TGFβ CONVERTS TH1 CELLS INTO TH17 CELLS THROUGH STIMULATION OF RUNX1 EXPRESSION UNDER INFLAMMATORY CONDITIONS IN INTESTINES

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Differentiated CD4⁺ T cells preserve plasticity to alter phenotypes under various conditions. Compared with other CD4⁺ T cell lineages, Th1 cells are relatively less studied in terms of the stability. It is unclear whether IFNγ⁺ Th1 cells can convert into IL-17⁺ Th17 cells. Accumulating evidence demonstrates that severity of colitis correlates with the presence of IFNγ⁺IL-17⁺CD4⁺ T cells in the intestinal lamina propria. IFNγ⁺ Th1 cells can potentially convert and contribute to the generation of IFNγ⁺IL-17⁺CD4⁺ T cells, in addition to the differentiation of naïve CD4⁺ cells and the conversion of IL-17⁺ Th17 cells. By using IFNγ-Thy1.1 CBir1 TCR-Tg reporter mice, whose TCR is specific for an immunodominant microbiota antigen CBir1, we demonstrated that transfer of purified CBir1-specific IFNγ⁺ Th1 cells induced colitis in Rag⁻/⁻ mice and converted into IL-17⁺ Th17 in the inflamed intestines. TGFβ and IL-6, but not IL-1β, IL-23, and hypoxia factors, regulated Th1 conversion into Th17 cells. TGFβ induction of transcriptional factor Runx1 is crucial for the conversion, in that silencing Runx1 by siRNA inhibited Th1 conversion into Th17 cells. Furthermore, by using ChIP assays, we demonstrated that TGFβ promoted histone H3K9 acetylation but inhibited histone H3K9 trimethylation of Runx1- and RORγt- binding sites on il-17 or rorc genes in Th1 cells and thus enhanced the accessibility of those binding sites. In conclusion, our data demonstrate that Th1 cells convert into Th17 cells under inflammatory conditions in intestines, and this conversion is mediated by TGFβ induction of Runx1.