Interleukin-6 (IL-6) is an inflammatory cytokine, the level of which is highly elevated in most, if not all, inflammatory states. IL-6 triggers cell type-specific responses and acts on target cells via a specific interleukin-6 receptor (IL-6R), which, together with IL-6, binds to and induces the dimerization of a second receptor subunit, gp130. IL-6 also binds to soluble IL-6R, and this complex interacts with gp130, regardless of IL-6R expression. This allows cells that do not express IL-6R and would be otherwise insensitive to IL-6 to respond to it. We have generated a constitutively active version of gp130 by forced leucine-zipper-mediated dimerization, named L-gp130. Once inserted into the Rosa26 locus of mice, L-gp130 can be activated in a cell-autonomous manner by crossing these mice with any Cre-recombinase transgenic mouse strain. Activation of gp130 in hepatocytes produced liver-specific effects such as the induction of acute-phase proteins, but it also had profound systemic effects on the immune system. Such local and systemic effects of interleukin-6 will be reviewed.

**Keywords:** cancer; inflammation; interleukin-6; pancreatitis; trans-signaling
removed from the cell membrane, as demonstrated in vitro [9] and in vivo [10]. The resulting soluble IL-6R (sIL-6R) binds the ligand IL-6 with an affinity similar to that of membrane-bound IL-6R [11,12], and the IL-6-sIL-6R complex can bind to gp130 even on cells that do not express IL-6R. This process, referred to as IL-6 trans-signaling (Fig. 1) [13], dramatically broadens the spectrum of IL-6 target cells [14]. IL-6 activities via membrane-bound IL-6R (classic-signaling), such as the hepatic acute-phase reaction [15], are protective and regenerative. On the other hand, IL-6 activities via sIL-6R are considered pro-inflammatory and are additionally involved in inflammation-associated cancer [3,7,8,16,17].

IL-6 trans-signaling can be mimicked by a designer cytokine called Hyper-IL-6, in which IL-6 is fused to the sIL-6R via a flexible peptide linker [18]. Since the affinity of IL-6 to the IL-6R is about 100 times lower than the affinity of the IL-6-sIL-6R complex for gp130, the Hyper-IL-6 protein is about 100 times more efficient in stimulating the target cells than the pair formed by IL-6 and sIL-6R (Fig. 2) [18].

IL-6 activity is the target of biologics in the therapy of autoimmune diseases such as rheumatoid arthritis [3,19]. Neutralizing monoclonal antibodies against IL-6 or IL-6R block both the classic signaling and the trans-signaling of IL-6 [5]. A designer protein of the extracellular portion of human gp130 fused to the constant portion of human IgG1 antibodies (sgp130Fc) selectively blocks IL-6 trans-signaling (Fig. 2) [3,20]. Bazedoxifene, a steroid analog clinically approved for the treatment of osteoporosis, was recognized to partly suppress IL-6- and IL-11-induced gp130 activity [21]. Recently, bazedoxifene was used to rescue activated fibroblasts and macrophages in nucleotide-binding oligomerization domain-containing protein 2 (NOD2)-driven Crohn’s disease, indicating that gp130 blockade might be beneficial to patients with NOD2 mutations [22]. NOD2 recognizes bacterial molecular patterns and stimulates the immune system. Mutations in NOD2 have been associated with inflammatory bowel disease [22].

 Forced dimerization of gp130 was achieved by removing the entire extracellular portion of gp130 and replacing it with a leucine zipper [23]. Transfection of this cDNA construct coding for L-gp130 into IL-6-dependent cells resulted in cytokine-independent growth of the cells (Fig. 2). Introducing the L-gp130 construct into murine embryonal stem cells permanently blocked their differentiation in the absence of cytokine leukemia inhibitory factor (LIF) [23], which also signals via the gp130 receptor subunit [4]. The L-gp130 cDNA construct has been introduced into the murine Rosa26 locus so as to allow conditional transcriptional activation of L-gp130 and cell-autonomous gp130 activity by breeding these mice with appropriate Cre-transgenic mouse strains [24]. Constitutive activation of gp130 in B cells or all hematopoietic cells resulted in the formation of aggressive B-cell cancers underlining the key role of gp130 in this neoplasia [24].

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**Fig. 1.** Classic signaling and trans-signaling of IL-6. (A) IL-6 binds to the membrane-bound IL-6R and the complex of IL-6 and IL-6R associates with gp130, leading to the dimerization of gp130, which initiates intracellular signaling. Importantly, only cells that express IL-6R can respond to IL-6 alone. (B) IL-6 binds to soluble IL-6R (sIL-6R). The complex of IL-6 and sIL-6R associates with gp130 triggering the same events described in (A). Importantly, the complex of IL-6 and sIL-6R can activate any cell type, since all cells in our body express gp130.
In this review article, I summarize the state of the art and the experimental approach to study local and systemic activities of the cytokine IL-6 in inflammatory diseases and tumorigenesis.

**The role of IL-6 in the hepatic acute-phase response**

The hepatic acute-phase response is an orchestrated release of proteins involved in the protection of the body including C-reactive protein (CRP), serum amyloid A (SAA), haptoglobin, fibrinogen, and complement C3 [15]. The cytokine IL-6 mainly via STAT3 activation has been recognized to be the major regulator of the hepatic acute-phase response in the liver [25]. In humans, the acute-phase proteins CRP and SAA have been demonstrated to dramatically increase up to 1000-fold during the acute-phase reaction [26]. CRP is a pentameric protein, which binds to lysophosphatidylcholine on apoptotic cells, which leads to the activation of the complement system. Elevated CRP levels during inflammatory states are used as important disease markers [27]. Several functions have been ascribed to SAA proteins, such as transport of cholesterol to the liver and recruitment of cells of the immune system. Moreover, SAA has been implicated in amyloidosis and other inflammatory diseases [28].

Recently, several novel functions have been recognized for SAA. It was shown that in a mouse model of pancreatic tumor formation, IL-6-induced activation of the STAT3 pathway in hepatocytes led to the secretion of SAA and subsequently to the formation of a metastatic niche for tumor cells [29]. Such an intercellular network was also detected in patients with pancreatic and colorectal tumors, which had metastasized into the liver. In mice deficient for SAA protein, no prometastatic niche formation in the liver was seen, indicating a functional role of this acute-phase protein in directing metastasis [29].

IL-6 has a functional role in the generation of TH17 cells, which are a subtype of CD4 helper T cells [30,31]. When naïve CD4-positive T cells are stimulated with TGFβ, the T cells differentiate into regulatory T cells. A combination of TGFβ and IL-6 stimulates naïve CD4-positive T cells to differentiate into TH17 cells [30,31]. TH17 cells play an important
role at mucosal barriers where they are involved in the protection from pathogenic bacteria and fungi [32].

It was recently shown by Lee et al. that SAA together with IL-6 directly induces mouse T cells to differentiate into TH\textsubscript{17} cells. The stimulation by SAA and IL-6 resulted in a gene signature of chronic inflammatory disease-associated genes [33]. These findings were confirmed for human CD4-positive T cells. The important role of SAAs was corroborated in inflammatory animal models. In the absence of all functional SAA genes, mice showed significantly ameliorated features of colitis as compared to littermate controls [33]. In the mouse model for the human disease multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), mice without functional SAA genes showed significantly delayed onset and milder symptoms of the disease as compared to wt mice [33].

These recent results illustrate how IL-6 coordinates the innate and acquired immune system. The hepatic acute-phase response is clearly an ancient defense reaction, which originates from activated macrophages and is induced primarily by IL-6. SAA as one of the major acute-phase proteins together with IL-6 seems to be essential for the differentiation of TH\textsubscript{17} cells and therefore for the maintenance of biologic interfaces and barriers, as shown in the examples of intestinal inflammation and encephalomyelitis [32,33].

**The role of IL-6 in pancreatitis-associated lung injury**

Acute pancreatitis is a serious disease often caused by gallstones or alcohol abuse, which in some patient can develop into multiple organ failure [34]. In these patients, a systemic activation of the immune system reminiscent of sepsis without involvement of infection is experienced, with a major complication being acute lung injury [35,36]. Elevated serum levels of IL-6 and hepatic acute-phase proteins such as CRP have been associated with acute pancreatitis [37]. In a mouse model using cerulein stimulation of pancreatic digestive enzyme secretion, severe acute pancreatitis with acute lung injury was observed [36,38]. In these mice, elevated IL-6 levels in serum and bronchoalveolar lavage fluid were detected [36]. Interestingly, 100% of IL-6\textsuperscript{-/-} mice [39] survived severe acute pancreatitis, whereas 40% of wt mice died, indicating that IL-6 is a mediator of lung injury associated with pancreatitis [36]. Interestingly, however, in the absence of IL-6, inflammation-associated damage in the pancreas was aggravated but acute lung injury was improved (Fig. 3) [36].

IL-6 can act via classic and trans-signaling [2]. In mice, which transgenically express the sgp130Fc protein, IL-6 trans-signaling is largely inhibited [40]. In these mice, as in IL-6\textsuperscript{-/-} mice, acute lung injury was significantly improved [36]. But in contrast to IL-6\textsuperscript{-/-} mice, inflammation-associated damage in the pancreas was reduced indicating that classic IL-6 signaling via the membrane-bound IL-6R is involved in protection of the pancreas from inflammatory insults [36]. Consequently, we observed 100% survival of animals treated with cerulein when the mice were injected with the recombinant sgp130Fc protein (Fig. 3) [20], which selectively blocks IL-6 trans-signaling without affecting IL-6 signaling via the membrane-bound IL-6R [3]. We have postulated before that IL-6 activities mediated via the soluble IL-6R are pro-inflammatory, whereas IL-6 activities mediated via the membrane-bound IL-6R are rather anti-inflammatory, protective, or regenerative [16,41].

**The role of IL-6 trans-signaling in cancer**

The membrane-bound metalloprotease ADAM17 is responsible for the release of the sIL-6R as demonstrated in vitro [9,42] as well as in vivo [10]. This sIL-6R together with IL-6 mediates IL-6 trans-signaling. ADAM17 on the other hand is also responsible for cleavage of TNF\textalpha{} [43] and ligands of the EGF-R [44], indicating that ADAM17 orchestrates three major signaling pathways, which all show systemic activity [12,45]. In addition, close to 100 substrates have been identified in vitro and few of these have been verified in vivo [12,45].

ADAM17\textsuperscript{-/-} mice are not viable [46] and conditional ADAM17 knock-out mice have been generated [47]. In many murine models of human diseases, it is, however, not completely clear in which tissue or cell type ADAM17 activity might be important since it might cleave substrates also from a different cell. Therefore, using tissue-specific knock-out mice, it is not always clear in which cell types to delete ADAM17 in a given disease model. We have generated ADAM17 hypomorphic mice, which in all tissues only expressed about 5% of ADAM17 compared to wt mice [48]. These mice were viable but were highly susceptible to experimental inflammatory bowel disease due to impaired activation of the EGF-R in the intestine [48].

The development of hepatocellular carcinoma has been linked with inflammation and EGF-R signaling [49]. Provocatively, in the diethylamino/nitrosamine/pheno-barbital hepatocellular carcinoma model, mice lacking EGF-R in macrophages develop far less tumors than wt mice [49]. Indeed, it was found that EGF-R in...
Macrophages was required to transcriptionally induce IL-6 expression, which triggered hepatocyte proliferation and development of hepatocellular carcinoma [49]. Later, it was shown in the same model of hepatocellular carcinoma that specific blockade of IL-6 trans-signaling was sufficient to completely block the development of hepatocellular carcinoma [50], indicating that IL-6 trans-signaling but not classic signaling was responsible for tumor formation in the liver (Fig. 4).

More recently, the cell-specific role of the EGF-R in two major colon cancer models has been analyzed [51]. When the EGF-R was conditionally deleted in intestinal epithelial cells, tumor growth was not affected. In contrast, when the EGF-R was knocked out in myeloid cells, significantly fewer and smaller tumors were observed [51]. Stimulation of the EGF-R in myeloid cells resulted in highly elevated levels of IL-6 in the serum of mice treated with dextran sodium sulfate (DSS), which causes colonic epithelial injury [51]. Recombinant IL-6 protected DSS-treated mice from colitis and neutralizing IL-6 activity with the help of a monoclonal antibody exacerbated intestinal inflammation [51]. The protective role of IL-6 in animal models of inflammatory bowel disease can be explained by the regenerative activity of IL-6 and subsequent intracellular STAT3 activation via the membrane-bound IL-6R on intestinal epithelial cells [16,52,53].

When ADAM17 hypomorphic mice were subjected to the same colon cancer models as the EGF-R conditional knock-out mice, almost no tumors were seen in the absence of ADAM17 [54]. Furthermore, after 6 months, the few tumors seen without ADAM17 were all low-grade dysplasias, whereas in the presence of ADAM17, an average of 3 low-grade dysplasias, 2 high-grade dysplasias, and 1 invasive carcinomas per analyzed animal developed [54] as quantified by the method of Boivin et al. [55]. We hypothesized that the IL-6 synthesized by myeloid cells upon EGF-R

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**Fig. 3.** The pancreatic—lung failure model of systemic IL-6 activity. Pancreatic injury induced by cerulein results in a massive secretion of pancreatic digestive enzymes, in turn leading to acute pancreatitis and subsequent acute lung injury, which is fatal in up to 50% of treated mice. In the IL-6−/− mice, pancreatitis is more pronounced, whereas acute lung injury is attenuated, indicating that IL-6 exerts a protective function on the pancreas and is also necessary for the inflammatory signals to reach the lungs. In sgp130Fc transgenic mice, pancreatic damage is reduced and no major lung injury is observed. Hence, IL-6 classic signaling appears to be involved in pancreatic regeneration, whereas the systemic spreading of the inflammation to the lungs depends on IL-6 trans-signaling.
stimulation was involved in tumor formation. Myeloid cells are known to shed the sIL-6R upon inflammatory stimuli [56] and the generated sIL-6R together with IL-6 could act via IL-6 trans-signaling on the intestinal epithelial cells and induce tumor formation. We therefore compared tumorigenesis in colon cancer models in IL-6−/− mice [39] and in mice, which transgenically express the sgp130Fc protein [40] and are therefore protected from IL-6 trans-signaling [54]. These results were confirmed in the azoxymethane colon cancer model, in which transgenic sgp130Fc mice were protected from lesions analyzed by colonoscopy [57] during the course of the experiment and showed minimal tumor formation as compared to wt mice [54].

From these experiments, it could be concluded that in hepatocellular carcinoma as well as in colon cancer, the IL-6 trans-signaling mechanism acted downstream of EGF-R activity and thus might offer a new therapeutic window relevant to patients who developed resistance to EGF-R blockade (Fig. 4) [58]. It should be analyzed whether such a mechanism might be also detectable in other tumor entities.

Interestingly, a recent report showed that in the pancreas, IL-6 trans-signaling is involved in epithelial memory of inflammation associated with transcriptional and epigenetic changes, which seems to be involved in tissue protection. This effect might, however, be associated with a promotion of tumorigenesis [59]. It will be important to analyze whether this phenomenon can also be found in other types of neoplasia.

Of note, using the ADAM17 hypomorphic mice, it was also shown that ADAM17 plays an important role in kidney fibrosis following kidney injury [60]. Furthermore, a decisive role of ADAM17 has been demonstrated in lung cancer [61], pulmonary emphysema [62], and atherosclerosis [63]. These reports underline the involvement of ADAM17 in multiple signaling pathways, which are disease relevant [12,45].

**Cell-autonomous activation of gp130**

The responses of different tissues and cells to the cytokine IL-6 are highly diverse. The response of an organism to IL-6 is the sum of these diverse responses. In order to better define tissue- or cell-specific IL-6 responses, we have generated a constitutively active gp130 molecule. At the cDNA level, we have replaced the entire extracellular portion of gp130 by the leucine zipper portion of the c-jun transcription factor [64] to force dimerization of gp130 (Fig. 2) [23]. When the cDNA coding for the dimerized gp130 protein L-gp130 was transfected into mammalian cells, the L-gp130 protein was expressed at the cell surface and was tyrosine phosphorylated without stimulation. When L-gp130 cDNA was transfected into IL-6-dependent pro-B-cells, the cells autonomously proliferated without cytokine stimulation. The spontaneous differentiation of murine embryonic stem cells is completely blocked when the cells are treated with the cytokine LIF [65]. LIF is a member of the IL-6 family of cytokines and acts via a receptor complex, which contains gp130 [2]. When LIF is replaced by the combination of IL-6 and sIL-6R, the differentiation of murine embryonic stem cells is also inhibited [66].
When murine embryonic stem cells were stably transfected with an L-gp130 cDNA, the cells maintained an undifferentiated phenotype in the absence of LIF [23]. These experiments demonstrated that dimerization of gp130 was sufficient to activate gp130 and that the activation was stable for many cell divisions [23].

The L-gp130 cDNA was retrovirally introduced into murine bone marrow cells. Upon transplantation into lethally irradiated syngeneic recipients, the mice developed myeloma with organ damage, lytic bone lesions, monoclonal gammopathy, and kidney injury. The myeloma could be transplanted into syngeneic recipients, which led to dramatically reduced latency of disease [67]. These results indicated that gp130 activity alone was sufficient for the development of the disease.

We introduced the L-gp130 cDNA into the ROSA26 locus of C57BL/6 mice. In these mice, transcription of L-gp130 can be activated by crossing the animals with transgenic mice expressing the cre-recombinase under the transcriptional control of a tissue- or cell-specific promoter. The cre-recombinase removes a stop cassette, which is flanked by loxP sites, and thereby activates the transcription of L-gp130 [24]. When L-gp130 was activated in B cells, mature B-cell malignancies were observed, underlining the importance of gp130 signaling in the hematopoietic system [24].

With the help of different cre-transgenic mice, the expression of L-130 was activated in distinct liver cell types such as hepatic stellate cells, cholangiocytes/liver progenitor cells, and hepatocytes [68]. All mice showed highly elevated mRNA levels of L-gp130 and the expression was restricted to the targeted cell types. The activation of gp130 was visualized by STAT3 phosphorylation. Interestingly, upon L-gp130 expression, we did not observe significant changes in cholangiocytes/liver progenitor cell or hepatic stellate cell numbers, indicating that gp130 activation alone did not suffice to change cellular homeostasis. L-gp130 expression in hepatocytes resulted in massive STAT3 phosphorylation and strongly enhanced expression of acute-phase protein genes such as SAA and serum amyloid P, which turned out to be stable for more than 1 year [68].

Surprisingly, the activation of gp130 in hepatocytes resulted in an expansion of the myeloid compartment of the liver. Numbers of inflammatory macrophages were significantly increased and infiltrating monocytes were polarized to the M1 phenotype. Strikingly, we observed two Kupffer cell populations, which were characterized by the production of IL-6 and IL-10, respectively. In control animals, only one Kupffer cell population was detected, which secreted neither IL-6 nor IL-10. When mice with gp130 activation in hepatocytes were challenged with bacteria, significantly fewer life bacteria were detected in spleen and liver as compared with wt animals, indicating that gp130 activation alone provides protection from bacterial infection. After 1 year, persistent hepatocyte gp130 activation led to the deposition of SAA in colon, kidney, and spleen, reminiscent of patients with amyloidosis [68]. These results indicate that the cytokine IL-6 via gp130 activation not only exerts local effects but has also the potential to generate systemic changes in different organs and cell types.

Conclusions

The examples described above demonstrate the local and systemic nature of the activities of the cytokine IL-6. The current molecular tools (Fig. 2) have helped researchers to decipher the multifaceted functions of the cytokine IL-6 and to ascribe them to the activities of membrane-bound or soluble IL-6R. This has led to the development of a new therapeutic approach that blocks the inflammatory activities of IL-6 without compromising its protective and regenerating effects [3,16]. This approach has very recently shown efficacy in phase II clinical trials in patients with inflammatory bowel disease [17].

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Conflict of interest

SR-J has acted as a consultant and speaker for Abb-Vie, Chugai, Genentech Roche, Roche, Pfizer, and Sanofi. He also declares that he is an inventor on patents owned by CONARIS Research Institute, which develops the sgp130Fc protein Olmikicept together with the company I-Mab. SR-J has stock ownership in CONARIS. None of these relationships are relevant to the work published in this manuscript.

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