

## Supplement Review

# The paradigm of IL-6: from basic science to medicine

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### Chapter summary

IL-6 is a pleiotropic cytokine with a wide range of biological activities in immune regulation, hematopoiesis, inflammation, and oncogenesis. Its activities are shared by IL-6-related cytokines such as leukemia inhibitory factor and oncostatin M. The pleiotropy and redundancy of IL-6 functions have been identified by using a unique receptor system comprising two functional proteins: an IL-6 receptor (IL-6R) and gp130, the common signal transducer of cytokines related to IL-6. Signal transduction through gp130 is mediated by two pathways: the JAK-STAT (Janus family tyrosine kinase-signal transducer and activator of transcription) pathway and the Ras mitogen-activated protein kinase pathway. The negative regulators of IL-6 signaling have also been identified, although the physiological roles of the molecules are not yet fully understood. The pathological roles of IL-6 have also been clarified in various disease conditions, such as inflammatory, autoimmune, and malignant diseases. On the basis of the findings, a new therapeutic approach to block the IL-6 signal using humanized anti-IL-6R antibody for rheumatoid arthritis, Castleman's disease, and multiple myeloma has been attempted.

**Keywords:** cytokines, gp130, interleukin-6, SOCS, rheumatoid arthritis

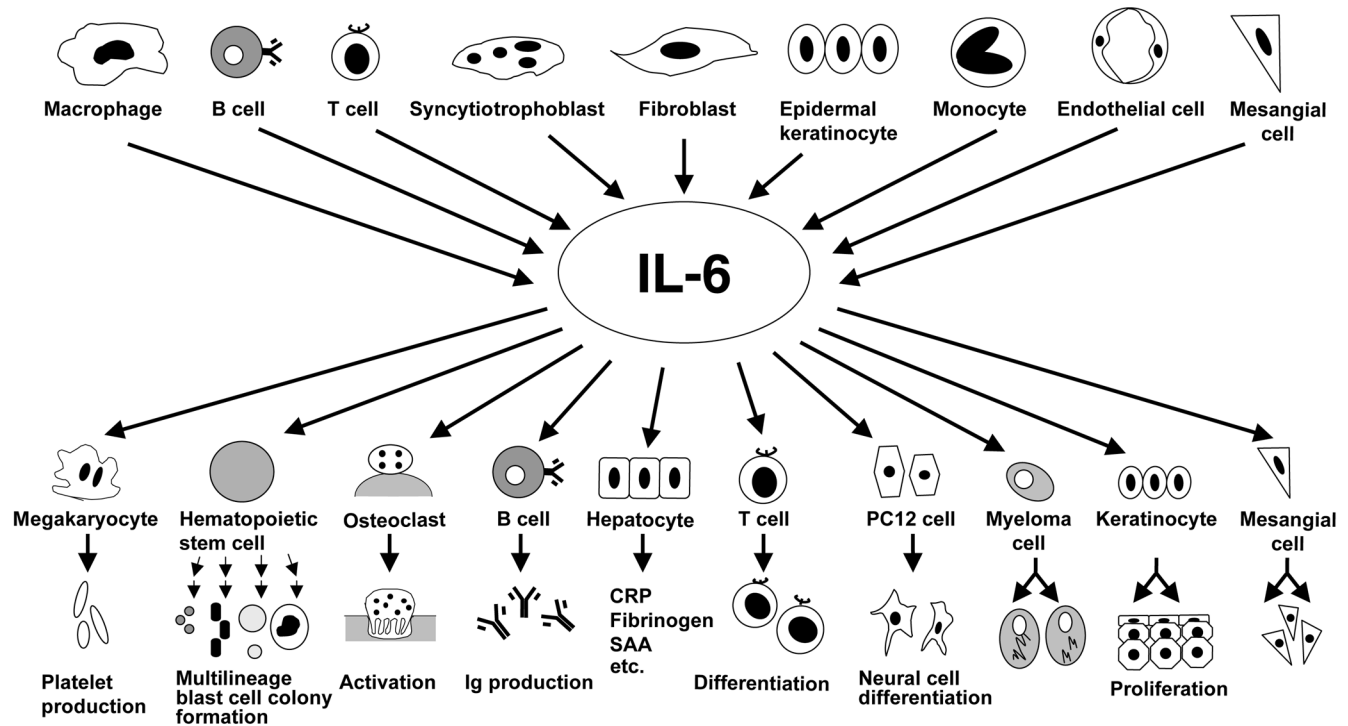
### Identification of IL-6 and its pleiotropic functions

IL-6 was originally identified as an antigen-nonspecific B-cell differentiation factor in the culture supernatants of mitogen- or antigen-stimulated peripheral blood mononuclear cells that induced B cells to produce immunoglobulins [1,2], and was named B-cell stimulatory factor 2 (BSF-2). The cDNA encoding human BSF-2 was cloned in 1986 [3]. Simultaneously, IFN- $\beta$ 2 [4,5] and a 26-kDa protein [6] in fibroblasts were independently cloned by different groups and found to be identical to BSF-2. Later, a hybridoma/plasmacytoma growth factor [7-10] and a hepatocyte-stimulating factor [11-13] were also proven to be the same molecule as BSF-2. Although various names

have been used for this molecule because of its multiple biological activities, it is now known as IL-6.

A pleiotropic cytokine with a wide range of biological activities (Fig. 1), IL-6 is produced by various types of lymphoid and nonlymphoid cells, such as T cells, B cells, monocytes, fibroblasts, keratinocytes, endothelial cells, mesangial cells, and several tumor cells [14]. It induces growth of T cells and differentiation of cytotoxic T cells [15-19] by augmenting the expression of IL-2 receptor [15] and the production of IL-2 [20]. IL-6 acts synergistically with IL-3 to support the formation of multilineage blast cell colonies in hematopoiesis [21-25]. IL-6 also induces differentiation of macrophages [26], megakaryocytes [27-29], and

Figure 1



IL-6-producing cells and biological activities of IL-6. IL-6 is produced by lymphoid and nonlymphoid cells, such as T cells, B cells, monocytes, fibroblasts, keratinocytes, endothelial cells, mesangial cells, and several kinds of tumor cell (top of figure). IL-6 also has a wide range of biological activities on various target cells (bottom of figure).

osteoclasts [30]. In the acute-phase reaction, this cytokine stimulates hepatocytes to produce acute-phase proteins such as C-reactive protein (CRP), fibrinogen,  $\alpha_1$ -antitrypsin, and serum amyloid A [12,13], and it simultaneously suppresses albumin production [11]. It causes leukocytosis and fever when administered *in vivo* [31] and also acts as a growth factor for renal mesangial cells [32], epidermal keratinocytes [33,34], and various types of tumor cells, for example, in plasmacytoma [8], multiple myeloma [35], and renal cell carcinoma [36].

Although IL-6 has pleiotropic effects on various target cells, some of the biological activities are also mediated by other cytokines, such as leukemia inhibitory factor (LIF) and oncostatin M (OSM). The pleiotropy and redundancy of IL-6 functions can be identified by using a unique receptor system of cytokines [14].

**Identification and characterization of IL-6R as the specific receptor of IL-6, and of gp130 as the common signal transducer of the IL-6 superfamily**

We and our colleagues identified the two components of IL-6 receptor (IL-6R), an 80-kDa IL-6-binding protein ( $\alpha$  chain) and a 130-kDa signal transducer known as gp130

( $\beta$  chain), in 1988 and 1990 [37–39], respectively. Although IL-6 cannot directly bind to gp130, it can bind to IL-6R to generate the high-affinity complex of IL-6/IL-6R/gp130. Furthermore, the complex of IL-6 and soluble IL-6R can generate IL-6-mediated signal transduction [38,39]. Another feature of cytokines is the redundancy of their functions. For example, IL-6, LIF, and OSM all induce macrophage differentiation in the myeloid leukemia cell line M1 [40–43] and acute-phase protein synthesis in hepatocytes [11,12,44–46]. An important finding as regards cytokine receptors is that one constituent of a given cytokine receptor is shared by several other cytokine receptors [47]. For example, gp130 is in fact shared by the receptors for such cytokines of the IL-6 superfamily as ciliary neurotrophic factor (CNTF), LIF, OSM, IL-11, and cardiotrophin-1 [14,48,49]. Thus, the molecular mechanisms of redundancy in functions of cytokines of the IL-6 superfamily can be explained at least in part by the sharing of gp130 among their receptors.

Investigations of the IL-6R system have provided evidence that the combination of IL-6 and soluble IL-6R can act on cells that express gp130 but not IL-6R [48]. A complex consisting of a soluble cytokine receptor and its corresponding cytokine acquires different target specificity from

the original cytokine and should therefore express different functions from those of the original cytokine. In fact, we found that doubly transgenic mice expressing human IL-6 and IL-6R showed myocardial hypertrophy [50], indicating that the combination of IL-6 and soluble IL-6R acts on heart muscle cells that express gp130, an action that IL-6 cannot exert by itself. The action leads to the induction of cardiac hypertrophy, so that the effect is similar to that of cardiotrophin-1. This combination of cytokine and its soluble receptor may contribute to the generation of the functional diversity of cytokines in a wide range of other receptor systems and may also play a pathological role in various diseases in which an increase in the serum-soluble form of various cytokine receptors has been reported.

### Clarification of multiple signal cascades in IL-6 signal

As the cytoplasmic domain of most cytokine receptors, including gp130, does not have an intrinsic catalytic domain, one of the most controversial issues before 1993 was the identification of catalytic molecules that associate with cytokine receptors. This issue was resolved by the discovery of several Janus family tyrosine kinases (JAK1, JAK2, JAK3, Tyk-2), which are involved in the transduction of cytokine and hormone signals [51–53]. Furthermore, the signal transducer and activator of transcription (STAT) was found to play a central role in a variety of cytokine signal cascades. Our group and others found that JAK1, JAK2, and Tyk-2 are activated and are tyrosine-phosphorylated in response to IL-6, CNTF, LIF, and OSM [14], and also identified and characterized STAT3 [54]. IL-6 activates STAT1 and STAT5 in addition to STAT3. In the absence of JAK1, the activation of transcriptional factor STATs following stimulation by IL-6 is not effective as long as both JAK2 and Tyk-2 are activated. This finding suggests that there is a hierarchy among gp130-associated JAKs [55].

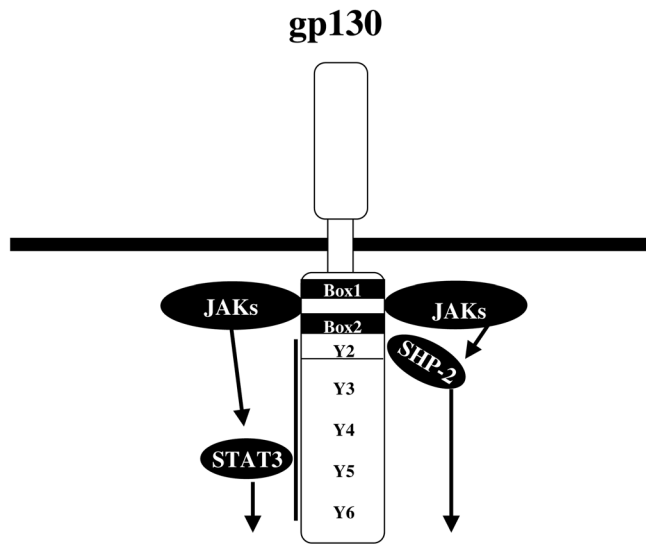
Several research groups, including ours, have identified two types of IL-6 response element (IL-6RE) in the genes encoding acute-phase proteins. The presence of type I IL-6RE, which is a binding site for NF-IL-6 (nuclear factor for IL-6 expression), IL-6DBP (IL-6 vitamin-D-binding protein), and C/EBP $\beta$  [56–59], has been confirmed in the genes for CRP, hemopexin A, and haptoglobin. The binding activity of NF-IL-6 is probably induced by IL-6 through the increased expression of the NF-IL-6 gene rather than through its post-translational modification. Type II IL-6RE is contained in the fibrinogen,  $\alpha_2$ -macroglobin,  $\alpha_1$ -acid glycoprotein, and haptoglobin genes. IL-6 triggers the rapid activation of a nuclear factor, known as the acute-phase response factor, which binds to type II IL-6RE [60]. Purification and molecular cloning of this factor revealed that it is identical to STAT3 [54,61].

We clarified that human gp130 has 277 amino acid residues in its cytoplasmic domain, which contains two

motifs, Box1 and Box2, conserved among the cytokine receptor family (Fig. 2) [39,62,63]. The membrane-proximal region containing Box1 and Box2 was found to be sufficient for the activation of JAK through gp130 [64]. Furthermore, human gp130 has six tyrosine residues in its cytoplasmic domain. Finally, the tyrosine phosphorylation of Src homology protein 2 tyrosine phosphatase-2 (SHP-2), a phosphotyrosine phosphatase, and that of STAT3 depend on the second tyrosine residue (Y2) from the membrane, and on any one of the four tyrosine residues (Y3, Y4, Y5, Y6) in the carboxy terminus that have a glutamine residue at the third position behind tyrosine (Y-X-X-Q) (see Fig. 2) [65,66].

It is known that IL-6 induces growth arrest and macrophage differentiation in the murine myeloid leukemic cell line M1. The essential role of STAT3 in the IL-6-induced macrophage differentiation of M1 cells was demonstrated by using dominant negative forms of STAT3 [67], which inhibit both IL-6-induced growth arrest and macrophage differentiation in M1 transformants. Blocking STAT3 activation inhibits IL-6-induced repression of c-Myb and c-Myc, but not EGR-1 induction [68], while IL-6 enhances the growth of M1 cells when STAT3 is suppressed. Thus, IL-6 simultaneously generates growth-enhancing signals as well as growth-arrest and differentiation-inducing signals, but the former are apparent only when STAT3 activation is suppressed. As for the growth signals, a 65-amino-acid region proximal to the transmembrane domain was found to be sufficient for generating a growth response by using gp130 transfectants of an IL-3-dependent proB-cell line BAF/BO3 [14,63]. However, the membrane-proximal region of 68 amino acids is not sufficient for the induction of tritium thymidine ( $^3\text{H}$ -Tdr) uptake when cells are starved of IL-3. For cell growth, the membrane-proximal region containing 133 amino acid residues is both required and sufficient [69]. Furthermore, at least two distinct signals are required for gp130-induced cell growth: a cell cycle progression signal dependent on the second tyrosine residue, Y2, and possibly mediated by SHP-2, and an antiapoptotic signal dependent on the third tyrosine residue, Y3, and mediated by STAT3 through induction of BCL-2. However, our recent study using mice with STAT3 deficiency in a T-cell-specific manner has revealed that STAT3 activation is involved in IL-6-dependent T cell proliferation through prevention of apoptosis without the need for BCL-2 induction [70]. Thus, STAT3 plays pivotal roles in gp130-mediated signal transduction regulating cell growth, differentiation, and survival. In addition to the JAK–STAT signal transduction pathway, it is known that the Ras mitogen-activated protein (MAP) kinase pathway is also activated through SHP-2 [69] or Shc [71]. Furthermore, nonreceptor tyrosine kinases, such as Btk, Tec, Fes, and Hck [72,73] are activated through the IL-6 receptor, as well as through a variety of other cytokine receptors [74], although the biological significance of these signal transduction pathways remains to be

Figure 2



Schematic structure of gp130. Binding of IL-6 to IL-6R induces homodimerization of gp130, activating JAK associating with gp130 at Box1. This is followed by the tyrosine phosphorylation of the distal part of gp130 and recruitment of STAT3. STAT3 is then tyrosine-phosphorylated by JAK. SHP-2 on the second tyrosine (Y2) residue of gp130 activates the MAP kinase pathway. JAK, Janus family tyrosine kinase; SHP-2, Src homology protein 2 tyrosine phosphatase-2; STAT, signal transducer and activator of transcription; Y(2,3, etc.), (second, third, etc.) tyrosine residue (from the membrane).

clarified. Several distinct signal transduction pathways are generated through different regions of the cytoplasmic domain of gp130. The expression pattern of these signaling molecules determines which set of signaling pathways is activated in a given cell. Furthermore, these signaling pathways may interact with each other and contribute to a variety of biological activities. In fact, a recent study reported that knock-in mutation mice lacking SHP-2 signal showed sustained gp130-induced STAT3 activation; this finding indicates a negative regulatory role of SHP-2 for STAT3 activation [75]. These knock-in mice also displayed splenomegaly and lymphadenopathy and an acute-phase reaction. In contrast, all known mice deficient in the STAT3 binding site, such as the gp130-deficient mouse, died perinatally [75]. However, it has also been reported that mice deficient in STAT3 signal displayed a severe joint disease in association with mitogenic hyper-responsiveness of the synovial cells to the IL-6-family cytokines. This hyper-responsiveness was the result of sustained gp130-mediated SHP-2 activation due to a lack of the SHP-2 inhibitor induced by STAT3 [76].

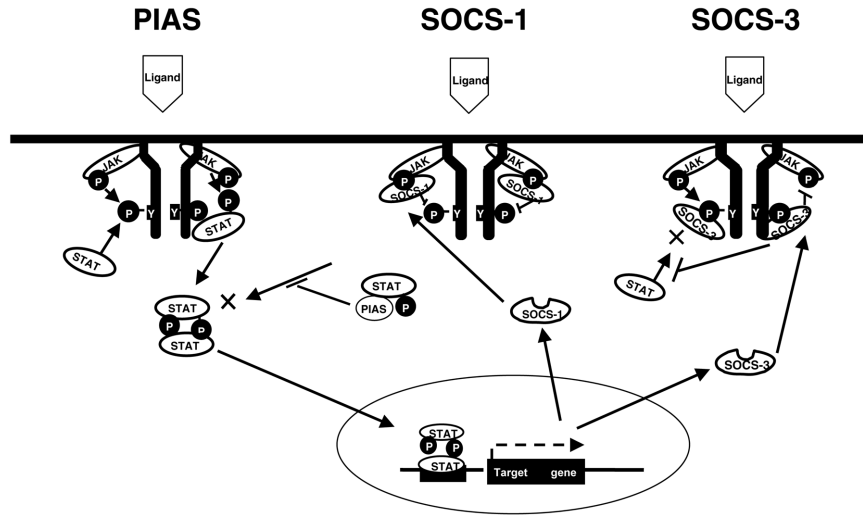
### Identification of new inhibitors of IL-6 signaling

Cytokine signaling, including that of IL-6, is negatively regulated with respect to both magnitude and duration. Recently, it has been found that at least two new families

of inhibitors contribute to the negative regulation of cytokine signaling: the suppressor of cytokine signaling (SOCS) and the protein inhibitors of activated STATs (PIAS) (Fig. 3). In 1997, two other groups and ours identified SOCS-1, also known as SSI-1 (STAT-induced STAT inhibitor 1) or JAB-1 (JAK-binding protein 1), as a negative regulatory molecule of IL-6 signaling on the basis of its binding to JAK [77–79]. Subsequently, database searches have shown that the SOCS family now includes eight members (CIS and SOCS1–SOCS7), all of which are characterized by a central SH2 domain flanked by an N-terminal region containing a conserved motif known as the SOCS box [77,80–82]. mRNA of SOCS-1, SOCS-2, and SOCS-3 is induced by cytokines such as IL-6, IFN- $\gamma$ , IL-4, and granulocyte-colony-stimulating factor and several other members, and they inhibit cytokine-activated JAK–STAT signal pathways [83–85]. However, the factors that induce mRNA of the other SOCS families, such as SOCS-4–7, have not been clarified and their functions have not been thoroughly characterized.

SOCS-1 and SOCS-3 are especially well known as inhibitors of cytokine signaling [86], acting through different mechanisms. SOCS-1 directly interacts with JAKs, and thus inhibits their catalytic activity. SOCS-3 also inhibits JAK activity (but only partially in comparison with SOCS-1) although the augmentation of its effect in the presence of receptors suggests that SOCS-3 inhibits cytokine signaling by binding to the receptor complex. In the IL-6 signal cascade, the SHP-2 interaction site of gp130 has also been shown to be a SOCS-3 contact site, so that SOCS-3 may compete for the SHP-2–gp130 interaction site [86,87]. Gene-targeting mice of the SOCS family were used to show that SOCS-2 and SOCS-3 are critical molecules for, respectively, GH/IGF-1 and EPO signaling *in vivo* [88,89]. In particular, mice deficient in SOCS-2 exhibit gigantism, reduced production of major urinary proteins, increased local production of IGF-1, and accumulation of collagen in the dermis, while SOCS-3-deficient mice die at 12–16 days of age because of erythrocytosis by deregulation of fetal liver hematopoiesis. However, a recent study of SOCS-3-deficient mice showed that SOCS-3 was required for placental development but not for normal hematopoiesis in the mouse embryo [90].

Two groups of researchers, including ours, initially reported that SOCS-1-deficient mice are born healthy but with growth disclose various kinds of abnormalities, including stunted growth, fulminant hepatitis with serious fatty degradation, and mononuclear cell infiltration of several organs, and die within 3 weeks after birth [91,92]. Subsequently, it was reported that SOCS-1 is a key molecule for IFN- $\gamma$  actions *in vivo* as seen in SOCS-1-deficient mice that also lack the IFN- $\gamma$  gene (SOCS-1/IFN- $\gamma$  doubly deficient mice) [93,94]. However, it was also found that

**Figure 3**

Molecular mechanism of inhibition by new cytokine inhibitors. **(Left)** PIAS inhibits DNA-binding activity of STATs through association with activated them. **(Center)** SOCS-1 inhibits catalytic activity of JAKs by direct interaction with them. **(Right)** SOCS-3 inhibits catalytic activity of JAKs by binding to receptor complex. JAK, Janus family tyrosine kinases; P, phosphorylation; PIAS, protein inhibitors of activated STATs; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; Y, tyrosine residue.

SOCS-1 *in vitro* inhibits activation of STAT6 by IL-4 stimulation [92], and that SOCS-1 *in vivo* inhibits TNF- $\alpha$  and insulin signaling [95,96]. In a recent study of SOCS-1/STAT1 and SOCS-1/STAT6 doubly deficient mice, we found that the physiological role of SOCS-1 is essential for inhibition of crosstalk in cytokine signaling, particularly for IFN- $\gamma$ -induced inhibition of STAT6 [97]. SOCS-1-deficient mice feature an intact IL-6 signaling pathway, suggesting that SOCS-3 may act as a crucial inhibitor of IL-6 signaling *in vivo*.

Unlike the SOCS family, PIAS proteins constitute a family of constitutively expressed negative regulators of STATs. Five members of this family have been identified with the yeast two-hybrid method and by a search of the expressed sequence tag database: PIAS-1, PIAS-3, PIAS-X $\alpha$ , PIAS-X $\beta$ , and PIAS-Y [98,99]. They all share homology and contain several highly conserved domains, including a putative zinc-binding motif and a highly acidic region. PIAS-1 and PIAS-3 have been identified as specific inhibitors of STAT signal pathways [98,99]. Overexpression studies have shown that PIAS-1 associates only with activated STAT1 dimers and inhibits their DNA-binding activity, but that no monomeric forms of STAT1 are present [99]. Similarly, PIAS-3 associates specifically with activated STAT3 but not with STAT1, resulting in the blocking of all STAT3-mediated gene transcriptions, and is especially well known as an inhibitor of IL-6 signaling in M1 cell lines [98]. The constitutive expression of PIAS proteins implies that their physiological role differs from that of SOCS proteins, which are induced by

cytokine stimulation. So far, however, the differences in the physiological roles of these two families of proteins are not well known.

### Application of anti-IL-6R antibody to clinical medicine

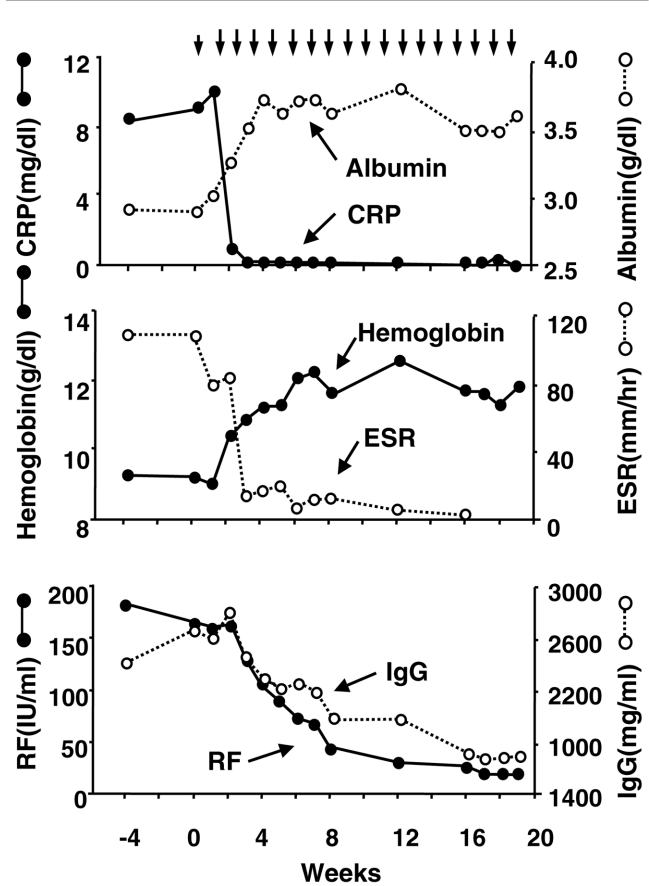
Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by destructive changes in bone and cartilage of affected joints as well as the emergence of rheumatoid factors. Although the exact causes of RA remain unknown, immunological dysregulation by inflammatory cytokines has been shown to be involved in its development [100]. IL-6 is one of these cytokines and uncontrolled IL-6 overproduction appears to be responsible for the clinical symptoms and abnormal laboratory findings in RA [101]. Because of the B-cell differentiation factor activity of IL-6, overproduction of IL-6 is responsible for the increase in serum  $\gamma$ -globulin and the emergence of rheumatoid factors. IL-6 as a hepatocyte-stimulating factor causes an increase in CRP, serum amyloid A, and erythrocyte sedimentation rate and a decrease in serum albumin [11–13]. On the other hand, IL-6 as a megakaryocyte differentiation factor causes thrombocytosis [22,27,28]. Since IL-6 in the presence of soluble IL-6R activates osteoclasts to induce bone absorption [30], IL-6 may be involved in the osteoporosis [102] and destruction of bone and cartilage associated with RA. In fact, a large amount of IL-6 has been observed in both sera and synovial fluids from the affected joints of patients with RA [103–106]. Blockade of the IL-6 signal may thus constitute a new therapeutic strategy for RA.

Wendling *et al.* reported that the administration of mouse antihuman IL-6 monoclonal antibodies to patients with RA resulted in amelioration of RA symptoms and improvement of laboratory findings [107]. However, such therapeutic effects were transient, because murine antibodies were found to be highly immunogenic in humans, especially when they were administered repeatedly. To be effective as therapeutic agents administered to patients in repeated doses, mouse antibodies must therefore be engineered to look like human antibodies. A humanized anti-IL-6R antibody was constructed by grafting the complementarity-determining regions (CDRs) from mouse PM-1, a specific monoclonal antibody against human IL-6R, into human IgG to re-create a properly functioning antigen-binding site in a reshaped human antibody [108]. *In vitro*, humanized anti-IL-6R antibody is equivalent to both mouse and chimeric PM-1 in terms of antigen binding and growth inhibition of IL-6-dependent myeloma cells [108,109]. Furthermore, it looks very much like a human antibody and can therefore be expected to be a poor immunogen in human patients [110].

The *in vivo* effect of humanized anti-IL-6R antibody on the development of collagen-induced arthritis was examined in cynomolgus monkeys because it cross-reacts with the monkey IL-6R [111]. Intravenous administration of humanized anti-IL-6R antibody (10 mg/kg once a week) significantly inhibited the onset of joint inflammation and the elevation of serum CRP and fibrinogen levels and erythrocyte sedimentation rate that were induced by immunization with bovine type II collagen with a complete adjuvant.

On the basis of the above findings, we administered humanized anti-IL-6R antibody to RA patients whose active disease was resistant to conventional therapy using methotrexate, various disease-modifying antirheumatic drugs, and corticosteroids, with the permission of the Ethical Committee of Osaka University Medical School. Low-grade fever and fatigue disappeared and CRP and fibrinogen levels were normalized within 2 weeks after the start of humanized anti-IL-6R antibody treatment (50 mg twice a week) (Fig. 4). This was followed by reduction of morning stiffness, improvement of the swollen-joint score and the pain and tenderness score, and reduction of anemia, thrombocytosis, and hypoalbuminemia. A score of ACR20 on the American College of Rheumatology scale was achieved in 7 of 8 patients after 8 weeks of treatment and ACR50 in 4 of 8 patients after 8 weeks. The treatment was well tolerated and no major side effects were observed. These data indicate that humanized anti-IL-6R antibody is useful for the treatment of RA. Phase I clinical trials in the United Kingdom and a phase I/II study in Japan also proved the safety and the efficacy of humanized anti-IL-6R antibody [112,113]. Double-blind, randomized, placebo-controlled phase II studies for the use of the antibody to treat RA are now in the progress both in Europe and in Japan. In addition to RA, various other IL-6-related

Figure 4



Representative clinical course of an RA patient treated with humanized anti-IL-6R antibody. A 51-year-old woman with RA was given humanized anti-IL-6R antibody intravenously (50 mg twice a week). Although she had active disease refractory to conventional treatment with drugs including methotrexate and prednisolone, treatment with humanized anti-IL-6R remarkably improved her condition. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

diseases such as Castleman's disease, multiple myeloma, mesangial proliferative glomerulonephritis, psoriasis, and Kaposi's sarcoma are possible targets of humanized anti-IL-6R antibody.

**Conclusion**

IL-6 participates in immune response, hematopoiesis, and acute-phase reactions. On the other hand, deregulation of IL-6 production has been implicated in the pathogenesis of a variety of diseases, including plasmacytoma/myeloma and several chronic inflammatory proliferative diseases. Future studies on the regulation of IL-6 expression and clarification of the molecular mechanisms of IL-6 functions, as well as of inhibitors of IL-6 signal, should provide information critical to a better understanding of the molecular mechanisms of these diseases and the development of new therapeutic methods such as antibody therapy.

## Glossary of terms

BSF = B-cell stimulatory factor; CNTF = ciliary neurotrophic factor; IL-6RE = IL-6 response element; LIF = leukemia inhibitory factor; NF-IL-6 = nuclear factor for IL-6 expression; OSM = oncostatin M; PIAS = protein inhibitors of activated STATs; SHP-2 = SH2-containing protein tyrosine phosphatase-2; SOCS = suppressor of cytokine signaling; Y(2,3, etc.) = (second, third, etc.) tyrosine residue (from the membrane).

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