Seminars in Immunology 26 (2014) 88–96

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

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

Toshio Tanaka[a,b], Masashi Narazaki[c], Atsushi Ogata[b,c], Tadamitsu Kishimoto[d,*]

[a] Department of Clinical Application of Biologics, Osaka University Graduate School of Medicine, Osaka University, Osaka 565-0871, Japan
[b] Department of Immunopathology, World Premier International Immunology Frontier Research Center, Osaka University, Osaka 565-0871, Japan
[c] Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, Osaka University, Osaka 565-0871, Japan
[d] Laboratory of Immune Regulation, World Premier International Immunology Frontier Research Center, Osaka University, Osaka 565-0871, Japan

ARTICLE INFO

Keywords:
IL-6
Autoimmunity
Inflammation
Tocilizumab

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.

* Corresponding author at: Laboratory of Immune Regulation, World Premier International Immunology Frontier Research Center, Osaka University, 8F IFReC Building, 3-1 Yamada-oka, Suita City, Osaka 565-0871, Japan. Tel.: +81 6 6879 4957; fax: +81 6 6879 4958.
E-mail address: kishimoto@ifrec.osaka-u.ac.jp (T. Kishimoto).

1044-5323/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.smim.2014.01.009

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],