Toll-like receptor 4 signaling by follicular dendritic cells is pivotal for germinal center onset and affinity maturation.

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Details

Abstract

Germinal centers (GCs) are specialized microenvironments where antigen-activated B cells undergo proliferation, immunoglobulin (Ig) class switch recombination, somatic hypermutation (SHM), and affinity maturation. Within GCs, follicular dendritic cells (FDCs) are key players in driving these events via direct interaction with GC B cells. Here, we provide in vivo evidence that FDCs express and upregulate Toll-like-receptor (TLR) 4 in situ during germinal center reactions, confirm that their maturation is driven by TLR4, and associate the role of FDC-expressed TLR4 with quantitative and qualitative affects of GC biology. In iterative cycles of predictions by in silico modeling subsequently verified by in vivo experiments, we demonstrated that TLR4 signaling modulates FDC activation, strongly impacting SHM and generation of Ig class-switched high-affinity plasma and memory B cells. Thus, our data place TLR4 in the heart of adaptive humoral immunity, providing further insight into mechanisms driving GCs arising in both health and disease.

Beteiligte Forschungseinheiten

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