

REVIEW

Role of gp130-mediated signalling pathways in the heart and its impact on potential therapeutic aspects

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IL-6-type cytokines bind to plasma membrane receptor complexes containing the common signal transducing receptor chain gp130 that is ubiquitously expressed in most tissues including the heart. The two major signalling cascades activated by the gp130 receptor, SHP2/ERK and STAT pathways, have been demonstrated to play important roles in cardiac development, hypertrophy, protection and remodelling in response to physiological and pathophysiological stimuli. Experimental data, both *in vivo* and *in vitro*, imply beneficial effects of gp130 signalling on cardiomyocytes in terms of growth and survival. In contrast, it has been reported that elevated serum levels of IL-6 cytokines and gp130 proteins are strong prognostic markers for morbidity and mortality in patients with heart failure or after myocardial infarction. Moreover, it has been shown that the local gp130 receptor system is altered in failing human hearts. In the present review, we summarize the basic principles of gp130 signalling, which requires simultaneous activation of STAT and ERK pathways under the tight control of positive and negative intracellular signalling modulators to provide a balanced biological outcome. Furthermore, we highlight the key role of the gp130 receptor and its major downstream effectors in the heart in terms of development and regeneration and in response to various physiological and pathophysiological stress situations. Finally, we comment on tissue-specific diversity and challenges in targeted pharmacological interference with components of the gp130 receptor system.

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Abbreviations: AngII, angiotensin II; CCL5, chemokine, CC motif, ligand-5; CT-1, cardiotrophin-1; ERK, extracellular signal-regulated kinase; ES cell, embryonic stem cell; gp130, glycoprotein-130; IFN- γ , interferon- γ ; IL-6, interleukin-6; IL-11, interleukin-11; JAK, Janus kinase; LIF, leukaemia inhibitory factor; MAPK, mitogen-activated protein kinase; MHC, myosin heavy chain; NF- κ B, nuclear factor- κ B; OSM, oncostatin M; PI3K, phosphatidylinositol-3-kinase; SHP2, SH2 domain-containing cytoplasmic protein tyrosine phosphatase; sIL-6R, soluble IL-6 receptor; SOCS, suppressor of cytokine signalling; STAT, signal transducer and activator of transcription; TNF- α , tumour-necrosis factor- α .

Introduction

The glycoprotein-130 (gp130), the central signal transducer of the interleukin-6 (IL-6)-related cytokines, is widely expressed in the mammalian organism, including the developing and adult heart. Activation of gp130 in the heart by IL-6 type cytokines occurs during embryogenesis, in response to inflammation, pressure overload and ischaemic injury thereby inducing signalling via three major pathways: (1) the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, (2) the Ras/mitogen-activated

protein kinase (MAPK and extracellular signal-regulated kinase(ERK)) signalling pathway and (3) the phosphatidylinositol-3-kinase-dependent (PI3K)/Akt pathway (Figure 1) (Hirano *et al.*, 1997; Hirota *et al.*, 1999; Funamoto *et al.*, 2000; Heinrich *et al.*, 2003; Fischer and Hilfiker-Kleiner, 2007).

In recent years, it has been reported that the serum concentration of IL-6 increases after myocardial infarction (Rattazzi *et al.*, 2003), and that levels of circulating IL-6 and soluble IL-6 receptor (sIL-6R) are elevated in patients with congestive heart failure (Tsutamoto *et al.*, 1998; Buzas *et al.*, 2004), as well as in hypertrophic and dilative cardiomyopathy (Buzas *et al.*, 2004). Furthermore, systemic IL-6 levels correlate with the severity of left ventricular dysfunction and are strong independent predictors of subsequent clinical outcomes in patients with heart failure and after myocardial

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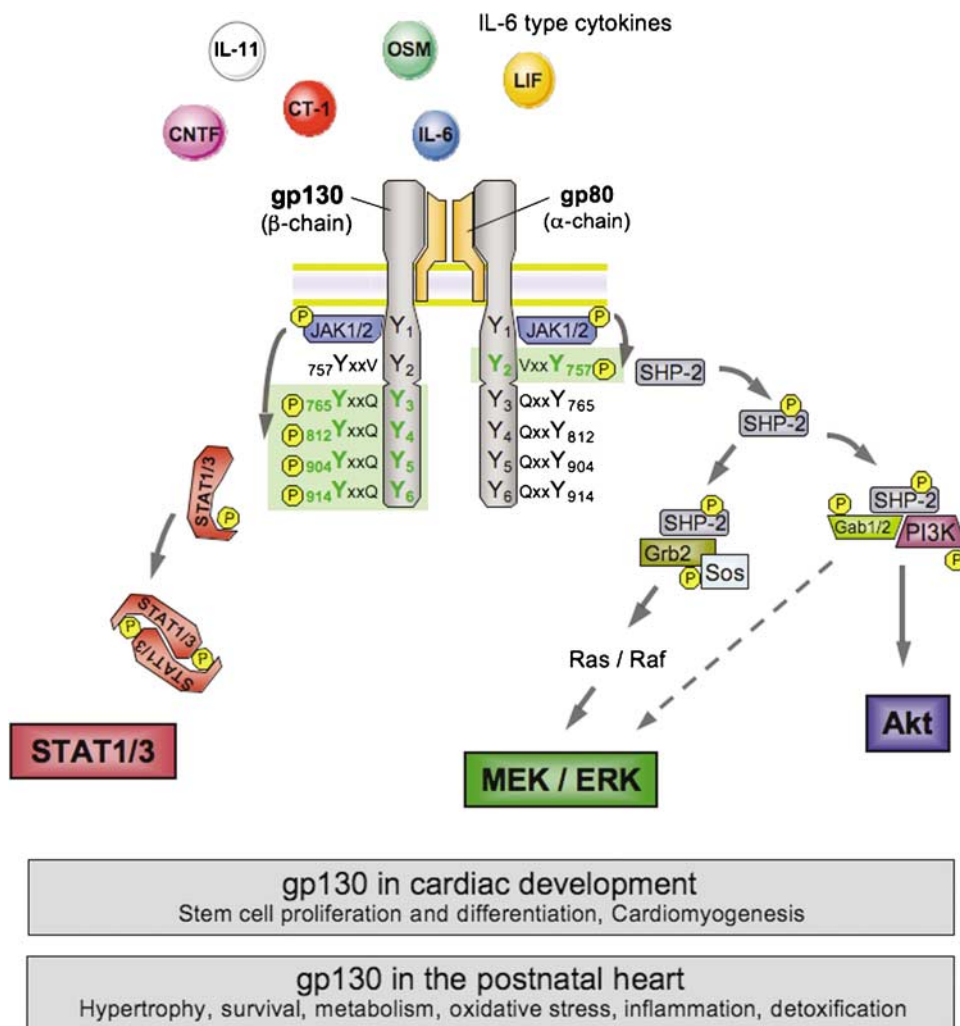


Figure 1 Role of glycoprotein 130 (gp130) downstream signalling in the heart. Scheme of gp130 receptor activation showing interleukin-6 (IL-6) type cytokines binding to their transmembrane receptor α -subunits, which induces homodimerization of the gp130 receptor β -subunits or heterodimerization of gp130 with either one of the structurally and functionally similar leukaemia inhibitory factor (LIF) receptor and oncostatin M (OSM) receptor β -subunits. Following dimerization of the gp130 receptor complex, Janus kinase-1/2 (JAK1/2) constitutively connected to the intracytoplasmic membrane proximal regions of the receptor subunits are catalytically activated and themselves transphosphorylate tyrosine residues in the gp130 receptor intracellular domain. Subsequently, two major intracellular signalling cascades are triggered, the signal transducer and activator of transcription (STAT)-1/3 pathway and the SH2 domain-containing cytoplasmic protein tyrosine phosphatase (SHP2)/MEK/extracellular signal-regulated kinase (ERK) pathway. Via the formation of complexes with growth factor receptor binding protein-2 (Grb2)-associated binding protein-1/2 (Gab1/2) and phosphatidylinositol-3-kinase (PI3K), SHP2 activation furthermore initiates the Akt pathway and additionally enhances MEK/ERK signalling. Activation of gp130-mediated signalling plays essential roles in stem cells and cardiomyogenesis. In the adult heart, it is involved in numerous physiological and pathophysiological processes. MEK, mitogen-activated protein kinase (MAPK)/ERK kinase.

infarction (Roig *et al.*, 1998; Tsutamoto *et al.*, 1998; Maeda *et al.*, 2000; Orus *et al.*, 2000; Birks *et al.*, 2001; Rattazzi *et al.*, 2003). Similarly, plasma levels of the IL-6 type cytokine, leukaemia inhibitory factor (LIF) and soluble gp130 receptor significantly increase in association with the severity of heart failure (Hirota *et al.*, 2004). More recently, our laboratory has explored the IL-6/gp130/JAK/STAT signalling cascade in patients with end-stage heart failure and showed that this signalling cascade is altered at the levels of ligands, receptors and downstream signalling molecules (Podewski *et al.*, 2003). For example, cardiac expression of IL-6 is reduced whereas the expression of LIF is elevated (Eiken *et al.*, 2001; Podewski *et al.*, 2003). The expression of cardiotrophin-1 (CT-1), another member of the IL-6 cytokine family, is not altered

(Podewski *et al.*, 2003). At the receptor level, gp130 expression is not different, but failing hearts display enhanced gp130 activation (tyrosine phosphorylation). The expression of JAK2 and tyrosine kinase-2, the next downstream signalling molecules of the gp130 receptor, are also not altered, but surprisingly their activation state (tyrosine phosphorylation) is diminished in failing hearts. Most strikingly, both expression and activation of the effector signalling molecule of the IL-6/gp130/JAK/STAT cascade, STAT3, is severely reduced in failing hearts (Podewski *et al.*, 2003).

Until recently, only limited information is available on the expression in failing human hearts of the suppressor of cytokine signalling (SOCS) proteins that serve as negative

regulators of gp130/JAK/STAT signalling. SOCS3 is transcriptionally upregulated by STAT transcription factors and, in line with lower STAT3 activity, its expression appeared to be attenuated in terminally failing human hearts (Podewski *et al.*, 2003).

In general, observations taken from patient studies are mainly descriptive and do not identify the causative functional roles of individual factors or signalling pathways. In this regard, the biological consequence of IL-6 type cytokine expression and its respective downstream signalling mechanisms in human cardiac pathophysiology has not yet been resolved. It has been suggested that systemically increased IL-6 type cytokine signalling may contribute to the progression of heart failure and its thrombotic complications (Chin *et al.*, 2003) pointing to a deleterious role of IL-6 type cytokine signalling in patients. In contrast, a growing body of experimental work suggests that IL-6-related cytokine signalling contributes to compensatory hypertrophy, provides cardioprotection and promotes neovascularization (Hirota *et al.*, 1999; Negoro *et al.*, 2000; Yamauchi-Takahara and Kishimoto, 2000, 2002; Jacoby *et al.*, 2003; Hilfiker-Kleiner *et al.*, 2004). In particular, the analysis of transgenic mice harbouring knockouts for specific components of the gp130 receptor system shed light on the specific roles of the gp130 receptor system for various cardiovascular cell types and the myocardium itself.

In the current review, we highlight the key role of the gp130 receptor and its major downstream signalling mediators in the heart in terms of cardiac development and postnatal physiology. Moreover, we summarize the basic principle of gp130 signalling and try to place experimental findings and clinical observations in relation to each other to explain potential discrepancies of expected beneficial versus observed detrimental roles of gp130 signalling within the pathophysiological situations of the cardiovascular system.

The gp130 receptor signalling system

The IL-6 type cytokines, comprising IL-6, IL-11, LIF, oncostatin M (OSM), ciliary neurotrophic factor, CT-1 and cardiotrophin-like cytokine are a family of mediators with pleiotropic effects in the organism. They are involved in inflammatory and immunologic processes (May *et al.*, 2003) as well as in haematopoiesis, liver and neuronal regeneration, embryonic development and cardiovascular physiology as reviewed by Heinrich *et al.* (1998), Ernst and Jenkins (2004) and Fischer and Hilfiker-Kleiner (2007). Hence, they activate target genes involved in growth, differentiation, survival, apoptosis and proliferation. With the shared use of the gp130 receptor, the biological functions of IL-6 family cytokines are largely overlapping as reviewed by Ernst and Jenkins (2004).

Interleukin-6 type cytokines bind to plasma membrane receptor complexes containing the common signal-transducing receptor chain gp130. IL-6, IL-11 and ciliary neurotrophic factor first bind specifically to their respective α -receptor subunits, and only the complex of cytokine and α -receptor efficiently recruits the signalling receptor subunits (Pennica *et al.*, 1995), which was reviewed by Heinrich *et al.*

(1998), Ernst and Jenkins (2004) and Fischer and Hilfiker-Kleiner (2007). The binding of a ligand to its receptor induces homodimerization of gp130 (upon binding of IL-6 and IL-11) or heterodimerization of gp130 with LIF receptor (following binding of LIF, ciliary neurotrophic factor, cardiotrophin-like cytokine and CT-1) or OSM receptor (for OSM), respectively (Pennica *et al.*, 1995), which was reviewed by Fischer and Hilfiker-Kleiner (2007). Receptor binding of all IL-6 cytokines induces dimerization of gp130 receptor β -subunits, which triggers activation of non-overlapping intracellular signalling cascades by phosphorylation of multiple, highly conserved tyrosine residues (Y) within the cytoplasmic domain of the gp130 receptor via constitutively associated JAK family members (Figure 1). Subsequent signal transduction via gp130 involves three major downstream pathways: (1) the JAK/STAT1/3 pathway, (2) the Ras/ERK1/2 signalling pathway and (3) the PI3K/Akt pathway (Figure 1) (Kunisada *et al.*, 1996; Hirano *et al.*, 1997; Oh *et al.*, 1998; Hirota *et al.*, 1999; Heinrich *et al.*, 2003). Phosphorylation of a single-membrane proximal Y residue (Y757) within the cytoplasmic domain of the gp130 receptor is necessary and sufficient for recruitment of the SH2 domain-containing cytoplasmic protein tyrosine phosphatase (SHP2), its subsequent tyrosine phosphorylation and activation of the Ras/ERK1/2 cascade (Figure 1). In this regard, tyrosine phosphorylation of SHP2 provides docking elements for the adaptor protein growth factor receptor binding protein-2, which is constitutively associated with the Ras/GTP exchange factor, Sos as reviewed by Ernst and Jenkins (2004). In addition, tyrosine-phosphorylated SHP2 can form a complex with the scaffolding proteins growth factor receptor binding protein-2-associated binding protein-1/2 and the p85 subunit of PI3K, which leads to activation of the Akt pathway and might also feed into the Ras/ERK1/2 cascade (Figure 1) as reviewed by Ernst and Jenkins (2004). By contrast, docking of STAT proteins (mainly STAT1 and 3) to the C-terminal phosphotyrosine residues within the gp130 receptor results in tyrosine phosphorylation of the STAT1/3 proteins by the activated JAKs with subsequent homo- and heterodimerization and nuclear translocation where STAT transcription factor complexes eventually induce transcription of specific sets of target genes (Figure 1) (Funamoto *et al.*, 2000; Negoro *et al.*, 2001a; Osugi *et al.*, 2002), which was reviewed by Fischer and Hilfiker-Kleiner (2007).

In summary, the expression pattern of IL-6 cytokines may vary among different developmental stages, cell types and stress situations; however, their biological functions in terms of gp130 receptor-mediated signalling seem to be largely overlapping.

Modulation of the cellular response to gp130-mediated signalling: fine-tuning JAK/STAT and SHP2/ERK signalling is the key issue

There is evidence that balanced versus unbalanced activation of gp130 downstream signalling may play a key role between beneficial organ protection and regeneration, and detrimental tumorigenesis and organ failure. For example, prolonged gp130-mediated STAT3 activation promotes liver progenitor cell proliferation, whereas gp130-mediated ERK1/2 activation suppresses this process, suggesting that gp130 signalling

acts as an important switch between liver regeneration and tumorigenesis (Yeoh *et al.*, 2007). In the heart, it has been reported that early blockade of gp130-mediated STAT3 signalling negatively affects susceptibility to viral infection (Yajima *et al.*, 2006). Moreover, sufficient activation of gp130/STAT3 signalling plays an important role for increasing cardiomyocyte cell survival until specific immune responses begin to clear the virus (Yajima *et al.*, 2006). Along these lines, it has been shown that gp130-mediated STAT3 activation is transducing important hypertrophic and cytoprotective effects in the heart (Hirota *et al.*, 1999; Jacoby *et al.*, 2003). In contrast, overexpression of the negative regulator of gp130/STAT activation, SOCS3, in the pressure-overloaded heart has been shown to promote the transition between cardiac hypertrophy and failure, further supporting the important role of an intact gp130/STAT cascade for cardioprotection (Yasukawa *et al.*, 2001). Additional data from transgenic mouse lines imply that gp130-mediated JAK/STAT signalling is required throughout life, because systemic ablation of gp130-mediated JAK/STAT activation (gp130^{ΔSTAT}) leads to reduced life spans, impaired humoral and mucosal immune and hepatic acute phase responses, failure of blastocyst implantation, impaired gastrointestinal wound healing, degenerative joint disease, increased numbers of haematopoietic progenitor cells, thrombocytopenia, leukocytosis and Th2-biased immune response (Ernst and Jenkins, 2004).

As found in mice with defective gp130-mediated JAK/STAT activation, mice with systemic deficiency for gp130-mediated SHP2/ERK (gp130^{Y757}) activation develop various systemic defects, which are, however, of a different nature. These mutant mice develop splenomegaly, lymphadenopathy, enhanced hepatic acute phase and thymus-dependent immune responses, Th1-biased immune response and auto-

immune arthritis (Jenkins *et al.*, 2005). Interestingly, it is thought that the majority of organ defects in gp130^{Y757} mice are not direct consequences of deficient gp130-mediated ERK activation, but rather result from sustained gp130-mediated STAT1/3 activation (Ernst and Jenkins, 2004). This feature is explained by the fact that the Y757 residue serves not only for SHP2 activation, but also for the recruitment of SOCS3 protein to the gp130 receptor (Figure 2) (Ernst and Jenkins, 2004; Johnston, 2004). Specifically, SOCS3 competes with SHP2 for the phosphorylated Y757 docking site, thereby reducing the availability of the phosphorylated tyrosine of the SHP2 docking site and, as a consequence, attenuating gp130-mediated ERK signalling. In addition, as mentioned previously, SOCS proteins serve as negative regulators of JAK/STAT signalling. They harbour an SH2 domain and a COOH-terminal SOCS box and inhibit JAK signalling upon binding to phosphorylated tyrosine residues of the cytokine receptors such as gp130 and/or directly to JAK. Moreover, SOCS proteins are implicated in destabilizing their interacting partners as they can function as the substrate-recruiting component of ubiquitin ligases, thereby not only affecting the activation state of STATs, but also their protein levels (Johnston, 2004).

The lack of STAT3 protein degradation in the absence of SOCS3 binding together with the notion that the JAK/STAT1/3 axis upregulates STAT3 expression explains at least in part the hyperactive state of JAK/STAT signalling in gp130^{Y757} mice. Moreover, even when gp130 receptor activation ceases, increased levels of unphosphorylated STAT3 protein can drive a second, delayed wave of gene expression in the absence of tyrosine phosphorylation, including chemokine, CC motif, ligand-5; IL-6; intercellular adhesion molecule-1 and IL-8 that do not respond directly to phosphorylated STAT3 (Figure 2) (Yang *et al.*, 2005). Here, a

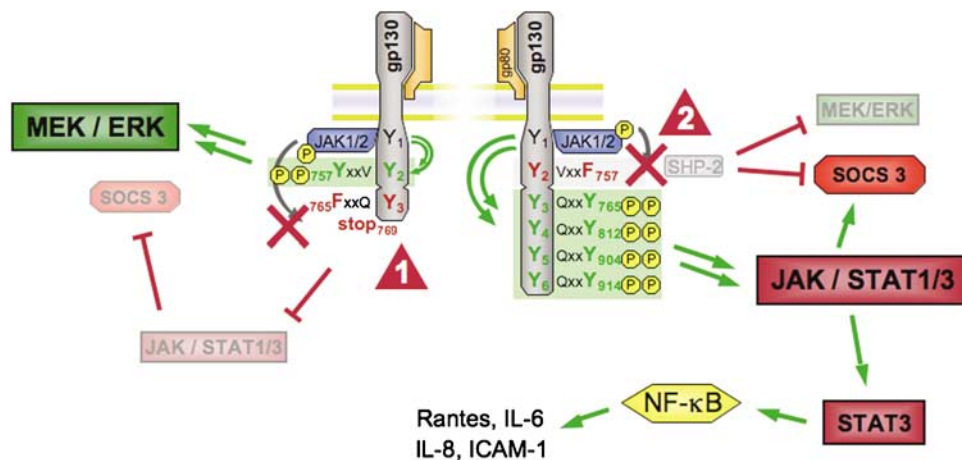


Figure 2 Mutations in the glycoprotein 130 (gp130) receptor lead to an imbalance in downstream signalling pathways. Detailed schematic view of the gp130 receptor structure shows tyrosine 757 (Y757) necessary for SH2 domain-containing cytoplasmic protein tyrosine phosphatase (SHP2) phosphorylation and suppressor of cytokine signalling (SOCS)-3 binding. A point mutation (Y757→F757, tyrosine→phenylalanine) abolishes binding of SHP2 and SOCS3 (arrowhead 1) and leads to uncontrolled Janus kinase (JAK)/signal transducer and activator of transcription (STAT) activation with exaggerated STAT3 activation. As a consequence, proinflammatory pathways, that is nuclear factor-κB (NF-κB) activation, are promoted. The left side displays a truncated gp130 intracellular domain incapable of binding and activating the STAT1/3 pathway (arrowhead 2) from its membrane-distal phosphotyrosine residues. This mutant form is characterized by the substitution of Y765 by F765 and is truncated at the C-terminal side of amino acid 768. Deficient STAT1/3 signalling in this model is accompanied by enhanced signalling via the SHP2/MEK/extracellular signal-regulated kinase (ERK) pathway. ICAM, intercellular adhesion molecule-1. MEK, mitogen-activated protein kinase (MAPK)/ERK kinase.

transcription factor complex with unphosphorylated nuclear factor- κ B (NF- κ B) activates many genes responsive to unphosphorylated STAT3. These κ B-dependent genes are activated upon accumulation of the complex of unphosphorylated STAT3 and NF- κ B in the nucleus binding to the κ B elements of promoters and may partially account for the proinflammatory phenotype resulting from prolonged and excessive STAT3 activation as observed in gp130^{Y757} mice. Moreover, interactions among phosphorylated and unphosphorylated forms of STAT3 and NF- κ B as well as binding of unphosphorylated STAT3 to various other transcription factors such as c-Jun and the glucocorticoid response element have been reported. It may, therefore, be that the upregulation of unphosphorylated STAT3 is important for the entire physiological functions of the group of cytokines that use the common gp130 receptor subunit to phosphorylate STAT3 (Yang *et al.*, 2007a).

Taken together, the simultaneous activation of STAT and ERK pathways by gp130 receptor stimulation appears essential for a balanced biological outcome in many physiological and pathophysiological settings, especially as STAT and ERK signalling induce partly contradictory or at least conflicting responses (Ernst and Jenkins, 2004; Jenkins *et al.*, 2005; Yeoh *et al.*, 2007). Disturbance of this 'signalling orchestration' may lead to an exaggerated activation of a single pathway causing an unrestrained biological response with ultimately pathophysiological outcomes.

The gp130 receptor system plays a crucial role in early heart development and might therefore be important for cardiac regeneration

The heart is among the first organs to be formed and to function during development. Embryos with a homozygous null mutation for gp130 die between 12.5 days postcoitum and term (Yoshida *et al.*, 1996). On 16.5 days postcoitum and later, they show hypoplastic ventricular myocardium without septal and trabecular defect. The subcellular ultrastructures in cardiomyocytes deficient in gp130 appear normal, but the cardiac phenotype indicates a role in the expansion of the compact layer of the ventricular myocardium. The gp130 ligands LIF and CT-1 are expressed at high levels during the course of cardiogenesis and promote proliferation and survival of embryonic cardiomyocytes implicating that the gp130 receptor system plays an essential role for the cardiac development, potentially by regulating cardiomyogenesis, cardiomyocyte survival and growth (Sheng *et al.*, 1996).

In recent years, the nature of the postnatal heart as a terminally differentiated organ which—due to the negligible rates of cardiomyocyte proliferation and the quantitatively insignificant replenishment by endogenous progenitor cells—is incapable of endogenous repair and myocardial regeneration, generated the objective of replacing damaged myocardial tissue by *ex vivo* expanded and differentiated stem or progenitor cells. Current research focuses on suitable cell types and modes of transplantation, the determination of the cardiac stem cell niche microenvironment and, importantly, the inducers and pathways of stem cell

proliferation and directed differentiation into the main myocardial cell types including cardiomyocytes. In this regard, it is worth mentioning that upregulation of IL-6 and activation of STAT3 have been implicated in the G0/G1 cell cycle phase transition and induction of proliferation of hepatocytes after hepatectomy. Mice deficient in either IL-6 or the transcription factor NF-IL-6 display a disturbed proliferative response during liver regeneration partly resulting in liver failure associated with lack of STAT3 activation and decreased expression of adaptor-related protein complex-1, Myc and cyclin D1 mRNA (Streetz *et al.*, 2000; Wallenius *et al.*, 2000). However, it is currently unclear whether knowledge of regenerative aspects of gp130-mediated signalling in the liver can, at least in part, help to decipher modulation of cell cycle progression and cellular division in other organs in the adult, such as the heart.

Differential gp130 signalling as a switch in directing stem cell fate
It is known that murine embryonic stem (ES) cells can be maintained in an undifferentiated state on a feeder layer of mouse embryonic fibroblasts or in the presence of LIF. Murine ES cells require LIF-mediated gp130 activation or alternatively induced gp130 dimerization (Stuhlmann-Laeisz *et al.*, 2006) for self renewal and, most importantly, STAT3 downstream signalling has been identified as the key pathway in the gp130 system that prevents differentiation of ES cells and keeps them in an undifferentiated state (Matsuda *et al.*, 1999). Likewise, gp130 and activation of its downstream mediator STAT3 have been proven to be mainly responsible for the expansion of haematopoietic precursor cells in the fetal mouse aorto-gonado-mesonephros region (Takizawa *et al.*, 2003). However, it is very likely that other (gp130-independent) paracrine signalling pathways play additional roles in the maintenance of 'stemness' and the determination of stem cell fate (Dani *et al.*, 1998). In line with their murine counterparts, human ES cells have a functioning gp130 receptor system that displays robust activation of its major signalling pathways JAK/STAT, MEK (MAPK/ERK kinase)/ERK and PI3K/AKT in response to IL-6 type cytokine stimulation. However, activation of gp130-dependent signalling and the JAK/STAT3 pathway in human ES cells leads to the loss of markers of pluripotency, indicating that the maintenance of an undifferentiated state in human ES cells is independent of STAT3 signalling (Daheron *et al.*, 2004; Sumi *et al.*, 2004) and potentially depends on pathways not related to the gp130 receptor system (Dani *et al.*, 1998). Although inhibition of the gp130 receptor-triggered MAPK pathway stabilizes the STAT3-mediated conservation of stemness in murine ES cells, activation of the ERK1/2 pathway in turn leads to the loss of pluripotency and the onset of differentiation. For example, concurrent addition of bone morphogenetic protein-2 and LIF induces the expression of cardiomyocyte markers such as connexin-43, Mef2c, Tbx5, Nkx2.5, GATA-4 and myosin heavy chain (MHC) in murine ES cells as early as 2–4 days in culture, with STAT3 and ERK1/2 playing prominent roles in this determination of cell fate (Rajasingh *et al.*, 2007). From these experimental data, it is possible that the balance and cross talk between STAT3 and MAPK

signalling account for the induction of cardiomyocyte differentiation in ES cells (Burdon *et al.*, 2002; Humphrey *et al.*, 2004).

A potentially important role of gp130 signalling may also exist in adult stem cells sources. In this regard, it has recently been shown that spermatogonial stem cells are able to differentiate into cardiomyocytes and are therefore viewed as potential candidates to regenerate the injured heart (Guan *et al.*, 2006, 2007). Spermatogonial stem cells continuously divide in the testis to support spermatogenesis throughout the life of adult male animals. As very few spermatogonial stem cells are present *in vivo*, it is necessary to expand these cells *in vitro* for potential therapeutic use. A recent report found that the addition of LIF to newborn testis cell cultures enhanced the formation of germ cell colonies. Interestingly, ciliary neurotrophic factor, but not OSM, had the same effect (Kanatsu-Shinohara *et al.*, 2007). No phenotypic or functional difference was found between spermatogonial stem cells that had been maintained in the absence of LIF, indicating that LIF *per se* does not alter the stemness of spermatogonial stem cells (Kanatsu-Shinohara *et al.*, 2007). These data suggest that LIF/gp130 signalling could be useful in the initiation and expansion of spermatogonial stem cell cultures for later therapeutic use.

Interestingly, recent data also hint at a role of differential gp130 receptor downstream signalling in adult tissue-committed cell plasticity. Specifically, it was found that OSM induces epithelial-to-mesenchymal transition of proximal tubular cells into myofibroblasts during tubulo-interstitial kidney fibrosis in a gp130-dependent manner, involving phosphorylation of STAT1 and STAT3 as well as activation of ERK1, ERK2 and ERK5 (Schramek *et al.*, 2003; Nightingale *et al.*, 2004; Pollack *et al.*, 2007). The promotion of myofibroblast differentiation from resident, tissue-specific cells might also be induced by other cytokines that activate STAT3 or the MAPK pathway and are produced during inflammatory reactions. Moreover, this transdifferentiation mechanism of tissue-committed cells could play an important role in remodelling processes in response to pathological influences such as ischaemia in various organs and tissues, including the heart.

Thus, knowledge of the influence of the gp130 receptor system on embryonic development, cell proliferation or differentiation decisions generated in embryonic or adult stem cells may help to elucidate the mechanisms to expand stem cells and to drive cell fate determination. In addition, it will be of major interest to characterize the role of gp130-dependent signalling in the microenvironment of organ-specific stem cell niches, especially the composition of gp130-dependent paracrine factors that regulate adult stem cell biology and tissue/organ homeostasis to optimize regeneration processes.

Deciphering gp130-mediated effects in cardiomyocytes: hypertrophy, survival, metabolic regulation

The activation of gp130 signalling by distinct members of the IL-6 type family of cytokines, namely CT-1, LIF and

potentially IL-11, promotes cardiomyocyte survival (Fischer and Hilfiker-Kleiner, 2007; Kimura *et al.*, 2007) and induces cardiomyocyte hypertrophy *in vitro* with a predominant increase in myocardial cell length by addition of new sarcomeric units in series (Wollert *et al.*, 1996; Wollert and Chien, 1997; Wang *et al.*, 2001; Ancey *et al.*, 2003). Current data suggest that there is some ligand specificity in terms of gp130-mediated downstream signalling in cultured cardiomyocytes. LIF-induced gp130-mediated cardiomyocyte hypertrophy has been mainly ascribed to the activation of Ras/ERK1/2 signalling (Kodama *et al.*, 2000). In contrast, growth factor receptor binding protein-2-associated binding protein 1/SHP2 interaction appears to play a crucial role in gp130-dependent hypertrophic stimulation of cardiomyocytes through the activation of ERK5 (Nakaoka *et al.*, 2003). In line with this observation, CT-1-induced cardiomyocyte hypertrophy strongly depends on MEK5/ERK5 signal transduction, and appears only partly based on JAK/STAT and Ras/ERK1/2 pathways (Takahashi *et al.*, 2005), and is completely independent of PI3K/AKT signalling (Tian *et al.*, 2004).

Apart from its role in cardiomyocyte hypertrophy and survival, gp130 signalling upon LIF stimulation seems to alter cardiomyocyte metabolism. Indeed, it was reported that LIF induces contractile dysfunction and an increase in anaerobic energy metabolism in isolated cardiomyocytes, in part mediated by reduced expression of components in the ATP synthase complex and insulin-like growth factor-binding proteins 1 and 6 (Florholmen *et al.*, 2004a,b), thereby suggesting an involvement of gp130 signalling in maladaptive responses of the cardiac muscle. In contrast, oxidative stress is likely to impair protective IL-6 type cytokine signalling. In detail, it was shown that the generation of reactive oxidant species in cardiomyocytes blocks STAT3 signalling of the IL-6 type cytokines by targeting JAK1 (Kurdi and Booz, 2007). Specifically, activation of JAK1 is reduced and JAK1 association with both gp130 and LIF receptor is impaired in the presence of oxidative stress, leading to decreased phosphorylation of LIF receptor and gp130. These findings indicate that IL-6 type cytokine signalling may be redox-sensitive, thereby hinting at a new pathophysiologically relevant regulative mechanism in gp130 downstream pathways in cardiomyocytes.

Cardiac gp130 signalling under physiological conditions

Cardiomyocyte gp130 receptor signalling is not essential for normal postnatal cardiac growth, but plays an essential role in the ageing myocardium

To study the role of gp130 in adult organs and to circumvent embryonic and fetal lethality, mice with conditional knockouts or cell-specific overexpression are generated. In the heart, organ-specific overexpression or knockouts can be achieved by driving the gene of interest under a cardiomyocyte-specific promoter, such as the α -myosin heavy chain (α -MHC) or the myosin light chain 2 (mlc-2v) promoter.

Mice with cardiomyocyte-specific overexpression of the gp130 receptor do not develop a specific cardiac phenotype, at least no hypertrophy or cardiac failure have been

described to date in these mice, despite a slightly increased activation state of downstream signalling molecules STAT3 and ERK1/2 (Tone *et al.*, 2000). Mice with a cardiomyocyte-specific deficiency for gp130 receptor during fetal (Hirota *et al.*, 1999) or in early postnatal development (α -MHC-Cre^{tg/-} and gp130^{flox/flox}) (Fischer and Hilfiker-Kleiner, 2007) are viable and display normal postnatal cardiac development and cardiac function up to the age of 6 months. We have recently shown that gp130 activity in cardiomyocytes is required to protect the mice from age-related heart failure (Fischer and Hilfiker-Kleiner, 2007). In line with a cardio-protective role of gp130-mediated STAT activation, mice with a cardiomyocyte-specific deletion of STAT3 display spontaneous age-related heart failure and increased mortality beyond 12 months of age (Jacoby *et al.*, 2003; Hilfiker-Kleiner *et al.*, 2004).

Taken together, these observations suggest that certain endogenous gp130 ligands are present in the unstressed adult heart and might be responsible for baseline activation of the gp130 receptor under normal conditions. This baseline activation does not induce cardiac hypertrophy but seems essential for cardiac protection in ageing mice.

Role of gp130 signalling in physiological cardiac hypertrophy

Physiological cardiac hypertrophy occurs in response to growth, exercise or pregnancy, where increase in cardiomyocyte size is paralleled by a proportional growth of the vasculature and the capillary network and is usually not accompanied by cardiac fibrosis (Olson, 2004). Regular exercise induces anti-inflammatory effects with elevated levels of IL-6, which is thought to suppress oxidative stress and the production of proinflammatory cytokines, that is, tumour-necrosis factor- α (TNF- α) via activation of gp130-mediated signalling (Petersen and Pedersen, 2006). In addition, exercise-induced production and release of IL-6 from myofibres may contribute to abrogate an atherogenic lipid profile, which is often associated with chronic cardiac diseases (Petersen and Pedersen, 2006). However, there is little information on a direct role for gp130 in the heart during exercise.

Reversible physiological growth of heart also takes place in women during pregnancy, where ventricular hypertrophy, diastolic dysfunction and longer QT-interval dispersion develop as a result of volume overload as well as increased stretch and force demand (Eghbali *et al.*, 2005). Sex hormones, for example, oestrogens, seem to play an important role in adaptation processes of the maternal heart during pregnancy (Eghbali *et al.*, 2005). Serum levels of components of the IL-6/gp130 receptor system are also altered during pregnancy. For example, serum levels of OSM, the soluble LIF receptor sgp190 and of the sIL-6R are increased during pregnancy (Matsuzaki *et al.*, 1995; Pitard *et al.*, 1998; Ogata *et al.*, 2000). Furthermore, we have recently shown that activation of gp130 downstream mediator STAT3 plays an essential role for the protection of the maternal heart from postpartum cardiomyopathy (Hilfiker-Kleiner *et al.*, 2007). We therefore closely monitored female mice harbouring cardiomyocyte-specific deletions of the gp130 receptor for signs of peri- or postpartal heart

failure and mortality. We did, however, not observe any pregnancy-associated mortality in these female mice (D Hilfiker-Kleiner, unpublished data), suggesting that gp130 might not be the main mediator of myocardial STAT3 activation during remodelling processes in the peripartal phase.

Role of gp130 signalling in cardiac pathophysiology

Activation of gp130 signalling modulates cardiomyocyte hypertrophy and survival in vivo

Continuous activation of gp130 in the heart, achieved by combined overexpression of both IL-6 and its receptor, is capable of inducing cardiac hypertrophy *in vitro*, but also *in vivo* without additional stimuli (Hirota *et al.*, 1995). Importantly, STAT3, the major downstream signalling molecule of gp130, is sufficient to induce cardiomyocyte hypertrophy, and thereby plays a key role for gp130-mediated cardiomyocyte hypertrophy *in vitro* (Kunisada *et al.*, 1998) and *in vivo* (Hirota *et al.*, 1999; Kunisada *et al.*, 2000) as determined in transgenic mice with cardiac-specific overexpression of the STAT3 gene. Although the activation of the MEK5/ERK5 and p38 MAPK pathways has been ascribed to the mediation of eccentric, maladaptive cardiac hypertrophy, the gp130/JAK/STAT axis is implicated in concentric hypertrophy (Miyamoto *et al.*, 2004).

Interestingly, it could recently be demonstrated that IL-6 is an essential component of angiotensin II (AngII)-mediated hypertension and activation of the myocardial gp130/STAT3 axis leading to cardiac hypertrophy (Coles *et al.*, 2007). However, activation of STAT3 and development of cardiac hypertrophy in response to AngII stimulation appear to depend on classic IL-6 signalling via the membrane-bound cognate IL-6 receptor, whereas AngII-mediated hypertension is mediated by agonistic complexes of IL-6 with the sIL-6R that bind to the gp130 receptor, a mechanism referred to as IL-6 trans-signalling (Coles *et al.*, 2007).

Remarkably, recent data hint on further influences that impact on the phenotypic peculiarity of gp130-mediated hypertrophy. For instance, CT-1-induced hypertrophy was found to be markedly modified by the renin-angiotensin system in a STAT3-dependent manner. Furthermore, it appears that the gp130 receptor system and the renin-angiotensin system compound one another in their hypertrophic effects *in vivo*, with the extent of gp130-mediated hypertrophy being determined by the level of endogenous hypertensive preactivation, probably resulting in an exaggerated induction of angiotensinogen expression in response to CT-1 stimulation (Lopez *et al.*, 2006).

Moreover, the gp130 receptor system plays an important role in the transition of left ventricular hypertrophy to overt heart failure. Intriguingly, Lopez *et al.* (2007) found that the loss of LIF receptor abundance in cardiomyocytes from failing hearts of spontaneously hypertensive rats compared with non-failing hearts with left ventricular hypertrophy accounts for diminished CT-1-mediated cytoprotective signalling and protection from apoptotic and non-apoptotic cell death induced by AngII. In this framework, neuro-humoral agonists such as AngII, aldosterone and noradrenaline

seem to be causally involved in LIF receptor downregulation, which proved to be sufficient for reduction of protective gp130-dependent mechanisms (Zvonic *et al.*, 2005).

Cardiac adaptation to pressure overload depends on gp130 signalling

While initial *in vivo* studies foreshadowed the involvement of gp130 activation and downstream JAK/STAT signalling in pressure overload-induced hypertrophy (Pan *et al.*, 1998), the pivotal role of gp130 in initiation of cardiac hypertrophy in response to biomechanical stress was demonstrated in mouse models with cardiomyocyte-specific deletion of gp130. Although the function and structure of gp130-deficient hearts is normal under basal conditions, acute pressure overload induces a rapid progress to cardiac dilation and dysfunction due to the absence of compensatory hypertrophy and intense loss of contractile myocardium caused by massive cardiomyocyte apoptosis (Hirota *et al.*, 1999). Similarly, the expression of a dominant-negative mutant of gp130 in the heart leads to marked attenuation of pressure overload (thoracic aortic constriction)-induced cardiac hypertrophy and a reduction of concomitant STAT3 activation (Uozumi *et al.*, 2001).

Closely associated with the myocardial STAT3 activation pattern in response to pressure overload is the biphasic induction of SOCS3, a gene transcriptionally upregulated by an activated gp130/JAK/STAT signalling cascade (Yasukawa *et al.*, 2001). As described before, SOCS3 subsequently interrupts JAK/STAT (Ernst and Jenkins, 2004), but it also attenuates the activity of two other gp130-mediated signalling pathways, Ras/ERK and PI3K/Akt (Johnston, 2004). Therefore, upregulation of SOCS3 in the pressure-overloaded heart represents a key modulator of gp130-mediated cardiomyocyte hypertrophy and survival (Yasukawa *et al.*, 2001). Moreover, it can be hypothesized that in a balanced system, inhibition of gp130 signalling by SOCS3 in cardiomyocytes may ensure the termination of the hypertrophic growth without interfering with survival. In unbalanced situations, that is in SOCS3 overexpressing mice, insufficient hypertrophic growth, disturbed sarcomeric organization and enhanced cardiomyocyte apoptosis may result. In turn, attenuated SOCS3 expression due to insufficient activation of STAT3 may cause enhanced Ras/ERK and PI3K/Akt signalling, leading to exaggerated and unlimited cardiomyocyte hypertrophy and subsequent heart failure.

In conclusion, activation of gp130-mediated signalling upon stress-induced ligand stimulation in cardiomyocytes seems to be a key determinant of hypertrophic growth, survival, metabolisms and function both *in vitro* and *in vivo*. Moreover, current experimental data strongly suggest that a well-balanced gp130 receptor system is indispensable for compensatory hypertrophic growth, cardioprotection and prevention of heart failure in response to neurohumoral and mechanical stress factors.

In response to ischaemia, gp130 drives cardioprotective signalling

In post-ischaemic myocardial remodelling, gp130 activation through several cytokines of the IL-6 type family was proven to confer beneficial effects. For instance, persistent

activation of the gp130 receptor by administration of the IL-6/sIL-6 receptor complex inhibits cardiomyocyte apoptosis and restricts infarct sizes after ischaemia followed by reperfusion (Matsushita *et al.*, 2005). In addition, LIF and CT-1 not only promote cardiomyocyte hypertrophy and survival (Kodama *et al.*, 1997; Yasukawa *et al.*, 2001), but also seem to be involved in myocardial wound healing and neovascularization (Zou *et al.*, 2003; Freed *et al.*, 2005; Takahashi *et al.*, 2005), activation of cardiac fibroblasts (Tsuruda *et al.*, 2002) and restriction of the post-infarction remodelling process (Wang *et al.*, 2002). As a result, overexpression of LIF in experimental models resulted in preserved left ventricular function and geometry following myocardial infarction (Zou *et al.*, 2003; Berry *et al.*, 2004). Likewise, IL-11 administration was shown to reduce cardiac ischaemia/reperfusion injury by exerting both hypertrophic as well as cytoprotective signals via the gp130 downstream targets STAT3 and ERK1/2 (Kimura *et al.*, 2007). Interestingly, it has also been assumed that LIF released by infiltrating macrophages activated by cardiac tissue degradation products might play a cardioprotective role in the early inflammatory reaction following ischaemia (Trial *et al.*, 2004).

Different gp130 downstream pathways are involved in the cardioprotective effects following myocardial infarction. Mainly an efficient STAT3 signalling appears to be essential for the restriction of cardiac damage induced by ischaemia/reperfusion injury and myocardial infarction (Negoro *et al.*, 2000; Hilfiker-Kleiner *et al.*, 2004). Indeed, myocardial expression of IL-6 is rapidly induced following myocardial ischaemia (Yamauchi-Takahara *et al.*, 1995; Roy *et al.*, 2006) and the gp130/JAK2/STAT3 axis is triggered within minutes after ischaemia and remains activated up to 7 days post myocardial infarction (Fischer and Hilfiker-Kleiner, 2007). The gp130/STAT3-mediated cytoprotective signalling during ischaemia/reperfusion is to a considerable part based upon the scavenging of reactive oxygen species generation via the induction of the antioxidative enzyme manganese superoxide dismutase (Negoro *et al.*, 2001a). Further, protective mechanisms of gp130/STAT3 signalling initiated by IL-6, LIF or OSM include the induction of vascular endothelial growth factor expression and subsequent neovascularization in response to tissue ischaemia or inflammation (Funamoto *et al.*, 2000; Weiss *et al.*, 2003; Rega *et al.*, 2007).

Despite these positive effects of the gp130/STAT3 cascade, it has also been reported that the JAK/STAT axis is involved in unfavourable changes after infarction, such as alteration of gene activity that may underlie early diastolic dysfunction (that is, upregulation of phosphatase 1 and downregulation of p16-phospholamban) as well as downregulation of Kv4.2 gene expression that may underlie increased arrhythmogenicity of the post-infarction heart (El-Adawi *et al.*, 2003). It was recently shown that IL-6 is a causative factor in the development of depressed cardiac function and increased proinflammatory signalling following trauma-haemorrhage injury. In this setting, both blockade of endogenous IL-6 and administration of antibodies against the IL-6 receptor significantly attenuated cardiac NF- κ B, intercellular adhesion molecule-1, CINC-1, -3 and myeloperoxidase activity and resulted in an improvement of cardiac output (Yang *et al.*, 2006, 2007b). These studies suggest again that only a

precise control of gp130 signalling ensures a physiological outcome not only in the pressure-overloaded heart, but also after myocardial infarction and in the haemorrhagically damaged heart. Indeed, SOCS proteins are upregulated after myocardial ischaemia and one study emphasizes a positive role of SOCS3 to prevent early post-ischaemic myocardial dysfunction by modulating TNF- α -induced IL-6/gp130/STAT3 activity (Wang *et al.*, 2006). This report shows that a deficiency of TNF- α receptor-1 prevented TNF- α -mediated cardiac dysfunction and was associated with reduced IL-6 levels, attenuated STAT3 phosphorylation and upregulated SOCS3 (Wang *et al.*, 2006).

The gp130 receptor system and inflammatory diseases of the heart
Deduced from mouse models, gp130-mediated STAT3 activation seems to play a major role in the preservation of cell survival during virally conditioned myocardial inflammation as cardiac-specific gp130 knockout mice display an increase in susceptibility to viral infection of cardiomyocytes (Yajima *et al.*, 2006). Furthermore, it has been shown that gp130-mediated stimulation of cardiomyocytes has a cytoprotective effect against virus infection in culture that can be attenuated by SOCS3 (Yajima *et al.*, 2006).

In fact, a rather more detrimental role of SOCS proteins emerged from studies in myocarditis models, where, for example, transgenic mice with cardiomyocyte-specific overexpression of SOCS3 display a marked increase in susceptibility to viral infection despite an intact interferon (IFN)-mediated antiviral response (Yajima *et al.*, 2006). In addition, cardiomyocyte-specific transgenic expression of SOCS1 inhibits enterovirus-induced signalling of JAK/STAT, with accompanying increase in viral replication, cardiomyopathy and mortality in Cocksackie virus-infected mice (Yasukawa *et al.*, 2003). The major difference from SOCS3 is that SOCS1 is not induced by the IL-6 type cytokines, but is strongly induced by IFN- γ and modulates the effects of IFN- γ *in vivo* (Hanada *et al.*, 2006; Qin *et al.*, 2006; Zimmerer *et al.*, 2007; Zitzmann *et al.*, 2007). Considering the essential role of IFN- γ for host defence mechanisms, cardiac SOCS1 may play a particularly important role in virally induced heart disease (Metcalf *et al.*, 2000). In this regard, SOCS1/JAB is likely to mediate the protective effect of CT-1 against lipopolysaccharide-induced left ventricular dysfunction *in vivo* (Tanimoto *et al.*, 2005). In addition, SOCS1 does not seem to affect the gp130-mediated Ras/ERK and PI3K/Akt signalling, suggesting that gp130/JAK/STAT signalling plays the major protective role in cardiac inflammatory disease. In line with the notion of STAT3 as an important host defence pathway, mice with cardiomyocyte-specific deletion of STAT3 display increased susceptibility to endotoxin (lipopolysaccharide)-induced myocardial inflammation, resulting in extensive fibrosis and increased cardiomyocyte apoptosis (Jacoby *et al.*, 2003).

Thus, gp130/JAK/STAT signalling appears to play an important role in protecting the heart from viral and bacterial infection by preserving adult cardiomyocytes until specific immune responses begin to clear the virus. However, it has been reported that during viral myocarditis, continuous and excessive production of IL-6 promotes myocardial

injury by breaking down both cytokine networks and viral clearance (Tanaka *et al.*, 2001), again suggesting the necessity for a tight regulation of the gp130 receptor system.

Activation of gp130 protects against the cardiotoxicity of doxorubicin

The anthracycline doxorubicin is an anticancer drug known to cause severe cardiac toxicity by generating free radicals, which accelerate oxidative stress (Shioji *et al.*, 2002). Cardiomyocyte survival in doxorubicin-induced apoptosis through PI3K/Akt phosphorylation and Bcl-xL/caspase-3 interaction is regulated by gp130 (Negoro *et al.*, 2001a). Activation of gp130 inhibits doxorubicin-induced cell death in cardiomyocytes, resulting in the restoration of PI3K/Akt activities and in the inactivation of caspase-3. STAT3 signalling, possibly mediated by gp130 receptor activation, also plays a major protective role in doxorubicin-mediated cardiotoxicity (Kunisada *et al.*, 2000; Jacoby *et al.*, 2003). In general, it is assumed that gp130-mediated protection against doxorubicin-induced cardiotoxicity mainly results from protection against oxidative stress and in a direct upregulation of anti-apoptotic defence mechanisms via STAT3 (Negoro *et al.*, 2001b; Jacoby *et al.*, 2003). It is also conceivable that elevated levels of immunomodulators such as IFN- γ and TNF- α play an additional role in the mediation of cardiotoxic effects under conditions with decreased STAT3 activation (Numata *et al.*, 2007).

Challenges for directed pharmacological interventions in the gp130 receptor system: observing the changes or changing the observed?

The physiological activation of gp130-mediated signalling, especially via its main downstream effector STAT3, in response to various cardiac burdens such as pressure overload, cardiotoxic agents, and ischaemia and its relevance for the cardiac adaptation to these pathophysiological conditions (Hirota *et al.*, 1999; Jacoby *et al.*, 2003; Hilfiker-Kleiner *et al.*, 2004) gave rise to the idea of additionally enhancing gp130 signalling and STAT3 activation via ligand-induced activation following cardiac injury and of enhancing STAT3 function in the heart during the transition from compensated states to cardiac failure. As described previously, administration of the IL-6/sIL-6 receptor complex, but not IL-6 or its soluble receptor alone, was shown to inhibit cardiomyocyte apoptosis and to restrict infarct sizes after cardiac ischaemia/reperfusion injury (Matsushita *et al.*, 2005). This strengthened the possibility that activation of the gp130 receptor by IL-6 might be a future strategy in cardiovascular therapy, even in cases where the targeted receptor might not necessarily be expressed on cardiomyocytes, but may be activated by transsignalling. However, the finding that the complete knock-down of IL-6 did not influence infarct sizes or left ventricular function, remodelling and survival in mice did not fully support this concept (Fuchs *et al.*, 2003). Other gp130 ligands or factors signalling via JAK/STAT such as angiotensin may either be downregulated or act in a compensatory manner to exert cellular effects within a certain homeostatic range. In

contrast, the promotion of myocardial injury by excessive release of IL-6 (Tanaka *et al.*, 2001) suggests that high levels of circulating IL-6 following myocardial infarction or in patients with dilative cardiomyopathy might not only be a marker for the severity of ongoing inflammatory reactions but might also represent an active contributor to sustained damage during myocardial inflammation. Therefore, instead of ligand-induced activation of the gp130 receptor, it might turn out to be more practical to recognize and modulate activity of downstream targets of gp130-mediated pathways, that is, increasing STAT3-dependent manganese superoxide dismutase or vascular endothelial growth factor signalling in the heart, to restrict acute or chronic damage.

It should be taken into account that interventions targeting components of the gp130 receptor system in other organs might also affect its tightly controlled downstream pathways in the heart. For instance, it is known that in contrast to balanced STAT3 signalling, which is required for adaptive responses of cell proliferation, survival and metabolism of various organs to changing environmental influences, persistent STAT3 activation is frequently associated with malignant transformation and is one of the causative molecular abnormalities in oncogenesis as reviewed by Turkson (2004). Aberrant STAT3 activation is known to promote uncontrolled growth and survival through dysregulation of gene expression, including cyclin D1, c-Myc, Bcl-xL and Mcl-1, thereby contributing to oncogenesis (Turkson, 2004). Moreover, recent studies reveal that persistently active STAT3 induces tumour angiogenesis by upregulation of vascular endothelial growth factor and modulates immune functions in favour of tumour immune evasion (Turkson, 2004). Furthermore, IL-6-induced, gp130-mediated activation of STAT3 and the Notch-3 pathway have been found to be critical hallmarks in breast tumorigenesis (Guo *et al.*, 2006; Berishaj *et al.*, 2007; Sansone *et al.*, 2007). Moreover, IL-6 has been ascribed a causative role in STAT3 activation by mutant EGF receptors in lung carcinogenesis (Berishaj *et al.*, 2007). Thus, IL-6 and STAT3 emerged as novel targets for cancer therapy and are currently under investigation (Zaki *et al.*, 2004). Recent studies meanwhile demonstrated that inhibition of STAT3 activation, that is by means of small molecule STAT3 decoys, is capable of inducing apoptosis, and decreasing proliferation and STAT3-mediated gene expression of tumour cells both *in vitro* and *in vivo* (Leong *et al.*, 2003; Xi *et al.*, 2005). In addition, Selander *et al.* (2004) recently showed that blockade of gp130 signalling in a mouse tumour model efficiently inhibited tumour growth and metastasis, emphasizing the use of pharmacological inhibition of gp130 signalling in patients with breast cancer. Taken together, the targeted disruption of gp130-dependent signalling pathways appears to be a promising novel therapeutic strategy for the treatment of cancers characterized by constitutive STAT3 activation. However, one has to take into account the relevance of a tightly controlled gp130 receptor system in the heart while employing therapeutic strategies for other entities such as cancer treatment involving downregulation or inhibition of STAT3 signalling. Here, the maintenance of a balanced gp130 signalling in the heart should be considered equally important and specific treatment strategies should be developed aiming at

protection of the heart from adverse side effects associated with systemic downregulation of gp130/STAT3 signalling during antitumour therapy. In turn, displayed against the necessity of an intact, physiologically regulated gp130 receptor system in the heart for the protection against pathophysiological stress such as ischaemia, mechanical stress and cytotoxic agents, a potential oncogenic effect has to be considered and should be carefully investigated.

In the light of these controversies, it is especially important to define further those gp130/STAT3-dependent downstream mediators that may specifically serve as prime targets for novel therapies to treat heart failure, without increasing the risk for malignancies.

Conclusion

The gp130 receptor system plays an essential role for cardiac development, potentially by regulating cardiomyogenesis, cardiomyocyte survival and growth. In experimental models, gp130 receptor signalling has been shown to be essential for cardiac development and for cardioprotection against physiological and pathophysiological stress. In addition, the understanding and directed manipulation of gp130-dependent signal transduction pathways is a prerequisite for cell type-specific pre-commitment that may eventually facilitate stem- and progenitor cell-based therapies for myocardial repair and regeneration.

Importantly, beneficial effects of gp130 signalling seem to require well-balanced circuits of STAT and ERK signalling pathways, where negative feedback mechanisms, that is, SOCS proteins play an important role. Failure in this orchestration of signalling results in loss of cardiac cells, maladaptive hypertrophy and cardiac dysfunction and may explain discrepancies between reported beneficial and protective roles of the gp130 receptor system in experimental models and the association of activated gp130 receptor system components with adverse clinical outcomes in patients with heart failure or after myocardial infarction (Roig *et al.*, 1998; Tsutamoto *et al.*, 1998; Maeda *et al.*, 2000; Orus *et al.*, 2000; Birks *et al.*, 2001; Rattazzi *et al.*, 2003; Buzas *et al.*, 2004; Hirota *et al.*, 2004). The attenuated STAT3 activation and reduced SOCS3 expression observed in patients with end-stage heart failure (Podewski *et al.*, 2003) may reflect disturbance of the physiological activity of the gp130 signalling system. In its consequence, balanced gp130 signalling appears to be cardioprotective, whereas imbalanced gp130 signalling contributes more to maladaptation and heart failure.

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Conflict of interest

The authors state no conflict of interest.

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