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Commentary

Biological effects of interleukin-6: Clinical applications in autoimmune diseases and cancers

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ABSTRACT

Interleukin-6 (IL-6) is a pro-inflammatory cytokine involved in the pathogenesis of various autoimmune and chronic inflammatory diseases. Binding of IL-6 to its receptor (IL-6R) initiates both classical- and *trans*-signaling pathways. A number of autoimmune diseases are characterized by overproduction of IL-6. Tocilizumab, a humanized monoclonal antibody against IL-6R, blocks IL-6-mediated signaling and has been approved for the treatment of rheumatoid arthritis and Castleman's disease. IL-6 levels are also upregulated in various tumors, and the levels of circulating IL-6 are associated with prognosis in cancer patients. The major issues covered in this commentary include (1) how IL-6-mediated biological effects may lead to the pathogenesis of autoimmune diseases and cancers, (2) the rationale of developing anti-IL-6 strategies for therapeutic purposes, (3) recent advances in anti-IL-6 therapeutics (clinical benefits and adverse events), (4) current knowledge about clinical trials evaluating newly emerging anti-IL-6 treatments, (5) strategies to improve anti-IL-6 therapeutics from both basic and clinical aspects. This commentary provides a useful overview of the role of IL-6 in both autoimmune diseases and cancers from the laboratory as well as clinical perspectives.

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1. Introduction: IL-6 and the IL-6-mediated signaling pathway

In immune system, T cells play a crucial role in regulating the proliferation and differentiation of B cells into antibody-forming cells in response to stimuli. Nevertheless, certain T cell functions can be replaced or compensated by signalings mediated by soluble factors like lymphokines or monokines secreted by T cells as well as non-T cells. Human B-cell differentiation factor-2 (BSF-2) is a secreted soluble factor which could induce final maturation of B cells to become immunoglobulin-secreting cells. Purification and cloning showed that BSF-2 was a cytokine containing 184 amino acids (26 kDa), which was later named as interleukin (IL)-6 [1]. IL-6 is produced by a number of immune and non-immune effector cells, including T and B cells, fibroblasts, monocytes, keratinocytes, mesangial cells, glial cells, endothelial cells as well as many tumor cells [2,3]. IL-6 production could be induced by a variety of stimuli such as cytokines, including IL-1, tumor necrosis factor (TNF), and platelet-derived growth factor (PDGF), as well as bacterial and viral infections [3]. The IL-6 receptor (IL-6R) is mainly expressed in immune effector cells such as T and B cells, monocytes, macrophages, and neutrophils as well as certain non-immune effector cells such as pancreatic islet cells and hepatocytes [4].

IL-6R exists in the transmembrane form and a soluble form. The soluble form is likely a proteolytically cleaved product of the transmembrane form of IL-6R, or an alternatively splicing product of IL-6R mRNA [2]. The cytoplasmic domain of IL-6R is very short and does not contain any unique sequence or kinase domain. Binding of IL-6 to its either soluble or transmembrane receptor

Abbreviations: IL-6, interleukin-6; JAK, Janus kinase; STAT, signal transducer and activator of transcription; PI3K, phosphoinositide 3-kinase; RA, rheumatoid arthritis; Th, T-helper; TNFα, tumor necrosis factor α; IFN, interferon; AKT/PKB, protein kinase B; NF-κB, nuclear factor-kappaB; AP-1, activator protein-1; MAPK, mitogen activated protein kinase; ERK, extracellular signal-regulated kinase; EAE, experimental autoimmune encephalomyelitis; VEGF, vascular endothelial growth factor; ABCG, ATP-binding cassette transporter G; ER, estrogen receptor; PCNA, proliferating cell nuclear antigen; ZEB-1, beta-catenin/zinc finger E-box binding homeobox 1; LMP1, latent membrane protein 1; Tff3, trefoil factor 3; Hsp, heat shock protein; CA-IX, carbonic anhydrase 9; MMP, matrix metalloproteinase.

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formed a complex with signal-transducing receptor subunit gp130 and triggered its signaling pathway [2]. In addition to transmitting signal for IL-6, gp130 also mediated signaling by other cytokines such as oncostatin M, IL-11, leukemia inhibitory factor, ciliary neurotrophic factor and cardiotrophin-1 [2]. The signal initiated by the IL-6/transmembrane IL-6R/gp130 complex is called the classical signaling pathway, while the signal initiated by the interaction between soluble IL-6R/IL-6 and gp130 is called the *trans*-signaling pathway [3]. It was shown that the half-life of plasma IL-6 was significantly longer, and the IL-6 concentration required to induce the expression of acute phase proteins was significantly lower in transgenic mice expressing soluble human IL-6R compared to control animals [5]. Predictably, the classical pathway is confined to cells that express both IL-6R and gp130 on their surface whereas the *trans*-signaling pathway is open to all cells expressing gp130 which is a much wider range.

The formation of the IL-6/IL-6R/gp130 complex triggers the activation of a number of downstream signaling pathways. Activation of the Ras/mitogen activated protein kinases (MAPKs) mediates the phosphorylation and activation of nuclear factor (NF)-IL6 which binds to the IL-6-responsive element in the promoter region of acute phase genes to induce production of acute phase proteins [2]. The IL-6/IL-6R/gp130 complex also activates Janus kinases (JAKs) such as JAK-1, JAK-2 and tyrosine kinase 2 as well as downstream transcriptional factors like signal transducers and activators of transcription (STAT)1 and STAT3 and the enzyme phosphatidylinositol 3-kinase (PI3K). Translocation of activated STATs to the nucleus mediates the regulation of a number of genes, while activated PI3K in turn activates serine/threonine kinase protein kinase B/AKT. IL-6-mediated activation of both JAK/STATs/PI3K and Ras-Raf/MAPK kinase/extracellular signal-regulated kinases (ERK)1/2 pathways can induce very broad immune reactions [3].

2. Biological effects of IL-6 in immunity

Several biological effects of IL-6 in regulating immune response in different systems/organs are briefly summarized in Table 1.

2.1. IL-6 regulates differentiation of T-helper cells

T-helper (Th) cells are crucial in nearly all autoimmune-mediated diseases. Stress or environmental factors induce activation and differentiation of T cells toward specific groups of cells with different effector functions. The Th-1 cells and Th-2 cells are mainly responsible for clearing intracellular pathogens and extracellular pathogens, respectively. The Th-2 cells also mediate reactions to allergens. The most potent antigen-presenting cells, the dendritic cells (DCs), secrete IL-6 and inhibit the differentiation of T cells toward the Th-2 phenotype, suggesting that IL-6 plays a dominant negative role in Th-2-cell development [6].

The Th-17 cells represent a group of T cells distinct from Th-1 and Th-2 cells [7], which are associated with clinical manifestations in a number of autoimmune diseases [8]. IL-6 together with another cytokine transforming growth factor-beta (TGF-β) worked together to preferentially promote differentiation of Th-17 cells from naïve T cells in animal studies [9]. However, the regulation of Th-17 cell differentiation is complex. Inhibition of IL-6 signaling in a mouse model of collagen-induced arthritis during the early phase of disease induction effectively suppressed Th-17 induction and development of arthritis; however, blockade of IL-6 signaling 2 weeks after induction of arthritis did not suppress Th-17 differentiation or the symptoms of arthritis [10]. These data indicated that IL-6 was only required for the initial differentiation of Th-17 cells from naïve T cells, but not for the maintenance of Th-17 cells once their differentiation process completed [10].

Table 1
Biological effects of interleukin (IL)-6 in immunity.

Major targets	Main effects	References
T-helper cells	Negatively regulated Th-2 response	[6]
	Inhibited TGF-β-induced Treg differentiation	[17]
	Together with TGF-β promoted differentiation of Th-17 cells from naïve T cells	[9]
	In combination with IL-1β, TGF-β, and IL-23 led polarization of naive Vγ9Vδ2 T cells to producing IL-17	[14]
Hematopoietic system	Controlled proliferation and differentiation of the progenitor cells of many hematopoietic lineages	[18]
	Controlled leukemic multipotent progenitor cell fate and regulated the development of chronic myelogenous leukemia	[19]
	Promoted and prevented lymphoma development by acting distinct stages of hematopoietic development	[20]
	Induced activation of T and B cells and hematopoiesis and lupus-like autoimmune manifestations in Lyn-deficient mice	[21]
Nervous system	Was required for myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis	[23]
	B cell-specific IL-6 regulated Th17 responses in experimental autoimmune encephalomyelitis	[24]
	Maintained plasmablast-like B cells survival and increased autoantibody production in patients with neuromyelitis optica	[25]
	Induced the CD4(+) T follicular helper cell-differentiation program and exacerbated autoimmune reaction	[26]
Cardiovascular system	Was constitutively produced in cardiac myxomas	[27]
	Aggravated severity of autoimmune myocarditis induced by cardiac α-myosin peptide immunization	[30]
	Increased severity of angiotensin II-induced cardiac fibrosis	[31]
	Was protective in viral-induced autoimmune myocarditis	[33]
Respiratory system	Exacerbated pleural exudation and polymorphonuclear cell infiltration in immune-mediated lung damage	[36]
	Increased death rate in acute pancreatitis-associated acute lung injury in mice	[37]
	Induced Th-17 cell differentiation within the lung and caused lung damage	[38]
Liver	Induced production of a variety of acute phase proteins	[2]
	Protected liver from damage in concanavalin A-induced T cell-mediated hepatitis	[39]
	Was protective in liver injury induced by bacterial hepatotoxin stimulation or partial hepatectomy	[40]
	Down-regulated expression of liver cytochrome P450 3A4 enzyme	[41]
Gastrointestinal system	Prevented apoptosis of intestinal mucosal T cells in Crohn's disease	[44]
	Protected wound healing from colon injury by inducing epithelial proliferation	[45]
Kidney	Increased severity and inflammatory cell infiltration in kidney in lupus-prone mice	[46]
	Activated *trans*-signaling pathway to exacerbate immune-mediated kidney damage in Lyn-deficient mice	[47]
	Upregulated proliferation of macrophages that accumulated and caused damage in the kidney	[48]

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