

Toll like receptors: a new hope on the horizon to treat multiple sclerosis

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Evolving data have shown that the toll like receptors (TLRs) family of innate immune receptors has an important role in driving the activation and inhibition of pathogenic pathways involved in multiple sclerosis (MS). While developing clinical trials targeting MS by TLRs modulators are of considerable interest, several of them have failed. Herein, the various consequences of TLRs pathways activation and the potential of targeting these receptors for therapeutic purposes are described. In particular, different aspects of TLR based therapies are discussed, in order to develop more efficacious and safe therapies targeting inflammatory and autoimmune diseases, especially MS.

Multiple sclerosis (MS), as a chronic immune-mediated inflammatory and neurodegenerative disease of the CNS, mostly affects young and active population of the society, representing a leading cause of disability in this group, therefore imposing a huge disease burden on health care systems [1]. Neurodegeneration is a fundamental aspect of MS pathogenesis, recognized by loss of axons, dendrites and neurons. Primary inflammatory demyelination is the main cause of neurodegeneration during early stages in MS [2,3]. MS can affect any part of the CNS, and the clinical manifestations can be sensory, motor or visual disturbances, urinary or stool incontinence and gait disorders [1].

In the past few years, extensive efforts have been made to tackle MS. Although approving interferon beta-1 β in the early 1990s as the first treatment to reduce the rate of relapses was a major breakthrough in MS therapy, we have so far met with limited success in clinical trials targeting MS pathogenesis, and a definite and reliable cure is yet to be found [4]. Lack of proper understanding of pathological processes underlying MS might be the reason behind this failure.

Despite the fact that MS etiology is unknown, the striking opinions advocate

the immune nature of MS. Epidemiological studies highlight that predisposing genetic factors and/or environmental insults, such as a viral infection, might be required to trigger the MS pathology. Activation of innate and adaptive immune systems has been observed during the degenerative processes of MS.

Microglial cells as 'CNS-resident macrophages' can play a dichotomous role in the pathogenesis of MS; both neuro-destructive and neuro-protective. In addition, activation of CD4⁺ autoreactive T cells and differentiation into Th1 phenotype is one of the major events in the course of the disease. Furthermore, other components of the immune system, such as antibodies, complement system, CD8⁺ T cells and factors produced by innate immune cells are of serious importance [5].

Basically, the function of the immune system relies on innate immune receptors, sensing the pathogenic components of self or non-self and danger signals. This critical differentiation is recognized by a limited number of germline-encoded receptors, called pattern recognition receptors (PRRs). PRRs encompass a wide range of receptors, including toll-like receptors (TLRs), membrane-bound C-type lectin receptors (CLRs), nucleotide – binding

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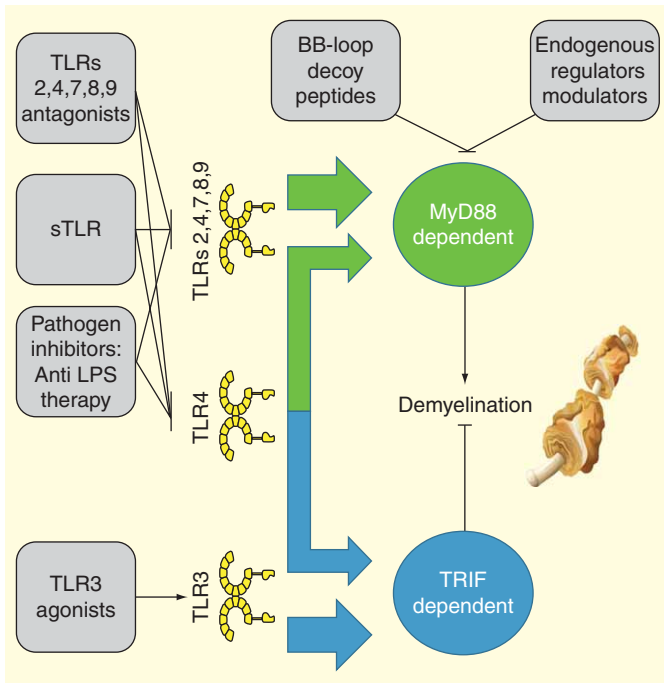


Figure 1. The role toll-like receptor-mediated signaling pathways in multiple sclerosis and their possible therapeutic targets.

sTLR: Soluble TLRs; TLR: Toll like receptor.

oligomerization domain-like receptors (NLRs) and retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) [6].

TLRs as important PRRs are able to sense both pathogens through the exogenous pathogen-associated molecular patterns (PAMPs), and tissue injury through the endogenous danger-associated molecular patterns (DAMPs). Such an interaction can trigger the transcriptional activation of pro-inflammatory cytokines through two major pathways; MyD88-dependent pathway and TRIF-dependent pathway. All TLRs signal through MyD88-dependent pathway, except TLR3 and endosomal retained TLR4, which signal through TRIF-dependent pathway [7–9]. Activation of these pathways and subsequent production of pro-inflammatory cytokines could play a crucial role in the pathogenesis of autoimmune diseases, including MS.

Investigations into the role of TLR signaling pathways in MS have revealed potential targets for interventions in clinical and pre-clinical studies (FIGURE 1). Mounting evidences suggest an ameliorative role of TRIF-dependent pathway and a detrimental role of MyD88-dependent pathway in MS. In line with this, activation of TRIF-dependent pathway and inhibition of MyD88-dependent pathways might be a promising opportunity to close the gaps in evidence-based, effective and affordable treatments for all MS patients. Indeed, our team systemically reviewed the TLRs modulators possibly exerting ameliorative effects in MS pathology. Since the clinical evidences on these compounds are limited, there should be more trials investigating the efficacy of them [10,11].

As already mentioned, TLR3-TRIF pathway might exert ameliorative properties in this context. Therefore, TLR3 agonists

such as Poly I:C12U (Ampligen) might be a promising approach for targeting MS pathogenesis [12,13]. On the contrary, inhibiting MyD88-dependent pathway by TLR 2, 4, 7, 8, 9 antagonists can also be efficacious. Another approach that could be used for inhibition of MyD88-dependent pathway is administration of pathogen inhibitors such as anti LPS therapy and soluble TLRs (sTLR) [14]. Furthermore, TLRs tolerance approach can be considered for chronic and prophylactic purposes [15].

On the other hand, focusing on the downstream pathways of TLRs can be a novel way to treat MS. We can interfere and consequently inhibit MyD88-dependent signaling cascade, through the administration of BB-loop decoy peptides, and modulators of endogenous regulators, such as short form of MyD88 (sMyD88), IRAKM, suppressor of cytokine signaling-1 (SOCS1), the Toll-interacting protein (TOLLIP), phosphoinositide 3-kinase (PI3K) and A20 [16,17].

Although we have several safe and efficacious compounds modulating TLR function, there has been little success on TLR modulator-based trials in autoimmune disorders. Most of these trials have not targeted downstream signaling pathways shared between TLRs, such as MyD88 and TRIF. In other words, in most of the cases, only one specific TLR has been targeted [11]. In order to come toward making TLR modulator-based therapy a realistic goal, we should probably consider targeting multiple TLRs or the common downstream signaling pathways by specific modulators.

TLR modulators, as with all drugs, come with a price of adverse events. Systemic administration of such compounds may cause a number of side effects that should be seriously and carefully considered.

In addition, we may have to administer these immunomodulatory drugs for long-term periods (if not life-long) to chronically dampen the pathogenic cascades involved in MS neuropathogeny. Therefore, we should consider the complications of chronic immunosuppression such as major infections with lethal outcomes and increased risk of cancers. Several adverse effects of previously used immunomodulatory drugs (e.g., corticosteroids, IFN β -1b, IFN β -1a and natalizumab) have already been reported in the treatment of MS [18,19]. Indeed, complications of TLRs modulators are yet to be specified, though they seem less theoretical than supposed.

The current advances in the field of MS pathophysiology should provide the impetus to bring these new TLR modulators to the clinical trials to establish evidence. However, a long path may still lie ahead before such therapies make their way into routine clinical use.

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