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Review article

Multiple sclerosis: Skin-induced antigen-specific immune tolerance

Paula Wildner, Krzysztof W. Selmaj*

Department of Neurology, Medical University of Lodz, Lodz, Poland

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ABSTRACT

Multiple sclerosis (MS) is a highly prevalent demyelinating disorder, presumed to be driven by an autoimmune response toward the central nervous system (CNS) components. All currently available treatments modulate the immune system globally and besides the reduction of disease activity, they may also impose considerable disturbances on the immune protective mechanisms. Thus, induction of antigen-specific immune tolerance remains the ultimate goal of MS therapy. Such approach carries promising therapeutic perspectives and, above all, a desirable safety profile. Several studies have been performed to evaluate highly selective, antigen-induced, therapies for experimental autoimmune encephalomyelitis (EAE) and MS. These trials have also indicated the importance of the antigen administration route. The continued efforts to develop efficient and safe MS therapy gave rise to the idea of incorporating the skin immune system in order to modulate autoimmunity in MS. Skin is the largest immunological organ of human body, and thus provides ample opportunities to modify immune responses. Skin dendritic cells have a significant ability to modulate the immune reactions, promoting either immunity or tolerance. Their capacity to induce tolerance has already been described in several experimental models of MS. In a one-year, double-blinded, placebo-controlled study assessing the effectiveness of transdermal myelin peptides patches, significant changes in the morphology of Langerhans cells (LCs) and shifts in the dendritic cell (DC) populations in the draining lymph nodes have been observed. In addition, patients treated with myelin patches showed a decreased brain inflammatory activity on MRI and a reduced relapse rate. In this review, we further discuss the potential to use skin-induced immune tolerance for MS treatment, with a particular focus on dermal DCs.

1. Introduction

Multiple sclerosis (MS) is the most common acquired demyelinating condition of the central nervous system (CNS). The etiology of this disease remains unknown. However, pathogenetic events are believed to be driven by an autoimmune response against myelin components. The risk of developing MS is determined by genetic as well as environmental factors. Although current therapies have been proven partially effective in reduction of disease activity, they globally affect the immune system and might impose a serious risk for patients' immune protection. Thus, induction of highly selective therapies which target only MS related mechanisms, seems to be the ultimate goal in MS treatment. One option in this direction is induction of immune tolerance toward myelin and/or other CNS components involved in MS autoimmune reactions. Skin is the largest immunological organ of human body and thus provides ample opportunities to modify immune responses, both suppress and potentiate them. Among the variety of cells which make up the skin immune system, dendritic cells (DCs) are believed to be of primary importance. DCs are professional antigen-presenting cells (APCs) and they have a significant ability to modulate

Abbreviations: AHR, airway hyperresponsiveness; APC, antigen presenting cell; APL, altered peptide ligand; BBB, blood-brain barrier; CD, cluster of differentiation; CNS, central nervous system; cDC, conventional dendritic cell; CIA, collagen-induced arthritis; CII, type II collagen; CS, contact sensitivity; CSF, cerebrospinal fluid; CSSS, cyanoacrylate skin surface stripping; DC, dendritic cell; DISC, death-inducing signaling complex; DLN, draining lymph nodes; DN, double negative; DNFB, dinitrofluorobenzene; DNP-BSA, 2,4-dinitrophenylated bovine serum albumin; DNTB, 2,4-dinitrothiocyanobenzene; EAE, experimental autoimmune encephalomyelitis; EC, epicutaneous; ECS, extracellular spaces; EDSS, Expanded Disability Status Scale; HLA-DR, human leukocyte antigen - antigen d related; HSP, heat shock protein; IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; INF, interferon; ISF, interstitial fluid; LC, Langerhans cell; LPS, lipopolysaccharide; MBP, myelin basic protein; MHC, major histocompatibility complex; MOG, myelin oligodendrocyte protein; MRI, magnetic resonance imaging; mRNA, messenger RNA; MS, Multiple sclerosis; MyD88, Myeloid differentiation primary response gene 88; NK, natural killer cell; NKT, natural killer T cell; OVA, ovalbumin; PBS, phosphate-buffered saline; PC-BSA, phosphorylcholine conjugated to bovine serum albumin; pDC, plasmacytoid dendritic cell; PLP, myelin proteolipid protein; PRR, pattern recognition receptor; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TDI, transdermal immunization; T1D, type 1 diabetes; Tc, cytotoxic T cell; Tfh, follicular helper T cell; TGF-β, transforming growth factor beta; Th, T helper cell; TLR, toll-like receptor; TNBS, 2,4,6-trinitrobenzenesulfonic acid; TNP-Ig, 2,4,6-trinitrophenyl-conjugated mouse immunoglobulin; Tr, regulatory T cell; Treg, regulatory T cell

* Corresponding author at: Department of Neurology, Laboratory of Neuroimmunology, Medical University of Lodz, Kopcinskiego 22, 90-153 Lodz, Poland.
E-mail address: kselmaj@afazja.am.lodz.pl (K.W. Selmaj).

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the immune response, promoting either immunity or tolerance. Therefore, DCs' altered function and phenotype may play a crucial role in pathogenesis of autoimmune diseases, including MS (Comabella et al., 2010; Coutant and Miossec, 2016). Accordingly, DCs in MS patients manifest notable changes in phenotype and function (Nuyts et al., 2013; Bayas et al., 2009). Thus, targeting DCs represents a promising strategy in MS treatment. In this review we shall evaluate the potential to use skin-induced immune tolerance for MS treatment and highlight the role of DCs in this process.

2. Mechanisms of antigen-specific immune tolerance

Antigen-specific immune tolerance is a state of unresponsiveness toward certain antigen induced by a prior exposure to that antigen. This phenomenon protects the immune system from destructive responses mediated by this antigen, while the global protective immunity remains preserved (Van Brussel et al., 2014). The endogenous development of tolerance toward self antigens involves the central and peripheral arms. The early mechanisms of central tolerance comprise the processes prior to T and B cells maturation and their release to circulation, which occur within the core immune organs, namely the thymus and the bone marrow. Subsequent maturation processes, which make up the peripheral tolerance, are aimed to suppress auto-reactive immune cells, which escaped the central tolerance process, and take place in the secondary lymphoid organs and/or at the sites of inflammation (Bolon, 2012; Xing and Hogquist, 2012). The induction of immune tolerance is dependent on variable factors such as the route of antigen administration, the dose schedule and the use of adjuvants. Only slight alterations in abovementioned factors may alter the triggered type of response: tolerance or immunity (Miller et al., 2007).

In the periphery, immune tolerance can be induced by several mechanisms (Fig. 1), such as anergy, deletion or suppression by regulatory T cells (Tregs) (Pearson et al., 2017). T cell anergy is generated in the presence of a TCR signal and concurrent absence of a second signal mediated the CD28 ligation (Xing and Hogquist, 2012). Anergy can also be driven by the CLTLA4-B7 ligation. CTLA-4 binds B7 family costimulatory molecules with high avidity and transduces a negative signal, therein preventing cell cycle progression (Tivol et al., 1995). Another route promoting anergy of self-reactive $CD4^+$ T cells is presentation of self peptides on immature APCs which lack expression of costimulatory molecules. The level of costimulatory molecule expression on APCs is regulated by numerous mechanisms such as presence or absence of inflammation or infectious agents (Podojil and Miller, 2009). T-cell deletion in the periphery due to activation-induced cell death follows the activation of Fas by FasL or certain antibodies and involves the formation of the death-inducing signaling complex (DISC) and downstream activation of apoptotic caspases (Xing and Hogquist, 2012). CD4 + CD25 + Foxp3 + Tregs are a vital component of peripheral tolerance. The suppression of activated T cells by Tregs can be mediated by the production of anti-inflammatory cytokines, such as IL-10, IL-35, and TGF-β, cytolysis, metabolic disruption and affecting the maturation or function of DCs (Vignali et al., 2008).

Development of peripheral tolerance critically depends on the presence and availability of antigen in secondary immunological organs. In case of MS, it remains elusive how CNS antigens enter the peripheral compartment of immune system in the light of immune privilege status of the brain which has been described long time ago. The immune privilege is conditioned mainly by the blood-brain barrier (BBB) and the absence of conventional lymphatics in the CNS. The lymphatic drainage of CNS includes the drainage of cerebrospinal fluid (CSF) and interstitial fluid (ISF) to lymph nodes. The main routes for the CSF drainage are channels within the cribriform plate of the ethmoid bone, connecting the subarachnoid space with lymphatic vessels in the nasal mucosa (Johnston et al., 2004). Spinal subarachnoid space is drained to the lumbar lymph nodes (Kida et al., 1993). It has been shown that T cells and APC from the CSF flow to the deep cervical lymph nodes (Goldmann et al., 2006; Hatterer et al., 2006; Hatterer et al., 2008). Interestingly, myelin and axonal antigens have been observed in the deep cervical lymph nodes after axonal injury and autoimmune demyelination (de Vos et al., 2002; Fabriek et al., 2005; Mutlu et al., 2007; Cserr et al., 1981). The ISF has been demonstrated to drain from the brain via bulk flow along white matter fibre tracts and along perivascular pathways (Engelhardt et al., 2016). The flow of ISF via the ECS is diffusion dependent (Nicholson et al., 2011). Until now, it remains not fully understood why a remarkable predominance of the CSF drainage to deep cervical lymph nodes in comparison with superficial lymph nodes is observed. APC from the CNS accesses the spleen via blood. In an animal model of MS, performed on marmoset monkeys, high amounts of cells transporting proteolipid protein, as well as cells with myelin basic protein have been found within the spleens (de Vos et al., 2002). Studies performed in experimental autoimmune encephalomyelitis (EAE), have shown that the lymph nodes draining CNS promote demyelination. In one study excision of cervical lymph nodes resulted in a mitigation of relapses and spinal cord pathology (van Zwam et al., 2007). In another studies, deep and superficial cervical lymph nodes have been removed (Furtado et al., 2008; Phillips et al., 1997) leading to an EAE delay and a less severe disease. Besides the pernicious role of cervical lymph nodes in EAE/MS pathology, it is highly probable that they also play an important role in the induction of tolerance (Moingeon, 2013; Wolvers et al., 1999). It is supposed that immune tolerance and immune responses are triggered subsequently or simultaneously in the cervical lymph nodes and they depend upon the interaction between T cells and APCs (Engelhardt et al., 2016). A vital role of lymphatic endothelium is also underlined. Lymphatic endothelium is presumed to secrete immunosuppressive factors and therefore hinder T cell function and DCs maturation. Transendothelial transport regulates the delivery of antigens within lymph nodes. Endothelial cells are able to induce T cell tolerance via antigen presentation in the context of co-inhibitory molecules (Card et al., 2014). Remarkably, it has been proven that B cells which populate the CNS mature in the draining cervical lymph nodes as well. It was shown that B cells move freely across the tissue barrier and that the B cell maturation occurs mainly outside the CNS in the secondary lymphoid tissue (Stern et al., 2014). Recently, a group from our research center suggested that CNS derived exosomes might also contribute to communication between CNS and peripheral immune system. It has been found that serum exosomes, both from MS patients and controls, contain major myelin peptides and proteins (Galazka et al., 2017). These abovementioned findings implicate that the bidirectional flow of immune cells between the CNS and the cervical lymph nodes might emerge the key means to achieve antigen-specific immune tolerance.

3. Antigen-induced immune tolerance in MS

Until now, several attempts to induce antigen-specific immune tolerance in EAE/MS have been made (Steinman, 2015). For the first time, antigen-specific therapy for neuroinflammation was investigated in the Martin Kies laboratory. In this study, EAE was restrained with encephalitogenic proteins from homologous brain (Shaw et al., 1960). More recently, attempts to induce antigen-specific tolerance in MS have involved the use of altered peptide ligand (APL) (Table 2). The epitope was first characterized by Wucherpfenig et al. (1997). Although several trials with APL have been managed, they did not meet the expectations (Bielekova et al., 2000; Kappos et al., 2000). In a phase 2 study including 142 patients, 5 mg of APL was given subcutaneously for 4 months. The treatment resulted in a Th2 shift of immune response and a reduction of volume and number of enhancing lesions in MRI (Kappos et al., 2000). However, the study was stopped because of a high rate of hypersensitivity reactions. In another phase 2 study, a few patients developed exacerbations of multiple sclerosis (Bielekova et al., 2000). Trials with native MBP peptides constituted another approach. An attempt to induce tolerance to myelin basic protein was made with an