Extended Abstract
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Advancements in Genetic Engineering

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Sphingosine-1-phosphate [S1P] is a potent bioactive sphingolipid molecule. In response to a stimulus, S1P is produced intracellularly by the action of two sphingosine kinases, and then it is exported to the extracellular environment or acts as an intracellular second messenger. S1P binds to its cognate G-protein coupled receptors, which are known as S1P receptors. There are five S1P receptors that have been identified in vertebrates. By activating S1P receptors, S1P controls a variety of physiological and pathological processes including cell migration, angiogenesis, vascular maturation, inflammation, and invasion, metastasis, and chemoresistance in cancer. S1P has emerged as a critical regulator of leukocyte migration and plays a central role in lymphocyte egress from the thymus and secondary lymphoid organs. In the current review article, we summarize the current understanding of the emigration of lymphocytes and other leukocytes from bone marrow, thymus and secondary lymphoid organs to the circulation, as well as the clinical implications of modulating the activity of the major S1P receptor, S1PR1. Sphingosine-1-phosphate [S1P] is a sphingolipid metabolite and a potent signalling molecule that regulates diverse cellular processes including cell proliferation, survival, differentiation and migration. Intense research by many groups has provided a comprehensive understanding of the role of S1P signalling in diverse physiological processes. These include but are not limited to metazoan and mammalian development, reproduction, angiogenesis, vascular maturation, inflammation, the response to ischemic injury, leukocyte migration, and cancer progression, metastasis, invasiveness and chemoresistance [3]. S1P exerts most of its biological actions by serving as a ligand for five G protein-coupled receptors [GPCRs] known as S1P receptors 1-5 [S1PR1-5]. After the discovery that the phosphorylated form of FTY720, an immunosuppressive compound, is an analogy of S1P and binds to four of the five S1PRs, the major role that S1P signalling plays in lymphocyte trafficking was recognized and the potential to target this pathway for therapeutic benefit envisaged. In fact, FTY720 [Galena] has now been approved by the Food and Drug Administration for the treatment of multiple sclerosis and is being evaluated in the treatment of other autoimmune diseases, demonstrating the clinical utility of targeting S1P signalling for the purpose of immunomodulation. Although the regulation of T cell egress from the thymus by S1P/S1PR1 signalling is the most well-characterized and pharmacologically exploited of its known functions, the regulation of hematopoietic cell trafficking is a leitmotif of S1P signalling.

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