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Epigenetic Regulation of the Expression of Il12 and Il23 and Autoimmune Inflammation by the Deubiquitinase Trabid

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ABSTRACT

The pro-inflammatory cytokines interleukin-12 (IL-12) and IL-23 drive and amplify helper T-cell responses to microbial infection and other danger signals. However, deregulated activity of these cytokines has been linked to a range of inflammatory diseases, including multiple sclerosis, psoriasis and Crohn's disease. Here we reported that the production of IL-12 and IL-23 is under control of Trabid (encoded by *Zranb1*), an intracellular protein whose cellular function is still largely unclear. By using a gene-targeting approach, we found that Trabid deficiency in DCs and macrophages impaired the induction of IL-12 and IL-23 without affecting the induction of many other cytokine-encoding genes. Consistent with that, Trabid deficiency impaired production of the TH1 and TH17 subsets of inflammatory T-cells, which rendered mice refractory to the induction of experimental autoimmune encephalomyelitis (EAE), an autoimmune neuroinflammatory disease dependent on TH1 and TH17 cells. To investigate the mechanism underlying the effect of Trabid on inflammatory T-cell responses, we go on to analyze the effects of Trabid deficiency on Toll-like receptor (TLR)-stimulated DCs *in vitro*. Our results showed that *Zranb1*-deficient DCs have no defects in signaling via NF-κB or mitogen-activated protein kinases or in the nuclear translocation of various transcription factors of the NF-κB family. However, Trabid facilitated TLR-induced histone modifications at the promoters of IL-12 and IL-23, which involved deubiqutination and stabilization of the histone demethylase Jmjd2d. Our findings highlight an epigenetic mechanism for the regulation of IL-12 and IL-23 and establish Trabid as an innate immunological regulator of inflammatory T-cell responses.

Keywords: Epigenetic, Interleukin 12, Inflammation, Deubiquitinase Trabid

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