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Perspective

# Sphingosine-1-Phosphate Signaling in Immune Cell Trafficking and Autoimmune Disease: A Pathway Under the Spotlight

**Isabella M. Keane***

*Department of Immunology, Karolinska Institute, Stockholm, Sweden*

## DESCRIPTION

The immune system relies on precise spatial and temporal coordination of cell movement to function effectively. Among the molecular mediators guiding immune cell migration, Sphingosine-1-Phosphate (S1P) has emerged as a central player. A bioactive lipid metabolite, S1P operates through five G-protein-coupled receptors (S1PR1–S1PR5) to control cell trafficking, vascular integrity and immune surveillance. While the physiological importance of S1P signaling is well established, its dysregulation has been increasingly linked to autoimmune diseases, where inappropriate immune activation and migration drive pathology. S1P is generated intracellularly by the phosphorylation of sphingosine *via* sphingosine kinases (SphK1 and SphK2) and is exported to the extracellular space, where it creates a gradient essential for directing immune cell movement. High concentrations of S1P are maintained in blood and lymph, while tissues and lymphoid organs typically have lower levels. This gradient enables naïve lymphocytes to exit thymus and lymph nodes by engaging S1PR1, facilitating their recirculation and surveillance roles.

In autoimmune disorders such as Multiple Sclerosis (MS), Inflammatory Bowel Disease (IBD) and Systemic Lupus Erythematosus (SLE), this carefully orchestrated trafficking is disrupted. Aberrant expression or activity of S1P receptors can lead to excessive egress of lymphocytes from lymphoid tissues into circulation, allowing them to infiltrate peripheral tissues and exacerbate inflammation. In MS, for instance, autoreactive T cells escape immune checkpoints and invade the Central Nervous System (CNS), resulting in demyelination and neuronal injury. Here, the S1P pathway does not merely facilitate movement but plays a pathogenic role in disease progression. The therapeutic relevance of this signaling axis has been underscored by the success of S1P receptor modulators. Fingolimod (FTY720), the first-in-class S1PR modulator approved for MS, acts as a functional antagonist of S1PR1. Once phosphorylated *in vivo*, fingolimod binds to S1PR1 on lymphocytes, causing its internalization and degradation. This traps lymphocytes in lymph nodes, reducing their circulation and preventing them from reaching inflamed CNS tissues. Clinical trials have demonstrated fingolimod's efficacy in reducing relapse rates and MRI lesion activity in relapsing-remitting MS, validating S1P signaling as a viable therapeutic target.

Since then, newer S1P receptor modulators such as siponimod, ozanimod and ponesimod have been developed, offering improved selectivity, safety and pharmacokinetics. These next-generation drugs target specific S1P receptors, primarily S1PR1 and S1PR5, minimizing off-target effects associated with non-selective modulation. Their expanding application in diseases beyond MS such as ulcerative colitis and psoriasis highlights the versatility of this pathway in controlling immune cell dynamics across diverse tissues. Despite these advances, several questions remain. How does chronic modulation of S1P signaling affect immune homeostasis in the long term? Could prolonged lymphocyte sequestration impair host defense against infections or malignancies? Moreover, the tissue-specific roles of less-studied receptors like S1PR2–S1PR5 in autoimmune settings are not yet fully understood. Emerging evidence suggests that these receptors may influence not only lymphocyte trafficking but also cytokine production, endothelial barrier function and innate immune cell behavior.

Additionally, S1P signaling interacts with other key immunological pathways, including chemokine receptors, integrins and adhesion molecules. These intersecting networks may offer novel therapeutic entry points or reveal synergistic strategies. For instance, combining S1PR modulators with targeted biologics (e.g., anti-IL-17 or anti-TNF agents) could enhance efficacy or address treatment-resistant disease subsets. Understanding these relationships will be critical as we attempt to personalize therapies based on disease phenotype and patient immune profiles. Beyond pharmacological modulation, research is also investigating the role of diet, microbiome-derived metabolites and lipid metabolism in shaping S1P signaling. Altered lipid homeostasis in autoimmune patients may influence S1P synthesis and gradient formation, potentially offering opportunities for lifestyle-based interventions or metabolic therapies.

**Correspondence to:** Isabella M. Keane, Department of Immunology, Karolinska Institute, Stockholm, Sweden, E-mail: isabella.kane@ki.se

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## CONCLUSION

Sphingosine-1-phosphate signaling sits at a critical junction of immunological regulation, bridging lipid metabolism, receptor biology and immune cell trafficking. Its role in maintaining immune homeostasis is as significant as its contribution to autoimmunity when dysregulated. The clinical impact of S1P receptor modulators, particularly in multiple sclerosis, has transformed our approach to managing immune-mediated diseases and demonstrated that targeting immune cell migration is a viable and powerful strategy. Yet, much remains to be uncovered. A deeper understanding of receptor subtype function, context-specific signaling, and long-term immunological consequences is essential. As next-generation therapies evolve, a more refined and integrative approach to manipulating S1P signaling could lead to safer, more precise and more effective treatments for a range of autoimmune disorders. Continued exploration of this pathway holds great promise not only for suppressing inappropriate immune responses but also for restoring the balance essential to immune resilience.