

The Effects of Fingolimod on T Cells and the Central Nervous System in the Pathogenesis of Multiple Sclerosis

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Abbreviations

CCR7: C-C Chemokine Receptor Type 7; CNS: Central Nervous System; S1P: Sphingosine 1-Phosphate; S1P₁: Sphingosine 1-Phosphate Receptor Subtype 1; T_N: Naïve T Cell

Knowledge of the immunopathology of multiple sclerosis (MS) within the central nervous system (CNS) continues to evolve and has been enhanced greatly by an understanding of the mode of action and effects of disease modifying therapies (DMTs). It is widely accepted that T cells play a critical role in the pathogenesis of MS, and immune cell infiltrates found in active CNS lesions are dominated by T cells and antigen-presenting cells [1,2]. Auto reactive T cells that migrate across the blood-brain barrier (BBB) are activated locally by immune cells in the CNS (microglia and astrocytes), leading to CNS inflammation (Figure 1) [3,4]. Indeed, the approved high-efficacy DMTs natalizumab and fingolimod exert effects on T cells by targeting facets of T-cell migration [5].

A recent review article evaluated the evidence for the CNS effects of fingolimod [6]. In relapsing forms of MS, fingolimod causes central memory T cells and naïve T cells to be retained, reversibly, in lymph nodes, and hence reduces the recirculation of autoreactive lymphocytes and their migration into the CNS [7-10]. Specifically, fingolimod is a sphingosine 1-phosphate (S1P) receptor modulator that binds to the S1P₁ receptor subtype on the surface of naïve and central memory T cells that express CC-chemokine receptor type 7 (CCR7⁺ T cells), and causes the S1P₁ receptor to be internalized by the cell [7,11]. This functional blockade of the S1P signalling pathway by fingolimod inhibits the egress of CCR7⁺ T cells from lymph nodes (Figures 1 and 2) [8,11]. Levels of effector memory T cells, which are CCR7⁻, are largely unaffected by fingolimod, so immune surveillance, and therefore protection from infection, is preserved [12].

The high efficacy of fingolimod in relapsing forms of MS [13-15] cannot be accounted for solely by prevention of peripheral T-cell circulation into the CNS. It is also likely to be attributable in part to direct interactions with neural cells expressing S1P receptors [16]. For example, both *in vitro* and *in vivo* evidence indicates that fingolimod has a direct effect on astrocytes, oligodendrocytes, neurones, microglia and dendritic cells [6]. Delivery of therapeutic biomolecules into the CNS is of course restricted by the BBB and the blood-spinal cord barrier [17,18]. However, the lipophilic nature of fingolimod allows it to cross these barriers and reach the CNS following oral administration [19].

In addition to the wealth of evidence for the direct role played by T cells in the immunopathology of MS, evidence is also accumulating for the role of B cells. B cells activate pro-inflammatory T cells, secrete pro-inflammatory cytokines and produce autoantibodies to myelin [20,21]. Moreover, recent data show that B-cell-targeted therapy ameliorates disease activity; however, whether B cells are directly involved in the pathogenesis of MS is unclear [20,21]. Fingolimod treatment exerts positive effects on B cells in MS; it increases the number of circulating regulatory B cells, which are protective in autoimmune disease, and has been shown to enhance regulatory B-cell migration across the BBB, while simultaneously reducing the number of circulating naïve and memory B cells [6]. More recent data show that fingolimod corrects the imbalance between regulatory

and effector B-cell functions both by direct effects and indirect partitioning effects on B-cell subpopulations [22].

In conclusion, the efficacy of DMTs that target T cells in MS reinforces the importance of the role of T cells in disease pathogenesis. It is also clear that in MS the interplay between T-cell and B-cell subtypes within the CNS is complex [6]. Further understanding of the specific roles of T cells within the MS brain may be important in informing future immunotherapeutic strategies for individuals with the disease.

Figure 1: Central memory T cells (T_{CM}) and naïve T cells (T_N) recirculate between blood and the lymphatic system via the lymph nodes. When an antigen is encountered in the lymph node, T cells are activated and proliferate; T_N cells develop into T_{CM} cells, which can develop further into effector memory T cells (T_{EM}), depending on the level of antigenic stimulation. In MS, abnormally stimulated antigen-presenting cells (APC) activate lymphocytes in the lymph nodes against myelin proteins. These myelin protein-primed auto reactive lymphocytes egress from lymph nodes into the blood, where they are re-stimulated by APCs, such as macrophages (Mac), to infiltrate the CNS via the blood-brain barrier (BBB). In the CNS, activated T_{CM} differentiate into T_{EM} on re-encountering the auto-antigen. A pro-inflammatory loop is therefore set up, leading to the accumulation of activated T cells, Mac, B cells and antibody-producing plasma cells. These activated cells release toxic inflammatory mediators, including pro-inflammatory cytokines, antibodies, glutamate, nitric oxide and complement – a process which ultimately leads to breakdown of the myelin sheath.

Figure 2: Fingolimod inhibits sphingosine 1-phosphate (S1P) receptor signalling, preventing lymphocyte egress from lymph nodes. Fingolimod binding to S1P receptors on central memory T cells (T_{CM}) causes them to internalize and degrade their own S1P receptors, resulting in T_{CM} cells that are not responsive to S1P signals. While fingolimod is bound to the S1P receptors, any new S1P receptors produced inside the cell, as part of the normal regeneration process common to all cell types, remain in a state of arrest. Therefore, any S1P signal does not cause the T_{CM} cells to leave the lymph node. Fingolimod therefore prevents these autoreactive T_{CM} cells from migrating into circulation and entering the central nervous system. In contrast, the levels of peripheral effector memory T cells (T_{EM}), which are important in containing locally invading pathogens and preserving immunosurveillance, are largely unaffected by fingolimod therapy.

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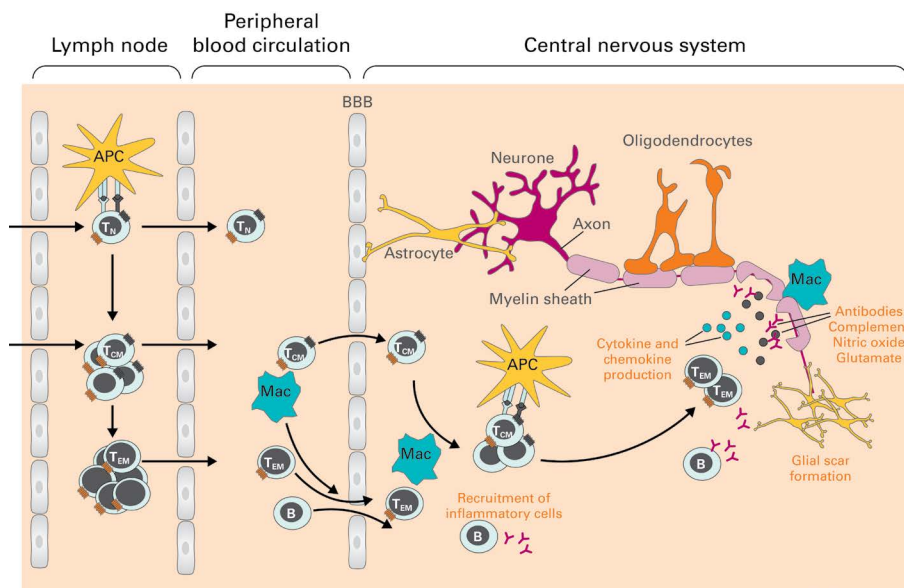


Figure 1: Overview of the involvement of T cells in the immune cascade in multiple sclerosis.

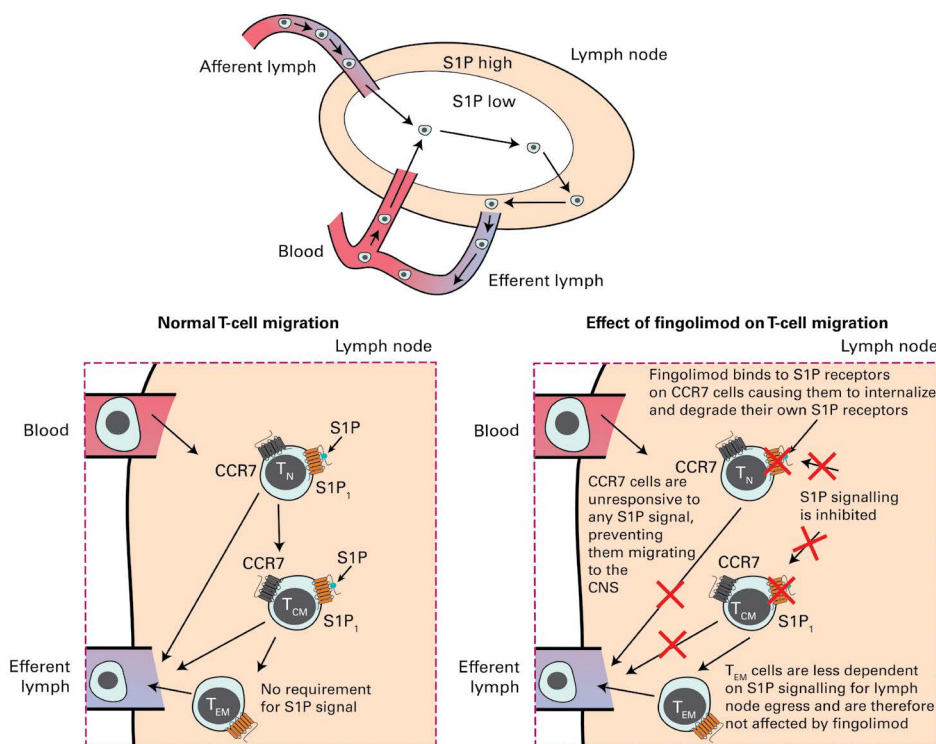


Figure 2: Fingolimod prevention of T cell migration into the CNS (adapted from Jeffery et al. with permission) [12].

Figure legends:

Figure 1: Overview of the involvement of T cells in the immune cascade in multiple sclerosis.

Figure 2: Fingolimod prevention of T cell migration into the CNS (adapted from Jeffery et al. with permission).

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