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Chronic upper airway inflammation related to high Th2 cytokines in Mendelian susceptibility to mycobacterial disease case

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ABSTRACT

In this report, we have described a child suffering from Mendelian susceptibility to mycobacterial disease (MSMD) owing to an autosomal recessive, complete T-bet deficiency, which impairs IFN-γ production by innate and innate-like adaptive, but not mycobacterial-reactive purely adaptive lymphocytes. In this study, we explored the persistent upper airway inflammation (UAI) and blood eosinophilia in this patient. Unlike the wild-type (WT) T-bet, the mutant form of T-bet from this patient did not inhibit the production of T helper 2 (Th2) cytokines, including IL-4, IL-5, IL-9, and IL-13, when overexpressed in Th2 cells. Moreover, *Herpesvirus saimiri* immortalized T cells from the patient produced abnormally large amounts of Th2 cytokines, and the patient had markedly high plasma IL-5 and IL-13 concentrations. Finally, the patient's $CD4^+$ αβ T cells produced most of the Th2 cytokines in response to chronic stimulation, regardless of their antigen specificities, a phenotype reversed by the expression of WT T-bet. T-bet deficiency thus underlies the excessive production of Th2 cytokines, particularly IL-5 and IL-13, by $CD4^+$ αβ T cells, causing blood eosinophilia and UAI. The MSMD of this patient results from defective IFN-γ production by innate and innate-like adaptive lymphocytes, whereas the UAI and eosinophilia result from excessive Th2 cytokine production by adaptive $CD4^+$ αβ T lymphocytes.

Keywords: MSMD, Th2 cytokines, UAI