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Poster Abstract

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DNA methylation silences IL-4 and type 2 cytokines in CD8 T cells

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During T cell development, cell fate decisions direct the potential of a T cell such that CD4 T cells mount effector responses characterized by IFN- γ or IL-4 production (Th1 or Th2 cells, respectively), and CD8 T cells mount effector responses characterized by cytotoxicity and the production of IFN- γ . We addressed the role of DNA methylation in regulating appropriate cytokine gene expression in mature T cells by utilizing mice that have a selective loss of DNA methyltransferase 1 (Dnmt1) in T cells at the DP stage of development (CD4 Cre Dnmt1 2lox mice). T cell development in these mice appears normal. However, upon activation CD8 T cells lacking Dnmt1 and DNA methylation expressed IL-4 at levels equivalent or greater than CD4 T cells. This correlated with profound demethylation of the IL-4 locus and modified histone structure consistent with accessible chromatin. Dnmt1^{-/-} CD8 T cells also increased expression of IL-13 and IL-5, two other cytokines characteristic of Th2 and Tc2 effector cells. The increase in type 2 cytokine expression was not due to changes in the expression of key transcription factors. Nonetheless, Dnmt1^{-/-} T cells appropriately up- and down-regulated the expression of GATA-3, T-bet and type 2 cytokines when placed in polarizing culture conditions. Our results demonstrate that DNA methylation is essential for silencing cell-autonomous type 2 cytokine expression in the CD8 lineage, and suggest that early changes in IL-4 transcription are imposed relative to the transcriptional threshold set by the level of DNA methylation.