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REVIEW ARTICLE

The Biology of Interleukin-6

By Tadamitsu Kishimoto

B CELLS ARE the only eukaryotic cells that are able to produce antibody molecules. Their growth and differentiation into antibody producing cells require the presence of T cells and macrophages; the function of these cells was found to be replaced by soluble factors.[1-3] In the early 1980s it was shown that at least two different kinds of factors were required in the regulation of B cell response, one for growth of activated B cells, B-cell growth factor (BCGF), and the other for antibody induction in B cells, B-cell differentiation factor (BCDF).[4-6] Since then, a variety of factors regulating the B cell response have been reported in the human and murine systems. Finally, in 1986 the cDNAs for three B-cell stimulatory factors have been cloned; interleukin-4 (IL-4) (BCGF1/BSF1) for the early activation of resting B cells,[7,8] IL-5 (BCGFII) for the growth of activated B cells,[9] and IL-6 (BCDF/BSF2) for the final differentiation of B cells into antibody producing cells[10] (Fig 1).

Human IL-6 (BSF2) was originally identified as a factor in the culture supernatants of mitogen or antigen-stimulated peripheral mononuclear cells, which induced immunoglobulin production in Epstein Barr virus (EBV) transformed B-cell lines or in *Staphylococcus aureus* Cowan 1 (SAC) stimulated normal B cells.[11] This molecule was found to be separable from other factors, such as IL-2 and BCGFs, and the establishment of human T cell hybridoma generating BSF2 activity confirmed that this is a distinct molecule from other cytokines.[6] BSF2 was purified to homogeneity from the culture supernatant of a human T-cell leukemia virus type 1 (HTLV-1) transformed T-cell line and its partial *N*-terminal amino acid sequence was determined.[12] Based on these findings, the cDNA encoding human BSF2 was cloned.[10]

Approximately at the same time, the molecular cloning and the nucleotide sequences of the molecules termed interferon β_2 (IFNβ_2)[13] and 26 Kd protein were reported[14] and the results revealed that BSF2, IFNβ_2, and 26 Kd protein were identical. In 1980, an inducible mRNA species of about 13S encoding for a novel human fibroblast-type interferon (IFN), named IFNβ_2 was reported.[15] The isolated cDNA clone for such an induced mRNA was trancribed in vitro into a protein of 26 Kd. One group detected an antiviral activity that was neutralized with anti-IFNβ_2 and thus called this molecule IFNβ_2.[15] On the other hand, another group could not detect any antiviral activity in this protein[16] and its interferon activity was controversial until recombinant molecules became available. In 1987 recombinant IL-6 (r IL-6) was shown to have no IFN activity and to have antigenically and functionally no relations with IFNβ.[17]

Growth factors for plasmacytomas/myelomas have been reported by several investigators.[18,20] In 1986, *N*-terminal amino acid sequence of a human cytokine that showed hybridoma/plasmacytoma growth factor activity was determined and the result again showed that the factor was identical with BSF2/IFNβ_2/26 Kd protein.[21] Subsequently, the cDNA cloning of murine hybridoma/plasmacytoma growth factor was completed and the sequence indicated that it was the murine homologue of IL-6/BSF2.[22,23] Therefore, all the results demonstrated that IL-6 has the growth activity in plasmacytoma/myeloma cells.

The other major activty of IL-6 is induction of acute phase proteins in hepatocytes. The studies with IL-6 and anti–IL-6 antibody carried out by Gauldie et al[24] and Andus et al[25] clearly demonstrated that IL-6 functioned as a hepatocyte stimulating factor (HSF) and induced the production of major acute phase proteins.

As described, the molecular cloning of the cDNA of IL-6 indicated that the function of IL-6 is not restricted to B lineage cells but shows a wide variety of biological activities on various tissues and cells. Table 1 summarizes the activities exerted by molecules identified to be identical to IL-6.

STRUCTURE OF IL-6

Human IL-6 consists of 184 amino acids with two potential N-glycosylation sites and four cysteine residues.[10] Comparison of the cDNA sequence of human IL-6 with that of murine shows a homology of 65% at the DNA level and of 42% at the protein level.[26] The position of four cysteine residues is completely conserved and nine amino acid residues (no. 56 through 65) between two cysteine residues (no.

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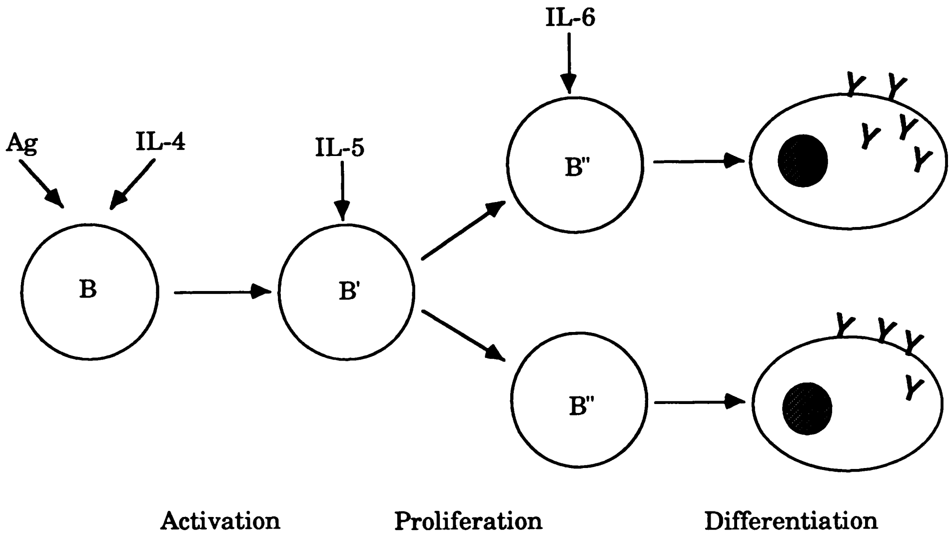

Fig 1. Process of B-cell differentiation and interleukins involved in the process.

50 and 73) are identical, suggesting that the cysteine-rich middle region of the mature protein may play a critical role in IL-6 activity.[26] Recently, a biologically active recombinant IL-6 gene was chemically synthesized on the basis of the human IL-6 cDNA sequence.[27] The result showed that a cysteine-free, bioengineered rIL-6 protein was active, suggesting that the primary sequence of IL-6 might contain the information necessaary to fold the peptide chain into an active conformation and cysteine residues might not be required.

The sequence of IL-6 was compared with other known proteins. Only G-CSF shows a significant homology with IL-6[10]; the position of four cysteine residues of IL-6 match with those of G-CSF. This suggests a similarity in the tertiary structure of these two molecules and may indicate some functional similarity as described later. Furthermore, the gene organization of IL-6 shows a distinct similarity with the G-CSF gene[28]; both genes have the same number of exons and introns and the size of each exon is strikingly similar (Fig 2). Taken together, these findings suggest that the genes for IL-6 and G-CSF might be evolutionarily derived from a common ancestor gene.

REGULATION OF THE IL-6 EXPRESSION

IL-6 is produced by various types of lymphoid and nonlymphoid cells, such as T cells, B cells, monocytes, fibroblasts, keratinocytes, endothelial cells, mesangium cells, and several tumor cells, as summarized in Table 2. The production of IL-6 by T cells requires the presence of monocytes, while monocytes produced IL-6 in the absence of an apparent stimulus in in vitro culture.[29] The peak of IL-6 mRNA in monocytes was achieved five hours following culture, whereas that of T cells was at 24 to 48 hours after culture initiation, suggesting that IL-6 produced by monocytes and T cells with different kinetics may exert distinct effects, at different phases of the immune responses.

Table 1. Molecules Identical to IL-6

B-cell stimulatory factor 2
Interferon $\beta 2$
26 Kd protein
Myeloma/plasmacytoma growth factor
Hepatocyte stimulating factor
Macrophage granulocyte inducing factor 2
Cytotoxic T-cell differentiation factor

The production of IL-6 in various cells is positively or negatively regulated by a variety of signals. IL-6 production in T cells is induced by T cell mitogens or antigenic stimulation in the presence of direct contact with macrophages.[29] Lipopolysaccharide (LPS) enhances IL-6 production in monocytes and fibroblasts.[29,30] A variety of cytokines, including IL-1, tumor necrosis factor (TNF), platelet-derived growth factor (PDGF), and IFNβ as well as serum, poly(I)poly(C), and cycloheximide also enhance the expression of the IL-6 gene in different cell types.[31] Phorbol esters, which activate protein kinase C,[32] and agents that increase intracellular cAMP[33] also enhance the accumulation of IL-6 mRNA. Various viruses induce IL-6 production in fibroblasts[34] or in the CNS.[35] Human immunodeficiency virus induces IL-6 production in monocytes.[36] Glucocorticoids negatively regulate the IL-6 gene expression in various tissues and cells.[30]

The chromosomal DNA segments of human[28] and mouse[26] were isolated. The comparison revealed that the sequence similarity in the coding region is about 60%, whereas the 3′ untranslated region and the first 300 bp sequence of the 5′ flanking region are highly conserved (~90%), suggesting the importance of the regulation of the IL-6 gene expression. Sequences similar to transcriptional enhancer elements such as the c-fos serum responsive element (SRE) and the consensus sequences for cAMP induction (CRE), activator protein 1 binding (AP-1) and the glucocorticoid receptor binding (GRE) were identified within the highly conserved 5′-flanking regions of the genes as shown in Fig 3.[26] These sequences may play an important role in transcriptional activation of the IL-6 gene.

Noteworthy is the striking similarity of transcriptional regulation between the IL-6 and the c-fos genes. First, both genes are induced rapidly without requirement of prior protein synthesis. Second, a very broad range of stimuli

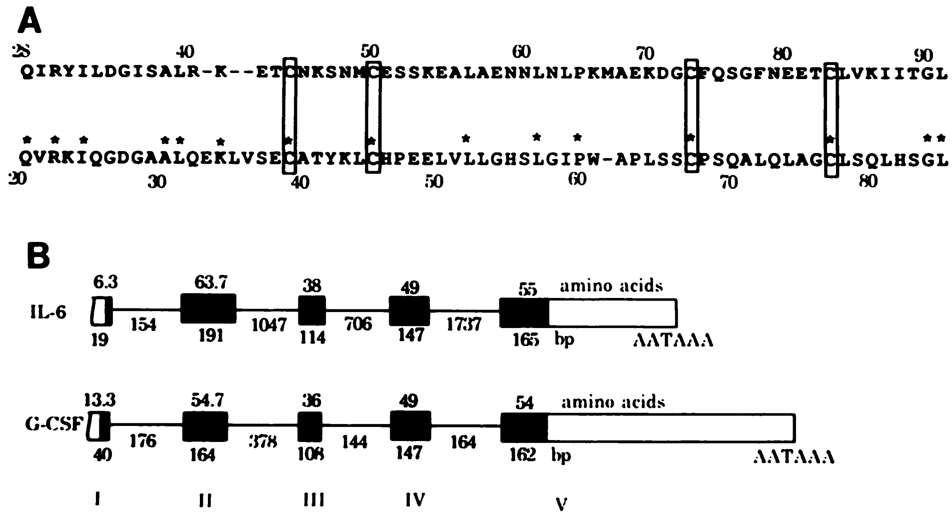

Fig 2. Comparisons of the amino acid sequence (A) and the gene organization (B) between IL-6 and G-CSF.

modulate the gene expression in various tissues and cells. These data suggest that both genes are likely to share some cis-acting 5′ regulatory elements. In fact, the region involved in IL-6 induction is mapped within the IL-6 promotor region (−180/−123 bp), which is homologous to c-fos SRE. Nuclear factor(s) that recognize a 14 bp dyad symmetry were identified within the c-fos SRE homology (Akira et al, submitted). However, the dyad symmetry of the IL-6 promotor is quite different from the dyad symmetry of the c-fos promotor, suggesting that the nuclear factor(s) binding to these dyad symmetries must be different from each other. The transcriptional regulation of the IL-6 gene is quite similar to that of the c-fos and these two genes have probably developed to use the common modular structure in order to respond to a variety of external stimuli common in the two genes. However, the precise regulation is different and specific between the two genes.

BIOLOGIC FUNCTION OF IL-6

Immune system. IL-6 was originally identified as T cell-derived lymphokine that induces final maturation of B cells into antibody producing cells.[11,12] The studies with the IL-6 confirmed the activity of IL-6 on B cells. Thus, IL-6 could augment the production of IgM, IgG, and IgA in Pokeweed mitogen (PWM)-stimulated peripheral mononuclear cells (PBL) (Fig 4).[37] IL-6 was also effective in in vivo antibody production in mice primed to sheep RBCs (SRBC).[38] As shown in Fig 4, the intraperitoneal administration of 10 μg rIL-6 every other day could augment anti-SRBC secondary antibody response more than tenfold. The study with anti–IL-6 antibody demonstrated that IL-6 is one of the essential factors for antibody production in B cells;[37] anti–IL-6 almost completely abrogated PWM-induced Ig-production in PBL. However, mitogen-induced proliferation of B cells was not affected at all by anti–IL-6 antibody, indicating that IL-6 is not involved in the growth of activated B cells. This shows a marked contrast to the fact that IL-6 is a potent growth factor for myeloma/plasmacytoma cells as described later.

Effect of IL-6 is not restricted to B cells, it can also act on T cells. IL-6 receptors are expressed on activated but not resting B cells, while resting T cells express IL-6 receptors,[39] indicating that IL-6 acts only on the final maturation stage of activated B cells, but can be effective on resting T cells. In fact, IL-6 was shown to induce IL-2 receptor[40] as well as IL-2 production[41] in mitogen-stimulated T cells and thymocytes. IL-6 promoted the growth of PHA-stimulated thymocytes and peripheral T cells.[42-45] The IL-6–induced growth of T cells was found to be partly inhibited by anti–IL-2 or anti-Tac antibody indicating that IL-6 can directly induce the growth of T cells. The thymocyte costimulatory activity of the macrophage- or T cell-derived conditioned medium was largely abrogated by anti–IL-6 antibody.[46] Previously, it was thought that the thymocyte costimulatory activity was exerted mainly by IL-1. However, the results obtained with rIL-6 and anti–IL-6 antibody strongly suggest that IL-6 is an

Table 2. Producer Cells of IL-6

Normal Cells	Cell Lines	Tumor Cells
T cells	T-cell lines (HTLV-1 transformed)	Cardiac myxoma cells
B cells	U937 (Monocyte cell lines)	Myeloma cells
Monocytes	P388D1 (Monocyte cell lines)	Hypernephroma
Fibroblasts	MG63 osteosarcoma cell line	
Keratinocytes	T24 bladder carcinoma line	
Endothelial cells	A549 lung carcinoma line	
Astrocytes	SK-MG-4 glioblastoma line	
Bone marrow stroma cells	U373 astrocytoma line	
Mesangial cells		

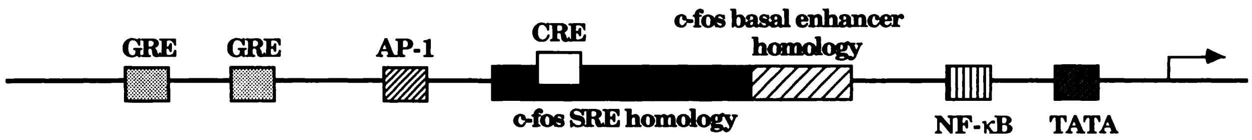

Fig 3. Transcriptional control element motifs identified in the 5′ promotor region of the IL-6 gene. CRE, glucocorticoid responsive element; AP-1, AP-1 binding element; CRE, cyclic AMP responsive element; c-fos SRE, c-fos serum responsive element; NF-κB, NF-κB binding element.

essential accessory factor for T-cell activation and proliferation.

IL-6 induced not only proliferation but also the differentiation of cytotoxic T cells (CTL) in the presence of IL-2 from murine as well as human thymocytes and splenic T cells.[47,48] Previously, the requirement of a factor(s) other than IL-2 for CTL induction was reported in various experimental systems and they were called CDF, KHF, etc. The result obtained with rIL-6 and anti–IL-6 has confirmed that these factors are identical with IL-6. IL-6 induced serine esterases required for the expression of cytotoxic function, showing its critical role in cytotoxic T-cell differentiation.[47]

Hematopoiesis. The positive effect of IL-6 on hematopoiesis was first described by Ikebuchi et al.[49] It was found that IL-3 and IL-6 acted synergistically to support the formation of multilineage blast cell colonies in murine spleen cell cultures. The appearance of multilineage blast cell

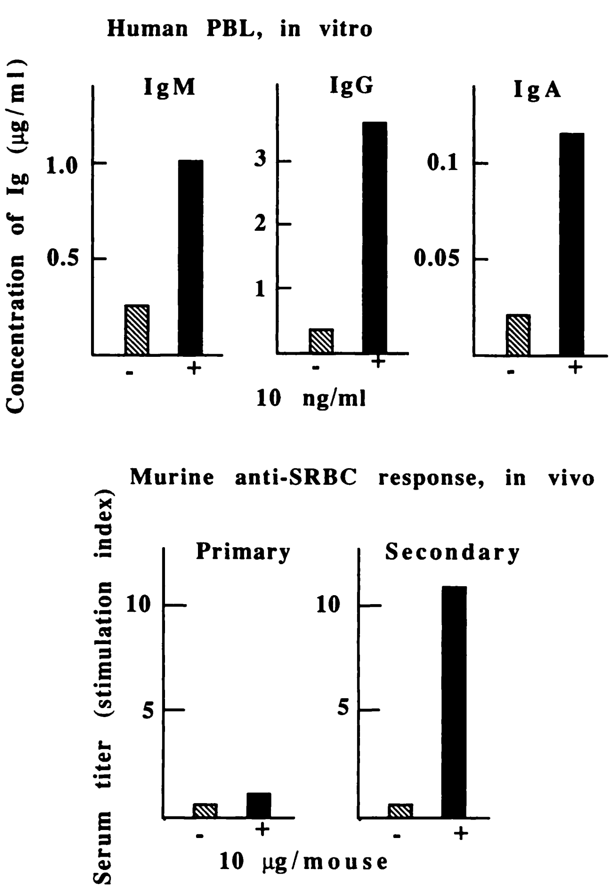

Fig 4. Effect of rIL-6 on in vitro and in vivo antibody production.

colonies by IL-3 was significantly hastened by the addition of IL-6, suggesting that IL-6 activate hematopoietic stem cells at the G_0 stage to enter into the G_1 phase. Similar results were observed by Koike et al.[50] They showed that IL-6 and IL-3 in serum free cultures increased multilineage blast cell colonies but not single or oligolineage colonies, indicating that IL-6 acts on the multipotent progenitors but not on the more mature progenitors. Addition of IL-6 to cultures with a low concentration of IL-3 resulted in a significant increase in the number as well as the size of colonies, suggesting that the other mechanism of synergism of IL-6 may be the enhancement of the susceptibility of multipotent progenitors to IL-3, possibly by upregulating IL-3 receptors.

Stanley et al[51] presented evidence that hematopoietin-1 (H-1), which was purified from culture supernatants of a human bladder carcinoma cell line, 5637, possessed synergistic activity with IL-3 in support of proliferation of hematopoietic progenitors. Recently, Mochizuki et al[52] and Moore and Warren[53] reported that IL-1α and IL-1β accounted for the H-1 activity of the 5637 supernatant. When highly purified human marrow progenitors (My10$^+$ cells) were used, IL-6 and IL-3 showed a synergy for the proliferation of progenitors, while IL-1α revealed no synergism with IL-3.[54] As bone marrow stroma cells produce large amounts of IL-6 following stimulation with IL-1, these results suggest an indirect effect of IL-1 in part mediated by IL-6.

The synergistic action of IL-6 with IL-3 for the proliferation of multilineage progenitor cells suggests a potential role for IL-6 in bone marrow transplantation. Short-term liquid culture of murine nonadherent marrow cells with IL-6 and IL-3 was found to increase the number of CFU-S approximately fivefold. When 2×10^5 nonadherent bone marrow cells were transplanted to lethally irradiated recipients, the survival rate at day 30 was only 20%. However, when these cells were precultured with IL-6 plus IL-3 before transplantation, the survival rate increased to 90% (Okana et al, submitted). If this culture system is also efficient for expanding human stem cells, it may be used in bone marrow transplantation.

Human and murine myeloid leukemic cell lines, such as human histiocytic U937 cells and mouse myeloid M1 cells can be induced to differentiate into macrophages and granulocytes in vitro by several synthetic and natural products. Several factors have been identified that can induce differentiation of leukemic cells, such as G-CSF,[55] MG1-2,[56] and leukemia inhibitory factor (LIF).[57] Recently, IL-6 was also shown to induce the differentiation of M1 cells into macrophages;[58] IL-6 enhanced phagocytosis and expression of Fcγ and C3d receptors and its effect was much more potent than that of vitamin D_3.[58] Sachs et al recently reported that MGI-2 was identical with IL-6. LIF was also molecularly cloned and found to be a novel factor having no similarity with either G-CSF or IL-6.[57] However, noteworthy is that LIF can induce a large amount of IL-6 in M1 cells. At present, it is not known whether the effect of LIF on M1 cells is direct or indirect through IL-6 production.

Acute phase reactions. The acute phase response is a systemic reaction to inflammation or tissue injury. It is characterized by leukocytosis, fever, increased vascular permeability, alterations in plasma metal and steroid concentration, along with increased levels of acute phase proteins. The biosynthesis of acute phase proteins by hepatocytes is regulated by several factors: IL-1, TNF, and HSF. IL-1 was originally considered to be the major acute phase regulator, although it could only partially elicit the full acute phase response. The studies with rIL-6 and anti–IL-6 antibody demonstrated that IL-6 could function as HSF and the HSF activity in monocyte conditioning medium was exerted by IL-6 molecule.[24,25] IL-6 could induce a variety of acute phase proteins, such as fibrinogen, alpha-1-antichymotrypsin, alpha-1-acid glycoprotein, haptoglobin in human hepatoma cell line, HepG2. In addition to those proteins, it induced serum amyloid A, C-reactive protein, and alpha-1-antitrypsin in human primary hepatocytes.[59] In vivo administration of IL-6 in rats induced typical acute phase reactions similar to that induced by the injection of turpentine. Moreover, IL-6–induced expression of mRNAs for acute phase proteins was more rapid than that induced by turpentine.[60] The results confirmed the in vivo role of IL-6 in acute phase reaction. It was also reported that serum level of IL-6 correlated well with that of C-reactive protein and fever in patients with severe burns, supporting the causal role of IL-6 in acute phase response.[61]

Neural system. IL-1 stimulation of glioblastoma cells or astrocytoma cells was found to induce the expression of IL-6 mRNA, suggesting certain effects of IL-6 on nerve cells. Nerve growth factor (NGF) was shown to induce a phenotypic shift in chromaffin cells and their neoplastic counterpart, PC12 cell line, resulting in neural differentiation accompanied by chemical, ultrastructural, and morphological changes. IL-6 was also found to induce the typical differentiation of PC12 cells into neural cells.[62] In fact, in the presence of IL-6, the cell viability was maintained and a change in morphology to neurite-extending cells was observed after several days. Furthermore, IL-6 was found to induce the transient expression of c-fos proto-oncogene and an increase in the number of voltage-dependent Na^+ channels in PC12 cells. The differentiation induced by IL-6 is similar to that observed with NGF, although IL-6 and NGF use completely different receptors on PC12 cells, Moreover, it was found that PC12 cells express about 1,200 IL-6 receptors per cell with a Kd value of $\sim 1.8 \times 10^{-9}$ mol/L.

IL-6 could show its effect on hypothalamo-pituitary-adrenal axis in vivo. Intravenous (IV) administration of IL-6 into rats increased the plasma level of adrenocorticotropic hormone 30 minutes after the injection.[63] The injection of anticorticotropin-releasing hormone ten minutes before IL-6 completely abolished the IL-6–induced increase of ACTH, suggesting that IL-6 stimulated the secretion of ACTH through the cortiocotropin-releasing hormone. IL-6 showed a synergistic effect with glucocorticoid on the induction of acute phase proteins.[59] Thus, IL-6–induced secretion of ACTH may have a positive feed back loop on acute phase reaction. On the other hand, glucocorticoid is a potent inhibitor in the induction of IL-6 production in various cells. Therefore, the interaction of IL-6 with neuro-endocrine system may regulate positively and negatively acute phase reactions and immune responses.

IL-6 was found to be produced in a murine CNS by infection with lymphocytic choriomeningitis virus or with vesicular stomatitis virus.[35] Both virus-infected microglial cells and astrocytes produced IL-6.[64] The production of IL-6 may explain the mechanisms leading to the intrathecal antibody production by B cells having infiltrated the brain tissue. It was also found that IL-6 induced an increase in the secretion of a neurotrophic factor, nerve growth factor by astrocytes. Thus, IL-6 production may be involved in repair mechanism besides antibody production in the course of viral infection.

RECEPTORS AND SIGNAL TRANSDUCTION

IL-6 provides multiple signals on various tissues and cells. As summarized in Table 3, these signals can be divided into three categories: (*a*) induction of differentiation or specific gene expression such as Ig induction in B cells or the induction of acute phase proteins in hepatocytes; (*b*) stimulation of cell growth, such as the induction of myeloma/plasmacytoma growth or T cell growth; and (*c*) inhibition of cell growth, such as inhibition of growth of myeloid leukemia cells or breast cancer cells. In order to know the mechanism how a single cytokine can provide multiple signals, the molecular structure of the specific receptor should be revealed.

The number of cytokine receptors is usually in the order of 10^2 to 10^3, which is 100-fold less than that for hormone or growth factor receptors. The IL-6 receptor is not exceptional as shown in Table 4. As expected from its pleiotropic function, receptors are expressed on various cells, such as activated B cells, resting T cells, B lymphoblastoid cell lines, myeloma cell lines, hepatoma lines, and monocyte cell lines. The number of the receptors is between 10^2 and 10^3 and a myeloma cell line, U266, expresses the maximum number of receptors, approximately 1 to 2×10^4, which may fit for the activity of IL-6 as myeloma growth factor.[39]

cDNA for IL-6 receptor has been cloned by using high

Table 3. Multiple Signals Provided by IL-6

Induction of differentiation or specific gene expression
Ig-induction in B cells
Induction of acute phase proteins in liver cells
Induction of cytotoxic T-cell differentiation
Induction of neural cell (PC12) differentiation
Activation of hematopoietic stem cells from G_0 to G_1
Stimulation of cell growth
Induction of the growth of myeloma/plasmacytoma cells
Induction of T cell growth
Induction of mesangial cell growth
Inhibition of cell growth
Growth inhibition of myeloid leukemia cells (M1 cells)
Growth inhibition of breast carcinoma cell lines

Table 4. IL-6 Receptor Expressed on Various Cells

Cells	No. of Receptor/Cell
Activated B cells	~500
Resting B cells	Nondetectable
Resting T cells	~300
EBV-transformed B-cell lines	200–3,000
Burkitt's lymphoma lines	Nondetectable
Myeloma cells and cell lines	100–20,000
Hepatoma cell lines	2,000–3,000
Myeloid leukemia cell lines	2,000–~3,000
Rat pheochromocytoma (PC12)	~1,000

efficiency COS cell expression vector.[65] As shown in Fig 5, the receptor consists of 468 amino acids with a single transmembrane segment. The intracytoplasmic portion consists of 82 amino acids and it does not have a tyrosine kinase domain, although IL-6 is a potent growth factor for myeloma cells. Comparison of the sequence shows that IL-6 receptor belongs to the C2 set of the Ig superfamily and first hundred amino acids formed an Ig-like domain. Noteworthy is that all the receptors for cytokines so far cloned, PDGF,[66] CSF-1,[67] IL-1,[68] and IL-6[65] belong to the C2 set of the Ig superfamily. IL-6 receptor has five possible *N*-glycosilation sites and the molecular weight (mol wt) of mature protein is 80 Kd. Crosslinking experiments with ^{125}I–IL-6 showed that only a single polypeptide chain with 80 Kd mol wt is involved in the binding with IL-6. However, the binding of IL-6 with the 80 Kd IL-6 receptor triggers the association of the second nonligand binding polypeptide chain with 130 Kd mol wt (Taga et al, submitted). The mutated IL-6 receptor without intracytoplasmic portion could transmit the IL-6 signal, indicating that the second nonligand binding chain is responsible for the signal transduction. Therefore, IL-6 receptor consists of two polypeptide chains, a ligand-binding chain and a nonligand binding, signal transducing chain, the results suggest a novel mechanism for the signal transduction. Physicochemical properties of IL-6 and its receptor are summarized in Table 5.

IL-6 AND DISEASES

Multilple myelomas/plasmacytomas. As described, IL-6 is a potent growth factor for myeloma/plasmacytoma cells, suggesting a possible involvement of IL-6 in the generation of myeloma/plasmacytoma. The study with myeloma cells freshly isolated from the bone marrow of myeloma patients demonstrated that IL-6 is an autocrine growth factor for human myeloma cells.[69] In fact, (*a*) IL-6 augments the in vitro growth of myeloma cells, (*b*) myeloma cells produce IL-6, and (*c*) anti–IL-6 inhibits the spontaneous growth of myeloma cells. In 26 cases of myelomas tested, 12 cases that were at the early clinical stage were responsive to IL-6 for their growth, but myeloma cells derived at late clincal stages were refractory to IL-6 stimulation.[70] These results suggest that IL-6 is an essential autocrine growth factor for myeloma cells and its dyregulated expression may be involved in the oncogenesis of human multiple myelomas.

This was further confirmed by transgenic mice carrying the human IL-6 gene conjugated with the Ig enhancer (Eμ-IL-6). The transgenic mice showed the generation of plasmacytomas (Suematsu et al, submitted for publication). However, these plasmacytoma cells were polyclonal and not transplantable. Furthermore, they did not show the c-myc translocation. Therefore, the result suggests that constitutive expression of IL-6 in B lineage cells induces polyclonal proliferation of IL-6 dependent plasmacytomas and a second event such as c-myc translocation during continuous proliferation may transform cells into monoclonal and transplantable plasmacytomas.

In 1962, Potter and Boyce demonstrated the induction of plasmacytomas in BALB/c mice by intraperitoneal injection of mineral oil.[71] Plasmacytomas were generated exclusively in oil-induced granulomatous tissues that produced a large

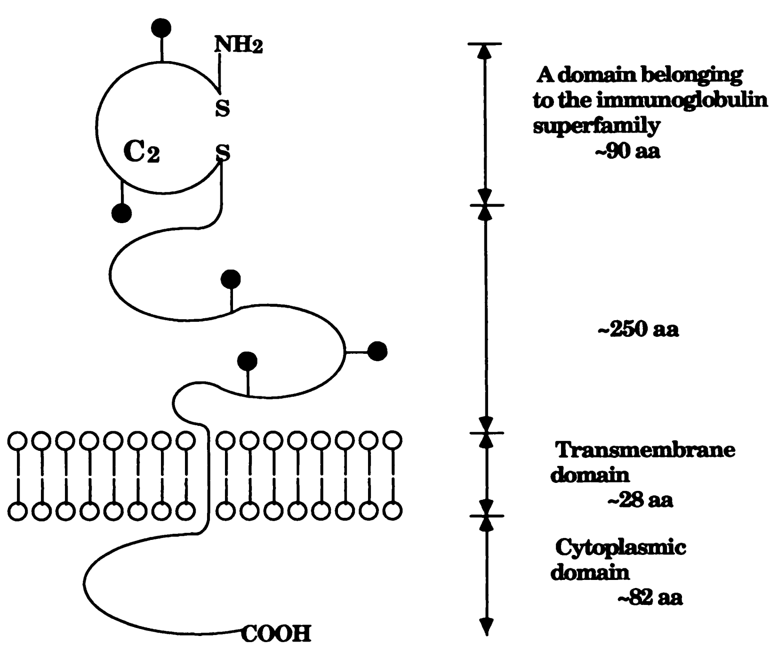

Fig 5. Schematic model of IL-6 receptor, a member of immunoglobulin super family.

Table 5. Physicochemical Properties of Human IL-6 and IL-6R

	IL-6	IL-6R
Apparent molecular weight (Kd)	21	80
Number of amino acids		
Total	212	468
Mature protein	184	449
N-glycosylation sites	2	5
Transmembrane segment		Single
Intracytoplasmic portion		82 amino acid
Sequence homology	G-CSF	Ig superfamily
		No tyrosine kinase domain
Genomic structure	5 exons	Not known
Chromosomal location	Chromosome 5	Not known

amount of plasmacytoma growth factor. As described, plasmacytoma growth factor was molecularly cloned and shown to be a murine homologue of IL-6.[22,23] Therefore, the study performed by Potter and Boyce as well as the observations made in the transgenic mice with the Eμ-IL-6 gene indicate an essential role of IL-6 in the oncogenesis of murine plasmacytomas.

Castleman's disease. In 1956, Castleman et al reported a group of patients with a large, benign hyperplastic mediastinal lymph node that resembled thymomas.[72] Since then, a syndrome consisting of fever, anemia, hyper γ-globulinemia and increase in acute phase proteins in association of consistent benign hyperplastic lymph nodes has been called Castleman's disease. The affected lymph nodes are characterized by massive infiltration of plasma cells. Sometimes, patients develop monoclonal gammapathy and finally multiple myelomas. Of particular interest is that the above mentioned clinical abnormalities disappear after excision of the affected lymph node. The germinal center of hyperplastic lymph nodes of patients with Castleman's disease were found to produce constitutively large quantities of IL-6 with no significant production of other cytokines (Yoshizaki et al, submitted). Dramatic clinical improvement and decrease in serum IL-6 were observed following surgical removal of the involved lymph node. Considering the multiple biological activities of IL-6, the aberrant constitutive expression of IL-6 by the germinal center B cells in the affected lymph nodes can explain the symptoms of this rare disease and the abnormal regulation of IL-6 expression may be the primary event in the pathogenesis of Castleman's disease.

Lennert's T-cell lymphoma. IL-6 was shown to be involved in the in vitro as well as in vivo growth of Lennert's T lymphoma cells.[73] Lennert's lymphoma is a special variant of non-Hodgkin's lymphoma characterized by a massive infiltration of macrophage-derived epithelioid histiocytes. A T lymphoma cell line established from a patient with Lennert's lymphoma showed macrophage-dependent growth and the function of macrophages could be replaced with macrophage-derived soluble factor(s). IL-6 supported the in vitro growth of such an established T-cell line and anti–IL-6 antibody could completely neutralize the activity of macrophage-derived factor. Considering the massive infiltration of macrophges in lymphoma tissues, the evidence suggests that macrophage-derived IL-6 may be involved in the in vivo growth of Lennert's lymphoma.

Polyclonal B-cell activation and autoimmune diseases. Cardiac myxoma is a benign intraatrial heart tumor and interestingly patients often show autoimmune symptoms and autoantibody production, which disappear after surgical removal of myxoma cell.[74] Study with cardiac myxoma cells demonstrated that they constitutively produced large amounts of IL-6.[75] Several other cancers also aberrantly produced IL-6 and patients showed autoantibody production. The results suggest that abnormal production of IL-6 in vivo may induce polyclonal B cell activation and autoantibody production.

These observations suggest that abnormal expression of IL-6 may contribute to the generalized autoimmune disease, such as rheumatoid arthritis. In fact, high levels of IL-6 were detected in synovial fluid from the joints of patients with active RA.[76] The synovial cells as well as the infiltrated T and B cells constitutively produced IL-6. The overproduction of IL-6 can explain the local as well as the generalized symptoms of RA, such as infiltration of plasma cells into synovial tissues, autoantibody production and elevation of acute phase proteins including CRP and serum amyloid A. IL-6 was found to be a growth factor for EBV-transformed B lymphoblastoid cells. This may explain the presence of abnormally elevated numbers of circulating EBV-infected B cells in RA patients. Diseases related to the abnormal expression of IL-6 are summarized in Table 6.

SUMMARY AND FUTURE PROSPECTS

Most cytokines involved in the regulation of the immune responses and hematopoiesis have been molecularly cloned. The studies with recombinant molecules clearly demonstrate that the function of these cytokines is not specific to a certain lineage of cells as originally expected but they show a wide variety of biological functions on various tissues and cells. One of the most typical examples of these multifunctional cytokines is IL-6. As described, it regulates immune responses, hematopoiesis, and acute phase reactions, indicating that it plays a central role in host defense mechanism. Among many cytokines, IL-6 is the first one, the abnormal expression of which is directly related to the pathogenesis of several diseases, such as myeloma/plasmacytoma, Castleman's disease, and mesangium proliferative glomerulonephritis, in which IL-6 functions as an autocrine growth factor for kidney mesangium cells. Therefore, the study on the regulatory mechanism of the IL-6 gene expression is indispensable for unraveling the molecular pathogenesis of those diseases. Neutralization of IL-6 with specific inhibitors may be applied for the treatment of such diseases. Soluble receptors are possible candidates as the specific inhibitor.

The signal transduction through cytokine receptors may be unique: (*a*) the number of receptors is approximately

Table 6. Deregulation of IL-6 Expression and Diseases

Myelomas and plasmacytomas
Castleman's disease
Rheumatoid arthritis
Mesangial proliferative glomerulonephritis
Cardiac myxoma

100-fold less than that of hormone or growth factor receptors and (*b*) any known biochemical reactions, such as phosphatidyl inositol turnover, tyrosine phosphorylation, and Ca^{++}-ion influx, are not invoked following stimulation with cytokines. Recently, cDNAs for cytokine receptors, such as IL-6, IL-1 and γ-IFN have been cloned. The receptor molecules do not have any unique structure for the signal transduction, such as tyrosine kinase domain. Therefore, the presence of associated molecules for the signal transduction is assumed. In fact, IL-6 stimulation triggers the association of the IL-6 receptor with a nonligand binding signal transducer. The unique mechanism of signal transduction through cytokine receptors will hopefully be elucidated in the near future.

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