Therapeutic antibodies that target inflammatory cytokines in autoimmune diseases

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Abstract

Inflammatory cytokines are key regulators of immune responses. Persistent and excessive production of inflammatory cytokines underscores the development of autoimmune diseases. Therefore, neutralizing inflammatory cytokines or antagonizing their receptor function is considered as a useful therapeutic strategy to treat autoimmune diseases. To achieve the success of such a strategy, understanding of the complex actions of these cytokines and cytokine networks is required. In this review we focus on four inflammatory cytokines—tumor necrosis factor α (TNFα), interleukin-6 (IL-6), IL-23 and IL-17—and dissect how the dysregulation of these cytokines regulates autoimmune diseases. On the basis of pre-clinical and clinical data, we specifically discuss the therapeutic rationale for targeting these cytokines and describe the potential adverse effects.

Introduction

Since interferon (IFN) was discovered in 1957 ([1, 2](#)), more than 90 inflammatory cytokines and their corresponding receptors have been identified ([3, 4](#)). These cytokines are produced by various cell types, and regulate immune responses, wound healing, angiogenesis, hematopoiesis and tissue remodeling. An appropriate inflammatory response is vital to host defense, whereas excessive or persistent production of inflammatory cytokines results in immunopathology such as inflammatory or autoimmune diseases.

Although inflammatory cytokines exert variable effects at different stages of different autoimmune diseases, not all of them are effective or promising targets for the treatment of these diseases. Here we outline some of the most effective treatments for autoimmunity including those targeting tumor necrosis factor α (TNFα), interleukin-6 (IL-6), IL-23 and IL-17, and discuss the underlying biological mechanisms. We also discuss the future challenges in the development of cytokine-targeted drugs on the basis of pre-clinical and clinical data.

Cytokines in autoimmune diseases

Upon infection or injury, keratinocytes, macrophages, dendritic cells (DCs) and other cells are activated to produce inflammatory cytokines ([5–9](#)). These inflammatory cytokines in turn act back on macrophages and DCs to induce more inflammatory cytokines, chemokines and other antimicrobial mediators ([10–12](#)). Subsequently, chemokines recruit myeloid

DCs, neutrophils and T cells to the site of infection or injury to further amplify inflammatory responses to protect hosts from microbial infections or to repair tissue damage ([13, 14](#)). However, under certain circumstances, possibly due to the presence of autoreactive T cells in the case of autoimmunity, there is uncontrolled production of inflammatory cytokines. Work for the past 10 years has revealed a vital role of T helper 17 (T_h17) cells in autoimmune diseases.

For example, in psoriasis, IL-6, together with TGFβ, induces naive CD4$^+$ T cells to differentiate into IL-17-producing T cells ([15–17](#)), and the persistent production of TNFα and other inflammatory cytokines activates macrophages and keratinocytes to constantly produce chemokines such as CCL20 and CCL27 to recruit immune cells including myeloid DCs, neutrophils and T_h17 cells to lesional skin of patients with psoriasis ([18–22](#)). Among these immune cells, DCs are further activated by TNFα to produce IL-23 ([23, 24](#)). IL-23, on one hand, directly activates a subset of IL-23-receptor-expressing macrophages and DCs, resulting in the production of inflammatory cytokines such as TNFα and IL-1 ([25–27](#)). On the other hand, IL-23 not only promotes T_h17 cells to become highly pathogenic but also activates $\gamma\delta$ T cells; both cell types produce IL-17A, IL-17F, IL-6 and TNFα ([26, 28–30](#)). IL-17 activates epithelial cells (e.g. keratinocytes), endothelial cells and fibroblasts to produce a variety of inflammatory cytokines ([31–33](#)), chemokines ([34](#)) and antimicrobial peptides/proteins (AMPs) ([35–37](#)).

In addition, IL-17 synergizes with other inflammatory cytokines including TNFα and IL-1β to further induce the expression of inflammatory cytokines and chemokines (38). The inflammatory cytokines induced by IL-17 promote the expansion of IL-17-producing γδ T or T$_h$17 cells whereas the chemokines recruit more neutrophils or IL-17-producing T cells to sites of inflammation in the skin (30, 39, 40); these processes result in a feed-forward mechanism to further amplify local inflammatory responses to incite cytokine storms, thus leading to the inflammatory manifestation of psoriatic skin (Fig. 1).

Taken together, the inflammatory circuit of TNFα, IL-6, IL-23 and IL-17 plays a critical role in host defense and tissue repair, whereas the dysregulation of this inflammatory circuit leads to the development of autoimmune diseases such as psoriasis.

Targeting inflammatory cytokines in autoimmune diseases

Given the importance of TNFα, IL-6, IL-23 and IL-17 in the development and pathogenesis of inflammatory and/or autoimmune diseases, lots of efforts have been spent on targeting these cytokines to treat these diseases. Accumulating pre-clinical and clinical studies show that blocking TNFα, IL-6, IL-23, IL-17 or their corresponding receptors by use of neutralizing antibodies is highly effective in the treatment of multiple autoimmune diseases such as psoriasis, rheumatoid arthritis (RA) and inflammatory bowel disease (IBD; Table 1). In particular, targeting the IL-23–IL-17 axis has been the most successful strategy for the treatment of psoriasis in the past decade.

Tumor necrosis factor α

TNFα is one of most avidly studied and clinically targeted cytokines in the treatment of autoimmune diseases. To date,

TNFα blockers are still the best-selling cytokine-targeting drug type on the market. TNFα is expressed by several cell types including keratinocytes, macrophages, monocytes, neutrophils, and T lymphocytes while its receptors, TNF receptor 1 (TNFR1; also known as p60) and TNFR2 (also known as p75), are ubiquitously expressed. Deregulated production of TNFα and its TNFRs is detrimental and has been associated with sepsis and several other inflammatory and autoimmune diseases including RA, psoriasis and colitis.

In the early 1970s, TNFα was discovered as a potent muscle-wasting (or cachexic) factor with potent anticancer activity (41, 42). This discovery stimulated great enthusiasm in the treatment of cancer. Unexpectedly, the administration of TNFα to patients caused hypotension and hepatic damage (43). The failure of TNFα in cancer treatment made scientists shift their attention to the field of sepsis as macrophage-derived TNFα was found to be one of two primary inflammatory cytokines in the pathogenesis of septic or endotoxin shock (44). However, the inhibition of TNFα with neutralizing antibodies or soluble TNFα receptor in patients with sepsis was either ineffective or made survival outcomes worse (45, 46).

Although anti-TNFα therapies failed in the treatment of cancer and sepsis, the first clinical trial of a TNFα inhibitor succeeded in the treatment of RA in 1992 (47). This success subsequently led to five approved TNFα-blocking biologicals (Table 1)—infliximab, etanercept, adalimumab, certolizumab and golimumab (48). Infliximab is an IgG1 mouse–human chimeric antibody and was the first TNFα-targeted drug to be approved, in 1998 (49). This was followed by the approval of the TNFR2–F$_c$ (crystallizable fragment of immunoglobulins) IgG1 chimera protein etanercept (50). Adalimumab was the first fully human antibody targeting TNFα and was approved in 2002 (51). Certolizumab pegol is a new, polyethylene glycol-conjugated, humanized F$_{Ab}$ (antigen-binding fragment of immunoglobulins) of a TNFα-specific monoclonal antibody
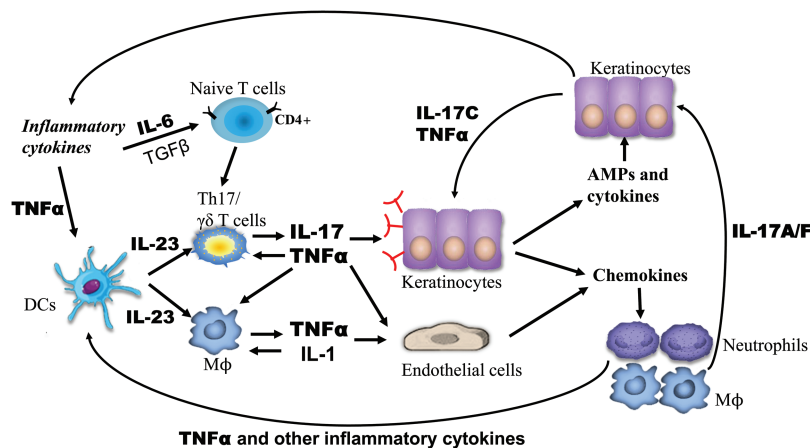

Fig. 1. The inflammatory circuit of TNFα, IL-6, IL-23 and IL-17 in the pathogenesis of psoriasis. The persistent production of TNFα and other inflammatory cytokines activates DCs to produce IL-23, and IL-6, together with TGFβ, induces naive CD4+ T cells to differentiate into IL-17-producing T cells. IL-23 directly activates macrophages (Mφ) to produce inflammatory cytokines such as TNFα and IL-1; IL-23 also promotes T$_h$17 cell differentiation into highly pathogenic T$_h$17 cells and activates γδ T cells, both cell types constantly produce IL-17A, IL-17F, IL-6 and TNFα. IL-17 activates epithelial cells (e.g. keratinocytes) and endothelial cells to produce a variety of inflammatory cytokines, chemokines and AMPs. The inflammatory cytokines induced by IL-17 promote the expansion of IL-17-producing γδ T or T$_h$17 cells whereas the chemokines recruit more neutrophils or IL-17-producing T cells to sites of inflammation in the skin, which produces a positive feed-forward mechanism and further amplifies local inflammatory responses to incite cytokine storms in psoriasis.

Table 1. Antibody-based biologics targeting TNFα, IL-23, IL-17 or their corresponding receptors

Biologic	Developers	Type of agent	Indications	Stage
TNFα				
Infliximab (Remicade®)	Janssen Biologics (Philadelphia, PA, USA)	Chimeric TNFα-specific antibody	Rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis, Crohn's disease, ulcerative colitis	Approved
Etanercept (Enbrel®)	AMGen (Thousand Oaks, CA, USA) / Pfizer (New York, NY, USA)	Human TNFR2–Fc fusion protein	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, ankylosing spondylitis	Approved
Adalimumab (Humira®)	Abbott Laboratories (Chicago, IL, USA)	Human TNFα-specific antibody	Rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis, Crohn's disease	Approved
Certolizumab pegol (Cimzia®)	UCB (Brussels, Belgium)	Human pegylated F_{Ab} TNFα-specific antibody	Rheumatoid arthritis, Crohn's disease	Approved
Golimumab (Simponi®)	Janssen Biologics	Human TNFα-specific antibody	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	Approved
IL-6				
Tocilizumab (Actemra®/RoActemra®)	Hoffmann—La Roche (Basel, Switzerland)	Humanized IL-6R-specific mAb	Rheumatoid arthritis, juvenile rheumatoid arthritis, Crohn's disease, Castleman's disease	Approved
Siltuximab (Sylvant®)	Janssen Biologics	Chimeric (mouse–human) IL-6-specific mAb	Multicentric Castleman's disease	Approved
Sarilumab	Sanofi (Paris, France)	Fully human IL-6Rα-specific mAb	Rheumatoid arthritis / Ankylosing spondylitis	Phase III / Phase II
Olokizumab	UCB	Humanized IL-6-specific mAb	Rheumatoid arthritis	Phase II
Sirukumab	Janssen Biologics	Fully human IL-6-specific mAb	Rheumatoid arthritis	Phase II
IL-23				
Ustekinumab (Stelara®)	Janssen Biologics	Human IL-12/IL-23- specific antibody targeting the p40 subunit	Psoriasis, psoriatic arthritis / Crohn's disease / Rheumatoid arthritis	Approved / Phase III / Phase III
Tildrakizumab	Merck (Kenilworth, NJ, USA) / Sun Pharmaceuticals (Mumbai, India)	Fully human mAb targeting IL-23 p19	Psoriasis / Crohn's disease	Phase III / Phase I
Guselkumab	Janssen Biologics	Fully human mAb targeting IL-23 p19	Psoriasis / Psoriatic arthritis	Phase III / Phase II
BI-655066	Boehringer Ingelheim GmbH (Ingelheim am Rhein, Germany)	Humanized mAb targeting IL-23 p19	Psoriasis, Crohn's disease, ankylosing spondylitis	Phase II
LY3074828	Eli Lilly & Co. (Indianapolis, IN, USA)	Humanized mAb targeting IL-23 p19	Psoriasis	Phase I
IL-17				
Secukinumab (Cosentyx®)	Novartis International AG (Basel, Switzerland)	Fully human mAb targeting IL-17A	Psoriasis / Psoriatic arthritis, ankylosing spondylitis / Rheumatoid arthritis, multiple sclerosis	Approved / Phase III / Phase II
Ixekizumab	Eli Lilly	Humanized mAb targeting IL-17A	Psoriasis, psoriatic arthritis / Rheumatoid arthritis	Phase III / Phase III
Brodalumab	AMGen / AstraZenenca (London, UK)	Fully human mAb targeting IL-17RA	Psoriasis, psoriatic arthritis	Phase III
CNTO6785	Janssen Biologics	Fully human mAb targeting IL-17A	Rheumatoid arthritis	Phase II
Bimekizumab	UCB	Humanized mAb targeting IL-17A and IL-17F	Psoriasis, psoriatic arthritis	Phase I
SCH-900117	Merck	Fully human mAb targeting IL-17A	Rheumatoid arthritis	Phase I

(mAb) and was approved in 2008 (52). Golimumab, another fully human antibody, was approved in 2009 (53).

It is reasonable to speculate that all these five TNFα-blocking biologicals would be effective in the treatment of autoimmune diseases associated with overproduction of TNFα, such as psoriasis, RA, multiple sclerosis (MS) and IBD (54, 55). However, not all patients have responded equally to each medication. Despite the impressive positive effects of blockade of TNFα in psoriasis, psoriatic arthritis and RA (51), anti-TNFα agents worsened disease in patients with MS (56) and etanercept failed to treat patients with IBD (57).

The basis for these differential effects of TNFα blockade might be due to the heterogeneity of RA, MS and IBD. In addition, all five TNFα-blocking biologicals have been reported to be effective in the treatment of RA, but about one-third of patients with RA treated with anti-TNFα agents did not respond (58). This difference might be dependent on the genetic makeup of patients and different mechanisms underlying the pathogenesis of RA. Moreover, TNFα is at the upstream of the inflammatory cytokine cascade. This early release inflammatory cytokine is at key steps of disease development but may not be fundamental to the disease pathogenesis in some cases as recent detailed studies indicate that both the timing and the duration of TNFα expression are important in determining the pathogenic roles of TNFα (59, 60).

Thus, determining the appropriate stage of disease at which to intervene is crucial. Moreover, the systemic blockade of soluble TNFα and membrane-bound TNFα by using neutralizing antibodies has been indicated to enhance cancer risk and susceptibility to infections (61, 62).

Interleukin-6

IL-6, like TNFα, is a key mediator in the immune system and produced by various haematopoietic and non-haematopoietic cells. Its receptor consists of a membrane-bound IL-6Rα and the accessory molecule glycoprotein 130 (gp130; also known as IL-6Rβ). The expression of membrane-bound IL-6Rα is restricted mainly to cells of the immune system and to hepatocytes, whereas gp130 is ubiquitously expressed. IL-6 also has a key role in the development of autoimmune models such as experimental autoimmune encephalomyelitis (EAE), collagen-induced arthritis (CIA), RA, IBD and psoriasis. In IL6-deficient mice, arthritis development was completely inhibited (63) and the severity of IBD was strikingly reduced (64), suggesting that targeting IL-6 holds therapeutic potential in the treatment of these autoimmune diseases. Therefore, multiple neutralizing antibodies targeting IL-6 and its receptor have been developed (Table 1). To date, tocilizumab (humanized IL-6R-specific mAb) has been approved, in combination with methotrexate, to treat RA (65); and siltuximab (chimeric IL-6-specific mAb) has been approved for multi-center trials of Castleman's disease treatment (66). Sirukumab (fully human IL-6-specific mAb), olokizumab (humanized IL-6-specific mAb) and sarilumab (fully human IL-6Rα mAb) are under Phase-II or -III study in patients with RA (67–69).

Despite the great potential of targeting IL-6 and IL-6R, caution is warranted given that IL-6 bound to soluble IL-6Rα, a form generated by proteolytic cleavage of membrane-bound IL-6Rα by the metalloproteinases TNFα-converting enzyme

or alternatively spliced mRNA, can induce *trans*-signaling by associating with the accessory molecule gp130 in a multitude of cell types that do not express membrane-bound IL-6Rα (4). Therefore, the antibodies directed against IL-6Rα will target both membrane-bound and soluble forms of the receptor, which may be outweighed in some cases by adverse effects. In such cases, targeting signaling molecules such as JAKs downstream of IL-6R might be more effective. Thus, tofacitinib, a small-molecule therapeutic targeting JAK1 and JAK3, has proved to be significantly effective (70). Moreover, IL-6 plays a critical role in host defense against microbial infections (71, 72) and plays a protective role during neural and liver injury (73, 74). Long-term IL-6 neutralization may increase susceptibility to bacterial and viral infections or may cause mortality in patients with ischemic neural damage or alcoholic cirrhosis.

The IL-23–IL-17 axis

The discovery of the IL-23–IL-17 immune axis has led to defining a new lineage of T helper cells—T_h17 cells. This new T-cell subset plays a key role in the pathogenesis of multiple autoimmune diseases as T_h17 cells are one of major producers of IL-17 (75).

Interleukin-23.   IL-23 is a heterodimeric cytokine composed of the p19 and the p40 subunits, and shares the p40 subunit with IL-12, which contains another subunit—p35. Given its key role in driving pathogenic T_h17 and γδ T cells to produce high levels of IL-17 (Fig. 1), neutralizing antibodies have been developed that target IL-23. The anti-p40 subunit therapy targeting IL-12 was first evaluated in patients with Crohn's disease (CD) in 2000 and provided benefit in this disease (76). Subsequent studies demonstrated that, in patients with psoriasis, levels of mRNA for the p40 of IL-12 or IL-23 and for the p19 of IL-23 were higher in lesions of psoriasis patients than in non-lesional and normal skin, whereas mRNA for p35 of IL-12 was present but decreased in lesional skin (77). Moreover, pre-clinical models of psoriasis illustrated that IL-23 exposure in murine skin drove the excessive growth and abnormal differentiation of keratinocytes, whereas IL-12 did not promote the same pathology (77, 78).

The evidence suggests that targeting the p40 of IL-12 indeed inhibits IL-23 and that inhibiting p40 might be effective to treat psoriasis, too. Therefore, two therapeutic mAbs targeting the p40 subunit, Ustekinumab and briakinumab, were used in treatment of psoriasis (Table 1). Both Ustekinumab and briakinumab were effective in Phase III clinical trials for the treatment of psoriasis and psoriatic arthritis (4). Ustekinumab also showed benefits in the treatment of moderate to severe CD when it was administered as maintenance therapy (79), but failed to prevent inflammation in patients with MS (80).

To date, Ustekinumab has been approved to treat psoriasis and psoriatic arthritis (81). However, briakinumab was withdrawn pending further analysis as major adverse cardiac events occurred in a higher number of patients receiving briakinumab compared with those receiving placebo in some Phase III trials (81, 82). Besides Ustekinumab and briakinumab, several IL-23-specific antibodies antagonizing the p19 subunit including tildrakizumab, guselkumab,

LY2525623, AMG139, BI-655066 and LY3074828 (Table 1) have been developed (81). Tildrakizumab and guselkumab have completed Phase II trials for psoriasis. LY2525623 was terminated in Phase II for complexities in development but not safety concerns. AMG139, BI-655066 and LY3074828 are in early stages of development (81).

Although IL-23 is redundant in host defense to many pathogens, it is important for host responses against *Mycobacterium* and *Candida* infections as IL-23-dependent IL-17A and IL-17F play key roles in protecting hosts from these infections (83, 84). Therefore, treatment of autoimmune diseases with IL-23 antagonists carries the risk of impaired host defense responses to pathogens. Moreover, IL-12 can act on both innate and adaptive lymphoid cells such as natural killer cells and CD8$^+$ cytotoxic T lymphocytes, and these cells then produce IFNγ to prevent tumor initiation, growth and metastasis (85, 86). In contrast, IL-23 increases tumor cell proliferation, survival and invasion by activating signal transducer and activator of transcription 3 (STAT3) and the overexpression of IL-23 in mice is sufficient to induce rapid (3–4 weeks) *de novo* development of intestinal adenomas (85, 87, 88). Therefore, the risk of breakdown in tumor surveillance by antagonizing the IL-12/IL-23 p40 subunit is of particular concern. To achieve both efficacy and safety in the treatment of autoimmune diseases by targeting IL-23, the intricate cellular and molecular mechanisms of those diseases warrant further investigation. Meanwhile, clinical testing is required to determine whether a specific disease mechanism also operates in humans.

Interleukin-17.   As a key effector cytokine produced by pathogenic T$_h$17 and $\gamma\delta$ T cells, IL-17 plays a crucial role in the pathogenesis of multiple autoimmune diseases such as psoriasis, RA, MS, IBD and myocarditis (89–91) and has been thought as one of the best targets in the treatment of autoimmune diseases (92). Therefore, several monoclonal antibodies targeting IL-17A and IL-17RA have been developed (Table 1). The Phase II proof-of-concept studies for secukinumab (a fully human IL-17A-specific monoclonal antibody) (93), ixekizumab (a humanized IL-17A-specific antibody) (94) and brodalumab (a fully human IL-17RA-specific monoclonal antibody) (95) showed that each drug was highly effective and helped around 80% of treated patients to achieve a 75% reduction in the Psoriasis Area and Severity Index (PASI) (96).

To date, secukinumab has been approved for the treatment of plaque psoriasis, whereas isekizumab and brodalumab are in Phase III trials (92). Beyond psoriasis, secukinumab, isekizumab and brodalumab are currently in pipeline, with trials in psoriatic arthritis and RA still ongoing. Other drug candidates targeting IL-17A include CNTO6785, SCH-900117 and bimekizumab. All these candidates are in either Phase II or Phase I clinical trials (97).

Although both IL-17A and IL-17RA are good targets in the treatment of autoimmune diseases, a key question remains: targeting which one—the cytokine or the receptor—is more effective? From a pharmacokinetic point of view it may be easier to block the cytokine than the receptor. IL-17 is readily available in the circulation, whereas the receptor resides in the membrane of many cell types and the corresponding neutralizing antibodies need to gain access to the relevant tissue before the receptor can be neutralized (92). Therefore, it is reasonable to speculate that targeting the ligand would be more straightforward than the receptor. However, IL-17RA is the most common signaling subunit in the IL-17 pathway. It can form heterodimeric receptor complex with most other IL-17 receptors. Therefore, targeting IL-17RA might be an effective way to disrupt the pathway if multiple IL-17 cytokines are contributing to a disease rather than a particular cytokine. Recent positive results for brodalumab in Phase III trials in psoriasis have confirmed this hypothesis (97).

Similar to targeting IL-23, the rates of adverse events including infections need to be considered due to a crucial role of IL-17A in the control of extracellular but not intracellular bacterial infections and fungi (98). To avoid the adverse effects, blocking T$_h$17 cell responses but not universal IL-17 cytokine signaling might be safer. Therefore, targeting RORγt, a key transcription factor that determines the lineage commitment of T$_h$17 cells, might be an alternative option. Several small molecules including digoxin and ursolic acid have been developed to antagonize RORγt activity (99, 100). However, off-target effects of these small molecules must be under key consideration.

Conclusions

Over the past two decades, targeting inflammatory cytokines and their receptors has produced multiple highly successful drugs in the treatment of autoimmune diseases such as RA, psoriasis and colitis. Although the potential of inflammatory cytokines and their receptors as drug targets is clearly established, how to select the key players in specific autoimmune diseases or pivotal regulators of cytokine circuits is still under debate. Therefore understanding the intrinsic cellular and molecular mechanisms of each cytokine in different disease settings is required to select a specific inflammatory target with better efficacy and safety profiles in the treatment of each autoimmune disease. Additionally, although the general principles in defining good anti-inflammatory targets are well established (3), the redundancy in the actions of many inflammatory cytokines that will limit the efficacy of single neutralizing agents requires us to pay careful attention.

We should point out that not all agents work as expected; some work better than others in certain diseases. Thus, the heterogeneity and complexity of human autoimmune diseases needs to be considered. Since mouse models cannot exactly resemble all types of human diseases, innovative translational studies on human patients are urgently required.

In addition, we need to keep in mind that inflammatory cytokines are also critical to maintain effective host defense or prevent tumorigenesis. Therefore, blocking cytokines to prevent autoimmune diseases might make patients more susceptible to infection or risk causing decreased tumor surveillance.

Clearly, there is much to be done to dissect the complex and highly interactive effects of inflammatory cytokines. With most of cytokines unstudied in human diseases, we are optimistic that many new, even better and safer ways of treating autoimmune diseases will emerge.

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