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## Abstract

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





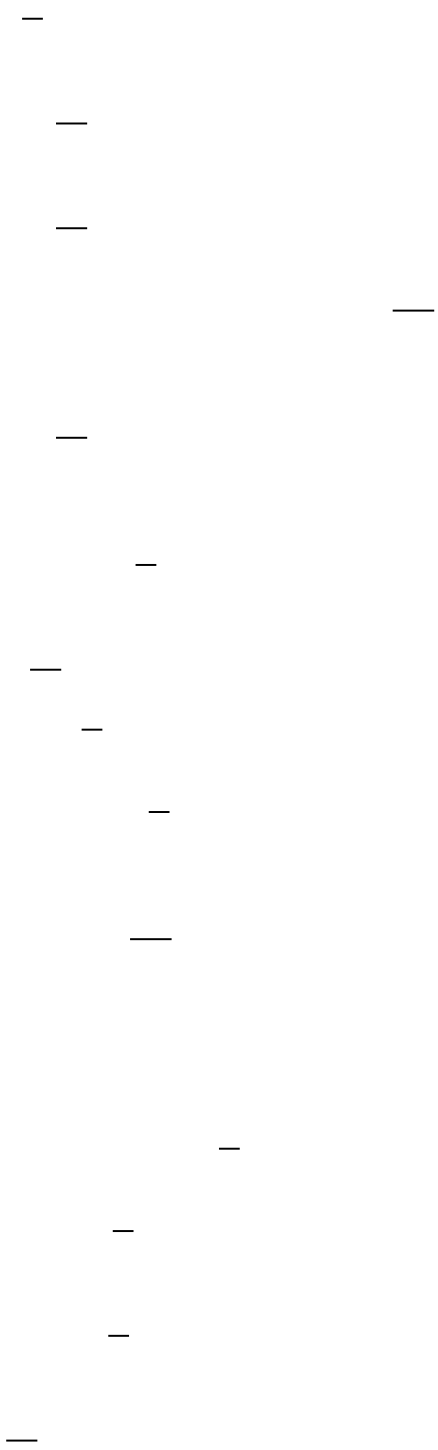
S1P degrading enzymes are expressed in the thymus [27,29,48,80]. LPP3 expression in thymic epithelial cells and endothelial cells but not in hematopoietic cells is required to maintain the S1P gradient and thymic egress [80]. S1P lyase is highly expressed in the thymus, and partial or complete loss of S1P lyase hampers T cell egress, possibly by destroying a local gradient [27,29,79]. The cellular compartment containing the SPL activity required to maintain low thymic S1P remain unanswered. S1P is produced intracellularly and, therefore, must be exported to activate S1PR1. Spnster 2 [Spns2] has emerged as one of main cell surface transporters facilitating S1P export. Spns2 is required for S1P transport from vascular endothelial cells and promotes thymic egress [87-89]. Two recent studies investigating whether Spns2 regulates plasma or lymph S1P levels have revealed conflicting results [39,40]. Both the studies have shown that loss of Spns2 causes reduced plasma S1P levels. However, the S1P levels in lymph were reduced [39] in one case and in the other were elevated [40]. This discrepancy could be due to different mouse models used in the studies. Mendoza and colleagues have used a conditional knockout mouse model, where Spns2 disruption is driven by Tie2-Cre promoter, whereas Nagahashi et al. [40] have used Spns2 null mice.

### T cell egress from lymphoid and nonlymphoid tissues

After thymic egress into the blood, mature naïve T cells must travel to the secondary lymphoid organs including spleen, lymph nodes [LNs] and Peyer's patches [PPs]. The egress of T lymphocytes from LNs is well defined [reviewed in ref. 28]. Lymph enters the LNs via afferent lymphatic vessels that are connected to macrophage-enriched medullary sinuses through the subcapsular sinuses (Figure 2B). Lymph percolates through the medullary sinuses before leaving the LN via the efferent lymphatic duct. Lymphocytes exit via medullary sinuses and the efferent lymphatic duct. A multistep model of LN egress has been proposed [90,91], in which cortical sinus 'probing' by T cells is followed by S1PR1-dependent entry of lymphocytes into the sinus. Cortical sinuses are present in the LN cortex closer to the surrounding T zone stroma, and they are often blind-ended and initiate near high endothelial venules [HEVs]. The cells then flow into medullary sinuses and the efferent lymph, which contains high levels of S1P produced by lymphatic endothelium [48,61]. After surveying a secondary lymphoid organ for several hours, T cells must exit to travel to other lymphoid organs and continue the surveillance program. Egress from the spleen results in T cell entry into the blood, whereas T cells egress from LNs and PPs directly into the lymph. Lymph carries cells back to the blood via the thoracic and right lymphatic ducts [28]. Egress must be regulated during the immune response. Within the first few hours after an inflammatory stimulus, lymphocyte egress from the responding lymphoid organ is transiently arrested to facilitate antigen encounter by rare cognate cells [28]. The number of antigen-specific lymphocytes must be expanded before they exit as effector(e r)13(es)5.1(p)-9(p)7(h) and if S1P prod(s a)9(n)4((n)19(t)-5(ig)8.2na)19(t)6(e 1K(h)4(e l)7(y)







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