The adaptor TRAF5 limits the differentiation of inflammatory CD4+ T cells by antagonizing signaling via the receptor for IL-6

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The family of 6 TNF receptor-associated factors (TRAFs) function as adaptor proteins for the TNF receptor superfamily, the Toll-like receptor family, and the RIG-I-like receptor family by associating with the intracellular domains of these receptors to mediate downstream signaling events. Our previous data shows that allergic lung inflammation mediated by inflammatory CD4+ T cells is more exaggerated in Traf5-/- mice than in wild-type mice and suggests that TRAF5 has a function that has not been delineated in detail in CD4+ T cells (So et al., J Immunol 2004). In this study, we have identified a novel attribute of TRAF5 in IL-6 signaling pathway. In the presence of IL-6, naïve Traf5-/- CD4+ T cells produced more IL-17 than did wild-type CD4+ T cells and developed a pronounced Th17 phenotype both in vitro and in vivo. Accordingly, Th17-associated experimental autoimmune encephalomyelitis (EAE) was greatly exaggerated in Traf5-/- mice than in wild-type mice, and Traf5-/- CD4+ T cells induced exaggerated EAE in TRAF-sufficient recipient mice. Surprisingly, TRAF5 constitutively associated with the signal-transducing receptor gp130 and suppressed recruitment and activation of STAT3 in response to IL-6. The finding provides a new perspective on the lineage commitment of CD4+ T cells and an explanation why TRAF5 exhibits an anti-inflammatory function in CD4+ T cells.

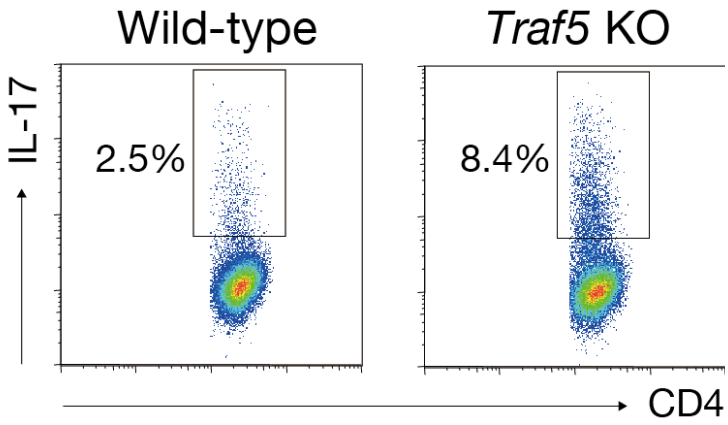

Figure 1. Traf5 KO CD4+ T cells exhibit enhanced Th17 development. Recall IL-17A production in activated CD4+ T cells generated from naïve wild-type or Traf5 KO CD4+ T cells (OT-II T cells) stimulated for 5 d with 0.1 μM OVA323-339 peptide antigen and wild-type splenic antigen-presenting cells in the presence of 10 ng/ml of IL-6, then restimulated for 5 h with PMA and ionomycin

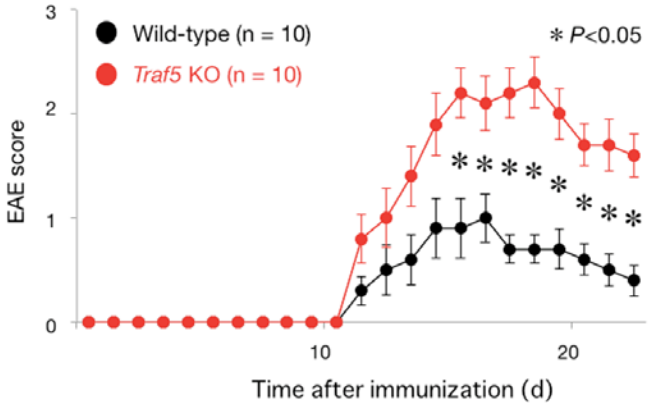

Figure 2. TRAF5 serves an inhibitory role in experimental autoimmune encephalomyelitis (EAE). Wild-type or Traf5 KO mice were subcutaneously immunized with MOG33-55 peptide antigen in CFA on day 0 and received intraperitoneal injection of pertussis toxin on days 0 and 2. Clinical signs of EAE in these mice monitored over 22 d.

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