The two facets of gp130 signalling in liver tumorigenesis

Dirk Schmidt-Arras1 · Eithan Galun2 · Stefan Rose-John1

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Abstract

The liver is a vital organ with multiple functions and a large regenerative capacity. Tumours of the liver are the second most frequently cause of cancer-related death and develop in chronically inflamed livers. IL-6-type cytokines are mediators of inflammation and almost all members signal via the receptor subunit gp130 and the downstream signalling molecule STAT3. We here summarize current knowledge on how gp130 signalling and STAT3 in tumour cells and cells of the tumour micro-environment drives hepatic tumorigenesis. We furthermore discuss very recent findings describing also anti-tumorigenic roles of gp130/STAT3 and important considerations for therapeutic interventions.

Keywords IL-6 · gp130 · STAT3 · Hepatocellular carcinoma (HCC) · Cholangiocarcinoma (CCA) · Tumour micro-environment · Anti-tumour immunity · Inflammation

Introduction

The family of IL-6-type cytokines

The cytokine Interleukin-6 (IL-6) was originally cloned as a B-cell stimulating factor [1] but was subsequently shown to be identical with hepatocyte stimulating factor [2], indicating that the cytokine may have very different activities within the human body. Today, we know that IL-6 is not only important for the activation of the immune system and the orchestration of innate and acquired immune response [3, 4] but also plays a role in the maintenance of the central nervous system [5] and in the regulation of metabolism [6, 7].

Biochemically, IL-6 is a four-helical protein with a typical up-up-down-down topology, which is shared by many cytokines [8, 9]. On target cells, IL-6 binds to the IL-6 receptor (IL-6Rα), which belongs to the class of hematopoietic receptors [8]. The complex of IL-6 and IL-6Rα associates with a second receptor protein, glycoprotein 130 kDa (gp130), which upon dimerisation initiates signal transduction within the cell (Fig. 1a) [10]. Interestingly, gp130 is also a signalling receptor of the cytokines IL-11, IL-27, IL-35, ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), leukaemia inhibitory factor (LIF), oncostatin M (OSM), and cardiotrophin-like cytokine (CLC) (Fig. 1a) [9]. These cytokines form the family of IL-6-type cytokines [9]. Of these cytokines, LIF, OSM, and CNTF have been identified as additional hepatocyte stimulating factors responsible for the induction of the hepatic acute-phase protein induction [11]. Consequently, intracellular signal transduction pathways of all these cytokines are very similar although not identical [12].

gp130 signal transduction

Dimerisation of gp130 by the IL-6 and IL-6Rα complex leads to activation of the tyrosine kinase JAK1, which is constitutively bound to gp130. JAK1 phosphorylates the five tyrosine residues within the cytoplasmic portion of gp130. The membrane proximal tyrosine is the docking site for the phosphatase
SHP2, which initiates the MAPK pathway and the PI3K pathway (Fig. 1b). The four membrane distal phosphotyrosine residues recruit STAT1 and STAT3, which upon phosphorylation homo- or heterodimerise and translocate to the nucleus where they act as transcription factors for STAT target genes (Fig. 1b). One of the earliest STAT target genes codes for the protein SOCS3, which is recruited to the membrane proximal tyrosine residue from where it inhibits JAK1 activity and prevents SHP2 binding (Fig. 1b). Thereby, SOCS3 provides negative feedback inhibition of gp130 activation [10]. In addition to the above mentioned signalling pathways, it was found that Src family tyrosine kinases are recruited to the cytoplasmic portion of gp130 and that this signal transduction is independent of receptor- and STAT3-phosphorylation. Src family kinases phosphorylate the transcriptional co-activator YAP (yes-associated protein) leading to activation of YAP target genes and tissue growth [13]. Interestingly, the JAK/STAT pathway and the YAP pathway are strongly activated in the regenerating liver [13, 14].

The cellular landscape of IL-6 family cytokine sender and receiver in the liver

The liver consists of different cell types. Hepatocytes, the liver parenchymal cells represent the largest cellular mass of the liver and fulfil multiple functions, including a central function in body metabolism, detoxification, and the synthesis of bile and plasma proteins. Biliary epithelial cells (BECs) are lining the intra- and extrahepatic bile ducts. Both epithelial lines can be the origin of hepatic tumours. The liver also harbours different inflammatory cells of the adaptive and the innate immune system, among them the Kupffer cells (KCs), that are liver-resident macrophages derived from the foetal yolk sac. Hepatic stellate cells (HSCs) are found in the perisinusoidal space.
space and serve as lipid and vitamin A storage. Upon liver damage, HSCs differentiate into collagen-secreting myofibroblasts [15].

Under physiological conditions, expression of IL-6 family cytokines is barely detectable in the liver. However, upon infection, challenge with microbial antigens or tissue damage, levels of IL-6 and IL-11, and OSM can increase tremendously. Under these conditions, myeloid cells, in particular, KCs are the major source of IL-6 and OSM. However, it was also demonstrated that non-parenchymal cells recruited via IL-17 are important sources of IL-6 during liver regeneration [16] and hepatic fibrosis [17]. During chronic liver disease also senescent hepatocytes and BECs secrete IL-6 (see also below), while OSM is secreted by hepatic progenitor cells [18]. IL-11 is secreted by activated HSCs [19] [20] and lipiddloaded hepatocytes [20] in the course of non-alcoholic fatty liver disease (NAFLD).

The signal-transducing subunit gp130 of IL-6 family receptor complexes is ubiquitously expressed in the body. Expression of gp130 in hepatocytes seems to be downregulated by bile acids which may contribute to hepatocyte death during cholestasis [21]. While gp130 is ubiquitously expressed in the liver, response to a particular cytokine family member is limited by the expression of its cognate receptor.

IL-6 needs to bind to the IL-6Rα in order to induce dimerisation of gp130 and initiation of intracellular signalling [9]. The membrane-bound IL-6Rα is subject to limited proteolysis by proteases such as ADAM10 and ADAM17 [22, 23], and in this way, generated soluble IL-6Rα still binds IL-6 and can elicit IL-6 signals on cells, which do not express IL-6Rα [9]. This mode of signalling has been named IL-6 trans-signalling [24]. The IL-6 trans-signalling pathway not only vastly enlarges the spectrum of IL-6 target cells but also increases the signalling strength and prolongs IL-6 signals on cells, which do express the IL-6Rα [25] due to the typically higher expression of gp130 as compared to IL-6Rα [9].

In the liver, all cell types are able to respond to IL-6, and expression of IL-6Rα was detected on hepatocytes, BECs [26], and HSCs [27]. Using a novel mouse model of cell-autonomous gp130 activation, we recently showed that hepatocytes but not BECs or HSCs react most prominently to gp130 activation [28]. However, this does not exclude that, under pathological conditions, IL-6-type cytokines regulate biological behaviour of BECs or HSCs.

**Physiological role of IL-6 family cytokines in the liver**

IL-6 regulates multiple functions in the liver, including infection defence, metabolism, and regeneration. In the acute phase of an infection, plasma levels of inflammatory cytokines such as TNFα, IL-1β, and IL-6 sharply increase, followed by enhanced secretion of proteins belonging to the family of acute-phase proteins (Fig. 1c) [29]. These proteins are able to prevent systemic spreading of an infection by pathogen opsonisation, enhancing blood coagulation and complement activation and the initiation of adaptive immunity. The necessity of IL-6/gp130 signalling for the induction of acute-phase proteins was initially demonstrated in mice deficient for IL-6 [30]. By using mice either deficient for gp130 [31–33] or with cell-autonomous gp130 activation [28], it was shown that gp130 activation in hepatocytes is sufficient to trigger acute-phase proteins secretion. There is experimental evidence that production of acute-phase proteins is even enhanced by IL-6 trans-signalling [28, 34, 35]. Recently, inactivating mutations in IL6ST, encoding gp130 [36] and inactivating mutations in IL6RA [37] were observed and demonstrated that, also in humans, IL-6/gp130 signalling is essential for the secretion of acute-phase proteins. Through the induction of hepcidin in hepatocytes, IL-6/gp130 signalling impairs ferroportin-mediated iron release from intestinal epithelial cells to further dampen bacterial infections [38, 39]. Furthermore, gp130 signalling in hepatocytes induces the mobilisation and recruitment of neutrophils via the secretion of the neutrophil attractant CXCL1 in mice or the functional orthologue IL-8 in humans [28, 33, 40].

The liver has a unique capacity to regenerate and IL-6 was identified as a major driver of liver regeneration. Shortly after hepatectomy, liver vein levels of TNFα increase, followed by a strong induction of IL-6 [41]. Consistently, IL-6-deficient mice display impaired liver regeneration [42]. IL-6 promotes liver regeneration by two means: prevention of hepatocyte cell death and stimulation of hepatocyte proliferation (Fig. 1c). While IL-6-deficient mice display a marked reduction in hepatocyte proliferation [42], administration of recombinant IL-6 acts as a direct hepatocyte mitogen [43]. This indicates that albeit other growth factors such as HGF contribute to liver regeneration, IL-6 is a key regulator of liver regeneration. IL-6/gp130 signalling was shown to prevent hepatocyte apoptosis upon DNA damage through stabilisation of Mcl-1 and the prevention of p53 stabilisation [44, 45]. Activation of the PI3K/AKT pathway contributes to the anti-apoptotic effect of IL-6/gp130 signalling in hepatocytes [46, 47].

Albeit hepatocytes express IL-6Rα and therefore respond to IL-6 classic signalling, hepatocyte proliferation, and hence, liver regeneration is enhanced by IL-6 trans-signalling. This observation can be explained by the fact that hepatocytes express far more gp130 than IL-6Rα. Consequently, in the presence of IL-6Rα and soluble IL-6Rα (sIL-6R), a larger fraction of gp130 molecules is stimulated than by IL-6 alone [46, 48–50].

While earlier reports demonstrated that recombinant human IL-11 protects from hepatocyte damage induced by oxidative stress, drugs, or ischemia/reperfusion [51–54], more recent reports show that IL-11 rather promotes liver damage via ROS production [20], activates HSCs [19, 20], and hence, promotes liver fibrosis in the setting of chronic liver disease. Similarly, OSM was shown to prevent hepatocyte damage by...
oxidative stress [55–57] and to promote hepatic fibrosis by upregulation of TGFβ and PDGF in hepatic macrophages [58], and by stimulating myofibroblast migration [59].

**Pro-tumorigenic roles of IL-6/gp130**

**Regulation of IL-6 secretion during tumorigenesis**

Hepatic tumours, in particular HCC, are classical examples of inflammation-driven cancers [60], and composition of the tumour-associated immune compartment is key to carcinogenesis and metastasis [61]. Tumour-associated myeloid cells, in particular KCs, were identified as major source for IL-6 [62, 63]. Expression and secretion of IL-6 in KCs are suppressed by activated oestrogen receptor (ER) α which explains at least in part the gender disparity in HCC formation in humans [62].

A common requirement for the secretion of IL-6 from tumour-associated macrophages (TAM) of the intestine and the liver is an autocrine EGFR activation loop [64, 65]. Interestingly, EGFR overexpression [66] and upregulation of EGFR ligands such as transforming growth factor (TGF) α [67] and epiregulin (EREG) [68] were reported in human and murine HCC.

Obesity is linked to an increased risk of tumour development and was shown to promote HCC formation via enhanced TNF α and IL-6 secretion [69]. Alterations in the intestinal microbiota composition called “dysbiosis” are common to obesity, age-dependent inflammation [70], and chronic liver disease [71]. Venous blood that drains from the intestine first passes the liver and KCs serve as gatekeepers that protect against intestinal-derived pathogens. Microbiota-associated molecular patterns (MAMPs) are sensed by toll-like receptors (TLR) on KCs leading to recruitment of the adaptor molecule MyD88 and/or TIR domain-containing adapter molecule 1 (TICAM-1/TRIF) and activation of downstream signalling (Fig. 2a). It was shown that, during HCC formation, intestinal dysbiosis enhanced EREG secretion in a TLR4-dependent manner [68]. It is therefore not surprising that KC-mediated IL-6 secretion during hepatic carcinogenesis is hampered in mice deficient for MyD88 or toll-like receptor (TLR) 4 [62, 72]. In this context, the serine-threonine protein kinase (STK) 4 counteracts TLR signalling and concomitant IL-6 secretion through phosphorylation of the TLR downstream signalling molecular IRAK1 [73] and is therefore considered as tumour suppressor for HCC [74].

B-Cells are present in HCC [61] and were shown to undergo immunoglobulin class switch recombination [75]. IgG secreted by these plasma cells binds to Fcy receptor on TAMs thereby enhancing IL-6 secretion [75]. Similarly, BEC autoreactive antibodies in patients with primary sclerosing cholangitis, a chronic liver disease that predisposes to cholangiocarcinoma formation, bind to and induce secretion of IL-6 from BECs [76].

Cancer-associated fibroblasts (CAFs) are key components of the tumour micro-environment [77]. Also in the liver, HCC often develops in cirrhotic liver that is promoted by activated HSCs [15, 78]. During liver fibrosis, HSCs are a cellular source of IL-6, and IL6 transcription is enhanced via the hepatic leukaemia factor (HLF) transcription factor (Fig. 2a) [27]. CAFs isolated from prostate cancer [79] and intrahepatic cholangiocarcinoma were also shown to highly secrete IL-6 [80].

Senescent cells secrete diverse molecules, including cytokines such as IL-6, which is called the senescence-associated secretory phenotype (SASP). During chronic liver disease, hepatocytes can become senescent. Both senescent hepatocytes [81, 82] and cholangiocytes [83] were shown to secrete IL-6. Consequently, surveillance of senescent hepatocytes is the key to the prevention of HCC formation [84]. But also non-senescent hepatocytes were shown to upregulate IL6 expression via co-binding of nuclear factor (NF)-κB and the polycomb repressor complex (PRC) 2 member enhancer of zeste homolog (EZH) 2 [85].

**Effect of IL-6 on (pre-)malignant hepatic cells**

Serum levels of IL-6 are high in chronic liver disease predisposing to hepatocarcinogenesis, suggesting that IL-6/gp130 signalling is a major driver of hepatocarcinogenesis. And indeed, not only IL-6-deficient [62] mice but also mice with hepatocyte-specific gp130-deficiency [91] display strongly impaired tumour formation not only in a murine DNA damage-driven HCC model but also in an obesity-driven liver tumour model. Furthermore, hepatocyte carcinogenesis was shown to be accelerated via enhanced genomic instability [92, 93]. While impaired DNA damage response during chronic inflammation is mainly mediated by TNF α [70, 94], survival and proliferation of genomic unstable hepatocytes are driven by gp130 trans-signalling by preventing...
p53-induced hepatocyte apoptosis (Fig. 2b) [45, 93, 95]. Not only IL-6 but also IL-11 seems to contribute to gp130-driven carcinogenesis as it was demonstrated that recurrence of experimental HCC upon hepatectomy was impaired in IL11ra-deficient mice [96].

Albeit the cellular origin of HCC is still under debate, the occurrence of cells with a liver stem/progenitor cell phenotype was reported in human and experimental HCC [63, 89, 97] that were able to reconstitute hepatic tumours in transplantation experiments [89]. These cells were termed HCC progenitor cells (HcPCs). HcPCs seem to depend on inflammatory signalling, and ectopic lymphoid structures in the liver were shown to promote survival and outgrowth of HcPCs [97]. During an early stage of hepatocarcinogenesis, HcPCs depend on paracrine IL-6 derived from KCs or TAMs [63, 89], while at a later stage of carcinogenesis, HcPCs develop an autocrine IL-6 loop through Lin28B-mediated suppression of the inhibitory miRNA let7 (Fig. 2b) [89]. Furthermore, in metastatic HCC, establishment of an autocrine IL-11 loop promotes metastatic colonisation (Fig. 2b) [90].
Similar to carcinogenic hepatocytes, proliferation and stemness of intrahepatic cholangiocarcinoma (CCA) cells are enhanced by IL-6/gp130 signalling through the upregulation of EZH2 that mediates histone H3 methylation (Fig. 2b) [80]. This correlates with enhanced expression of gp130 and IL-6Rα in CCA cells as compared to BECs [98]. The observation that proliferation of human CCA cell lines is reduced in the presence of a neutralising anti-IL-6 antibody [98] suggests that CCA cells also can adopt autocrine IL-6/gp130 signalling.

The fact that constitutive activation of the gp130/STAT3 pathway is found in inflammatory liver adenoma and hepatic tumour progenitor cells suggests that constitutive activation of gp130 in hepatocytes or liver progenitor cells is sufficient to drive liver tumorigenesis. In order to address this hypothesis, we previously generated an artificial constitutive active gp130 variant by replacing the extracellular domain of gp130 with the c-Jun leucine zipper [99], which we termed “Lgp130”. We generated mice with a Cre-inducible expression cassette in the ROSA26 locus. When Lgp130 was expressed in B-cells, it was sufficient to drive B-cell malignancies [100]. However, when Lgp130 was expressed in hepatocytes, we did not observe tumour formation in aged mice, despite persistent gp130/STAT3 activation [28]. These data suggest that gp130/STAT3 signalling alone does not confer malignant transformation. However, constitutive gp130 signalling was able to promote oncogenic transformation in human foetal hepatocytes when combined with DNA double strand breaks [95].

**Effect of IL-6 on tumour micro-environment**

The tumour micro-environment of hepatic tumours is composed of different inflammatory cells, and there is growing interest in the application of immunotherapeutic in hepatic cancers [61]. For the detailed inflammatory composition of HCC tumour micro-environment, the reader is referred to recent excellent reviews [61, 101, 102]. There is increasing evidence that IL-6 family cytokines are involved in shaping the inflammatory component of HCC tumour micro-environment. Different CD4+ T helper (Th) subpopulations, including Th17, were recently identified in hepatocarcinogenesis [113]. While there is clear evidence that IL-6 contributes to hepatic tumour formation, the role of other IL-6 family cytokines is less clear. However, there is evidence that OSM and CLC contribute to hepatic tumorigenesis, while LIF and IL-27 rather seem to play a tumour suppressive role.

Expression of inhibitory molecules including programmed cell death protein (PD)-1 and T cell immunoglobulin and mucin domain (TIM) 3 is increased on CD4+ and CD8+ T-cells in HCC tissue [61]. Inhibitory molecules on T cells guard against auto-reactivity but are also a sign of T cell exhaustion, a state of lymphocyte dysfunction. Tumour cells use this mechanism to evade surveillance through the adaptive immune system. IL-6 was shown to promote expression and stability of T cell inhibitory molecules. In HCC cell lines, IL-6 increased the surface localisation of PD-L1 (Fig. 2c), the ligand for the inhibitor molecule PD-1. gp130/JAK activation induced PD-L1 phosphorylation, and in tum, altered glycosylation that resulted in an enhanced stability of PD-L1 on the cell surface [109]. Furthermore, CAFs isolated from HCC were shown to recruit and activate neutrophils [110] via secretion of IL-6 and induction of STAT3 activity in neutrophils (Fig. 2c). These activated neutrophils [110], also myeloid-derived suppressor cells [85], dampened an anti-tumour T-cell response through the upregulation of PD-L1 (Fig. 2c). Similarly, IL-6 derived from glioblastoma cells induced PD-L1 in tumour-associated myeloid cells [111]. It is therefore not surprising that combination of anti-PD-1 antibodies with anti-IL-6 antibodies impairs the immunosuppressive tumour micro-environment and is a promising strategy also for the therapy of HCC [110, 112, 113].

Interestingly, it was recently shown in a murine model of primary sclerosing cholangitis that IL-17 from Th17 cells promotes the expression of PD-L1 on BECs [114] thereby not only dampening auto-inflammation on one side but also potentially preventing proper anti-tumour response in cholangiocarcinoma.

KCs were suggested to promote survival of liver sinusoidal cells in an IL-6/gp130-dependent manner [115]. Accordingly, it was shown that tumour vascularisation in murine HCC models is enhanced by IL-6 trans-signalling [45, 116] and thereby further promoting hepatic tumourigenesis (Fig. 2c).

IL-6 signalling also plays an essential role for the preparation of a hepatic metastatic niche. On one hand, IL-6 induced PD-L1 expression on colorectal cancer cells thereby blunting anti-tumour effector function of CD8+ T cells [117]. On the other hand, gp130/STAT3-dependent secretion of SAA protein by hepatocytes promotes metastatic colonisation of pancreatic cancer cells in the liver [118].

**The impact of other IL-6 family cytokines on hepatocarcinogenesis**

While there is clear evidence that IL-6 contributes to hepatic tumour formation, the role of other IL-6 family cytokines is less clear. However, there is evidence that OSM and CLC contribute to hepatic tumorigenesis, while LIF and IL-27 rather seem to play a tumour suppressive role.
The OSMR is expressed on HcPCs and proliferation and hepatocytic differentiation of these cells is promoted by OSM [119]. Neutrophils that accumulate in hepatic tumour tissue produce OSM upon paracrine stimulation with TNFα secreted by TAMs [120]. As a consequence, OSM is hypothesized to promote hepatocarcinogenesis and intrahepatic metastasis. CLC, secreted by CAFs, was recently identified to accelerate hepatocellular carcinogenesis [121] and engagement of CNTFR induces MAPK activation in HCC cell lines in vitro [122].

Expression of LIFR is lost during malignant progression of hepatic tumours [123], suggesting that LIF plays a tumour suppressive role. However, little is known on the underlying mechanisms.

Expression of IL-27 is upregulated in HCC patients [124]. In HCC cell lines, IL-27 induces robust STAT1 rather than STAT3 phosphorylation and a STAT1-dependent expression profile [125]. As a consequence, IL-27 induced expression of MHC I, suggesting more effective antigen presentation, but also, expression of PD-L1 was elevated [126]. However, the effect of IL-27 on growth of hepatic tumours in vivo is far from being understood, as IL-27 did not prevent the orthotopic growth of an HCC cell line in mice [127].

**Anti-tumorigenic roles of IL-6/gp130/STAT3**

The fact that IL-6 is a pleiotropic cytokine with a unique ligand–receptors interaction and natural “built-in” shed and intracellular inhibitors make it not unexpected that its effect on tumorigenesis is context-dependent and not “monochromatic”. Although most investigations show the pro-tumorigenic effect of IL-6, it also encounters several properties that directly or indirectly execute its anti-tumorigenic properties.

Numerous mechanisms and associations were reported between increased IL-6 expression and signalling and levels and suppression of tumorigenesis. These include the following: 1. the role of IL-6 in liver fibrosis, 2. the role of IL-6 in senescence, and 3. the tumour suppressive effects of STAT3.

**Prevention of hepatic fibrosis**

Fibrosis is a complexed condition involving different cytokines, including IL-6 [128]. Liver fibrosis is perceived as a contributing factor to the development of liver injury, and vice versa, liver injury, which is usually the initiating event, causes the development of liver fibrosis [129]. Furthermore, fibrosis is a significant factor for liver disease outcome and a risk for the development of hepatocellular carcinoma (HCC) [78]. It was already shown 20 years ago that IL6 deficiency causes enhanced liver fibrosis upon the development of liver injury [130]. IL-6 KO mice are shown to be more susceptible to liver steatosis and injury under a high-fat diet [131, 132]. In a CCl4 model of liver fibrosis, the attenuation of fibrosis by sorafenib correlated with increased STAT3 phosphorylation in hepatocytes which was dependent on KC-derived IL-6 [133]. In addition, it was shown that, upon deletion of STAT3 in hepatocytes, there is an exacerbation of liver fibrosis during cholestasis. Unidentified factors released from hepatocytes, dependent on STAT3, play a protective role in liver fibrogenesis through an inhibitory effect on activated HSCs (Fig. 3a) [134]. The mechanism of how IL-6 prevents and reverses hepatic fibrosis is still under investigations. One proposed mechanism is that bipotential murine oval liver cells, thought to be hepatic progenitors, secret IL-6 which could induce the apoptosis of HSCs [135]. In alcoholic liver disease in humans, it was also suggested that IL-6 has an anti-fibrotic effect through the STAT3 signalling pathway [136]. An additional potential mechanism is through the inhibition of inflammation in specific cases, as was reported in the lipopolysaccharide/d-galactosamine (LPS/d-Gal)-induced acute liver injury in rodent model, in which IL-6 has an anti-injury property [137]. Alcoholic liver disease is associated with HCC [138]. The protective role of IL-6 was also shown in an ethanol-induced oxidative stress model in which hepatocytes via induction of metallothionein protein expression dependent on IL-6 were protected against ethanol injury also by other mechanisms [139, 140].

**Direct anti-tumour effects**

The pleiotropic nature of IL-6 mediates many cellular phenotypes, which are context-dependent. These are involved in metabolism, differentiation, and survival. Heme oxygenase-1 (HO-1) has a number of anti-injury properties mediated by catabolic by-products such as biliverdin, which suggests that HO-1 is a tissue protector. A recent report shows that HO-1 is a tumour suppressor gene, which is induced by IL-6 [141].

STAT3, although perceived as a traditional target for treating cancer, until today, this is not translated into clinical usage [142]. This is also true for the use of STAT3 inhibitors for the treatment of HCC. None of the STAT3 inhibitors passed phase III clinical studies for HCC. Lysosomes are recognized today as pivotal in many cellular processes. Cellular transformation is associated with lysosomal modifications, potentially also promoting tumorigenesis [143]. STAT3 mediates lysosomal-mediated programmed cell death in mammary epithelial cells, by formation of large vacuoles containing triglyceride, inducing leakage of cathepsins which culminates in cell death [144]. Altogether, this teaches us that STAT3 phosphorylation downstream to IL-6 signalling could suppress breast cancer development and progression.

The role of STAT3 is also dichotomic. In the liver, STAT3 is activated in cholangiocytes enhancing cholangiocytic cancer stem cell for proliferation downstream to the signalling of CD24 and NANOG [145]. Loss of STAT3 in lung and pancreatic cancers was associated with mesenchymal transition of epithelial cells and an aggressive tumour phenotype. Whereas, STAT3 activation conferred a differentiated cells epithelial phenotype and reversed the
cancerous phenotype [146]. STAT3 was also shown to encounter tumour suppressive effects in other types of tumours including papillary thyroid carcinoma [147], glioblastoma [148], in colon carcinoma STAT3 suppresses the development of ApcMin cancer possibly through the downregulation of Snail-1, suppressing an epithelial-mesenchymal transition of colorectal cancer cells [149, 150]. A similar observation was reported in KRAS mutation induced lung adenocarcinoma, in which disruption of STAT3 induced tumorigenesis [151]. Furthermore, in smokers with KRAS mutation, lung adenocarcinoma STAT3 correlated with poor survival and advanced malignancy. The experience and disappointment with STAT3 inhibitors were also apparent for prostate cancer. Prostate cancer is the most frequent cancer in males, and the phosphatase and tensin homologue (PTEN) gene is the most frequently mutated gene in this malignancy. Mice with a conditional mutation of PTEN in the prostate epithelium are a commonly used mouse model for prostate cancer. Unexpectedly, genetic inactivation of STAT3 or IL-6 in prostate-specific PTEN knock-out mice led to accelerated tumour progression and metastasis [152]. This result helped to explain the result from clinical trials, in which patients with advanced prostate cancer were treated with a neutralizing IL-6 antibody without any significant survival advantage [153]. In the prostate-specific PTEN knockout mouse model, it was shown that the loss of IL-6/STAT3 signalling bypassed cellular senescence by disrupting the ARF-p53 axis indicating that alternative reading frame protein (ARF) was a novel STAT3 target gene [152]. In line with the animal studies, it was shown in prostate cancer patients that loss of STAT3 and ARF correlated with increased risk of tumour recurrence. These results yield a molecular explanation how the IL-6/STAT3 axis, which in many tumours has an oncogenic potential, can also act in the maintenance of senescence and thereby act as a tumour suppressor (Fig. 3b) [152].

In a Myc-dependent breast cancer mouse model, STAT3 deficiency was associated with enhanced epithelial-to-mesenchymal transition and metastasis, indicating a potential anti-metastatic property of STAT3 [154]. In summary, although STAT3 is perceived a pro-tumorigenic mediator of signalling upon its phosphorylation, growing number of reports teach to the fact that the role of STAT3 in tumorigenesis is more context-dependent.

**Effect of IL-6/gp130 signalling on CCA**

Intrahepatic cholangiocarcinoma is a very aggressive cancer and the second most common among liver cancers. Recent publications report quite controversial findings on the role of
IL-6 in cholangiocarcinoma. IL-6 is proposed to be secreted from CAFs of this tumour, inducing epigenetic changes in cholangiocytes and thereby enforcing a malignant transformation driving the initiation of intrahepatic cholangiocarcinoma [80]. However, a recent report observed a negative correlation between IL-6 levels and intrahepatic cholangiocarcinoma [155]. In addition, farnesoid X receptor (FXR), which is downregulated in intrahepatic-cholangiocarcinoma cell lines and human samples, has a negative correlation with aggressiveness and poor prognosis of patients with intrahepatic-cholangiocarcinoma. FXR expression was negatively correlated with IL-6 in intrahepatic cholangiocarcinoma tissues. FXR inhibited intrahepatic cholangiocarcinoma aggressiveness through the suppression of IL-6 [156]. However, it was shown that inhibition of IL-6 trans-signalling by the administration of recombinant sgp130Fc reduced cholangiocarcinoma cell line viability and induced apoptosis, whereas both migration and proliferation increased [157]. In one type of cholangiocarcinoma, carcinoma of the gallbladder (GBC), IL-6R α (gp80), was downregulated and correlated positively with an improvement of overall survival. Overall, these complex observations of the role of IL-6 in human cholangiocarcinoma, showing both pro-tumorigenic and anti-tumorigenic properties, are “reproduced” in other types of cancers as well. These complexed observations render a simple therapeutic approach. This complexity imposes a case-by-case investigation and understanding prior to developing therapeutic approaches.

### Regulation of tumour cell senescence

Senescence is initiated following an external stress imposed on the tissue. In the liver, this could be inflammation, infection, or metabolic strain. Senescent cells arrest in the cell cycle, encounter morphological changes, and produce a specific and complex secretome, the senescence-associated secretory phenotype (SASP) [158]. The development of DNA damage leads to cell cycle arrest through the activation of p53, and the induction of p21^{CIP1} and p16^{INK4a} inhibits cyclin-dependent kinases CDK4, CDK6, and CDK2 in some cases. IL-6 is a major component of the SASP response although it is now known that SASP could harbour hundreds of protein and non-protein substances with inflammatory and immunological properties [159]. Induction of senescence in cancer opens an opportunity to treat the malignancy with senolytic agents that selectively induce cell death in senescent cells [160]. This was recently shown to be effective in liver cancer [161]. Although the role of IL-6 in senescence-induced anti-tumour effects was reported in non-HCC [162], the role of IL-6 in senescence-mediated anti-tumour effects in different types of liver cancers is still under investigation and seems to be dependent on the tumour type (E.G., personal communication). However, in some pathological conditions upon stress, senescence develops, as in alcoholic liver disease. It was recently shown that M2 macrophages trigger hepatocyte senescence and enhance alcohol-induced hepatocyte senescence, as indicated by increased β-galactosidase activity, elevated CDKN1A mRNA expression, and induction of nuclear p21. This group identified IL-6 as the mediator of M2-induced hepatocyte senescence. Senescent hepatocytes might display protective effect against alcoholic liver disease, a pre-malignant condition upon becoming chronic [163].

### Therapeutic considerations

In the intensive investigations on the role of the IL-6/STAT3 pathway, although unfolded many mechanistic understandings related to the development of liver cancer and other malignancies, no single drug was yet approved that is based on these mechanistic findings. However, specific targets and approaches interfering with the IL-6/STAT3 pathway are highlighted and are potentially important to indicate in this review. The potential contribution of senescence to the development of HCC has been investigated in an effort to identify new therapeutic targets against HCC. Senolytic agents were shown to have a beneficial effect on HCC [161] but, at the same time, warranted further investigations [164].

There are some recent developments in the applications of kinase inhibitors (sorafenib [165] and lenvatinib [166]) and immunotherapies for HCC [61, 167]. However, these encounter many side effects and escapes from treatments and are currently indicated for a more advanced disease. Due to the intensive cancer surveillance programs worldwide, many small tumours are detected in patients with cirrhosis at relatively early stages [168]. For these patients, regional approaches including partial/segmental hepatectomy (PHx), transcatheter arterial chemoembolisation (TACE), and radiofrequency ablations (RFA) gained ground as an important approach for treating HCC local/regional disease [169]. However, these approaches are also associated with high recurrence frequency. We have shown in the MDR2 KO mice model [170], which simulates inflammation-induced chronic liver injury and cancer, that there is an enhanced hepatocarcinogenesis following PHx [92]. This occurs with enhanced DNA damage response, increased genomic instability, escape of cell-cycle arrest, and senescence and causes tumour growth acceleration subsequent to PHx, causing HCC recurrence. In a recent investigation, to unfold the enhanced carcinogenic effect of PHx, it revealed that, under these inflammatory conditions, there is a striking increase in hepatocytes bearing micronuclei, a marker of genomic instability, which is suppressed by IL-6 blockade [93]. The vast majority of patients in the western world develop HCC on the background of cirrhosis, rendering PHx as a preferred therapeutic approach. However, PHx in cirrhotic patients is associated with high mortality. This leads to the development of...
alternatives. RFA is a potential therapeutic approach for small size tumours in cirrhotic livers [171]. However, RFA is associated with HCC recurrence [172]. Based on these observations, we have recently dissected the mechanism of this recurrence in vitro and in vivo models, showing a panel of inflammatory mediators responsible for enhanced hepatocyte proliferation and HCC recurrence in mouse models exposed to RFA, including STAT3, IL-6, c-MET, COX-2, and heat shock proteins [173–182]. All these are currently undergoing further investigation to identify the preferred therapeutic approach in combination of RFA to suppress HCC recurrence.

Perspective, future research

In the past decades, IL-6 has emerged as an important mediator of tissue inflammation and regeneration. It was therefore not surprising that IL-6 and STAT3 which act as the major transcription factor downstream of the IL-6 receptor complex were initially considered tumour promoters in many cancer types including the liver. Several cell types and mechanisms in the tumour micro-environment of the liver were identified to regulate the expression and secretion of IL-6.

However, more recent research has shed more light on the complexity of IL-6 signalling in cancer including liver. It turned out that IL-6 not only has tumour-promoting effects but acts also in tumour prevention. Therefore, future research has to unveil a more detailed picture on the kinetics and cellular context of IL-6 signalling in order to precisely distinguish between pro- and anti-tumorigenic effects of IL-6 signalling. This might include epigenetic mechanisms, the identification of co-dependencies, and a more detailed understanding of its role in anti-tumour immunity.

Consequently, we will be able to design novel therapeutics that are able to block tumorigenic effects of IL-6 without affecting its physiological role in infection defence and tissue regeneration.

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Declarations

Conflict of interest

S.R.-J. is an inventor of patents owned by the CONARIS Research Institute, which develops the sgp130Fc protein together with Ferring Pharmaceuticals, and he has stock ownership in CONARIS. No conflicts of interest, financial or otherwise, are declared by E.G. and D.S.-A.

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