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NON-CANONICAL NOTCH SIGNALING REGULATES ACTIVATION AND DIFFERENTIATION OF PERIPHERAL CD4+ T CELLS

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Abstract
Cleavage of the Notch receptor via a γ-secretase, results in the release of the active intra-cellular domain of Notch that migrates to the nucleus and interacts with RBP-$J_{K,}$ resulting in the activation of downstream target genes. This canonical Notch signaling pathway has been documented to influence T-cell development and function. However, the mechanistic details underlying this process remain obscure. In addition to RBP-J_K, the intra-cellular domain of Notch also interacts with other proteins in the cytoplasm and nucleus, giving rise to the possibility of an alternate, RBP-J_K independent Notch pathway. However, the contribution of such RBP-J_K

independent, “non-canonical” Notch signaling in regulating peripheral T-cell responses is unknown. We specifically demonstrate the requirement of Notch1 for regulating signal strength and signaling events distal to the T-cell receptor in peripheral $CD4^+$ T cells. By using mice with a conditional deletion in Notch1 or RBP-J_K, we show that Notch1 regulates activation and proliferation of $CD4^+$ T cells independently of RBP-J_K. Furthermore, differentiation towards T_H1 and *i*Treg lineages is also Notch dependent but RBP-J_K independent. Our data provide evidence that non-canonical regulation of these processes likely occurs through NF-$_K$B. Additionally, we also provide evidence suggestive of cross-talk between Notch and the mTOR pathway. Notch1, but not RBP-J_K, is required for phosphorylation of several substrates directly downstream of mTORC2. Collectively, these striking observations demonstrate that many of the cell intrinsic functions of Notch occur independently of RBP-J_K. This reveals a previously unknown, novel role of non-canonical Notch signaling in regulating peripheral T-cell responses.