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Biomarkers of the Innate and Adaptive Immune System Responsible for the Pathogenesis of Multiple Sclerosis - A Narrative Review

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Abstract

Introduction: Multiple Sclerosis (MS) is a complex neurodegenerative disease whose pathophysiology involves demyelinating changes, axon injury, oligodendrocytic death, neuron apoptosis, and inflammation and demyelination of both white and gray brain matter.

Discussion: The role of T cells/B cells has been fairly well documented in MS patients. Analysis of inflammatory infiltrates reveals that CD8+ T cells are found in active lesions while B cells are mainly concentrated in the meninges. Secretory B cell products play an important role in the apoptosis of neurons and the death of oligodendrocytes in MS patients. However, MS cannot be characterized by immune responses; there are genomic components as shown by gene knockout studies. Although there is no cure for MS, it has recently been discovered that increased doses of melatonin may have therapeutic effects.

Conclusion: While the research of MS is ongoing, it is clear that the role of innate and adaptive immunity should not only be the central factor in further understanding the progression of the disease but also the focus of future therapeutic targets. In this review, we focus primarily on immune responses characterized by lesion analysis and inflammatory response in MS patients.

Keywords: Multiple sclerosis; Innate immunity; Adaptive immunity; Biomarker; T cell; B cell; Interleukin

Abbreviations: MS: Multiple Sclerosis; CNS: Central Nervous System; GWAS: Genome-Wide Association Studies

Introduction

Multiple Sclerosis (MS) involves an immune-mediated process in which an abnormal response of the immune system is directed against the body's Central Nervous System (CNS). Demyelination and inflammation are the primary factors of MS, affecting the formation of plaque in the CNS. This results in MS's clinical manifestations, which are vision impairment, fatigue, weakness, depression, numbness, bowel changes, loss of muscle coordination and bladder dysfunction. Depending on the affected areas of the CNS, most MS patients will experience phases of deteriorations, flare-ups or exacerbations before the emergence of a new symptom [1,2]. The cause or etiology of MS is not fully understood. However, there is a likely correlation between various factors, influenced by genetic and environmental dynamics. Despite this, research confirms that MS is an autoimmune disease. These studies are corroborated by Genome-Wide Association Studies (GWAS), which identify over 100 MS risk loci, numerous of which intersect in many gene activations of other autoimmune diseases [3,4].

Diseases that cause dysregulation in the immune system are at the highest risk of causing contraction of MS. The progression of MS is found to be correlated with various biomarkers including immune cells and members of the IL1 cytokine family [5]. In this review we attempt to identify the role of innate and adaptive immunity and provide a comprehensive role of biomarkers in the pathogenesis of MS. In addition, we hope to highlight possible strategies/therapeutic targets in order to slow the progression of the disease and improve the quality of life of MS patients.

Discussion

The role of innate immunity in multiple sclerosis

Multiple sclerosis is generally accepted as an autoimmune disease that causes neurodegeneration in the brain; however, some recent studies have suggested that neurodegeneration in progressive MS may be independent of inflammation. In a study exploring the validity of these claims, researchers investigated the correlation between neurodegeneration, inflammation, and disease development in MS stages. They studied 67 MS autopsies from various phases of the disease, comparing it to 28 controls free of neurological disease and brain lesions. Analysis of inflammatory infiltrates in relation to lesion activity revealed that T cells are actually the source of the most prominent inflammation in the active lesions. Moreover, T-cell infiltration in the meninges was highly noticeable in comparison to the cortical parenchyma, which had little to no T cell infiltrates. It is also interesting to note that CD8 and CD4 positive T cell infiltration supported previous studies, which found that CD8 positive T cells infiltrate the most in MS lesions. Similarly, B-cells and HLA-D-positive microglia cells and macrophages revealed a comparable pattern of inflammation; B-cells were mainly seen in meninges, with only a few isolated in the parenchyma in concentrations ten times lower than T cells. The most intense inflammation was found in patients with relapsing/acute disease, followed by patients in which the disease was progressing. T- and B-cell occurrence was similar in those patients, but plasma cell ratio was different-they were seen more prominently in patients suffering from a progressive form of the disease [6].

Link between the adaptive and innate immunity

Factors that trigger inflammation are crucial for the pathogenesis of MS. Given this, single nucleotide polymorphisms play an important role as they can amplify the expression of inflammatory cytokines and mediators. Multiple studies have indicated that MS patients have high pro-inflammatory and inflammatory cytokine serum levels. One of the most potent and crucial components of innate immunity is the IL-1 family [7]. Vigne and colleagues found that IL-36α, IL-36β, and IL-36γ, members of the IL-1 family are crucial in the production of pro-inflammatory cytokines as most CD4 T lymphocytes and murine bone marrow-derived dendritic cells constantly expressed IL-36R. This was substantiated by high levels of IL-6, IL-12, IL-1β, IL-23 and TNF-α seen in bone marrow-derived dendritic cells. These pro-inflammatory cytokines were affected by IL-36 more than any other IL-1 cytokine. IL-36 was also found to stimulate the production of IFN-γ, IL-17 and IL-4 by CD4 T cells. This clearly demonstrates the key role that IL-36R ligands play, not only in the relationship between innate and adaptive immunity, but also in the stimulation of T-helper responses [8].

Importance of serum level of interleukin 36 in relapsing-remitting MS

In a study recruiting 49 relapsing remitting MS patients and 41 healthy individuals, researchers evaluated the implications of Interleukin (IL)-36 in the pathogenesis of MS. The results of their study indicated that there is a significantly higher concentration of IL-36 serum levels in patients with MS [9]. In a separate study examining the expression of IL-36 colonic epithelial cells in patients suffering from inflammatory bowel syndrome, it was revealed that ulcerative colitis patients had higher expression of IL-36α and IL-36γ in comparison with IL-36β. Monocytes plasma cells and T cells were the main sources of this increased expression of IL-36α and IL-36γ. IL-36α is found to be largely responsible for the formation of acute phase proteins and expression of CXC chemokine, along with the stimulation of MyD88 adaptor proteins TRAK1, IRAK1 and TRAF6 [in conjunction with IL-36γ. This stimulation of adaptor proteins triggers activation of AP-1, NF-κB and phosphorylation of MAPKs. Furthermore, it was found that siRNAs and MAPK inhibitors for c-Jun, AP-1 and NF-κB considerably downregulated IL-36-induced expression of the XCX chemokine [10].

Melatonin effects in peripheral t-helper lymphocytes in RR-MS

Melatonin is known to be a modifier of T helper (Th) 1, Th17 and Treg, the presence of which, along with increased Th22 cells in peripheral blood, are associated with MS progression. In fact, the gene encoding the Th22 receptor il22ra2 actually makes patients more susceptible to MS disease [11]. In a 2017 study, researchers investigated the effects of in vitro administration of melatonin on T-helper (Th) 1, Th9, Th17, T22, and Treg responses.

Results of the study showed that melatonin effectively decreased: CNS infiltration of T cells expression of adhesion molecules and the following chemokines: IL2, IL12, IFN-gamma, and TNF.

In-vitro melatonin in phytohemagglutinin-stimulated peripheral blood mononuclear cells showed a reduced Th1 response. In addition to Th1, Th9 and Th22 responses were also found to be reduced by melatonin treatment [12]. The study further suggested that blocking IL9, IFN gamma, TNF, and IL17A could be potential forms of treatment since all these cytokines increase T-cell infiltration of the CNS, causing oligodendrocytic and neuronal death [12]. Thus, melatonin may be able to improve the quality of life of MS patients through regulation of Th cells and chemokines.

Naïve, memory, and effector T cells in progressive MS

In order to better understand T-cell activation, researchers studied CD26-dipeptidyl peptidase IV and CD49d. CD26 is associated with T helper (Th) 17 cells and the activation of T cells while CD49d is seen when T cells enter the central nervous system. In one study to help determine the role of CD49 in the progression of MS, researchers used Natalizumab, a monoclonal antibody that attaches to the CD49d receptor. At the end of the 15-month treatment period with natalizumab, there was a statistically significant reduction of inflammatory mediators along with less damage to tissues CD28+ and CD4+ terminally

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differentiated effector memory T cells were increased in primary progressive MS patients [13].

Researchers analyzed the difference in percentages and absolute numbers of T cells before and after natalizumab treatment, along with their expression of CD26 and CD49d. They found that the absolute number of circulating CD4+ and CD8+ CD28+ EM and TEMRA T cells increased post-treatment, which is consistent with the idea that natalizumab prevents these T cell subsets from entering the CNS. Additionally, treatment of natalizumab decreased the percentage of cells expressing CD26 in all cell subsets of CD4+ and CD8+ T cells besides CD26+ CD28- TEMRA T cells, which already show the lowest expression of CD26 in untreated patients and controls. Lastly, they found a decrease in the frequency of T cells expressing CD49d in all cell subsets of CD4+ and CD8+ [13]. These findings encourage future studies to look into additional benefits that natalizumab may provide MS patients.

B lymphocytes role in MS

Lisak et al. [14] investigated the role of secretary B cells on the apoptosis of neurons and oligodendrocytes. Secretory products of B cells were taken from both patients with RRMS and control patients and then were treated onto oligodendrocytes. Investigators found that in the secretory product secreted from 13 MS patients, 58% oligodendrocytes died from exposure compared to only 4% in oligodendrocytes treated with secretary product in control patients. Human neurons, when treated with secretory products from RRMS patients, showed a similar trend with over half experiencing neuronal death compared to only ten percent of neurons when treated with control samples. As a result, it is evident that although the mechanism of B cell interaction is not fully understood, it plays a major role in cell death especially in RRMS patients and needs to be further investigated [14].

Hydroxylase effects on immunity

25-hydroxycholesterol (25-OHC) not only initiates a signaling cascade that suppresses the production of IgA but also has antiviral properties. While 25 OHC needs to be further investigated, 24S-Hydroxycholesterol 24S-OH-chol has been fairly well documented. Leoni and colleagues had shown that 24S-OH-chol is synthesized in the brain and its distribution through plasma may serve as a biomarker for the progression of MS. In a study conducted on 118 patients who suffered from MS it was demonstrated that older patients, presumably those who had suffered from MS for a longer duration, had reduced 24S-OH-chol plasma levels compared to age matched controls. As a result, the progression of MS may be correlated with a loss of neuronal cells that synthesize oxysterols [15].

The role of oxysterols

Chalmin and colleagues investigated both how oxysterols modulate/contribute to T lymphocyte morphology and play a role in MS autoimmunity through the use of MS Ch25h -/- mice models. Ch25h is a gene that is highly involved in both cholesterol and lipid metabolism. They reported that 16 days post immunization, only 15 % of Ch25h-/- mice developed MS and 43 % had remained symptom free. The Ch25h knockout had no influence on immune system activation in the periphery as CD 4+ T cells and wild type T cells with immunization of myelin oligodendrocyte glycoproteins revealed the same number of leukocytes, IFN-g, IL-17A and IgG proliferation. Moreover, the study demonstrated that Ch25h may actually intensify inflammatory signals and impair trafficking of CD 44+ and CD4 + T cells [16]. While here we have highlighted the importance of the CH25H gene, there are over 100 genetic markers that may increase the likelihood of MS in a given population.

Conclusion

Most of our current understanding of MS has been derived from investigating the role of T cells/B cells and cytokines. These essentially have served as biomarkers for the progression of MS and much of the clinical focus has been on finding ways to regulate them. Currently two of the most effective treatments available to clinicians are increased use of melatonin and administration of the monoclonal antibody Natalizumab, both of which work to regulate inflammation and cytokine activity. Current clinical trials have also noted the importance of immune system regulation in slowing down the progress of MS and as a result the majority of phase 3 clinical trials running today have a focus on immune regulation. While over 100 genetic markers have been discovered for MS, gene therapy has yet to become a viable form of treatment, but perhaps may be an alternative in the future.

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