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·Minireview·

Immunologic pathogenesis of multiple sclerosis

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Abstract: Multiple sclerosis (MS) is an autoimmune disease. The etiology and pathogenesis of MS remain unclear. At present, there are substantial evidences to support the hypothesis that genetics plays a crucial role. The people who have genetic predisposing genes easily develop immune-mediated disorder, probably in conjunction with environmental factors. The aim of this review is to describe recent observations regarding the immunologic pathogenesis of MS.

Keywords: multiple sclerosis; immunology; pathogenesis

1 Introduction

Multiple sclerosis (MS) is an autoimmune disease characterized by multifocal inflammation and damage involving the myelin sheath. The etiology and mechanism of MS remain unclear. In the light of the current consensus, the pathogenesis of MS is heterogeneous. At present, there are substantial evidences to support the hypothesis that genetics plays a crucial role. The people who have genetic predisposing genes easily develop immune-mediated disorder, probably in conjunction with environmental factors.

The viewpoint that MS is an autoimmune disease is derived primarily from studies on a single animal model, experimental autoimmune encephalomyelitis (EAE). The current knowledge of pathogenesis of MS is focusing on the functional disequilibrium of Th1 and Th2 cells, abnormal expression of Fas and Fas receptor (Fas/FasL), abnormal expression of costimulator, the effect of myelin basic protein (MBP) and IL-16 and myelin directed autoantibodies, all of which can contribute to the extent of tissue injury in MS (Fig. 1).

2 The functional disequilibrium of Th1 and Th2 cells

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Studies on animal models demonstrate that autoreactive T cells generated in the systemic compartment access the central nervous system (CNS) where they can result in inflammatory demyelination, namely MS, which is an immune-mediated disorder involving one or more antigens located in the myelin of the CNS[1,2]. Substantial qualitative differences appear in responses mediated by myelin-reactive T cells in patients with MS and healthy persons.

There are two subsets of T cells, categorised according to surface proteins they express and classes of main histocompability complex (MHC) protein they recognize. Helper T (Th) cells are $CD4^+$ and recognize MHC class II protein. Cytotoxic T (Tc) cells are $CD8^+$ and recognize MHC class I protein. There are also two sub-types of Th cells (Th1 and Th2 cells) since the cytokines of their secretion are different. Therefore, their functions are different. Secreted proinflammatory cytokines of myelin-specific T cells determine the ability of these cells in the CNS[3].

For the greatest part, Th1 cells mediate MS. The cytokines that Th1 cells produce include lymphotoxin, interferon-γ (IFN-γ), tumour necrosis factor β (TNF-β) and interleukin-2 (IL-2)[4]. IFN-γ and TNF-β can activate macrophages which can strip myelin and destroy oligodendrocyte. In addition, Th1 cells can secrete more proinflammatory cytokines, such as TNF-α and IL-12. IL-12 probably plays a role in the regulation of T-cell responses that have potential relevance to MS[5], while TNF-α may be directly cytotoxic to oligodendrocyte. Our studies demonstrated that IL-12/IFN-γ/NO axis played a critical role in the development of Th1-

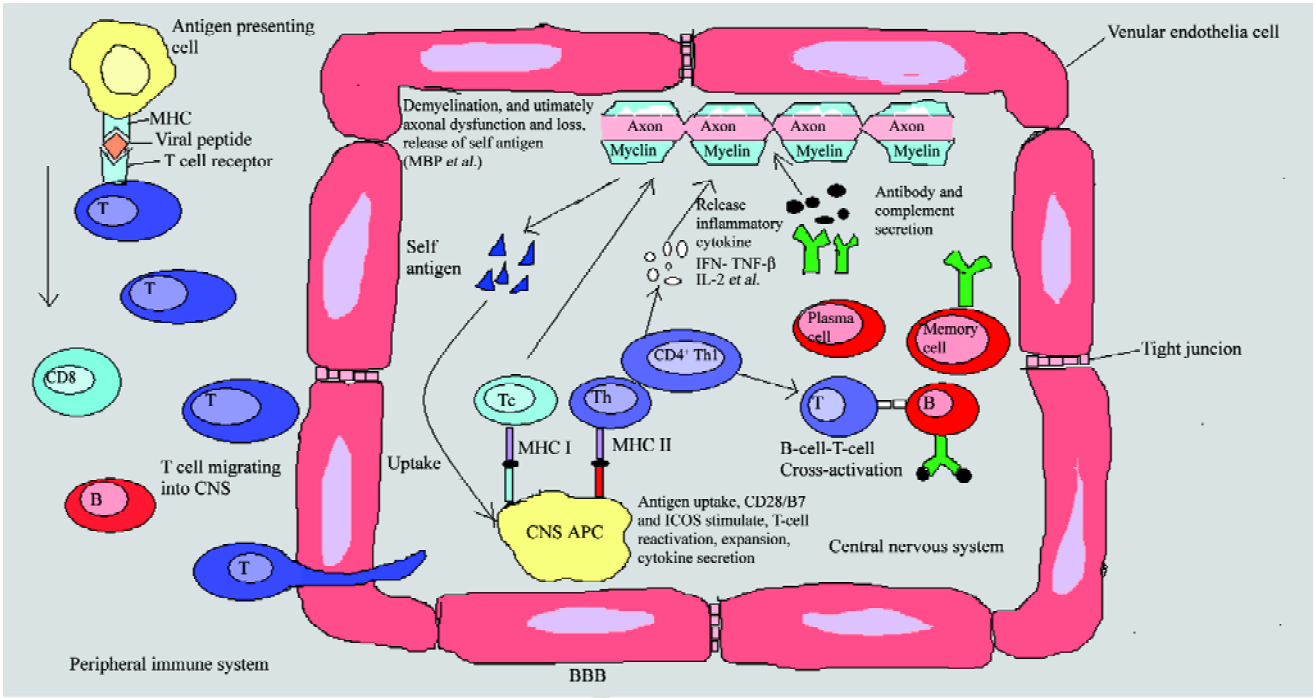

Fig. 1 The induction, inflammation, demyelination, and ultimately axonal dysfunction and loss in EAE/MS. According to this model, the cytokines produced as a result of inflammation, can lead to axonal energy rundown and loss[8].

mediated EAE[6]. Hedegaard *et al.* found that the MBP-induced CD4$^+$ T cell proliferation and production of IL-17 correlated with the number of active plaques on magnetic resonance images[7].

Alternatively, CD4$^+$ Th2 cells represent an antiinflammatory population of lymphocytes that produce large amounts of immunoregulatory cytokines (e.g. IL-4, IL-5, IL-6 and IL-10). IL-4 had been previously correlated with a polarized Th2 immune response, crucial in the differentiation of Th0 cells toward the Th2 pathway. IL-4 knockout mice are defective in development of Th2 cells. A report also suggested that IL-4 could suppress Th1 responses and protect mice from EAE[9]. Mice deficient in IL-10 production have a higher incidence of EAE and develop a more aggressive form of disease[10], while over expression of IL-10 suppresses the development of disease[10,11]. IL-5 plays no significant role in the development of EAE. An unknown cytokine could compensate for the absence of IL-5. However, IL-5 appeared to have immunomodulatory functions in MS[12]. The role of IL-6 in MS has not clearly been understood, particularly since IL-6 is a pleiotropic cytokine involved in the regulation of immune responses. A study showed that anti-IL-6 had no significant effect on EAE, but exogenous IL-6 inhibited EAE when delivered by the recombinant *vaccinia* virus system[13]. By contrast, Serada *et al.* found that IL-6 could induce the differentiation of Th17 cells from naive helper T cells *in vitro*[14]. Th17 is a new inflammatory helper T cell subset which produces IL-17A and is involved in the development and pathogenesis of collagen induced by arthritis (CIA) and EAE. They also indicated that anti-IL-6R mAb could inhibit the development of EAE and inhibit the induction of myelin oligodendrocyte glycoprotein (MOG) peptide-specific CD4$^+$, CD8$^+$, and Th17 T cells in inguinal lymph nodes. Thus anti-IL-6R mAb treatment might represent a novel therapy for human MS[14,15]. In addition, monocyte chemokine protein-1 (MCP-1) can drive Th0 cells to differentiate to Th2 and significantly inhibit the adoptive transfer of EAE. However, we found that the expression of MCP-1 mRNA increased prior to the appearance of clinical symptoms in EAE model[16]. In conclusion, Th2-mediated responses have beneficial effects on the severity and progression of MS[17], and are one of the major mechanisms underlying the induction of Ag-specific immune tolerance[18].

CD8$^+$ Tc cells have also been implicated in EAE and MS. CD8$^+$ T cells show a prominent clonal expansion within MS plaques and correlate better with the extent of acute axonal

injury than $CD4^+$ T cells[19]. Studies using murine models have demonstrated that $CD8^+$ T cells could exhibit an encephalitogenic potential *in vivo* and *in vitro*[20,21], leading to pathology in various ways, such as causing apoptosis of oligodendrocytes and releasing enzymes to destroy targeted cells.

3 Abnormal expression of Fas/FasL

Fas/FasL are members of the TNF superfamilies and known to trigger apoptosis. Fas is one of the most important molecules in regulating autoimmunity involving T cells. Ferrante *et al.* showed that the percentage of Apo-1/Fas-expressing immune cells was increased in MS patients compared with those in controls and that augmented expression of Apo-1/Fas was mostly evident on the surface of macrophages[22]. Importantly, it has been previously demonstrated that Fas function was defective in MS[23] and the disruption of Fas-FasL interaction in gld, as well as lpr mice, partially protected them from EAE[24]. Recently, Lopatinskaya *et al.* has demonstrated that as opposed to various cytokines and chemokine receptors, the two markers of apoptosis Fas and FasL may have predictive value for the progression of disability over a period of 10 years[25]. Hovelmever *et al.* generated mice deficient in Fas expression specifically in oligodendrocytes and further confirmed that Fas was a major initiator of oligodendrocyte apoptosis in EAE. Fas appeared to confer protection from demyelination and development of clinical disease [26]. A study confirmed that the percentage of CD69 increased and Fas expression decreased in $CD4^+$ $CCR5^+$ T cells in 41 MS patients[27]. The lower Fas expression in activated $CD4^+$ $CCR5^+$ T cells might contribute to the pathogenesis of disease by prolonging cell survival and favoring their migration into the CNS. In patients with MS, treatment with IFN-β may be mediated by Fas/FasL signaling. IFN-β could increase the expression of surface Fas and cytotoxic T lymphocyte antigen-4 (CTLA4) molecules, and the expression of the soluble forms of these molecules[28]. The increased Fas and CTLA4 molecules in MS patients may lead to inflammatory lymphocyte apoptosis, which suggests that Fas plays an important role in the lymphocyte apoptosis of EAE.

4 Abnormal expression of costimulatory molecules

The differentiation and activation of T cells need the contribution of double signals. The second signal is provided by antigen-presenting cells (APC) which belong to the dendritic cell lineage and are endowed with the complete repertoire of costimulatory molecules including members of the immunoglobulin-superfamily, such as CD28/B7 and ICOS, that enable the APC to present antigen to, and fully activate naive T cells[29]. Crucially, the balance of APC-derived cytokines determines the subset of regulatory or effector T cells into which a naive cell will differentiate. The interaction between CD28 and B7-1 was suggested to preferentially stimulate the production of IFN-γ which is biased towards the generation of Th1 cells, whereas CD28 triggering B7-2 should mainly secret IL-4 which favors the generation of Th2 cells[30]. In a study the expression of B7-H1 (B7-homologue1) in human CNS tissue was assessed and its adaptive immune responses in MOG_{35-55}-induced EAE were analyzed. The experiments showed a direct inhibitory role of APC-derived B7-H1 on the activation of MOG-specific effector cells and demonstrated the critical importance of B7-H1 as an immune-inhibitory molecule capable of down-regulating T cell responses and contributing to the confinement of immunopathological damage[31].

Abnormal expression of B7 can destroy the balance of Th1 and Th2 cells and result in the development of MS. However, Ferrante *et al.* reported that both B7-1 and B7-2 expressed in monocytes of MS patients, but the expression of B7-2 was induced earlier than that of B7-1 in most acute and chronic immune responses and the expression of B7-1 was not significant when compared with that of control group[22]. This result is not consistent with the super-expression of Th1 and the low-expression of Th2 in MS patients, indicating that there are possibly other costimulator pathways.

5 The effect of MBP

MBP is one of the proteins of the myelin sheath and one of the most important autoantigens to induce MS. Considerable data suggest that MBP plays a key role in the pathology of MS, although its mechanism of action has remained unclear. Antigenically related MBP has been isolated from the cerebrospinal fluid of patients with MS[32,33].

MBP can provoke MS through several pathways. It could activate both $CD4^+$ and $CD8^+$ T cells which play important roles in the pathogenesis of MS. In EAE, $CD4^+$ T cells recognizing MBP have been found to induce CNS pathology

characterized by extensive inflammation and mild demyelination[34]. It was known recently that $CD8^+$ T cells could recognize short peptides of MBP and induce EAE. But unlike the effect of $CD4^+$ T cells, $CD8^+$ T cells recognizing MBP-derived peptides directly contributed to severe CNS demyelination in EAE, presumably through induction of injury of oligodendrocytes[35]. Furthermore, MBP probably provoked the generation of IL-16 in the CNS. Beddison *et al.* presumed that IL-16 was a proinflammatory cytokine which could activate the process of demyelination[36]. Several evidences presented that microglial expression of proinflammatory molecules by MBP-primed T cell was gender-sensitive because female MBP-primed T cells induced the production of NO and other proinflammatory cytokines such as IL-1β, IL-1α, TNF-α and IL-6 which caused relatively more CNS damage in female MS patients than males[37].

6 The effect of myelin directed autoantibodies

In a genetically predisposed individual, an environmental trigger can lead to the development of antibodies against meylin-based antigen, such as anti-MOG and anti-MBP antibodies. These antibodies cross the blood-brain barrier from the systemic circulation to the CNS, and can activate macrophages or microglial cells. Meanwhile, complement and TNF-α are believed to cooperate in producing demyelination, but not initiate immune disorders[38].

Evidence from immunopathological studies suggests that antibody/complement-dependent mechanisms are involved in approximately 60% of MS cases[39]. MOG is the only protein known to induce a demyelinating autoantibody response in EAE. The passive transfer of demyelinating monoclonal anti-MOG antibodies into animals with EAE resulted in widespread demyelination and enhanced clinical disease[40]. Autoantibody/B-cell responses to MOG are enhanced in MS, but these responses are not disease specific. Do they mediate primary demyelination? To address this question, Lalive *et al.* used MOG-transfected cell lines in an attempt to identify potentially pathogenic MOG-specific antibodies in MS sera. Their study indicated that in the majority of patients the anti-MOG response was directed against linear peptide epitopes that were not accessible when the native protein was expressed on the cell surface. Only in a small percentage of cases there were antibodies that recognize the native protein[41]. A study suggested that autoantibody responses to MOG might only play a significant role in demyelination in a small subset of the MS population[42]. A recent observation provided the evidence that antimyelin antibodies have no role in the diagnosis of MS or in the identification of patients at high risk for the development of clinically definite disease[43]. So the definitive effect of anti-MOG and anti-MBP antibodies for MS is continuing to be attempted.

7 Conclusion

In the past few years the real improvement of the laboratory and analytical approaches to study MS has been achieved, leading to a better understanding of the complex immunopathogenesis and genetics of the disease, and the definite pathologic basis of demyelination. But the development of reliable and predictive genomic profiles has not been revealed, because there are some other reasons, such as experimental constraints and ethical considerations.

More importantly, understanding the underlying mechanisms may provide new, better therapeutic options that will help to prevent the development of MS. At present, therapeutic approaches targeting T cells have been successfully used, leading to immunosuppression or tolerance, such as the use of some agents including Imuran, Cytoxan, Methotrexate, Cladribine, and recently IFN-β, Glatiramer acetate and T-cell receptor peptide immunization. In recent years, stem cell transplantation has been proposed as a perfect treatment for MS including hematopoietic and mesenchymal stem cell transplantation[44,45]. However, it remains necessary to better understand the multiple basic genetic and immunological mechanisms in order to find more effective therapeutic tools to help prevent the development of MS.

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多发性硬化的免疫学发病机制

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摘要：多发性硬化是一种自身免疫性疾病，其发病机制至今还未阐明，目前认为可能是一些携有先天遗传易感基因的个体有易发生免疫调节功能紊乱的趋势，在后天环境中外因的作用下，诱发对中枢髓鞘成分的异常自身免疫应答而致病。本文综述了近年来的相关文献和科研成果，旨在探讨多发性硬化的免疫学发病机制。

关键词：多发性硬化；免疫学；发病机制