Editorial paper

Reumatologia 2025; 63, 2: 65–67
DOI: https://doi.org/10.5114/reum/204012

Interleukin-6 signalling: what rheumatologists should know and expect

Stefano Rodolfi[1,2], **Maria Maślińska**[3], **Carlo Selmi**[1,2]

[1]Department of Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Rozzano, Italy
[2]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy
[3]Early Arthritis Clinic, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland

Interleukin-6 (IL-6) is a pleiotropic cytokine with numerous biological activities in several organs and systems. First described in 1973 by Kishimoto et al. [1], it has been attributed several names in the subsequent years, as different scientific groups were isolating the same molecule in different biological scenarios. Subsequent cloning showed that these proteins were identical, and they were thus grouped under the current name of IL-6. This cytokine is now recognised as a central mediator of the innate and adaptive immune response, with an established role in promoting B- and T-cell differentiation and activation, immunoglobulin production by B cells, endothelial activation, secretion of other pro-inflammatory cytokines, and synthesis of acute phase reactants by the liver. In the last decades, the role of IL-6 in the pathogenesis of rheumatic and non-rheumatic inflammatory diseases has been recognised, and its pharmacological blockade has made its way into national and international recommendations for the treatment of rheumatoid arthritis, giant cell arteritis, juvenile idiopathic arthritis, adult-onset Still's disease, systemic sclerosis, Castleman's disease, cytokine release syndrome, neuromyelitis optica spectrum disorder, and severe coronavirus disease 2019 (COVID-19) [2]. The effects of IL-6 extend far beyond the modulation of the immune response, frequently with opposing effects depending on the context. A fundamental concept behind the pleiotropic and variable activity of IL-6, is that of the multiplicity of its signalling modalities. This cytokine can exert its biological functions via binding to a membrane-bound receptor (IL-6R), initiating the so-called "classical signalling", or to its soluble form (sIL-6R), via the so-called "trans-signalling". Both pathways lead to recruitment of the adaptor glycoprotein 130 (gp130) and initiation of intracellular signalling via the JAK/STAT3 pathway. Interleukin-6 family cytokines are cytokines that use gp130 as a receptor subunit, and they are therefore also called gp130 cytokines (Fig. 1) [3].

There is also a third signalling mechanism, called trans-presentation of uncertain significance in humans, in which dendritic cells present the membrane-bound IL-6/IL-6R complex from cell to cell to cognately interacting T cells, which respond through their own gp130 [3]. Under physiological conditions, the classical signalling predominates, and only cells expressing the membrane-

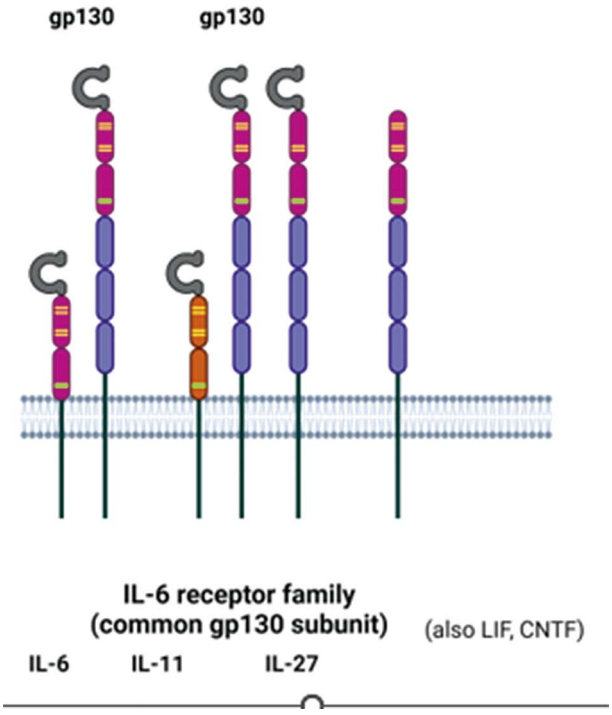

Fig. 1. Interleukin-6 receptor family.
CNTF – ciliary neurotrophic factor, gp130 – glycoprotein 130, IL – interleukin, LIF – leukaemia inhibitory factor
Source: Created in BioRender. https://BioRender.com/5bolsth

Address for correspondence
Stefano Rodolfi, Department of Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, via A. Manzoni 56, 20089 Rozzano, Italy, e-mail: st.rodolfi@gmail.com
Submitted: 01.04.2025; **Accepted:** 14.04.2025

bound IL-6R (hepatocytes, neutrophils, monocytes, macrophages, and some types of T lymphocytes) are activated to maintain the immune homeostasis. On the other hand, in a pro-inflammatory status, owing to the activity of matrix metalloproteases (including A disintegrin and metalloproteinase 17 – ADAM17) and alternative spicing, sIL6-R is generated and liberated from the membrane, and the balance shifts towards trans-signalling, which, being ubiquitously gp130 expressed, involves a significantly wider variety of cell types [4].

This accounts for the complexity of the effect of IL-6 on immune response, metabolism, haematopoiesis, bone and neural homeostasis, and tumourigenesis. In general terms we may assume that classical signalling is mainly responsible for the acute inflammatory, homeostatic, and pro-regenerative effects of IL-6, while disease is mediated by trans-signalling and trans-presentation [5]. In fact, the classical signalling is responsible for the acute inflammatory response involved in bacterial clearance, while trans-signalling inhibition mediates macrophage infiltration, endothelial activation, chemokine expression, reduced differentiation of CD4+ T cells into T regulatory cells, and induction (along with classical signalling and trans-presentation) and maintenance of a Th17 phenotype [6, 7]. This duality is maintained at the metabolic level, with classical signalling being associated with improved glucose control, greater insulin sensitivity, suppressed adipose tissue macrophage accumulation, and reduction of body weight, while trans-signalling is associated with insulin resistance, tissue macrophage accumulation, hepatic inflammation, and atherosclerosis [7, 8]. Furthermore, the same concepts apply to the role of IL-6 in cancer as acute signalling promotes antitumour adaptive immunity by regulating T-cell priming in lymphoid organs and inducing the migration of cytotoxic T cells to tumour-draining lymph nodes and vessels. Conversely, persistent IL-6 signalling in the tumour microenvironment supports cell survival, angiogenesis, endothelial-to-mesenchymal transition, and metastatic spread through activation of the JAK/STAT3 pathway and regulation of tumour-infiltrating stromal and immune cells, being recognised as a poor prognostic factor across several types of cancer [9]. It appears from the effect of selective blockade of trans-signalling in animal cancer models that this pathway is mostly responsible for the pro-oncogenic properties of IL-6 [10].

The currently available anti-IL-6 agents target either the IL-6 receptor (tocilizumab, sarilumab, satralizumab), or the cytokine itself (siltuximab, sirukumab, clazakizumab, olokizumab). Both approaches seem equally effective on the classical and trans-signalling pathways with comparable outcomes, although characterised by different pharmacokinetic properties and by the fact that anti-IL-6 antibodies fail to prevent trans-presentation [10, 11]. The general inhibition of IL-6 effects may thus account for some of the side effects attributable to IL-6 inhibition, such as increased incidence of bacterial infections, liver injury, dyslipidaemia, acute pancreatitis, and intestinal perforation [2]. In the last 2 decades, selective inhibitors of trans-signalling have been developed

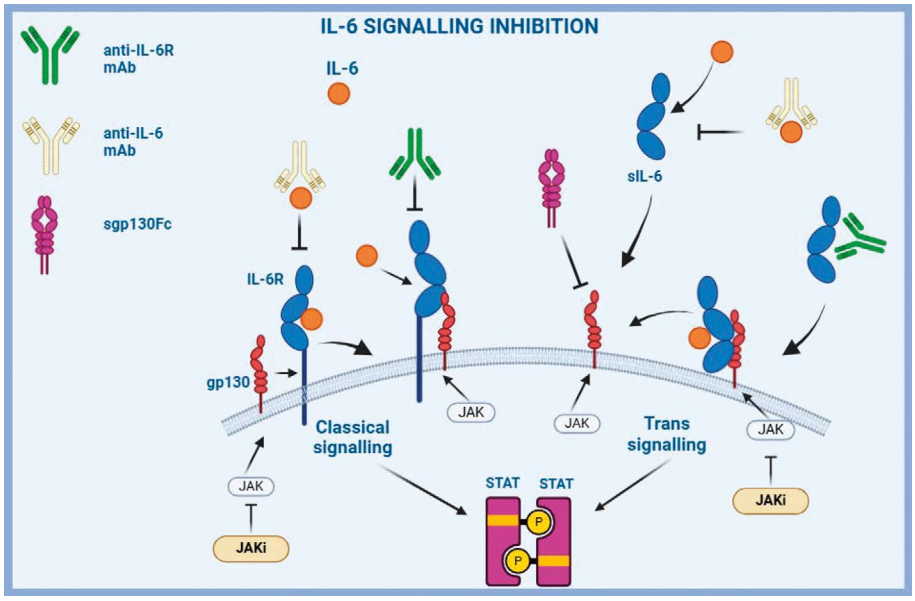

Fig. 2. Basic principles of IL-6 signalling and inhibition. Antibodies targeting IL-6 or IL-6 receptor block indistinctively classical and trans-signalling, while inhibitors of glycoprotein 130 (gp130), here represented by the pioneer sgp130Fc (i.e. olamkicept), selectively inhibit trans-signalling.

JAKi – Janus kinase inhibitor, mAb – monoclonal antibody.

in an attempt of overcome this hurdle, and they are well represented by olamkicept (sgp130Fc), a fusion protein of the extracellular portion of gp130 fused to the Fc portion of a human IgG1 antibody, tested in numerous preclinical trials on animal models of human and neoplastic diseases. Treatment with olamkicept in these settings proved to be at least as efficient as treatment with anti-IL-6 or anti-IL-6R agents, with possible advantages in animal models of sepsis, pancreatitis, bone fracture healing, and myocardial infarction [11]. Olamkicept proved to be safe and tolerated in phase I trials on IBD, with an effect superior to placebo in induction of remission in a recent phase IIb trial on active ulcerative colitis [12, 13]. Owing to these promising results, further phase II and III trials on olamkicept are planned for the near future [10]. However, gp130 is not unique to IL-6 but is employed as an adaptor molecule by other cytokines, including IL-11, which has been implicated in both physiological and pathological processes with a dual effect similar to IL-6 [14]. There is thereby a theoretical risk of inhibiting the beneficial effects of other cytokines along with IL-6 trans-signalling with olamkicept treatment, a risk that new-generation gp130 inhibitors, designed to have higher affinity for IL-6-sIL-6R complex, are trying to overcome [10]. Finally, IL-6 signalling can be blocked with JAK inhibitors; however, JAKs participate in the intracellular signalling of several cytokines; hence, selective IL-6 inhibition is not possible with these molecules. Figure 2 provides an overview of the 2 main signalling pathways of IL-6 and how they are inhibited via the available treatments.

In conclusion, modulating IL-6 activity represents the cornerstone treatment of some inflammatory diseases and a fascinating therapeutic opportunity even for non-rheumatic diseases that feature deregulated inflammation. Novel agents promise to target IL-6 in a more selective and safer way, and future trials will clarify at which level they may enter clinical practice.

Disclosures

Conflict of interest: The authors declare no conflict of interest.
Funding: No external funding.
Ethics approval: Not applicable.
Data availability: Not applicable.

References

1. Kang S, Narazaki M, Metwally H, Kishimoto T. Historical overview of the interleukin-6 family cytokine. J Exp Med 2020; 217: e20190347, DOI: 10.1084/jem.20190347.
2. Aletaha D, Kerschbaumer A, Kastrati K, et al. Consensus statement on blocking interleukin-6 receptor and interleukin-6 in inflammatory conditions: an update. Ann Rheum Dis 2023; 82: 773–787, DOI: 10.1136/ard-2022-222784.
3. Rose-John S. Local and systemic effects of interleukin-6 (IL-6) in inflammation and cancer. FEBS Lett 2022; 596: 557–566, DOI: 10.1002/1873-3468.14220.
4. McElvaney OJ, Curley GF, Rose-John S, McElvaney NG. Interleukin-6: obstacles to targeting a complex cytokine in critical illness. Lancet Respir Med 2021; 9: 643–654, DOI: 10.1016/S2213-2600(21)00103-X.
5. Rose-John S. Interleukin-6 signalling in health and disease. F1000Res 2020; 9: F1000 Faculty Rev-1013, DOI: 10.12688/f1000research.26058.1.
6. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta 2011; 1813: 878–888, DOI: 10.1016/j.bbamcr.2011.01.034.
7. Giraldez MD, Carneros D, Garbers C, et al. New insights into IL-6 family cytokines in metabolism, hepatology and gastroenterology. Nat Rev Gastroenterol Hepatol 2021; 18: 787–803, DOI: 10.1038/s41575-021-00473-x.
8. Feng Y, Ye D, Wang Z, et al. The Role of Interleukin-6 Family Members in Cardiovascular Diseases. Front Cardiovasc Med 2022; 9: 818890, DOI: 10.3389/fcvm.2022.818890.
9. Mohamed AH, Ahmed AT, Al Abdulmonem W, et al. Interleukin-6 serves as a critical factor in various cancer progression and therapy. Med Oncol 2024; 41: 182, DOI: 10.1007/s12032-024-02422-5.
10. Rose-John S, Jenkins BJ, Garbers C, et al. Targeting IL-6 trans-signalling: past, present and future prospects. Nat Rev Immunol 2023; 23: 666–681, DOI: 10.1038/s41577-023-00856-y.
11. Heink S, Yogev N, Garbers C, et al. Trans-presentation of interleukin-6 by dendritic cells is required for priming pathogenic TH17 cells. Nat Immunol 2016; 18: 74, DOI: 10.1038/ni.3632.
12. Wagner F, Schreiber S, Bagger Y, et al. Safety, tolerability, and pharmacokinetics of single- and multiple-ascending doses of olamkicept: Results from randomized, placebo-controlled, first-in-human phase I trials. Clin Transl Sci 2024; 17: e13832, DOI: 10.1111/cts.13832.
13. Zhang S, Chen B, Wang B, et al. Effect of Induction Therapy With Olamkicept vs Placebo on Clinical Response in Patients With Active Ulcerative Colitis: A Randomized Clinical Trial. JAMA 2023; 329: 725–734, DOI: 10.1001/jama.2023.1084.
14. Garbers C, Hermanns HM, Schaper F, et al. Plasticity and cross-talk of interleukin 6-type cytokines. Cytokine Growth Factor Rev 2012; 23: 85–97, DOI: 10.1016/j.cytogfr.2012.04.001.