Interleukin-10 (IL-10) is an anti-inflammatory cytokine protein that reduces immune responses and staves off autoimmune disease. Now, a research team led by Masato Kubo at the RIKEN Research Center for Allergy and Immunology, Yokohama, has identified a transcription factor called E4 promoter-binding protein (E4BP4) that is responsible for driving the expression of IL-10 in multiple types of immune cells.

The researchers investigated E4BP4 because of a unique property of a subset of immune cells called T helper type 1 (T\(_{H1}\)) cells, which generally enhance immune responses by secreting pro-inflammatory cytokines. However, under chronic stimulation with foreign antigens—that occur during chronic infection—T\(_{H1}\) cells can also produce cytokines, such as IL-10 and IL-13, which are normally made only by other immune-cell types. While the immune system is fighting the infection, IL-13 modulates allergic responses, and IL-10 prevents the immune system from attacking the body.

Kubo and colleagues compared genes expressed in T\(_{H1}\) cells with and without chronic antigen stimulation, and found that E4BP4 was expressed only in instances of chronic antigen stimulation. When they expressed E4BP4 in T\(_{H1}\) cells that had not been chronically infected, it induced production of IL-10 and IL-13 in conditions in which those cytokines would not normally occur (Fig. 1). E4BP4-deficient TH1 cells could not increase expression of IL-10 and IL-13 after chronic antigen stimulation. The researchers found that other T cell subsets also required E4BP4 to modulate the expression of IL-10, but not IL-13.

Transcription factors can control the expression of genes by binding to a region on the genomic DNA called the promoter. Kubo and colleagues observed that E4BP4 bound to the IL-13 promoter in T\(_{H1}\) cells that had been chronically stimulated with antigen. No binding occurred with TH1 cells lacking chronic stimulation. Kubo explains, however, that: "E4BP4 seems to regulate the expression of IL-10 in a totally different way by altering the chromosomal structure in the region of that gene."

Mice lacking IL-10 can spontaneously develop intestinal autoimmune disease. Interestingly, Kubo and his team found that E4BP4-deficient mice produced lower levels of IL-10 than control mice, and showed some symptoms of gastrointestinal inflammation along with diarrhea. The mice lacking E4BP4 also developed more severe symptoms of a neurological autoimmune disease caused by exposure to brain antigens. E4BP4 is therefore a key factor in preventing the immune system from attacking the body's own organs, and "induction of expression of E4BP4 may cure many types of autoimmune inflammatory diseases," says Kubo.

**More information:** Motomura, Y., et al. The
transcription factor E4BP4 regulates the production of IL-10 and IL-13 in CD4+ T cells. 


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