MS: What We Know and What We Need to Learn

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Multiple sclerosis (MS), the most common neurologic disease of young adults, is an autoimmune disease of the central nervous system (CNS), i.e. the brain and spinal cord. Myelin, the lipid-rich substance that envelops many axons, speeds transmission of electrical signals between neurons. In MS, the body's own immune system attacks myelin and oligodendrocytes, the cells that produce myelin in the CNS, and the resulting damage slows or completely stops nerve conduction.

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People with MS can have a variety of neurologic symptoms, including stiffness, visual impairment, bladder dysfunction, vertigo, clumsiness, altered sensation, and weakness. Specific symptoms correspond to the location of MS lesions, which can form anywhere in the CNS. For example, a lesion in the optic nerve can cause vision loss and pain worsened by eye movement; a lesion in the cerebellum can cause clumsiness and poor balance.

Most patients experience an initial "clinically isolated syndrome," symptoms seem to flare up and then ease off, returning to near-normal neurologic function before flaring up again later. This pattern of disease is known as relapsing remitting MS (RRMS). A subset of patients with RRMS disease develops secondary progressive MS (SPMS), in which the acute attacks grow worse, leading slowly to loss of function, usually walking, and accumulation of other disability. Patients with the rarest type, primary progressive MS (PPMS), have symptoms that worsen from the start; they don't experience discrete attacks.

In the body, bouts of localized inflammation cause the flares of RRMS, while neurodegeneration contributes to the progressive forms of the disease. Diagnosis of MS is based on a patient's medical history, physical exam, and MRI scans, seeing the presence of lesions, where they are, and how they change or increase over time. In early relapsing remitting disease there are frequent MS lesions with associated breakdown of the blood-brain barrier, as measured by gadolinium enhancement. In secondary progressive disease, there are little to no new MS lesions but instead, progressive loss of brain parenchymal volume [1].

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Over the past two decades, our understanding of MS has greatly expanded. We now have a good working model for RRMS, having identified many of the genetic and environmental factors that contribute to risk of developing the disease. In parallel with this deeper insight into pathogenesis has come the development of highly effective drugs that have dramatically altered the course of disease for many patients. However, we still don't know whether the early treatment of patients with relapsing remitting disease prevents secondary progressive MS.

We now know that MS pathogenesis is driven by cells of the adaptive immune system, the branch of the immune system whose lymphocytes (B cells and T cells) each respond only to a single specific antigen. Th17 cells, a subset of T cells that normally protect the body from extracellular bacteria and fungi, are crucial to initiating the disease. Studies of experimental autoimmune encephalomyelitis (EAE), a good animal model for investigating the immune basis of MS, suggest that autoreactive Th17 cells (Th17 cells that specifically recognize a body component as an antigen) cross the blood-cerebrospinal fluid (CSF) barrier by interacting with a specific protein expressed on the choroid plexus, a structure that produces CSF in the ventricles of the brain [2]. These autoreactive T cells then enter the periventricular parenchyma or the pia and subpial cortex of the brain. Once there, they release the cytokines IL-17 and IL-22, which increase blood-brain barrier permeability and initiate immune

cell penetration by additional autoreactive Th17 cells and other types of lymphocytes: Th1 cells, CD8 T cells, B cells and plasma cells [3].

Regulatory T cells (Tregs), a subpopulation of T cells that help maintain tolerance to self-antigens, are also critical in MS. Our group has shown that Tregs from MS patients are less able to suppress autoreactive T cells [4]. Additionally, we observed that patients with RRMS have an increased frequency of Th1-like, IFNγ-secreting, pro-inflammatory Tregs compared with healthy subjects. We showed both *in vitro* and *ex vivo* that these Tregs acquire their pro-inflammatory phenotype when they are stimulated in the presence of IL-12 [5]. Support for this mechanism *in vivo* comes from the observation in people with RRMS that IFN-β treatment decreases IL-12 levels and normalizes the frequency of IFNγ-secreting Tregs.

B cells and plasma cells, the immune cells that produce antibodies, have also long been recognized as important cell types in MS pathology. This is due in part to the oligoclonal bands, reflecting antibodies of different specificities, which are often seen in the spinal fluid of people with MS. In people with SPMS, clinicians have seen ectopic lymphoid follicle-like structures containing proliferating B cells in the membranes surrounding brain and spinal cord. A gradient of worsening neuronal loss near these meningeal follicles has been observed, suggesting that antibody-mediated cell death may be partially responsible for disease in the gray matter of the brain [6].

Researchers are striving to identify the self-antigens to which autoreactive lymphocytes respond in MS. Much work has focused on T cell reactivity to myelin antigens, specifically myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG). The general consensus is that there are several pathologic antigens involved in MS. Although initial autoreactivity may be specific to one particular antigen, the process of epitope spreading likely expands the pool of specific triggers of activated immune cells to include multiple epitopes of the target antigen and even additional antigens [7].

Genetic factors contribute to the development of MS; studies show high rates of disease concordance in twins and other first-degree relatives. Our knowledge of MS genetics has expanded dramatically in the past decade as a result of fundamental advances in human genetics. Genome-wide association studies (GWAS), large case-control studies designed to detect genetic variants that confer modest risk for common diseases, have now identified 194 MS-associated loci that, in aggregate, account for approximately half of the genetic risk for MS. Among these loci there is significant enrichment of genes linked to lymphocyte regulation.

In addition, approximately two-thirds of these susceptibility loci are shared with other autoimmune diseases, hinting that there may be common autoimmunity pathways [8]. These genetic variants are beneficial and apparently lead to increases in immune responsiveness. But, perhaps, too much of a good thing may be bad and lead to an autoimmune response.

While genetic risk is critical for MS onset, there are clearly environmental factors that influence the disease. One interesting epidemiological observation is that MS frequency varies with geography, but child immigrants tend to take on the risk level of the area to which they move. This has led many to suggest that early exposure to an environmental factor may be important. Epstein-Barr virus (EBV), the virus that causes infectious mononucleosis and countless milder infections, is an often-cited suspect.

Recently, our group has suggested that salt may play an important role in MS pathology. We showed that Th17 cells generated under high-salt conditions display a highly pathogenic pro-inflammatory phenotype, and that mice fed a high-salt diet develop a more-severe form of EAE [9]. Similarly, other researchers have found higher sodium intake to be associated with increased clinical and radiological disease activity in people with MS[10]. A recent paper identified melatonin, a hormone involved in maintenance of circadian rhythms, as a possible contributor to the seasonality of MS relapses; the authors showed that melatonin levels negatively correlate with MS activity in patients, and that melatonin limits development of EAE and blocks differentiation of pathogenic Th17 cells [11]. Thus, it is not bad genes or a bad environment but a poor interaction between genes and environment that cause MS.

Many of the advances in MS over the past two decades have revolved around the development of effective disease-modifying drugs, medications that target the underlying pathology of MS and that can alter long-term outcomes. Approved by the FDA in 1993, interferon beta-1b (IFN-β1b) was the first disease-modifying drug for MS. It changes the expression of many pro- and anti-inflammatory genes and reduces the number of immune cells that cross the blood-brain barrier. Glatiramer acetate, another early

MS drug, is a random polymer of four amino acids that drives T cells towards a non-inflammatory state. Both IFN-β and glatiramer acetate are administered by subcutaneous injection, reduce the annual relapse rate by about 30 percent, and have excellent long-term safety profiles [12].

Natalizumab, a monoclonal antibody that blocks T cells from crossing the blood-brain barrier, is one of the most effective MS drugs on the market. Administered by monthly intravenous infusion, natalizumab was shown to reduce the rate of clinical relapse at one year by 68 percent and decrease the accumulation/enlargement of MRI lesions over two years by 83 percent [13]. A very small but real number of natalizumab-treated patients developed progressive multifocal leukoencephalopathy (PML), a rare, often fatal, brain infection caused by reactivation of JC virus. For this reason, before starting natalizumab, patients should be tested for antibodies against JC virus, presence of which indicates previous infection and PML susceptibility.

Fingolimod is a highly effective oral drug, with 55-60 percent lower relapse rates compared with placebo. It works by trapping naive and central memory T lymphocytes in lymph nodes. Newer MS medications include the oral immunomodulatory drugs teriflunomide and dimethyl fumarate [12]. Recent studies with ocrelizumab, a monoclonal antibody directed against B cells, demonstrate a significant reduction in the relapse rate without serious side effects.

In summary, MS is a multifocal demyelinating disease of the CNS caused by an autoimmune response to self-antigens in genetically susceptible people. While our understanding of relapsing remitting disease and treatment options have expanded enormously in recent years, understanding the mechanism of secondary and primary progressive MS, including the neurodegenerative aspects of these diseases, remains a central question.

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