Transcription factor regulates protein that dampens immune responses

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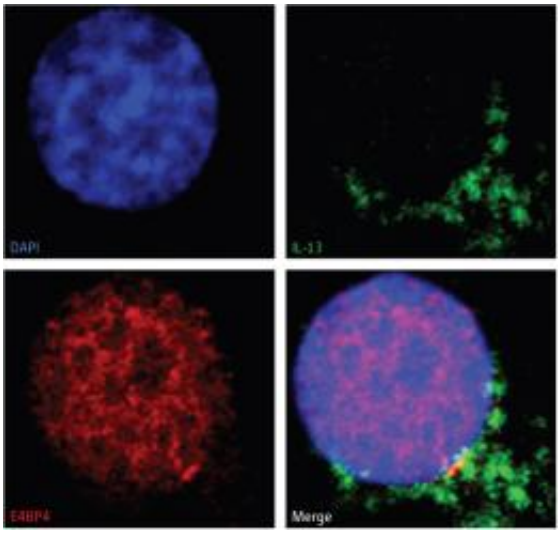

Figure 1: In T cells stained blue (top left), the transcription factor E4BP4 (red) regulates that production of IL-13 (green) and IL-10 (not shown). Credit: Reproduced from Ref. 1 Yasutaka Motomura et al.

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 regulations the production of IL-10 and IL-13 in CD4+ T cells. Nature Immunology 12, 450–459 (2011).

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