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Review

A new era for the treatment of inflammatory autoimmune diseases by interleukin-6 blockade strategy

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ABSTRACT

Interleukin-6 (IL-6) is a cytokine with redundant and pleiotropic activities, and its synthesis is tightly regulated by transcriptional and posttranscriptional mechanisms. When infections and tissue injuries occur, IL-6 synthesis is promptly induced and provides an emergent signal that contributes to host defense through the stimulation of acute-phase responses, immune reactions, and hematopoiesis. After the environmental stress is removed from the host, the production of IL-6 is terminated. However, dysregulated continual synthesis of IL-6 is involved in the development of chronic inflammatory autoimmune diseases. For this reason, tocilizumab, a humanized anti-IL-6 receptor antibody, was developed. Worldwide clinical trials have demonstrated the outstanding efficacy of tocilizumab in rheumatoid arthritis, systemic juvenile idiopathic arthritis, and Castleman's disease; thus, a new era has come for the treatment of these diseases, which were previously considered intractable. Moreover, favorable results from off-label use of tocilizumab strongly suggest that it will be widely applicable for various refractory inflammatory autoimmune diseases. In this context, the mechanism for the continual synthesis of IL-6 needs to be elucidated in order to investigate the pathogenesis of specific diseases and to facilitate the development of more specific therapeutic strategies.

1. Introduction

Interleukin 6 (IL-6) is a typical cytokine featuring redundant and pleiotropic activity. After successful cloning of the IL-6 gene, it was found that IL-6 exerts a variety of biological activities on responding cell populations through its binding to transmembrane IL-6 receptor (IL-6R) as well as soluble IL-6R (sIL-6R). The transient production of IL-6 contributes to host defense against infections and tissue injuries, and when the stress of infection or injury is removed, the synthesis of IL-6 is terminated. However, the dysregulated continuous production of IL-6 by a distinct cell population plays a pathological role in various inflammatory autoimmune diseases.

Tocilizumab is a humanized anti-IL-6R antibody (Ab). Clinical trials have shown that tocilizumab is greatly efficacious for the treatment of intractable diseases such as rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (sJIA), and Castleman's disease. Moreover, reports regarding off-label use of tocilizumab strongly suggest that the IL-6 blockade strategy is a promising therapeutic approach for other refractory inflammatory autoimmune diseases. In this review, we highlight the pathological role of IL-6 in inflammatory autoimmune diseases and discuss current evidence as well as future perspectives of IL-6 blockade therapy for inflammatory autoimmune diseases.

2. Discovery and biological function of IL-6

The gene encoding IL-6 was successfully cloned in 1986 on the basis of B-cell stimulatory factor 2 (BSF-2) activity, which induces the differentiation of activated B cells into Ab-producing cells [1]. Later, BSF-2 was found to be identical to hepatocyte-stimulating factor (HSF), hybridoma growth factor (HGF), and interferon (IFN) β2, and then the molecule became known as IL-6 [2]. Human IL-6 is made up of 212 amino acids, which includes a 28-amino acid signal peptide, and its gene has been mapped to chromosome 7p21. The core protein is about 20 kDa. Glycosylation accounts for the 21–26 kDa size of natural IL-6.

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2.1. Stimulation of acquired immunity

In the acquired immune response, IL-6 performs an important function (Fig. 1). IL-6, originally identified as BSF-2, induces the differentiation of activated B cells into immunoglobulin (Ig)-producing plasma cells, so that continuous over-expression of IL-6 results in hypergammaglobulinemia and autoantibody production. IL-6 also acts as a growth factor for hybridoma cells and myeloma cell lines. IL-6 transgenic mice exhibit polyclonal plasmacytosis in the spleen, lymph nodes, and thymus and have increased number of megakaryocytes in bone marrow [3]. Myeloma cells respond to IL-6 for growth, while some myeloma cells themselves are able to produce IL-6. Thus, IL-6 is an autocrine growth factor in some types of multiple myelomas [4]. Moreover, IL-6 can promote the survival of the plasmablast cell population, which secretes a pathological autoantibody, anti-aquaporin 4 (AQP4), in patients with neuromyelitis optica (NMO) [5].

IL-6 affects not only B cells but also T cells. IL-6 promotes specific differentiation of naïve CD4-positive T cells into effector T-cell subsets. IL-6 in combination with transforming growth factor (TGF)-β preferentially induces the differentiation of naïve CD4-positive T cells into Th17 cells [6], whereas IL-6 inhibits TGF-β-induced regulatory T cell (Treg) development [7]. The resultant predominance of Th17 cells over Treg caused by IL-6 may be responsible for the disruption of immunological tolerance and is thus pathologically involved in the development of inflammatory autoimmune diseases [8]. Indeed, in several autoimmune disease models, IL-6 blockade at the priming step suppresses the development of the imbalance of antigen-specific effector T-cell subsets and of autoimmune diseases irrespective of antigens immunized [9–11]. IL-6 also promotes T follicular helper cell differentiation as well as production of IL-21 [12], which also regulates Ig synthesis. In addition, IL-6 induces the differentiation of CD8-positive T cells into cytotoxic T cells [13].

2.2. Stimulation of acute-phase protein synthesis

After IL-6 is synthesized in a local lesion in the initial stage of inflammation, it rapidly induces hepatocytes to produce acute-phase proteins such as C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, haptoglobin, and α1-antichymotrypsin, whereas IL-6 reduces the production of fibronectin, albumin, and transferrin [14]. Increased levels of acute-phase proteins provide an emergent signal and contribute to the host defense. CRP and SAA are recognized as biological markers of inflammation occurring somewhere in the body, while their synthesis is mainly regulated by IL-6, since administration of tocilizumab leads to normalization of serum levels of these proteins [15,16]. Long-term expression of high levels of SAA leads to a serious complication, amyloid A amyloidosis [17]. IL-6-mediated production of hepcidin, which blocks the action of iron transporter ferroportin 1 in the gut and thus reduces serum iron levels, leads to hypoferremia and anemia associated with chronic disorders [18]. IL-6 also enhances zinc transporter Zip14 expression on hepatocytes and so induces hypozincemia, which often occurs in inflammation [19].

2.3. Other biological activities

IL-6 exerts other various effects, other than those on hepatocytes and lymphocytes, and these effects are frequently detected in chronic inflammatory diseases [2,20,21]. One of these effects is that when IL-6 is generated in bone marrow stromal cells, it stimulates the receptor activator of the nuclear factor kappa B (NF-kB) ligand (RANKL) [22], which is indispensable for the differentiation and activation of osteoclasts, which leads to bone resorption and osteoporosis [23]. IL-6 also induces excess production of vascular endothelial growth factor (VEGF), leading to angiogenesis and increased vascular permeability, which are pathological features of inflammatory lesions that are seen in synovial tissues of RA or edematous lesions of remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome [24] Moreover, it has been reported that IL-6 promotes keratinocyte proliferation [25] or the synthesis of collagen in dermal fibroblasts and their differentiation into myofibroblasts, which may account for skin fibrosis in patients with systemic sclerosis (SSc) [26]. In addition, IL-6 interacts with vascular endothelial cells, the endocrine system including the hypothalamic-pituitary-adrenal axis, neuropsychological systems, and other systems.

3. IL-6 signaling pathway

The IL-6R-signaling system is made up of two receptor chains and downstream signaling molecules [27]. The IL-6R constitutes the IL-6-binding chain, which occurs in two forms, 80 kDa transmembrane IL-6R and 50–55 kDa sIL-6R [28], while 130 kDa gp130 constitutes the signal-transuding chain [29]. The expression of transmembrane IL-6R is limited to cells such as hepatocytes and leukocytes, while sIL-6R without the cytoplasmic region is present in human serum, and after IL-6 binding to sIL-6R, the resultant complex induces the IL-6 signal on gp130-expressing cells [30]. The pleiotropic effect of IL-6 is explained by the broad range of gp130 expression on various cells [31]. After IL-6 binds to transmembrane IL-6R or sIL-6R, either the IL-6/transmembrane IL-6R or IL-6/sIL-6R complex induces homodimerization of gp130 [32] and triggers a downstream signal cascade, the classic signaling pathway or trans-signaling pathway, respectively [33,34]. The activated IL-6R complex is generated in the form of a hexameric structure comprising two molecules each of IL-6, IL-6R and gp130 [35]. Of these components, IL-6R is a unique binding-receptor for IL-6, whereas the signal-transducing chain gp130 is shared by members of the IL-6 family of cytokines, including leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), IL-11, cardiotrophin 1 (CTF1), cardiotrophin-like cytokine (CLC), IL-27, and IL-35. While each cytokine binds to its specific binding receptor, all of these cytokines use the same gp130 for their signal transmissions [36]. This molecular mechanism, in which the IL-6 family of cytokines uses a common signal-transducer, solved the long-standing mystery of why members of the IL-6 family of cytokines show functional redundancy.

Activation of gp130 in turn triggers activation of downstream signaling molecules, that is, the Janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3) pathway and the JAK-SH2-domain containing protein tyrosine phosphatase-2 (SHP-2)-mitogen-activated protein (MAP) kinase pathway. The induction of various sets of IL-6 responsive genes, including acute-phase proteins, is accounted for by the activation of the transcription factor STAT3, which also stimulates the expression of the suppressor of cytokine signaling 1 (SOCS1) and SOCS3. In this context, SOCS1 binds to tyrosine-phosphorylated JAK [37], whereas SOCS3 binds to tyrosine-phosphorylated gp130 to stop IL-6 signaling by means of a negative feedback loop [38].

4. Regulatory mechanism of IL-6 synthesis

IL-6 functions as a mediator for notification of the occurrence of some emergent event. IL-6 is generated in the infectious lesion, and in the event of tissue damage it sends out a warning signal to the entire body. The signature of exogenous pathogens, known as pathogen-associated molecular patterns (PAMPs), is recognized in the infected lesion by pathogen recognition receptors (PRRs) of immune cells such as monocytes and macrophages [39],

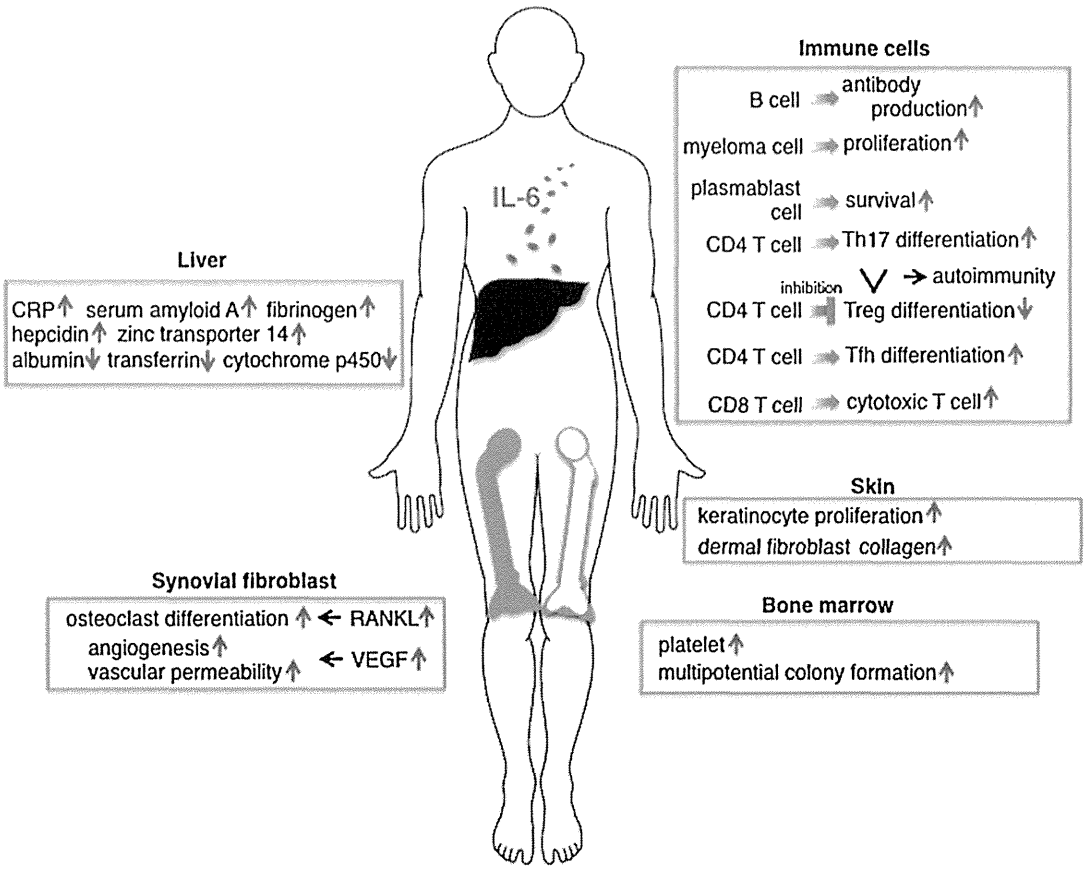

Fig. 1. Pleiotropic activity of IL-6. IL-6 has pleiotropic effects on immune cells, bone marrow cells, hepatocytes, and other types of cells. Dysregulation of IL-6 production contributes to pathological conditions. In hepatocytes, IL-6 induces the expression of acute-phase proteins including CRP, serum amyloid A, fibrinogen, hepcidin, and zinc transporter 14, whereas it inhibits production of albumin, transferrin, and cytochrome p450. IL-6 also plays a role in immune cells by promoting differentiation or proliferation of B and T cells. Moreover, IL-6 can stimulate several non-immune cells, such as synovial fibroblasts, bone marrow cells, and dermal cells. CRP, C-reactive protein; RANKL, receptor activator of nuclear factor of kappa B (NF-kB) ligand; VEGF, vascular endothelial growth factor; Treg, regulatory T cell; Tfh, T follicular helper cell.

while damage-associated molecular patterns (DAMPs), which are released from damaged or dying cells in noninfectious inflammation caused by burns or trauma, promote IL-6 synthesis [40]. Not only immune-competent cells but also mesenchymal cells, endothelial cells, fibroblasts, and many other cells are reportedly able to produce IL-6 in response to various stimuli [21]. IL-6 synthesis is tightly regulated both transcriptionally and posttranscriptionally [41].

4.1. Transcriptional regulation of IL-6

A number of transcription factors regulate IL-6 gene transcription. The functional cis-regulatory elements in the human IL-6 gene 5′ flanking region contain binding sites for NF-kB, specificity protein 1 (SP1), nuclear factor IL6 (NF-IL6), activator protein 1 (AP-1), and interferon regulatory factor 1 (IRF-1) [41,42]. Activation of cis-regulatory elements by stimulation with IL-1, tumor necrosis factor (TNF), Toll-like receptor (TLR)-mediated signal, and forskolin lead to activation of the IL-6 promoter.

An interesting finding is that some viral products enhance the DNA binding activity of NF-kB and/or NF-IL6, which results in an increase in IL-6 mRNA transcription [41]. These include the transactivator protein (Tax) derived from the human T lymphotropic virus 1 (HTLV-1), the transactivator of the transcription (TAT) protein of the human immunodeficiency virus 1 (HIV-1), and the human hepatitis B virus X protein.

In addition, some microRNAs directly or indirectly regulate transcription activity [41]. Interaction of microRNA-155 with the 3′-untranslated regions (UTR) of NF-IL6 suppresses NF-IL6 expression, while microRNA-146a/b indirectly suppresses transcription of IL-6 by targeting IL-1 receptor-associated kinase 1 (IRAK1).

4.2. Posttranscriptional regulation of IL-6

As for posttranscriptional regulation of cytokine expression, cytokine mRNA is controlled through both the 5′- and 3′-UTR [43]. Initiation of mRNA translation is affected by the 5′-UTR, and the stability of mRNA by AU-rich elements (AREs) located in the 3′-UTR [44]. A number of RNA-binding proteins and microRNAs bind to the 3′-UTRs and regulate the stability of IL-6 mRNA [41]. For example, IL-6 mRNA stabilization is promoted by MAP kinase (MAPK) p38α and by the Kaposi sarcoma-associated herpes virus (KSHV) open reading frame (ORF) 57 by competing with the binding of microRNA-608 to IL-6 mRNA. Other RNA-binding proteins such as tristetraprolin (TTP) and butyrate response factor-1 (BRF-1) and -2, however, promote IL-6 mRNA degradation, while IL-6 mRNA levels are reduced by microRNAs such as microRNA-365 and -608 through direct interaction with IL-6 3′-UTR.

In addition to these regulators, a nuclease known as regulatory RNase-1 (Regnase-1) destabilizes IL-6 mRNA, and Regnase-1 knockout mice spontaneously develop autoimmune diseases with splenomegaly and lymphadenopathy [45]. The inhibitor of NF-kB (IkB) kinase (IKK) complex controls IL-6 mRNA stability by phosphorylating Regnase-1 in response to IL-1 or TLR stimulation [46]. Phosphorylated Regnase-1 then undergoes ubiquitination and degradation. Regnase-1, when re-expressed in IL-1- or

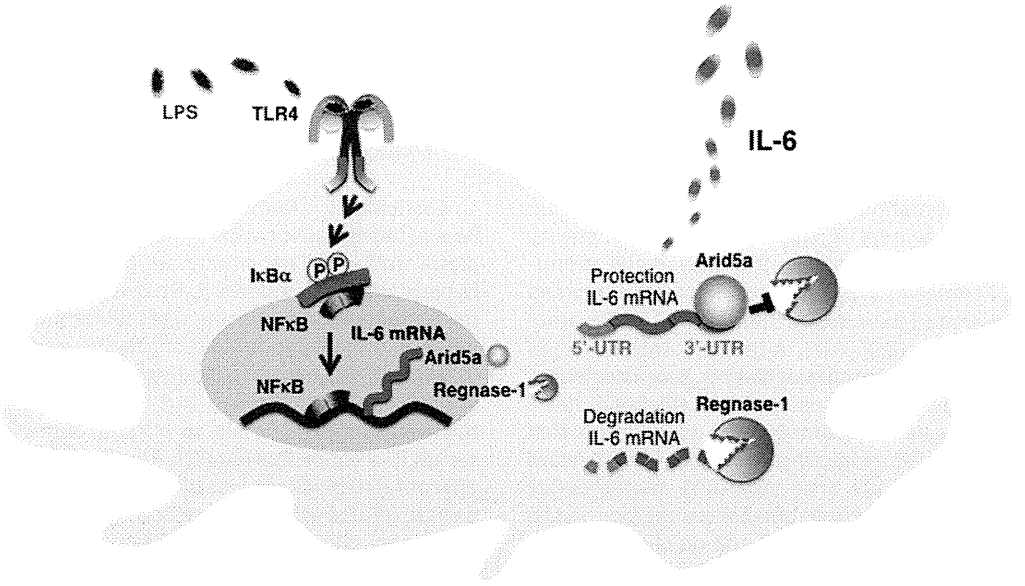

Fig. 2. Regulatory mechanism of IL-6 production. In the innate immune response, pathogen-associated molecular patterns are recognized by pathogen recognition receptors to induce proinflammatory cytokines; for example, TLR4 recognizes LPS, which is the component of the outer membrane of Gram-negative bacteria. TLR4 activates the NF-kB signaling pathway and promotes the transcription of IL-6 mRNA. Regnase-1 promotes IL-6 mRNA degradation, whereas Arid5a inhibits the destabilizing effect of Regnase-1. The balance between Arid5a and Regnase-1 is important for the regulation of IL-6 mRNA. LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; NF-kB, nuclear factor of kappa beta; IkB, inhibitor of NF-kB; UTR, untranslated region.

TLR-activated cells, exhibits delayed kinetics, and 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 IkBα, activating transcription, but also Regnase-1, releasing the "brake" on IL-6 mRNA expression.

In contrast, we have recently identified a novel RNA-binding protein, AT-rich interactive domain-containing protein 5a (Arid5a), which binds to the 3′-UTR of IL-6 mRNA, resulting in the selective stabilization of IL-6 but not of TNFα or IL-12 mRNA [47]. Arid5a expression is increased in macrophages in response to lipopolysaccharide (LPS), IL-1β, or IL-6 and is also induced under Th17-polarizing conditions in T cells. We also found that Arid5a gene deficiency abolishes increased IL-6 levels in LPS-injected mice and preferential Th17 cell development in experimental autoimmune encephalomyelitis. Furthermore, Arid5a counteracts the destabilizing function of Regnase-1 on IL-6 mRNA, indicating that the balance between Arid5a and Regnase-1 plays an important role in IL-6 mRNA stability and that the predominance of Arid5a over Regnase-1 promotes inflammatory processes and possibly induces the development of inflammatory autoimmune diseases (Fig. 2).

5. Pathological role of IL-6 in various inflammatory autoimmune diseases

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 recruitment of SOCS [37,38]. At the same time, IL-6 synthesis ceases, resulting in normalization of serum levels of acute-phase proteins such as CRP and SAA. However, dysregulated and persistent IL-6 production via mostly unknown mechanisms, one of which is, however, possibly due to an imbalance between Arid5a and Regnase-1, in certain cell populations leads to the development of various diseases. The first association of IL-6 with disease development was demonstrated in a case of cardiac myxoma. Fluid obtained from the myxoma tissue of a patient who presented with fever, polyarthritis, elevated CRP level, anemia, and hypergammaglobulinemia with positivity for anti-nuclear factor was cultured and found to contain a large quantity of IL-6, which suggested that IL-6 may contribute to chronic inflammation and autoimmunity [48]. Subsequent studies have demonstrated that dysregulation of IL-6 production occurs in the synovial fluids of RA [49], swollen lymph nodes of Castleman's disease [50], myeloma cells [4], and peripheral blood cells or involved tissues in various other inflammatory autoimmune diseases [21].

Moreover, the pathological role of IL-6 in disease development has been verified in animal models of diseases as well as the findings that IL-6 blockade by gene knockout or administration of anti-IL-6 or anti-IL-6R Ab can result in the preventive or therapeutic suppression of such disease development. For example, IL-6 blockade resulted in a reduction in susceptibility to Castleman's disease-like symptoms in IL-6 transgenic mice [51]. Similar effects were observed in models of RA [9,52,53] systemic lupus erythematosus (SLE) [54], SSc [55,56], inflammatory myopathies [57], experimental autoimmune encephalomyelitis [10], experimental autoimmune uveoretinitis [11], and other inflammatory autoimmune diseases.

6. A new era for the treatment of inflammatory autoimmune diseases by IL-6 blockade strategy

In view of the pathological role of IL-6 in various inflammatory autoimmune diseases, it was expected that IL-6 targeting would constitute a novel therapeutic strategy against these diseases [58,59]. Then, tocilizumab, a humanized anti-IL-6R monoclonal Ab of the IgG1 class, was generated by grafting the complementarity determining regions of a mouse anti-human IL-6R Ab onto human IgG1 [60]. Tocilizumab can block IL-6-mediated signal transduction by inhibiting IL-6 binding to transmembrane IL-6R and sIL-6R. Through numerous worldwide clinical trials, the outstanding efficacy, tolerability, and safety of tocilizumab were verified. Based on these clinical trial results, tocilizumab has been approved for the

treatment of RA in more than 100 countries [59,61], as well as for sJIA in Japan, India, the USA, and the EU [62,63], and for Castleman's disease [64,65] in Japan and India.

6.1. Efficacy of tocilizumab in rheumatoid arthritis

RA is an immune-mediated chronic disease, characterized by systemic and joint inflammation, which causes joint destruction and leads to great loss in activity of daily living (ADL) and quality of life (QOL) [66]. Worldwide clinical trials proved the prominent efficacy of tocilizumab in suppression of disease activity and protection of progression of joint destruction, as well as the ameliorative effect in ADL and QOL [67]. Although other biologics including TNF inhibitors, T-cell stimulator blocker, B-cell depletory, or IL-1R antagonist are currently used for RA, tocilizumab has a unique characteristic feature. Tocilizumab is the only biologic that as monotherapy proved to be more efficacious than the standard disease-modifying antirheumatic drug (DMARD), methotrexate [68,69]. The direct comparison of tocilizumab monotherapy and its combination therapy with methotrexate found no clinically relevant superiority of the combination strategy over the monotherapy [70]. Moreover, the direct comparison of tocilizumab and adalimumab, a fully human anti-TNFα Ab, showed that as monotherapy tocilizumab was superior to adalimumab, as determined by several indices of disease activity in RA patients for whom methotrexate was deemed inappropriate [71]. Indeed, the newest RA management recommendation by the European League Against Rheumatism (EULAR) indicates that tocilizumab is positioned as the first-line biologic that rheumatologists should choose, especially in patients for whom biological monotherapy must be initiated [72]. Tocilizumab is now indicated for moderate to severe RA patients by intravenous (IV) injection of 4 mg/kg (followed by an increase to 8 mg/kg, depending on clinical response in the USA) or 8 mg/kg every 4 weeks.

More recently, in addition to IV injection of tocilizumab, a subcutaneous (SC) injection option was developed [73,74]. The non-inferiority of TCZ-SC 162 mg weekly to TCZ-IV 8 mg/kg every 4 weeks was demonstrated in combination with DMARDs including methotrexate [73]. In addition, TCZ-SC monotherapy (162 mg biweekly without MTX) was also comparable in efficacy to TCZ-IV monotherapy [74]. Therefore, patients can choose the administrative route based on their preference.

6.2. Efficacy of tocilizumab in systemic juvenile idiopathic arthritis

sJIA is a subtype of chronic childhood arthritis that leads to joint destruction, functional disability, and growth impairment, accompanied by systemic inflammation [75]. IL-6 is markedly elevated in blood and synovial fluid of sJIA patients, and their IL-6 level is correlated with disease activity. A randomized, double-blind, placebo-controlled, withdrawal phase III trial for 56 patients with sJIA showed the American College of Rheumatology (ACR) Pedi 30%, 50%, and 70% responses in 91%, 86%, and 68% of the patients, respectively [62]. Based on its outstanding efficacy for JIA, tocilizumab was approved as the first biologic drug for the treatment of sJIA in Japan. 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, depending on body weight, every 2 weeks). At week 12, the primary endpoint (an absence of fever + an improvement of 30% or more in at least three of the six variables in the ACR core set for JIA) was met in significantly more patients in the tocilizumab-treated group than in the placebo group (85% vs. 24%, $P < 0.001$) [63]. At week 52, 82% or 59% of the patients who received tocilizumab attained 70% or 90% improvement, respectively. The striking responsiveness of sJIA to tocilizumab has led to the recognition of the start of a new era in the treatment of this disease, which had been long considered to be one of the most intractable juvenile diseases [76].

6.3. Efficacy of tocilizumab in Castleman's disease

Castleman's disease is a lymphoproliferative disease with benign hyperplastic lymph nodes characterized by follicular hyperplasia and capillary proliferation accompanied by endothelial hyperplasia. Dysregulated IL-6 expression generated by transgenic mice produced a syndrome resembling Castleman's disease [77], while IL-6 blockade inhibited inflammatory manifestations [51]. IL-6 was highly expressed in hyperplastic lymph nodes of patients with Castleman's disease and surgical removal of the solitary involved lymph node led to clinical improvement and reduced serum IL-6 concentration [50]. The first evidence of the beneficial effect of IL-6 blockade was observed in a patient with Castleman's disease treated with a mouse anti-IL-6 Ab [78]. Subsequently, two open-label clinical trials of tocilizumab for Castleman's disease showed its marked ameliorative effect in clinical symptoms and laboratory findings [64,65], leading to its approval as an orphan drug for Castleman's disease in Japan in 2005.

6.4. Additional candidate diseases for tocilizumab treatment

Case reports, series, and pilot studies of the off-label application of tocilizumab have provided favorable results indicating that tocilizumab may be used for the treatment of various intractable inflammatory autoimmune diseases [59,61]. Among candidate diseases, the results accumulated so far strongly suggest that IL-6 blockade may become an innovative therapeutic strategy for SSc, large-vessel vasculitis, polymyalgia rheumatica (PMR), amyloid A amyloidosis, NMO, adult-onset Still's disease (AOSD), and cytokine release syndrome.

SSc is a connective tissue disorder characterized by tissue fibrosis, vasculopathy, and immune abnormalities [79]. Numerous studies have analyzed the pathological mechanisms of SSc, but no effective treatment has yet been established. IL-6 is a therapeutic target cytokine in SSc because of its excessive expression in involved skin; IL-6 induces collagen production as well as α-smooth muscle actin (α-SMA) expression by dermal fibroblasts and promotes endothelial cell activation and apoptosis in endothelial cell-neutrophil co-cultures. Moreover, in SSc models immunized with DNA topoisomerase 1 and Freund's complete adjuvant or injected with bleomycin, IL-6 deficiency produced by either administration of anti-IL-6R Ab or gene knockout suppressed fibroblast activation, which resulted in reduced dermal fibrosis [55,56]. We observed beneficial effects of tocilizumab for two patients with SSc [80]. Histological analysis revealed the thinning of collagen fiber bundles and the reduction of activated myofibroblasts in the dermis after a 6-month treatment [56]. These findings indicate that IL-6 blockade strategy is a promising approach for the treatment of SSc. A phase II/III, multicenter, randomized, double-blind, placebo-controlled study is in progress to assess the efficacy and safety of tocilizumab versus placebo in patients with systemic sclerosis (NCT01532869).

The pathological significance of IL-6 has been well documented in forms of large-vessel vasculitis, such as giant cell arteritis (GCA) and Takayasu arteritis (TA) [81]. The serum concentrations of IL-6 are elevated at the onset and during clinical relapse, while tissue-infiltrating cells reportedly produce major quantities of IL-6 as well as Th1-type cytokine IFN-γ in patients with GCA and TA. Tocilizumab treatment has been reported to have rapid and prominent beneficial effects on 27 patients with GCA and 20 patients with TA, resulting in the successful tapering of corticosteroids for all GCA

patients except one. Moreover, tocilizumab even as monotherapy could induce disease remission in 5 patients with GCA. These results strongly suggest that IL-6 inhibition may become a novel therapeutic strategy for large-vessel vasculitis. Phase II and III, randomized, double-blind, placebo controlled studies of tocilizumab in patients with giant cell arteritis (NCT01450137 and NCT01791153) and a phase II open trial to evaluate the add-on efficacy of tocilizumab to corticosteroids in Horton's disease (GCA) (NCT01910038) are in progress.

PMR is a chronic inflammatory disorder that affects the elderly and is characterized by aching and morning stiffness in the shoulders, neck, and pelvic girdles [82]. PMR can occur in its isolated form or may be associated with GCA. Although its pathogenesis remains unknown, IL-6 has been identified as the only cytokine detected at a consistently high level in patients with the active form of the disease, and as the most sensitive indicator of disease activity. In fact, tocilizumab was clinically efficacious for 6 patients with PMR who relapsed repeatedly and experienced corticosteroid-related adverse events, resulting in the successful tapering of corticosteroids, while the treatment as monotherapy induced remission in 4 PMR patients with fresh onset of the disease. Two phase II clinical trials of tocilizumab in the treatment of polymyalgia rheumatica (NCT01396317 and NCT01713842) are under investigation.

A serious complication of chronic inflammatory diseases is amyloid A amyloidosis, in which amyloid fibril deposition causes progressive deterioration in various organs [16]. SAA, an acute phase protein produced in the liver mainly by IL-6, is an amyloid fibril precursor protein, and a sustained high concentration of SAA correlates with a progression of renal amyloid diseases. Previously, it was recognized that the only way to treat amyloid A amyloidosis is intensive therapy for the underlying chronic inflammatory diseases, but recently several therapeutic strategies have been proposed for the specific treatment of amyloid A amyloidosis. The inhibition of SAA synthesis appears to be the most suitable approach, since chronic suppression of serum levels of SAA (less than 10 mg/L) was found to lead to a regression or stabilization of the amyloid load [17]. Tocilizumab is the most powerful agent to inhibit SAA production, since its administration caused a marked reduction of serum concentrations of SAA irrespective of the underlying diseases [16,65]. Furthermore, case studies of amyloid A amyloidosis complicated with RA, JIA, vasculitis syndrome, Behcet's disease, and latent tuberculosis reported on the striking clinical effect of tocilizumab on gastrointestinal symptoms and renal function [16,83]. This evidence strongly suggests that IL-6 blockade may be an innovative strategy for amyloid A amyloidosis irrespective of the underlying diseases [16].

NMO is a chronic inflammatory disorder predominantly affecting the spinal cord and optic nerves, in which autoantibodies directed against AQP4 play a pathologic role [84]. Several studies have reported a marked increase of IL-6 in the cerebrospinal fluid of patients with NMO. Moreover, it was reported that the population of plasmablasts showing the $CD19^{int}CD27^{high}CD38^{high}CD180^{negative}$ phenotype was increased in the peripheral blood of NMO patients and that anti-AQP4 Abs were mainly produced by the plasmablasts [5]. IL-6 enhanced the survival of plasmablasts as well as AQP4 Ab secretion, whereas tocilizumab could lessen their survival. Indeed, clinical improvement and reduction of serum levels of anti-AQP4 Abs were reported in an NMO patient who received tocilizumab therapy [85]. Moreover, the prominent beneficial effects of tocilizumab in several other refractory NMO patients to conventional treatment regimens suggest that IL-6 blockade could be a novel therapeutic strategy for NMO.

As described before, tocilizumab was approved for the treatment of sJIA due to its outstanding efficacy [62,63]. AOSD is a chronic inflammatory disease characterized by four cardinal symptoms; spiking fever, evanescent maculopapular rash, arthritis, and leukocytosis [86]. Pathologically, it resembles sJIA and is considered to be an adult-onset type of sJIA. As expectedly, numerous case and pilot studies have shown that tocilizumab treatment improved clinical symptoms and signs of AOSD patients who had been refractory to conventional treatment and even biologics including TNF inhibitors and anakinra. These findings also indicate that tocilizumab may become a first-line biologic for the treatment of AOSD.

Cytokine release syndrome is a potentially fatal immune reaction induced by hyperactivation of T cells and macrophages. Experimentally, inhalation by mice of peroxidized phospholipids induced a cytokine storm resulting from a marked increase in the production of IL-6 but not TNF [87]. Two recent reports showed that the cytokine release syndrome, which occurred in two patients with acute lymphoblastic leukemia (ALL) treated with chimeric antigen receptor-modified T cells with specificity for CD19 (CTL019 cells) or in one ALL patient treated with blinatumomab, a CD19/CD3-bispecific T cell receptor-engaging Ab, could be rescued by tocilizumab [88,89], suggesting that IL-6 inhibition may become an innovative therapeutic approach for T cell-mediated cytokine release syndrome.

Furthermore, tocilizumab was reportedly efficacious for numerous other inflammatory autoimmune diseases [59,61,90]. These diseases comprise autoimmune diseases including SLE, polymyositis, relapsing polychondritis, autoimmune hemolytic anemia, acquired hemophilia, and Cogan's syndrome; chronic inflammatory diseases such as Crohn's disease, Behcet's disease, uveitis, RS3PE syndrome, graft-versus-host disease (GVHD), pulmonary hypertension, and IgG4-related disease; and autoinflammatory syndromes such as TNF receptor-associated periodic syndrome (TRAPS), chronic inflammatory neurological cutaneous articular syndrome (CINCA), and Schnitzler syndrome, as well as other diseases including atherosclerosis, type 2 diabetes mellitus, atopic dermatitis, sciatica, and amyotrophic lateral sclerosis. Further clinical evaluations are essential to determine additional indications for tocilizumab therapy.

7. Concluding remarks

On the basis of clarification of the whole picture of the IL-6-mediated signaling system, the pathological role of IL-6 in various diseases, and the progress in bioengineering techniques, a humanized anti-IL-6R monoclonal Ab was developed (Fig. 3). Clinical trials of tocilizumab started in the late 1990s, and this biologic was first approved for the treatment of Castleman's disease in 2005 in Japan, nearly 20 years after the successful molecular cloning of the IL-6 gene. During the following years, tocilizumab has become one of the first-line biologics for the treatment of moderate to severe RA in more than 100 countries and sJIA in Japan, India, the USA, and the EU, and is the only approved drug for Castleman's disease in Japan and India. This great success has evolved to a paradigm shift in the treatment of such diseases and has actually accelerated the development of other IL-6 inhibitors [33,91]. It is anticipated that during the next decade IL-6 inhibitors will be widely used for the treatment of various as yet intractable diseases, and its application will overcome the refractory nature of such diseases.

To achieve this goal, however, there are several hurdles to overcome. First, additional clinical trials will be needed to evaluate the efficacy and safety of tocilizumab for various diseases. The second hurdle is to clarify the mechanisms that render tocilizumab efficacious for phenotypically different diseases. In the case of RA, it has been demonstrated that tocilizumab treatment led to improvement in systemic and joint inflammatory markers [67,91,92]. Moreover, recent preliminary results indicate that tocilizumab treatment can

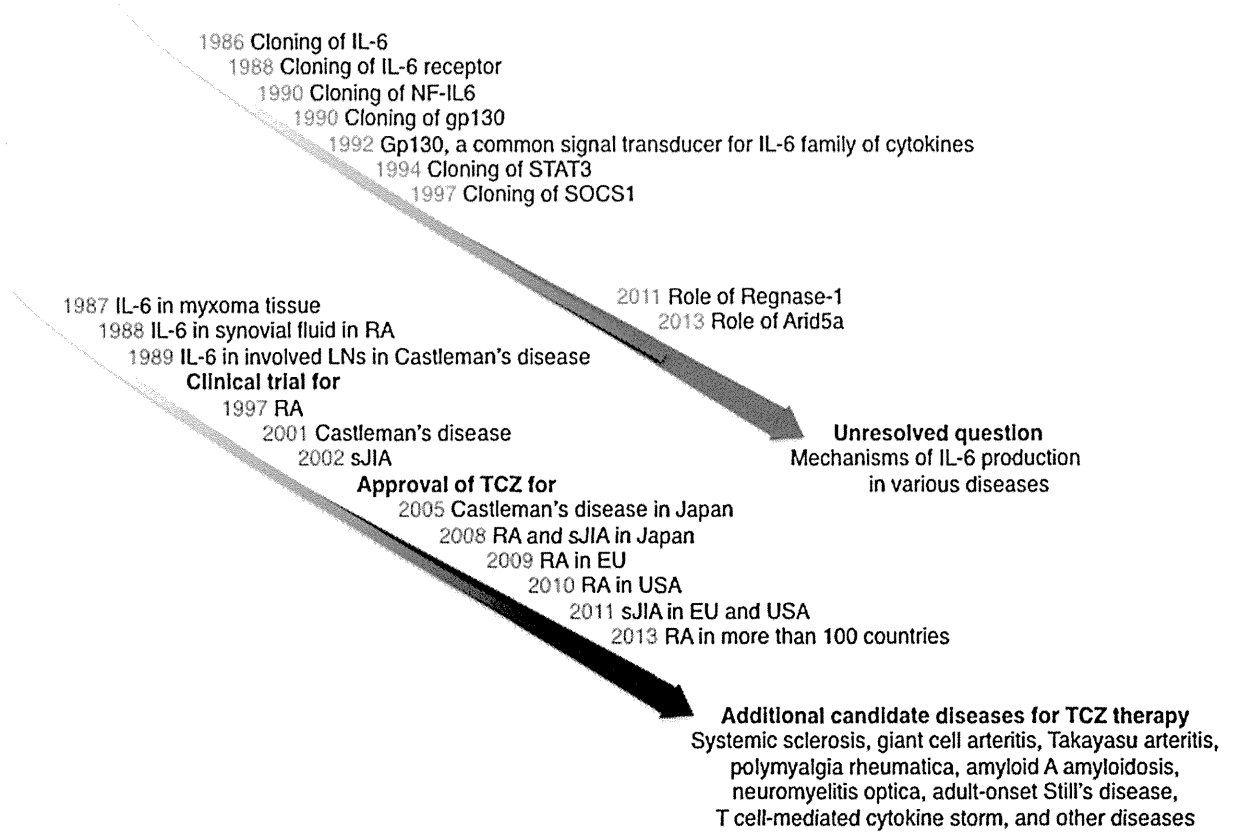

Fig. 3. Major discoveries in IL-6-related research and milestones of IL-6 targeting strategy for diseases. Basic research for IL-6 clarified its receptor system, signaling cascade, and the molecular basis of the characteristic features of cytokines, redundancy and pleiotropy. In parallel with the development of basic research, clinical studies revealed its pathological significance in disease development. These findings led to the concept that IL-6 blockade would constitute a novel therapeutic strategy for inflammatory autoimmune diseases. Indeed, tocilizumab, a humanized anti-IL-6R antibody became an innovative biologic for the treatment of refractory diseases such as RA, sJIA, and Castleman's disease. It is expected that this strategy would be widely applicable for other intractable diseases. NF-IL6, nuclear factor IL-6; STAT3, signal transducer and activator of transcription 3; SOCS1, suppressor of cytokine signaling 1; RA, rheumatoid arthritis; LNs, lymph nodes; sJIA, systemic juvenile idiopathic arthritis; TCZ, tocilizumab.

correct the imbalance between Th17 and Treg in peripheral blood CD4-positive T cells [93,94], while it was also demonstrated that the treatment caused a reduction in the capacity of T cells to produce IL-21 in association with a decreased level of serum IgG4 class anti-cyclic citrullinated peptide Ab in RA [95]. As described before, tocilizumab treatment was found to improve clinical symptoms and reduce serum anti-AQP4 Ab titers, perhaps by inhibiting cell survival of the plasmablasts secreting this Ab [5,85]. If IL-6 blockade can actually correct these immunological abnormalities such as the imbalance of effector CD4-positive T-cell subsets and autoantibody production, it will in fact be possible to use tocilizumab for the treatment of a wide variety of inflammatory autoimmune diseases.

Finally, although clarification of the whole picture of the IL-6-mediated signaling pathway solved the long-standing mystery of why IL-6 shows redundant and pleiotropic activity, we would like to emphasize that the mystery remains as to why IL-6 is persistently expressed in various diseases. Accurate and detailed analyses of proteins including Arid5a and Regnase-1 and of microRNAs that regulate IL-6 synthesis will be helpful for solving this mystery, while clarification of the mechanism(s) involved will inspire the identification of more specific target molecules and investigations into the pathogenesis of specific diseases.

Conflict of interest

T. Kishimoto holds a patent for tocilizumab and has received royalties for Actemra. T. Tanaka has received a grant and payment for lectures including service on speaker's bureaus from Chugai Pharmaceutical Co., Ltd. A. Ogata has received a consulting fee as a medical adviser and a grant and payment for lectures including service on speaker's bureaus from Chugai Pharmaceutical Co., Ltd. M. Narazaki has received payment for lectures including service on speaker's bureaus from Chugai Pharmaceutical Co., Ltd.

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Cancer Immunology Research

The Biology and Medical Implications of Interleukin-6

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Masters of Immunology

Cancer Immunology Research

The Biology and Medical Implications of Interleukin-6

Toshio Tanaka[1] and Tadamitsu Kishimoto[2]

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, chemokines, 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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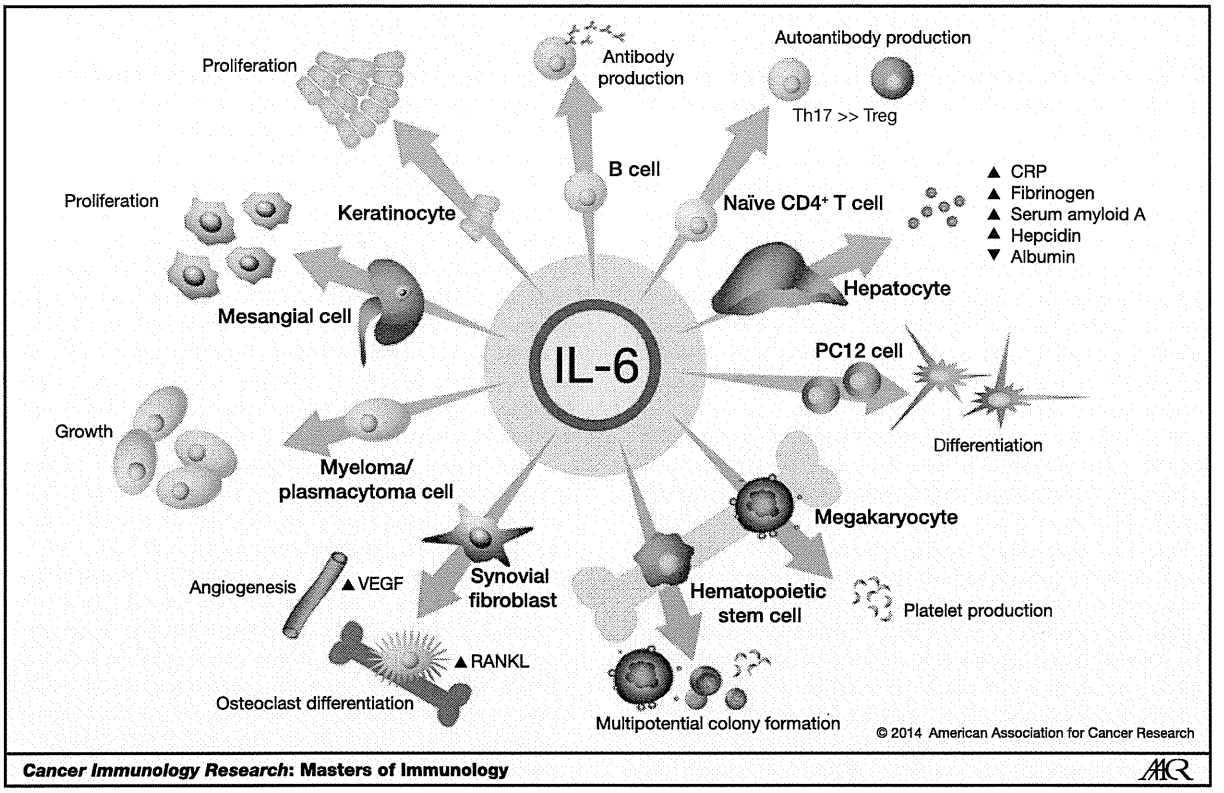

Figure 1. Pleiotropic activity of IL-6. IL-6 acts as a BSF-2, which induces activated B cells into antibody production. IL-6, combined with TGF-β, preferentially promotes the differentiation of naïve $CD4^+$ T cells into Th17 cells, but inhibits TGF-β–induced Treg development. As a consequence, Th17/Treg 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-β2, 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 α1-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-κB 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 pleiotropy 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-κB, 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-κB 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

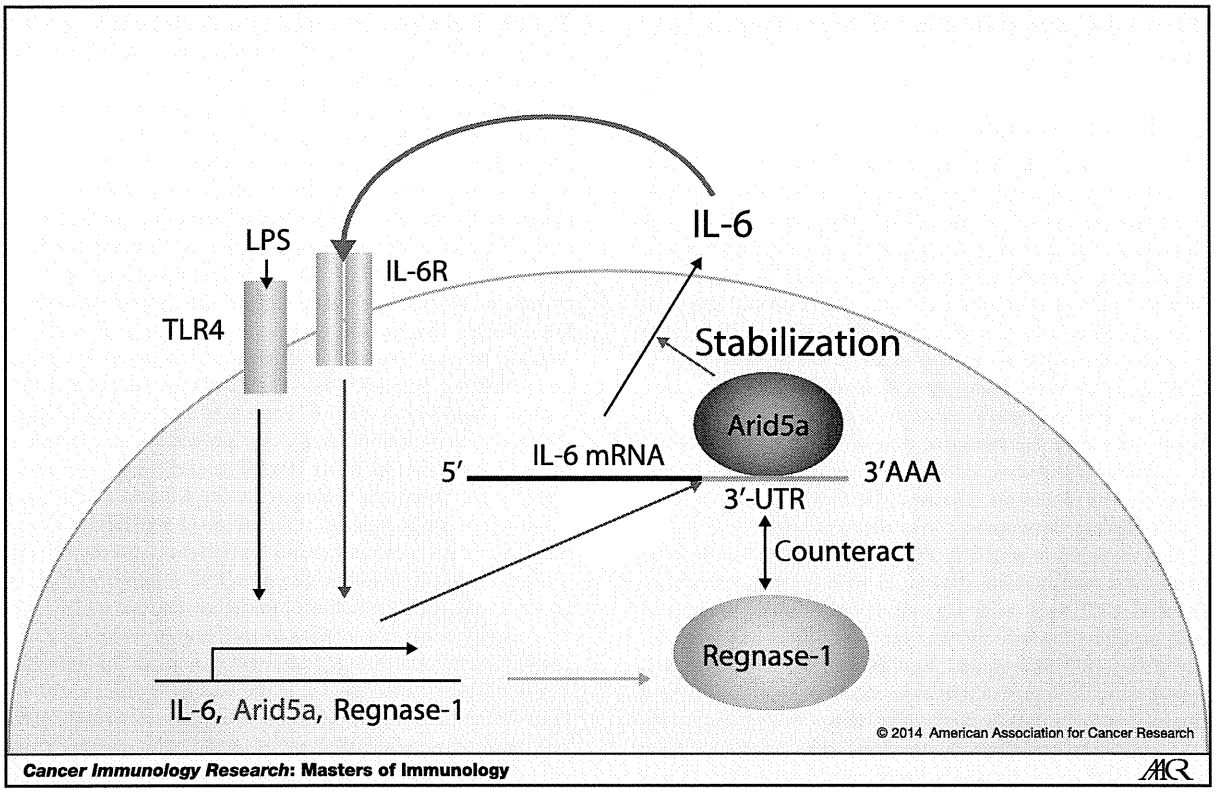

Figure 2. Arid5a counteracts the destabilizing effect of Regnase-1 on IL-6 mRNA. Regnase-1 accelerates IL-6 mRNA degradation, and Arid5a counteracts the destabilizing effect of Regnase-1. The balance between Arid5a and Regnase-1 thus plays an important role in IL-6 mRNA stability.

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 p38α 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 IκB 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 IκBα 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-1β, 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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REVIEW

Monoclonal antibodies in rheumatoid arthritis: comparative effectiveness of tocilizumab with tumor necrosis factor inhibitors

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Abstract: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent joint inflammation, systemic inflammation, and immunological abnormalities. Because cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 play a major role in the development of RA, their targeting could constitute a reasonable novel therapeutic strategy for treating RA. Indeed, worldwide clinical trials of TNF inhibiting biologic disease modifying antirheumatic drugs (bDMARDs) including infliximab, adalimumab, golimumab, certolizumab pegol, and etanercept as well as the humanized anti-human IL-6 receptor antibody, tocilizumab, have demonstrated outstanding clinical efficacy and tolerable safety profiles, resulting in worldwide approval for using these bDMARDs to treat moderate to severe active RA in patients with an inadequate response to synthetic disease modifying antirheumatic drugs (sDMARDs). Although bDMARDs have elicited to a paradigm shift in the treatment of RA due to the prominent efficacy that had not been previously achieved by sDMARDs, a substantial percentage of patients failed primary or secondary responses to bDMARD therapy. Because RA is a heterogeneous disease in which TNF-α and IL-6 play overlapping but distinct pathological roles, further studies are required to determine the best use of TNF inhibitors and tocilizumab in individual RA patients.

Keywords: interleukin-6, rheumatoid arthritis, adalimumab, biologic

Introduction to rheumatoid arthritis (RA) and the development of targeted therapies

RA, a chronic disease affecting 0.5%–1% of adults, is characterized by persistent synovitis, systemic inflammation, and immunological abnormalities.[1,2] Uncontrolled active RA causes joint damage, disability, diminished quality of life, and cardiovascular and other comorbidities. Although its exact pathogenesis is not fully understood, a multistep progression has been proposed for the development of RA.[1] Environment–gene interactions promote a loss of tolerance to self-antigens that contain a citrulline residue generated by posttranslational modification, leading to an anticitrulline response by both T-cells and B-cells. Thereafter, the inflammatory response becomes localized in the joints and synovitis is initiated and perpetuated by positive feedback loops, promoting systemic disorders. Lymphocytes, other inflammatory cells, and their products contribute to the development of RA. For instance, many cytokines have been implicated in the pathogenesis of RA, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-7, IL-15, IL-17A, IL-17F, IL-18, IL-21, IL-23, IL-32, IL-33, and granulocyte-macrophage colony stimulating factor.[1]

Because TNF-α is an important mediator responsible for joint inflammation and destruction, it was the first cytokine to be targeted in the treatment of RA.[2,3]

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