Biochimica et Biophysica Acta 1813 (2011) 878–888

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

The pro- and anti-inflammatory properties of the cytokine interleukin-6

Jürgen Scheller [a], Athena Chalaris [b], Dirk Schmidt-Arras [b], Stefan Rose-John [b,*]

[a] Institute of Biochemistry and Molecular Biology II, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany
[b] Institute of Biochemistry, Christian-Albrechts-University, Olshausenstrasse 40, D-24098 Kiel, Germany

ARTICLE INFO

Article history:
Received 10 December 2010
Received in revised form 23 January 2011
Accepted 27 January 2011
Available online 4 February 2011

Keywords:
IL-6 *trans-signaling*
sIL-6R
gp130
sgp130Fc
STAT3 activation
Inflammation associated cancer

ABSTRACT

Interleukin-6 is a cytokine not only involved in inflammation and infection responses but also in the regulation of metabolic, regenerative, and neural processes. In *classic signaling*, interleukin-6 stimulates target cells via a membrane bound interleukin-6 receptor, which upon ligand binding associates with the signaling receptor protein gp130. Gp130 dimerizes, leading to the activation of Janus kinases and subsequent phosphorylation of tyrosine residues within the cytoplasmic portion of gp130. This leads to the engagement of phosphatase Src homology domains containing tyrosin phosphatase-2 (SHP-2) and activation of the ras/raf/Mitogen-activated protein (MAP) kinase (MAPK) pathway. In addition, signal transducer and activator of transcription factors are recruited, which are phosphorylated, and consequently dimerize whereupon they translocate into the nucleus and activate target genes. Interestingly, only few cells express membrane bound interleukin-6 receptor whereas all cells display gp130 on the cell surface. While cells, which only express gp130, are not responsive to interleukin-6 alone, they can respond to a complex of interleukin-6 bound to a naturally occurring soluble form of the interleukin-6 receptor. Therefore, the generation of soluble form of the interleukin-6 receptor dramatically enlarges the spectrum of interleukin-6 target cells. This process has been named *trans-signaling*. Here, we review the involvement of both signaling modes in the biology of interleukin-6. It turns out that regenerative or anti-inflammatory activities of interleukin-6 are mediated by *classic signaling* whereas pro-inflammatory responses of interleukin-6 are rather mediated by *trans-signaling*. This is important since therapeutic blockade of interleukin-6 by the neutralizing anti-interleukin-6 receptor monoclonal antibody tocilizumab has recently been approved for the treatment of inflammatory diseases.

1. Introduction

Functional pleiotropy and redundancy are characteristic features of cytokines, which include interleukins, interferons, colony-stimulating factors, and many growth factors. Cytokines are produced by many different cell types and often show overlapping activities regulating proliferation or differentiation, depending on the type and developmental state of the target cells involved. The cytokines interleukin-6 (IL-6), IL-1, and TNFα are elevated in most, if not all, inflammatory states and have been recognized as targets of therapeutic intervention. This review will focus on the cytokine IL-6, for which also numerous activities outside of the immune system are known. Interestingly, it has been recognized that, although mostly regarded as a pro-inflammatory cytokine, IL-6 also has many regenerative or anti-inflammatory activities. The molecular mechanism of how one cytokine can act in a pro- and anti-inflammatory way is starting to emerge and will be discussed in this review article.

2. IL-6 family of cytokines

Members of the interleukin 6 (IL-6) family of cytokines include IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary inhibitory factor (CNTF), cardiotropin-1 (CT-1), cardiotrophin-like related cytokine and stimulating neurotrophin-1/B-cell stimulating factor 3 (NNT-1), neuropoietin (NPN), IL-27, and IL-31. With the exception of IL-31, all IL-6 type cytokines share the membrane glycoprotein gp130 as a common receptor and signal transducer subunit (reviewed in references 1 and 2). IL-6 and IL-11 initially bind to the membrane bound α receptors IL-6 receptor (IL-6R) or IL-11R, respectively. Subsequently, IL-6/IL-6R or IL-11/IL-11R complexes associate with gp130, leading to gp130-homodimer formation and signal initiation. Viral IL-6 (vIL-6) from the human herpes virus 8 (HHV-8) also signals via a gp130 homodimer but without the need of the αIL-6R [3]. LIF, CNTF, OSM, CT-1, NPN, and NNT-1 signal via gp130/LIF-R-heterodimeric receptor complexes [4]. In addition, OSM signals via a

Abbreviations: ADAM, a disintegrin and metalloprotease; AOM, azoxymethane; CBM, cytokine-binding module; DSS, dextran sodium sulfate; Ig, immunoglobulin; IL, interleukin; mAb, monoclonal antibody; mb, membrane bound; R, receptor; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; wt, wild type

* Corresponding author.
E-mail addresses: jscheller@uni-duesseldorf.de (J. Scheller), rosejohn@biochem.uni-kiel.de (S. Rose-John).

0167-4889/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2011.01.034

receptor complex consisting of gp130 and OSM-R. IL-27 has been shown to act via a gp130/WSX-1 heterodimeric receptor complex [5]. IL-31 is the only IL-6 type cytokine that does not require the receptor chain gp130 but instead induces the formation of a heterodimer of gp130-like receptor (GPL) together with the OSM-R. Like IL-6 and IL-11, other IL-6 type cytokines need additional specific α receptors, including the glycosylphosphatidylinositol (GPI)-anchored CNTF-R for CNTF, CLC, NPN, and NNT-1 as well as the soluble Epstein–Barr-virus induced Gene 3 (EBI-3) for p28 (IL-27). CT-1 has been described to act directly via a gp130/LIF-R heterodimer but an as yet unidentified CT-1 specific GPI-anchored receptor may also exist on neuronal cells [6,7].

Importantly, most soluble receptor molecules are antagonists and compete with membrane bound proteins for ligand binding, whereas the soluble receptors sIL-6R, EBI-3, and sCNTF-R of the IL-6 family are agonists.

3. The IL-6 receptor complex

The receptor complex mediating the biological activities of IL-6 consists of the IL-6 binding type I transmembrane glycoprotein termed IL-6R (also designated CD126 or gp80) and the type I transmembrane signal transducer protein gp130 (CD130). On target cells, IL-6 first binds to the membrane-bound non-signaling α-receptor IL-6R (mbIL-6R). This complex of IL-6 and IL-6R then binds to two molecules of gp130 and leads to IL-6-signal transduction, which includes activation of JAK/STAT, ERK, and PI3K signal transduction pathways.

IL-6 is a glycosylated protein of 21–28 kDa and has the typical four-helix bundle structure characteristic for all IL-6-type cytokines, made up of four long α-helices (A, B, C, D) arranged in an up-up-down-down topology. IL-6 has three distinct receptor-binding sites referred to as site 1 (contacting the IL-6R), site 2 (contacting gp130 between domain 2 and domain 3), and site 3 (contacting the domain 1 or Ig-like domain of gp130). Site 1 is formed by the C-terminal residues of helix D and the C-terminal part of the AB-loop and determines the specificity of IL-6R binding. Site 2, consisting of residues located in the middle of helices A and C, and site 3, consisting of residues located at the N-terminal part of the AB-loop (Site 3a) and the C-terminal residues of the D-helix (site 3b) are needed for the recruitment of two gp130 molecules.

In contrast to human IL-6, vIL-6 encoded by the human herpes virus 8 (HHV-8), which shares 25% amino acid sequence homology with human IL-6, can directly activate gp130 on cells without the requirement of the IL-6R [3,8]. Like in human IL-6, site 2 of vIL-6 binds to the domains 2/3 of gp130 whereas site 3 of vIL-6 interacts with Ig-like domain D1 of gp130. Interestingly, the amino acid residues forming site 2 and site 3 showed no conservation between human IL-6 and vIL-6.

Recently, the epitopes within the vIL-6 protein, which enable direct binding to gp130, were identified. Human/viral IL-6 chimeric proteins were constructed and tested for direct binding to gp130 [9]. An IL-6 chimera, which carried both gp130 interacting sites 2 and 3 of vIL-6, could not bind to gp130 in the absence of the IL-6R. In contrast, an IL-6 chimeric protein, containing only amino acids from site 3 of vIL-6 plus the loop between helices B and C (named site 3c), displayed the same functional properties as vIL-6. This human/viral IL-6 chimera could induce STAT3 phosphorylation as well as proliferation of a cell line dependent on IL-6 and soluble IL-6R. Since the crystal structure of vIL-6 in complex with gp130 revealed no interaction of site 3c with gp130 [8], requirement of this site for direct binding of vIL-6 to gp130 was surprising. Interestingly, a different IL-6 chimera, consisting of site 3c of vIL-6 alone, failed to activate gp130 in the absence of IL-6R. Therefore, site 3c together with sites 3a and 3b appeared to be the minimal requirement for activation of gp130 in the absence of the IL-6R [9].

The IL-6R is a glycosylated type I membrane 80 kDa protein. The Ig-like domain of the human IL-6R is not required for binding of IL-6 [10] but stabilizes the receptor during intracellular trafficking through the secretory pathway [11]. Binding of IL-6 to IL-6R is mediated by residues on domains 2 and 3 of the IL-6R. Interestingly, murine IL-6R lacking the Ig-domain was not able to bind IL-6 [12], pointing to a fundamental difference between human and murine IL-6. So far, it is unclear whether this difference explains the species specificity of human and murine IL-6; whereas human IL-6 binds to both, human and murine IL-6R, murine IL-6 exclusively binds to the murine IL-6R [13]. Shedding of the IL-6R and functional role of soluble IL-6R in a process called *trans-signaling* is described in Sections 4 and 5.

Gp130 is a glycosylated type I membrane protein of 130–150 kDa with 6 extracellular domains, a single transmembrane domain, and a cytoplasmic domain. Gp130 has an N-terminal Ig-like-domain (D1), followed by two cytokine binding domains (CBD; domain 2 and domain 3) and three fibronectin-like (FN III)-domains (domains 4–6). In addition to the physical interaction of gp130 and IL-6R [14], the Ig-like domain of gp130 binds to site 3 of IL-6 and the CBM-domains of gp130 interacting with site 2 of IL-6 [14]. The N-terminally located CBM-domain (domain 2) contains two pairs of conserved cysteines that form interstrand disulfide bonds. The C-terminally located domain 3 contains a conserved Trp-Ser-X-Trp-Ser (WSXWS) motif [15].

The membrane proximal domains of gp130 (domains 4–6) are required for transmitting the signal to the cytoplasmic domain. Deletion mutants lacking D4, D5, or D6 showed no or reduced signal transduction activities [16]. Furthermore, a study using single-particle electron microscopy of the symmetric IL-6/IL-6R/gp130-D1-D6 revealed that the COOH terminal portions of the cytokine binding domain of gp130 are approximately 100 Å apart. The COOH terminal portions of the membrane proximal fibronectin III domains are in close proximity, leading to close juxtaposition of the transmembrane domains of the cell surface expressed receptor, enabling activation of intracellular signaling [17]. After ligand binding, domains 4 and 5 are orientated at an angle of approximately 80°, resulting in an acute bend in the structure. Thus, the complete ectodomain of gp130 adopts a wide-open “C”-shape structure [18,19].

Of importance, gp130 receptors exist as preformed, inactive dimers at the cell membrane [20,21]. Also, the IL-6R exists as preformed dimer at the plasma membrane [22]. Therefore, the presumably loose and not adjusted association of the juxtamembrane and transmembrane domain regions in the preformed dimers are not sufficient to induce signal transduction. This finding is consistent with a cellular study in which insertion of one to four alanine residues to the juxtamembrane intracellular region of gp130 leads to successive impairment but not abolishment of signal transduction, indicating that the gp130/gp130 dimer not only needs to be positioned in close proximity but also needs to be aligned in a specific manner to allow for full activation of the receptor [23]. Gp130 lacks intrinsic kinase activity and it is non-covalently associated with Janus kinases (JAKs; JAK1, JAK2, and TYK2). These tyrosine kinases become autophosphorylated upon receptor engagement by IL-6 type cytokines and subsequently phosphorylate distinct tyrosine residues within gp130 [1]. In this view, cytokine binding results in reorganization of preformed receptor complexes in such a way that the JAKs are rearranged and juxtaposed, allowing their activation by cross-phosphorylation. This implies that, after ligand binding, only a subtle reorganization within the receptor complex has to occur to initiate intracellular signaling.

After ligand binding, the signaling complex is rapidly internalized, mediated by dileucine-like-motifs in the cytoplasmic domain of gp130 [24,25]. No internalization motifs have been identified within the cytoplasmic portion of the IL-6R. Interestingly, caspase activation by CD95L leads to degradation of the gp130 receptor chain and thereby to blunting of IL-6 signaling [26].

Functional and structural studies suggested that IL-6 forms a hexameric signaling complex containing two molecules of IL-6, IL-6R,

and gp130 ($IL\text{-}6_2/IL\text{-}6R_2/gp130_2$) [14,27]. However, an alternative activation model based on a tetrameric gp130 receptor complex ($IL\text{-}6_1/IL\text{-}6R_1/gp130_2$) was also proposed [27]. Cotransfection of two signaling-incompetent gp130 muteins in which one gp130 mutein (gp130ΔD1) is unable to interact with site 2 of IL-6 and the other gp130 mutein (gp130mutCBM) with site 3 restored IL-6 signaling, suggesting that only one of the two IL-6 binding sites in the gp130 homodimer is sufficient to induce the signaling cascade [28]. This result is not compatible with a hexameric receptor configuration. Interestingly, the dose response curves of IL-6 and IL-11, which signal via a homodimer of gp130, are bell-shaped, with high cytokine concentrations leading to a decline of the biological response [29,30]. These and other results suggest that low IL-6 concentrations might favor the formation of tetrameric $IL\text{-}6_1/IL\text{-}6R_1/gp130_2$ complexes whereas higher IL-6 concentrations lead to the formation of hexameric $IL\text{-}6_2/IL\text{-}6R_2/gp130_2$ complexes. Accordingly, CNTF, which signals via a tetrameric complex of $CNTF_1/CNTF\text{-}R_1/gp130_1/LIF\text{-}R_1$, and which, even at higher concentration cannot form hexameric signaling complexes, does not show a bell-shaped dose-response over a wide concentration range [31].

4. Generation of the soluble IL-6R

Soluble receptors have been discovered for many cytokines and are important regulators of inflammatory events by acting as agonists or antagonists of cytokine signaling. The soluble receptors of IL-1α ($sIL\text{-}1R_{II}$) and TNFα ($sTNFR_I$ and $sTNFR_{II}$) inhibit the biologic activity of their ligands and therefore act as antagonists [32–36]. In contrast, the sIL-6R amplifies IL-6-mediated signaling by activation of cell types, which express the signal transducer protein gp130 but lack mbIL-6R expression. Interestingly, only a few cell types express IL-6R on the cell surface and therefore respond to IL-6 alone. Such cells are macrophages, neutrophils, some types of T-cells and hepatocytes. In contrast to the IL-6R, gp130 is ubiquitously expressed [37–39]. The sIL-6R binds to IL-6 with comparable affinity as the mbIL-6R and the IL-6/sIL-6R complex acts agonistically on cells that express gp130 (Fig. 1). Activation of cells that only express gp130 *via* the IL-6/sIL-6R complex is called *trans-signaling* whereas activation of cells *via* the mbIL-6R in complex with IL-6 is called *classic-signaling* [33,38]. Activation of gp130 via *trans-signaling* is crucial for lymphocyte trafficking into the inflamed area by controlling chemokine expression [40,41]. Furthermore, IL-6 *trans-signaling* promotes T-cell proliferation during colon cancer development and is involved in regulating adhesion molecule expression on endothelial cells [42,43].

There are two major mechanisms leading to generation of the sIL-6R. The first involves proteolytic cleavage of the mbIL-6R and is dependent on a metalloprotease activity. The second mechanism is dependent on the transcription of an alternative spliced IL-6R-mRNA lacking the transmembrane and cytosolic domains [44,45]. Of note, alternative splicing results in a frame shift and leads to the generation of a novel COOH terminal protein sequence (GSRRRGSCGL), which, however, has no influence on the biological properties of the sIL-6R. So far, the alternative spliced mRNA coding for the soluble form of the IL-6R has only been described for humans but has not been identified in the mouse, indicating that the circulating murine sIL-6R is generated exclusively by limited proteolysis. The proteolytic cleavage of the IL-6R is catalyzed by Zn^{2+}-metalloproteases of the ADAM (a disintegrin and metalloprotease) family [40,46–48]. ADAM proteases are type-I transmembrane-proteins and are involved in limited proteolysis (shedding) of many cytokine receptors including $TNFR_{I+II}$, IL-1R, M-CSF receptor, and IL-6R [49,50]. Among the numerous ADAM proteases (the human genome contains 25 *ADAM* genes), ADAM10 and ADAM17 are the most related and share many substrates [51]. The IL-6R has been described as a substrate for ADAM17 as well as for ADAM10. Apparently, ADAM10 is responsible for the slow constitutive IL-6R shedding, whereas ADAM17, upon appropriate activation, causes rapid IL-6R proteolysis [47]. ADAM17 activation and subsequent cleavage of the IL-6R can be induced by the phorbol ester phorbol-12-myristate-13-acetate (PMA), which is a well characterized activator of protein kinase C (PKC) [44]. ADAM17 can also be activated by proinflammatory cytokines such as IL-1β and TNFα [52], by the bacterial toxins streptolysin O and hemolysin A [53], by cellular cholesterol depletion [47], and by the proteosome inhibitor bortezomib [54]. In a recent study, we identified apoptotic pathways as a physiological stimulus of IL-6R shedding [40]. Apoptosis plays an important role in regulating growth, tissue homeostasis, development, and immune responses. The induction of apoptosis is mediated by extrinsic and intrinsic pathways, which require the cooperation of a series of molecules including signal molecules and receptors, enzymes, and gene regulating proteins. Chalaris et al. demonstrated that intrinsic and extrinsic inductions of apoptosis by stimuli as diverse as DNA-damage, cytokine deprivation, UV irradiation, and Fas ligation resulted in ADAM17 mediated shedding of the IL-6R from the cell surface. Apoptosis-induced shedding of the IL-6R was caspase-dependent but PKC-, MAPK-, and ROS- independent. Inhibition of ADAM17 during apoptosis by small pharmacological inhibitors or by a dominant-negative ADAM17 variant resulted in inhibition of IL-6R shedding. The sIL-6R generated during apoptosis was biologically active and formed complexes with IL-6, resulting in IL-6 *trans-signaling* in non-apoptotic cells. Neutrophils have a short life span and die rapidly *via* apoptosis *in vivo* and *in vitro*. Primary human neutrophils shed the IL-6R after induction of apoptosis. Using the air pouch mouse model of acute inflammation, we demonstrated that apoptosis-induced shedding of the IL-6R by neutrophils facilitated formation of IL-6/sIL-6R complexes, which directed IL-6 *trans-signaling* on endothelial cells. These cells were hereby stimulated to secrete chemokines leading to recruitment of mononuclear phagocytic cells involved in the nonphlogistic removal of apoptotic neutrophils. Furthermore, blocking IL-6 *trans-signaling* by neutralizing antibodies or soluble gp130-Fc during acute inflammation resulted in normal influx of neutrophils but in severely impaired influx of monocytes into the

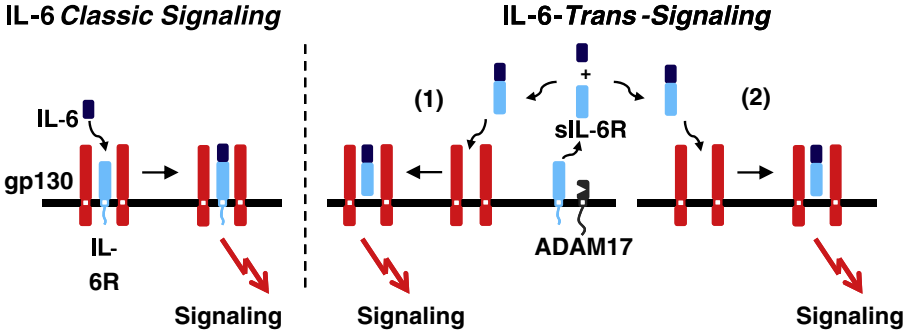

Fig. 1. *Classic-* and *trans-signaling* of IL-6. Cells that express both gp130 and the IL-6R are responsive to IL-6 (*classic signaling*). However, cells that express only gp130 can be activated by the IL-6/sIL-6R complex. Activation of cells by the IL-6/sIL-6R complex is termed *trans-signaling*. The sIL-6R is generated by proteolytic cleavage of the membrane bound precursor. The sIL-6R binds IL-6 with comparable affinity as the membrane bound form and mediates gp130 activation in an (1) autocrine or (2) paracrine manner.

inflamed area. Therefore, IL-6R shedding and subsequent IL-6 *trans-signaling* represent important steps for the resolution of inflammatory responses by controlling the recruitment of mononuclear phagocytes (Fig. 2). Thus, shedding of the IL-6R during neutrophil apoptosis may have profound effects on the outcome of the inflammatory response.

In a recent study, mice with a conditional targeted IL-6R gene were analyzed [55]. When the IL-6R gene was knocked down in hepatocytes, the serum levels of sIL-6R went down by 32%. Ablation of the IL-6R gene in hematopoietic cells, however, led to a reduction of sIL-6R serum levels by 60%. From these studies, it can be concluded that hepatocytes and hematopoietic cells are the main sources of sIL-6R found in the circulation [55].

Interestingly, a soluble form of the signal transducer protein gp130 (sgp130) was also detected in the circulation at relatively high concentrations (100–400 ng/ml in human plasma) [56–58]. Sgp130 is mainly produced by alternative splicing rather than limited proteolysis [59]. Since sgp130 can bind to the IL-6/sIL-6R complex in the circulation, it acts as a specific inhibitor of IL-6 mediated *trans-signaling* [60]. *Classic-signaling* via the mbIL-6R is not affected by sgp130. Of note, sgp130 is specific for the IL-6/sIL-6R complex since signaling of other IL-6-type cytokines like LIF and OSM were inhibited at 100–1000-fold higher concentrations and CNTF and IL-27 signaling were not affected at all [60–62]. We developed a chimeric designer cytokine receptor termed sgp130Fc. This fusion protein consists of the entire extracellular portion of gp130 fused to the Fc region of human IgG1. As sgp130Fc forms dimers, it acts as a potent inhibitor of IL-6 *trans-signaling* and has more than 10-fold higher inhibitory potential compared to the monomeric natural occurring sgp130 form [60]. Sgp130Fc was used in many mouse models of human diseases and showed highly beneficial therapeutic effects in antigen-induced arthritis, inflammatory bowel disease, and colon associated cancer [42,63,64]. Moreover, it was shown that sgp130Fc blocked migration of TH_{17} cells in a *Staphylococcus epidermidis* induced peritonitis model [65]. Recently, we generated transgenic mice, which expressed sgp130Fc under the control of the liver specific phosphoenol pyruvate carboxykinase (PEPCK) promoter. The sgp130Fc protein produced in hepatocytes and secreted in the circulation was detected at high concentrations (10–30 μg/ml). The sgp130Fc protein produced in these mice was fully functional and efficiently inhibited IL-6 *trans-signaling in vivo* [41]. In the air pouch model of acute inflammation, we demonstrated that leukocyte accumulation in sgp130Fc transgenic mice was profoundly impaired as compared to wt mice. In particular, neutrophil and macrophage infiltration was disturbed at later stages of inflammation, an effect which was accompanied by a reduced production of the CC chemokine MCP-1.

In a recent study, an IL-6R neutralizing mAB, which exclusively blocked IL-6 *trans-signaling*, was generated. Using this antibody, the authors showed that intra-articular neutralization of *trans-signaling* blocked local inflammatory responses [66]. The inhibition of collagen induced arthritis in mice using this antibody, however, was less effective than the inhibition by the *trans-signaling* inhibitor sgp130Fc, indicating that the IL-6R neutralizing mAB was less effective [64,66].

5. *Classic signaling* and *trans-signaling* of interleukin-6

With the help of the sgp130Fc protein [60] and the fusion protein of IL-6 and the sIL-6R named Hyper-IL-6 [67], the contribution of *classic-* and *trans-signaling* during IL-6 mediated responses was analyzed in numerous *in vitro* and *in vivo* studies. By comparing the *in vitro* and *in vivo* activities of IL-6 and Hyper-IL-6, we concluded that neural cells [68,69], neural stem cells [70], hematopoietic stem cells [71,72], liver progenitor cells [73], and murine embryonic stem cells [74] depend on the sIL-6R in their response to IL-6.

An important role of IL-6 in the regeneration of the liver had been suggested by the high levels of IL-6 secreted after partial hepatectomy [75]. Furthermore, IL-$6^{-/-}$ mice were shown to be impaired in liver regeneration after 2/3 hepatectomy [76]. Experiments with IL-6 transgenic mice and IL-6/sIL-6R double transgenic mice demonstrated that only the combination of IL-6 and sIL-6R but not IL-6 alone led to efficient hepatocellular proliferation, suggesting a decisive role of IL-6 *trans-signaling* in the regulation of liver regeneration [77–79]. Indeed, we could demonstrate that the application of Hyper-IL-6, but not of IL-6 alone, accelerated regeneration of the liver after partial hepatectomy [80] as well as after D-galactosamine induced liver damage [81,82].

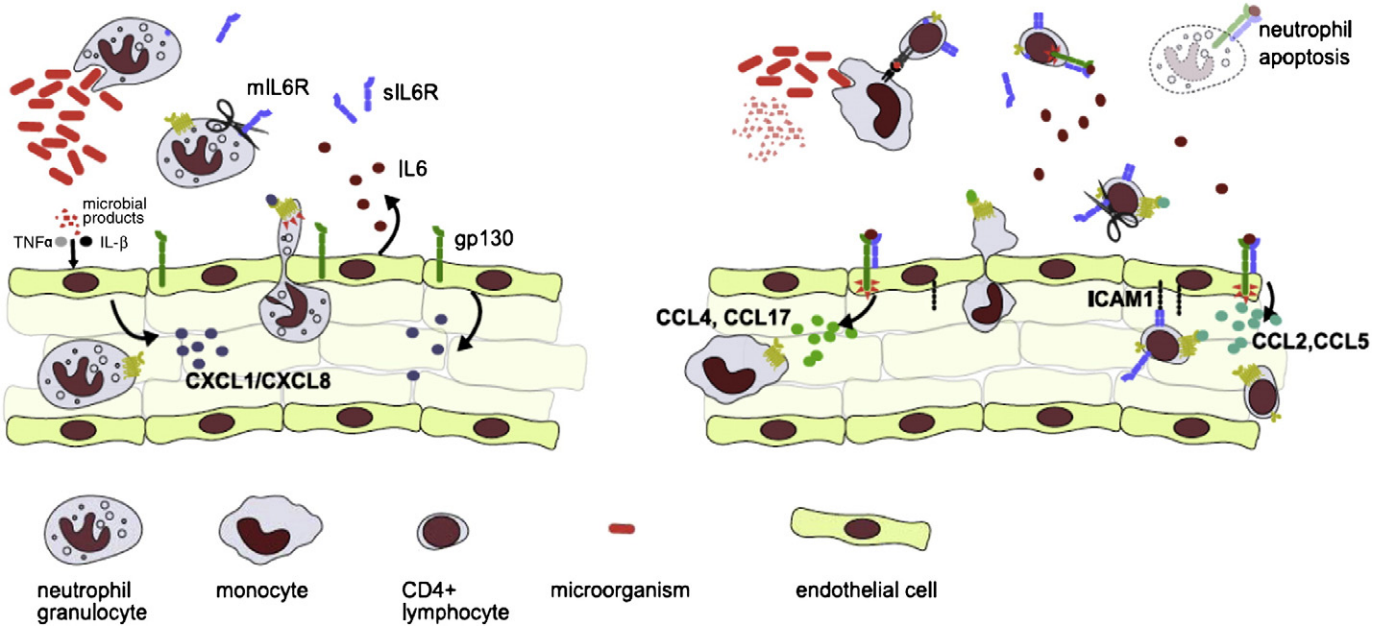

Fig. 2. Neutrophil apoptosis leads to shedding of IL-6R and to progression of the inflammatory process. Left panel: during the acute phase of inflammation, endothelial cells produce IL-6, as well as a plethora of chemokines, leading to the attraction of neutrophils. Upon infiltration to the site of inflammation, neutrophils produce soluble IL6 receptor (sIL6R) by proteolytic cleavage of the membrane bound form (mIL6R). Right panel: endothelial cells are subsequently stimulated via IL-6 *trans-signaling*, leading to a switch in chemokine expression from CXC chemokines such as KC to CC chemokines like MCP-1, resulting mainly in the attraction of monocytes and T-lymphocytes. In addition, L-selectin and ICAM-1 mediated tethering of leukocytes is enhanced. While IL-6 induces apoptosis of neutrophils and hence contributes to neutrophil clearance, maintenance of $CD4^+$ T_H17 cells is mediated by IL-6 *trans-signaling*.

These findings were supported by the fact that sgp130Fc inhibited hepatocellular proliferation and regeneration in the liver after chemically induced damage [83,84]. Interestingly, blocking classic interleukin-6 signaling but not interleukin-6 *trans-signaling* reduced concanavalin A-induced liver damage in mice [85].

In several models of chronic inflammatory bowel disease, it turned out that sgp130Fc was as effective as a neutralizing antibody against the IL-6R to block the inflammatory process [63]. This was later confirmed in a genetic model of ileitis in SAMP1/Yit mice [86]. Several mouse models of arthritis, namely antigen induced arthritis and collagen induced arthritis, were analyzed and it was shown that IL-6$^{-/-}$ mice were completely protected against the disease [64,87]. Interestingly, only injection of Hyper-IL-6 but not IL-6 alone was able to restore the disease in antigen induced arthritis, pointing to an involvement of *trans-signaling* in the development of this autoimmune disease [87]. The application of sgp130Fc completely blocked the development of arthritis in both animal models [64,87], underlining the importance of IL-6 *trans-signaling*. We could also show that, in a murine peritonitis model, which depended on the injection of sterile supernatants of *Staphylococcus epidermidis*, the progression from the neutrophilic to the mononuclear stage depended on IL-6 *trans-signaling*. This progression could be induced by the injection of Hyper-IL-6 and could be blocked by the application of sgp130Fc [88]. The induction of inflammatory colon cancer in the AOM/DSS model could be blocked to the same degree by the application of a neutralizing antibody against the IL-6R and by sgp130Fc, again demonstrating that the development of inflammation induced cancer depended on IL-6 *trans-signaling* [42]. These results were recently confirmed in a mouse model of colitis-associated cancer, in which mice were treated over 9 cycles with DSS without prior treatment with the mutagen AOM [89].

In patients with malignant ovarian cancer IL-6 *trans-signaling* on endothelial cells prevented chemotherapy-induced apoptosis, induced endothelial hyperpermeability, and increased transendothelial migration of ovarian cancer cells. Selective targeting of IL-6 *trans-signaling* in mice strongly reduced ascites formation in a xenograft model [90].

Interestingly, in a recent report, it was shown that IL-6$^{-/-}$ mice upon DSS treatment showed a higher inflammatory score than wt mice. This was explained by the positive effect of IL-6 on the regeneration of intestinal epithelial cells upon wounding brought about by the application of the irritant DSS [91]. A regenerative effect of IL-6 was already demonstrated in earlier studies with the enteric bacterial pathogen *Citrobacter rodentium* [92]. The importance of the regeneration of intestinal epithelial cells after DSS treatment was recently underlined by a study using mice, which expressed extremely low levels of the protease ADAM17, the enzyme known to be responsible for the cleavage of TNFα, IL-6R, and ligands of the EGF-R. In the absence of ADAM17 activity, the lack of EGF-R activity led to the complete absence of STAT3 phosphorylation and consequently of regenerative proliferation in the epithelium of the gut. Accordingly, a breakdown of the intestinal barrier and infiltration of immune cells was observed, which led to severe weight loss and death of mice [93].

In murine sepsis models, blockade of IL-6 *trans-signaling* was sufficient to rescue the mice from death [94,95]. Interestingly, in the caecum puncture ligation model, global IL-6 blockade was less beneficial than selective blockade of IL-6 *trans-signaling* with the sgp130Fc protein. This could be explained by the fact that sgp130Fc only blocks IL-6 bound to the sIL-6R. Since during sepsis, the levels of IL-6 markedly exceed the levels of sIL-6R, enough IL-6 is left active which can stimulate regenerative proliferation in the epithelium of the gut, whereas in the case of global IL-6 blockade, no active IL-6 is left [94].

These examples not only clearly demonstrated that the pro-inflammatory activities of IL-6 were dependent on *trans-signaling*. They also showed that IL-6 has regenerative activities, which, when absent, aggravated the development of the inflammatory process. Since intestinal epithelial cells express the mbIL-6R, it can be concluded that these regenerative (or anti-inflammatory) activities of IL-6 most likely depended on *classic-signaling* via the mbIL-6R [42].

6. Constitutive activation of gp130 by ligand independent dimerization

Besides the ligand-dependent activation of gp130 by IL-6 type cytokines, it can also be activated in a ligand-independent way by forced dimerization. Replacement of the entire extracellular domains of gp130 with the leucine zipper region of the c-jun protein created the chimeric receptor protein L-gp130 [96]. Upon retroviral transduction into an IL-3 and/or IL-6-dependent pre B-cell line, STAT3 as well as ERK1/2 phosphorylation was detected and the cells exhibited ligand-independent growth over several months. Furthermore, transfection of murine embryonal stem cells with L-gp130 led to up-regulation of the stem cell factor OCT-4 and thus suppression of differentiation [96].

In 2009, Rebouissou et al. described naturally occurring, ligand-independent, and constitutively active gain-of-function gp130 variants in inflammatory hepatocellular adenomas in humans. These variants had in-frame deletions in the domain 2 of gp130 (contacting site 2 of IL-6) resulting in a marked ligand-independent activation of the gp130 signaling pathway in inflammatory hepatocellular adenomas. The gain-of-function gp130 mutations in these human hepatocellular adenomas were linked to the activation of the acute inflammatory phase observed in malignant conversion of hepatocytes [97]. Interestingly, we had already observed liver adenoma formation in IL-6/sIL-6R double transgenic mice but not in IL-6 single transgenic mice [98], indicating that this process was induced by IL-6 *trans-signaling*.

Recently, Suthaus et al. showed that gp130 could also be activated in a rather different way of ligand-independent dimerization [99]. To achieve ligand-independent dimerization of homo- and heterodimeric gp130-type receptor complexes including gp130/gp130, gp130/LIFR, gp130/OSM-R, gp130/WSX-1, and OSM-R/GPL, a novel system based on IL-15/IL-15R-sushi domain was established, in which the entire extracellular domains of gp130 and other gp130-type receptors were replaced by IL-15 or the IL-15R. IL-15 binds with high affinity to the IL-15R [100]. A chimeric IL-15-gp130 receptor again led to receptor phosphorylation, subsequent STAT1/3 and ERK1/2 phosphorylation, and cytokine-independent growth of a factor-dependent pre B-cell line [99] which might be explained by the tendency of IL-15 to form dimers and multimers (Inken Lorenzen, personal communication [101]). However, fusion of IL-15 to truncated receptors including LIFR, OSM-R, WSX-1, and GPL did not show ligand-independent activation of the respective homodimeric receptor, although other reports showed that functional homodimerization of LIFR, OSMR, and GPL could be achieved by artificial ligand-induced systems [102,103]. Functional ligand-independent heterodimerization of gp130/LIFR, gp130/OSMR, gp130/WSX-1, and OSMR/GPL receptor complexes was achieved by co-expression of IL-15-LIFR, IL-15-OSMR, or IL-15-WSX-1 with IL-15R domain fused to gp130 (N-terminally truncated) or GPL (N-terminally truncated) and led to cytokine-independent growth of the respective factor-dependent pre B-cell lines [99]. In addition, functional homodimerization of LIFR/LIFR and GPL/GPL could be achieved by co-expression of IL-15-LIFR with IL-15R-sushi-LIFR and IL-15-GPL with IL-15R-sushi-GPL (unpublished data). It remains open whether such heterodimeric complexes will also be found *in vivo* as recently exemplified for the constitutive, ligand-independent somatic in-frame deletion variants of gp130 [97].

7. Activities of interleukin-6 *in vivo*

7.1. Interleukin-6 as an activator of the immune system

There are several lines of evidence suggesting that IL-6 plays a pivotal role during the transition from innate to acquired immunity. Acute inflammation is characterized by an initial infiltration of

neutrophils, which is then replaced by monocytes and T cells after 24–48 h in order to prevent increased tissue damage from the accumulation of neutrophil-secreted proteases and reactive oxygen-species at the site of inflammation. Endothelial cells as well as other vascular elements that are activated by microbial products, IL-1β or TNFα, produce various chemokines together with IL-6, leading to the attraction of neutrophils in the initial phase. Proteolytic processing of the IL-6R from invading neutrophils subsequently drives IL-6 *trans-signaling* in resident tissue cells, leading to a switch from neutrophil to monocyte recruitment by suppressing mainly neutrophil-attracting (CXCL1/Groα, CXCL8/IL-8, CX3CL1/fractalkine) and enhancing mainly monocyte-attracting chemokines (CCL2/MCP-1, CCL8/MCP-2, CXCL5/ENA-78, CXCL6/GCP-2) [88,104–106]. Moreover, cell adhesion molecules like ICAM-1, VCAM-1, and CD62E (E-selectin) on endothelial cells, as well as L-selectin (CD62L) on lymphocytes are upregulated by IL-6 *trans-signaling*, thereby enhancing leukocyte transmigration [43,105,107]. Besides its role in attracting monocytes, IL-6 *trans-signaling* has been shown to skew monocyte differentiation towards macrophages by upregulating M-CSF receptor expression [108]. Studies in signaling defective gp130 knock-in mice suggest that the level of M-CSFR expression is directly related to the extent of ERK activation, as overactivation of STAT3 suppressed M-CSFR expression [109]. The finding that IL-6 induces neutrophil apoptosis further supports the notion that IL-6 substantially contributes to the resolution of acute neutrophil infiltration [105].

Analysis of peritoneal inflammation in IL-6$^{-/-}$ mice revealed that IL-6 is necessary for T cell recruitment. IL-6 *trans-signaling* triggers the expression of T cell attracting chemokines (CCL4, CCL5, CCL17, and CXCL10), a process which could be blocked by sgp130Fc [110]. Moreover, IL-6 has been shown to rescue T cells from entering apoptosis, a process that seems to rely on STAT3-dependent upregulation of anti-apoptotic regulators (Bcl-2, Bcl-x_L) and modulation of Fas surface expression [63,104,111].

Besides its role in the recruitment and anti-apoptosis of T lymphocytes, IL-6 plays a crucial role in B and T cell differentiation. IL-6 was initially characterized as a factor that enhances antibody production in a B cell line [112] and supports growth of B lineage neoplasms [31,113]. Likewise, IL-6$^{-/-}$ mice have an impaired IgG production upon immunization with a T cell-dependent antigen [114]. More recently, it has been shown that IL-6 promotes B cell helper capabilities of CD4$^+$ T cells through increased IL-21 production [115,116].

Upon activation by antigen-presenting cells, naïve T-helper precursors can differentiate into T_H1, T_H2, or T_H17 and regulatory T (T_{reg}) cells. IL-6 has been shown to skew T cell differentiation towards T_H2 and T_H17. T_H2 cell differentiation is thereby governed by inducing the expression of IL-4 via upregulation of NFATc2 and by the suppression of IFNγ signaling via upregulation of SOCS1 [117,118]. Recently, it has been shown that IL-6 can strongly inhibit the TGFβ-mediated differentiation of naïve CD4$^+$ T-cells into regulatory T-cells (T_{reg}), which inhibit autoimmunity and protect against tissue injury. On the other hand, the combination of TGFβ and IL-6 induced the formation of IL-17 secreting T_H17 cells, a subset of T helper cells, distinct from T_H1 and T_H2 cells that are implicated in the induction of autoimmune diseases [119,120]. Interestingly, it was shown that only the combination of IL-6/sIL-6R but not IL-6 alone led to the efficient suppression of T_{reg} cells and the induction of T_H17 cells, indicating that IL-6 *trans-signaling* plays an important role in T-cell differentiation [121].

Interestingly, TGFβ enhanced IL-6 induced STAT3 phosphorylation by lowering the expression of SOCS3. *In vitro*, suppression of SOCS3 in naïve T cells enhanced IL-6 induced RORγt expression albeit to a lesser extent than when cells were stimulated with IL-6 and TGFβ [122]. These data support the notion that persistent STAT3 activation is needed to reverse the Foxp3-mediated repression of RORγt and RORα and thereby the differentiation and maintenance of T_H17 cells. In line with this is the finding that an IL-21 autocrine loop, which also leads to STAT3 activation, is established during the course of T_H17 differentiation. The induction of pathogenic T_H17 cell formation can also be induced by IL-6 in concert with IL-1β and IL-23. In these settings, IL-6 is important to upregulate the IL-23 receptor in naïve CD4$^+$ T-cells via a STAT3-dependent pathway [123].

Interestingly, whereas naïve T cells in the periphery express mbIL-6R, IL-6R is proteolytically shed from activated T cells. Therefore, differentiation of T_H17 cells is mediated via IL-6 *classic-signaling* whereas the maintenance of activated T_H17 cells has been shown to be strongly supported by IL-6 *trans-signaling* [65]. Together, these data suggest that, in the absence of any inflammatory insult, TGFβ suppresses the generation of effector T cells and induces T_{reg} cells. However, during inflammation or infection, IL-6 with the help of sIL-6R suppresses T_{reg} development and favors the differentiation of effector T_H17 cells (Fig. 3). This is in accordance with the findings that IL-6$^{-/-}$ mice are protected from experimental autoimmune encephalomyelitis.

7.2. Interleukin-6 and metabolic control

A role of IL-6 in the control of metabolism has been suspected based on several observations. The group of Pedersen found that muscle cells upon exercise secreted large amounts of IL-6 [124,125]. On the other hand, it was seen that adipocytes of obese individuals secrete IL-6, an activity which correlated with the adipocyte volume [126]. Therefore, obesity was regarded as a state of chronic, low-grade inflammation [127]. Strikingly, IL-6$^{-/-}$ mice were found to develop late onset obesity [128], although this finding could not be reproduced by other authors [129]. In a recent study, carefully comparing wt and IL-6$^{-/-}$ mice, it was demonstrated that mice in the absence of IL-6 develop glucose intolerance and insulin resistance. Furthermore, IL-6$^{-/-}$ mice exhibited signs of liver inflammation [130]. When the IL-6R gene was deleted only in hepatocytes, mice developed a reduction in insulin sensitivity and glucose tolerance [131]. Interestingly, these mice also developed liver inflammation, which could be blocked upon blockade of TNFα, suggesting a pivotal balance of IL-6 and TNFα signaling in the liver [131].

Of note, in patients receiving the IL-6R neutralizing mAb Actemra (tocilizumab), an increase in body weight of approximately 4 kg (7%) and marked hypertriglyceridemia and hypercholsterinemia during the treatment period was detected, implying a link between blockade of IL-6 signaling and impaired metabolic homeostasis in humans [132] These findings are reminiscent with the unexpected weight lowering effects of CNTF in clinical trials with patients suffering from motor neuron diseases [133]. Moreover, transgenic mice overexpressing IL-6 and sIL-6R, which showed massive stimulation of gp130 signaling pathway, were significantly smaller than wt mice and did not develop visible fat pads [78]. Given the mentioned results with mice lacking the hepatic IL-6R, and since hepatocytes express membrane bound IL-6R, it can be suspected that the effect of IL-6 on hepatic control of insulin sensitivity and glucose tolerance is mediated by IL-6 *classic-* rather than by *trans-signaling* [134]. It will therefore be interesting to see whether specific blockade of IL-6 *trans-signaling* by sgp130Fc will have an effect on insulin sensitivity and glucose tolerance.

7.3. Interleukin-6 and bone metabolism

Bone homeostasis is regulated by the balance of osteoblasts, which are building up bone and osteoclasts, which degrade bone. It was shown that osteoclast formation was triggered by IL-6 only in the presence of sIL-6R [135]. The importance of IL-6 was underlined by experiments with IL-6$^{-/-}$ mice, which were completely protected from bone loss after ovariectomy, which is a model for bone loss in females after menopause [136].

RANK ligand (RANKL) is an essential factor for osteoclastogenesis since it stimulates differentiation of myeloid precursor cells into osteoclasts by binding to its signaling receptor, RANK [137]. RANKL

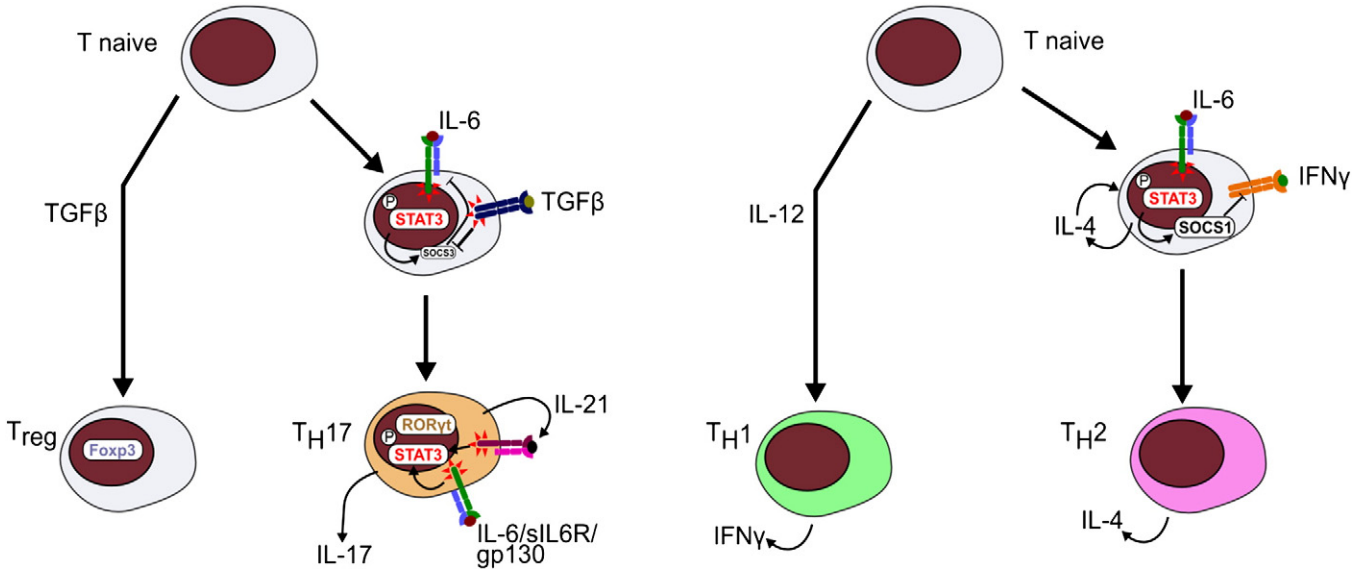

Fig. 3. Role of IL-6 in T-cell differentiation. Activation of STAT3 plays a central role during the development of T_H2 and T_H17 cells. Left panel: TGFβ alone induces the differentiation of naïve $CD4^+$ T-cells into regulatory T-cells (T_{reg}). TGFβ in combination with IL-6 triggers the differentiation of naïve T-cells towards T_H17 cells. TGFβ thereby enhances P-STAT3 levels via suppression of SOCS3. Differentiated T_H17 cells sustain elevated P-STAT3 levels either via gp130 *trans-signaling* or via an autocrine IL-21 loop. Right panel: IL-6 induces STAT3 activation in naïve T-cells. Consequently, IL-4 production as well as inhibition of IFNγ signaling via upregulated SOCS1 shifts the balance towards T_H2 formation.

expression was shown to be induced by IL-6/sIL-6R but not IL-6 alone via the JAK/STAT signaling pathway [137]. Accordingly, it was shown that neutralizing anti-IL-6 mAbs inhibited osteoclast formation. Interestingly, IL-6 levels and certain IL-6 gene polymorphisms have been associated with bone mineral density alterations in inflammatory disease [138]. Taken together, these data show that IL-6, most likely via IL-6 *trans-signaling*, plays an important role in the regulation of bone homeostasis.

7.4. Interleukin-6 and pain

It was shown that IL-6 in combination with sIL-6R sensitized rat skin nociceptors to heat *in vivo* and that heat-activated ionic current was modulated by IL-6 in rat sensory neurons [139,140]. Subsequently, using mice lacking gp130 in peripheral sensory neurons, it was demonstrated that IL-6/gp130 ligand-receptor complex induced heat hypersensitivity both *in vitro* and *in vivo*. This process was mediated by activation of PKC-δ via Gab1/2/PI3K and subsequent regulation of TRPV1, a member of the transient receptor potential (TRP) family of ion channels [141]. A key role for IL-6 signaling in pathological pain was confirmed using IL-$6^{-/-}$ mice. These mice failed to develop thermal hyperalgesia [142]. This effect of IL-6 is most likely mediated via IL-6 *trans-signaling* via the soluble IL-6R since sgp130Fc transgenic mice [41] reacted significantly slower than wt mice upon exposure to heat in a hot plate assay (PC Baier, T Schiffelholz, S Rose-John, J Scheller, unpublished results).

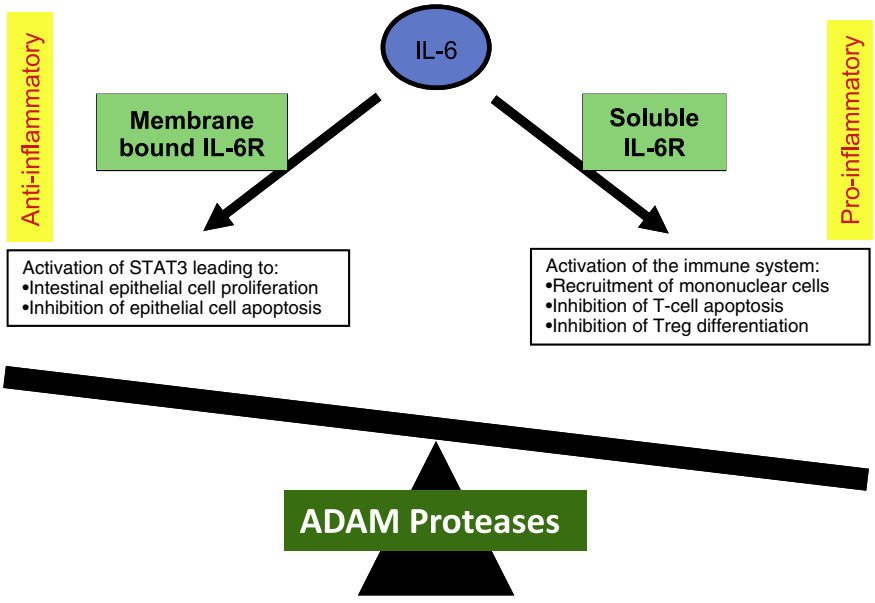

Fig. 4. Pro- and anti-inflammatory properties of IL-6. IL-6 is a pleiotropic cytokine with pro- and anti-inflammatory properties. In several mouse models, it was shown that IL-6 *classic signaling* mediates the activation of anti-inflammatory pathways on target cells. In a murine colon cancer model, IL-6 *classic signaling* is essential for the activation of STAT3-mediated signaling pathways which induce the regeneration of intestinal epithelial cells after DSS induced damage. In contrast, IL-6 *trans-signaling* is observed in chronic inflammatory disorders like Crohn's disease and rheumatoid arthritis. Trans-signaling leads to activation of the immune system by the recruitment of monocytes to the inflamed area. Trans-signaling on T-cells leads to inhibition of apoptosis, inhibition of T_{reg} differentiation, and differentiation of T_H17 cells.

These results demonstrate that beneficial results can be expected in patients upon administration of IL-6 neutralizing agents such as the IL-6R neutralizing mAb Actemra (tocilizumab), which has recently been approved for treatment of rheumatoid arthritis patients in Europe and in the United States.

8. Perspectives and conclusions

IL-6 is involved not only in the activation of the immune system but also in regenerative processes as well as in the regulation of metabolism, in the maintenance of bone homeostasis, and in many neural functions. It turned out that, in all cases tested, pro-inflammatory functions of IL-6 could be inhibited by sgp130Fc, which does not affect IL-6 responses via the mbIL-6R. On the other hand, functions of IL-6 such as metabolic control in the liver and regeneration of the epithelium in the intestine seem to be mediated via the mbIL-6R (Fig. 4). This view bears important consequences on the therapeutic blockade of IL-6 as a treatment of chronic inflammatory diseases. Patients with such diseases need to be treated for many years if not for their entire life span. In view of the complex biology of IL-6, long-term global blockade of this cytokine should be carefully considered. Whereas most IL-6 blocking agents block both *classic*- and *trans-signaling*, specific *trans-signaling* blockade is under development [143].

Acknowledgments

The work described in this review was funded by grants from the Deutsche Forschungsgemeinschaft, Bonn, Germany (SFB415, project B5; SFB841 and SFB877, projects A1 and A2) and by the Cluster of Excellence “Inflammation at Interfaces.”

References

[1] P.C. Heinrich, I. Behrmann, S. Haan, H.M. Hermanns, G. Muller-Newen, F. Schaper, Principles of interleukin (IL)-6-type cytokine signalling and its regulation, Biochem. J. 374 (2003) 1–20.
[2] J. Scheller, J. Grötzinger, S. Rose-John, Updating IL-6 classic- and trans-signaling, Signal Transduct. 6 (2006) 240–259.
[3] J. Müllberg, T. Geib, T. Jostock, S.H. Hoischen, P. Vollmer, N. Voltz, D. Heinz, P.R. Galle, M. Klouche, S. Rose-John, IL-6-receptor independent stimulation of human gp130 by viral IL-6, J. Immunol. 164 (2000) 4672–4677.
[4] T. Taga, T. Kishimoto, gp130 and the interleukin-6 family of cytokines, Annu. Rev. Immunol. 15 (1997) 797–819.
[5] S. Pflanz, L. Hibbert, J. Mattson, R. Rosales, E. Vaisberg, J.F. Bazan, J.H. Phillips, T.K. McClanahan, R. de Waal Malefyt, R.A. Kastelein, WSX-1 and glycoprotein 130 constitute a signal-transducing receptor for IL-27, J Immunol 172 (4) (2004) 2225–2231.
[6] D. Pennica, V. Arce, T.A. Swanson, R. Vejsada, R.A. Pollock, M. Armanini, K. Dudley, H.S. Phillips, A. Rosenthal, A.C. Kato, C.E. Henderson, Cardiotrophin-1, a cytokine present in embryonic muscle, supports long-term survival of spinal motoneurons, Neuron 17 (1996) 63–74.
[7] O. Robledo, M. Fourcin, S. Chevalier, C. Guillet, P. Auguste, A. Pouplard-Barthelaix, D. Pennica, H. Gascan, Signaling of the cardiotrophin-1 receptor. Evidence for a third receptor component, J. Biol. Chem. 272 (1997) 4855–4863.
[8] D.-C. Chow, X.-L. He, A.L. Snow, S. Rose-John, K.C. Garcia, Structure of an extracellular gp130-cytokine receptor signalling complex, Science 291 (2001) 2150–2155.
[9] N. Adam, B. Rabe, J. Suthaus, J. Grötzinger, S. Rose-John, J. Scheller, Unraveling viral interleukin 6 binding to gp130 and activation of STAT-signaling pathways independent of interleukin 6-receptor, J. Virol. 83 (2009) 5117–5126.
[10] H. Yawata, K. Yasukawa, S. Natsuka, M. Murakami, K. Yamasaki, M. Hibi, T. Taga, T. Kishimoto, Structure–function analysis of human IL-6 receptor: dissociation of amino acid residues required for IL-6-binding and for IL-6 signal transduction through gp130, EMBO J. 12 (1993) 1705–1712.
[11] P. Vollmer, B. Oppmann, N. Voltz, M. Fischer, S. Rose-John, A role for the immunoglobulin-like domain of the human IL-6 receptor: intracellular protein transport and shedding, Eur. J. Biochem. 263 (1999) 438–446.
[12] M.Y. Wiesinger, S. Haan, S. Wüller, M.E. Kauffmann, T. Recker, A. Küster, P.C. Heinrich, G. Müller-Newen, Development of an IL-6 inhibitor based on the functional analysis of murine IL-6Ralpha, Chem. Biol. 16 (2009) 783–794.
[13] J. Grötzinger, G. Kurapkat, A. Wollmer, M. Kalai, S. Rose-John, The family of the IL-6-type cytokines: specificity and promiscuity of the receptor complexes, Protein Struct. Funct. Genet. 27 (1997) 96–109.
[14] M.J. Boulanger, D.C. Chow, E.E. Brevnova, K.C. Garcia, Hexameric structure and assembly of the interleukin-6/IL-6 alpha receptor/gp130 complex, Science 300 (2003) 2101–2104.
[15] J.F. Bazan, Structural design and molecular evolution of a cytokine receptor superfamily, Proc. Natl Acad. Sci. USA 87 (1990) 6934–6938.
[16] I. Kurth, U. Horsten, S. Pflanz, A. Timmermann, A. Kuster, H. Dahmen, I. Tacken, P.C. Heinrich, G. Müller-Newen, Importance of the membrane-proximal extracellular domains for activation of the signal transducer glycoprotein 130, J. Immunol. 164 (2000) 273–282.
[17] G. Skiniotis, M.J. Boulanger, K.C. Garcia, T. Walz, Signaling conformations of the tall cytokine receptor gp130 when in complex with IL-6 and IL-6 receptor, Nat. Struct. Mol. Biol. 12 (2005) 545–551.
[18] Y. Xu, N.J. Kershaw, C.S. Luo, P. Soo, M.J. Pocock, P.E. Czabotar, D.J. Hilton, N.A. Nicola, T.P. Garrett, J.G. Zhang, Crystal structure of the entire ectodomain of gp130: insights into the molecular assembly of the tall cytokine receptor complexes, J. Biol. Chem. 285 (2010) 21214–21218.
[19] I. Lorenzen, W. Shang, M. Perbandt, M.V. Petoukhov, D. Svergun, G.H. Waetzig, S. Rose-John, R. Hilgenfeld, J. Grötzinger, The structure of the unliganded extracellular domain of the interleukin-6 signal transducer gp130 in solution, Eur J Cell Biol in press (2010).
[20] B. Giese, C. Roderburg, M. Sommerauer, S.B. Wortmann, S. Metz, P.C. Heinrich, G. Müller-Newen, Dimerization of the cytokine receptors gp130 and LIFR analysed in single cells, J. Cell Sci. 118 (2005) 5129–5140.
[21] S. Tenhumberg, B. Schuster, L. Zhu, M. Kovaleva, J. Scheller, K.J. Kallen, S. Rose-John, gp130 dimerization in the absence of ligand: preformed cytokine receptor complexes, Biochem. Biophys. Res. Commun. 346 (2006) 649–657.
[22] B. Schuster, W. Meinert, S. Rose-John, K.-J. Kallen, The human interleukin–6 (IL-6) receptor exists as a preformed dimer in the plasma membrane, FEBS Lett. 538 (2003) 113–116.
[23] J.S. Greiser, C. Stross, P.C. Heinrich, I. Behrmann, H.M. Hermanns, Orientational constraints of the gp130 intracellular juxtamembrane domain for signaling, J. Biol. Chem. 277 (2002) 26959–26965.
[24] Y. Wang, G.M. Fuller, Phosphorylation and internalization of gp130 occur after IL-6 activation of Jak2 kinase in hepatocytes, Mol. Biol. Cell 5 (1994) 819–828.
[25] E. Dittrich, S. Rose-John, C. Gerhartz, J. Müllberg, T. Stoyan, K. Yasukawa, P.C. Heinrich, L. Graeve, Identification of a region within the cytoplasmic domain of the interleukin-6 (IL-6) signal transducer gp130 important for ligand-induced endocytosis of the IL-6 receptor, J. Biol. Chem. 269 (1994) 19014–19020.
[26] D. Graf, K. Haselow, I. Münks, J.G. Bode, D. Häussinger, Caspase-mediated cleavage of the signal-transducing IL-6 receptor subunit gp130, Arch. Biochem. Biophys. 477 (2008) 330–338.
[27] J. Grötzinger, T. Kernebeck, K.-J. Kallen, S. Rose-John, IL-6 type cytokine receptor complexes: hexamer or tetramer or both? Biol. Chem. 380 (1999) 803–813.
[28] S. Pflanz, I. Kurth, J. Grötzinger, P.C. Heinrich, G. Müller-Newen, Two different epitopes of the signal transducer gp130 sequentially cooperate on IL-6-induced receptor activation, J. Immunol. 165 (2000) 7042–7049.
[29] M. van Dam, J. Müllberg, H. Schooltink, T. Stoyan, J.P. Brakenhoff, L. Graeve, P.C. Heinrich, S. Rose-John, Structure–function analysis of interleukin-6 utilizing human/murine chimeric molecules. Involvement of two separate domains in receptor binding, J. Biol. Chem. 268 (1993) 15285–15290.
[30] S. Viswanathan, T. Benatar, S. Rose-John, D.A. Lauffenburger, P.W. Zandstra, Ligand/receptor signaling threshold (LIST) model accounts for gp130-mediated embryonic stem cell self-renewal responses to LIF and HIL-6, Stem Cells 20 (2002) 119–138.
[31] K.-J. Kallen, J. Grötzinger, E. Lelièvre, P. Vollmer, D. Aasland, C. Renné, J. Müllberg, K.-H. Meyer zum Büschenfelde, H. Gascan, S. Rose-John, Receptor recognition sites of cytokines are organized as exchangeable modules: transfer of the LIFR binding site from CNTF to IL-6, J. Biol. Chem. 274 (1999) 11859–11867.
[32] J.G. Giri, J. Wells, S.K. Dower, C.E. McCall, R.N. Guzman, J. Slack, T.A. Bird, K. Shanebeck, K.H. Grabstein, J.E. Sims, et al., Elevated levels of shed type II IL-1 receptor in sepsis. Potential role for type II receptor in regulation of IL-1 responses, J. Immunol. 153 (1994) 5802–5809.
[33] S. Rose-John, P.C. Heinrich, Soluble receptors for cytokines and growth factors: generation and biological function, Biochem. J. 300 (1994) 281–290.
[34] S. Orlando, M. Sironi, G. Bianchi, A.H. Drummond, D. Boraschi, D. Yabes, A. Mantovani, Role of metalloproteases in the release of the IL-1 type II decoy receptor, J. Biol. Chem. 272 (1997) 31764–31769.
[35] J.J. Peschon, J.L. Slack, P. Reddy, K.L. Stocking, S.W. Sunnarborg, D.C. Lee, W.E. Russell, B.J. Castner, R.S. Johnson, J.N. Fitzner, R.W. Boyce, N. Nelson, C.J. Kozlosky, M.F. Wolfson, C.T. Rauch, D.P. Cerretti, R.J. Paxton, C.J. March, R.A. Black, An essential role for ectodomain shedding in mammalian development, Science 282 (1998) 1281–1284.
[36] P. Reddy, J.L. Slack, R. Davis, D.P. Cerretti, C.J. Kozlosky, R.A. Blanton, D. Shows, J.J. Peschon, R.A. Black, Functional analysis of the domain structure of tumor necrosis factor-alpha converting enzyme, J. Biol. Chem. 275 (2000) 14608–14614.
[37] H.H. Oberg, D. Wesch, S. Grussel, S. Rose-John, D. Kabelitz, Differential expression of CD126 and CD130 mediates different STAT-3 phosphorylation in CD4 + CD25- and CD25 high regulatory T cells, Int. Immunol. 18 (2006) 555–563.
[38] S. Rose-John, G.H. Waetzig, J. Scheller, J. Grotzinger, D. Seegert, The IL-6/sIL-6R complex as a novel target for therapeutic approaches, Expert Opin. Ther. Targets 11 (2007) 613–624.
[39] J. Scheller, S. Rose-John, Interleukin-6 and its receptor: from bench to bedside, Med. Microbiol. Immunol. 195 (2006) 173–183.
[40] A. Chalaris, B. Rabe, K. Paliga, H. Lange, T. Laskay, C.A. Fielding, S.A. Jones, S. Rose-John, J. Scheller, Apoptosis is a natural stimulus of IL6R shedding and contributes to the pro-inflammatory trans-signaling function of neutrophils, Blood 110 (2007) 1748–1755.

[41] B. Rabe, A. Chalaris, U. May, G.H. Waetzig, D. Seegert, A.S. Williams, S.A. Jones, S. Rose-John, J. Scheller, Transgenic blockade of interleukin 6 transsignaling abrogates inflammation, Blood 111 (2008) 1021–1028.
[42] C. Becker, M.C. Fantini, C. Schramm, H.A. Lehr, S. Wirtz, A. Nikolaev, J. Burg, S. Strand, R. Kiesslich, S. Huber, H. Ito, N. Nishimoto, K. Yoshizaki, T. Kishimoto, P.R. Galle, M. Blessing, S. Rose-John, M.F. Neurath, TGF-beta suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling, Immunity 21 (2004) 491–501.
[43] Q. Chen, D.T. Fisher, K.A. Clancy, J.M. Gauguet, W.C. Wang, E. Unger, S. Rose-John, U.H. von Andrian, H. Baumann, S.S. Evans, Fever-range thermal stress promotes lymphocyte trafficking across high endothelial venules via an interleukin 6 trans-signaling mechanism, Nat. Immunol. 7 (2006) 1299–1308.
[44] J. Mullberg, H. Schooltink, T. Stoyan, M. Gunther, L. Graeve, G. Buse, A. Mackiewicz, P.C. Heinrich, S. Rose-John, The soluble interleukin-6 receptor is generated by shedding, Eur. J. Immunol. 23 (1993) 473–480.
[45] J.A. Lust, K.A. Donovan, M.P. Kline, P.R. Greipp, R.A. Kyle, N.J. Maihle, Isolation of an mRNA encoding a soluble form of the human interleukin-6 receptor, Cytokine 4 (1992) 96–100.
[46] J. Mullberg, W. Oberthur, F. Lottspeich, E. Mehl, E. Dittrich, L. Graeve, P.C. Heinrich, S. Rose-John, The soluble human IL-6 receptor. Mutational characterization of the proteolytic cleavage site, J. Immunol. 152 (1994) 4958–4968.
[47] V. Matthews, B. Schuster, S. Schutze, I. Bussmeyer, A. Ludwig, C. Hundhausen, T. Sadowski, P. Saftig, D. Hartmann, K.J. Kallen, S. Rose-John, Cellular cholesterol depletion triggers shedding of the human interleukin-6 receptor by ADAM10 and ADAM17 (TACE), J. Biol. Chem. 278 (2003) 38829–38839.
[48] A. Chalaris, J. Gewiese, K. Paliga, L. Fleig, A. Schneede, K. Krieger, S. Rose-John, J. Scheller, ADAM17-mediated shedding of the IL6R induces cleavage of the membrane stub by gamma-secretase, Biochim. Biophys. Acta 1803 (2010) 234–245.
[49] R.A. Black, Tumor necrosis factor-alpha converting enzyme, Int. J. Biochem. Cell Biol. 34 (2002) 1–5.
[50] C.P. Blobel, Remarkable roles of proteolysis on and beyond the cell surface, Curr. Opin. Cell Biol. 12 (2000) 606–612.
[51] D.R. Edwards, M.M. Handsley, C.J. Pennington, The ADAM metalloproteinases, Mol. Aspects Med. 29 (2008) 258–289.
[52] N. Franchimont, C. Lambert, P. Huynen, C. Ribbens, B. Relic, A. Chariot, V. Bours, J. Piette, M.P. Merville, M. Malaise, Interleukin-6 receptor shedding is enhanced by interleukin-1beta and tumor necrosis factor alpha and is partially mediated by tumor necrosis factor alpha-converting enzyme in osteoblast-like cells, Arthritis Rheum. 52 (2005) 84–93.
[53] I. Walev, P. Vollmer, M. Palmer, S. Bhakdi, S. Rose-John, Pore-forming toxins trigger shedding of receptors for interleukin 6 and lipopolysaccharide, Proc. Natl Acad. Sci. USA 93 (1996) 7882–7887.
[54] A.M. Vahdat, K.S. Reiners, V.L. Simhadri, D.A. Eichenauer, B. Boll, A. Chalaris, V.R. Simhadri, K. Wiegmann, H.W. Krell, S. Rose-John, A. Engert, E.P. von Strandmann, H.P. Hansen, TNF-alpha-converting enzyme (TACE/ADAM17)-dependent loss of CD30 induced by proteasome inhibition through reactive oxygen species, Leukemia 24 (2010) 51–57.
[55] M.M. McFarland-Mancini, H.M. Funk, A.M. Paluch, M. Zhou, P.V. Giridhar, C.A. Mercer, S.C. Kozma, A.F. Drew, Differences in wound healing in mice with deficiency of IL-6 versus IL-6 receptor, J. Immunol. 184 (2010) 7219–7228.
[56] M. Narazaki, K. Yasukawa, T. Saito, Y. Ohsugi, H. Fukui, Y. Koishihara, G.D. Yancopoulos, T. Taga, T. Kishimoto, Soluble forms of the interleukin-6 signal-transducing receptor component gp130 in human serum possessing a potential to inhibit signals through membrane-anchored gp130, Blood 82 (1993) 1120–1126.
[57] M. Tanaka, M. Kishimura, S. Ozaki, F. Osakada, H. Hashimoto, M. Okubo, M. Murakami, K. Nakao, Cloning of novel soluble gp130 and detection of its neutralizing autoantibodies in rheumatoid arthritis, J. Clin. Invest. 106 (2000) 137–144.
[58] J.G. Zhang, Y. Zhang, C.M. Owczarek, L.D. Ward, R.L. Moritz, R.J. Simpson, K. Yasukawa, N.A. Nicola, Identification and characterization of two distinct truncated forms of gp130 and a soluble form of leukemia inhibitory factor receptor alpha-chain in normal human urine and plasma, J. Biol. Chem. 273 (1998) 10798–10805.
[59] J. Müllberg, E. Dittrich, L. Graeve, C. Gerhartz, K. Yasukawa, T. Taga, T. Kishimoto, P.C. Heinrich, S. Rose-John, Differential shedding of the two subunits of the interleukin-6 receptor, FEBS Lett. 332 (1993) 174–178.
[60] T. Jostock, J. Müllberg, S. Özbek, R. Atreya, G. Blinn, N. Voltz, M. Fischer, M.F. Neurath, S. Rose-John, Soluble gp130 is the natural inhibitor of soluble IL-6R transsignaling responses, Eur. J. Biochem. 268 (2001) 160–167.
[61] W. Hui, M. Bell, G. Carroll, Soluble glycoprotein 130 (gp130) attenuates OSM- and LIF-induced cartilage proteoglycan catabolism, Cytokine 12 (2000) 151–155.
[62] J. Scheller, B. Schuster, C. Holscher, T. Yoshimoto, S. Rose-John, No inhibition of IL-27 signaling by soluble gp130, Biochem. Biophys. Res. Commun. 326 (2005) 724–728.
[63] R. Atreya, J. Mudter, S. Finotto, J. Müllberg, T. Jostock, S. Wirtz, M. Schütz, B. Bartsch, M. Holtmann, C. Becker, D. Strand, J. Czaja, J.F. Schlaak, H.A. Lehr, F. Autschbach, G. Schürmann, N. Nishimoto, K. Yoshizaki, H. Ito, T. Kishimoto, P.R. Galle, S. Rose-John, M.F. Neurath, Blockade of IL-6 transsignaling abrogates established experimental colitis in mice by suppression of the antiapoptotic resistance of lamina propria T cells, Nature Med 6 (2000) 583–588.
[64] M.A. Nowell, A.S. Williams, S.A. Carty, J. Scheller, A.J. Hayes, G.W. Jones, P.J. Richards, S. Slinn, M. Ernst, B.J. Jenkins, N. Topley, S. Rose-John, S.A. Jones, Therapeutic targeting of IL-6 trans-signaling counteracts STAT3 control of the inflammatory infiltrate in experimental arthritis, J. Immunol. 182 (2009) 613–622.
[65] G.W. Jones, R.M. McLoughlin, V.J. Hammond, C.R. Parker, J.D. Williams, R. Malhotra, J. Scheller, A.S. Williams, S. Rose-John, N. Topley, S.A. Jones, Loss of CD4+ T cell IL-6R expression during inflammation underlines a role for IL-6 trans signaling in the local maintenance of Th17 cells, J. Immunol. 184 (2010) 2130–2139.
[66] R. Lissilaa, V. Buatois, G. Magistrelli, A.S. Williams, G.W. Jones, S. Herren, L. Shang, P. Malinge, F. Guilhot, L. Chatel, E. Hatterer, S.A. Jones, M.H. Kosco-Vilbois, W.G. Ferlin, Although IL-6 trans-signaling is sufficient to drive local immune responses, classical IL-6 signaling is obligate for the induction of T cell-mediated autoimmunity, J. Immunol. 185 (2010) 5512–5521.
[67] M. Fischer, J. Goldschmitt, C. Peschel, J.P. Brakenhoff, K.J. Kallen, A. Wollmer, J. Grotzinger, S. Rose-John, A bioactive designer cytokine for human hematopoietic progenitor cell expansion, Nat. Biotechnol. 15 (1997) 145-145.
[68] P. März, J.-C. Cheng, R.A. Gadient, P. Patterson, T. Stoyan, U. Otten, S. Rose-John, Sympathetic neurons can produce and respond to interleukin-6, Proc. Natl Acad. Sci. USA 95 (1998) 3251–3256.
[69] P. März, U. Otten, S. Rose-John, Neuronal activities of IL-6 type cytokines often depend on soluble cytokine receptors, Eur. J. Neurosci. 11 (1999) 2995–3004.
[70] O. Islam, X. Gong, S. Rose-John, K. Heese, Interleukin-6 and neural stem cells: more than gliogenesis, Mol. Biol. Cell 20 (2009) 188–199.
[71] J. Audet, C.L. Miller, S. Rose-John, J.M. Piret, C.J. Eaves, Distinct role of gp130 activation in promoting self-renewal divisions by mitogenically stimulated murine hematopoietic cells, Proc. Natl Acad. Sci. USA 98 (2001) 1757–1762.
[72] F. Walker, H.H. Zhang, V. Matthews, J. Weinstock, E.C. Nice, M. Ernst, S. Rose-John, A.W. Burgess, IL6/sIL6R complex contributes to emergency granulopoietic responses in G-CSF- and GM-CSF-deficient mice, Blood 111 (2008) 3978–3985.
[73] G.C. Yeoh, M. Ernst, S. Rose-John, B. Akhurst, C. Payne, S. Long, W. Alexander, B. Croker, D. Grail, V.B. Matthews, Opposing roles of gp130-mediated STAT-3 and ERK-1/ 2 signaling in liver progenitor cell migration and proliferation, Hepatology 45 (2007) 486–494.
[74] R.K. Humphrey, G.M. Beattie, A.D. Lopez, N. Bucay, C.C. King, M. Firpo, S. Rose-John, A. Hayek, Maintenance of pluripotency in human embryonic stem cells is Stat3 independent, Stem Cells 22 (2004) 522–530.
[75] C. Trautwein, T. Rakemann, M. Niehof, S. Rose-John, M.P. Manns, Acute-phase response factor, increased binding, and target gene transcription during liver regeneration, Gastroenterol 110 (1996) 1854–1862.
[76] D.E. Cressman, L.E. Greenbaum, R.A. DeAngelis, G. Ciliberto, E.E. Furth, V. Poli, R. Taub, Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice, Science 274 (1996) 1379–1383.
[77] M. Peters, S. Jacobs, M. Ehlers, P. Vollmer, J. Müllberg, E. Wolf, G. Brem, K.H. Meyer Test, The function of the soluble interleukin 6 (IL-6) receptor in vivo: sensitization of human soluble IL-6 receptor transgenic mice towards IL-6 and prolongation of the plasma half-life of IL-6, J. Exp. Med. 183 (1996) 1399–1406.
[78] M. Peters, P. Schirmacher, J. Goldschmitt, M. Odenthal, C. Peschel, H.P. Dienes, E. Fattori, G. Ciliberto, K.H. Meyer zum Büschenfelde, S. Rose-John, Extramedullary expansion of hematopoietic progenitor cells in IL-6/sIL-6R double transgenic mice, J. Exp. Med. 185 (1997) 755–766.
[79] P. Schirmacher, M. Peters, G. Ciliberto, E. Fattori, J. Lotz, K.H. Meyer zum Büschenfelde, S. Rose-John, Hepatocellular hyperplasia, plasmacytoma formation, and extracellular hematopoiesis in interleukin (IL)-6/soluble IL-6 receptor double-transgenic mice, Am. J. Pathol. 153 (1998) 639–648.
[80] M. Peters, G. Blinn, T. Jostock, P. Schirmacher, K.H. Meyer zum Büschenfelde, P.R. Galle, S. Rose-John, Combined interleukin-6 and soluble interleukin-6 receptor accelerates murine liver regeneration, Gastroenterol 119 (2000) 1663–1671.
[81] E. Galun, E. Zeira, D. Shouval, O. Pappo, M. Peters, S. Rose-John, Liver regeneration induced by a designed hIL-6/shIL-6R fusion protein reverses severe hepatocellular injury, FASEB J. 14 (2000) 1979–1987.
[82] N. Hecht, O. Pappo, D. Shouval, S. Rose-John, E. Galun, J.H. Axelrod, Hyper-IL-6 gene therapy reverses fulminant hepatic failure, Mol. Therap. 3 (2001) 683–687.
[83] C. Drucker, B. Rabe, A. Chalaris, E. Schulz, J. Scheller, S. Rose-John, Interleukin-6 trans-signaling regulates glycogen consumption after D-galactosamine-induced liver damage, J. Interferon Cytokine Res. 29 (2009) 711–718.
[84] J. Gewiese-Rabsch, C. Drucker, S. Malchow, J. Scheller, S. Rose-John, Role of IL-6 trans-signaling in CCl(4) induced liver damage, Biochim. Biophys. Acta 1802 (2010) 1054–1061.
[85] S. Malchow, W. Thaiss, N. Jänner, J. Gewiese-Rabsch, C. Garbers, K. Yamamoto, S. Rose-John, J. Scheller, Essential role of neutrophil mobilization in concanavalin A-induced hepatitis is based on classic IL-6 signaling but not on IL-6 trans-signaling, Biochim. Biophys. Acta 1812 (2011) 290–301.
[86] K. Mitsuyama, S. Matsumoto, S. Rose-John, A. Suzuki, T. Hara, N. Tomiyasu, K. Handa, O. Tsuruta, H. Funabashi, J. Scheller, A. Toyonaga, M. Sata, STAT3 activation via interleukin-6 trans-signaling contributes to ileitis in SAMP1/Yit mice, Gut 55 (2006) 1263–1269.
[87] M.A. Nowell, P.J. Richards, S. Horiuchi, N. Yamamoto, S. Rose-John, N. Topley, A.S. Williams, S.A. Jones, Soluble IL-6 receptor governs IL-6 activity in experimental arthritis: blockade of arthritis severity by soluble glycoprotein 130, J. Immunol. 171 (2003) 3202–3209.
[88] S.M. Hurst, T.S. Wilkinson, R.M. McLoughlin, S. Jones, S. Horiuchi, N. Yamamoto, S. Rose-John, G.M. Fuller, N. Topley, S.A. Jones, IL-6 and its soluble receptor orchestrate a temporal switch in the pattern of leukocyte recruitment, Immunity 14 (2001) 705–714.
[89] S. Matsumoto, T. Hara, K. Mitsuyama, M. Yamamoto, O. Tsuruta, M. Sata, J. Scheller, S. Rose-John, S. Kado, T. Takada, Essential roles of IL-6 trans-signaling in colonic epithelial cells, induced by the IL-6/soluble-IL-6 receptor derived from lamina propria macrophages, on the development of colitis-associated premalignant cancer in a murine model, J. Immunol. 184 (2010) 1543–1551.

[90] C.W. Lo, M.W. Chen, M. Hsiao, S. Wang, C.A. Chen, S.M. Hsiao, J.S. Chang, T.C. Lai, S. Rose-John, M.L. Kuo, L.H. Wei, IL-6 trans-signaling in formation and progression of malignant ascites in ovarian cancer, Cancer Res. 71 (2011) 424434.
[91] S. Grivennikov, E. Karin, J. Terzic, D. Mucida, G.-Y. Yu, S. Vallabhapurapu, J. Scheller, S. Rose-John, H. Cheroutre, L. Eckmann, M. Karin, IL-6 and STAT3 signaling is required for survival of intestinal epithelial cells and colitis associated cancer, Cancer Cell 16 (2009) 103–113.
[92] S.M. Dann, M.E. Spehlmann, D.C. Hammond, M. Iimura, K. Hase, L.J. Choi, E. Hanson, L. Eckmann, IL-6-dependent mucosal protection prevents establishment of a microbial niche for attaching/effacing lesion-forming enteric bacterial pathogens, J. Immunol. 180 (2008) 6816–6826.
[93] A. Chalaris, N. Adam, C. Sina, P. Rosenstiel, J. Lehmann-Koch, P. Schirmacher, D. Hartmann, J. Cichy, O. Gavrilova, S. Schreiber, T. Jostock, V. Matthews, R. Häsler, C. Becker, M.F. Neurath, K. Reiss, P. Saftig, J. Scheller, S. Rose-John, Critical role of the disintegrin metalloprotease ADAM17 for intestinal inflammation and regeneration in mice, J. Exp. Med. 207 (2010) 1617–1624.
[94] T. Barkhausen, T. Tschernig, P. Rosenstiel, M. Van Griensven, R.-P. Vonberg, M. Dorsch, A. Mueller-Heine, A. Chalaris, J. Scheller, S. Rose-John, D. Seegert, C. Krettek, G.H. Waetzig, Selective blockade of interleukin-6 trans-signaling improves survival in a murine polymicrobial sepsis model, Crit Care Med (2011) in press.
[95] C.J. Greenhill, S. Rose-John, R. Lissilaa, W. Ferlin, M. Ernst, P.J. Hertzog, A. Mansell, B.J. Jenkins, IL-6 trans-signaling modulates TLR4-dependent inflammatory responses via STAT3, J. Immunol. 186 (2011) 1199–1208.
[96] C. Stuhlmann-Laeisz, S. Lang, A. Chalaris, K. Paliga, E. Sudarman, J. Eichler, U. Klingmüller, M. Samuel, M. Ernst, S. Rose-John, J. Scheller, Forced dimerization of gp130 leads to constitutive STAT3 activation, cytokine independent growth and blockade of differentiation of embryonic stem cells, Mol. Biol. Cell 17 (2006) 2986–2995.
[97] S. Rebouissou, M. Amessou, G. Couchy, K. Poussin, S. Imbeaud, C. Pilati, T. Izard, C. Balabaud, P. Bioulac-Sage, J. Zucman-Rossi, Frequent in-frame somatic deletions activate gp130 in inflammatory hepatocellular tumours, Nature 457 (2009) 200.
[98] D. Maione, E. Di Carlo, W. Li, P. Musiani, A. Modesti, M. Peters, S. Rose-John, C. Della Rocca, M. Tripodi, D. Lazzaro, R. Taub, R. Savino, G. Ciliberto, Coexpression of IL-6 and soluble IL-6R causes nodular regenerative hyperplasia and adenomas of the liver, EMBO J. 17 (1998) 5588–5597.
[99] J. Suthaus, A. Tillmann, I. Lorenzen, E. Bulanova, S. Rose-John, J. Scheller, Forced homo- and heterodimerization of all gp130-type receptor complexes leads to constitutive ligand-independent signaling and cytokine-independent growth, Mol. Biol. Cell 21 (15) (2010) 2797–2807.
[100] I. Lorenzen, A.J. Dingley, Y. Jacques, J. Grotzinger, The structure of the interleukin-15 alpha receptor and its implications for ligand binding, J. Biol. Chem. 281 (2006) 6642–6647.
[101] N.A. Hanick, M. Rickert, L. Varani, A.J. Bankovich, J.R. Cochran, D.M. Kim, C.D. Surh, K.C. Garcia, Elucidation of the interleukin-15 binding site on its alpha receptor by NMR, Biochemistry 46 (2007) 9453–9461.
[102] A. Dreuw, S. Radtke, S. Pflanz, B.E. Lippok, P.C. Heinrich, H.M. Hermanns, Characterization of the signaling capacities of the novel gp130-like cytokine receptor, J. Biol. Chem. 279 (2004) 36112–36120.
[103] H.M. Hermanns, S. Radtke, C. Haan, H. Schmitz-Van de Leur, J. Tavernier, P.C. Heinrich, I. Behrmann, Contributions of leukemia inhibitory factor receptor and oncostatin M receptor to signal transduction in heterodimeric complexes with glycoprotein 130, J. Immunol. 163 (1999) 6651–6658.
[104] S.A. Jones, Directing transition from innate to acquired immunity: defining a role for IL-6, J. Immunol. 175 (2005) 3463–3468.
[105] G. Kaplanski, V. Marin, F. Montero-Julian, A. Mantovani, C. Farnarier, IL-6: a regulator of the transition from neutrophil to monocyte recruitment during inflammation, Trends Immunol. 24 (2003) 25–29.
[106] M. Romano, M. Sironi, C. Toniatti, N. Polentarutti, P. Fruscella, P. Ghezzi, R. Faggioni, W. Luini, V. van Hinsbergh, S. Sozzani, F. Bussolino, V. Poli, G. Ciliberto, A. Mantovani, Role of IL-6 and its soluble receptor in induction of chemokines and leukocyte recruitment, Immunity 6 (1997) 315–325.
[107] Q. Chen, W.C. Wang, R. Bruce, H. Li, D.M. Schleider, M.J. Mulbury, M.D. Bain, P.K. Wallace, H. Baumann, S.S. Evans, Central role of IL-6 receptor signal-transducing chain gp130 in activation of L-selectin adhesion by fever-range thermal stress, Immunity 20 (2004) 59–70.
[108] P. Chomarat, J. Banchereau, J. Davoust, A.K. Palucka, IL-6 switches the differentiation of monocytes from dendritic cells to macrophages, Nat. Immunol. 1 (2000) 510–514.
[109] B.J. Jenkins, D. Grail, M. Inglese, C. Quilici, S. Bozinovski, P. Wong, M. Ernst, Imbalanced gp130-dependent signaling in macrophages alters macrophage colony-stimulating factor responsiveness via regulation of c-fms expression, Mol. Cell. Biol. 24 (2004) 1453–1463.
[110] R.M. McLoughlin, B.J. Jenkins, D. Grail, A.S. Williams, C.A. Fielding, C.R. Parker, M. Ernst, N. Topley, S.A. Jones, IL-6 trans-signaling via STAT3 directs T cell infiltration in acute inflammation, Proc. Natl Acad. Sci. USA 102 (2005) 9589–9594.
[111] S.J. Curnow, D. Scheel-Toellner, W. Jenkinson, K. Raza, O.M. Durrani, J.M. Faint, S. Rauz, K. Wloka, D. Pilling, S. Rose-John, C.D. Buckley, P.I. Murray, M. Salmon, Inhibition of T cell apoptosis in the aqueous humor of patients with uveitis by IL-6/soluble IL-6 receptor trans-signaling, J. Immunol. 173 (2004) 5290–5297.
[112] T. Hirano, T. Taga, N. Nakano, K. Yasukawa, S. Kashiwamura, K. Shimizu, K. Nakajima, K.H. Pyun, T. Kishimoto, Purification to homogeneity and characterization of human B-cell differentiation factor (BCDF or BSFp-2), Proc Natl Acad Sci USA 82 (1985) 5490–5494.
[113] S. Suematsu, T. Matsuda, K. Aozasa, S. Akira, N. Nakano, S. Ohno, J. Miyazaki, K. Yamamura, T. Hirano, T. Kishimoto, IgG1 plasmacytosis in interleukin 6 transgenic mice, Proc. Natl Acad. Sci. USA 86 (1989) 7547–7551.
[114] M. Kopf, H. Baumann, G. Freer, M. Freudenberg, M. Lamers, T. Kishimoto, R. Zinkernagel, H. Bluethmann, G. Kohler, Impaired immune and acute-phase responses in interleukin-6-deficient mice, Nature 368 (1994) 339–342.
[115] O. Dienz, S.M. Eaton, J.P. Bond, W. Neveu, D. Moquin, R. Noubade, E.M. Briso, C. Charland, W.J. Leonard, G. Ciliberto, C. Teuscher, L. Haynes, M. Rincon, The induction of antibody production by IL-6 is indirectly mediated by IL-21 produced by CD4+ T cells, J. Exp. Med. 206 (2009) 69–78.
[116] F. Eddahri, S. Denanglaire, F. Bureau, R. Spolski, W.J. Leonard, O. Leo, F. Andris, Interleukin-6/STAT3 signaling regulates the ability of naïve T cells to acquire B-cell help capacities, Blood 113 (2009) 2426–2433.
[117] S. Diehl, M. Rincon, The two faces of IL-6 on Th1/Th2 differentiation, Mol. Immunol. 39 (2002) 531–536.
[118] M.H. Sofi, W. Li, M.H. Kaplan, C.H. Chang, Elevated IL-6 expression in CD4 T cells via PKCtheta and NF-kappaB induces Th2 cytokine production, Mol. Immunol. 46 (2009) 1443–1450.
[119] E. Bettelli, Y. Carrier, W. Gao, T. Korn, T.B. Strom, M. Oukka, H.L. Weiner, V.K. Kuchroo, Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells, Nature 441 (2006) 235–238.
[120] P.R. Mangan, L.E. Harrington, D.B. O'Quinn, W.S. Helms, D.C. Bullard, C.O. Elson, R. D. Hatton, S.M. Wahl, T.R. Schoeb, C.T. Weaver, Transforming growth factor-beta induces development of the T(H)17 lineage, Nature 441 (2006) 231–234.
[121] S. Dominitzki, M.C. Fantini, C. Neufert, A. Nikolaev, P.R. Galle, J. Scheller, G. Monteleone, S. Rose-John, M.F. Neurath, C. Becker, Cutting edge: trans-signaling via the soluble IL-6R abrogates the induction of FoxP3 in naïve CD4+CD25 T cells, J. Immunol. 179 (2007) 2041–2045.
[122] H. Qin, L. Wang, T. Feng, C.O. Elson, S.A. Niyongere, S.J. Lee, S.L. Reynolds, C.T. Weaver, K. Roarty, R. Serra, E.N. Benveniste, Y. Cong, TGF-beta promotes Th17 cell development through inhibition of SOCS3, J. Immunol. 183 (2009) 97–105.
[123] K. Ghoreschi, A. Laurence, X.P. Yang, C.M. Tato, M.J. McGeachy, J.E. Konkel, H.L. Ramos, L. Wei, T.S. Davidson, N. Bouladoux, J.R. Grainger, Q. Chen, Y. Kanno, W.T. Watford, H.W. Sun, G. Eberl, E.M. Shevach, Y. Belkaid, D.J. Cua, W. Chen, J.J. O'Shea, Generation of pathogenic T(H)17 cells in the absence of TGF-beta signalling, Nature 467 (2010) 967–971.
[124] B.K. Pedersen, M.A. Febbraio, Muscle as an endocrine organ: focus on muscle-derived interleukin-6, Physiol. Rev. 88 (2008) 1379–1406.
[125] B.K. Pedersen, A. Steensberg, C. Fischer, C. Keller, P. Keller, P. Plomgaard, M. Febbraio, B. Saltin, Searching for the exercise factor: is IL-6 a candidate? J. Muscle Res. Cell Motil. 24 (2003) 113–119.
[126] T. Skurk, C. Alberti-Huber, C. Herder, H. Hauner, Relationship between adipocyte size and adipokine expression and secretion, J. Clin. Endocrinol. Metab. 92 (3) (2007) 1023–1033.
[127] G.S. Hotamisligil, Inflammation and metabolic disorders, Nature Med. 444 (2006) 860–867.
[128] V. Wallenius, K. Wallenius, B. Ahren, M. Rudling, H. Carlsten, S.L. Dickson, C. Ohlsson, J.O. Jansson, Interleukin-6-deficient mice develop mature-onset obesity, Nat. Med. 8 (2002) 75–79.
[129] G.B. Di Gregorio, L. Hensley, T. Lu, G. Ranganathan, P.A. Kern, Lipid and carbohydrate metabolism in mice with a targeted mutation in the IL-6 gene: absence of development of age-related obesity, Am. J. Physiol. Endocrinol. Metab. 287 (2004) E182–E187.
[130] V.B. Matthews, T.L. Allen, S. Risis, M.H. Chan, D.C. Henstridge, N. Watson, L.A. Zaffino, J.R. Babb, J. Boon, P.J. Meikle, J.B. Jowett, M.J. Watt, J.O. Jansson, C.R. Bruce, M.A. Febbraio, Interleukin-6-deficient mice develop hepatic inflammation and systemic insulin resistance, Diabetologia 53 (2010) 2431–2441.
[131] F.T. Wunderlich, P. Ströhle, A.C. Könner, S. Gruber, S. Tovar, H.S. Brönneke, L. Juntti-Berggren, L.S. Li, N. van Rooijen, C. Libert, P.O. Berggren, J.C. Brüning, Interleukin-6 signaling in liver-parenchymal cells suppresses hepatic inflammation and improves systemic insulin action, Cell Metab. 12 (2010) 237–249.
[132] N. Nishimoto, Y. Kanakura, K. Aozasa, T. Johkoh, M. Nakamura, S. Nakano, N. Nakano, Y. Ikeda, T. Sasaki, K. Nishioka, M. Hara, H. Taguchi, Y. Kimura, Y. Kato, H. Asaoku, S. Kumagai, F. Kodama, H. Nakahara, K. Hagihara, K. Yoshizaki, T. Kishimoto, Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease, Blood 106 (2005) 2627–2632.
[133] P.D. Lambert, K.D. Anderson, M.W. Sleeman, V. Wong, J. Tan, A. Hijarunguru, T.L. Corcoran, J.D. Murray, K.E. Thabet, G.D. Yancopoulos, S.J. Wiegand, Ciliary neurotrophic factor activates leptin-like pathways and reduces body fat, without cachexia or rebound weight gain, even in leptin-resistant obesity, Proc. Natl Acad. Sci. USA 98 (2001) 4652–4657.
[134] M.A. Febbraio, S. Rose-John, B.K. Pedersen, Is interleukin-6 receptor blockade the Holy Grail for inflammatory diseases? Clin. Pharmacol. Ther. 87 (2010) 396–398.
[135] T. Tamura, N. Udagawa, N. Takahashi, C. Miyaura, S. Tanaka, Y. Yamada, Y. Koishihara, Y. Ohsugi, K. Kumaki, T. Taga, T. Kishimoto, T. Suda, Soluble interleukin-6 receptor triggers osteoclast formation by interleukin 6, Proc. Natl Acad. Sci. USA 90 (1993) 11924–11928.
[136] V. Poli, R. Balena, E. Fattori, A. Markatos, M. Yamamoto, H. Tanaka, G. Ciliberto, G.A. Rodan, F. Costantini, Interleukin-6 deficient mice are protected from bone loss caused by estrogen depletion, EMBO J. 13 (1994) 1189–1196.
[137] M. Hashizume, N. Hayakawa, M. Mihara, IL-6 trans-signalling directly induces RANKL on fibroblast-like synovial cells and is involved in RANKL induction by TNF-alpha and IL-17, Rheumatology 47 (2008) 1635–1640.
[138] H. Tilg, A.R. Moschen, A. Kaser, A. Pines, I. Dotan, Gut, inflammation and osteoporosis: basic and clinical concepts, Gut 57 (2008) 684–694.

[139] O. Obreja, M. Schmelz, S. Poole, M. Kress, Interleukin-6 in combination with its soluble IL-6 receptor sensitises rat skin nociceptors to heat, in vivo, Pain 96 (2002) 57–62.
[140] O. Obreja, W. Biasio, M. Andratsch, K.S. Lips, P.K. Rathee, A. Ludwig, S. Rose-John, M. Kress, Fast modulation of heat-activated ionic current by proinflammatory interleukin 6 in rat sensory neurons, Brain 128 (2005) 1634–1641.
[141] M. Andratsch, N. Mair, C.E. Constantin, N. Scherbakov, C. Benetti, S. Quarta, C. Vogl, C.A. Sailer, N. Uceyler, J. Brockhaus, R. Martini, C. Sommer, H.U. Zeilhofer, W. Müller, R. Kuner, J.B. Davis, S. Rose-John, M. Kress, A key role for gp130 expressed on peripheral sensory nerves in pathological pain, J. Neurosci. 29 (2009) 13473–13483.
[142] P.G. Murphy, M.S. Ramer, L. Borthwick, J. Gauldie, P.M. Richardson, M.A. Bisby, Endogenous interleukin-6 contributes to hypersensitivity to cutaneous stimuli and changes in neuropeptides associated with chronic nerve constriction in mice, Eur. J. Neurosci. 11 (7) (1999) 2243–2253.
[143] M. Kopf, M.F. Bachmann, B.J. Marsland, Averting inflammation by targeting the cytokine environment, Nat. Rev. Drug Discov. 9 (2010) 703–718.