

The Biology and Medical Implications of Interleukin-6

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Abstract

Cytokines are soluble mediators, which aid cell-to-cell communication in immune responses, and interleukin-6 (IL-6) is a prototypical cytokine featuring redundant and pleiotropic activity. The complete elucidation of the IL-6-mediated signal transduction system has provided a molecular basis for the characteristic features of cytokines. When tissue damage or inflammation due to infections or injuries occurs, IL-6 synthesis is promptly induced, contributing to the host defense through the stimulation of acute-phase immune reactions and hematopoiesis. The production of IL-6 is terminated when tissue homeostasis is restored. The synthesis of IL-6 is tightly regulated transcriptionally and posttranscriptionally. However, the dysregulated continual synthesis of IL-6 has been implicated in the development of various diseases, including autoimmune and chronic inflammatory diseases and cancers. Clinical trials using the humanized anti-IL-6 receptor monoclonal antibody tocilizumab have demonstrated the efficacy of IL-6 blockade for the treatment of refractory inflammatory diseases, such as rheumatoid arthritis, systemic juvenile idiopathic arthritis, and Castleman disease. Moreover, favorable results from the off-label use of tocilizumab strongly suggest that it may be applicable for the treatment of other refractory immune-mediated diseases, including cancer. Therefore, the mechanisms for the dysregulated synthesis of IL-6 need to be elucidated to understand the pathogenesis of the resultant diseases and to facilitate the development of effective therapeutic strategies. *Cancer Immunol Res*; 2(4); 288-94. ©2014 AACR.

Disclosure of Potential Conflicts of Interest

T. Tanaka has received honoraria for service on the speakers' bureau for Chugai Pharmaceutical Company. T. Kishimoto has ownership interest in a patent for Actemura.

CME Staff Planners' Disclosures

The members of the planning committee have no real or apparent conflicts of interest to disclose.

Learning Objectives

IL-6 is a prototypical cytokine with characteristic redundant and pleiotropic activity. The transcription of IL-6 is induced promptly upon tissue damage or inflammation and ceases when homeostasis is restored. The synthesis of IL-6 is tightly regulated; its dysregulation is implicated in the development of immune-mediated diseases and cancer. An understanding of the biology of IL-6 will inform the design of therapeutics against diseases associated with its dysregulated expression. Upon completion of this activity, the participant should have a basic knowledge of the potential medical implications of this pleiotropic cytokine.

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Introduction

Cytokines are soluble mediators that aid cell-to-cell communication in immune responses. They include IFNs, chemo-

kines, lymphokines, interleukins, TGF- β , colony-stimulating factors (CSF), and TNF and are characterized by functional redundancy and pleiotropy. Interleukins are cytokines that act primarily on leukocytes. To date, nearly 40 interleukins have been identified. Interleukin-6 (IL-6) is a prototypical cytokine. After the gene encoding IL-6 was cloned, the cytokine was found to exert a variety of biologic activities, some of which have proved redundant with those of other members of the IL-6 family of cytokines. The transient expression of IL-6 contributes to host defense against infections and tissue injuries by stimulating acute-phase immune response and hematopoiesis. When tissue homeostasis is restored, the synthesis of IL-6 ceases. However, the dysregulated continuous production of IL-6 by distinct cell populations plays a pathologic role in various diseases. Tocilizumab, a humanized anti-IL-6 receptor

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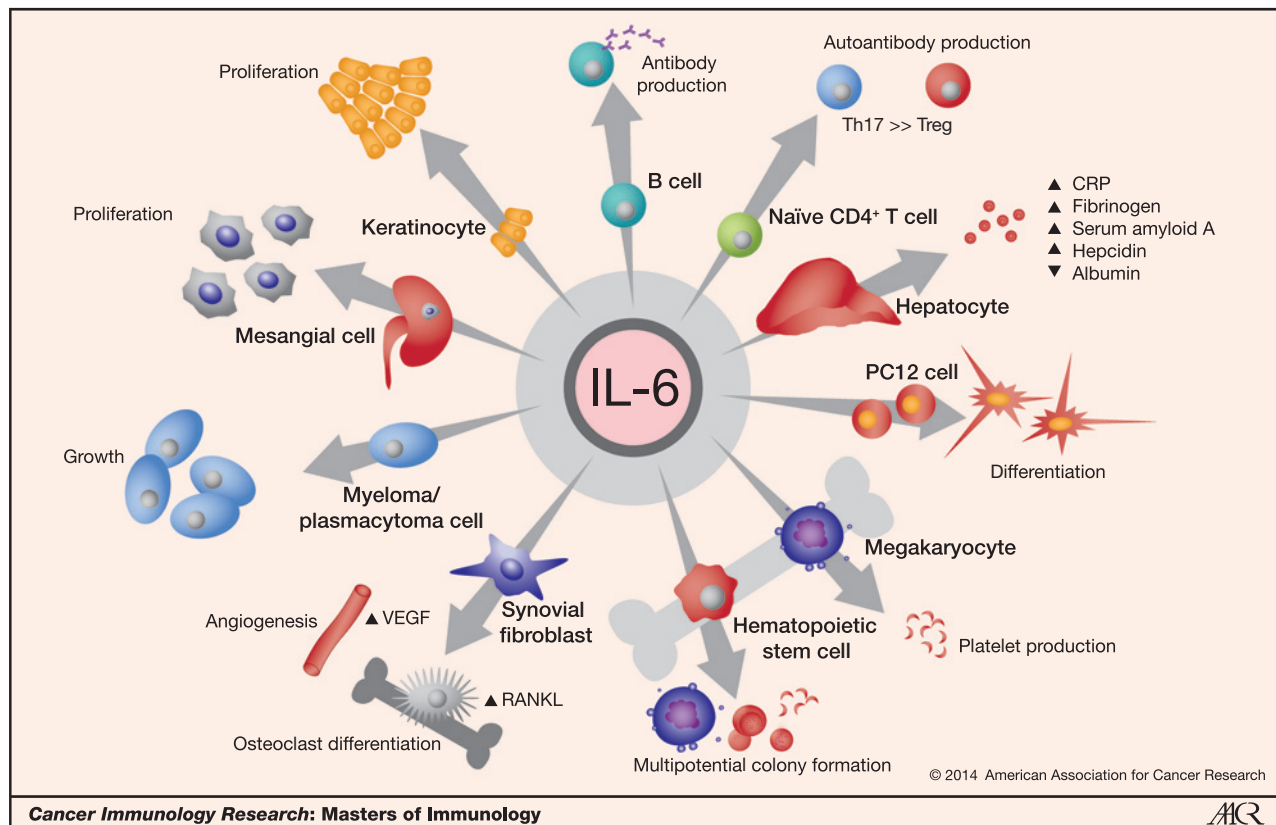


Figure 1. Pleiotropic activity of IL-6. IL-6 acts as a BSF-2, which induces activated B cells into antibody production. IL-6, combined with TGF- β , preferentially promotes the differentiation of naïve CD4⁺ T cells into Th17 cells, but inhibits TGF- β -induced Treg development. As a consequence, Th17/Treg imbalance may cause the onset and progression of immune-mediated diseases. IL-6 also induces production of acute-phase proteins, such as CRP, SAA, fibrinogen, and hepcidin, but reduces synthesis of albumin in hepatocytes. In bone marrow, IL-6 induces maturation of megakaryocytes into platelets and activation of hematopoietic stem cells. Moreover, IL-6 promotes the differentiation of osteoclasts and angiogenesis, stimulates collagen production by dermal fibroblasts, and stimulates the growth of myeloma cells and mesangial cells.

(IL-6R) antibody, was developed in response to the expectation that IL-6 blockade might be a novel therapeutic strategy for such diseases. Results from clinical trials have indicated that tocilizumab is highly efficacious for the treatment of some intractable inflammatory diseases, such as rheumatoid arthritis, systemic juvenile idiopathic arthritis (sJIA), and Castleman disease. Moreover, reports about the off-label use of tocilizumab strongly suggest that IL-6 blockade may be a promising therapeutic approach for other refractory autoimmune and inflammatory diseases and cancers.

This master primer focuses on the biology of IL-6, the medical implications of the progress in IL-6-targeting therapeutic strategy, and the future aspects of IL-6-related research.

Biologic Functions of IL-6

IL-6 was originally identified as B-cell-stimulating factor 2 (BSF-2) in the culture supernatants of mitogen- or antigen-stimulated peripheral blood mononuclear cells, which induced immunoglobulin production in Epstein-Barr virus-transformed B-cell lines or in *Staphylococcus aureus* Cowan 1-stimulated B cells (1). The gene encoding BSF-2 was cloned in 1986 (2). Subsequently, BSF-2 was found to be identical to the hepatocyte-stimulating factor, the hybridoma growth factor, and IFN- β 2, which was later found to lack antiviral activity; the molecule

became known as IL-6 (1). Human IL-6 consists of 184 amino acids with two potential N-glycosylation sites and four cysteine residues; the core protein is about 20 kDa, and glycosylation accounts for the 21- to 26-kDa size of natural IL-6.

In response to infections or tissue injuries caused by burns and traumas, IL-6 is promptly synthesized and activates an acute immune response (Fig. 1). IL-6 induces the differentiation of activated B cells into immunoglobulin-producing plasma cells and acts as a growth factor for hybridoma and myeloma cells. In addition to B cells, IL-6 also affects T cells by inducing the specific differentiation of naïve CD4⁺ T cells into effector T-cell subsets. In combination with TGF- β , IL-6 preferentially induces the differentiation of naïve CD4⁺ T cells into Th17 cells, but inhibits the TGF- β -induced development of regulatory T cells (Treg; refs. 3, 4). The pathogen-specific, effector Th17 cells eliminate extracellular pathogens from the host, and the IL-6-induced dominance of Th17 cells over Tregs may account for the disruption of the immune tolerance that is involved in the development of autoimmune and inflammatory diseases. Indeed, in several autoimmune disease models, IL-6 blockade at the priming step suppresses the development of the dominance of Th17 and/or Th1 over Tregs in antigen-specific effector T-cell subsets, and of the autoimmune diseases independent of the antigens used for immunization. Furthermore, IL-6 promotes T follicular

helper cell differentiation as well as the production of IL-21 (5), which also functions in the regulation of immunoglobulin synthesis.

IL-6 stimulates hepatocytes to produce acute-phase proteins, such as C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, hepcidin, and α 1-antichymotrypsin, and it reduces the production of fibronectin, albumin, and transferrin (6). The increase in the levels of acute-phase proteins issues an emergency stress signal and contributes to host defense. CRP and SAA are biomarkers of inflammation, and their synthesis is mainly regulated by IL-6, as the administration of tocilizumab leads to the normalization of the serum levels of these inflammation-related acute-phase proteins.

IL-6 exerts other effects that are detected frequently in chronic inflammatory diseases. Bone marrow stromal cells produce IL-6 that stimulates the receptor activator of NF- κ B ligand (RANKL), which is essential for the differentiation and activation of osteoclasts, leading to bone resorption and osteoporosis. IL-6 also induces the production of VEGFs, resulting in angiogenesis and increased vascular permeability, which are pathologic features of cancers and of inflammatory lesions in the synovial tissues of rheumatoid arthritis. Moreover, it has been reported that IL-6 promotes keratinocyte proliferation and the synthesis of collagen in dermal fibroblasts and their differentiation into myofibroblasts, which may account for skin fibrosis in patients with systemic sclerosis. Mesangial cell proliferation and matrix overproduction are characteristic features of glomerular diseases, and IL-6 has been found in matrix deposits and may be involved in mesangial cell proliferation. Finally, IL-6 has been shown to interact with and affect various cells and organ systems, including the vascular endothelial cells, the endocrine system of the hypothalamic-pituitary-adrenal axis, and the neuropsychologic system.

IL-6 Signaling Pathway

The multiple functions of IL-6 are initiated upon its binding to the IL-6R. The IL-6R-signaling system comprises two receptor chains and downstream signaling molecules (7). The IL-6R is composed of the IL-6-binding chain, which exists in two forms, an 80-kDa transmembrane IL-6R and a 50- to 55-kDa soluble IL-6R (sIL-6R; ref. 8), and a 130-kDa gp130 signal-transducing chain (9). sIL-6R is derived from the extracellular portion of the transmembrane IL-6R by either proteolytic cleavage of the proximal membrane moiety or by alternative splicing. The genetic polymorphism of the IL-6R gene 48892 A/C (rs8192284), which causes a functional amino acid change (Asp358Ala) in the proteolytic cleavage site of the IL-6R, influences the serum levels of sIL-6R and can be positively or negatively associated with several inflammatory diseases. The expression of the transmembrane IL-6R is limited to the surface of cells, such as hepatocytes and leukocytes, whereas the sIL-6R is present in the sera and tissue fluids. Upon binding to either the transmembrane IL-6R or the sIL-6R, the IL-6 cytokine-receptor complex induces the homodimerization of the IL-6R gp130 chains triggering the downstream signaling cascade.

Cytokines mediate intercellular communications in immune responses and are characterized by functional plei-

otropy and redundancy (10), but the molecular basis of these characteristic features remained unknown. However, the pleiotropic function of IL-6 can be explained by the broad range of gp130 expression in various cells. The activated IL-6R complex is a hexameric structure comprising two molecules each of IL-6, IL-6R, and gp130. Although IL-6R is a unique binding receptor for IL-6, the gp130 signal-transducing chain is shared by members of the IL-6 family of cytokines, which include the leukemia inhibitory factor, oncostatin M, ciliary neurotrophic factor, IL-11, cardiotrophin 1, cardiotrophin-like cytokine, IL-27, and IL-35 (11). Identification of the molecular mechanism by which the IL-6 family of cytokines uses the common signal-transducer gp130 has solved the long-standing mystery of the redundant function of the IL-6 family of cytokines (12).

Activation of gp130 in turn triggers the activation of downstream signaling pathways, such as the Janus-activated kinase (JAK)-STAT3 pathway and the JAK-SH2-domain-containing protein tyrosine phosphatase-2/mitogen-activated protein kinase (MAPK) pathway. The induction of various sets of IL-6-responsive genes is accounted for by the activation of the transcription factor STAT3, which also stimulates the activation of the genes encoding suppressor of cytokine signaling-1 (SOCS1) and SOCS3. Under these conditions, SOCS1 binds to tyrosine-phosphorylated JAK, whereas SOCS3 binds to tyrosine-phosphorylated gp130 to terminate IL-6 signaling by means of negative feedback loops (13).

Regulation of IL-6 Synthesis

IL-6 is synthesized promptly when infections or tissue injuries occur, providing a warning signal to the host. The signature of exogenous pathogens, known as pathogen-associated molecular patterns (PAMP), is recognized in the infected lesion by pathogen-recognition receptors of innate immune cells, such as monocytes and macrophages, while the damage-associated molecular patterns (DAMP) released from damaged or dying cells can initiate and perpetuate immune response in a noninfectious context. In addition to immune cells, other sources of IL-6 may include mesenchymal cells, endothelial cells, fibroblasts, and many others including tumor cells (14).

IL-6 synthesis is tightly regulated both transcriptionally and posttranscriptionally (15), and a number of transcription factors regulate IL-6 expression. The functional *cis*-regulatory elements in the human IL-6 gene 5' flanking region contain binding sites for NF- κ B, specificity protein 1 (SP-1), nuclear factor IL-6 (NF-IL-6), activator protein 1 (AP-1), and IFN regulatory factor 1 (IRF-1). Some viral products have been shown to enhance the DNA-binding activity of NF- κ B and/or NF-IL-6, resulting in an increase in IL-6 mRNA transcription (15). They include the transactivator protein derived from the human T lymphotropic virus 1, the transactivator of the transcription protein of the HIV 1, and the human hepatitis B virus X protein. In addition, some microRNAs (miRNA, miR) have been shown to regulate the transcription of IL-6, either directly or indirectly. For instance, miR-155 suppresses NF-IL-6 expression by directly interacting with the 3'-untranslated regions (UTR) of NF-IL-6, whereas miR-146a/b indirectly

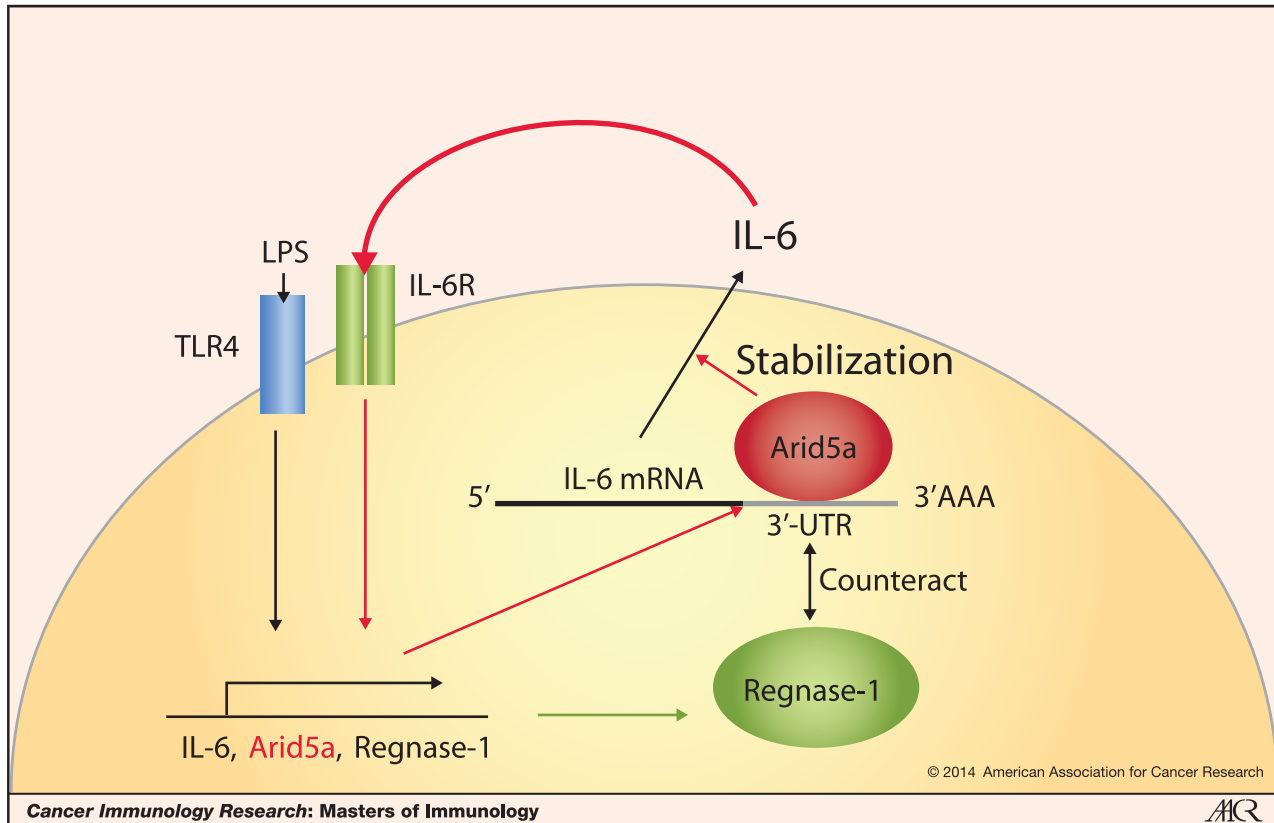


Figure 2. Arid5a counteracts the destabilizing effect of Regnase-1 on IL-6 mRNA. Regnase-1 accelerates IL-6 mRNA degradation, and Arid5a counteracts the destabilizing effect of Regnase-1. The balance between Arid5a and Regnase-1 thus plays an important role in IL-6 mRNA stability.

suppresses the transcription of IL-6 by targeting the IL-1 receptor-associated kinase 1.

Cytokine expression can be regulated posttranscriptionally; there are regulatory elements at both the 5'- and 3'-UTR of cytokine mRNAs (16). Initiation of mRNA translation is controlled via the 5'-UTR. Stability of the cytokine mRNA is controlled by the binding of RNA-binding proteins and miRNAs to the AU-rich elements located in the 3'-UTR. For example, IL-6 mRNA stabilization is promoted by the MAPK p38 α and the Kaposi sarcoma-associated herpes virus open reading frame 57, which competes with the binding of miR-608 to the 3'-UTR of the IL-6 mRNA. Other RNA-binding proteins, such as tristetraprolin and butyrate response factor-1 and -2, promote IL-6 mRNA degradation, and the levels of IL-6 mRNA are reduced by the binding of miR-365 and miR-608 to the IL-6 3'-UTR.

In addition to these regulators, a nuclease known as regulatory RNase-1 (Regnase-1) destabilizes IL-6 mRNA; Regnase-1 knockout mice spontaneously develop autoimmune diseases with splenomegaly and lymphadenopathy (17). The inhibitor of I κ B kinase (IKK) complex controls IL-6 mRNA stability by phosphorylating Regnase-1 in response to IL-1 or Toll-like receptor (TLR) stimulation (18). Phosphorylated Regnase-1 then undergoes ubiquitination and degradation. The kinetics of Regnase-1 is delayed, when reexpressed in IL-1- or TLR-activated cells, while Regnase-1 mRNA is negatively regulated

by Regnase-1 itself via a stem-loop region present in the Regnase-1 3'-UTR. These findings demonstrate that the IKK complex phosphorylates not only I κ B α activating transcription but also Regnase-1, releasing the "brake" on IL-6 mRNA expression.

Recently, we have identified a novel RNA-binding protein termed AT-rich interactive domain-containing protein 5a (Arid5a), which binds to the 3'-UTR of the IL-6 mRNA, resulting in the selective stabilization of IL-6, but not of TNF- α or IL-12 mRNA (19). The expression of Arid5a is increased in macrophages in response to lipopolysaccharide (LPS), IL-1 β , or IL-6, and it is also induced under Th17-polarizing conditions in T cells. We found that Arid5a gene deficiency eliminates the increase in the levels of IL-6 in LPS-injected mice and in the preferential Th17 cell development in experimental autoimmune encephalomyelitis (EAE). Furthermore, Arid5a counteracts the destabilizing effect of Regnase-1 on IL-6 mRNA (Fig. 2), indicating that the balance between Arid5a and Regnase-1 plays an important role in IL-6 mRNA stability. The predominance of Arid5a over Regnase-1 promotes prolonged IL-6 expression and potentially induces the development of various immune-mediated diseases and oncogenesis (Fig. 2). Indeed, a preliminary study has demonstrated that the expression of Arid5a in peripheral blood CD4⁺ T cells was significantly higher in patients with untreated rheumatoid arthritis than in healthy individuals (20). Moreover, blockade of IL-6 but not

of TNF- α resulted in a reduction in the level of Arid5a in CD4⁺ T cells.

Medical Implications of IL-6

The immediate and transient expression of IL-6 contributes to host defense against environmental stress factors such as infections and tissue injuries. When the source of stress is removed from the host, IL-6-mediated activation of the signal transduction cascade is terminated by negative regulatory systems, such as ligand-induced internalization and degradation of gp130, and the recruitment of SOCS (13), resulting in the normalization of serum levels of acute-phase proteins such as CRP and SAA. At the same time, IL-6 synthesis ceases. However, the dysregulated, persistent IL-6 production, via still mostly unknown mechanisms, one of which may be due to an imbalance between Arid5a and Regnase-1, leads to the development of various diseases. The first association of IL-6 with disease development was demonstrated in a case of cardiac myxoma, in which the fluid obtained from the myxoma tissue of a patient, who presented with fever, polyarthritis, elevated CRP level, anemia, and hypergammaglobulinemia with positivity for antinuclear factor, contained a large quantity of IL-6 (21). Subsequent studies have demonstrated that dysregulated IL-6 production also occurs in synovial fluids of rheumatoid arthritis, swollen lymph nodes of Castleman disease, myeloma cells, peripheral blood cells or tissues from patients with other diseases, and in many tumor cells (1, 22).

Moreover, the concept of a pathologic role for IL-6 in disease development has been supported by the findings that IL-6 blockade by gene knockout or by the administration of anti-IL-6 or anti-IL-6R antibody can result in preventive or therapeutic suppression of diseases in animal models. For example, IL-6 blockade resulted in a reduction in the susceptibility to Castleman disease-like symptoms in IL-6 transgenic mice, and inhibited disease development in animal models of rheumatoid arthritis, systemic lupus erythematosus (SLE), systemic sclerosis, inflammatory myopathies, EAE, experimental autoimmune uveoretinitis, and other immune-mediated diseases.

Because of the pathologic role of IL-6 described above, it was expected that IL-6 targeting would be a novel therapeutic strategy against these diseases (4, 21, 22). This led to the development of tocilizumab, a humanized anti-IL-6R monoclonal antibody of the immunoglobulin G1 (IgG1) class, which was generated by grafting the complementarity-determining regions of a mouse antihuman IL-6R antibody onto human IgG1 (23). Tocilizumab can block IL-6-mediated signal transduction by inhibiting IL-6 binding to both the transmembrane IL-6R and the sIL-6R.

The first clinical evaluation of the efficacy of tocilizumab involved the treatment of 7 patients with Castleman disease, a chronic inflammatory disease characterized by swelling of multiple lymph nodes with massive infiltration of mature plasma cells. These patients presented with severe inflammatory symptoms such as high fever, anemia, increased levels of acute-phase proteins, and hypergammaglobulinemia; in response to the administration of tocilizumab, the fever promptly diminished, the CRP levels became normalized, and

the hemoglobin levels increased (24). The efficacy of tocilizumab was confirmed in a clinical trial involving 28 other patients with Castleman disease (25), resulting in the approval of tocilizumab as an orphan drug for the Japanese market in 2005.

Next, through numerous clinical trials worldwide, the efficacy, tolerability, and safety of tocilizumab for rheumatoid arthritis were verified. On the basis of the results of these clinical trials, tocilizumab has been approved for the treatment of rheumatoid arthritis in more than 100 countries (4). In addition to tocilizumab, five TNF inhibitors and a T-cell stimulator blocker (abatacept) have been approved as first-line biologic therapy for patients with rheumatoid arthritis with inadequate responses to the standard disease-modifying antirheumatic drug (DMARD) methotrexate. However, tocilizumab possesses a unique feature: It is the only biologic therapy that as monotherapy has proved more efficacious than methotrexate or other DMARDs, and thus seems to be a potent antirheumatic biologic therapy. Clinical studies have demonstrated that the coadministration of TNF inhibitors and methotrexate is more efficacious for patients with rheumatoid arthritis than the administration of TNF inhibitors alone. In contrast, the ACT-RAY clinical trial showed that tocilizumab monotherapy was not inferior to tocilizumab combined with methotrexate, indicating that tocilizumab as monotherapy might be more effective for suppression of disease activity than TNF inhibitors (26). A direct comparison of tocilizumab and adalimumab, a fully human anti-TNF- α antibody, has demonstrated that tocilizumab monotherapy was superior to adalimumab monotherapy, as determined by several indices of disease activity in patients with rheumatoid arthritis (27), and the clinical efficacy of adalimumab for rheumatoid arthritis was equivalent to that of abatacept when used in combination with methotrexate (28).

sJIA is a subtype of chronic childhood arthritis that leads to joint destruction, functional disability, and growth impairment accompanied by systemic inflammation. IL-6 is markedly elevated in the sera and synovial fluids of patients with sJIA, and the levels of IL-6 correlate with disease activity. A randomized, double-blind, placebo-controlled phase III trial for 56 patients with sJIA resulted in American College of Rheumatology (ACR) pediatric criteria 30%, 50%, and 70% responses for 91%, 86%, and 68% of the patients, respectively (29). Subsequently, in a global phase III trial, 112 children with active sJIA and inadequate responses to nonsteroidal anti-inflammatory drugs and glucocorticoids were randomized to receive placebo or tocilizumab (8 or 12 mg/kg every 2 weeks, depending on body weight). At week 12, the primary endpoint (an absence of fever and an improvement of 30% or more in at least three of the six variables in the ACR core set for JIA) was met for significantly more patients in the tocilizumab-treated group than in the placebo group (85% vs. 24%; ref. 30). The responsiveness of sJIA to tocilizumab has led to the recognition that IL-6 blockade represents an important advancement in the treatment of this disease, which had been considered as one of the most intractable pediatric diseases.

Moreover, case reports, small series, and pilot studies of the off-label application of tocilizumab have produced favorable results, indicating that tocilizumab may be used for the

treatment of three classes of intractable inflammatory diseases (4, 21). The first class comprises autoimmune diseases, including systemic sclerosis, large-vessel vasculitis, SLE, polymyositis, neuromyelitis optica, relapsing polychondritis, autoimmune hemolytic anemia, acquired hemophilia, and Cogan syndrome. The second class consists of chronic inflammatory diseases such as adult-onset Still disease, amyloid A amyloidosis, cytokine release syndrome, Crohn disease, polymyalgia rheumatica, remitting seronegative symmetrical synovitis with pitting edema, Behçet disease, uveitis, graft-versus-host disease, pulmonary arterial hypertension, and IgG4-related disease. The third class entails autoinflammatory syndromes such as TNF receptor-associated periodic syndrome, chronic inflammatory neurologic cutaneous articular syndrome, and Schnitzler syndrome. In addition, other candidate diseases include atherosclerosis, type II diabetes mellitus, atopic dermatitis, sciatica, and amyotrophic lateral sclerosis. Finally, IL-6 blockade is a promising therapeutic strategy for some cancers as an increase in IL-6 levels has been associated with elevated cancer risk, and the levels of IL-6 may constitute a prognostic factor for several cancer types. In fact, IL-6 has been found to promote cancer progression by the induction of tumor angiogenesis, the inhibition of cancer cell apoptosis, and the perturbation of the tumor microenvironment; the cytokine has also been linked to cancer-associated cachexia (31). Taken together, these findings strongly suggest that more detailed clinical evaluations of tocilizumab therapy for a wide variety of diseases, including cancer, are warranted.

Concluding Remarks

On the basis of clarifying the IL-6-mediated signal transduction system, the pathologic role of IL-6 in various

diseases was delineated, and a specific pharmacologic inhibitor, the humanized anti-IL-6R monoclonal antibody tocilizumab, was developed. Clinical trials of tocilizumab started in the late 1990s, and this biologic therapy was first approved for the treatment of Castleman disease in Japan in 2005. Since that time, tocilizumab has been adopted as a first-line biologic therapy for the treatment of moderate to severe rheumatoid arthritis in more than 100 countries, for sJIA in Japan, India, the United States, and the European Union, and is the only approved drug for Castleman disease in Japan and India. These major successes have led to a paradigm shift in the treatment of such diseases and have accelerated the development of other IL-6 inhibitors (32). It is anticipated that during the next decade, IL-6 inhibitors will be widely used for the treatment of various intractable inflammatory diseases, and their application will overcome the refractory nature of such diseases. To achieve this goal, additional clinical trials will be needed to evaluate the efficacy and safety of IL-6 inhibitors.

Finally, although the delineation of the IL-6-mediated signal transduction pathway has answered the long-standing question of why cytokines exhibit functional redundancy and pleiotropy, but it remains an enigma as to why IL-6 is persistently expressed in various diseases. Further analyses of proteins, such as Arid5a and Regnase-1, and miRNAs that regulate IL-6 synthesis should lead to satisfactory answers, while the delineation of the mechanism(s) involved will result in the identification of more specific target molecules and investigations into the pathogenesis of these diseases.

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