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Review article

Biological role of Toll-like receptor-4 in the brain

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ABSTRACT

The Toll-like receptors (TLRs) are a family of microbe-sensing receptors that play a central role in the regulation of the host immune system. TLR4 has been described in the brain and seems to regulate some physiological processes, such as neurogenesis. TLR4 has also been reported to play a role during neurodegenerative disorders, including Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis and Parkinson's disease. This review is focused on reports concerning recent insights into the role and activation mechanisms of TLR4 in the brain, in pathological and physiological conditions, as well as the therapeutic benefit that could derive from TLR4 modulation.

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1. Introduction

Mammalian Toll-like receptors (TLRs) were initially discovered because of their sequence similarities to *Toll* involved in *Drosophila* dorsoventral embryonic development and antifungal immunity (Nüsslein-Volhard and Wieschaus, 1980; Steward et al., 1984; Lemaitre et al., 1996). In 1997, Medzhitov et al. cloned a human homolog of the *Drosophila* Toll protein, now known as TLR4, and showed that Toll signaling was able to stimulate adaptive immune responses (Medzhitov et al., 1997). Shortly after, the Toll gene was discovered to be an important component for the detection of microbes in *Drosophila melanogaster*, as well as demonstrations that TLR4 mediates the inflammatory response to lipopolysaccharide (LPS) in mice (Poltorak et al., 1998; Poltorak et al., 2000). This led to the identification of the target molecule of LPS on the cellular surface of macrophages. These discoveries substantially extended the knowledge of pathogen-mediated intra-cellular

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signal transduction, and were crucial for understanding the mechanisms that govern innate immunity (Bode et al., 2012).

In general, mammalian cells recognize the presence of pathogens through a group of receptor complexes, also termed pattern recognition receptors (PRR), that are specialized in detecting conserved molecular structures that are essential to the life cycle of a pathogen. These pathogen-borne molecular structures are also termed pathogen-associated molecular patterns (PAMP) (Takeda and Akira, 2005; Akira et al., 2006).

Thus, the term PRR encompasses a heterogeneous group of soluble, membrane-bound or cytoplasmic receptor structures involved in the detection of PAMPs. These molecular sensors are crucial to the initiation of innate immunity, constituting the first line defense against microorganisms (Bode et al., 2012).

Specifically, TLRs are a family of PRR that enable the recognition of conserved structural motifs in a wide array of pathogens. They are homologs of Toll, a receptor found in insects, involved both in establishing dorsoventral polarity during embryogenesis and in immune response against fungal infections (Hashimoto et al., 1988; Lemaitre et al., 1996). These receptors are type I integral membrane glycoproteins characterized by three major domains: (1) a leucine-rich extracellular domain; (2) a transmembrane domain; and (3) a cytoplasmic TIR domain homologous to that of the interleukin 1 (IL-1) receptor, termed the Toll/IL-1 receptor (TIR) domain (O'Neill and Dinarello, 2000). Ligand recognition by TLRs is mediated by the extracellular domain that harbors a leucine-rich repeat (LRR) composed of 19–25 tandem copies of the "xLxxLxLxx" motif (Jin and Lee, 2008).

To date, 10 members of the human receptors and about 13 mammalian TLRs have been described (Akira et al., 2006; McGuire et al., 2006) and more recently, 10 bovine TLRs have been mapped (McGuire et al., 2006). Among these, TLR1–TLR10 are conserved between humans and mice, although TLR10 is not functional in mice because of a retroviral insertion, whereas TLR11–13 are not present in humans (Akira et al., 2006; Beutler et al., 2007; Medzhitov, 2007).

The TLR family can be divided into extracellular and intracellular members. TLR1, TLR2, TLR4, TLR5, TLR6, and TLR11 are localized on the cell surface to recognize PAMPs. Conversely, TLR3, TLR7, TLR8, and TLR9 are intracellularly expressed in endosomal or lysosomal compartments and the endoplasmic reticulum (ER) (Bode et al., 2012). TLRs are described not only in the immune cells, such as macrophages, dendritic cells, B and T cells, but also in non-immune cells, including fibroblasts and epithelial cells (Wang et al., 2006).

In 1998, TLR-4 was identified as the signaling receptor for LPS or endotoxin from the outer membrane of Gram-negative bacteria (Poltorak et al., 1998). The TLR4 specificity for LPS from Gram negative bacteria has also been demonstrated with TLR4 knock-out mice (Hoshino et al., 1999). Furthermore, a mouse strain possessing a point mutation in the TLR4 gene was shown to be unresponsive to LPS (Poltorak et al., 1998).

There is accumulating evidence that not only does TLR4 activation affect the immune response against invading Gram-negative bacteria but it is also involved in the development and progression of a number of neurodegenerative diseases (Schröder and Schumann, 2005). In the CNS, constitutive expression of TLR4 transcripts has been described in distinct anatomical areas of the brain (Lacroix et al., 1998; Laflamme and Rivest, 2001). In this respect, it was reported that microglia but not astrocytes or oligodendrocytes express TLR4, and that TLR4 is required for LPS-induced oligodendrocyte death in vitro (Lehnardt et al., 2002). Recently, TLR2 has also been reported to be involved in neurodegeneration (Koedel et al., 2007; Okun et al., 2009; Ziegler et al., 2011). Among TLRs, TLR2 seems to be the most promiscuous TLR receptor capable of recognizing the widest set of different pathogens. TLR2 complexes with TLR1 or TLR6 are involved in the recognition of bacterial lipoproteins (Akira and Takeda, 2004; Gay and Gangloff, 2007). TLR2 can also interact with other molecules such as CD36 (Triantafilou et al., 2006) or CD14 (Yang et al., 1999; Flo et al., 2002) and can induce multimerization in response to different microbial ligands (Triantafilou et al., 2006). Interestingly, LPS is able to cause a robust transcriptional induction of TLR2 in the brain, but this receptor does not modulate the immune response to LPS in the brain (Naert et al., 2009).

By contrast, in the central nervous system (CNS), TLR4 has been reported to be constitutively expressed in microglia (Lehnardt et al., 2003) and its ligand, LPS, induces the production of inflammatory mediators including tumor necrosis factor alpha (TNF-α), IL-6, and nitric oxide (NO) (Akira and Takeda, 2004) via the nuclear factor κB (NF-κB) signaling pathway.

Considering the critical role of TLR4 in neuroinflammation and brain injury, the aim of this review is to focus on reports concerning recent insights into the role and activation mechanisms of TLR4 in the brain, not only in pathological events but also in physiological conditions, as well as the therapeutic benefit that could derive from TLR4 modulation.

2. TLR-4 signaling

In the host system, LPS capture is facilitated by the LPS binding protein (LBP) which transfers it to the receptor complex composed of CD14, MD-2 (or LY96) and TLR4. Upon LPS binding, TLR4 recruits, through its short intracellular TIR domain, adaptor molecules and kinases, thus initiating a downstream signaling cascade that culminates in the secretion of pro-inflammatory cytokines and chemokines (Takeuchi and Akira, 2002; Takeda and Akira, 2005). Activation of TLR4 by LPS induces two signaling pathways known as the myeloid differentiation primary response gene 88 (MyD88) dependent and independent pathways (Akira et al., 2006).

The MyD88 dependent pathway in TLR4 signaling requires the adaptor proteins TIRAP (TIR domain containing adaptor protein) and MyD88 to initiate a downstream cascade leading to nuclear translocation of the nuclear factor (NF)-κB and mitogen associated protein (MAP) kinase signaling pathways (such as the ERK-CREB pathway, the JNK-AP1 pathway, and the p38 pathways), resulting in the production of pro-inflammatory cytokines (Kagan and Medzhitovd, 2006). This leads to the rapid expression of inducible nitric oxide synthase (iNOS) and a wide variety of proinflammatory cytokines, chemokines, and their receptors, including tumor necrosis factor alpha (TNF-α), IL-1α, IL-1β, IL-1ra, IL-6, IL-8, IL-10, IL-12p40, IL-23, and macrophage inflammatory protein (MIP)-1α, and MIP-1β (Lee and Kim, 2007). These factors initiate the inflammatory response, increase vascular permeability, direct dendritic cells (DC) and macrophage migration from the periphery to the central lymphoid organs, and regulate various aspects of adaptive immunity development.

On the other hand, the independent signaling pathway is controlled by the adaptors TICAM (Toll-like receptor adaptor molecule) 1 or TRIF (TIR-domain-containing adaptor inducing interferon-β) and TICAM 2 or TRAM (TRIF-related adaptor molecule), which activate the transcription factor IRF3 (IFN regulatory factor 3) and the production of IFN-β and chemokine RANTES (Regulated on Activation Normal T cell Expressed and Secreted) (Yamamoto et al., 2003a,b).

TLR4 engagement leads to the production of neurotoxic molecules such as proinflammatory cytokines, NO, reactive oxygen species (ROS), and peroxynitrite (Xie et al., 2002). Moreover, LPS-activated microglia produce a large amount of glutamate, an important neurotransmitter which in some circumstances acts as a potent neurotoxin (Takeuchi et al., 2006). LPS challenge may also activate TLR4 on the microglia surface, leading to oligodendrocyte injury (Lehnardt et al., 2002). Recently, CNS-relevant in vitro and in vivo studies have highlighted the function of suppressor of cytokine signaling (SOCS) proteins under various neuroinflammatory or neuropathological conditions. SOCS1 and SOCS3 have been described as having a short half-life (1–2 h) and their expression levels are reported to increase rapidly following macrophage exposure to inflammatory cytokines and TLR ligands. Expression of SOCS1 and SOCS3 is regulated primarily by activation of STAT1 and STAT3, respectively, although their expression can be mediated through other signaling cascades, including the mitogen activated protein kinase

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