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Notch functions from the cytoplasm to the nucleus during T cell activation

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Abstract

Notch1 specifically upregulates expression of the cytokine interferon- γ in peripheral T cells through activation of NF- κ B. However, how Notch mediates NF- κ B activation remains unclear. NF- κ B activation occurs within minutes of TCR engagement and this activation is sustained for at least 48 hours following TCR signaling. We used either γ -secretase inhibitor (GSI) to prevent the cleavage and subsequent activation of Notch family members or siRNA against Notch1 to reduce endogenous expression of Notch1 specifically. We demonstrate that GSI blocked the later, sustained NF- κ B activation, but did not affect the initial activation of NF- κ B. Using biochemical approaches, as well as confocal microscopy, we show that the intracellular domain of Notch1 (N1^{IC}) directly interacts with NF- κ B and competes with I κ B α , leading to retention of NF- κ B in the nucleus, and that N1^{IC} can directly regulate IFN- γ expression through complexes formed on the IFN- γ promoter. Additionally, within the immunological synapse, cytosolic Notch1 associates with CARMA1 and BCL10, mediating a direct interaction among them. Upon TCR and CD28 stimulation, Notch1 directly interacts with PKC θ ; and the IKK complex, leading to IKK-mediated activation of NF- κ B. In the absence of Notch1, there is no formation of CARMA1/BCL10/Malt1 complex, which is required for IKK activation. Taken together, these data suggest that Notch1 plays two roles during T cell activation: as an activation scaffold in the cytoplasm and as a transcriptional activator in the nucleus. ^

Subject Area

Molecular biology|Immunology

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