The role of Notch in T cell activation and development

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Abstract

Notch is crucial for multiple stages of T cell development, including the $CD4^+CD8^+$ double positive (DP) to $CD8^+$ single positive (SP) transition, but regulation of Notch activation is not well understood. In this thesis, I explored the potential of p53, endocytosis, and Cbl-b to regulate Notch activation. p53 regulates Presenilin1 (PS1) expression, and PS1 cleaves Notch, releasing its intracellular domain (N^{IC}), leading to the expression of downstream targets, *e.g.* the *HES1* gene. One aim of this thesis was to determine if p53 regulates Notch activity during T cell development. I found that Notch1 expression and activation were negatively regulated by p53 in several thymoma lines. Additionally, N^{IC} was elevated in *Trp53* $^{-/-}$ thymocytes as compared to *Trp53* $^{+/+}$ thymocytes. To determine if elevated Notch1 activation in *Trp53*$^{-/-}$ thymocytes had an effect on T cell development, CD4 and CD8 expression were analyzed. The $CD4^+$ SP:$CD8^+$ SP T cell ratio was decreased in *Trp53* $^{-/-}$ splenocytes and thymocytes. This alteration in T cell development correlated with the increased Notch1 activation observed in the absence of p53. These data indicate that p53 negatively regulates Notch1 activation during T cell development. Skewing of T cell development toward $CD8^+$ SP T cells in *Trp53*$^{-/-}$ mice is reminiscent of the phenotype of N^{IC}-overexpressing mice. Thus, I suggest that p53 plays a role in T cell development, in part by regulating Notch1 activation. In the second aim of my thesis I present preliminary data showing that endocytosis does not appear to be involved in mammalian Notch activation although there is evidence in *Drosophila* for a positive endocytic role in Notch activation. The ability of Cbl-b to regulate Notch activation was the final aim of this thesis. Cbl-b, like Notch, has been shown to play a role in regulating the T cell signaling threshold. With this aim, I wanted to address the possibility of Cbl-b regulating T cell signaling via regulating Notch activation. Due to technical difficulties I was only able to obtain preliminary data suggesting that Cbl-b does positively regulate Notch activation in peripheral T cells. In this dissertation I have shown that Notch activation is regulated by controlling the expression of cellular components needed for cleavage, not just by encountering ligand on neighboring cells. ^

Subject Area

Molecular biology|Immunology

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