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Lymphatic control of B cell follicle formation in the developing lymph node

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Lymph nodes (LNs) are structured into B cell follicles and T cell zones ensuring optimal immune responses. B cell follicle organization relies on the CXCL13 chemokine produced by the follicular dendritic cells (FDCs) and the marginal reticular cells (MRCs), both constituting the B cell-associated stroma. However, the underlying cellular and molecular mechanisms for the generation of FDCs and MRCs, and thus B cell follicles, are incompletely understood. Here, we explored the function of the Receptor Activator of NF-kB (RANK) expressed by the lymphatic endothelial cells (LECs) in the maturation of B cell-associated stroma and the formation of B cell follicles.
By combining different microscopy approaches and flow cytometry to study LN organization in mice whose LECs were rendered RANK-deficient perinatally, we uncovered a severe defect in B cell follicles that was associated with an absence of MRCs and FDCs and a reduction in B cell numbers. Sinusoidal macrophages, T cells and lymphoid tissue inducer (LTI) cells were also found diminished. This disorganization was not found upon RANK depletion in adult mice, suggesting a critical temporal window for RANK signaling in LEC to support LN development. However, in contrast to LNs, lymphocytes were more abundant in blood suggesting a dysregulation in the cell egress from secondary lymphoid organs. Indeed, a partial restoration of the wild-type phenotype was observed when lymphocyte egress was reduced by treatment of newborn mice with fingolimod. Therefore, the data support the notion that RANK triggers lymphatic closure for prolonged lymphocyte residence to allow the necessary hematopoietic – stroma crosstalk for formation of MRCs and FDCs and generation of B cell follicles.
As organized lymphoid tissue is important for an efficient immune response, these insights could open new therapeutical avenues for autoimmune diseases or cancer.