

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

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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 Trabad (encoded by *Zranb1*), an intracellular protein whose cellular function is still largely unclear. By using a gene-targeting approach, we found that Trabad 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, Trabad 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 Trabad on inflammatory T-cell responses, we go on to analyze the effects of Trabad deficiency on Toll-like receptor (TLR)-stimulated DCs *in vitro*. Our results showed that *Zranb1*-deficient DCs have no defects in signaling via NF- κ B or mitogen-activated protein kinases or in the nuclear translocation of various transcription factors of the NF- κ B family. However, Trabad facilitated TLR-induced histone modifications at the promoters of IL-12 and IL-23, which involved deubiquitination and stabilization of the histone demethylase Jmjd2d. Our findings highlight an epigenetic mechanism for the regulation of IL-12 and IL-23 and establish Trabad as an innate immunological regulator of inflammatory T-cell responses.

Keywords: Epigenetic, Interleukin 12, Inflammation, Deubiquitinase Trabad

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