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INSIGHTS

S1PR1, an endothelial-immune influencer

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Lymphatic dysfunction has been associated with tertiary lymphoid structure (TLS) formation in the mesentery. However, our understanding of TLS formation is mainly focused on inflammatory signaling. Here, Geng et al. (https://doi.org/10.1084/jem.20241799) show that lymphatic endothelial cell (LEC) S1P/S1PR1 signaling plays a role in mesenteric TLS formation in the absence of subclinical inflammation and, importantly, is a key regulator of lymphatic valve development.

Tertiary lymphoid structures (TLSs) can have multiple roles in immune system response, and their prognostic relevance is context dependent (Zhao et al., 2024). For example, in most cancers, TLSs are linked to a positive prognosis, whereas in autoimmune diseases, they are not. The immune cell composition of TLSs varies according to their maturation state, ranging from small B cell aggregates to fully developed mature TLSs with high endothelial venules (HEVs) and germinal centers, which are structurally and functionally similar to B cell follicles in secondary lymphoid organs (SLOs) (Barone et al., 2016; Sautès-Fridman et al., 2016). SLOs in the body are connected by lymphatic vessels (LVs), which are important for SLO development (Bovay et al., 2018). One key feature of LVs is their intraluminal lymphatic valves, which help prevent lymph backflow and are crucial for proper lymphatic function. The study by Geng and colleagues demonstrates that the lymphatic-specific deletion of sphingosine 1-phosphate receptor-1 (S1PR1) hinders the development of lymphatic valves and ultimately results in the formation of TLSs in the ileum (Geng et al., 2025).

The main source of lymph S1P is from the lymphatic endothelial cells (LEC), and S1P/S1PR1 signaling pathway is implicated in immune cell egress from SLOs and lymphangiogenesis (Weigel et al., 2023; Yoon et al., 2008). S1PR1 is also among the many factors that are indispensable for LV function (Geng et al., 2017; Geng et al., 2020), but its role in lymphatic valve development was not clear. Moreover, whether the lymphatic valves are important to TLS formation is still not well-defined. In the current study, Geng et al. show that S1PR1 is necessary for postnatal lymphatic valve development and function, as its deletion in LECs specifically leads to fewer and more leaky lymphatic valves in the ileum-draining mesenteric LVs. S1PR1 acts through the regulation of FOXC2 and CX37, critical molecules in proper valve formation. In *S1PR1*$^{i\Delta LEC}$ mice, the ileum drainage is defective and leads to the formation of TLSs in pre-collecting and collecting LVs. The activation of the S1P/S1PR1 pathways is shown to occur in an autocrine manner, where LEC-derived S1P orchestrates both lymphatic valve development and TLS formation. Thus, the take-home messages from this study are that the S1P/S1P1R signaling pathway is necessary for lymphatic valve development, and its continuous activation is needed to prevent TLSs from forming in the ileum (Geng et al., 2025).

The lymphatic system plays critical roles in both the maintenance of tissue fluid balance and in the transport of antigen and immune cells to organize immune responses. The phenotype caused by the deletion of S1PR1 from LECs highlights both of these functions and shows that they are interrelated. As lymphatic system biology is becoming more comprehensively studied than ever before, the role of LVs in multiple disease processes is coming to light. The role of properly functioning LVs has become clear in resolving inflammatory diseases, aiding in the recovery from myocardial infarction, and in preventing the buildup of waste products in the brain that are associated with neurodegenerative diseases (Petrova and Koh, 2020). Further, the role of the lymphatic system in driving cancer progression is well established (Lei et al., 2024). In spite of a clear need, we still do not have any therapeutics that target the lymphatic system to help in treating these conditions.

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Lymphatic dysfunction can arise from many pathologies in the LVs, from the alteration of initial LV endothelial cells that cause them to be "zippered" closed and unable to absorb interstitial fluid, to the inability of lymphatic muscle cells to drive lymph flow. In this study, the lymphatic S1P/S1PR1 pathway is shown to be a key regulator of lymphatic valve development, and shows that with abnormal LV formation, lymphatic function is impaired. As there are different root causes of lymphatic dysfunction in different disease settings, there will not be a single therapeutic strategy to correct lymphatic dysfunction. Thus, there is a need to develop tools to identify the type of lymphatic

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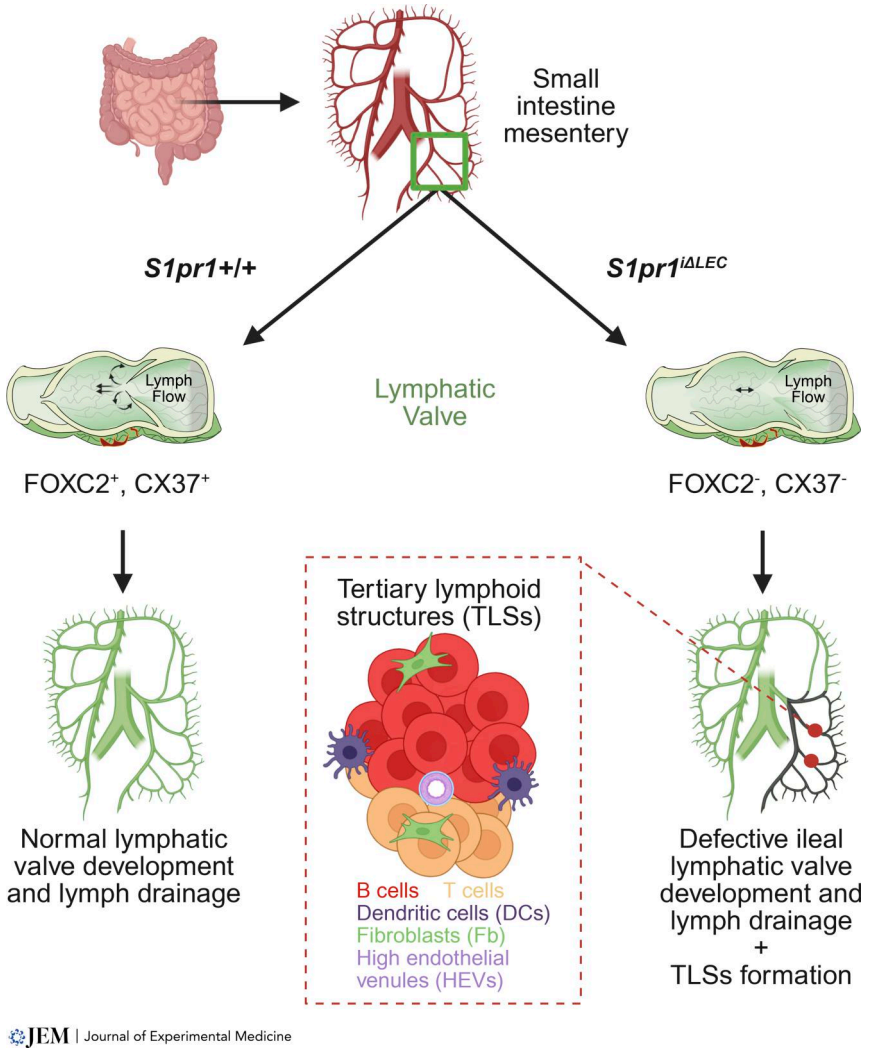

Schematic illustration of Geng et al. (2025) key findings. S1PR1 plays a role in lymphatic valve development by regulating FOXC2 and CX37. S1PR1 deletion in LECs disrupts lymphatic valve development and function, and leads to the formation of TLSs in the mesenteries. Created in BioRender.

dysfunction involved in a disease process and therapeutic strategies to correct the underlying lymphatic dysfunction. The work presented in Geng et al. shows that S1PR1 is a potential target to improve lymphatic function and points to possible strategies to induce or block TLS formation in cancer or autoimmune diseases, respectively. The ability to translate these findings is helped by the fact that there are already Food and Drug Administration–approved S1PR1 inhibitors available.

TLSs are known to arise upon chronic inflammation. Several studies have shown that early events of TLS formation occur similarly to the formation of SLOs, where lymphoid tissue inducers orchestrate the process with the help of lymphoid tissue organizers (Barone et al., 2016). However, what role the vasculature plays and which types of vessels are required is still not clear. In the work of Geng et al., dysfunctional lymphatic valves are shown to lead to mesenteric TLS formation in an initially non-inflamed situation. The formation of TLSs in the absence of inflammation shows that inflammatory signaling is not a prerequisite for the initiation of TLS formation, which is also true for SLO formation during development. It is possible that TLSs formed in the absence of inflammation might have different properties and potential to generate immune responses compared with TLSs that form in inflammatory conditions or cancer. Impaired lymphatic function might limit the ability of antigen and antigen-presenting cells to reach a lymph node, so in these circumstances, TLSs might begin to form to provide more local and accessible lymphoid tissue to prevent pathogenic infections.

Understanding the different types of TLSs and their mechanisms of formation might further allow the beneficial regulation of TLS in cancer. TLS classification generally relies on the immune cell composition, yet the presence of stromal cells and specialized vessels called HEVs is equally important. TLS classification is relevant for their function and prognosis in several cancers. Moreover, the spatial distribution of TLSs in tumors also affects response to immune therapy, such as in colorectal and hepatic cancer (Sautès-Fridman et al., 2019). HEVs are an important conduit for immune cells, and their presence is associated with fully mature TLSs. However, there are many unanswered questions. Does the presence or absence of LVs also affect the immune cell composition of the TLS? Does tumor-associated lymphangiogenesis correlate with the presence or absence of TLS? In contrast to most tumors, the presence of TLSs in other diseases is underappreciated. For example, in atherosclerosis, the presence of TLS signifies severe inflammation (Milasan et al., 2015). Moreover, proper lymphatic drainage of cholesterol near the artery is shown to be atheroprotective (Martel et al., 2013). The current new knowledge from Geng et al. that S1PR1 inhibition leads to TLS formation further shows the importance of the lymphatic system in disease and opens possible doors for studying this pathway in atherosclerosis-associated TLS formation.

TLSs are emerging as important modifiers of immune responses, sometimes beneficial and at other times exacerbating pathology. TLSs also offer new therapeutic opportunities to modify disease. By continuing to expand our understanding of the mechanisms of TLS formation and their activity in various disease states, therapies that modify TLS will become a nearer reality. The work presented in Geng et al. is another significant step in the process of using TLS to influence disease outcomes.

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References

Barone, F., et al. 2016. *Front. Immunol.* https://doi.org/10.3389/fimmu.2016.00477

Bovay, E., et al. 2018. *J. Exp. Med.* https://doi.org/10.1084/jem.20180217

Geng, X., et al. 2017. *Dis. Model Mech.* https://doi.org/10.1242/dmm.030825

Geng, X., et al. 2020. *JCI Insight*. https://doi.org/10.1172/jci.insight.137652

Geng, X., et al. 2025. *J. Exp. Med.* https://doi.org/10.1084/jem.20241799

Lei, P.-J., et al. 2024. *Front. Immunol.* https://doi.org/10.3389/fimmu.2024.1449291

Martel, C., et al. 2013. *J. Clin. Invest.* https://doi.org/10.1172/JCI63685

Milasan, A., et al. 2015. *Future Sci. OA*. https://doi.org/10.4155/fso.15.61

Petrova, T.V., and G.Y. Koh. 2020. *Science*. https://doi.org/10.1126/science.aax4063

Sautès-Fridman, C., et al. 2016. *Front. Immunol.* https://doi.org/10.3389/fimmu.2016.00407

Sautès-Fridman, C., et al. 2019. *Nat. Rev. Cancer*. https://doi.org/10.1038/s41568-019-0144-6

Weigel, C., et al. 2023. *J. Biol. Chem.* https://doi.org/10.1016/j.jbc.2023.104775

Yoon, C.M., et al. 2008. *Blood*. https://doi.org/10.1182/blood-2007-11-125203

Zhao, L., et al. 2024. *Signal Transduct. Target Ther.* https://doi.org/10.1038/s41392-024-01947-5