Journal of the Neurological Sciences xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

Emerging immunopharmacological targets in multiple sclerosis

Mojtaba Farjam [a], Guang-Xian Zhang [b], Bogoljub Ciric [b], Abdolmohamad Rostami [b,*]

[a] Non-communicable Diseases Research Center, Department of Medical Pharmacology, School of Medicine, Fasa University of Medical Sciences, Fasa, Iran
[b] Department of Neurology, Thomas Jefferson University, Philadelphia, PA 19107, USA

ARTICLE INFO

Article history:
Received 3 November 2014
Received in revised form 9 September 2015
Accepted 10 September 2015
Available online xxxx

Keywords:
Neuroimmunology
Immunotherapy
Multiple sclerosis

ABSTRACT

Inflammatory demyelination of the central nervous system (CNS) is the hallmark of multiple sclerosis (MS), a chronic debilitating disease that affects more than 2.5 million individuals worldwide. It has been widely accepted, although not proven, that the major pathogenic mechanism of MS involves myelin-reactive T cell activation in the periphery and migration into the CNS, which subsequently triggers an inflammatory cascade that leads to demyelination and axonal damage. Virtually all MS medications now in use target the immune system and prevent tissue damage by modulating neuroinflammatory processes. Although current therapies such as commonly prescribed disease-modifying medications decrease the relapse rate in relapsing-remitting MS (RRMS), the prevention of long-term accumulation of deficits remains a challenge. Medications used for progressive forms of MS also have limited efficacy. The need for therapies that are effective against disease progression continues to drive the search for novel pharmacological targets. In recent years, due to a better understanding of MS immunopathogenesis, new approaches have been introduced that more specifically target autoreactive immune cells and their products, thus increasing specificity and efficacy, while reducing potential side effects such as global immunosuppression. In this review we describe several immunopharmacological targets that are currently being explored for MS therapy.

Contents

* Corresponding author at: Department of Neurology, Thomas Jefferson University, 901 Walnut Street, Philadelphia, PA 19107, USA.
E-mail address: a.m.rostami@jefferson.edu (A. Rostami).

http://dx.doi.org/10.1016/j.jns.2015.09.346
0022-510X/

1. Introduction

Multiple sclerosis (MS) is a neurodegenerative disease of the central nervous system (CNS) that has devastating clinical outcomes in many patients. MS is a leading cause of neurological disability in young adults and in the middle-aged population [1]; it imposes an incredibly high socio-economic burden on society [2], with medication making up a great share of these costs [3,4]. The majority of patients experience a relapsing-remitting (RR) clinical course, and gradual accumulation of neurological deficits can eventually cause permanent disabilities. A minority of patients suffer from a progressive clinical course characterized from the beginning by steady disease progression without remissions (primary progressive MS; PPMS), and there is no evidence that any treatment works in this type of MS or in secondary progressive MS (SPMS) [5]. Even in RR-MS, which can be treated using several immunomodulatory medications, treatment outcomes have not been reported as unequivocally effective for all patients, i.e., the outcomes show wide inter-individual variations, likely due to the non-homogenous nature of the disease course. The scientific strategy of choice for treating these types of disease is to better understand their pathophysiology.

It has been suggested that MS pathogenesis is initiated by activation of myelin antigen-specific T and B cells in the periphery [6,7]. While the origin of activation of these immune cells is not known, it has been proposed that certain autoantigens or organisms with peptide homology to these antigens might trigger this process [1,8]. These myelin-reactive cells, upon migrating into the CNS, encounter autoantigens, become reactivated, and an inflammatory cascade ensues that result in demyelination and axonal injury [9]. In this scenario, T cells appear to play an important role, although B cells also contribute [10]. Thus, targeting T cells, B cells and mediators involved in their activation provides major routes for therapeutic interventions in MS. Current treatment options basically target the immune system to modulate disease.

While a number of drugs for MS therapy are being developed, the longlasting neuroprotective efficacy of current drugs has not been confirmed [11]. In almost all cases, immunopharmacology has been the basis for drug design and development. To date, there are several approved medications for MS, including interferon beta (IFN-β) 1a, IFN-β 1b, glatiramer acetate, mitoxantrone [12], natalizumab [13,14], fingolimod, triflunomide, dimethyl fumarate [15] and a recently approved medication, alemtuzumab [16]. These drugs, mainly through modulating or interfering with different aspects of immune responses, reduce the relapse rate or decrease the need for steroids during exacerbations. However, in many patients, the response to some drugs is suboptimal, and for other medications, safety is a concern. Moreover, there is debate on how and to what extent these medications can modify the long term course of the disease. Furthermore, the lack of curative modalities and low rate of compliance in taking medication are therapeutic issues in MS [17]. The cost effectiveness of these drugs in MS is also under debate.

Current understanding of the immunopathogenesis of MS has identified novel immunological processes and molecules that could be pharmacologically modulated in order to provide more effective and less toxic drugs; new MS therapies are being investigated and clinical trials are underway, based on the fine immunological processes underlying MS. The effectiveness of every target in MS therapy is controversial, and T cells, B cells, their crosstalk mechanisms, and a handful of inflammatory mediators and processes are being studied.

In the following sections, a brief review is presented of therapies targeting immune system components, with the goal of providing novel immunopharmacological treatment options for MS.

2. Targeting T cells in MS

T cells provide important targets for MS therapy. Different T cell types and their surface markers have been experimentally targeted based on the immunopathology of MS. In the periphery, as well as the CNS, autoreactive T cells differentiate into several subtypes of T cells including proinflammatory cytokine secreting T-helper (Th) 1 and recently discovered Th17 cells, both of which contribute to the development of autoimmune response [18]. In contrast, Th2 and regulatory T cells (Tregs) are anti-inflammatory. T cell-directed therapies could be effective if stages of T cell activation at different phases of MS pathogenesis are properly targeted (Table 1).

2.1. Targeting CD4 + T cells

It is believed that autoreactive CD4 + T cells play a central role in MS pathogenesis. Thus, CD4 + T cell targeting with anti CD4 + antibody (cM-T412) was tested as a therapeutic option, and clinical trials with this antibody were performed in RRMS patients [19,20]. In the trials, reduction of relapse rate was observed in patients treated with this antibody, and side effects were limited; however, its efficacy in reducing T2/FLAIR lesions in MRI was not shown. Based on this report, it was concluded that this strategy has no long-term clinical benefits [21]. The reason for its ineffectiveness is not known, but it has been suggested that this strategy leads to depletion of all CD4 + T cells. While a

Table 1
Targeting T and B cells in MS.

Targeting T and B cells in multiple sclerosis			
Pharmacological target	Experimental results if available	Clinical outcomes	References
Targeting markers on T cells			
CD4 + T cells	Effective in EAE	No long-term benefits	[21,177]
CD52 + cells	Effective in EAE	FDA-approved drug (Alemtuzumab)	[16,178]
CD25 (IL-2R)	Effective in EAE	Drug under study (daclizumab)	[39,179]
Targeting T cell activation in MS			
Altered peptide ligands			
MBP	Effective in EAE	No evidence of clinical benefit to date	[51,54]
MOG	Effective in EAE	No evidence of clinical benefit to date	[59,61]
Targeting T cell co-stimulatory pathways			
CD40/CD40L	Effective in EAE	Studies discouraged due to suspected risks of adverse effects	[69–70]
CD28:B7	Effective in EAE	Reported safe in phase I trials	[78–79]
Targeting markers on B cells			
CD20	Effective in EAE	Clinical trials ongoing On Rituximab	[91,180]

Please cite this article as: M. Farjam, et al., Emerging immunopharmacological targets in multiple sclerosis, J Neurol Sci (2015), http://dx.doi.org/10.1016/j.jns.2015.09.346