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A New Era for Immunotherapeutic Approaches in Multiple Sclerosis Treatment

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Abstract

Recent studies have shown that many pathological conditions, including neurodegenerative disorders, are always the result of innate immune dysregulations. In multiple sclerosis (MS), innate immunity has shown induce proinflammatory responses, mainly mediated by specific innate immune receptors, as well as Toll-like receptors (TLRs). Interestingly, whereas activation of TLR-MyD88 dependent signaling pathway induces inflammation and MS progression, TLR3 activation MyD88 independent seems to play a beneficial effect, probably due to its ability to enhance endogenous IFN-β production, that in turn down regulates proinflammatory responses. Consequently, new therapeutic approaches based on TLR up and/or down regulation could offer promising results. In addition to several classes of TLR antagonists represented by different types of antibodies, nanobodies, mimetic molecules and RNA-selective interference compounds, TLR3 agonists appear particularly interesting due to their capability of inducing IFN-β production. Among these, Ampligen® shows early promise, since it has shown positive results in several phase III trials for the treatment of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), an illness that shows remarkable levels of similarity with MS.

Introduction

The recent advances in understanding the important role played in the central nervous system (CNS) by innate immune cells, such as resident microglia and newly recruited bone-marrow derived cells, that allow active interactions between the immune and nervous systems [1], suggested invaluable mechanisms for several pathological conditions, including the neurodegenerative disorders, most of them have shown to be mainly caused by immune dysregulations. In multiple sclerosis (MS), innate immunity has recently shown to play a major role both in the initiation and progression of the disease, by influencing the effector functions of T and B cells [2-4]. In particular, numerous and recent studies have shown that inappropriate responses of specific receptors expressed by innate immune cells, as well as Toll-like receptors (TLRs), contribute to modulate MS course. Whereas the activation of most TLRs, including TLR2, TLR4, TLR7, and TLR9 through MyD88-dependent signaling pathway, mediates MS progression, TLR3 activation, through MyD88-independent and TRIF-dependent pathway, has shown to protect from the murine model of MS, represented by experimental autoimmune encephalomyelitis (EAE) [5-6]. The positive role played by TLR3 activation is probably due to its capability of inducing, through a MyD88-independent pathway, endogenous IFN-β production, that appears to directly increase expression and concentration of anti-inflammatory agents while down regulating the expression of proinflammatory cytokines. Altogether, the recent advances obtained by the researchers about the role of TLR biology in MS have led to potential new therapeutic approaches to counteract the disease, manly based on TLR up and/or down regulation with specific agonists and/or antagonists and by inhibiting intracellular proteins involved in the cascade signaling pathways [7]. Novel therapeutics able to modulate immune responses through TLRs has been developed by several international companies. The most known class of TLR antagonists is represented by different types of murine, humanized and recombinant antibodies already approved for clinical use in other diseases. Among these, the class of nanobodies (VHH-based single variable domains) with very long complementary determining regions 3 (CDR3), are capable of inhibiting efficiently different protein antigens. Due their small size (12-15 kDa), nanobodies have several additional advantages compared to conventional antibodies (150-160 kDa), such as their extreme stability towards changes in temperature and chemical environments, and resistance to extreme pH levels. Because of their reduced size, nanobodies can penetrate tissues and cells faster than the conventional antibodies, being also capable of breaking through the brain's blood barrier, abilities that make them suitable for CNS therapies.

Other receptor antagonists are represented by mimetic molecules of short amino acid sequences, able to prevent the interaction of prototype proteins with their partners. Among these, specific "decoy peptides" have shown to block selectively TLR signaling pathways, by inhibition of TIR-TIR interactions via structural mimicry, due to three-dimensional fold similarities with TIR structures of specific TLRs [8]. Mimetic TLR inhibitors have been also developed to prevent homo- or hetero-dimerization of TLRs. Antagonistic molecules directed against intracellular TLRs, including TLR3, TLR7 and TLR9, are mainly represented by single stranded DNA or RNA molecules. Among these, the aptamers, obtained by "in vitro" selection processes from combinatorial libraries, have been widely used in various biomedical applications. In particular, the aptamers obtained using immunoprecipitation strategy together to exponential enrichment (SELEX), appear to selectively inhibit endosomal TLR-mediated pathways responsible for inappropriate or excessive inflammation in multiple diseases [9-10]. More recently, small RNA-selective interference compounds have been obtained by using predictive modeling methods [11]. These novel techniques will allow to also obtaining efficient interference RNA-based TLR modulators [12].

Altogether, the modulation of TLR expression with small molecules acting as TLR-agonists/antagonists represents an innovative and attractive approach in MS therapy. The use of TLR-targeting drugs is also promoted by their fewer side effects and lower or no toxicity, compared with other drugs commonly used in MS treatment. This represents an important feature, since MS is a chronic disease that requires long-term treatments.

Among the most promising immunotherapeutics TLR-targeting suitable to be used in MS therapy, TLR3 agonists play a leading role, mainly due to their capability of inducing endogenous IFN-β production [13-16]. TLR3 is triggered by dsRNA with a minimum size of at least 50 base pairs and by specific endogenous ligands, as well as the endosomial microtubule regulator stathmin [17]. Much recent evidence supports the positive role showed by TLR3/TRIF mediated pathway. In EAE mice, TLR3 stimulation induces the inhibition, IL27-mediated, of Th17 cells, that are known to play a critical role in the disease [18-20]. In addition, high levels of IFN, that significantly reduced disease severity, were detected in EAE mice inoculated intraperitoneally with the synthetic TLR3 agonist poly (I): poly (C) acid [21].

Among the investigational compounds TLR3-targeting, the mismatched double-stranded RNA molecule Ampligen® [22] could offer promise in MS therapy. Ampligen® is a mismatched dsRNA with a high specificity of binding to TLR3, with a subsequent selective activation of genes for IFNs, 2-5 adenylate synthetase, and protein kinase (p68) [23,24]. In contrast to the original molecule, developed in the 1960s by Merck and Co. to reduce tumor formation, and that resulted extremely toxic, the new compound was modified by Johns Hopkins University researchers and made less toxic by adding uridylic acid molecules at specific intervals along the dsRNA chain, so obtaining a particular dsRNA, denoted poly (I): poly (C12U), wherein one of the two polyribonucleotides is polyriboinosinic acid and the other is polyribocytidyl C12, uridylic acid. This new compound, called Ampligen® (for AMPLIfied GENetic activity), capable of stimulating IFN production like poly (I): poly (C), had smaller and rugged molecular structure, and appeared more resistant to molecular unfolding, including denaturation and branching, and this led to an increase in bioactivity, due to higher ability to bind TLR3.

Ampligen® is currently in phase III clinical trial in the treatment of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), an illness that shows remarkable levels of similarity with MS. Indeed, both disorders, show remarkable phenomenological and neuroimmune overlaps [25]. The neuroimmune similarities between MS and CFS/ME are mainly based on shared immunoinflammatory oxidative and nitrosative stress, autoimmune and mitochondrial pathways. Other remarkable levels of similarity concern "the findings produced by neuroimaging techniques, that appear quite similar in both illnesses and show decreased cerebral blood flow, atrophy, gray matter reduction, whit matter hyperintensities, increased cerebral lactate and choline signaling, and lowered acetyl-aspartate levels" [26]. However, the main evidence base supporting the use of Ampligen® in MS therapy is because TLR3 stimulation leads to endogenous induction of IFNβ that has shown to prevent inflammation and demyelination and to also possess neuroprotective activity [27]. In addition, unlike the exogenous IFN used in MS therapy, it does not induce neutralizing antibodies that reduce effectiveness [28,29].

Conclusions and Future Directions

Despite the several therapies proposed to treat MS, none of them has shown to be completely effective. In every case, a strong inflammatory response, TLR-mediated, appears to contribute to this autoimmune disease. Then, a selective inhibition of specific TLRs can provide a proposing device to prevent initiation and progression of MS. In contrast, TLR3 stimulation can improve the MS course, due its ability to enhance IFNβ production. We can conclude that TLR modulation with small molecules acting as TLR-agonists/antagonists might represent an alternative and attractive approach in MS therapy. Another winning point of TLR-targeting drug is that they not show important side effects and toxicity compared with drugs commonly used in MS treatment. This represents an important feature in the therapy of this chronic autoimmune disease that always involves young people who will be compelled to continue the therapy for the rest of their lives.

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