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Paradoxical effects of targeting TNF signalling in the treatment of autoimmunity

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Abstract

Adalimumab, an anti-TNF monoclonal antibody used to treat rheumatoid arthritis and other autoimmune disorders, paradoxically enhances the capacity of TNF to expand TNF receptor type II-expressing regulatory T cells. This provocative finding opens a new avenue for exploring the mechanisms that underlie efficacy, non-responsiveness and adverse effects associated with therapeutic targeting of TNF signalling.

Although inappropriately named for its capacity to induce haemorrhagic necrosis in experimental cancers, TNF has proved to be a master proinflammatory cytokine. In addition to being rapidly expressed at high levels at sites of inflammation, TNF seems to induce a complicated inflammatory cascade, initiating the expression of proinflammatory mediators such as IL-1, IL-6, IL-8 and granulocyte–macrophage colony-stimulating factor (GM-CSF). The idea that TNF could act as a master stimulator of inflammation led to the successful development of anti-TNF therapy for autoimmune diseases. The beneficial therapeutic effects of such treatment further substantiated the notion that TNF has a pivotal role in some autoimmune diseases¹. Anti-TNF biologic agents have become a first-line treatment for patients with rheumatoid arthritis (RA), and they are widely used in the treatment of patients with other chronic autoimmune inflammatory diseases, such as Crohn disease, psoriasis, psoriatic arthritis, ankylosing spondylitis and juvenile RA. The success of anti-TNF biologic agents is a prime example of how basic research can be translated into therapeutic benefits for patients.

In an effort to dissect the immunological mechanisms underlying the anti-inflammatory effect of anti-TNF biologic agents, their effects on CD4⁺FOXP3⁺ regulatory T (T_{reg}) cells have inevitably been a focus of investigation, as T_{reg} cells have an indispensable roles in

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Competing interests statement

The authors declare no competing interests.

immunological homeostasis and in the prevention of autoimmune responses. A study by Michael Ehrenstein's group in 2004 was the first to show that treatment with infliximab, a chimeric monoclonal antibody (mAb) directed against TNF, increased the number and function of T_{reg} cells in patients with RA². This stimulatory effect of anti-TNF treatment on T_{reg} cells implied that TNF inhibits T_{reg} cell activity. Conversely, compelling evidence now indicates that TNF preferentially activates and expands T_{reg} cells through its interactions with TNF receptor type II (TNFR2, also known as TNF receptor superfamily member 1B and CD120b)³.

How is it possible that both TNF and anti-TNF mAbs boost T_{reg} cell activity? This question is answered in a 2016 study by Nguyen and Ehrenstein⁴, which found that the anti-TNF mAb adalimumab, unlike the TNFR2–Fc fusion protein etanercept, could bind to membrane-bound TNF (mTNF) expressed on monocytes from patients with RA. Adalimumab binding upregulated expression of mTNF, thus increasing its capacity to activate T_{reg} cells via TNFR2 (REF. 4). This unexpected enhancement of TNF signalling indicates that adalimumab paradoxically acts as an agonist of TNF activity, rather than neutralizing or blocking it. This finding is similar to previous reports showing that anti-IL-2 mAbs and IL-15 receptor- α (IL-15R α)–Fc chimeric complexes are agonistic and markedly increase the biological activity of IL-2 and IL-15, respectively⁵.

TNF is initially expressed as mTNF, which is released in a soluble form (sTNF) after proteolytic cleavage. mTNF is known to preferentially bind to TNFR2, whereas sTNF preferentially binds to TNFR1, which has a well-established role in the pathogenesis of inflammation. TNFR1 is expressed by a wide variety of cell types, whereas TNFR2 is primarily, but not exclusively, expressed by T_{reg} cells. Presumably, the complex of anti-TNF mAb and mTNF protects mTNF from enzymatic cleavage and degradation, and thus provides more sustained stimulation to TNFR2-expressing T_{reg} cells.

Adalimumab is known to interact with both mTNF and sTNF, whereas etanercept only interacts with sTNF. It is therefore interesting to hypothesize that although both drugs inhibit the sTNF–TNFR1 proinflammatory pathway, only adalimumab has the capacity to also activate TNFR2-expressing T_{reg} cells. The ability of adalimumab to reduce inflammation by activating T_{reg} cells might help to clarify reports of adalimumab having better efficacy and tolerability than etanercept across a wide range of autoimmune indications⁶.

Nevertheless, etanercept is proven to be effective in the treatment of RA and other autoimmune disorders⁷. As etanercept does not expand T_{reg} cells⁴, direct inhibition of pathogenic effector T (T_{eff}) cells is likely to be its main mechanism of action. Although T_{eff} cells express markedly lower levels of TNFR2 than do T_{reg} cells, T_{eff} cell expression of TNFR2 can be upregulated upon activation, and this upregulation has important functional implications⁸. Inhibition of T_{eff} cell proliferation by anti-TNF mAbs is replicated by anti-TNFR2 mAbs but not by anti-TNFR1 mAbs (unpublished observations). Furthermore, T_{eff} cells deficient in TNFR2 are less responsive to T-cell receptor stimulation (unpublished observations). Thus, inhibition of TNF–TNFR2 costimulatory signalling in T_{eff} cells should have an antagonistic effect on T_{eff} cells and thereby contribute to the clinical efficacy of biologic agents that target this signalling pathway.

As described above, T_{reg} cell activation and expansion are stimulated by TNF–TNFR2 signalling. Indeed, the exacerbation of psoriasis in mice after TNF blockade is associated with reduced numbers of T_{reg} cells in the draining lymph nodes⁹. Furthermore, simultaneous blockade of TNFR1 and TNFR2, but not blockade of TNFR1 alone, causes a decrease in the number of T_{reg} cells in the draining lymph nodes and spleen, consequently enhancing the activity of pathogenic T_{eff} cells in mice with collagen-induced arthritis¹⁰. Thus, a consequence of suppressing pathogenic T_{eff} cells with biologic agents that inhibit TNF signalling is the concomitant impairment of T_{reg} cell activity. Conversely, when acting as an agonist, the anti-TNF mAb–mTNF complex has the potential to activate TNFR2-expressing pathogenic T_{eff} cells in addition to activating T_{reg} cells. These two possibilities might help to explain why up to 40% of patients are unresponsive to therapies that block TNF signalling, with some experiencing adverse effects such as exacerbation of disease (as seen in multiple sclerosis) or even the induction of new autoimmune responses. Therefore, the frequency and function of T_{reg} cells and T_{eff} cells should be carefully evaluated in these patients.

The powerful T_{reg}-cell-promoting effect of TNF–TNFR2 signalling should be harnessed in the treatment of autoimmunity, transplant rejection and graft-versus-host disease. The most straightforward approach could be the use of TNFR2 agonists to expand T_{reg} cells in patients (FIG. 1). Although such an approach could also activate and expand TNFR2-expressing pathogenic T_{eff} cells, these cells express lower levels of TNFR2 than do T_{reg} cells, and so T_{reg} cells should outcompete T_{eff} cells. Furthermore, TNFR2-expressing autoreactive T_{eff} cells are highly activated, so TNFR2 agonists could trigger activation-induced cell death. Alternatively, selective blockade of TNFR1 (FIG. 1) could ‘divert’ all of the TNF so that higher concentrations are available to bind TNFR2, consequently expanding T_{reg} cells while blocking TNFR1-mediated proinflammatory events. As TNFR1 is more widely expressed than TNFR2, TNFR1 antagonists are likely to cause more adverse effects than TNFR2 agonists. An appropriate anti-TNF mAb that can complex with mTNF and deliver a potent stimulatory signal to T_{reg} cells, as described by Nguyen and Ehrenstein⁴, is also worth exploring (FIG. 1). In addition, agents that upregulate mTNF expression could also preferentially activate and expand T_{reg} cells, and thus should be studied (FIG. 1).

Taken together, recent research has advanced our understanding of the mechanisms by which biologic agents that target TNF signalling mediate their effects in autoimmune disorders, highlighting their effects on pathogenic T_{eff} cells and protective T_{reg} cells. Our ability to tip the balance of T_{eff} cell and T_{reg} cell activity in favour of immunosuppression will be the key to developing safer and more effective biological treatments for autoimmune diseases in the future.

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Figure 1 | Expansion of regulatory T cells by targeting of TNF receptor type II.

CD4⁺FOXP3⁺ regulatory T (T_{reg}) cells constitutively express higher levels of TNF receptor type II (TNFR2) than do effector T (T_{eff}) cells. Membrane-bound TNF (mTNF) preferentially binds to TNFR2, and consequently activates and expands T_{reg} cells, a function that could be therapeutically exploited for the treatment of autoimmunity, transplant rejection and graft-versus-host disease. Strategies to promote TNFR2-induced activation and expansion of T_{reg} cells include treatment with TNFR2 agonists, TNFR1 antagonists, an anti-mTNF monoclonal antibody (mAb) or agents that can upregulate mTNF expression on antigen-presenting cells (such as monocytes, macrophages and dendritic cells). AICD, activation-induced cell death.