Noncanonical NF-κB in effector and regulatory T cells
Susan E. Murray, Fanny Polesso, Alexander M. Rowe, and David C. Parker
Department of Molecular Microbiology and Immunology
Oregon Health & Science University, Portland, Oregon

In lymphocytes, signals from antigen, cytokine, and innate immune receptors cause immediate, transient activation of NF-κB through the canonical pathway by triggering IκB degradation. A second, non-canonical or “alternative” NF-κB pathway has been described downstream of some members of the TNFR family. Slow, sustained activation of NF-κB through this IκB-independent non-canonical pathway governs the formation of secondary lymphoid organs (downstream of LTβR) and determines the fate of B cells (downstream of BAFFR). Little is known of the role of the non-canonical NF-κB pathway in T cell function, although T cells express a number of costimulatory TNFR family members, including OX40, 4-1BB, CD27, GITR, CD30, DR3, and HVEM, many of which have been shown to activate the non-canonical pathway in transfected cell lines. These costimulatory TNFRs are known to provide essential signals for function and survival of activated T cells after antigen recognition. NF-κB-inducing kinase (NIK) is an essential kinase in non-canonical NF-κB activation. Peripheral T cell populations are normal in the absence of NIK, but developmental defects in NIK-deficient mice have obscured the role of NIK during in vivo T cell responses to antigen. We show that NIK is not necessary for TCR signaling or activation of canonical NF-κB signaling in T cells downstream of the TNFR family member OX40 (CD134), but it is necessary for non-canonical NF-κB signaling downstream of OX40. NIK-deficient T cells are nearly completely unresponsive to OX40-mediated induction of effector cytokines and cytokine receptors in vivo. Moreover, NIK-deficient donor CD4 T fail to mediate graft-versus-host disease and fail to survive as memory CD4 and CD8 T cells following LCMV infection. Modest overexpression of NIK in T cells from a conditional transgene leads to rapid fatal autoimmunity characterized by hyperactive effector T cells and poorly suppressive Foxp3+ regulatory T cells. These results suggest that the non-canonical NF-κB pathway is activated downstream of the costimulatory TNFR family members in T cells, that it is necessary for the costimulatory activity of TNFR family members in vivo, and that independent activation of the non-canonical NF-κB pathway mimics some of the costimulatory activities of the TNFR family members, including blocking the function of regulatory T cells. Inhibition of this pathway by drugs acting specifically on enzymes in the pathway (IKK1 and/or NIK and the IAPs that regulate NIK protein levels) has the potential to block ongoing immune reactions that are dependent on internal danger signals resulting from inflammation and tissue damage, such as allergy, autoimmune disease, transplant rejection, and graft-versus-host disease, without blocking immunity to infectious agents driven by antigen receptors and innate receptors for microbial products through the canonical NF-κB pathway and other signaling pathways.


