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Narrative Review

Immunopathology of Multiple Sclerosis

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ABSTRACT

After decades of experimental and clinical investigations regarding to immunomodulatory therapies for multiple sclerosis (MS) point to exact immunological pathogenesis that drive disease relapses, progression, and remission. In this regard, we shed a light on our current information on multiple sclerosis immunopathogenesis, assess strong hypotheses about the role of the immune system in the disease and clarify key controversies that are still unresolved. Recent clinical recognitions in the field of immunology, and the increasing advances with respect to the role of inflammation as a pivotal component of demyelination, are shaping our findings of disease immunopathogenesis, and we evaluate the concepts for improved efficacy of current treatments of MS in the future.

Keywords: Multiple sclerosis, Molecular biomarker, Pathogenesis, Immune system, Blood.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the brain and spinal cord that is known as a common cause of severe physical disability in young people which afflicts approximately 2.5 million people worldwide (1). MS is accompanied with a major personal and socioeconomic burden: the mean age of disease onset is 30 years and it has been reported that 25 years after diagnosis, approximately half of patients need permanent use of a wheelchair. The disease has a heterogeneous manifestation that can include sensory and visual dysfunctions, motor disturbances, fatigue, pain and cognitive problems (2). The heterogeneity of clinical symptoms associates with the spatiotemporal dissemination of lesions within the central nervous system (CNS) (3). These plaques are a hallmark for diagnosis of MS and are created by immune cell infiltration via the blood–brain barrier (BBB) into the CNS that increases inflammation, demyelination, gliosis and neural damages, leading to dysfunction of neuronal signaling (4). T cells are present early in lesion formation, and the disease is known to be autoimmune, caused by autoreactive lymphocytes that stimulate aberrant mechanisms against CNS antigens, the exact nature of which, however, remains unknown.

Infiltration of immune cells into the CNS which is particularly found in the relapsing-remitting type of the disease has been the main aim of currently available treatments for MS. Although these wide variety of immunomodulatory therapies decrease immune cell function and entry into the CNS and reduce relapse rate, they are often correlated with complications (5). These vary from mild symptoms and the development of other autoimmune diseases to malignancies and even sever opportunistic infections such as progressive multifocal leukoencephalopathy, suggesting the need to find

more specific treatments that can be efficaciously reduce inflammation and the symptoms of the patients but without inducing such significant adverse events.

Similarly, it has been increasingly showed that although the long-standing treatments established for MS can reduce relapse rate, they do not substantially reduce the progression of the disease and neuroinflammatory damages. This supports the idea that there is some degree of conflicts between the processes driving overt relapses and those driving chronic progression. Therefore, secondary progressive disease may not be a temporally distinct phase of the condition arising as a direct result of the relapsing-remitting disease but may instead be the consequence of other underlying pathophysiological mechanisms. This is also in association with the existence of the relapse-free, primary progressive type of MS (6, 7).

The combination of relapses and disability progression has considerable information for our knowledge of disease pathways and for therapeutic design, as there are currently no treatments approved to specifically treat primary or secondary progressive types of MS (8). Although disease progression is not greatly affected by the common immunomodulatory treatments, which target peripheral immune cell function and entry into the CNS, immunological involvement has an important role in this process: there is another inflammatory component existing in the CNS that is only marginally affected by peripheral immune control and that is associated to gradual neuroaxonal loss and damage of myelin-producing oligodendrocytes (9). This CNS-resident inflammatory component of the disease is less well known but is likely to involve continuous activation of innate immune cells; these cells have been shown to exist in demyelinated loci, but they are also present diffusely throughout normal parts of white matter of the CNC, and their numbers associate with tissue damage (10).

Investigation of the distinct roles of the immune system in the events that induce MS development and those that associated with disease progression is thus complicated by the multicellular pathophysiology contributed to infiltrating adaptive and innate immune cells, as well as CNS-resident innate immune cells with neuroinflammatory activity and by the chronic nature of the disease that increases over a period of many decades.

In this study, we assess how our findings of the involvement of the immune system in inducing the development of MS is being constructed by the ongoing interrogation of genetic predisposition and environmental risk factors. We evaluate the changing role of peripheral immune system including role of effector and regulatory lymphocytes and innate immune cells in inducing pathogenesis as the disease takes its course, and we discuss regarding CNS-resident innate cells as emerging part of the disease contributors to chronic neuroinflammation. Therefore, in this review we aimed to summarize current evidence regarding multiple sclerosis immunopathology, the outstanding clinical needs, and the possible biomedical challenges for the future.

What Causes Multiple Sclerosis?

The exact triggers of MS, and whether these are different from one patient to the next, still remains unknown, but the disease is thought to arise in genetically susceptible subjects, with accidental events and environmental risk factors affecting disease penetrance. It has been estimated that genetic variation accounts for approximately 30% of the overall risk of MS development, and with the development of genome-wide association studies (GWASs), more than 100 distinct genetic locations have been detected as being correlated with MS, totally explaining approximately 30% of the genetic part of the condition (11). Despite the fact that non-genetic risk factors have a proportionately larger role than genetic factors to immunological heterogeneity in MS patients (12), comparatively less progress has been obtained in elucidating environmental risk factors of MS, perhaps reflecting the problems of accurately interpreting complex, and sometimes confounding, epidemiological findings (13). Without a specific predominant exogenous risk factor, it is an open question whether MS is initiated in the periphery or in the CNS. In the peripheral model, autoreactive T cells that are activated at peripheral parts of the body infiltrate into the CNS along with activated B cells and monocytes. This model is in line with the technique used to provide the MS-like disease experimental autoimmune encephalomyelitis (EAE) in rats: emulsified CNS antigen is injected along with immune stimulants, leads to the production of pathogenic CD4+ T helper 1 (TH1) cells and TH17 cells in the draining lymph nodes (14, 15). These types of cells then circulate and ultimately perform

their effector roles within the CNS, having crossed the BBB at the choroid plexus.

On the other hand, CNS-intrinsic model may induce disease development, with the traffic of autoreactive lymphocytes occurring as a secondary phenomenon. It is unknown what these CNS-intrinsic events might be, although supposed mechanisms include inflammatory responses to an as yet unclear CNS viral infection or to mechanisms leading to primary neurodegeneration, similar to those that have been shown in Alzheimer disease or Parkinson disease (16). However, adding support for either model of MS etiology from other neurological disorders guarantees a closer consideration of how approved MS risk factors compare to those for other common autoimmune and neurodegenerative diseases.

Genetic Predisposition

The majority of candidate genes for susceptibility to MS are supposed to be immunological. Therefore, the considerable overlap in associated genomic locations between MS and other autoimmune diseases is predictable (17) and may show some sharing of predisposing immunological mechanisms, thereby supporting the peripheral model of MS development. However, in some patients this is only an apparent overlap: for instance, the same variant in the gene region encoding tumour necrosis factor receptor 1 (TNFR1) makes susceptibility to MS but confers protection against ankylosing spondylitis, consistent with the side effects of treatments targeting the TNFR1 pathway, which increase MS relapse rate but suggest efficacy in ankylosing spondylitis (18). Despite this finding, efforts to obtain a more comprehensive interpretation of the genetic evidence have led to the construction of interactome networks using the possible candidate genes assigned to each associated region. For MS, such analyses show the involvement of interleukin-2 (IL-2), interferons (IFNs) and nuclear factor-κB signalling, among numerous other immunological mechanisms, in disease susceptibility (18).

These data are consistent with pre-GWAS findings regarding immunological processes in MS, but the more critical use of GWAS findings to dissect disease pathways needs more in-depth evaluations. Epigenetic, transcriptomic and immunoprofiling (19) investigations are just beginning to add clarification on how the variants associate with immune cell subset-specific differences in the regulation of gene expression, as most related genetic variants are non-coding and many join to gene enhancers or repressors in involved immune cells. However, associations do not necessarily reflect causality. Currently, a more detailed, but not definitive, knowledge of genetically determined disease mechanisms has been found for only a handful of correlated loci, such as the *HLA-A*02:01* and *HLA-DRB1*15:01* variants (28,29), and the genes encoding the α-chains of the IL-2 and IL-7 receptors (20, 21). The findings show central tolerance processes, as well as peripheral differences in effector T cell function due to changed cytokine responsiveness, cytokine synthesis and homeostatic proliferation, in MS susceptibility.

Although still limited, the current evidence regarding the functional implications of MS-related genetic polymorphisms is that the *HLA* polymorphisms primarily define the CNS specificity of the MS by influencing the T cell repertoire, whereas the non-*HLA* polymorphisms more broadly affect the threshold of immune cell activation, thereby ultimately changing the probability of a CNS-directed autoimmune response being mounted.

Consequently, strikingly few genetic correlations are shared between MS and other neurodegenerative diseases such as Alzheimer disease and Parkinson disease (22). This suggests that non-immunological, primary neurodegenerative mechanisms are less likely to promote the development of MS, although role of genetic factors in disease severity or subtypes of the disease may yet show a role for neurological genes. Interestingly, however, disease risk correlations in the *HLA* region have also been shown for the other neurodegenerative diseases (22), even though T cell does not have a role in pathogenesis of these diseases, and thus more studies are required to establish the significance of these results.

The genetic basis of MS is associated with the prominent role of the immune system in disease susceptibility. The clinical importance of detecting the specific phenotypic consequences of MS-related polymorphisms has now initiated to be recognized, and this plethora of polymorphisms can serve as a platform for interrogating human immune system diversity (23, 24): to improve our knowledge of disease immunopathogenesis, to find more targeted treatment approaches and to even uncover novel immunological mechanisms that can be harnessed for therapeutic aims.

Environmental Factors

In consistent with the established roles of MS genetic risk factors in the direct development of autoreactivity and in the broader change of thresholds of immune cell activation, the environmental risk factors that have role in disease development may also fall into two similar categories.

Those environmental risk factors more directly affect the triggering of autoreactive T cells are often supposed to be viral or microbial in nature and exert their effects through molecular mimicry (25). Tolerance breakdown may also be occurred through the environmental factor-driven production of novel autoantigens (26). Furthermore, direct modification and generation of relevant antigens, environmental risk factors such as CNS-tropic infectious agents may also accelerate the release of sequestered CNS antigens into the periphery, as has been shown in recent study of a model of Theiler's murine encephalomyelitis virus infection (27).

Environmental risk factors with a more modulatory role may indirectly change the activation thresholds of autoreactive T cells by inducing a pro-inflammatory condition. Interestingly, peripheral inflammation by infection may also have a direct effect on the CNS: locally produced cytokines can induce afferent nerve endings, circumventricular organ and choroid plexus innate immune cells can react to circulating pathogen-related molecular patterns (28), and pro-inflammatory cytokines at high concentrations in the circulation can be infiltrated across the BBB and can activate signalling in perivascular macrophages (29). The outcome of this connection between immune system and CNS is postulated to typically involve the proinflammatory activation of microglial cells. This poses the provocative question of whether, in some subjects, MS can develop indirectly from peripheral inflammation that induces microglia-dependent neurodegeneration, without the need for a CNS-directed autoreactive response to be mounted.

It has been shown than many non-*HLA* genetic risk factors for MS probably influence a multitude of immunological mechanisms, environmental risk factors that affect any one of these different mechanisms may also be associated with disease development. Similarly, there may be just as numerous different environmental risk factors for MS as there are genetic risk factors. To date, the evaluated environmental factors implicated in MS variably, but not exclusively, include vitamin D, human cytomegalovirus infection (30) and irregularity of circadian rhythm. However, smoking and Epstein–Barr virus (EBV) infection remain the best-approved environmental risk factors although it should be considered that the modest impact of their individual effects on overall MS risk is comparable to that of any single associated genetic risk factors (30).

There is promising evidence that high levels of EBV-specific antibodies associate with increased MS risk, as does a history of infectious mononucleosis (31). Different mechanisms for the role of EBV infection in MS development have been suggested. One hypothesis is that inappropriate regulation of latent EBV infection results in viral reactivation in the CNS, leading to EBV-transformed B cells in the meningeal and perivascular space expressing viral proteins that could trigger effector T cells (32). Moreover, chronic viral infection can result in an increase in the presence of virus-specific memory T cells, and this increase may be emphasized in MS; indeed, homeostatic peripheral T cell proliferation in response to an accelerated thymic involution has been shown in patients with relapsing-remitting MS (33). However, there is conflicting findings regarding whether EBV RNA or protein increases in the CNS of patients with MS (34), and there is controversy regarding this hypothesis. A second hypothesis proposes that EBV may instead have a more general role in immune system dysregulation, which is in keeping with the association of EBV infection with the increased risk of developing other autoimmune diseases, such as systemic lupus erythematosus (35).

As the extent of the human virome is just beginning to be appreciated, our knowledge of viral involvement in MS is still in its early stages. This is equally true for the bacterial microbiome, the genome of which is approximately 100-times larger than the human genome, and which varies in composition based on environmental factors such as diet and exposure to different factors (35). EAE investigations have shown that changes to the gut microbiota, for example, can change the incidence and severity of CNS inflammation and ensuing development of the disease (36). However, a direct association between the microbiota and MS in humans has yet to be established.

Although finding the many environmental risk factors that may change MS risk and comprehending their mode of action shows a particularly significant challenge, the assumed ease of modifying exogenous effects and human behaviour to reduce disease risk or severity is an interesting prospect for future medical treatment.

Chronic Multicellular Disease Development

The multifactorial characteristics of MS including a potential deluge of different genetic and environmental factors at its inception unfolds through a complex, highly multicellular pathophysiological mechanism that evolves throughout the duration of the disease progression.

Autoreactive T Cells

The generation of T cells within CNS plaques is measurable in the early stages of MS (37), and the long-appreciated *HLA* correlations with the disease are seemed to reflect the presentation of specific CNS autoantigens to autoreactive T cells. As demyelination is a key characteristic of MS neuropathology, myelin protein-derived autoantigens have been assumed to be the main autoreactive targets. Myelin basic protein (MBP), proteolipid protein and myelin oligodendrocyte glycoprotein (MOG), for example, have been shown to be recognized by circulating CD4+ T cells in patients with MS but also in healthy subjects, and there is conflicting results regarding potential differences in the frequency and avidity of these cells between the two groups (38). This controversy and also the absence of a dominant T cell autoantigen in MS, may be due to technical limitations in recognizing such autoantigens, to inter-patient variation, or to epitope spreading (39), but unbiased combinatorial library screening methods and antigen-tolerizing methods may ease to further clarify anti-myelin immune mechanisms in the disease (40).

In EAE model of MS, entered CD4+ T cells are re-activated in the CNS by antigen-presenting cells (APCs), including CD11c+ dendritic cells (DCs), with the initiated inflammatory mechanism resulting in monocyte recruitment into the CNS, as well as naive CD4+ T cell activation through epitope spreading that increases the inflammation (52). TH1 cells and TH17 cells are the main CD4+ T cell subsets involved in disease, and thus altering of T cell differentiation away from these subsets and towards a TH2 cell phenotype has been a main therapeutic concept and is known to be a mechanism of action of the first-line, disease-modifying treatments such as IFNβ, glatiramer acetate (Copaxone; Teva and Sanofi–Aventis), and dimethyl fumarate (Tecfidera; Biogen) (41).

However, the exact role of TH1 cells versus TH17 cells in MS pathogenesis is unclear: conflicting results of investigations variably report the predominance of one cell type over the other at onset of the disease and during subsequent relapses and progression (42), and compared with controls, patient myelin-reactive peripheral CD4+ T cells expressing CC-chemokine receptor 6 (CCR6) reveal enhanced expression of both the respective TH1 and TH17 cell signature cytokines IFNγ and IL-17A (37). Moreover, some lesional CD4+ T cells have an intermediate phenotype, expressing both IFNγ and IL-17A. Despite these controversial findings, the failure of a Phase II clinical trial in cases with RRMS following the use of ustekinumab (Stelara; Janssen) (43) was not anticipated. Suggested reasons have included a putative inability of the drug to infiltrate via the BBB and influence directly in the CNS, and a decreased importance for IL-12 and/or IL-23 at subsequent stages of disease. The hypothesis for the ustekinumab study, based partly on EAE trials, has also been questioned; although EAE studies are indispensable for studying disease mechanisms, interspecies immunological differences have been detected, including the essential presence of IL-23 in TH17 cell activation in mice but not in humans (44). Furthermore, the activity of TH17 cells seems to differ between mice and humans. TH17 cell-mediated granulocyte–macrophage colony-stimulating factor (GM-CSF) synthesis has a role in chronic inflammation in EAE, whereas TH1 cells and other cell subsets are the first-line producers of this cytokine in MS patients (45).

Autoreactive B Cells

Compared with T cells, activated B cell numbers in the CNS vary more throughout disease process. Clonally activated B cells can be detected in the meninges, parenchyma and CSF, and intrathecal B cells synthesize antibodies that are measurable in the CSF and are of diagnostic value. Numbers of antibody-secreting B cells are increased with age in cases with primary or secondary progressive MS (46). The meninges of MS patients with secondary progressive disease often contain tertiary lymphoid structures of accumulated plasma cells, B cells, T

cells and follicular DCs (FDCs) (47), which are a result of long-term inflammation as seen in other chronic inflammatory or infectious diseases. By contrast, primary progressive disease is known by diffuse meningeal infiltration without such structures. Despite initial investigations that certain autoantigens are known by pathogenic B cells in subgroups of patients, these results still await approval (48). Furthermore, other autoimmune neurological disorders, such as myasthenia gravis, neuromyelitis optica and autoimmune encephalitis, present with a clinical uniformity (49) that is absent in the subgroup of cases with antibody-positive MS.

In the absence of recognized autoantigens, the process controlling B cell activation, selection and affinity maturation have been a matter of speculation. However, the recent usage of next-generation sequencing technologies to analyse B cell receptor diversity has yielded the characterization of B cell clonotypes in the peripheral parts of the body and the CSF of MS patients, and such investigations show that antigen-experienced B cells can undergo maturation in draining cervical lymph nodes before infiltration into the CNS (50). These data suggest a therapeutic potential for the peripheral intervention on specific B cell subtypes (50). Recently, Phase II clinical trials have revealed that CD20-specific monoclonal antibodies rituximab (51) or ocrelizumab are effective to reduce relapse numbers. These treatments decrease the majority of B cell subsets but not autoantibody-producing terminally differentiated plasma cells, and they may thus be effective to reduce B cell-mediated antigen presentation and other non-autoantibody-related pathogenic associations such as pro-inflammatory IL-6 production (52).

Defective Regulatory Cells

The presence and function of autoreactive B cells and T cells in MS may be due to the defective activity of regulatory cells, such as forkhead box P3 (FOXP3)-expressing CD4+ regulatory T (TReg) cells81 and IL-10-producing T regulatory type 1 (TR1) cells (53). Although few such cells exist in the CNS of MS patients, disease-associated HLA class II polymorphisms could skew thymic selection such that the regulatory T cells that are released into the periphery inappropriately suppress autoreactive effector T cells (54). On the other hand, dysfunction of peripheral suppressor cells could be indirectly occurred by the dysregulation of tolerogenic APCs, as reported in EAE (55). Non-*HLA* genetic correlations, such as variation in the *BACH2* gene region, may also have a role in changing TReg cell activity, as the transcription factor BACH2 has a pivotal role in the generation of these cells and exerts its effects as a super-enhancer for T cell identity (56). However, MS patients with immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), who have a FOXP3 deficiency, do not develop CNS-associated autoimmunity, and therefore TReg cell dysfunction in MS patients may be an acquired rather than a primary defect (57).

Inflammation in Progressive Neurodegeneration

The majority of current immunomodulatory treatments decrease number of relapse but not necessarily long-term MS progression, it has been shown that autoimmune response-instigated neuroaxonal injury initiates a potentially self-sustaining chronic neurodegenerative mechanism. This proceeds even in the absence of continued immune cell immigration from the periphery, which eventually wanes regardless of treatment, possibly due to immune cell exhaustion correlated with chronic antigenic exposure (58). Although neurodegeneration in MS is considered to be the culmination of a cascade of events occurring in axons and neurons including oxidative stress mechanisms, energy disturbances, ionic imbalances, and the failure of neuroprotective and regenerative process (59). Chronic CNS neuroinflammation may strengthen these mechanisms through the activation of cells that have become or are already present within the CNS.

Previously immigrating adaptive immune cells may have a role in long-term neuroinflammation in MS through the eventual generation of tertiary lymphoid structures within the CNS (60). However, it is becoming increasingly clear that CNS-resident cells that sense homeostatic disturbances, mainly microglia and astrocytes, can also synthesize a range of neurotoxic inflammatory mediators (such as cytokines, chemokines and reactive oxygen species) that trigger and increase neuroaxonal damage and thus neurodegeneration. Furthermore, these cells are likely to contribute to in MS-related CNS neuroinflammation not only during the later process of the disease when immune cell immigration from the periphery subsides but also from the outset. Even after the very first initiation of the disease, increases in the numbers and activation status of microglia and macrophages can be detected in plaques and in the

normal-appearing white matter of CNS (61). Furthermore, as neuroaxonal degeneration develops, microglia in the vicinity of axons emanating from distally damaged neurons may become activated; these neurons may hence make the nucleus of new plaque formation and may also have a role in the general brain atrophy that is seen in early disease (62). Considerably, the important role of microglia versus monocyte-derived macrophages throughout the course of MS has not been fully clarified owing to the problems in distinguishing these two morphologically and functionally similar cell types.

Conclusion

The current evidence regarding MS immunopathology has been consistently varied since the establishment of the first immunomodulatory treatment for the condition, and therefore hypotheses regarding the mechanisms underscoring the triggers and long-term development of the MS remain to be definitively explained, although these hypotheses are now better defined.

Maybe most significantly, the appreciation of MS as the pathophysiological intersection between interlinked but not entirely interdependent autoimmune and neurodegenerative mechanisms has set imminent research challenges. There is a dire need to meaningfully combine rapidly emerging technologies and results with existing neuroimmunological clinical evidence in order to interrogate the multicellular interplay that unfolds within the CNS throughout disease development. For better understanding of the pathophysiology of MS, further studies of immunology and neurology in MS through the assessment of neuroinflammation as a whole in order to better determine which inflammatory and neurodegenerative process are truly distinct but occur in parallel and which are inextricably correlated, so as to aid the design of more effective therapeutic interventions.

An aim for future treatment of MS may thus be the simultaneous, early targeting of peripheral immune cell activity and of CNS-intrinsic neuroinflammation, potentially through combinatorial treatments designed to effectively and specifically alter these two immunological parts of the disease, along with the provision of neuroprotective or neuroregenerative treatments. Improved disease treatment and potential patient satisfaction for more directed healthcare provision are also much-anticipated aims and may become tangible as we move into the ‘immune informatics’ era and as large-scale, common health resources become increasingly accessible.

Declarations

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Author Contribution

Melika Salari: Study design, data collection, writing draft of study.

Niloofar alsadat Nourian: Study design, data collection, writing draft of study.

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Conflict of interest

There is no conflict of interest.

Data Availability

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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