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Review article

Chronoinflammaging in Alzheimer; A systematic review on the roles of toll like receptor 2

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ABSTRACT

Aging is associated with a range of chronic low-grade inflammation (Chronoinflammaging) which may play a significant role in some chronic inflammatory based diseases, such as Alzheimer disease (AD). However, the events which lead to the induction of chronoinflammaging in AD are yet to be clarified. It has been proposed that the recognition of endogenous ligands by pathogen recognition receptors (PRRs) may be involved in the induction of chronoinflammaging. Toll like receptors (TLRs) are a family of PRRs which recognize endogenous damage associated molecular patterns (DAMPs) and subsequently induce inflammation. Therefore, TLRs are worthy of investigation to elucidate their roles in chronoinflammaging associated AD. This review article explores the main roles played by TLR2 in the pathogenesis of chronoinflammaging in patients suffering from AD.

Contents

1. Introduction

Chronoinflammaging is defined as a chronic inflammation in elderly humans [51]. Previous investigations demonstrated that increased production and release of endogenous non-microbial molecules, known as damage associated molecular patterns (DAMPs), as well as the malfunction of immunoregulatory factors are the main mechanisms responsible for the induction/stimulation of chronoinflammaging [37,52]. The complication is significantly associated with several age-related disorders such as age-related muscle wasting, type 2 diabetes, kidney dysfunctions, atherosclerosis, Alzheimer's/Parkinson's diseases and so on [7,9,32]. Therefore, chronoinflammaging appears to have a role associated with Alzheimer disease (AD) and it is possible that there is a correlation

Abbreviation: NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; AP-1, activator protein 1; PAMPs, pathogen associated molecular patterns; DAMPs, damage associated molecular patterns; MYD88, myeloid differentiation primary response; PRR, pathogen recognition receptor; TIR, toll/interleukin-1 receptor; LRRs, leucine-rich repeats; HSP60, heat shock protein 60; LPS, lipopolysaccharide; HMGB-1, high-mobility group box-1; Aβ, β-amyloid; DCs, dendritic cells; AD, Alzheimer disease; TLRs, toll like receptors; MAPKs, mitogen-activated protein kinases; PI3K/AKT, phosphatidylinositol 3-kinase/AKT; JNK, c-Jun N-terminal kinases; NF-κB, nuclear factor-κB; SOCS, suppressor of cytokine signaling; MAL, MyD88 adapter-like; IRAK1, interleukin-1 receptor-associated kinase 1; Dok, downstream of kinase; ERK, extracellular signal-regulated kinase; CD, cluster of differentiation; TNF, tumor necrosis factor; AP-1, activator protein 1.

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with increased production of DAMPs in the elderly humans. Additionally, it has been documented that DAMPs induce human cells to produce inflammatory factors via interactions with pathogen recognition receptors (PRRs), which are the corresponded receptors [5]. Thus, PRRs may play key roles in the induction of chronoinflammaging in patients suffering from AD. PRRs consist of several immune receptors which recognize DAMPs and pathogen associated molecular patterns (PAMPs) including toll like receptors (TLRs) [40,43]. TLRs are innate immune cell receptors which are presented either on the cytoplasmic membrane or in intra cellular vesicles [22]. TLR2, like other TLRs, can be considered as potential candidates for recognition of endogenous DAMPs and subsequent induction of chronoinflammaging. TLR2 induces immune cell activation via the myeloid differentiation primary response (MYD88) dependent pathway [46]. Thus, a hypothesis regarding the roles played by TLR2 in the induction of chronoinflammaging in AD has been raised by investigators. Therefore, this review addresses current information regarding the roles played by TLR2 in induction of chronoinflammaging in AD and its complications.

2. Alzheimer and chronoinflammaging

Aging is a period of human life which is associated with disability in personal life functions but is not considered as a disease [12]. According to the WHO definition, age of more than 60 years is considered as aging [2]. Nowadays, aged populations are increasing world-widely and it appears that more than 1200 million elderly humans will be alive by the end of 2030 [18]. Elderly individuals represent the largest population at risk of chronic inflammation associated diseases such as AD [12]. AD is an aging related disorder which is defined as declination in episodic memory [11]. AD is a progressive neurodegenerative dementia and is associated with the accumulation of harmful extracellular and intracellular neuritic plaques and tangles in the brain, respectively [11]. Several proteins, including β-amyloid (Aβ), a 4-kDa protein, are pathologically deposited in the plaques [4] and this is commonly associated with disease progression, however, this hypothesis is currently being challenged [36]. Although, the main mechanisms responsible for induction of AD are yet to be clarified, investigators believe that the deposited proteins play key roles in induction and deterioration of AD [4]. It seems that induction of inflammation by the proteins, especially Aβ, can be considered as an important factor involved in the pathogenesis of AD [4]. TLR2 has been identified as a receptor for Aβ, and this has been supported by several investigations in humans [6,17,34,57] and animals [8,47]. Richard et al., also confirmed the role of TLR2 in the recognition of Aβ [41]. TLR2 can also recognize microbial amyloids, a molecule similar to human Aβ [6,34]. Therefore, TLR2, as the receptor of Aβ, may participate in the pathogenesis of AD which is discussed below.

3. Toll-like receptor 2

TLR2 is a cell surface receptor for endogenous DAMPs and exogenous PAMPs. It is also known as TIL4 and CD282 and was first defined and characterized in 1998 [42]. TLR2 is expressed on the cytoplasmic membrane of several cell systems including polymorphonuclear cells, monocytes and macrophages, endothelial cells, dendritic cells (DCs), activated B lymphocytes, epithelial cell lines and hepatocytes [14,38,54].

The gene encoding TLR2 is highly conserved and is located on 4p32. Three dimensional structures showed that TLR2 is a type I transmembrane protein, and, like other TLRs, consists of three main domains including, leucine-rich repeats, hydrophobic transmembrane and toll/interleukin-1 receptor domains. TLR2 can recognize DAMPs and PAMPs in either homodimeric or heterodimeric (with TLR1/6) forms [55]. The most characterized ligands for TLR2 are: lipoteichoic acid, bacterial peptidoglycan, porins, lipoprotein, bacterial triacylated lipopeptides, viral hemagglutinin and glycoproteins, high mobility group box 1 protein, human glycosaminoglycan hyaluronan, heat shock proteins and β-defensin-3 [1,5,23,35]. Recently, new agonists for TLR2, such as synthetic triacylated lipopeptide Pam3CSK4 have also been identified [49]. After activation by forming TLR2/ligand interactions, several intracellular signaling pathways, which lead to the induction of inflammation, are activated including; MAPK and MYD88 dependent signaling pathways. Conversely, pathways that lead to the suppression of immune cell activation, including the PI3K/AKT pathway (as inducers of anti-inflammatory molecules such as IL-10) and SOCS [16,26,31] are also activated. Activation of the MAPKs and MYD88 dependent signaling pathways and PI3K/AKT pathway happens after recruitment of MYD88 and MAL (TIRAP) to the TIR domain of TLR2 [15]. Investigations also demonstrated that TLR2/TLR2 ligands interactions led to the suppression of IRAK1, a crucial factor for production of other TLR-induced type I interferons [30]. Therefore, it appears that TLR2 plays dual roles in both the induction and inhibition of immune responses against DAMPs and PAMPs. Although, the main mechanisms responsible for the controversial functions of TLR2 are unclear it seems that the concentration of TLR2 ligands may be considered as a determining factor [5]. Additionally, it seems that TLR2 has a negative feedback mechanism to regulate its functions. For instance, TLR2 increases downstream of kinase (Dok)1 and Dok2 tyrosine phosphorylation [10]. Phosphorylated Dok1 and 2 are important regulatory factors which block TLR2 dependent ERK and NF-κB pathways [10]. Fig. 1 illustrates the intracellular signaling pathways of TLR2.

4. TLR2 and Alzheimer

Tang et al., identified that TLR2 was up-regulated in neurons in response to energy deprivation and this may have a role in the pathogenesis of AD [48]. However, the investigations revealed that TLR2 plays dual roles in AD including the clearance of deposited Aβ, and the induction of expression of pro-inflammatory molecules in response to β-amyloid. TLR2 is not only able to recognize deposited Aβ but can also be considered as a receptor for microbial amyloids which are similar to Aβ [6,34]. Accordingly, there are some limited studies which reported a positive role of TLR2 in protection of AD. Richard et al., revealed that TLR2 clears Aβ and subsequently delays the cognitive declination in an animal model of AD [41]. The roles of TLR2 in phagocytosis of Aβ in AD have also been documented by Tahara et al. [47] and Chen et al. [8]. Based on these investigations, the positive roles of TLR2 in the prevention of AD have been explored in animal models. While, the investigations on the human have revealed that TLR2 has negative roles in AD and can be considered as inducer/stimulator of the diseases. Accordingly, investigators confirmed the roles played by TLR2 in the recognition of Aβ and induction of inflammation in the brain during AD [17,57]. As mentioned previously, Aβ plays important roles in the pathology of AD via its inflammatory and neurotoxic effects [57] as well as the induction of neuroinflammatory complications in the later stages of the disease [13]. Another study in humans demonstrated that deficiencies in TLR2 are associated with either reduced Aβ triggered inflammatory activation or increased Aβ phagocytosis [29]. Therefore, it seems that TLR2 can be used by microglia cells for the induction of Aβ related inflammation but not for phagocytosis of Aβ in the pathologic condition [29] and these pathways can be considered as mechanisms for the induction of AD in humans [13]. Interestingly, the correlation of TLR2 with the induction of AD has been reported by Zhang and colleagues who claim that TLR2 expression is increased in the peripheral blood mononuclear cells from AD patients [60]. Furthermore, up-regulation of TLR2 in AD, but not in other brain related diseases such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB), has also been reported by investigations on human models [24,44]. Hill et al., demonstrated that in AD patients the TLR2 receptor was responsible for detecting human microbial amyloids such as CsgA and curli, and endogenous Aβ 42 peptides, which is accumulated in AD [19]. Based on the aforementioned investigations it seems that TLR2 plays pathologic roles in induction/stimulation of AD in human. Interestingly, some investigations on animal models support these conclusions. For example, Chen et al.,