Check for updates

REVIEW

Interleukin-6 signalling in health and disease [version 1; peer review: 3 approved]

Stefan Rose-John

Biochemical Institute, Christian-Albrechts-Universitaet zu Kiel, Olshausenstrasse 40, D24098 Kiel, Germany

V1 First published: 20 Aug 2020, 9(Faculty Rev):1013
<https://doi.org/10.12688/f1000research.26058.1>Latest published: 20 Aug 2020, 9(Faculty Rev):1013
<https://doi.org/10.12688/f1000research.26058.1>**Abstract**

Biochemically, interleukin-6 belongs to the class of four-helical cytokines. The cytokine can be synthesised and secreted by many cells. It acts via a cell surface-expressed interleukin-6 receptor, which is not signalling competent. This receptor, when complexed with interleukin-6, associates with the signalling receptor glycoprotein 130 kDa (gp130), which becomes dimerised and initiates intracellular signalling via the Janus kinase/signal transducer and activator of transcription and rat sarcoma proto oncogene/mitogen-activated protein kinase/phosphoinositide-3 kinase pathways. Physiologically, interleukin-6 is involved in the regulation of haematopoiesis and the coordination of the innate and acquired immune systems. Additionally, interleukin-6 plays an important role in the regulation of metabolism, in neural development and survival, and in the development and maintenance of various cancers. Although interleukin-6 is mostly regarded as a pro-inflammatory cytokine, there are numerous examples of protective and regenerative functions of this cytokine. This review will explain the molecular mechanisms of the, in part opposing, activities of the cytokine interleukin-6.

Keywords

gp130, sgp130Fc, IL-6, IL-6R, sIL-6R, trans-signalling, ADAM17

Open Peer Review**Approval Status** ✓ ✓ ✓

	1	2	3
version 1	✓	✓	✓
20 Aug 2020			

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Elke Roeb**, Justus Liebig University, Giessen, Germany
2. **Hana Algül**, Technical University of Munich, Munich, Germany
3. **Jacqueline Bromberg**, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Stefan Rose-John (rosejohn@biochem.uni-kiel.de)

Author roles: **Rose-John S:** Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: Stefan Rose-John has acted as a consultant and speaker for AbbVie, Amgen, Janssen, Chugai, Roche, Genentech, Roche, Pfizer, Eli Lilly, and Sanofi. He also declares that he is an inventor on patents owned by CONARIS Research Institute, which develops the sgp130Fc protein (olamkicept), and he has stock ownership in CONARIS.

Grant information: The work of Stefan Rose-John has been supported by grants of the Deutsche Forschungsgemeinschaft Bonn, Germany, under the grant numbers CRC841, project C1, and CRC877, project A1, and by the German Excellence Cluster "Inflammation at Interfaces".

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2020 Rose-John S. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Rose-John S. **Interleukin-6 signalling in health and disease [version 1; peer review: 3 approved]** F1000Research 2020, 9(Faculty Rev):1013 <https://doi.org/10.12688/f1000research.26058.1>

First published: 20 Aug 2020, 9(Faculty Rev):1013 <https://doi.org/10.12688/f1000research.26058.1>

Introduction

Interleukin-6 (IL-6) is considered one of the most prominent pro-inflammatory cytokines¹. Blockade of IL-6 by the neutralising monoclonal antibody tocilizumab has been approved in more than 100 countries for the treatment of patients with autoimmune disorders such as rheumatoid arthritis². Additionally, the cytokine storm sometimes encountered when cancer patients are treated with chimeric antigen receptor (CAR) T-cells³ could be effectively treated with the antibody tocilizumab, leading to US Food and Drug Administration (FDA) approval of the drug for this condition. Even more recently, it has been recognised that many patients experience a similar cytokine storm upon infection with SARS-CoV-2 (COVID-19) virus⁴ and that these patients could also be treated with tocilizumab⁵. These new data led to a rekindled general interest in the cytokine IL-6.

IL-6 was initially discovered and cloned in the Kishimoto laboratory as a B-cell stimulatory factor⁶. Immediately after the molecular cloning, it was evident that IL-6 was identical to hepatocyte stimulating factor⁷, hybridoma-plasmacytoma growth factor⁸, interferon β ⁹, and 26 kDa protein¹⁰. This already indicated the pleiotropic nature of the cytokine. Later on, it was also recognised that IL-6 shows profound activities in the brain^{11,12}, in the regulation of metabolism^{13,14}, in the response of the body to exercise¹⁵, and in the development and maintenance of various cancers¹⁶.

This review article gives a short overview of the complex biology of IL-6 and explains how one cytokine can have extremely different biologic effects on different cells and in different physiologic states of the human body¹⁷.

The interleukin-6 receptor complex

The four-helical cytokine IL-6 (Figure 1) on cells binds to a membrane-bound IL-6 receptor (IL-6R), and the complex of IL-6 and IL-6R associates with a second receptor protein, glycoprotein 130 kDa (gp130), which dimerises and initiates intracellular signalling via the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) and rat sarcoma proto oncogene (ras)/mitogen-activated protein kinase and phosphoinositide-3 kinase pathways (Figure 2)¹⁸. Importantly, IL-6 exhibits only a measurable affinity to the IL-6R but not to gp130, and the IL-6R does not bind on its own to gp130. It is only the complex of IL-6 and IL-6R that binds to gp130 and induces its dimerisation (Figure 2). All cells in the body express gp130, but only a few cells such as hepatocytes and some leukocytes express IL-6R. It follows that cells that express only gp130 but not IL-6R cannot be stimulated by IL-6¹.

Noteworthy, gp130 is a component of the receptor complexes of the so-called gp130 cytokine family, which besides IL-6 comprises IL-11, ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC), leukaemia inhibitory factor (LIF), oncostatin M (OSM), and IL-27. For details, please refer to recent reviews^{19,20}.

It has, however, been noticed that the membrane-bound IL-6R can be cleaved by the membrane-bound metalloprotease a

Figure 1. Four-helical topology of the interleukin-6 (IL-6) protein. IL-6 belongs to the family of four-helical cytokines. The figure shows the four helices with the connecting loops. The A-B and the C-D loops are long enough to reach the length of a helix, whereas the B-C loop is short. Consequently, IL-6 has an up-up-down-down topology, meaning that helices A and B point upwards, whereas helices C and D point downwards. This topology is common to most cytokines such as IL-2, IL-4, IL-7, IL-11, IL-15, leukaemia inhibitory factor, oncostatin M, growth hormone, leptin, and many others.

disintegrin and metalloprotease 17 (ADAM17) to generate a soluble IL-6R (sIL-6R)²¹. To a minor extent, the human—but not the murine—sIL-6R can be generated by translation from a differentially spliced mRNA²². Intriguingly, the sIL-6R can still bind IL-6, and the complex of IL-6 and sIL-6R can associate with gp130 and induce signalling, even on cells that lack the membrane-bound IL-6R²³. This process has been named IL-6 trans-signalling (Figure 3)²⁴. Strikingly, following this paradigm, IL-6 can, in the presence of sIL-6R, stimulate any cell in the body since all cells express gp130¹⁷.

Interestingly, most IL-6R-expressing cells including hepatocytes express far more gp130 than IL-6R molecules. Therefore, stimulation of such cells with IL-6 alone will only lead to engagement of few gp130 molecules, whereas stimulation with the complex of IL-6 and sIL-6R will stimulate all cellular gp130 proteins. A threshold for a given response might not be reached with IL-6 stimulation but only with stimulation of all gp130 molecules via IL-6 trans-signalling. This might be an explanation for the observed differences in signalling between trans-signalling and classical signalling that lead to different phenotypes²⁵.

Molecular tools to elucidate the functions of interleukin-6

The concept of IL-6 trans-signalling has been corroborated by the use of two designer proteins. The first such protein consists of IL-6 covalently fused to the sIL-6R via a 40 Å flexible peptide linker, which allowed the placement of IL-6

Figure 2. Stimulation of target cells by interleukin-6 (IL-6). IL-6 (orange) first binds to the IL-6 receptor (IL-6R) (red). The complex of IL-6 and IL-6R associates with glycoprotein 130 kDa (gp130) (blue), which dimerises and leads to intracellular signalling. It is important to note that IL-6 and IL-6R alone exhibit no measurable affinity to gp130. Only the complex of IL-6 and IL-6R binds to and activates gp130. Therefore, IL-6 cannot stimulate cells that do not express IL-6R. Signalling occurs via the signal transducer and activator of transcription (STAT) 1/STAT3, Yamaguchi sarcoma viral oncogene homolog (YES)/YES-associated protein (YAP), phosphoinositide-3 kinase (PI3K)/AKT, and rat sarcoma proto oncogene (RAS)/mitogen-activated protein kinase (MAPK) pathways. JAK, Janus kinase.

at the correct distance to reach the IL-6 binding site of the sIL-6R. This protein was called Hyper-IL-6 (Figure 3A)²⁶. This protein was shown to stimulate gp130-expressing cells *in vitro* and *in vivo*, and it was shown that liver regeneration²⁷, stimulation of neural cells²⁸, and expansion of hematopoietic cells²⁹ was far more efficient in the presence of Hyper-IL-6 as compared to IL-6 alone³⁰.

While Hyper-IL-6 demonstrated only the biologic potential of IL-6 trans-signalling, these experiments did not prove that this process occurred *in vivo*. A second soluble protein was designed, which consisted of the entire extracellular portion of gp130 covalently fused to the Fc region of human IgG1 (Figure 3B). The resulting protein, named soluble gp130Fc (sgp130Fc), turned out to exhibit similar properties as membrane-bound gp130: it did not bind IL-6 or IL-6R alone, but it bound with high affinity the complex of IL-6 and sIL-6R^{31,32}. Consequently, the sgp130 protein *in vitro* and *in vivo* specifically inhibited IL-6 trans-signalling without compromising IL-6 signalling via the membrane-bound IL-6R, i.e. classic signalling³². The sgp130Fc protein could be used to define IL-6-mediated biologic responses, which were dependent on classic or trans-signalling. This was accomplished by comparing the treatment of animals with sgp130Fc or with neutralising antibodies against IL-6 or IL-6R, which blocked all IL-6 signalling (Figure 3C, D). Using animal models of human inflammatory diseases or inflammation-associated cancer, it turned out that autoimmune disorders and inflammation-associated cancers were mainly driven by IL-6 trans-signalling whereas regenerative and protective activities of IL-6 were mediated by classic IL-6 signalling via the membrane-bound IL-6R (Figure 4)²⁰.

Physiologic and pathophysiologic functions of interleukin-6

Under homeostatic conditions, IL-6 levels in the circulation are as low as 1–5 pg/ml, but during inflammatory states these levels can rise more than 1,000-fold, and under extreme conditions leading to sepsis IL-6 levels in the µg/ml range have been reported³³. IL-6 is produced by myeloid cells upon Toll-like receptor stimulation together with the cytokines IL-1β and tumor necrosis factor α (TNFα), which, via a feed-forward loop, lead to an immense amplification of IL-6 production during inflammatory conditions³⁴. There is perhaps no other protein in the human body whose level can go up by six orders of magnitude. This lets us conclude that IL-6 is the major alarm signal in the human body in response to infection, inflammation, and possibly cancer³⁵.

However, under normal conditions, IL-6 plays an important role in organ/cellular homeostasis. Mice in which the IL-6 gene has been ablated (IL-6 knockout mice) become obese late in life¹³, cannot regenerate their liver upon hepatectomy³⁶, and show no signs of osteoporosis upon ovariectomy³⁷, indicating roles for IL-6 in body weight regulation, liver physiology, and bone metabolism. In pathophysiologic states, however, there are marked differences between IL-6 knockout mice and wild-type mice. IL-6 knockout mice are completely protected in animal models of rheumatoid arthritis³⁸ and multiple sclerosis³⁹, indicating a key role for IL-6 in these autoimmune disorders.

With the help of the sgp130Fc protein and of neutralising monoclonal antibodies, it was possible to selectively block IL-6 trans-signalling or to block all IL-6 signalling, respectively.

Figure 3. Designer proteins to probe for modes of interleukin-6 (IL-6) signalling. (A) Hyper-IL-6 is a fusion protein between IL-6 and soluble IL-6 receptor (sIL-6R). (B) sgp130Fc is a fusion protein of the extracellular portion of glycoprotein 130 kDa (gp130) and the constant part of a human immunoglobulin G1 (IgG1) antibody. (C) IL-6 can signal via the membrane-bound IL-6R (classical signalling) and via the sIL-6R (trans-signalling). Hyper-IL-6 can be used to mimic IL-6 trans-signalling. (D) The sgp130Fc protein does not interfere with classical IL-6 signalling, but it specifically blocks IL-6 trans-signalling.

Using this approach, it was shown that classic IL-6 signalling via the membrane-bound IL-6R was responsible for the defence of the body against bacteria^{40,41}, intestinal regeneration upon polymicrobial sepsis⁴², prevention of aortic rupture in animal models of abdominal aortic aneurysm⁴³, and healing of bone fractures^{44,45}, indicating that these important processes are severely compromised under blockade of global IL-6 activity⁴⁶. It has been hypothesised that the same might apply for the treatment of COVID-19 patients⁴⁶ (Figure 4).

Besides being the major alarm signal in the human body, IL-6 plays a dominant role in various types of cancer. One important reason could be that IL-6, via stimulation of the STAT3 pathway, is a prominent growth factor of many cancer cells. The following scenario has been worked out in pancreatic cancer⁴⁷. It was noted that in the *Kras*^{G12D} model, the massive activation of the STAT3 pathway, which led to

tumour progression, was induced by tumour-infiltrating myeloid cells, which stimulated the neoplastic cells via IL-6 trans-signalling⁴⁷. Selective blockade of this pathway by the sgp130Fc protein blocked progression of pancreatic intraepithelial neoplasias to pancreatic ductal adenocarcinomas⁴⁷, indicating a prominent role for IL-6 trans-signalling in the development of pancreatic cancer. In the murine APC^{min/+} model of colon cancer, it was established that the genetic deletion of ADAM17, which is responsible for generating not only sIL-6R but also soluble TNF α and soluble ligands of the epidermal growth factor receptor (EGFR), resulted in completely abrogated tumour development¹⁶. Moreover, the formation of neoplasias stimulated ADAM17 on macrophages, leading to EGFR ligand cleavage and subsequent EGFR stimulation. These macrophages now produced IL-6 and sIL-6R, which led to the outgrowth of the tumours. Again, selective blockade of the IL-6 trans-signalling pathway by the sgp130Fc protein blocked tumour development in the APC^{min/+} model and an additional mouse model of colon cancer¹⁶. This was highly reminiscent of a study in liver cancer, in which it was shown that the EGFR expressed in macrophages but not EGFR in hepatocytes was involved in the development of hepatocellular carcinoma⁴⁸. Apparently, macrophage activation may be an important step in the initiation and progression of tumours via the IL-6 trans-signalling pathway²⁰ (Figure 4).

Therapeutic targeting of interleukin-6 activity

Therapeutic targeting of the pro-inflammatory cytokine TNF α was introduced as an efficient strategy to treat patients with autoimmune disorders such as rheumatoid arthritis and inflammatory bowel disease⁴⁹. Subsequently, blockade of the biologic activity of the cytokine IL-6 was shown to be an efficient treatment for patients with rheumatoid arthritis and other autoimmune diseases², and it was shown that blocking IL-6 activity was more efficient than blocking TNF α in a monotherapy trial⁵⁰. Blockade of IL-6 activity with the IL-6R neutralising monoclonal antibody tocilizumab was also highly effective in the treatment of patients with CAR T cell-induced severe cytokine release syndrome⁵¹. In patients with severe COVID-19 disease, the administration of tocilizumab resulted in a marked improvement of the condition in the majority of patients: the fever subsided, C-reactive protein decreased, and oxygen intake could be lowered. No obvious adverse reactions were observed. These preliminary data indicated that tocilizumab is a candidate for effective treatment of COVID-19 patients^{5,52}. Interestingly, treatment of COVID-19 patients with the IL-6R neutralising monoclonal antibody sarilumab resulted in no significant difference in clinical improvement and mortality⁵³.

Summary

The discovery that the pro-inflammatory activities of IL-6 are mediated by IL-6 trans-signalling whereas the protective and regenerative activities of IL-6 rely on classic signalling via the membrane-bound IL-6R suggested that the sgp130Fc protein might be an ideal candidate for a more specific mode of cytokine blockade as opposed to global cytokine inhibition²⁰. It was shown in appropriate animal models that blockade of IL-6 trans-signalling was indeed superior to global IL-6 blockade in a bone healing model^{44,45}, in a sepsis model⁴², in abdominal

Figure 4. Pro- and anti-inflammatory activities of interleukin-6 (IL-6). Left, anti-inflammatory and protective activities of the cytokine IL-6 are associated with signalling via the membrane-bound IL-6 receptor (IL-6R). Right, pro-inflammatory activities of the cytokine IL-6 are associated with signalling via the soluble IL-6R (sIL-6R). The membrane-bound metalloprotease a disintegrin and metalloprotease 17 (ADAM17) orchestrates the pro- and anti-inflammatory activities of IL-6. Treg, regulatory T cell.

aortic aneurysm models⁴³, and in bacterial infection models^{40,41}. The sgp130Fc protein was expressed and purified according to GMP regulations. Phase I clinical trials were successfully performed with healthy individuals, and a phase II clinical trial is presently ongoing in patients with inflammatory bowel disease⁵⁴. The future will tell whether this elegant therapeutic approach, which was successfully tested in many animal models, leads to a novel paradigm in cytokine-blocking therapies in patients with autoimmune disorders⁴⁶. Similarly, blockade of trans-signalling while leaving classical signalling intact may prove to be beneficial for patients experiencing “cytokine storms” from COVID-19 or CAR T-cell therapies. Finally, we suggest that malignancies promoted by high levels of trans-signalling could be contained by this therapeutic modality.

Abbreviations

ADAM17, a disintegrin and metalloprotease 17; EGFR, epidermal growth factor receptor; gp130, glycoprotein 130 kDa; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; ras, rat sarcoma proto oncogene; sgp130Fc, soluble gp130-Fc fusion protein, which under the name of olamkicept is in phase II clinical trials; sIL-6R, soluble IL-6R; STAT, signal transducer and activator of transcription; TNF α , tumor necrosis factor α ; YAP, YES-associated protein; YES, Yamaguchi sarcoma viral oncogene homolog.

Acknowledgements

I thank all past and current colleagues of our laboratory for many helpful discussions.

References

1. Kishimoto T: **Interleukin-6: From basic science to medicine--40 years in immunology.** *Annu Rev Immunol.* 2005; **23**: 1–21.
[PubMed Abstract](#) | [Publisher Full Text](#)
2. Tanaka T, Narazaki M, Ogata A, *et al.*: **A new era for the treatment of inflammatory autoimmune diseases by interleukin-6 blockade strategy.**

Semin Immunol. 2014; **26**(1): 88–96.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)

3. Teachey DT, Lacey SF, Shaw PA, *et al.*: **Identification of Predictive Biomarkers for Cytokine Release Syndrome after Chimeric Antigen Receptor T-cell Therapy for Acute Lymphoblastic Leukemia.** *Cancer Discov.* 2016; **6**(6): 664–79.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

4. Moore JB, June CH: **Cytokine release syndrome in severe COVID-19.** *Science*. 2020; **368**(6490): 473–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
5. Xu X, Han M, Li T, et al.: **Effective treatment of severe COVID-19 patients with tocilizumab.** *Proc Natl Acad Sci U S A*. 2020; **117**(20): 10970–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Faculty Opinions Recommendation](#)
6. Hirano T, Taga T, Yamasaki K, et al.: **Molecular cloning of the cDNAs for interleukin-6/B cell stimulatory factor 2 and its receptor.** *Ann N Y Acad Sci*. 1989; **557**: 167–78, discussion 17880.
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Gauldie J, Richards C, Harnish D, et al.: **Interferon beta 2/B-cell stimulatory factor type 2 shares identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute phase protein response in liver cells.** *Proc Natl Acad Sci U S A*. 1987; **84**(20): 7251–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
8. Brakenhoff JP, de Groot ER, Evers RF, et al.: **Molecular cloning and expression of hybridoma growth factor in Escherichia coli.** *J Immunol*. 1987; **139**(12): 4116–21.
[PubMed Abstract](#)
9. Zilberstein A, Ruggieri R, Korn JH, et al.: **Structure and expression of cDNA and genes for human interferon-beta-2, a distinct species inducible by growth-stimulatory cytokines.** *EMBO J*. 1986; **5**(10): 2529–37.
[PubMed Abstract](#) | [Free Full Text](#)
10. Haegeman G, Content J, Volckaert G, et al.: **Structural analysis of the sequence coding for an inducible 26-kDa protein in human fibroblasts.** *Eur J Biochem*. 1986; **159**(3): 625–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Rothaug M, Becker-Paulky C, Rose-John S: **The role of interleukin-6 signaling in nervous tissue.** *Biochim Biophys Acta*. 2016; **1863**(6 Pt A): 1218–27.
[PubMed Abstract](#) | [Publisher Full Text](#)
12. Willis EF, MacDonald KPA, Nguyen QH, et al.: **Repopulating Microglia Promote Brain Repair in an IL-6-Dependent Manner.** *Cell*. 2020; **180**(5): 833–846.e16.
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Wallenius V, Wallenius K, Ahren B, et al.: **Interleukin-6-deficient mice develop mature-onset obesity.** *Nat Med*. 2002; **8**(1): 75–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Findeisen M, Allen TL, Henstridge DC, et al.: **Treatment of type 2 diabetes with the designer cytokine IC7Fc.** *Nature*. 2019; **574**(7776): 63–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
15. Pedersen BK, Febbraio MA: **Muscles, exercise and obesity: Skeletal muscle as a secretory organ.** *Nat Rev Endocrinol*. 2012; **8**(8): 457–65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
16. Schmidt S, Schumacher N, Schwarz J, et al.: **ADAM17 is required for EGF-R-induced intestinal tumors via IL-6 trans-signaling.** *J Exp Med*. 2018; **215**(4): 1205–25.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
17. Rose-John S: **The biology of interleukin-6 in the 21st century.** *Semin Immunol*. 2014; **26**(1): 1.
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Schaper F, Rose-John S: **Interleukin-6: Biology, signaling and strategies of blockade.** *Cytokine Growth Factor Rev*. 2015; **26**(5): 475–87.
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Jones SA, Jenkins BJ: **Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer.** *Nat Rev Immunol*. 2018; **18**(12): 773–89.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
20. Garbers C, Heink S, Korn T, et al.: **Interleukin-6: Designing specific therapeutics for a complex cytokine.** *Nat Rev Drug Discov*. 2018; **17**(6): 395–412.
[PubMed Abstract](#) | [Publisher Full Text](#)
21. Müllberg J, Schooltink H, Stoyan T, et al.: **The soluble interleukin-6 receptor is generated by shedding.** *Eur J Immunol*. 1993; **23**(2): 473–80.
[PubMed Abstract](#) | [Publisher Full Text](#)
22. Lust JA, Donovan KA, Kline MP, et al.: **Isolation of an mRNA encoding a soluble form of the human interleukin-6 receptor.** *Cytokine*. 1992; **4**(2): 96–100.
[PubMed Abstract](#) | [Publisher Full Text](#)
23. Mackiewicz A, Schooltink H, Heinrich PC, et al.: **Complex of soluble human IL-6-receptor/IL-6 up-regulates expression of acute-phase proteins.** *J Immunol*. 1992; **149**(6): 2021–7.
[PubMed Abstract](#)
24. Rose-John S, Heinrich PC: **Soluble receptors for cytokines and growth factors: Generation and biological function.** *Biochem J*. 1994; **300**(Pt 2): 281–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
25. Rose-John S: **The Soluble Interleukin 6 Receptor: Advanced Therapeutic Options in Inflammation.** *Clin Pharmacol Ther*. 2017; **102**(4): 591–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
26. Fischer M, Goldschmitt J, Peschel C, et al.: **I. A bioactive designer cytokine for human hematopoietic progenitor cell expansion.** *Nat Biotechnol*. 1997; **15**(2): 142–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Galun E, Zeira E, Pappo O, et al.: **Liver regeneration induced by a designer human IL-6/sIL-6R fusion protein reverses severe hepatocellular injury.** *FASEB J*. 2000; **14**(13): 1979–87.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. März P, Otten U, Rose-John S: **Neural activities of IL-6-type cytokines often depend on soluble cytokine receptors.** *Eur J Neurosci*. 1999; **11**(9): 2995–3004.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. Audet J, Miller CL, Rose-John S, et al.: **Distinct role of gp130 activation in promoting self-renewal divisions by mitogenically stimulated murine hematopoietic stem cells.** *Proc Natl Acad Sci U S A*. 2001; **98**(4): 1757–62.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. Rose-John S: **Interleukin-6 Family Cytokines.** *Cold Spring Harb Perspect Biol*. 2018; **10**(2): a028415.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
31. Horsten U, Schmitz-Van de Leur H, Müllberg J, et al.: **The membrane distal half of gp130 is responsible for the formation of a ternary complex with IL-6 and the IL-6 receptor.** *FEBS Lett*. 1995; **360**(1): 43–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Jostock T, Müllberg J, Ozbek S, et al.: **Soluble gp130 is the natural inhibitor of soluble interleukin-6 receptor transsignaling responses.** *Eur J Biochem*. 2001; **268**(1): 160–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Waage A, Brandtzaeg P, Halstensen A, et al.: **The complex pattern of cytokines in serum from patients with meningococcal septic shock. Association between interleukin 6, interleukin 1, and fatal outcome.** *J Exp Med*. 1989; **169**(1): 333–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
34. Tanaka T, Narazaki M, Kishimoto T: **IL-6 in Inflammation, Immunity, and Disease.** *Cold Spring Harb Perspect Biol*. 2014; **6**(10): a016295.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Faculty Opinions Recommendation](#)
35. Rose-John S: **IL-6 trans-signaling via the soluble IL-6 receptor: Importance for the pro-inflammatory activities of IL-6.** *Int J Biol Sci*. 2012; **8**(9): 1237–47.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
36. Cressman DE, Greenbaum LE, DeAngelis RA, et al.: **Liver Failure and Defective Hepatocyte Regeneration in Interleukin-6-Deficient Mice.** *Science*. 1996; **274**(5291): 1379–83.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Poli V, Balena R, Fattori E, et al.: **Interleukin-6 deficient mice are protected from bone loss caused by estrogen depletion.** *EMBO J*. 1994; **13**(5): 1189–96.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
38. Alonzi T, Fattori E, Lazzaro D, et al.: **Interleukin 6 is required for the development of collagen-induced arthritis.** *J Exp Med*. 1998; **187**(4): 461–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
39. Okuda Y, Sakoda S, Bernard CC, et al.: **IL-6-deficient mice are resistant to the induction of experimental autoimmune encephalomyelitis provoked by myelin oligodendrocyte glycoprotein.** *Int Immunol*. 1998; **10**(5): 703–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
40. Hoge J, Yan I, Jänner N, et al.: **IL-6 controls the innate immune response against Listeria monocytogenes via classical IL-6 signaling.** *J Immunol*. 2013; **190**(2): 703–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
41. Sodenkamp J, Waetzig GH, Scheller J, et al.: **Therapeutic targeting of interleukin-6 trans-signaling does not affect the outcome of experimental tuberculosis.** *Immunobiology*. 2012; **217**(10): 996–1004.
[PubMed Abstract](#) | [Publisher Full Text](#)
42. Barkhausen T, Tschernig T, Rosenstiel P, et al.: **Selective blockade of interleukin-6 trans-signaling improves survival in a murine polymicrobial sepsis model.** *Crit Care Med*. 2011; **39**(6): 1407–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Paige E, Clément M, Lareyre F, et al.: **Interleukin-6 Receptor Signaling and Abdominal Aortic Aneurysm Growth Rates.** *Circ Genom Precis Med*. 2019; **12**(2): e002413.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. Kaiser K, Prystaz K, Vikman A, et al.: **Pharmacological inhibition of IL-6 trans-signaling improves compromised fracture healing after severe trauma.** *Naunyn-Schmiedeberg Arch Pharmacol*. 2018; **391**(5): 523–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
45. Prystaz K, Kaiser K, Kovtun A, et al.: **Distinct Effects of IL-6 Classic and Trans-Signaling in Bone Fracture Healing.** *Am J Pathol*. 2018; **188**(2): 474–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Magro G: **SARS-CoV-2 and COVID-19: Is interleukin-6 (IL-6) the 'culprit lesion' of ARDS onset? What is there besides Tocilizumab? SGP130Fc.** *Cytokine X*. 2020; **2**(2): 100029.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Faculty Opinions Recommendation](#)
47. Lesina M, Kurkowski MU, Ludes K, et al.: **Stat3/Socs3 activation by IL-6 transsignaling promotes progression of pancreatic intraepithelial**

- neoplasia and development of pancreatic cancer. *Cancer Cell*. 2011; **19**(4): 456–69.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
48. Lanaya H, Natarajan A, Komposch K, *et al.*: **EGFR has a tumour-promoting role in liver macrophages during hepatocellular carcinoma formation.** *Nat Cell Biol*. 2014; **16**(10): 972–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
[Faculty Opinions Recommendation](#)
 49. Sacre SM, Andreaskos E, Taylor P, *et al.*: **Molecular therapeutic targets in rheumatoid arthritis.** *Expert Rev Mol Med*. 2005; **7**(16): 1–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
 50. Gabay C, Emery P, van Vollenhoven R, *et al.*: **Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): A randomised, double-blind, controlled phase 4 trial.** *Lancet*. 2013; **381**(9877): 1541–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
 51. Le RQ, Li L, Yuan W, *et al.*: **FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome.** *Oncologist*. 2018; **23**(8): 943–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Faculty Opinions Recommendation](#)
 52. Campochiaro C, Della-Torre E, Cavalli G, *et al.*: **Efficacy and safety of tocilizumab in severe COVID-19 patients: A single-centre retrospective cohort study.** *Eur J Intern Med*. 2020; **76**: 43–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Faculty Opinions Recommendation](#)
 53. Della-Torre E, Campochiaro C, Cavalli G, *et al.*: **Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: An open-label cohort study.** *Ann Rheum Dis*. 2020.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Faculty Opinions Recommendation](#)
 54. **Safety and Efficacy of TJ301 IV in Participants With Active Ulcerative Colitis.** *ClinicalTrials*. 2020.
[Reference Source](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. **Jacqueline Bromberg**
Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
Competing Interests: No competing interests were disclosed.
2. **Hana Algül**
Comprehensive Cancer Center Munich, University Hospital Klinikum rechts der isar, Mildred-Scheel-Chair of Tumor Metabolism, Technical University of Munich, Munich, Germany
Competing Interests: No competing interests were disclosed.
3. **Elke Roeb**
Department of Gastroenterology, Justus Liebig University, Giessen, Germany
Competing Interests: No competing interests were disclosed.

Comments on this article

Version 1

Reader Comment 24 Aug 2020

Andrew Taylor-Robinson, School of Health, Medical & Applied Sciences, Central Queensland University, Brisbane, Australia

IL-6 is well-documented as an inflammatory cytokine that has been demonstrated to play a leading role in cytokine storm syndrome. Studies have shown that an imbalance in molar concentrations of IL-6, membrane-bound IL-6 receptor (IL-6R) and its soluble form (sIL-6R) can lead to up-regulation of IL-6-mediated trans-signalling, thereby initiating formation of a cytokine storm. This has been expertly reviewed by the author¹.

Together with sIL-6R, a soluble form of glycoprotein 130 (sgp130) constitutes an IL-6 neutralizing buffer system². ADAM Metalloproteinase Domain 17 (ADAM17), also known as tumour necrosis factor- α converting enzyme (TACE), is a membrane-bound enzyme that cleaves IL-6R to produce

sIL-6R and which is responsible for disrupting fine tuning of the neutralizing buffer system³.

In relation to the role of IL-6 in the pathogenesis of the severe manifestations of COVID-19, the article touches on this briefly. In order to develop an effective therapeutic strategy for COVID-19 new investigations should consider approaches that can provide control over both viral replication and cytokine imbalance.

Disease fatality associated with Ebola, dengue and SARS-CoV infections in humans is attributed to a cytokine storm that is triggered by excessive pro-inflammatory responses. ADAM-17 could be the keystone molecule involved in regulating IL-6 class switching and through this in controlling pro- and anti-inflammatory responses to viral antigenic stimuli. Therefore, ADAM-17 should be considered as a potential target molecule for novel antiviral drug discovery that would regulate host reactivity to infection and thereby limit or prevent fatal outcomes⁴.

Translating this rationale to SARS-COV-2 infection, my colleagues and I have recently analysed the different factors involved in these complex clinical manifestations as an interactive model⁵. In light of the insights gained we proposed that if administered along with antivirals a combination of ADAM17/TACE prodomain inhibitor (TPD), sgp130Fc protein (a recombinant form of sgp130) and anti-coagulant may promote enhanced outcomes in COVID-19 patient recovery.

References

1. Rose-John S: IL-6 trans-signaling via the soluble IL-6 receptor: Importance for the pro-inflammatory activities of IL-6. *Int J Biol Sci*. 2012; **8**(9): 1237–47. doi:10.7150/ijbs.4989
2. Jostock T, Müllberg J, Özbek S, *et al.*: Soluble gp130 is the natural inhibitor of soluble interleukin-6 receptor transsignaling responses. *Eur J Biochem*. 2001; **268**(1): 160–7. doi:10.1046/j.1432-1327.2001.01867.x
3. Scheller J, Chalaris A, Garbers C, *et al.*: ADAM17: a molecular switch to control inflammation and tissue regeneration. *Trends Immunol*. 2011; **32**(8): 380–7. doi:10.1016/j.it.2011.05.005
4. Mahmud-Al-Rafat A, Majumder A, Taufiqur Rahman KM, *et al.*: Decoding the enigma of antiviral crisis: does one target molecule regulate all? *Cytokine*. 2019; **115**(1): 13–23. doi:10.1016/j.cyto.2018.12.008
5. Mahmud-Al-Rafat A, Muzammal Haque Asim M, Taylor-Robinson AW, *et al.*: A combinational approach to restore cytokine balance and to inhibit virus growth may promote patient recovery in severe COVID-19 cases. *Cytokine*. 2020; **136**(2020): 155228. doi:10.1016/j.cyto.2020.155228

Andrew W. Taylor-Robinson

Professor of Immunology/Haematology & Research Coordinator, Infectious Diseases
School of Health, Medical & Applied Sciences, Central Queensland University, Australia

Competing Interests: No competing interests disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research