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AUTOIMMUNE DISEASE

A human antibody selectively targets regulatory T cells

> an effective immunotherapy for autoimmune diseases in humans would likely require targeting multiple axes of the immune system

At low doses, IL-2 induces the proliferation and functional activation of regulatory T (T_{reg}) cells, which suppress autoimmune responses and transplant rejection in mouse models. In a new paper in *Nature Medicine*, Trotta *et al*. identified a human anti-IL-2 antibody that mimics these effects and might be useful for treating human autoimmune diseases.

Previous studies in mice and humans have reported that low-dose IL-2 induces the expansion of T_{reg} cells, which controls the immunopathology of autoimmune diseases such as type 1 diabetes. At high doses, however, IL-2 treatment also induces the unwanted expansion of effector T (T_{eff}) cells. However, a mouse monoclonal antibody (JES6-1) that binds to mouse IL-2 and alters its affinity for CD25 (a component of the trimeric IL-2 receptor (IL-2R) that is expressed at different levels by T_{reg} cells and T_{eff} cells) improves the selectivity of IL-2 treatment so that T_{reg} cells are preferentially upregulated.

To generate human monoclonal antibodies that bind to human IL-2 (hIL-2), the researchers first screened a proprietary phage display library. They then carried out IL-2 binding assays, monitored the selective activation of IL-2–IL-2R signalling and studied binding between human anti-IL-2 antibody–hIL-2 complexes and different IL-2R receptor subunits to select antibodies that (in a complex with hIL-2) selectively promote T_{reg} cell proliferation. The antibody F5111.2 minimally reduced the response of T_{reg} cells to hIL-2 while substantially reducing IL-2 signalling in T_{eff} cells. Interestingly, structural analysis of the F5111.2 antigen-binding fragment (Fab) in complex with hIL-2 revealed that, although the binding site in IL-2 and the conformational change induced by antibody binding differed between F5111.2 and JES6-1, the overall effect of these antibodies on IL-2 was similar, suggesting a conserved biology.

In vivo analyses in a humanized mouse model of type 1 diabetes (NOD mice) revealed that the F5111.2–hIL-2 complex produced a selective increase in the T_{reg} cell population compared with other immune cells. Importantly, treating NOD mice with the F5111.2–hIL-2 complex for 5 days led to diabetes remission in 50% of mice after 1 week and maintained normoglycaemia in most mice after 4 weeks, compared with minimal effect of an isotype-matched antibody–hIL-2 complex or low-dose hIL-2. Similar therapeutic efficacy was also demonstrated in mouse models of experimental autoimmune encephalitis and graft-versus-host disease.

The authors conclude that an effective immunotherapy for autoimmune diseases in humans would likely require targeting multiple axes of the immune system, such as depletion of T_{eff} cells combined with enhancement of T_{reg} cells.

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