Regulation of Notch signaling by the E3 ubiquitin ligase Cbl-b and its role in CD4+ T cell anergy

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Abstract

Notch signaling is an evolutionarily conserved pathway that mediates a variety of cell fate decisions. In the immune system, the Notch pathway plays an important role throughout the life of T cells. Currently, the role of Notch signaling in peripheral T cells is being actively investigated. The Notch pathway has already been shown to be important for proliferation, IL-2 production and helper T cell differentiation following peripheral T cell activation. In this study, we show that the E3 ubiquitin ligase Cbl-b regulates Notch protein levels by targeting it for proteosomal degradation. Notch and Cbl-b associate with each other in bulk splenocytes and when co-transfected in 293T cells. Cbl-b co-expression led to reduction in the activity of a Notch reporter construct and enhanced the ubiquitination of the Notch protein. We have also used various deletion mutants of Notch and Cbl-b to localize the interacting regions on both proteins. ^ T cell anergy is a state of T-cell hyporesponsiveness following incomplete activation. Cbl-b has been shown to be upregulated in anergic T cells and is crucial for anergy induction. As Notch is important for effector functions of peripheral T cells, our discovery that Cbl-b negatively regulates Notch signaling has led us to investigate the role of Notch in anergy induction. Using an ex-vivo system to induce anergy in CD4+ T cells we show that Notch expression is down regulated upon induction of anergy. Also, Notch and CSL bind to the IL-2 promoter and positively regulate transcription and Notch also augments NF-κB binding to this promoter. Finally, we show that Notch expression during anergy induction rescues cytokine production and proliferation of these cells upon restimulation. Our findings suggest a novel role for Notch signaling in opposing the establishment of anergy.^

Subject Area

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