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Targeting lymphotoxin depletes pathogenic T cells

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Abstract

A monoclonal antibody directed against lymphotoxin- α (LT- α) expressed by pathogenic T cells can prompt the clearance of these cells from the body (pages 766–773). The findings bring us one step closer to targeting only the cell populations that cause harm in autoimmune diseases while leaving beneficial arms of the immune system largely intact.

Over the last ten years, the treatment options for individuals with autoimmune disorders have improved dramatically. A range of protein-based therapeutic agents have entered the market that specifically target the signaling pathways that cause conditions such as rheumatoid arthritis and multiple sclerosis. These therapies include agents that directly neutralize inflammatory cytokines, interfere with T cell activation or lead to the depletion of specific cell types known to be involved in these diseases.

Although the benefits of these therapies are indisputable, they can come at a high price to the patient. In addition to targeting the pathological inflammation, these immunotherapeutic agents can also interfere with normal host defense against infection and malignancy¹. Therefore, enhancing target specificity has been one of the primary goals of the field.

In this issue of *Nature Medicine*, Chiang *et al.*² report the identification of an antibody that specifically targets activated T cell subsets involved in autoimmunity and propose that this new approach may lead to a substantial improvement over current treatments.

We rely on our immune system to fight infection and to clear cells that have died or that have become malignant, but the same mechanisms that protect us can also bring harm. When the complex balance of regulation and responsiveness breaks down, lymphocytes begin to attack self antigens, leading to autoimmune destruction of the tissue. Consequently, therapeutic agents that target autoimmune cells tend to be detrimental to normal antimicrobial defense, because the same functions underlie both the normal and the pathologic immune processes. For example, tumor necrosis factor- α (TNF- α), which is a therapeutic target in rheumatoid arthritis and several other autoinflammatory diseases, is expressed by almost all cells of the immune system. TNF- α is essential in defending against infection by stimulating phagocytosis of bacteria and production of antimicrobial peptides. It is not possible to neutralize the TNF- α that inflames a rheumatoid joint without also neutralizing the TNF- α that protects from tuberculosis, and consequently, tuberculosis poses a serious threat to the health of patients receiving anti-TNF- α therapy.

After microbial or other antigenic stimuli, a common precursor T cell gives rise to T helper cells known as T helper type 1 (T_H1; interferon- γ -producing), T_H17 (interleukin-17 (IL-17)-

producing) and T_H2 (IL-4-, IL-5- and IL-13-producing) cells. Each of these T helper cell subsets has a distinct role in fighting particular types of infections^{3,4}. However, each can also be involved in immune responses that damage healthy tissue. T_H2 cells participate in allergies and asthma, whereas T_H1 and T_H17 cells are commonly involved in autoimmune disorders.

Chiang *et al.*² set out to identify a specific marker of T helper cells in their activated state. To accomplish this needle-in-a-haystack task, they performed a genome-wide search using the immune response *in silico* (IRIS) database⁵. This database was developed from a vast microarray study and features only genes shown to be specifically expressed in immune cells.

From this search, they uncovered an unexpected candidate in the somewhat enigmatic cytokine lymphotoxin- α (LT- α)². LT- α was first characterized as a secreted homotrimer (LT- α 3) but has since been found as a membrane-bound heterotrimer with LT- β , predominantly as the molecule LT- α 1 β 2 (Fig. 1). Secreted LT- α 3 binds the TNF receptors TNFRI and TNFRII and shares many of the functions of TNF- α . LT- α 1 β 2 binds its own unique receptor, LT- β receptor (LT β R). In addition to overlapping functions between LT- α 3 and TNF- α , the creation of LT β R-deficient mice revealed a crucial, nonredundant role for this cytokine in the formation of secondary lymphoid tissues, such as the spleen and lymph nodes, and of germinal centers where B cells proliferate and mature after activation.

On the basis of their IRIS search, Chiang *et al.*² examined the expression of LT- α 1 β 2 on the various T cell subsets. They confirmed that T_H1 and T_H17 cells express high amounts of LT- α 1 β 2 on their surface, which was maintained as the cells produced their hallmark inflammatory cytokines IFN- γ and IL-17. Expression LT- α 1 β 2 on T_H2 cells was lower than on T_H1 and T_H17 cells and was rapidly lost after activation. This observation indicated that it might be possible to selectively target activated T_H1 and T_H17 cells, which are thought to have the most substantial role in autoimmunity, while sparing T_H2 cells.

Chiang *et al.*² developed a monoclonal antibody against LT- α that could stably bind LT- α 1 β 2 expressed on the cell surface, leading to a process known as antibody-dependent cellular cytotoxicity. In this process, phagocytes such as macrophages recognize and eliminate antibody-coated cells (Fig. 1). Herein lies the novelty of this approach. Rather than simply neutralizing the action of LT- α , this monoclonal antibody ‘tags’ LT- α 1 β 2-expressing T cells, leading to their clearance by phagocytes. Although soluble LT- α 3 was also neutralized, this interaction did not seem necessary for the therapeutic efficacy of the antibody. Mutations in the antibody that do not induce phagocytosis also rendered the antibody therapeutically ineffective, despite binding LT- α 3. Importantly, Chiang *et al.*² found that this antibody bound LT- α 1 β 2 without interfering with its interaction with LT β R, leaving intact a major function of this cytokine in maintaining lymphoid tissue structure and function.

Depletion of activated T_H1 and T_H17 cells by this monoclonal antibody against LT- α was found to be effective at reducing autoimmune disease symptoms in mouse models of multiple sclerosis (experimental autoimmune encephalomyelitis) and rheumatoid arthritis (collagen-induced arthritis). The treatment decreased the expression of proinflammatory cytokines and relieved other symptoms of these conditions, even when administered after the onset of disease. Although disease amelioration was partial, it was similar to that achieved in the mouse model of rheumatoid arthritis by treatment with anti-TNF- α , currently a clinical standard of care for the condition².

Whether targeting LT- α will prove to be a better “mouse trap” for the treatment of autoimmune diseases than currently available options remains to be determined and depends not only on efficacy but also on side effects. Regimens for therapeutic targeting of T cells are already in use clinically or are in advanced stages of development¹. Although it is clear that these regimens are effective therapies, some agents can lead to general T cell depletion without distinguishing

between activated and nonactivated T cells, leaving the patient markedly immunocompromised.

Other, more specific agents that attempt to target only activated T cells may inadvertently deplete cells with similar surface markers that have protective, regulatory functions. For example, the IL-2 receptor (CD25) that is expressed by all activated T cells is also shared by T regulatory cells, whose role is to control immune responses, including those mediated by T_H1 and T_H17 cells^{6,7}. Thus, treatment with CD25-specific antibodies has the potential to also deplete the beneficial T regulatory population.

The monoclonal antibody against LT- α developed by Chiang *et al.*² may be able to home in on activated T_H1 and T_H17 while sparing other elements of the immune system. The expression of LT- α 1 β 2 is limited largely to T cells, with low expression on B cells and natural killer cells that in this study appeared to be insufficient to trigger antibody-induced depletion. Regulatory T cells and T_H2 cells were similarly unaffected by the antibody. Finally, by leaving the binding of LT- α 1 β 2 to its receptor intact, this treatment lacks the deleterious effects on splenic architecture and germinal center formation of another LT-targeting agent, LT β R fusion protein, which was specifically developed to block the interaction between LT- α 1 β 2 and its receptor and has shown mixed results in clinical trials².

The selectivity and specificity of the LT- α -specific antibody for T_H1 and T_H17 cells, combined with its lack of deleterious effects on lymphoid tissue architecture, lowers the likelihood of serious side effects, suggesting the approach of Chiang *et al.* may be a promising future addition to the arsenal of biologics for treatment of debilitating autoinflammatory conditions.

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Figure 1. Schematic of binding of LT- α -specific antibody (anti-LT- α). The monoclonal antibody identified by Chiang *et al.*² blocks the interaction between LT- α 3 and TNFRI and TNFRII but not the binding of LT- α 1 β 2 to LT β R, FcR, Fc receptor.