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Review

Targeting interleukin-6 in autoimmune uveitis

Marina Mesquida [a,b,*,1], Blanca Molins [b,1], Víctor Llorenç [a], Maite Sáinz de la Maza [a], Alfredo Adán [a]

[a] Uveitis Unit, Institut Clinic d'Oftalmologia, Hospital Clinic de Barcelona, Universitat de Barcelona, Spain
[b] Fundació Clínic per a la Recerca Biomèdica, IDIBAPS, Barcelona, Spain

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ABSTRACT

Interleukin-6 (IL-6) is a key cytokine that is strongly up-regulated during infection and inflammation. Featuring pleiotropic activity, IL-6 is responsible for the induction of hepatic acute-phase proteins, trafficking of acute and chronic inflammatory cells, differentiation of adaptive T cell responses, homeostatic regulation, and tissue regeneration. Dysregulated IL-6 production has been associated with the development of a wide variety of systemic immune-mediated, chronic diseases, and even certain types of cancer. From the ocular perspective, significant elevation of IL-6 has been found in ocular fluids derived from diabetic macular edema, retinal vein occlusion, and refractory/chronic uveitis patients. During the last decade, tocilizumab, a neutralizing monoclonal antibody (mAb) that targets the IL-6 receptor (IL-6R), has been approved for the treatment of rheumatoid arthritis in >100 countries worldwide. Furthermore, it has been reported to be effective for the treatment of a number of autoimmune diseases including uveitis and its associated macular edema. Currently numerous candidate molecular strategies targeting the IL-6 signaling pathways are in progress through clinical trials in various disorders. Herein we discuss the basic biology of IL-6 and its pathological role in the development of immune-mediated conditions, particularly focusing on inflammatory eye diseases. It also provides an overview of the on-going clinical trials with the new anti-IL-6 mAbs and their potential use in the clinical practice.

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* Corresponding author at: Uveitis Unit, Ophthalmology Department, Hospital Clínic de Barcelona, Ophthalmology Clinical Research Unit, Fundació Clínic per a la Recerca Biomèdica, IDIBAPS, Sabino de Arana, 1, PC 08028 Barcelona, Spain.
E-mail address: mesquida@clinic.ub.es (M. Mesquida).
[1] Contributed equally to this work with: Marina Mesquida, Blanca Molins.

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1. Introduction

Interleukin-6 (IL-6) was identified three decades ago by Kishimoto and colleagues as a T cell-derived factor inducing activated B cells to differentiate into antibody-producing cells [1]. IL-6 is a soluble mediator formerly known as B-cell stimulatory factor (BSF-2), interferon (IFN)-beta 2, and hepatocyte stimulating factor, based on the above stated function, antiviral activity, and acute phase protein synthesis, respectively [2]. When the BSF-2 complementary DNA was successfully cloned in 1986 [3], it turned out that these molecules with different names studied by various groups were in fact identical, resulting in the single name IL-6 [2]. Since its molecular discovery, major advances have taken place in understanding the biology of IL-6 and its fundamental role in inflammation, immune regulation, hematopoiesis, host defense, homeostasis, and tissue regeneration. IL-6 is often referred to as a pleiotropic cytokine being produced by a wide range of hematopoietic and somatic cells that influences numerous cell types with multiple biological functions. However, abnormal IL-6 production has been associated with the development of a wide variety of systemic immune-mediated, chronic diseases, and even neoplasms [1]. From the ocular perspective, significant elevation of IL-6 has been found in aqueous (AqH) or vitreous humour derived from diabetic macular edema (DME), retinal vein occlusion (RVO), and refractory/chronic uveitis patients [4–6]. Over the last decade, tocilizumab, a humanized monoclonal antibody (mAb) that binds the IL-6 receptor (IL-6R), has gained approval for the treatment of rheumatoid arthritis (RA) in >100 countries worldwide [7]. It is also approved for the treatment of systemic and polyarticular juvenile idiopathic arthritis (sJIA and pJIA, respectively), and for Castleman's disease in Japan. Furthermore, it has been reported to be effective in various immune-mediated disorders including non-infectious uveitis and its associated macular edema [4]. Due to the clinical success of IL-6-blockade, a number of new biologics targeting IL-6 signaling are currently being tested in clinical trials or in pre-clinical studies. It is expected that this strategy will have wider applicability in numerous immune-mediated diseases [7–9].

2. IL-6 biology

2.1. IL-6 signaling pathways

Human IL-6 is a 26 kDa protein made up of 212 amino acids codified by a gene located in chromosome 7p21 [7]. The biology and signaling of IL-6 are now better comprehended principally due to the outstanding work of Dr. Tadamitsu Kishimoto from Osaka University and Dr. Stefan Rose-John from the University of Kiel. IL-6 triggers signal transduction after binding the IL-6 receptor (IL-6R). There are two forms of the IL-6R, the 80 kDa transmembrane receptor protein and the 55 kDa soluble form (sIL6-R). During the so-called classic signaling, IL-6 binds its cognate transmembrane IL-6R forming the IL-6/IL-6R complex [7–9]. Signaling is only initiated when the IL-6/IL-6R complex associates with a second protein, the 130 kDa transmembrane glycoprotein named gp130 [10]. The association of gp130 with IL-6/IL-6R leads to the formation of the high affinity activated IL-6/IL-6R/gp130 complex, adopting a hexameric structure consisting of two molecules each of IL-6, IL-6R and gp130, thereby triggering the initiation of the intracellular signal transduction pathway via activation of Janus kinase (JAK) and signal transducer and activator of transcription 3 (STAT3) as well as the JAK-SHP2-Ras-mitogen activated protein kinase (MAPK) pathways, eliciting the downstream signal cascade leading to specific changes of intra-nuclear gene expression of various sets of IL-6-responsive genes [10]. The activation of STAT3 in turn induces the suppressor of cytokine signaling 1 (SOCS1) and SOCS3, which bind tyrosine-phosphorylated JAK and gp130 respectively, to stop IL-6 signaling by means of a negative feedback loop, as a mechanism of counter-regulation [11,12].

In the last years a new paradigm in IL-6 signaling has been elucidated [12,13]. In addition to the signaling through the membrane-bound IL-6R (classic signaling), IL-6 can provide signal transduction in cells lacking the cognate transmembrane IL-6R through binding the sIL-6R in association with gp130, in the so-called trans signaling pathway [13]. While it is known that almost all cells of the body express gp130, only few cells possess the transmembrane IL-6R, mainly hepatocytes and some leukocyte subpopulations (monocytes, neutrophils, T cells, and B cells). In trans signaling, IL-6 binds the sIL-6R, and the IL-6/sIL-6 complex subsequently binds gp130 on cells that do not express the transmembrane IL-6R (and are therefore unable to respond to IL-6 in the absence of sIL-6R) [12]. In other words, this pathway allows cells that do not express surface IL-6R to respond to the presence of IL-6 [13].

To ensure that IL-6/sIL-6R trans signaling is tightly regulated, there is counter-regulation by a soluble form of gp130 (sgp130), present at high concentrations in serum of healthy individuals (range, 250–400 ng/ml), as part of the physiological IL-6 buffer in the blood [13,14]. This natural inhibitor forms a complex with IL-6/sIL-6R, preventing the binding of IL-6/sIL-6R to membrane-bound gp130 [12–14].

It is believed that the pleiotropic effect of IL-6 derives from the broad range of cells expressing gp130, which highlights the importance of trans signaling [13]. The signal-transducing protein gp130 is shared by all members of the IL-6 cytokine family (including IL-35, IL-27, IL-11, leukemia inhibitory factor, oncostatin M, ciliary neurotrophic factor, among others). The fact that all the IL-6 family members use gp130 as a common signal transducer suggests why the aforementioned cytokines display pleiotropy and redundancy [14]. In summary, IL-6 binding to its transmembrane receptor leads to the activation of the so-called classic signaling pathway, whereas the IL-6/sIL-6R complex triggers the so-called trans signaling pathway. Various studies have shown that classic signaling via the membrane-bound receptor is regenerative and protects from bacterial infections, whereas trans signaling via the soluble receptor is proinflammatory [15]. Therefore, it has been hypothesized that the sole blockade of IL-6 trans signaling may be more beneficial than global IL-6 inhibition, maintaining the regenerative functions of IL-6 and specifically suppressing only pathophysiologic inflammatory activity [13,15]. Fig. 1 depicts IL-6 signaling pathways.

2.2. IL-6 biological functions

IL-6 is an essential mediator in host defense against environmental stress, alerting about the occurrence of an emergent event and sending out a warning sign to the entire body [9]. Under physiological conditions IL-6 is barely detectable in serum (1–5 pg/ml), although its levels can increase >100,000-fold during early phases of inflammation [8,9]. A myriad of cell types in the body can synthesize IL-6, including cells of the innate immune system such as neutrophils and monocytes/macrophages. As mentioned, IL-6 is important in the integrated host defense against numerous pathogens including bacteria, fungi, viruses and mycobacteria [16]. During infectious inflammation, IL-6 is promptly produced by monocytes and macrophages after the stimulation of Toll-like receptors (TLRs) with distinct pathogen-associated molecular patterns (PAMPs) [17]. In non-infectious inflammation such as burn or traumatic injury, damage-associated molecular patterns (DAMPs) from injured or dying cells stimulate TLRs to produce IL-6 [17]. PAMPs and DAMPs stimulate a number of signaling pathways including NF-κB, and upregulate the transcription of the mRNA of inflammatory cytokines such as IL-6, tumour necrosis factor alpha (TNF-α), and IL-1β. TNF-α and IL-1β in turn can activate transcription factors to synthesize IL-6 [13]. The local encounter of these innate immune cells with danger signals in early stages of the immune response is thereby translated into systemic dissemination of IL-6 through the bloodstream and the rapid elevation of serum IL-6 levels [8]. Liver hepatocytes respond to the IL-6 stimulus inducing the synthesis of acute-phase proteins such as C-reactive protein (CRP), serum amyloid A, fibrinogen, haptoglobin, and alpha-1-antichymotrypsin [18]. CRP is a well-known biomarker of inflammation and is used as such in clinical laboratory tests. Importantly, its expression principally depends on IL-6 [19]. Alpha-1-

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