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Multiple Sclerosis on behalf SFSEP

# Progress in understanding the pathophysiology of multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) arises in people who have a genetic susceptibility to environmental factors and events, which ultimately trigger the disease. It is thought that peripheral immune cells are mobilized and enter the CNS through the impaired blood–brain barrier in the subarachnoid space, as acute lesions show large numbers of macrophages and CD8+ T cells and, to a lesser extent, CD4+ T cells, B cells and plasma cells. Demyelination is mostly localized to focal lesions in early relapsing–remitting (RR) MS, whereas other areas of white matter appear normal. Over time, T-cell and B-cell infiltration becomes more diffuse and axonal injury more widespread, leading to self-perpetuating atrophy in both white and gray matter. With disease progression, inflammatory processes are predominantly driven by the action of CNS resident microglia cells. In addition, there is evidence that meningeal lymphoid-like structures can form and contribute to late-stage inflammation. In general, however, despite dynamic changes over time in MS pathology, lesions do not appear to differ significantly in the different classic forms of MS already identified. While all treatments approved for MS management target inflammatory components of RRMS, the B-cell-depleting antibody ocrelizumab is the first such treatment approved recently for primary progressive (PP) MS. However, recent pathological and imaging findings have prompted reconsideration of the clinical phenotypes of MS patients proposed by Lublin's 2013 classification, including clinical and MRI signs of activity, and new imaging biomarkers of remyelination are now being investigated for new strategies of MS management.



## 1. Introduction

The field of multiple sclerosis (MS) research continues to suffer from a fundamental lack of understanding of the initial mechanisms behind the disease, which has led to disease classifications based on natural history [1], and an incomplete view of the processes responsible for its initiation and development. From a clinical point of view, in 85% of patients, MS starts as a 'relapsing–remitting' form (RRMS), characterized by the presence of clinical relapses usually followed by functional recovery. After a variable period of time, 50% of RRMS patients enter a progressive phase of disease, called 'secondary-progressive' MS (SPMS), whereas the remaining MS patients follow a progressive course from the outset and are called 'primary-progressive' MS (PPMS) [2].

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## 2. Inflammation and demyelination are hallmarks of MS

The pathology of MS is characterized by inflammation, demyelination, reactive gliosis and neuroaxonal damage. Relapses coincide with the presence of inflammatory demyelinating lesions within the central nervous system (CNS) that are detectable by magnetic resonance imaging (MRI). These lesions are hallmarks of the disorder, and are due to the infiltration of peripheral immune cells into the brain and spinal cord.

Early lesions show invading peripheral immune cells and leakages in the blood–brain barrier (BBB). Macrophages predominate the infiltrate, followed by CD8+ T cells, whereas lower numbers of CD4+ T cells, B cells and plasma cells may also be found [3]. Although the T-cell composition of infiltrates does not change as the disease develops, the relative proportion of B and plasma cells increases [4]. Microglia and macrophages maintain a chronic state of activation throughout the disease [3], forming plaques that involve loss of myelin sheaths and oligodendrocytes.

Because the CNS is relatively separated from the immune system and lymphatic organs, this is considered an argument for peripheral initiation of adaptive immune responses against CNS antigens, with ensuing CNS barrier infiltration. However, even in a healthy CNS, memory T cells traffic through cerebrospinal fluid (CSF), indicating a capacity for intrinsic CNS immune surveillance [5,6].

A major challenge in the field of pathology is the result of recent developments in imaging technology. For the first time, tools permitting investigation of the dynamic evolution of brain and spinal cord damage during the course of disease are now available, and have led to several revelations. First, it became clear that focal white-matter (WM) lesions were only part of the spectrum of MS pathology. In early disease, there is little overt damage to the brain and spinal cord in areas outside of focal lesions referred to as 'normal-appearing white matter' (NAWM), while general brain atrophy was noted [7,8]. Second, spectroscopy data confirmed early pathological observations that not only myelin, but also axons and neurons, were affected by the disease process, as illustrated by the magnitude of neurodegenerative events in MS lesions [9]. The neurodegenerative process then gradually becomes self-perpetuating, resulting in irreversible disability [10,11].

Although axons and neurons are mostly preserved in early MS, ongoing disease leads to gradual neuroaxonal loss correlating with patient disability. The associated brain atrophy is accompanied by ventricular enlargement, and astrocytes form multiple sclerotic glial scars in white-matter lesions. Demyelinating areas in white matter can be partially repaired by remyelination, although demyelination is also found in gray matter of the cortex, nuclei and spinal cord [12].

## 3. MS is an autoimmune disease

MS is considered an autoimmune condition initiated by autoreactive immune cells that cross the BBB and target the CNS. The immunological component is the most well-understood etiopathological aspect of MS, and its importance has been emphasized by the findings of large-scale genetic analyses [2,13], identification of the Epstein–Barr virus (EBV) as an environmental contributor to MS [14,15] and studies of animal models in which the MS-like experimental autoimmune encephalomyelitis (EAE) can be induced through immune activation [10].

The strongest genetic determinant is the human leukocyte antigen *(HLA)-DRB1*15:01* allele, which most likely determines the CNS specificity of the condition, whereas >100 non-HLA-associated loci may function to alter immune-cell-activation thresholds in a non-antigen-specific fashion [13,16]. MS shares the same paradigm (genetic and environmental components) as other inflammatory diseases, but also has some differences. Indeed, even today, the initial biological target for a potent adaptive immune response remains an enigma.

High levels of EBV-specific antibodies are associated with robust evidence of increased MS risk, such as a history of infectious mononucleosis [15,17]. In fact, inadequate regulation of latent EBV infection could lead to viral reactivation in the CNS, resulting in EBV-transformed B cells in meningeal and perivascular effector T cells [18]. In addition, chronic viral infection can lead to an increase in the number of virus-specific memory T cells [19], although whether EBV ribonucleic acid (RNA) or EBV protein is present in the CNS of MS patients remains controversial [18,20]. Furthermore, EBV may play a more general role in immune-system dysregulation, thereby explaining why EBV infection also correlates with the risk of having other autoimmune diseases, such as systemic lupus erythematosus (SLE) [21].

As with other autoimmune disorders like inflammatory bowel disease (IBD) and especially Crohn's disease, other environmental factors, such as tobacco use and the microbiota, can influence MS development [22–25]. However, whether and how nicotine acts on the immune system in MS is still subject to discussion. Nicotine appears to bind to different subunits of nicotine acetylcholine receptors expressed on crucial immune-system cells, such as T and B cells, dendritic cells and microglia/macrophages. Nevertheless, while nicotine injections have been found to improve EAE symptoms, mice given cigarette smoke condensate manifest a worsened disease course [26,27].

Certain triggering factors related to the onset and perpetuation of MS could be associated with gut microbiota. In fact, it is becoming clear that different commensal microorganisms have the ability to: (i) elicit proinflammatory and anti-inflammatory responses in the host; (ii) mimic some CNS proteins, such as myelin proteins; (iii) communicate through a complex web of metabolites and neurotransmitters; and (iv) continuously activate the innate immune system, leading to chronic immune stimulation. Two recent studies have shown an increased abundance of *Akkermansia muciniphila* in MS patients compared with shared-household controls and monozygotic twin pairs without MS [24,28]. In another study, *A. muciniphila* was reported to have both regulatory and proinflammatory properties [29].

While autoimmune lesions can be reproduced under experimental conditions, none of the various EAE models have replicated the entire range of heterogeneity observed in MS patients. However, murine EAE models can still provide a platform for testing specific hypotheses related to both genetic and environmental disease risks. EAE is typically characterized by disseminated encephalomyelitis in which demyelination and

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