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Review Article

Toll-like Receptors in Multiple Sclerosis: From Immunobiology to Therapeutics

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Abstract
Multiple sclerosis (MS) is an autoimmune demyelinating disorder of the central nervous system (CNS). The pathophysiology of MS is not completely understood, and it involves multiple immune mechanisms and pathways. Toll-like receptors (TLRs) play a significant role in modulating chemokine and cytokine secretion, which are critical to CNS autoimmunity and regulation. Recent studies claimed that modulating TLRs can be considered a revolutionary in immunotherapeutic approaches to treating MS. This manuscript will review the current evidence on the role of TLRs in the pathogenesis of MS. We will start by introducing TLRs and their function in the immune system. Then we will proceed to discuss the role of TLRs in the pathogenesis of autoimmune disorders, particularly the main goal of our study: MS. Then we will elucidate TLR pathways in MS to better illustrate a perspective for targeting TLRs as a therapeutic method for MS. Finally, we will elaborate on the possible role of TLRS in the treatment of MS.

Keywords: Multiple Sclerosis; Toll-Like Receptor; TLR, Autoimmune Disorder, Treatment

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune condition leading to demyelinating lesions in the central nervous system. It is the most prevalent neurological disabling disorder, which can lead to cognitive or physical disabilities (1). Based on the progression and activity of the disease, it is traditionally classified into three major groups: primary progressive MS (PPMS), secondary progressive MS (SPMS), and relapsing-remitting MS (RRMS). This classification is important to define proper modifying therapy (2). Although the primary cause of MS is unknown, the interaction between T cells and antigen-presenting cells (APCs), which leads to the onset of the adaptive immune response, plays a signifi-

cant role in MS onset and progression (3). Some studies have highlighted the role of microglia, astrocytes, and dendritic cells as potential roles of APCs in the pathogenesis of MS (4). Multiple risk factors have been implicated in MS, such as smoking (5), diet (6), deficiency of vitamins such as B12 and D (7), exposure to carbon monoxide (CO) (8), UV radiation (9), Mycoplasma pneumoniae, and Epstein Barr virus (10).

Worldwide, over 2.8 million people suffer from MS, and the highest prevalence rate is observed in Europe (almost 133 per 100,000 people), with females being three times more affected than males (11). These data show the significance of MS among neurological disorders, especially if taking into account the high number of years lived with disability (YLD). Currently, the treatment of MS is mainly symptomatic based on its stage and progression (12). Toll-like receptors (TLRs) play a significant role in inflammatory pathways in order to link innate immunity with adaptive immunity consequently. They can directly regulate inflammatory reactions and activate innate and adaptive immune responses, which leads to the elimination of pathogens (13, 14). Identification of toll genes and their protein in Drosophila leads to the discovery of TLR, and its naming returns to its similarity with toll proteins known as the receptors on the cell surface (15, 16).

In this manuscript, we will review the evidence implicating TLRs in the pathogenesis of multiple sclerosis. Importantly, TLRs have been seen as promising therapeutic targets for MS, and related molecules are now in clinical trials.

What are TLRs?

TLRs are a class of immunological receptors that detect the molecular signature of microbial pathogens (17). Prior to the discovery of TLRs, innate immunity was thought to be a primitive component of the immune system. In other words, immunologists referred to it as the first stage of a more complex immunity response (adaptive immunity) or being involved in the body's systemic response, such as fever. Although the mechanisms for producing innate immune components such as cytokines were known, the mechanisms for boosting antiviral interferon expression were not. TLR discovery offered molecular insight into these mechanisms and paved the way for the discovery of other receptor families in innate immunity. For instance, the first discovered TLR was Drosophila melanogaster Toll-1, which was recognized based on its role in embryonic dorsal-ventral polarity specification (18). TLR discovery also indicated promising future immunological research directions (19) and resulted in the awarding of the Nobel Prize in 2011 to Bruce Beutler and Jules Hoffmann (20).

TLRs are found in both innate immune cells like macrophages and dendritic cells and non-immune cells like epithelial cells and fibroblast cells. TLRs are divided into two subfamilies based on their location: intracellular TLRs and cell surface TLRs. TLR3, TLR7, TLR8, TLR9, TLR11, TLR12, and TLR13 are intracellular TLRs that are found in the endosome. Cell surface TLRs include TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10. Nucleic acids derived from viruses and bacteria are recognized by intracellular TLRs. Intracellular TLRs can also recognize self-nucleic acids in disease conditions such as autoimmunity. TLRs on cell surfaces recognize microbial membrane components, including proteins, lipids, and lipoproteins (21-23). TLRs are all synthesized in the endoplasmic reticulum (ER), transported to the Golgi complex, and then trafficked to intracellular compartments such as the endosome or cell surface. The localization of intracellular TLRs appears to be critical for recognizing ligands and preventing TLR exposure to self-nucleic acids, which could lead to autoimmunity (24, 25). UNC93B1 (a multi-pass transmembrane protein) and PRAT4A regulate the trafficking of intracellular TLRs from the ER to endosomes (ER-resident protein) (26, 27). Asparaginyl endopeptidase and cathepsins K, L, S, H, and B lead nucleic acid-sensing TLRs to proteolytic cleavage in the endosome, where they become functional and begin signaling (28, 29).

Function of TLRs

The innate immune response is based on the recognition of a group of microbial components known as PAMPs (pathogen-associated molecular patterns) by pattern recognition receptors (PRRs). PRRs allow the human immune system to distinguish between self-antigen and non-self antigens. TLRs are a type of PRRs that are involved in recognizing danger and activating innate im-

mune system responses. TLRs recognize pathogens in B lymphocytes, macrophages, mast cells, eosinophils, dendritic cells, neutrophils, endothelium, adipocytes, cardiomyocytes, and epithelial cells. TLR stimulation increases the synthesis of pro-inflammatory cytokines and anti-bacterial substances. It also stimulates dendritic cell maturation, which increases the expression of MHC antigens and co-stimulatory molecules, making antigen presentation more effective. When innate immunity is insufficient to eliminate pathogens, TLR-activated antigen-presenting cells (APCs) release high levels of pro-inflammatory cytokines such as IL-6, IL-12, TNF-alpha, and chemokines. As a result, the expression of co-stimulatory molecules rises, triggering the adaptive immune response. TLRs also play an important role in immune response regulation by influencing $CD4^+$ $CD25^+$ T regulatory cells, which leads to immune response suppression (17, 30). See **Table 1** for information on the functions of different types of TLRs.

Table 1. Functions of TLRs

Type of TLR	Function
TLR1	Collaborating with TLR2 leads to the recognition of various pathogen-associated molecular patterns (21)
TLR2	Collaborating with TLR1 or TLR6 leads to the recognition of various pathogen-associated molecular patterns (21)
TLR3	Recognition of self-RNAs conjugated from damaged cells, small interfering RNAs, and double-standard RNA of the virus (31-33)
TLR4	Recognition of bacterial lipopolysaccharide (21)
TLR5	Recognition of bacterial flagellin (34)
TLR6	Collaborating with TLR2 leads to the recognition of various pathogen-associated molecular patterns (21)
TLR7	Recognition of viral single-standard RNA (35)
TLR8	Response to bacterial and viral RNA (36)
TLR9	recognition of hemozoin and viral and bacterial DNA (37)
TLR10	Collaboration with TLR2 leads to the recognition of ligands of listeria, sensing influenza A virus (38, 39)
TLR11	Recognition of flagellin (40)
TLR12	Recognition of profilin from toxoplasma gondii (41)
TLR13	Recognition of bacterial 23S rRNA (42)

Role of TLRs in the Pathogenesis of Autoimmune Diseases

Several immune mechanisms can result in immunological tolerance loss during adaptive response differentiation, uncontrolled self-reactive T and B cell activation, and, as a result, autoimmune conditions. Some of these mechanisms will be discussed in continue: TLRs are found in a variety of immune cells, including T and B cells. TLR signaling plays an important role in adaptive system activation through APC costimulatory molecule upregulation and adaptive immune system activation. TLRs are known to be a critical link between innate and adaptive immune responses; thus dysregulation of TLR signaling or continuous activation of TLRs may lead to autoimmunity pathogenesis (43-45).

T helper 1 and T helper 17 or $IL\text{-}17^+$ IFN^+ $CD4^+$ T cells have been shown to play a major role in autoimmune diseases (46). T helper 17 cells have been discovered in the gut of Crohn's disease patients. These cells produce IL-17 and IFN-gamma (47). Auto-reactive T helper1 transfer into naive recipients results in experimental autoimmune uveitis (EAU), which is not inhibited by anti-IL-17 antibodies (48). TLR signaling in the innate immune system can indirectly promote T cell proliferation and differentiation via regulatory cytokine production and dendritic cell maturation (49). Lipopolysaccharide, a TLR4 ligand, promotes IL-17 production by antigen-specific memory T cells (50). TLR signaling in T cells can also regulate the function of cytokines and promote their production (51). Regulatory $CD4^+$ $CD25^+$ T (Treg) cells play an important role in autoimmune conditions as well, as they can suppress the immune system's response to self and nonself antigens. TLR signaling has been shown to regulate $CD4^+$ $CD25^+$ T-reg cells in immunosuppression by altering the balance between T-reg cells and $CD4^+$ Th cells (52). TLR2 activation can result in T-reg suppression resistance by increasing IL-2 production (53). Because of their reaction to cellular components, antibodies play

an important role in the function of B cells in autoimmune diseases (54). TLR9 inhibitory oligonucleotides have a role in abolishing autoreactive B cell responses, which are known as the source of autoantibodies (55). As a coreceptor for autoreactive B cells, TLR7 plays an important role in the breakdown of tolerance and the production of autoantibodies (56). TLR9 signaling causes IgG production by directly affecting naive cells. TLR9 signaling can also cause IFN-alpha production by indirectly affecting plasmacytoid dendritic cells, which increases IgM production and increases the likelihood of autoimmune conditions (57).

TLRs in the Pathogenesis of MS

In the context of MS, dendritic cells, B cells, natural killer cells, $CD4^+$ $CD8^+$ T cells, and monocytes can migrate into the central nervous system, causing myelin and axon damage. When dendritic cells' TLR2 or TLR4 bind endogenous ligands, IL-1, IL-6, and IL-12 are produced, stimulating naive T cell differentiation to Th17 and Th1 cells, which secrete IL-17 and IFN-gamma, respectively. As a result, leukocyte transformation in the blood-brain barrier (BBB) is facilitated, and CNS damage occurs (58, 59).

TLR-MyD88 (myeloid differentiation primary response 88) signaling plays a role in MS pathogenesis by activating Th1 cells, Th17 cells, dendritic cells, and B cells, as well as increasing the secretion of pro-inflammatory cytokines. TLR signaling can also damage the BBB and increase the expression of vascular cell adhesion molecules and BBB-expressed adhesion molecules in response to endogenous danger-associated molecular patterns and pathogen-associated molecular patterns. This damages the blood-brain barrier and exacerbates MS (60). TLR1 is expressed on CHP-212 and NT2-N neuron cell lines and is recognized by reverse transcription polymerase chain reaction (RT-PCR) on microglia in relation to the role of different types of TLRs in MS (61, 62). It is also down-regulated in MS patients (in their peripheral blood mononuclear cells) but up-regulated in IFN-beta-treated patients (63). TLR2 is expressed on astrocytes, microglia, oligodendrocytes, and endothelial cells in the CNS, as well as infiltrating cells in MS. It is upregulated in MS patients' mononuclear cells, cerebrospinal fluid, and demyelinating lesions (62, 64). Microglia, oligodendrocytes, and astrocytes all express TLR3. TLR3 ligation increases the production of anti-inflammatory cytokines like IL-10 while decreasing the production of pro-inflammatory cytokines like IL-23 and IL-12. Several TLR3 studies, however, have found no link between TLR3 and multiple sclerosis (62, 65, 66). TLR4 expression increases in CSF mononuclear cells in MS patients compared to healthy people, but studies have found no link between TLR4 and multiple sclerosis (67, 68).

TLR5 expression in microglia is recognized by RT-PCR, and there is little data on the relationship between TLR5 and MS (62). TLR6 is detected by RT-PCR in CSF microglia and endothelial cells. Then, a study found a link between TLR6 and improvement with IFN-beta treatment in men but not in women (69). TLR7 mRNA expression was found to be increased in 11 MS patients in a study of 61 patients (70). TLR8 mRNA expression increases with the onset of multiple sclerosis (similar to TLR7). RT-PCR detects it in microglia (62, 70). TLR9-expressing plasmacytoid dendritic cells are found in demyelinating lesions of MS patients. In response to TLR9 ligation, these cells secrete IFN-alpha, which is elevated in untreated MS patients. TLR9 expression in patients with multiple sclerosis is reduced by IFN-beta treatment (70-72). Regarding TLR10 and TLR11, there are no available data.

The principal TLR adaptor is Myeloid differentiation factor 88 (MyD88). The MyD88 signaling pathway has been linked to the onset of autoimmune diseases such as multiple sclerosis through antigen-presenting regulation of DCs and B and T cell activation. PAMPs can stimulate TLRs 1, 2, 4, 5, and 6 on the cell surface. As a result of the interaction between MyD88 and IRAK-4 (IL-1 receptor-associated kinase-4), IRAK-1 and IRAK-2 are recruited and phosphorylated. IRAKs are activated after leaving MyD88 and interacting with TRAF6 (tumor necrosis factor receptor-associated factor 6), which leads to the activation of TAK1, TAB2/3, IB, and MAPK (mitogen-activated protein kinase), followed by AP-1 and nuclear factor-B translocation. Stimulating TLR3, 7, 8, and 9 in endosomes can result in the recruitment of IRAK1, IRAK4, TRAF6, and MyD88, as well as the translocation of IRF7 (interferon-regulatory factor 7) and the production of interferons (60).

Therapeutic Strategies in MS

Therapeutic strategies for MS have evolved significantly over the last few decades, and several immunomodulatory therapies have been successfully established. Advances in immunobiology, pathophysiology, and biotechnology, as well as the development of magnetic resonance imaging, have contributed to this advance.

The activation of CNS-autoreactive T-cells in the periphery, processes of demyelination, and T-cell adhesion and penetration into the CNS were all considered as immunological therapeutic targets (73). Corticosteroids such as intravenous methylprednisolone and oral prednisone have been used to reduce neuroinflammation, and plasma exchange was used if steroids were not effective. There are several disease-modifying therapies for relapsing-remitting multiple sclerosis, including interferon-beta, glatiramer acetate, and oral medications: fingolimod, teriflunomide, and siponimod, dimethyl fumarate and diroximel fumarate are taken twice daily. Cladribine is a second-line treatment for patients suffering from relapsing-remitting multiple sclerosis. In terms of infusion treatments, ocrelizumab is a humanized monoclonal antibody drug that is the only FDA-approved disease-modifying therapy for treating primary-progressive and relapse-remitting MS. Another example of therapy is natalizumab, which can prevent potentially harmful immune cells from migrating to the CNS. Alemtuzumab is another drug that reduces MS relapses by limiting leukocyte nerve damage.

Regarding symptomatic management, physical therapy can help with leg weakness and gait issues caused by MS. Muscle relaxants, such as tizanidine and baclofen, can help to alleviate uncontrollable and painful muscle spasms. Amantadine and modafinil can help with MS-related fatigue, and serotonin reuptake inhibitors can help with MS-related depression. Dalfampridine can be used to improve walking speed in some MS patients (12).

Generally, current treatments for MS focus on reducing inflammation, modifying the immune response, and managing symptoms. However, many of these therapies have limitations. For instance, disease-modifying drugs have shown efficacy in reducing relapse rates and slowing disease progression, but they often come with adverse effects and are not universally effective for all patients. Some individuals might experience breakthrough disease activity despite being on treatment. This is where TLRs come into the picture. TLRs are components of the innate immune system that play a crucial role in recognizing pathogens and initiating immune responses. Research suggests that TLRs may also contribute to autoimmune processes, including MS.

Targeting TLRs as potential therapeutic methods in MS holds promise for several reasons. Firstly, TLRs can modulate the immune response and potentially restore immune tolerance in MS patients. Secondly, TLR agonists or antagonists could potentially reduce inflammation and promote remyelination, addressing key aspects of MS pathology. Lastly, there is evidence that TLR signaling can influence neuroregeneration and neuroprotection, which could be beneficial in the context of MS. It is important to note that research on TLR-based therapies in MS is still in its early stages, and more studies are needed to fully understand the potential benefits and risks. However, by exploring TLR-targeted approaches, researchers and clinicians aim to develop novel and more effective treatment options for MS (74, 75).

Considering TLRs as a Target for Therapeutic Goals

Considering TLRs as a therapeutic goal for MS is based on the possibility of downregulating immune system responses with TLR agonists and antagonists (76). Because studies show that improper TLR stimulation can cause inflammation and autoimmunity, scientists strived to develop TLR antagonists and agonists. Another approach is to inhibit intracellular proteins that are involved in different signaling pathways. This approach, however, cannot significantly reduce the immune system's response. For example, despite the fact that the MyD88 pathway is present in nearly all TLR pathways, inhibiting its function does not completely inhibit immune response (76, 77). Some TLRs can suppress autoimmune responses, which lead to the precipitation of autoimmune conditions. This can be used as a therapeutic target by increasing the activity of these TLRs with agonists such as TLR3 (78). CQ-07001, which is an endogenous protein in humans, is an excellent

TLR3 agonist and a promising anti-inflammatory drug candidate. TLR3-dependent immune responses can be induced by poly (I: C). However, in vivo studies have revealed that this method can result in toxic side effects such as renal failure and shock (79). Because overstimulating TLRs can cause a variety of immunological diseases such as arthritis, atherosclerosis, and asthma, some TLR inhibitors may be considered for use in the treatment of autoimmune disorders (e.g. TLR-2, 4, and 9)(80-82).

TLR antagonists inhibit TLR activation by blocking or binding to their signals. TLR2, 4, 7, and 9 antagonists can be used as a therapeutic method to slow the progression of MS. TLR2 signaling inhibition can reduce IL-8 and IL-6 secretion (83). LPS is one of the most important pathogens for TLR4. LPS can cause inflammatory responses and may play a role in the pathogenesis of MS. Anti-LPS agents can be used to inhibit TLR4, which is a promising treatment option for MS (84). For example, GNbAC1 is a monoclonal antibody in humans that targets MS-related endogenous retroviruses, and randomized clinical trials indicate a promising future for using this as a therapeutic target for MS (85-87).

Ibudilast is a phosphodiesterase-4 inhibitor and an antagonist for TLR4 activation. It inhibits the production of IL-6 and TNF-alpha (both proinflammatory cytokines), reducing glial cell activation and, as a result, neuroinflammation (88). Another example is TAK-242, a natural LPS mimic that by binding to Cys747, can inhibit TLR4 signaling (89). Another monoclonal antibody in use today is NI-0101, which, when bound to a specific TLR epitope, can disrupt TLR4 dimerization and block signaling (90).

TLR9 and TLR7 are important in the activation of autoreactive B cells and, as a result, in autoimmune conditions (91, 92). CpG-52364 is their antagonist, and studies have shown that it can help with autoimmunity (93). By removing nonessential nucleotides, IRS 869 and IRS 661 become TLR9 and TLR7 antagonists, respectively. According to investigations, they can alleviate the symptoms of autoimmune disease (94-96).

Conclusion

In conclusion, targeting TLRs represents a promising strategy for the treatment and better prognosis of multiple sclerosis. TLR modulation can potentially alleviate inflammation, mitigate autoimmune responses, and halt disease progression. However, further research and clinical trials are necessary to fully understand the efficacy and safety of TLR-targeted interventions in MS management.

Conflict of Interest

The authors declare no conflicts of interest

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