanke and Kielian, 2011). Thus, TLRs serve as the first line of defense against pathogens, and their activations result in the death or disposal of the invading pathogen. Moreover, in recent decades, increasing evidence has suggested the involvement of TLRs in AD.

In this review, the key evidence supporting the important roles of microglia in AD is summarized. Additionally, we elucidate the influences of manipulating microglial TLRs on AD pathology, including the operations of TLRs gene in AD animal models. Finally, the genetic polymorphisms that suggest the disruption of TLRs in the brains of patients with AD are illustrated.

2. Microglial activation in AD

As early as the 1990s, various postmortem experiments demonstrated microglial activations in the brains of AD patients, especially in the vicinity of amyloid-β (Aβ) peptide-containing plaques (McGeer et al., 1987; Styren et al., 1990; Wisniewski et al., 1992). Ultrastructural analyses demonstrated individual microglia extending their finger-like processes into the core of plaques (Wisniewski et al., 1992), suggesting a specific microglia-Aβ association and indicating that Aβ may be the major driving force for microglial activation. Furthermore, the development of in vivo positron emission tomography (PET) imaging has greatly expanded our understanding of microglial activation in AD. Several studies reported an increased activated microglial load in AD brains, and this increase was directly correlated with the degree of cognitive deficits (Edison et al., 2008; Okello et al., 2009; Versijpt et al., 2003; Yasuno et al., 2012).

Additionally, activated microglia have been detected in various animal models. For instance, in the AβPP, P301S and triple-transgenic (3 × Tg-AD) mice, an increased number of activated microglia labeled by immunostaining were reported (Bellucci et al., 2004; Bornemann et al., 2001; Janelsins et al., 2005), and ultrastructural analysis showed microglia extending finger-like processes into Aβ fibrils (Stalder et al., 2001), similar to findings reported in the human brain (Wisniewski et al., 1992). Lines of in vivo PET imaging studies have further demonstrated the activation and both Aβ-driven and age-dependent activation occur (Meyer-Luehmann et al., 2008; Rapic et al., 2013; Venneti et al., 2009).

Microglial activation in AD is suggested to be heterogeneous, and Aβ plaques are considered to be the major driving forces. Numerous in vitro experiments have demonstrated the Aβ-induced microglial expression of inflammatory factors, including pro-inflammatory cytokines, chemokines, ROS, reactive nitrogen species and acute phase proteins (Mandrekar-Colucci and Landreth, 2010). Most of these factors were found to be neurotoxic

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