# Review

# Interleukin 6 and liver regeneration

## IL-6 and its biological function

The multifunctional cytokine interleukin 6 (IL-6) was cloned in 1986. Since then, our understanding of its role in the regulatory functions in the immune system has grown steadily. IL-6 is a typical pleiotropic cytokine that acts on various cells. It is commonly produced at local tissue sites and is released in almost all situations of homeostatic perturbation, which include endotoxaemia, trauma, and acute infection. In addition, circulating IL-6, together with tumour necrosis factor α (TNF-α) and interleukin 1 (IL-1), is required for induction of the acute phase response which comprises fever, corticosteroid release, and hepatic production of acute phase proteins which are mostly protease inhibitors. Overall, induction of the acute phase response by IL-6 has been regarded as part of an attempt to maintain homeostasis. Apart from its role in inflammation, IL-6 induces differentiation and development of B cells, T cells, myeloid cells, megakaryocytes, osteoclasts, neural cells, and hepatocytes. IL-6 acts as a growth factor for renal cell carcinoma and Kaposi's sarcoma, and promotes the growth of haematopoietic stem cells.

Apart from the cytokine itself, the IL-6 family comprises IL-11, ciliary neurotrophic factor (CNTF), cardiotropin (CT-1), oncostatin M (OSM), leukaemia inhibitory factor (LIF), and the novel neurotrophin 1/B cell stimulating factor 3 (NNT-1/BSF-3), which all share the common signal transducer gp130 as part of their receptors. Except for CNTFR, the IL-6-type cytokine signalling receptors are type I membrane proteins (extracellular N terminus, one transmembrane domain). This receptor family is defined by the presence of at least one cytokine binding molecule (CBM), a set of four conserved tyrosine residues, and a tryptophan-serine-X-tryptophan-serine (W-S-X-S-W) motif, located outside the transmembrane domain. Signal transduction after ligand binding is elicited by homodimerisation of gp130 in the case of IL-6 and IL-11, by heterodimerisation of gp130 and LIFR in the case of LIF, CNTF and CT-1, or by heterodimerisation of gp130 and OSMR in the case of OSM.[1] Thus the molecular mechanism of redundancy between the family members can be explained because all members use at least one gp130 molecule for signal transduction.

## The cytokine signalling complex

The IL-6 receptor complex consists of an 80 kD IL-6 binding glycoprotein termed IL-6R or gp80 and the signal transducer gp130. A complex of IL-6 bound to gp80 interacts on target cells with at least one gp130 molecule, thereby triggering homodimerisation of the intracellular domains of two gp130 molecules.[2] It remains to be elucidated whether the membrane bound complex consists of a single IL-6 and gp80 protein interacting with two gp130 molecules or if two of each of the molecules interact as a hexamer.

Besides their role as membrane bound proteins, gp80 and gp130 also occur as shedded receptors (limited proteolysis of the membrane bound form) in serum. In several conditions, such as human immunodeficiency infection, multiple myeloma, and juvenile chronic arthritis, elevated levels of soluble (s) gp80 have been observed. An alterna-

tive mechanism for generation of soluble receptors is secretion of the proteins after translation of an alternatively spliced mRNA. Sgp80 and sgp130 have different functions. Sgp80 bound IL-6 can interact with membrane bound gp130 and thus trigger activation of intracellular signalling pathways. This can lead to an enhanced IL-6 mediated response. Additionally, through this mechanism, primary IL-6 unresponsive cells expressing only gp130 and no gp80 can be activated through the sgp80/IL-6 complex. This process has been called "transsignalling".[3] The shedded signal transducer sgp130 itself can bind the IL-6/sgp80 complex. This trimary complex is no longer able to interact with membrane bound gp130. In this case sgp130 acts as an antagonist. In vitro experiments revealed that especially in cells lacking membrane bound IL-6R, sgp130 was a potent antagonist if these cells were stimulated with IL-6/sgp80 complexes. This antagonism was markedly enhanced by addition of sgp80.[4] Currently it is unclear if under physiological conditions sgp80 acts as an agonist as relatively high concentrations of soluble gp130 (300 μg/ml) have also been found in human blood.[5] The artificial protein, hyper-IL-6 (H-IL-6) was designed by covalently linking IL-6 to soluble gp80.[6] This artificial molecule causes a 10-fold increased STAT3 dependent gene transcription (haptoglobin) in hepatocytes[7] in vitro and in vivo. These results indicate a promising role for this designer cytokine in influencing pathophysiological conditions.

## Intracellular signal cascades activated by the gp130 receptor complex

In 1994 it was found that IL-6-type cytokines use tyrosine kinases of the Janus kinase (JAK) family for signal transduction.[8][9] Dimerisation of the intracellular domains of two gp130 molecules brings the receptor associated JAKs (JAK1, JAK2, and TYK) into close proximity, leading to activation via inter- or intramolecular phosphorylation and activation. The intracellular part of gp130 contains different tyrosine residues that become phosphorylated by activated JAK kinases. Phosphotyrosines can interact with SH2 domains of several proteins. These proteins are phosphorylated by JAK kinases and presumably by other non-receptor associated tyrosine kinases.[10][11]

From the cell membrane the six tyrosines of the human gp130 molecule are in positions 42, 118, 126, 173, 262, and 274 (fig 1). Phosphorylation of the four distal tyrosines (tyrosine 126, 173, 262, and 274) activates STAT (signal transducers and activators of transcription) proteins. Phosphotyrosine 126 and 173 specifically recruit STAT3; 262 and 274 bind STAT 1 and 3.[12] Apart from activation of STATs via tyrosine 118, the Ras-Map kinase cascade can be induced.[13]

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**Abbreviations used in this paper**: IL-6, interleukin 6; TNF-α, tumour necrosis factor α; TNF-RI, TNF receptor 1; CNTF, ciliary neurotrophic factor; CT-1, cardiotropin; OSM, oncostatin M; LIF, leukaemia inhibitory factor; NNT-1/BSF-3, neurotrophin 1/B cell stimulating factor 3; CBM, cytokine binding molecule; STAT, signal transducers and activators of transcription; TGF-β, transforming growth factor β; Con-A, concanavalin A; JAK, Janus kinase; C/EBPb, CCAAT enhancer binding protein β; NFκB, nuclear factor κB; AP-1, activated protein 1; NF-IL-b, nuclear factor-interleukin 6.
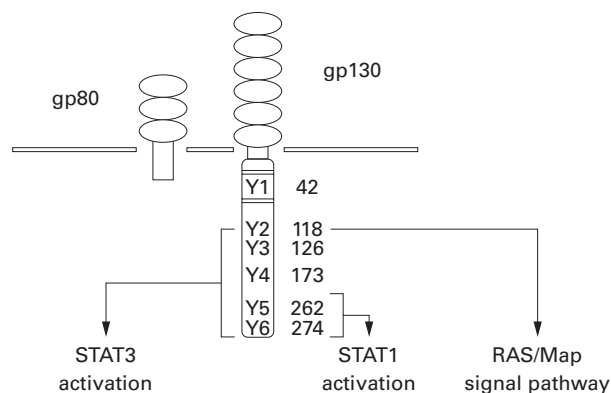
*Figure 1   Intracellular cascades of the gp130 receptor. After interleukin 6 (IL-6) binding to gp80, two gp130 molecules homodimerise and activate JAK kinases which in turn phosphorylate the intracellular tyrosines of the gp130 receptor. Via the different phosphotyrosines, STAT1/3 and Ras dependent pathways are activated in the cell.*

To date, seven mammalian STAT genes have been cloned. STATs are a family of cytoplasmic proteins that are activated to participate in gene control when cells encounter various extracellular polypeptides. STAT activity is predominantly regulated by post-translational modifications such as tyrosine and serine phosphorylation. There are a growing number of reports also demonstrating STAT activation via receptor tyrosine kinases (epidermal growth factor receptor, PDGFR, insulin receptor, c-met, and G-protein coupled receptors such as angiotensin II receptor). STAT activation is terminated by dephosphorylation or proteolytic degradation. Additionally, SH2 domain containing proteins (SOCSs) were found to inhibit IL-6 induced receptor phosphorylation and STAT activation.[14] Internalisation of the IL-6 receptor complex is another mechanism of rapidly removing circulating cytokines.[15]

STATs consist of 750–850 amino acids and distinct domains within the molecule. Biochemical and molecular studies have defined a tetramerisation domain and a leucine zipper-like domain at the N-terminus, a DNA interaction domain in the middle, an Src homology 3 (SH3)-like domain, an SH2 phosphotyrosine binding domain, and a transactivation domain at the C-terminus. They can interact with receptors, other transcription factors, the transcription machinery, and a tyrosine phosphatase.[16] Immediately after tyrosine phosphorylation, STATs build homo- and heterodimers. This interaction ensues at their SH2 domains.[17] The activated STAT dimers translocate to the nucleus where they recognise DNA binding sites in the promoter of their target genes.[18] STAT binding sites are often in close proximity to binding sites for other transcription factors, suggesting a combined action of these factors in gene regulation. For STAT3, cooperativity with CCAAT enhancer binding protein β (C/EBPβ),[19] nuclear factor κB (NFκB),[20] activated protein 1 (AP-1),[19] and growth factor[21] has been reported. STAT3-DNA binding sites were shown in the promoters of acute phase genes in hepatocytes.[1 2 22] Other examples of genes which become activated by IL-6 via STAT3 are transcription factors such as Jun-B, c-fos, interferon regulatory factor 1, and C/EBPδ, and a variety of other genes such as heat shock protein hsp90 and bcl-xl.

## Modulation of cell proliferation and apoptosis by IL-6

Specific functions in different tissues have been linked to the action of gp130 dependent signalling cascades. These experiments showed a role for gp130 in cell proliferation, cell differentiation, and regulation of apoptosis, mainly by

promoting antiapoptotic effects.[13 23–26] As these functions have been linked to specific cell systems, it seems likely that gp130 dependent signalling cascades work in a tissue specific manner.

Activation of STAT3 in B cells and human myeloma cells causes activation of antiapoptotic genes such as bcl-2 and bcl-xl, protecting from Fas dependent apoptosis.[23] Similar results were found in T cells. STAT3 deficient T cells were severely impaired in IL-6 induced proliferation which was due to the profound defect in IL-6 mediated prevention of apoptosis. However, antiapoptotic bcl-2 was normally expressed in STAT3 deficient T cells. These data indicate that IL-6 drives bcl-2 independent pathways in T cells thereby enhancing proliferation of these cells.[27] In hepatocytes, IL-6 protects from transforming growth factor β (TGF-β) induced apoptosis[28] by blocking TGF-β induced activation of caspase 3 via rapid tyrosine phosphorylation of phosphatidylinositol 3 kinase (PI 3 kinase) which consecutively activated the protein kinase Akt. The antiapoptotic activity of IL-6 was partially inhibited by a dominant negative mutant of STAT3 suggesting that additional gp130 dependent pathways are involved in this process.

Via the second intracellular tyrosine of gp130, the Ras-Map kinase pathway is stimulated, thereby regulating cell proliferation. This mitogenic activity was first found in pre-B cells.[13] In cells of neuronal origin (PC 12 cells) it was shown that the Ras-Map kinase pathway promotes cell differentiation while activation of STAT3 blocked differentiation.[26] IL-6 has an antiproliferative effect in melanoma cells. STAT3 activates pathways leading to enhanced expression of p27. Thereby cell cycle progression is blocked.[29] Besides, p27 IL-6 via STAT3 induces p21-WAF/CIP1 in melanoma cells. Recent data indicated that transcriptional relevant STAT3 DNA binding sites are present in the p21 promoter[30] which are activated after IL-6 stimulation. Bromberg and colleagues[31] reported that substitution of two cysteine residues within the SH2 domain of STAT3 produces a molecule that dimerises spontaneously, binds to DNA, and activates transcription. The mutated STAT3 molecule caused cellular transformation in immortalised fibroblasts, suggesting a new possible oncogenic role for STAT3.[31]

## Importance of IL-6 during liver regeneration

The role of IL-6 dependent signalling in the liver was mainly attributed to induction of the acute phase response.[22 32 33] However, interesting results were obtained when activation of IL-6 dependent genes was investigated after two thirds hepatectomy.[34] In rats, it has been shown that TNF-α and then IL-6 serum levels are elevated during the first hours while DNA synthesis in hepatocytes starts 24 hours after hepatectomy. After the increase in IL-6 serum levels, strong activation of the transcription factors STAT3 and C/EBPβ/nuclear factor-interleukin 6 (NF-IL-6) has been described, resulting in enhanced transcription of their target genes.[35–40] These results indicate that these factors might be involved in triggering G0/G1 phase transition of hepatocytes after hepatectomy.

Further evidence for the essential role of IL-6 and thus its intracellular targets for liver regeneration become obvious by using IL-6 −/− and C/EBPβ/NF-IL-6 −/− knockout mice. Both mice revealed an impaired proliferative response during liver regeneration.[41 42] Additionally, in IL-6 −/− mice, liver failure occurred after hepatectomy. In these animals the G1 phase was abnormal which resulted in a reduced rate of DNA synthesis. This observation correlated with a lack of STAT3 activation and decreased expression of AP-1, Myc, and cyclin D1 mRNA levels. Injection of IL-6 before hepatectomy rescued the pheno-
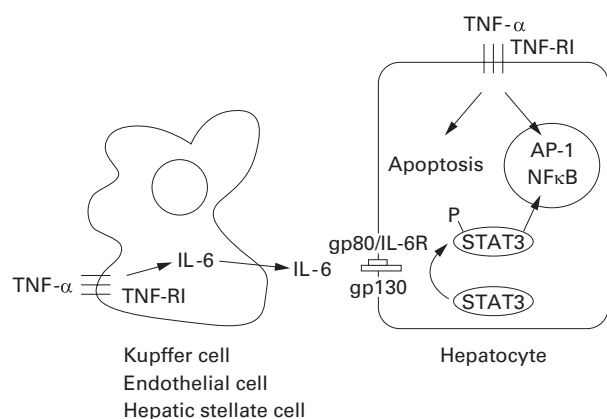
*Figure 2   The role of interleukin 6 (IL-6) in hepatocyte proliferation after partial hepatectomy. After partial hepatectomy, tumour necrosis factor α (TNF-α) activates IL-6 expression, most likely in Kupffer cells. TNF-α and IL-6 via the gp80/gp130 receptor complex in turn activate intracellular pathways in liver cells which are essential for triggering hepatocyte proliferation after hepatectomy.*

type by normalising hepatocyte proliferation and preventing liver damage. These results indicate that IL-6 is of fundamental importance for liver regeneration and that activation of STAT3 during this process is exclusively mediated by the gp130 receptor.[41]

The essential role of IL-6 for liver regeneration was further confirmed in TNF receptor 1 (TNF-R1) knockout mice.[43] In these mice, NFκB activation was impaired after partial hepatectomy and there was no increase in IL-6 serum levels. As a result, TNF-R1 knockout mice showed a defect in liver regeneration comparable with IL-6 −/− mice. As shown for IL-6 −/− animals and also for TNF-R1 −/− mice, IL-6 injection restored the capacity of hepatocytes to proliferate after partial hepatectomy.[41] Based on the results found in the IL-6 −/− and TNF-R1 −/− animals, a model was constructed to define the role of TNF-α and IL-6 during liver regeneration (fig 2). After hepatectomy, TNF-α initially becomes elevated and activates expression of IL-6, most likely via NFκB. The pathways which are then activated through gp130 in liver cells appear to be essential for priming hepatocytes in contrast with cell cycle progression.

More evidence for the role of IL-6 in hepatocyte proliferation came from experiments using double transgenic animals expressing IL-6 and gp80 under the control of liver specific promoters. In these mice hepatocyte proliferation was evident in the periportal areas. These mice developed hyperplastic nodules that closely mimicked human nodular regenerative hyperplasia of the liver, a disorder characterised by diffuse micronodular transformation of the hepatic parenchyma and formation of liver adenomas.[44 45]

In contrast to physiological doses of IL-6 for hepatocyte proliferation, a different effect is apparent after hyperstimulation of IL-6 in mice following partial hepatectomy. Interestingly, these mice showed a delay in cell cycle progression by over expressing the two protein kinase inhibitors p21 and p27.[46] Therefore, the experiments performed in the hepatectomy model revealed a dose dependent effect of IL-6 on hepatocyte proliferation. Hyperstimulation during liver regeneration seems to delay cell cycle progression.[47]

The functional relevance of IL-6 dependent signalling for regulation of different physiological and pathophysiological conditions in the liver was confirmed in other animal models. IL-6 protects from liver ischaemia and promotes hepatocyte proliferation after reperfusion.[48] Stimulation with IL-6 diminished concanavalin A (Con-A) dependent liver failure.[49] In this model of T cell dependent liver failure, IL-6, interferon γ, and TNF-α were elevated whereby IL-6 peaked six hours after injection. The first markers of the S phase were detected at 24 hours, correlating with STAT3 activation leading to restitution of the organ during regeneration of the Con-A treated liver.[50] Other models, such as tetrachloride induced liver injury, sepsis after caecal ligation,[51] and after ligation of the bile duct[52 53] display a protective role for the cytokine IL-6 dependent intracellular pathways.

## Physiological role of the gp130 signal transducer for the liver

Animals lacking the common signal transducer gp130 are not viable. Embryos with target disruption of gp130 die between 12.5 days post-coitum and birth. Gp130 −/− embryos showed hypoplastic ventricular myocardium because cardiomyocytes showed reduced proliferation. Additionally, gp130 −/− embryos had impaired development of pluripotent stem cells in the fetal liver.[54]

There is evidence that the gp130 molecule has a direct role during liver development.[55] Gp 130 −/− mice in another genetic background (ICR mice) survived longer compared with the strain used by Yoshida *et al* and only died soon after birth.[56] In contrast with newborn mice, accumulation of intracellular glycogen was greatly reduced in the liver of gp130 −/− mice. The phenotype is similar to that reported for C/EBPα −/− mice, suggesting a requirement for both gp130 and C/EBPα signalling pathways for fetal liver development.[55] Kamiya *et al* showed that OSM, a cytokine of the IL-6 family, in combination with glucocorticoid, induced maturation of fetal hepatocytes, as evidenced by morphological changes that closely resembled more differentiated hepatocytes and accumulated intracellular glycogen.

To further investigate the role of gp130 in adult mice, conditional gene targeting of the signal transducer (using the Cre-lox system[57]) was performed. These mice exhibited Schwann cell decompensation, degeneration of peripheral nerves, myocardial abnormalities, and defects in haematopoesis, while B cell development was not affected. The livers of these animals showed morphological abnormalities associated with a decreased ability to synthesise acute phase response proteins.

New approaches to study the role of gp130 in specific tissues were performed by expressing the Cre recombinase under the control of a tissue specific promoter. Using this approach, gp130 was specifically deleted in cardiomyocytes. These mice did not exhibit compensatory cardiac hypertrophy during aortic pressure overload. Instead they displayed rapid onset of dilated cardiomyopathy and massive induction of myocyte apoptosis. Thus these experiments demonstrated that gp130 activated signal cascades mediated cardiac hypertrophy and drove antiapoptotic pathways.[58] A similar approach to better define the role of gp130 for hepatocytes in vivo is not yet established.

## Future prospects

Since the cloning of IL-6 more than 10 years ago, much progress has been made in understanding IL-6 dependent intracellular pathways. In the liver, apart from controlling the acute phase response, IL-6 appears to contribute to hepatocyte proliferation and activation of protective pathways. In the future, the use of target disrupted animals will help to further define the relevance of gp130 dependent pathways in vivo during different pathophysiological conditions. This knowledge will help to identify the exact

molecular targets of IL-6 dependent mechanisms under these conditions and will result in the development of new therapeutic approaches for humans also.

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