Topological Small-World Organization of the Fibroblastic Reticular Cell Network Determines Lymph Node Functionality

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Fibroblastic reticular cells (FRCs) form the cellular scaffold of lymph nodes (LNs) and establish distinct microenvironmental niches to provide key molecules that drive innate and adaptive immune responses and control immune regulatory processes. Here, we have used a graph theory-based systems biology approach to determine topological properties and robustness of the LN FRC network in mice. We found that the FRC network exhibits an imprinted small-world topology that is fully regenerated within 4 wk after complete FRC ablation. Moreover, in silico perturbation analysis and in vivo validation revealed that LNs can tolerate a loss of approximately 50% of their FRCs without substantial impairment of immune cell recruitment, intranodal T cell migration, and dendritic cell-mediated activation of antiviral CD8+ T cells. Overall, our study reveals the high topological robustness of the FRC network and the critical role of the network integrity for the activation of adaptive immune responses.