

# Multiple Sclerosis

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## INTRODUCTION

Multiple sclerosis (MS) is a chronic, demyelinating, neurodegenerative disorder of the central nervous system (CNS). It is the most common cause of non-traumatic neurological damage among young adults, affecting approximately 0.24% of the North American population.<sup>1,2</sup> Canada has the world's highest rate of MS, with over 100,000 Canadians affected by the disease.<sup>3</sup> Although there is evidence that suggests an autoimmune process initiates the disease and that demyelination results from myelin-targeted inflammation, the complex pathogenesis of MS remains poorly understood. There is currently no cure for MS.<sup>1</sup>

## PATHOPHYSIOLOGY OVERVIEW

There are several phenotypes of MS: primary and secondary progressive MS, which involve uninterrupted disease progression; relapsing-remitting MS (RRMS), which consists of intermittent periods of active inflammation; and progressive-relapsing MS (PRMS), which exhibits continuous progression with occasional relapse.<sup>1,4</sup>

One commonality linking all forms of MS is lymphocyte-mediated perivascular inflammation, occurring primarily in the white matter. The resulting diffused or randomly distributed demyelination and axonal loss lead to inflammatory lesions, otherwise known as demyelinating plaques. Depending on the location of the plaques, neurological symptoms vary. These symptoms include vision and hearing impairment, sensory and proprioceptive deficits, motor deficits, depression, pain, fatigue, and cognitive impairment.<sup>1,5,6</sup> The CNS has the ability to partially counteract demyelination by mounting an anti-inflammatory response which may be partly responsible for the intermittent remission characteristic of RRMS and PRMS.<sup>5</sup> It is unknown why a similar anti-inflammatory response is not seen in progressive forms of MS.

While the exact mechanism that triggers MS remains elusive, epidemiological evidence has identified environmental factors, including exposure to the Epstein-Barr virus, to be a risk factor.<sup>7,8</sup> In addition, variations in the human leukocyte antigen gene also influence likelihood of MS onset.<sup>9</sup>

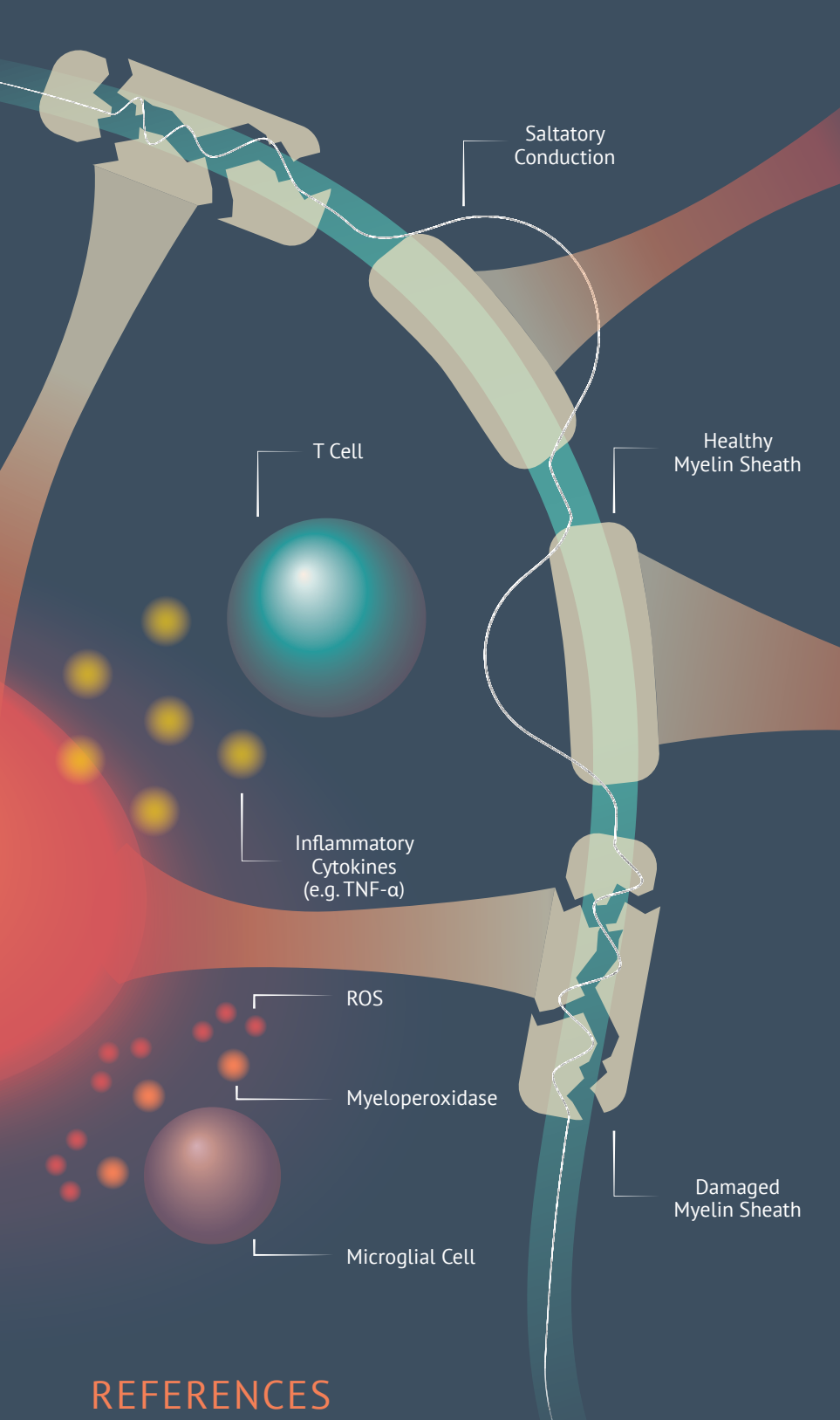
Oligodendrocyte

## AUTOIMMUNE DEMYELINATION

The myelin sheath is a specialized lipid-rich organelle produced, maintained, and regenerated by a type of glia called the oligodendrocyte. Myelin sheaths surround neuronal axons for the dual purpose of insulation and enhanced transmission. Demyelination is the characteristic neuropathology of MS, and results from autoimmune destruction of the myelin sheaths.<sup>5,6</sup> The current prevailing hypothesis states that CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes initiate and propagate an autoimmune attack on oligodendrocytes.<sup>1</sup> This process begins when T lymphocytes and B lymphocytes infiltrate the CNS. Once inside, they can be activated by myelin components presented by antigen presenting cells such as dendritic cells and microglia. Upon activation, a variety of potent pro-inflammatory cytokines with myelinotoxic effects are released, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>10</sup> This complex inflammatory process results in myelin sheath destruction, which

induces localized astrogliosis (abnormal increases in astrocyte population and size). In progressive MS, demyelination is invariably associated with microglial activation. These CNS-specific immune cells express molecules that facilitate the production of reactive oxygen species (ROS), such as myeloperoxidase and NADPH oxidase. In turn, ROS act to accelerate oligodendrocyte injury.<sup>11</sup>

The primary result of demyelination is perturbed impulse conduction. In properly myelinated axons, action potentials leap between unmyelinated regions of the axon known as the nodes of Ranvier, resulting in fast saltatory conduction. In the absence of healthy myelin, action potential conduction becomes diffuse, slow, and weak.<sup>12</sup> Additionally, demyelinated neurons become more excitable, generating abnormal impulses that produce symptoms of ataxia and tonic spasms characteristic of MS.<sup>10</sup>



## AXON DEGENERATION

In addition to demyelination, white matter inflammation in MS also causes axon degeneration, which is mediated by several mechanisms including mitochondrial injury, hypoxia, and membrane ionic imbalance. Demyelination exposes the mitochondria within the axons to ROS, which can mutate mitochondrial DNA, decreasing their rate of energy production. This can manifest in axonal degradation through numerous pathways, such as reduced axonal oxygen consumption, termed histotoxic hypoxia; release of apoptosis-inducing factors; and the activation of calpains, which can cause degradation of cytoskeletal proteins and axons.<sup>5</sup> The mechanisms involved in axonal degeneration are complex, and more research is needed to develop effective therapeutic interventions to counter axonal damage occurring in MS.<sup>13</sup>

## FUTURE RESEARCH

Currently, researchers have not reached a consensus on the primary trigger for the autoimmune attack, nor have they completely delineated the mechanism behind anti-inflammatory CNS activities underlying disease remission. Moreover, since no reliable imaging or pathological characteristics exist to distinguish between early RRMS and progressive forms of the disease, further research is necessary to determine differences between the phenotypes via molecular analysis of cerebrospinal fluid samples from MS patients. Despite this gap, immunomodulatory treatments, such as the interferon beta protein, have proven to be effective in reducing the relapse rate of MS by inhibiting the activation of myelin reactive T cells. Future research priorities for MS treatment include elucidating neuroprotection mechanisms and exploring combination therapies.<sup>10</sup>

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