PROTEIN KINASE CΔ PROMOTES TRANSITIONAL B CELL-NEGATIVE SELECTION AND LIMITS PROXIMAL B CELL RECEPTOR SIGNALING TO ENFORCE TOLERANCE.

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Significance Statement

The presented model illustrates the role of Protein kinase cδ in B cell receptor (BCR) signaling at distinct stages of B cell development. Developing B cells exit the bone marrow and migrate to the spleen as transitional 1 (T1) B cells. T1 B cells are highly sensitive to antigen-induced apoptosis, a trait that allows self-reactive cells that encounter antigen to be clonally deleted from the B cell repertoire. T1 B cellsenter the spleen via the periarteriallymphoid sheath (PALS) andundergo an importantstep of negative selection, a process that is frequently disrupted in lupus patients. Our studies show that the kinase Protein kinase cδ is required to activate a pro-apoptotic Ca2+-dependent pathway to Erk activation in bone marrow transitional B cells as well as splenic T1 B cells. PKCdthus couples BCR signaling to apoptosis at these developmental stages(1-3).

As T1 cells migrate from the PALS into the splenic follicle and become T2 cells their signaling properties change substantially. These B cells lose the ability to activate the Ca2+-Erk pathway, they are less sensitive to antigen-induced apoptosis and instead they tune their antigen responsiveness by downregulating surface IgM(BCR) levels in a manner proportional to antigen reactivity. We have shown that, in addition to facilitating negative selection of T1 B cells, Protein kinase cδ acts as a negative regulator of BCR signaling throughout development and in mature B cells by at least two distinct mechanisms: 1- Protein kinase cδ sets the threshold of antigenic signaling required for surface IgM downregulation, a key mechanism that dampens the responsiveness of anergic B cells; and 2- Protein kinase cδ negatively regulates proximal BCR signaling. As a consequence of these roles, Protein kinase cδ deficiency leads to an abnormally autoreactive B cell repertoire that is additionally hyperresponsive to antigen stimulation, leading to severeautoimmune pathology.

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3. Limnander A, Zikherman J, Lau T, Leitges M, Weiss A, Roose JP. Protein kinase cδ promotes transitional B cell negative selection and limits proximal BCR signaling to enforce tolerance. Mol Cell Biol. 2014. doi: 10.1128/MCB.01699-13. PubMed PMID: 24515435.

Illustration below made by Anna Hupalowska.

Journal Reference

Limnander A, Zikherman J, Lau T, Leitges M, Weiss A, Roose JP.

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Abstract

PProtein kinase cδ deficiency causes autoimmune pathology in humans and mice and is crucial for the maintenance of B cell homeostasis. However, the mechanisms underlying autoimmune disease in Protein kinase cδ deficiency remain poorly defined. Here, we address the antigen-dependent and -independent roles of Protein kinase cδ in B cell development, repertoire selection, and antigen responsiveness. We demonstrate that Protein kinase cδ is rapidly phosphorylated downstream of both the B cell receptor (BCR) and the B cell-activating factor (BAFF) receptor. We found that Protein kinase cδ is essential for antigen-dependent negative selection of splenic transitional B cells and is required for activation of the proapoptotic Ca(2+)-Erk pathway that is selectively activated during B cell-negative selection. Unexpectedly, we also identified a previously unrecognized role for Protein kinase cδ as a proximal negative regulator of BCR signaling that substantially impacts survival and proliferation of mature follicular B cells. As a consequence of these distinct roles, Protein kinase cδ deficiency leads to the survival and development of a B cell repertoire that is not only aberrantly autoreactive but also hyperresponsive to antigen stimulation.

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