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Immune Modulating Peptides for the Treatment and Suppression of Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a neurodegenerative disease in which the immune system recognizes proteins of the myelin sheath as antigenic, thus initiating an inflammatory reaction in the central nervous system. This leads to demyelination of the axons, breakdown of the blood-brain barrier, and lesion formation. Current therapies for the treatment of MS are generally non-specific and weaken the global immune system, thus making the individual susceptible to opportunistic infections. Antigenic peptides and their derivatives are becoming more prevalent for investigation as therapeutic agents for MS because they possess immune-specific characteristics. In addition, other peptides that target vital components of the inflammatory immune response have also been developed. Therefore, the objectives of this review are to (a) summarize the immunological basis for the development of MS, (b) discuss specific and non-specific peptides tested in EAE and in humans, and (c) briefly address some problems and potential solutions with these novel therapies.

Keywords

Multiple Sclerosis; Experimental Autoimmune Encephalomyelitis; Peptide; Antigen; Bifunctional Peptide Inhibitor

1 MULTPLE SCLEROSIS

1.1 Disease Introduction

Multiple sclerosis (MS) is the most common immune-mediated disease of the central nervous system. It is characterized by severe demyelination, axonal injury, lesion formation in the brain and spinal cord, blood-brain barrier (BBB) opening, and inflammatory immune cell infiltration [1]. MS is a very heterogeneous disease with very diverse pathological and clinical manifestations. Some of the clinical symptoms include loss of balance and coordination, visual and sensory impairment, fatigue, and cognitive difficulties [2]. The pathogenesis of the disease is not well understood, and there are a multitude of factors that may cause the onset of this disease. Genetic factors may play a major role, and it has been shown that a particular class-II allele of the major histocompatibility complex (MHC) may increase the risk for developing MS [3, 4]. Other studies have indicated a correlation between pathogenic infections and the development of the disease. This is believed to be

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caused by a phenomenon known as molecular mimicry or bystander activation [5]. Some links have been made between various different viruses to MS, such as the Epstein-Barr virus [6, 7] and varicella zoster virus [8], as well as bacterial pathogens such as chlamydia pneumonia [9–11]. However, there is no direct evidence of the link between pathogenic infections and MS. Currently, the most widely accepted hypothesis is that MS is an autoimmune disease that affects genetically pre-disposed individuals afflicted with an environmental pathogen [12].

Diagnosis of MS is complicated and unfortunately the majority of the current treatments are non-specific. The most common diagnostic tool for MS is magnetic resonance imaging (MRI). MRI has become a very important tool in diagnosis and monitoring of disease progression and is crucial for devising proper treatment plans. It is used to look for white matter lesion formation, particularly in the pons and the cerebellum [13], and the development of “black holes” that are a hallmark of severe demyelination and axonal damage [14]. There are currently eight FDA-approved therapies for the treatment of MS. Four forms of IFN-β therapies are being used for treatment, but their mechanism of action remains unknown [15]. It is believed that they work primarily by inducing an anti-inflammatory response [16]. Another commonly used therapeutic agent is glatiramer acetate (Copaxone), which is a polymer made up of a random mixture of four amino acids (alanine, glutamic acid, lysine, and tyrosine) [17]. The proposed mechanism of action of Copaxone is the diversion of the T cell response from type-1 (T_H1) to type-2 helper (T_H2) T cells. Mitoxantrone is an alternative drug that works primarily by inhibiting the proliferation of immune cells [16]. A monoclonal antibody (mAb) called natalizumab (Tysabri) is also being used to treat MS; it binds the α4β1 integrin [18] to inhibit the migration of lymphocytes into the BBB, thus preventing the infiltration of immune cells into the central nervous systems (CNS). Fingolimod (Gilenya), which prevents lymphocytes from exiting the lymph nodes and keeping them at the periphery so they cannot reach the CNS, is the latest FDA-approved drug [19].

1.2 Cellular Mechanisms and Role of Cytokines

The body has protective mechanisms in the thymus to prevent and eliminate any autoreactive T cells by a process known as central tolerance [20]. If autoreactive T cells fail to become tolerant by resident antigen presenting cells (APC) in the thymus, they can escape to the periphery, thus making the individual susceptible for the development of an autoimmune disease. However, the body has back-up protective peripheral-tolerance mechanisms to prevent these autoreactive T cells from proliferating and attacking self-components [21]. In the case of MS, it is proposed that both the central and peripheral tolerance mechanisms fail to induce tolerance or anergy to myelin-specific T cells. Furthermore, under yet unknown conditions, these myelin-reactive T cells can cross the BBB to enter the CNS via adhesion molecule interactions [22, 23]. Once in the CNS, these T cells become re-activated by resident APC such as microglia, macrophages, and dendritic cells (DC) and induce an inflammatory response in the CNS [20, 24]. DC play a crucial but contradictory role in the body; they are important both for maintaining peripheral tolerance and inducing an immunogenic response. It has been reported that DC can pick up myelin proteins and present them to T cells in the periphery [25–27]. DC have a strong presence in the inflammatory lesions of MS patients [28] and thus are key players in the reactivation of autoreactive T cells in the CNS [29]. In addition, DC have been implicated in epitope spreading [30]. The contribution of B cells to the development and progress of MS is not very clear. However, a phase II clinical trial using rituximab, a monoclonal antibody which depletes B cells, was beneficial to MS patients, therefore suggesting that B cells have a role in the pathogenesis of disease [31], and myelin-specific antibodies have been found in the cerebrospinal fluid (CSF) of MS patients [32].

In the past, MS was believed to be solely a $CD4^+$ T_H1 disease; recently, evidence has strongly suggested that $CD4^+$ type-17 T cells (T_H17) have a key role in its pathogenesis [33]. The contribution of T_H17 and/or T_H1 cells to the disease has not been fully elucidated, but the balance between these two T cell subsets has an important role in determining the location of the lesions within the brain [24]. MS is traditionally thought to be purely a $CD4^+$-mediated disease with little appreciation of the contribution of $CD8^+$ T cells. Myelin-specific $CD8^+$ T cells have been found in greater amounts in the lesions of MS patients but not healthy individuals [34–36]; this is unlike myelin-specific $CD4^+$ T cells, which are found in both MS and healthy individuals [37]. In addition, the depletion of $CD4^+$ cells has no effect on disease progression, but depletion of both $CD4^+$ and $CD8^+$ T cells has beneficial effects [38]. Like $CD4^+$, $CD8^+$ T cells are activated in the periphery and can cross the BBB under inflammatory conditions. Activation of $CD8^+$ in the periphery is accomplished through cross-presentation, which means APC that do not synthesize myelin proteins can present antigens to $CD8^+$ T cells in the context of the MHC-I molecule [39]. Activation in the CNS occurs via resident APC, and it still remains unclear which types of APC are involved [24]. $CD8^+$ T cells exert their effector function in the CNS through the production of soluble inflammatory mediators as well as direct cell lysis [24, 34, 35]. Therefore, contributions from both $CD4^+$ and $CD8^+$ are probably important in the development and pathogenesis of disease, and the different involvement of both T cells is proposed to be the reason behind the broad heterogeneity of the disease [24]. Autoreactive T cells can recognize several proteins of the myelin sheath as antigenic. The most common antigenic proteins in MS patients are myelin basic protein (MBP); myelin proteolipid protein (PLP), which makes up 50% of total myelin protein; and myelin oligodendrocyte glycoprotein (MOG), which is found on the outside of myelin sheath [5]. Identifying these autoantigens has become important for developing antigen-specific therapies as well as for induction of the disease in animal models for studying MS.

Currently, the widely accepted model for T-cell activation and induction of an inflammatory response is the “two-signal” model [40, 41]. The model proposes that two signals, an antigen-specific and a “danger” signal, must be delivered to T cells by APC such as an activated or mature DC (mDC). The maturation of an immature DC (iDC) is triggered by the phagocytosis of an insoluble antigen [42, 43]. Next, the antigen is broken down into small peptides, processed, and presented by the APC to a T cell via the MHC-II/T cell receptor (TCR) interaction; this is known as Signal 1. During the maturation process, the phenotype of DC changes and expresses costimulatory molecules and adhesion molecules on its surface (Figure 1). The presence of the costimulatory molecules, also known as Signal 2, informs the T cell of “danger” and, thus, the T cell differentiates into a pro-inflammatory phenotype to initiate an inflammatory response. One of the most important costimulatory signals is delivered via the B7/CD28 protein interaction and is a positive or activation signal [44, 45]. This interaction is vital for the activation of T cells in MS and its animal model, experimental autoimmune encephalomyelitis (EAE). A second pair of costimulatory molecules that have been shown to have a major role in the development of helper T cells are the CD40/CD154 (also referred to as CD40/CD40L) receptors [46]. A study in B7-deficient mice showed that the CD40/CD154 signal can sufficiently deliver the costimulatory signal in the absence of the B7/CD28 interaction [47]. Inhibitory (negative) signals can be delivered to T cells to inhibit its activation via the B7/CTLA-4 interaction [48]. Cell adhesion molecules also function to activate T cells, most notable molecules are intercellular adhesion molecule-1 (ICAM-1) and leukocyte function-associated antigen-1 (LFA-1) [49]. Another important group of molecules, which play a big role in influencing the T_H1/T_H2 balance in MS, are the inducible costimulator (ICOS) molecule and its ligand (ICOSL) [50]. It has been reported in the EAE model, that the ICOS/ICOSL interaction can induce mucosal tolerance by upregulating T_H2 and regulatory cytokines [51, 52]. Following the delivery of Signal 1 and 2, a phenomenon known as the immunological synapse (IS)

must take place to complete the activation of T cells [53, 54]. The formation of the IS involves the translocation between Signal 1 molecules (TCR/MHC-II-Ag complex) and the adhesion molecules (ICAM-1/LFA-1 complex). Because it is believed that the formation of the IS is vital for the activation of T cells, IS could be an important target for developing therapeutics aimed at suppressing the immune response.

All the immune responses involved in the pathogenesis and treatment of MS are mediated via a complex network of cytokines. During steady-state conditions (i.e., homeostasis), there is a balance between pro- and anti-inflammatory cytokines. In MS, inflammatory cytokines are responsible for the pathogenesis of the disease in the periphery as well as within the CNS. The function of each cytokine has not been fully elucidated due to the dynamic network and complex nature of the cytokine milieu. For the development and progression of disease, the pro-inflammatory cytokines are key players. There are several cytokines involved in the inflammatory response, particularly T_H1 cytokines such as IL-12, IFN-γ, and TNF-α as well as T_H17 cytokines such as IL-23 and IL-17 [24]. The exact contribution of each of these cytokines remains unclear and difficult to sort out. The involvement of IL-12 and IFN-γ was established by their heightened expression in the CNS and CSF of MS patients with increased clinical activity [55]. In addition, the roles of TNF-α and IFN-γ were determined when peripheral blood mononuclear cells (PBMC) isolated from MS patients secreted significant amounts of them [56–61]. IL-17 transcripts were found in CNS lesions of MS patients, thus indicating a major role of IL-17 in disease pathogenesis [33]. Immunotolerance is believed to be maintained by a group of suppressor (T_H2) and regulatory T cells (T_{reg}) that produce anti-inflammatory cytokines such as IL-2, IL-4, and IL-10 [62]. During the disease state, it has been reported that PBMC isolated from MS patients secrete no or low amounts of the anti-inflammatory cytokines [62]. Moreover, during ongoing disease there is a shift towards the production of pro-inflammatory cytokines. Therefore, a major strategy for treating an inflammatory disease like MS is shifting the balance towards the production of anti-inflammatory cytokines such as the ones secreted by T_{reg} and T_H2 cells.

1.3 Experimental Autoimmune Encephalomyelitis

The EAE animal model is used to study the underlying disease pathogenesis of MS and develop new therapies. EAE can be induced either by adoptive transfer of myelin-specific T cells or by the administration of a CNS homogenate or specific myelin proteins/peptides in the presence of an adjuvant such as complete Freund's adjuvant (CFA) [63]. In order to facilitate EAE induction and produce more reliable and consistent disease, pertussis toxin can be injected following the CFA/antigen injection [64]. Also, more recently, a new clone of transgenic mice possessing $PLP_{139-151}$ specific TCR has been shown to develop spontaneous EAE [65]. The EAE model mimics MS in several ways such as the development of multiple CNS lesions, destruction of the myelin sheath, and the breakdown of the BBB. Similar to MS, various immune cells are involved in the disease pathogenesis. Macrophages, microglia cells, DC, B-cell antibodies, and both $CD4^+$ and $CD8^+$ have vital roles in the development of the inflammatory response and tissue destruction [66]. The model has been very useful in studying the mode of action of four therapies currently on the market for the treatment of MS such as glatiramer acetate (Copaxone) [67], mitoxantrone [68], natalizumab (Tysabri) [69], and, most recently, fingolimod (Gilenya) [70–74]. It is important to recognize the limitations of the animal model as most successes in that model did not translate to humans [75]. In addition, many of the adverse side effects observed in clinical trials, from therapies initially tested in EAE, could not have been predicted from the animal model [76]. No one model of EAE mimics the heterogeneous pathology of MS and, therefore, more work must be done in order to more closely mimic the human disease. Nevertheless, EAE played a key role in understanding many pathogenic aspects of the

disease and led to the development of four important MS therapeutics; thus, its contribution in the past must not be undermined. For these reasons, the EAE animal model is continuously being used to test and develop new therapies for MS.

2 PEPTIDE TREATMENTS FOR MS

Most of the current therapies for MS do not regulate specific immune cells and they normally suppress the general immune response, which leads to many adverse side effects from opportunistic infections. Thus, there is a need to develop therapeutic agents that specifically control the myelin-reactive immune response for maintaining host capability to protect against foreign pathogens provided by the general immune response. Peptides are excellent specific inhibitors of protein-protein interactions and, therefore, are valuable specific modulators of protein-mediated signaling of the immune system. In this section, many of the current myelin-specific peptides being tested for the treatment of MS will be discussed. In addition, important advances in the development of non-specific peptides that have efficacy in the EAE animal model will be discussed.

2.1 Antigenic Peptides

Specific immunotherapy (SIT) has been used for about a century to induce tolerance for the treatment of allergies such as hay fever [77] and, more recently, seasonal allergic rhinitis [78], asthma [79], bee venom [80], peanuts [81], cow milk [82], and birch pollen [83]. The strategy behind allergen- or antigen-SIT is to administer the antigenic protein/peptide in a proper dose to modulate the immune response and reduce the immunogenicity towards a particular allergen/antigen [84]. The goal of SIT is to induce T cell anergy, activate T_{reg}, or promote a shift from a T_H1 phenotype to T_H2 phenotype [85]. Translating this strategy for inducing tolerance to treat autoimmune diseases has been the focus of many research groups. In this section, the successes of antigenic-SIT in the MS animal model and difficulties in applying the technology to humans will be discussed. In addition, some of the mechanistic aspects of this therapy will be discussed.

Tolerance induction via the mucosal route has been studied extensively in the EAE model. There are numerous studies showing that oral administration of myelin proteins or peptides is an effective way for inducing tolerance, by causing either T cell clonal anergy or induction of the regulatory immune response. It is reported that this depends on the dose of the administered antigen [86–88]. The attractive aspect of the oral route is that it mimics naturally induced tolerance to ingested antigens (with the exception of food allergies), in addition to its ease of administration. Studies reporting suppression of disease with whole proteins has been reported [89, 90] and, more importantly, there are numerous studies showing that induction of tolerance to suppress EAE can be achieved using small protein fragments and peptides. In one study, MBP fragments (1–37, 44–89, and 90–170) suppressed the disease significantly [91]. The oral administration of guinea pig-MBP_{68-88} suppressed rat-MBP_{68-88}-induced EAE in Lewis rats [92]. Other reports showed that MBP and MBP peptide suppressed PLP-induced EAE, suggesting that bystander suppression is possible via the oral route [93]. Lastly, another study showed that feeding animals with $PLP_{139-151}$ peptide induced T-cell clonal anergy and prevented the onset of EAE [94]. Unfortunately, the success in the EAE animal model could not be translated to MS patients. One phase-III clinical trial conducted to test the efficacy of orally administered bovine-myelin containing MBP and PLP showed no significant difference between the treatment and placebo groups (reviewed in ref. [95]). Thus, even though studies conducted in humans have proven that administration of antigen via the oral route is a safe method, no studies have reported any significant benefit so far. The other mucosal route used to deliver antigens is nasal administration. Studies using MBP whole protein [96, 97], MBP peptides [98], and a mixture of myelin peptides ($PLP_{139-151}$, MBP_{1-11}, MBP_{89-101}) [99] have induced peripheral

tolerance and prevented the onset of EAE but, similar to the oral route, no significant benefit in humans has been reported.

Other routes that have been more successful in attenuating MS and EAE were intravenous (i.v.) and transdermal administration. There have been several reports indicating the successful suppression of EAE after i.v. administration of MOG (41–60) and MBP peptides [100] and whole MBP [101, 102]. When the MBP_{82-98} peptide fragment was tested in MS patients, it generally reduced anti-MBP antibodies and significantly delayed the progression of disease in a particular sub-group of MS patients with the HLA haplotype DR2/DR4 [103]. Another study indicated that i.v. administration of MBP_{85-96}, but not intrathecal or subcutaneous administration, led to undetectable amounts of MBP autoantibodies in the CSF for several months post-treatment [104]. More recently, transdermal delivery of myelin antigens has shown some clinical benefit following the success observed in EAE. MBP_{Ac1-11} [105] and whole MBP [106] delivered transdermally protected mice from developing EAE. A small study conducted in patients diagnosed with relapsing-remitting MS was performed to test the immunological modulation caused by a mixture of three peptides (MBP_{85-99}, MOG_{35-55}, and $PLP_{139-151}$) via an adhesive skin patch. Myelin-specific T cell responses were completely eliminated after only four months of treatment [107]. In addition, there was an up-regulation in the production of IL-10 and a down-regulation of TGF-β and IFN-γ in the MS patients, indicating a shift towards an immunotolerant state. These results are promising and may show clinical efficacy if tested on a larger scale. So far, translating efficacy from the EAE animal model to MS treatment has proven to be a difficult task. This is probably due to the complexity and heterogeneity of human autoimmune diseases. Many factors must be considered when trying to apply antigenic-SIT for the treatment of human autoimmune disease such as dosing amount and frequency, route of administration, and specificity of antigens administered.

As described previously, the inflammatory response is initiated by a mDC due to exposure to an insoluble antigen. The uptake and processing of an insoluble antigen leads to the activation of a DC and the presentation of the antigen in presence of costimulatory molecules, thus inducing an inflammatory response. The immunological basis for antigenic-peptide therapy is that when the peptide is given in a soluble state, it binds directly to empty MHC-II molecules on the surface of iDC [108]. Because iDC do not have surface costimulatory molecules, the presentation of antigen by the MHC-II on an iDC in the absence of costimulatory signal(s) causes the naïve T cells to differentiate to T_{reg} cells after their interactions with antigen-presenting iDC [43]. Activation and proliferation of T_{reg} cells influences the balance of the immune response to restore tolerance by shifting from an effector T cell response (T_H1) to an immune-suppressor (T_H2) or an immune-regulatory response (Figure 2).

2.2 Altered Peptide Ligands

Altered peptide ligands (APL) are another group of peptides that are proposed to cause antigen-specific immunosuppression. These are molecules that are similar in sequence to native peptides with one or more amino acid modification(s) and can bind to MHC-II molecules and engage with the TCR to alter or inhibit the delivery of signal to the T cell. Thus, these molecules act as antagonists to produce T cell anergy or as partial agonists to produce incomplete activation of T cells. Incomplete activation of T cells will cause a shift from a pro-inflammatory T cell response (T_H1 and T_H17) to a regulatory/suppressor T cell response (T_H2 and T_H3) [109]. APL with sequence modifications in MBP_{1-9} [110], MBP_{87-99} [111, 112], and $PLP_{139-151}$ [113–117] have been shown to attenuate disease in the EAE model. In a phase I clinical trial, an APL from MBP_{83-99} showed a T_H2 bias and produced anti-inflammatory cytokines; the peptide was well-tolerated by the patients in this trial [118]. However, when this APL was tested in two separate phase II clinical trials, there

was no significant clinical benefit seen in treated patients [119, 120]. In one of the clinical trials, there was no difference observed in the small group of treated patients and the study was terminated due to adverse side effects from the treatment; in addition 3 of 8 patients experienced exacerbations of disease [119]. In the other clinical trial, hypersensitivity reactions were also present and no clinical differences between the APL-treated and the placebo groups were observed, albeit there was a reduction in the number and volume of gadolinium-enhanced CNS lesions [120].

Glatiramer acetate (Copaxone) is a random polymer of four amino acids (poly(YEAK)$_n$) that has been shown to modulate the immune response by competing with MBP epitopes for MHC binding as well as causing TCR antagonism [121]. Therefore, it is the only APL on the market for the treatment of MS. Following the success of Copaxone, similar molecules have been developed and tested in the EAE model. A poly(EYYK)$_4$ peptide that was developed to bind to the MHC-II binding pocket was shown to inhibit EAE in Lewis rats [122]. Other molecules such as poly(FYAK)$_n$ and poly(VWAK)$_n$ also ameliorated both MBP$_{85-99}$- and PLP$_{139-152}$-induced EAE in mice [123, 124]. However, one study indicated that Copaxone has no beneficial effects on disease progression and the risk of developing relapses; and therefore, its clinical use may be questionable [125]. It should also be noted that the efficacy observed from these short amino acid polymers in the animal model may not be translatable to humans.

2.3 Bifunctional Peptide Inhibitors

Our group has developed a novel group of bifunctional peptide inhibitors (BPI), which target APC and are proposed to selectively inhibit an immunogenic response towards a specific antigen. BPI molecules are composed of an antigenic peptide covalently linked to an adhesion peptide [126]. It is proposed that the antigenic peptide fragment of the BPI molecule binds to MHC-II molecules and the adhesion peptide binds simultaneously to an adhesion protein on the surface of the APC. The linker is made up of either aminocaproic acid or polyethylene glycol (PEG) to ensure simultaneous binding of the antigenic peptide portion as well as the adhesion peptide (LABL) to their respective receptors on the surface of the APC. The original length of the linker was estimated upon docking of the antigenic peptide and LABL peptide to X-ray structures of MHC-II [127] and ICAM-1, respectively [128–130]. As mentioned earlier, a step necessary for the activation of a pro-inflammatory T cell response is the formation of the immunological synapse, which occurs at the interface of APC and T cells and is the translocation of Signal 1 and adhesion proteins [40, 41, 53, 54]. The hypothesis is that BPI molecules bind to both MHC-II (Signal 1) and ICAM-1 (adhesion protein) on the surface of APC to tether both molecules and prevent the formation of the immunological synapse, thus altering the differentiation and proliferation of T cells from an inflammatory to a regulatory phenotype.

Several BPI molecules consisting of various antigens and adhesion peptides have been developed for the suppression of autoimmune diseases in animal models. A GAD-BPI molecule composed of GAD$_{208-217}$ and LABL peptides suppressed Type-1 diabetes in the non-obese diabetes mouse model [131]. GAD-BPI significantly suppressed insulitis and lowered blood glucose levels compared to control. Currently, CII-BPI composed of a collagen-II antigenic peptide (CII$_{256-270}$, CII$_{707-721}$, or CII$_{1237-1249}$) conjugated to LABL peptide attenuated clinical signs of rheumatoid arthritis in the collagen-II-induced model (unpublished data). More importantly, PLP-BPI, composed of PLP$_{139-151}$ conjugated to LABL, was the first BPI molecule to suppress EAE and modulate the immune response by increasing the proliferation of TGF-β-, IL-4-, and IL-10-producing CD4$^+$CD25$^+$ T cells, indicating a shift towards a suppressor and regulatory immune response [132–134]. Other studies with PLP-BPI showed that it can also suppress disease when injected three times (s.c.), or when dosed in a controlled release fashion [135]. Current studies prove that PLP-

BPI is effective when administered prior to induction of disease, or even after the appearance of clinical signs. Recently, PLP-cIBR, which contains cIBR7 peptide from the D1 domain of ICAM-1, was shown to be more potent than the parent PLP-BPI. A new MOG-BPI molecule composed of MOG_{38-50} can suppress MOG-induced EAE in the mouse model. Finally, a multivalent BPI molecule composed of both MOG_{38-50} and $PLP_{139-151}$ has been shown to suppress disease significantly in both MOG_{38-50}- and $PLP_{139-151}$-induced EAE. The value of the multivalent BPI molecule is that it can suppress disease regardless of the inciting antigen as well as attenuate new antigenic responses created by epitope spreading.

In summary, BPI molecules have excellent efficacy in suppressing EAE and other autoimmune diseases in animal models. Current studies indicate that BPI molecules down-regulate the production of pro-inflammatory cytokines and increase the production of regulatory cytokines. These results suggest that BPI molecules promote a shift towards a regulatory and suppressor immune response. However, more studies need to be done to elucidate the mechanisms of action of BPI molecules.

2.4 Other Peptides

A novel group of non-antigen-specific peptide inhibitors that bind to B7 on the surface of T cells and prevent the delivery of the costimulatory signal are derived from the sequence of the CD28 costimulatory protein on the surface of APC [44, 45]. The presentation of an antigen in the absence of a costimulatory signal will lead to T cell anergy, therefore inhibiting the inflammatory response (Figure 3). Peptides derived from the conserved region of CD28 containing the motif MYPPPY bind to B7 and have suppressed EAE in B10.PL mice [136]. A similar but shorter peptide that showed efficacy in prolonging cardiac allograft rejection [137] was tested in our laboratory, and results indicated significant suppression of $PLP_{139-151}$-induced EAE in SJL/J mice (unpublished data).

Another approach to suppressing the immune response is targeting the CD4 molecule on the surface of $CD4^+$ T cells. $CD4^+$ T cells are known to have a key role in the pathogenesis of disease and, therefore, preventing their activation would be a valuable target for attenuating any $CD4^+$-mediated immune response such as in MS. A cyclic peptide complementary to the CDR3-like region of CD4 [138] and another peptide designed based on the D1-CC′ loop region [139] were developed and found to suppress EAE effectively. However, it must be noted that safety will be a major concern when developing molecules that target molecules like CD4, since the CD4 molecule is important for the general immune defense mechanisms. Another immunomodulatory peptide known as RDP58 inhibits T_H1 cytokines [140] as well as upregulates heme-oxygenase-1 [141, 142]. It has been shown that heme-oxyhenase-1 has a protective role in EAE [143, 144]; therefore, when combined with the inhibition of T_H1 cytokines, RDP58 significantly lowered the incidence of EAE in Lewis rats [145].

Recently, new peptides have been developed for the treatment of MS by evaluating them in EAE animal models. First, IIIM1 is a 9-amino acid peptide derived from histone $H2A_{36-44}$ that possesses anti-inflammatory activity and suppressed MOG- and PLP-induced EAE [146, 147]. When administered orally, this peptide reduced the production of pro-inflammatory cytokines such as IL-17, IFN-γ, IL12, and IL-23 and promoted T_{reg} cell proliferation accompanied by an increase in TGF-β and IL-10 production. Secondly, four peptides that bind to the first two extracellular loops (ECL1 and ECL2) of the CC chemokine receptor 5 (CCR5) have been shown to significantly reduce the infiltration of monocytes and lymphocytes into the spinal cord and attenuated EAE in mice [148]. CCR5 has been shown to contribute significantly to the pathogenesis of disease by its role in the activation and migration of leukocytes [149]. Peptides targeting CCR5 have a mechanism of action similar to that of Tysabri, a monoclonal antibody used for the treatment of MS [150].

Thirdly, glucocorticoid-induced leucine zipper- (GILZ) peptides that bind to nuclear factor-kappa B (NF-κB) can modulate T-cell activation and induce an anti-inflammatory immune response to suppress the progression of EAE in mice [151]. GILZ peptides were derived from the binding sequence of GILZ to the p65 subunit of NF-κB [151]. GILZ-peptides inhibit the function of NF-κB and suppress the activation of inflammatory cytokines [152]. Finally, it has recently been proposed that treatment of MS can be achieved by modulating toll-like receptors (TLR) because TLR play an integral part in the development of MS and EAE [153–156]. Gambuzza et al. described different types of TLR that are involved in progression of MS and EAE and illustrated several peptides that modulate TLR and can potentially suppress disease [156].

3 SAFETY CONCERNS

A major safety concern involving antigen or antigen-derived therapies is the risk of developing anaphylaxis, which is a severe hypersensitivity reaction. Two clinical trials with an APL were terminated due to hypersensitivity reactions that developed in the patients [119, 120]. An anaphylactic reaction can occur from the initial burst of immune cell activation and proliferation accompanied by a storm of cytokine release. The generally accepted mechanism for induction of anaphylaxis is due to the release of inflammatory mediators that are triggered by cross-linking of IgE molecules bound to FcεRI on mast cells. This can lead to life-threatening symptoms such as tissue edema, leukocyte recruitment, excessive mucous production, and bronchoconstriction [157, 158]. Anaphylaxis has been observed in numerous EAE models after treatment with myelin peptides [159, 160], but when the peptides were administered in combination with an anti-IgE antibody, onset of anaphylaxis was inhibited. The route of administering the peptides plays a major role in mitigating the risk of developing hypersensitivity reactions. It is thought that i.v. injections have the greatest risk for developing anaphylaxis since the antigen becomes accessible to the systemic circulation immediately. S.c. and intradermal injections are believed to have a lower incidence of anaphylaxis, and mucosal administration is the safest [109]. It should be noted, however that induction of EAE by priming with myelin peptide in the presence of CFA leads to the production of IgE molecules [161], thus fostering a hypersensitivity response. This is in contrast to what occurs in MS patients, in which there is production of IgG antibodies [104]. To prevent side effects, Wraith et al. suggested that antigenic peptides could be delivered in a fashion similar to the way that allergens are delivered for the treatment of allergies [84]. In this case, the antigenic peptide should be administered by gradually increasing the dose to avoid rapid induction of anergy or activation of T_{reg} that leads to side effects.

4 CONCLUSIONS

MS pathogenesis is very complex, involving many different branches of the immune system, and still remains to be fully elucidated. Current treatments for MS are generally non-specific, leading to suppression of the general immune response to fight pathogenic infections. Therefore, there is a need to develop more antigen-specific treatments that avoid this general suppression. Recently, antigen-specific treatments such as antigenic peptides, APL, and bifunctional peptide inhibitors have been very successful in suppressing EAE in animal models. Unfortunately, many of these successes in animal models have not been yet translated to humans in treating MS; this is partly due to the generation of hypersensitivity reactions upon treatment with the antigenic peptides. In addition, the mechanisms of action of antigenic peptides and their derivatives in suppressing autoimmune diseases such as EAE and MS are not yet fully understood. Thus, more research needs to be done to elucidate their mechanisms of action and delineate why these antigenic peptides and their derivatives induce side effects such as hypersensitivity reactions. It has been shown that the method of

delivery and dosing schedule could reduce side effects. In the future, studies performed to develop novel delivery methods and dosing schedules of antigenic peptide therapies will be carried out to improve the efficacy and safety profiles of peptide therapies for MS.

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Abbreviations

EAE	experimental autoimmune encephalomyelitis
BPI	bifunctional peptide inhibitor

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Highlights

1. The immunological basis for the onset of MS is summarized.
2. Specific and non-specific peptides tested in EAE and in humans are discussed.
3. Some problems and potential solutions with these novel therapies are addressed.

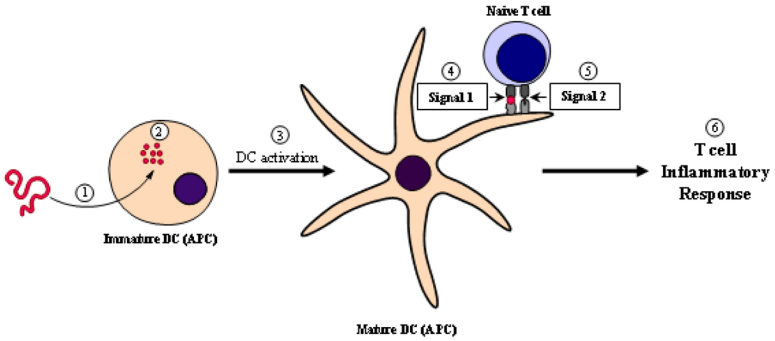

Figure 1.

Activation of a T cell inflammatory response. 1) A steady-state APC such as an immature DC internalizes an insoluble protein antigen. 2) The antigen is then processed and broken down into immuno-dominant peptides that can be presented by the MHC-II molecule on the surface of the APC. 3) Internalization and processing of the antigen triggers the activation of the DC, thus forming a mature DC (mDC). 4) Presentation of the antigen by the mDC in the context of the MHC-II molecule to the TCR on a naïve T cell is known as Signal 1. 5) mDC expresses costimulatory molecules which delivers an activation signal to naïve T cells this is known as Signal 2. 6) The presentation of an antigen in presence of costimulatory signals triggers the development of a T cell inflammatory response towards that antigen.

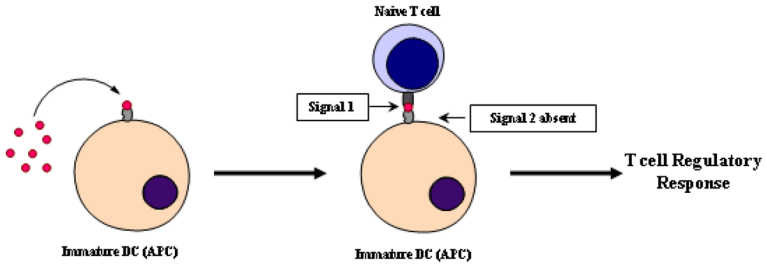

Figure 2.
Administration of soluble peptide antigens induces a T cell regulatory immune response. Soluble peptides can bind directly to empty MHC-II molecules on the surface of iDC avoiding internalization and processing of the antigen. Presentation of the antigen in absence of Signal 2 by an iDC leads to an antigen-specific regulatory response.

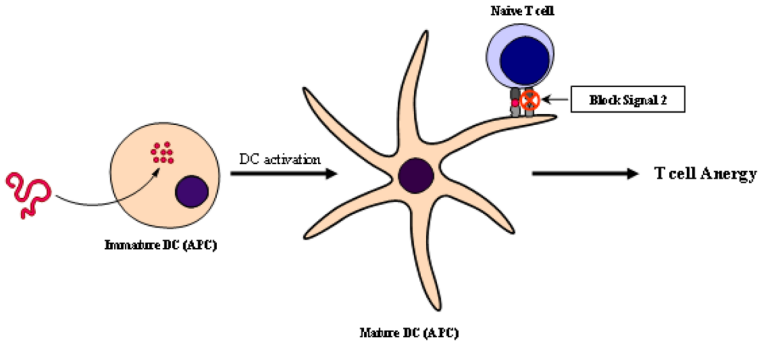

Figure 3.
Presentation of antigen with Signal 2 blockade causes improper activation of T cells thus leading to T cell anergy.