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Innate immune regulation of autoimmunity in multiple sclerosis: Focus on the role of Toll-like receptor 2

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ABSTRACT

Innate immunity relies on a set of germline-encoded receptors including Toll-like receptors (TLRs) that enable the host to discriminate between self and non-self. Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS). Infections are thought to play an important role in disease susceptibility. The role of innate immunity in MS has been recently appreciated. TLR2, a member of the TLR family, forms heterodimers with either TLR1 or TLR6 and detects a wide range of microbial as well as self-derived molecular structures. It may thus be important both in fighting infection and in activating autoimmunity. In this review, we discuss innate regulation of autoimmunity in MS with a focus on the role of TLR2 signaling.

1. Introduction

Innate immune system is the first line of host defense, hard-wired in germline-encoded receptors called pattern recognition receptors (PRRs), which enable the host to fight a vast array of invading pathogens. Innate immunity has evolved several strategies of self/nonself discrimination that are based on the ability of the PRRs to recognize and bind to conserved pathogen associated molecular patterns (PAMPs) produced by the microbes (either pathogenic or non-pathogenic) but not the host (Medzhitov and Janeway, 2002). Upon PAMP recognition, PRRs initiate a series of signaling cascades that execute the first line of host defensive responses necessary for killing infectious microbes. Innate immune response to infection is faster, while it lacks memory and specificity that makes it less effective in case of a second infection with the same pathogen (Akira and Hemmi, 2003). In the continuous fight of the host against invading pathogens a more specific and sustained immune response is needed which is defined as adaptive immunity. PRR signaling induces maturation of dendritic cells (DCs) and thus contributes to inducing adaptive immunity (Kawai and Akira, 2011). The two main arms of adaptive immunity are T cells (cellular immunity mediated by cytokines and chemokines) and B cells (humoral immunity mediated by antibodies). In addition to antigen-MHC binding to the TCR (signal 1), a costimulatory signal (signal 2) such as engagement of CD28 on T cells with CD80/86 (B7) or CD54 (ICAM-1) on APCs is required for the activation of T cells, which can then activate B cells as well (Fallarino et al., 2016). Inflammatory cytokines, such as e.g., IL-12 and type-I interferons for effector function of CD8+ and Il-1β for effector function of CD4+ T cells (Gran et al., 2013; Fallarino et al., 2016; Pettus and Wurz, 2008) may function as 'signal 3' to modify the phenotype of induced immune responses. Innate immune receptors like PRRs are thus essential for bridging the innate and adaptive immunity. Activation of PRRs by PAMPs upregulates expression of B7 molecules on APCs which is necessary for lymphocyte activation (signal 2) and also induce effector cytokines like IL-1, IL-12 and IFNs necessary for T cell effector functions (signal 3) (Medzhitov and Janeway, 1997).

PRRs are categorized according to their function (endocytic or signaling PRRs), localization and their ligand specificity. The families of PRRs involved in PAMP recognition and the control of innate immunity include TLRs, membrane-bound C-type lectin receptors (CLRs), cytosolic proteins such as nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and retinoic acid-inducible gene 1 (RIG-I)-like receptor (RLRs) (Kawai and Akira, 2011; Elinav et al., 2011). Cross talk between TLRs and other PRRs is being investigated (Kawai and Akira, 2011).

TLRs were the first identified family of PRRs. TLRs are type I transmembrane glycoproteins with a tri-modular structure which include extracellular leucine rich repeats (LRR) responsible for PAMP binding, a transmembrane domain and the intracellular Toll-interleukin (IL)-1 receptor (TIR) domain which interacts with adaptor proteins and mediates the downstream signaling (Podda et al., 2013). There are about 13 TLRs known to date. Both humans and mice express TLR1–TLR9.

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Humans, but not mice, express TLR10 and mice exclusively express TLR11–TLR13 (Chaturvedi and Pierce, 2009). TLR1, TLR2, TLR4, TLR5 and TLR6 are localized on the cell surface and exclusively recognize microbial membrane components whereas TLR3, TLR7, TLR8 and TLR9 are expressed on endosomes and recognize nucleic acids (Blasius and Beutler, 2010). Recently, it was shown that TLR11, a relative of TLR5 expressed on the cell surface, is also expressed in intracellular compartments (Pifer et al., 2011), but is not considered functionally active in human cells. TLR13 is also expressed in intracellular vesicles with yet unknown ligands (Blasius and Beutler, 2010). TLRs differ from each other in terms of ligand specificities, expression patterns, and possibly, in the target genes they can induce (Janeway Jr and Medzhitov, 2002). Ligand induced activation leads to the formation of TLR homo- and heterodimers; most of the TLRs form homodimers except for TLR2, which form heterodimer with TLR1or TLR2. Downstream signaling requires the recruitment of several adaptor proteins containing Toll/interleukin-1 receptor (TIR) domains. To date, five distinct TIR domain containing adaptor proteins are known: MyD88, MAL/TIRAF, TRIF, TRAM and SARM (Takeuchi and Akira, 2010; O'Neill and Bowie, 2007). MyD88 is considered as the most important adaptor protein in TLR signaling as MyD88-deficient mice were reported to have an impaired ability to signal through TLRs and, consequently, their APCs are unresponsive to TLR ligands (Kawai et al., 1999; Kaisho et al., 2001). The idea that MyD88 is essential for responses against a broad range of microbial ligands was strengthened when MyD88-deficient mice were reportedly failed to produce TNF or IL-6 when exposed to IL-1 or microbial ligands recognized by TLR2, TLR4, TLR5, TLR7 or TLR9 (Weiner, 2008). This led to categorizing TLRs as either MyD88 dependent or MyD88 independent. All the TLRs except TLR3 signal through a MyD88-dependent pathway to activate the transcription factor NF-kB leading to the expression of proinflammatory cytokine genes. TLR3 signals through Myd88-independent pathway and requires TRIF as an adaptor to activate type 1 IFN genes while TLR4 uses both MyD88 dependent and TRIF-dependent pathways (Akira, 2003).

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease of the central nervous system (CNS) characterized by inflammation and neurodegeneration. The etiology of MS is unknown however both genetic and environmental factors are thought to be involved (Xia et al., 2016). Inflammation in MS is mediated by peripheral myelin reactive CD4 + T cells (Bielekova et al., 2004) that express adhesion molecules facilitating their interactions with ligands present on vascular endothelial cells, resulting in transmigration to the CNS compartment (McQualter and Bernard, 2007). Once in the CNS, myelin reactive CD4 + T cells may be reactivated and lead to the characteristic demyelination and progressive axonal pathology (McQualter and Bernard, 2007). In recent years, genome-wide association studies (GWAS) and the genetic and epigenetic fine mapping studies showed that MS is an immune-mediated disease where both adaptive and innate immune cells are involved in the processes of inflammation, demyelination and neurodegeneration (Sawcer, 2011; Farh et al., 2015).

Adaptive immunity, specifically T cells and then B cell responses, have been the central focus in MS immunology research for the last few decades and they remain the major target for many of the MS immunomodulatory and immunosuppressive treatments (Constantinescu and Gran, 2014). Experimental autoimmune encephalomyelitis (EAE), the animal model of MS is considered a T-cell mediated disease with a peripheral trigger and subsequent blood brain barrier (BBB) breakdown and immune effector damage in the CNS (Constantinescu et al., 2011; Bert et al., 2011). Recent studies suggested that the innate immune system also plays a crucial role in MS, both in the initiation and the progression of the disease principally by modulating effector functions of T and B cells (Weiner, 2008). There are reports about expression of innate immune receptors like TLRs in a wide variety of cells of the innate and adaptive immune system in the periphery and within the CNS both in MS and EAE and levels of several TLRs were found to be elevated in MS lesions (Gran et al., 2013; Bsibsi et al., 2002). Innate immune cells such as dendritic cells (DCs) and tissue macrophages express PRRs including TLRs that recognize PAMP and subsequently produce pro-inflammatory cytokines and can serve as antigen-presenting cells (APCs) to prime naïve T cells to recognize antigens in the presence of T cell stimuli and co-stimulatory molecules (Takeda and Akira, 2005). Thus, TLRs play a role in linking the innate to the adaptive immune response (Fallarino et al., 2016). Depending on the specific TLR evaluated, TLR expression on CNS cells has been demonstrated to contribute to oligodendrocyte and neuron death (Lehnardt et al., 2003) or in other cases to be neuroprotective (Bsibsi et al., 2006).

A growing body of literature suggests a central role of the PRRs including TLRs for the development of autoimmune diseases (Marsland and Kopf, 2007). In addition to PAMPs derived from bacteria and viruses, TLR can also bind endogenous ligands and danger associated molecular patterns (DAMPs) produced as a result of tissue damage (Midwood et al., 2009). The role of different TLRs has been studied in relation to MS and its animal model EAE (Midwood et al., 2009).

Compared to other TLRs, TLR2 can sense the widest range of PAMP and endogenous ligands. TLR2 is ubiquitously expressed by immune (both innate and adaptive) cells, endothelial cells, epithelial cells and nervous system cells (Cameron et al., 1997; Bsibsi et al., 2002; Carson et al., 2006; Chang et al., 2009). The role of TLR2 in MS and other autoimmune and inflammatory diseases has been extensively investigated (Keogh and Parker, 2011; Midwood et al., 2009; Pålsson-McDermott and O'Neill, 2007). TLR2 could possibly play a dual role as both a proinflammatory and an anti-inflammatory molecule in MS. TLR2 was proposed to be at the crossroad of infection and autoimmunity (Borrello et al., 2011). In the context of MS, TLR2 is an important innate immune checkpoint which could be a potential target for therapeutic interventions (Hossain et al., 2015). In the next part of this review, we aim to give an overview of the innate immune regulation of autoimmunity, focus on the dichotomous role of TLR2 as both proinflammatory and anti-inflammatory receptor and discuss some aspects of regulation of TLR2 signaling and its effects relevant to MS.

2. Innate immune regulation of autoimmunity within the CNS and in the context of MS

For many years, the CNS has been considered 'immune privileged' as heterologous tissues that are rapidly rejected by the immune system when grafted in sites such as the skin were able to escape immune rejection when grafted into the CNS. This phenomenon was explained by several facts such as Pthe presence of the blood-brain barrier (BBB) which separates the CNS and the arterial blood flow, the lack of draining lymphatics, and the immunological features of CNS resident myeloid cells (microglia) (Carson et al., 2006). CNS autoimmunity and neurodegeneration were thought to result from immune cells encountering CNS antigens in the periphery. Our understanding of the mechanisms of immune privilege is being refined. Peripheral immune cells (e.g., Th17 cells) can cross the BBB to enter the uninflamed CNS (Reboldi et al., 2009) and the CNS is directly connected to secondary cervical lymph nodes via a standard lymphatic drainage system that can promote the generation of peripheral immune responses (Louveau et al., 2015; Aspelund et al., 2015). Thus, the current view is that the CNS is not immunologically inert, but rather interactive with peripheral immune components, CNS-resident innate immune cells (mainly microglia and astrocytes) are not incompetent but actively maintain a tolerogenic CNS environment and their functions are in part regulated by neurons and glial cells (Carson et al., 2006). Neurons promote a quiescent state of microglial cells by expressing ligands such as CD22, CD200, and CX3CL1 (fractalkine) (Carson et al., 2006). In mice lacking CD200 expressed on neurons, microglia show an activated phenotype that is associated with more severe disease in the EAE model (Hoek et al., 2000). Furthermore, there is evidence that neurodegeneration and demyelination can occur even in the absence of substantial infiltration of peripheral immune cells (Bø et al., 2003). Of note, inflammation within