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INVITED REVIEW

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Survival pathways in hypertrophy and heart failure: The gp130-STAT3 axis

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Abstract Circulating levels of interleukin (IL)–6 and related cytokines are elevated in patients with congestive heart failure and after myocardial infarction. Serum IL-6 concentrations are related to decreasing functional status of these patients and provide important prognostic information. Moreover, in the failing human heart, multiple components of the IL-6-glycoprotein (gp)130 receptor system are impaired, implicating an important role of this system in cardiac pathophysiology.

Experimental studies have shown that the common receptor subunit of IL-6 cytokines is phosphorylated in response to pressure overload and myocardial infarction and that it subsequently activates at least three different downstream signaling pathways, the signal transducers and activators of transcription 1 and 3 (STAT1/3), the Src-homology tyrosine phosphatase 2 (SHP2)-Ras-ERK, and the PI3K-Akt system. Gp130 receptor mediated signaling promotes cardiomyocyte survival, induces hypertrophy, modulates cardiac extracellular matrix and cardiac function. In this regard, the gp130 receptor system and its main downstream mediator STAT3 play a key role in cardioprotection.

This review summarizes the current knowledge of IL-6 cytokines, gp130 receptor and STAT3 signaling in the heart exposed to physiological (aging, pregnancy) and pathophysiological stress (ischemia, pressure overload, inflammation and cardiotoxic agents) with a special focus on the potential role of individual IL-6 cytokines.

Key words heart – signaling – hypertrophy – gp130 – cytokines

Introduction

It has been reported that serum levels of interleukin-6 (IL-6) cytokines (IL-6, leukemia inhibitory factor, LIF, and cardiotrophin-1, CT-1) are elevated in patients with cardiac insufficiency and that IL-6 is a strong prognostic marker for the morbidity and mortality in patients with heart failure or after myocardial infarction [57, 118, 148, 149]. In addition, serum levels of soluble glycoprotein (gp) 130, the common receptor subunit of all IL-6 cytokines, correlate with the severity of left ventricular dysfunction [6, 44, 57, 162].

Analysis in various knockout mouse models demonstrated that the gp130 receptor system plays a key functional role for cardioprotection against physiological and pathophysiological stress by promoting cardiomyocyte survival, inducing compensatory hypertrophy and preserving cardiac function [8, 50, 56, 64]. The characteristic phenotype of gp130-deficient mouse hearts displays a critical role of gp130 in the transition between compensatory cardiac hypertrophy and heart failure and implies that ligands operating via gp130 may prove to be important in adaptative or maladaptive processes of the heart in response to stress.

In various cell types including cardiomyocytes sub-

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sequent signal transduction via gp130 involves three major downstream pathways: The JAK (Janus kinase) – STAT (signal transducer and activator of transcription) axis, the Ras-Raf mitogen-activated protein kinase (MAPK, MEK/ERK) signaling cascade, and the phosphatidylinositol 3-kinase-dependent (PI3K/AKT) pathway [38, 47, 54, 56, 77, 102]. Each of these gp130 downstream signaling pathways has been demonstrated to play an important role in cardiac physiology. Particularly STAT3-dependent downstream signaling of gp130 holds a key role in cardiac hypertrophy and protective effects during its maladaptive transition to heart failure such as cardiac angiogenesis and prevention of cardiomyocyte apoptosis [51, 64, 78, 107].

In the current review, we summarize data on the role of individual IL-6 cytokines in cardiac pathophysiology and highlight the key functional role of gp130-STAT3 signaling for cardiac adaptation and protection in response to various forms of stress.

General overview on gp130 signaling

The IL-6-type cytokines, comprising IL-6, Interleukin-11 (IL-11), LIF, oncostatin M (OSM), ciliary neurotrophic factor (CNTF), CT-1 and cardiotrophin-like cytokine (CLC) are a family of helix bundle cytokines with pleiotropic effects in the organism [47, 48, 72]. Generally, they are involved in inflammatory and immunologic processes as well as in hematopoiesis, liver and neuronal regeneration, embryonic development and cardiovascular physiology. Through activation of target genes involved in growth, differentiation, survival, apoptosis, and proliferation IL-6 type cytokines play a key role in cellular and tissue homeostasis [13, 72].

With the shared use of the signal transducer gp130, the biological functions of IL-6 family cytokines are largely overlapping (Fig. 1). 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, CNTF, CLC, OSM and CT-1) or OSM receptor (for OSM), respectively [103, 110, 112]. These differences in the mechanisms of receptor recruitment might reflect a structural difference of the IL-6 type cytokines, as the cytokines with a straight A helix (IL-6, IL-11) signal via gp130 homodimers whereas the cytokines with a kinked A helix signal via LIFR–gp130 or OSMR–gp130 heterodimers (Fig. 1). Human OSM has the exceptional capability to recruit two different receptor complexes, as it binds to both LIFR–gp130 and OSMR–gp130 heterodimers (Fig. 1).

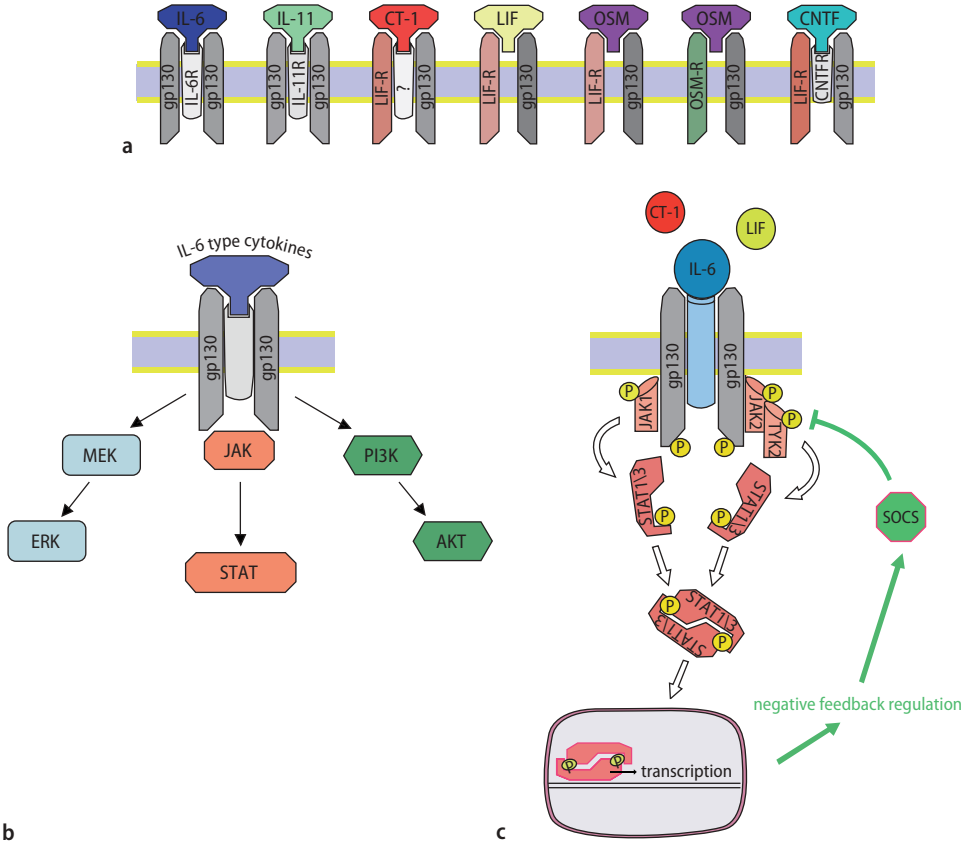

Fig. 1 Scheme depicting gp130 receptor system. **A** Cytokines of the IL-6 family bind to the common receptor unit gp130 inducing complex formation with ligand specific receptor subunits. **B** Upon ligand binding gp130 receptor dimers activate JAK/STAT, Ras-Raf-MEK/ERK and the PI3K/AKT signaling cascades. **C** Following tyrosine phosphorylation of JAKs, STAT proteins are recruited to the gp130 receptor and are phosphorylated. Subsequently STAT proteins form homo- or heterodimers, translocate to the nucleus and activate transcription. Among the genes transcriptionally upregulated by STAT3 are the SOCS proteins. SOCS-1 and SOCS-3 interact with the kinase domain of various JAK proteins or the cytoplasmic phosphotyrosine residue (phospho-Tyr759) of the respective receptor resulting in the inhibition of STAT protein phosphorylation thereby inducing a negative feedback regulation of STAT activation

Subsequent signal transduction via gp130 involves three major downstream pathways the activation of which is controlled by distinct regions of the gp130 receptor: the JAK- STAT axis, the Ras-Raf-MEK/ERK signaling cascade, and the PI3K/AKT pathway [38, 47, 54, 56, 77, 102] (Fig. 1).

All IL-6-type cytokines potently activate STAT3, and to a minor extent STAT1 through their common receptor subunit gp130 [48]. The initial interaction in the activation of the JAK/STAT signaling axis is the binding of IL-6-type cytokines to their corresponding plasma membrane receptor. Subsequently, following dimerization of the gp130 receptor complex, JAK1, JAK2, JAK3, and Tyk2 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 [74, 96]. This allows the recruitment of STAT proteins to the gp130 receptor complex via recognition of its phosphotyrosines by the STAT SH2 domains and results in the phosphorylation of STAT proteins at single carboxyterminal tyrosine residues by the activated JAK kinases. The phosphorylated STAT proteins then detach from their receptor and undergo homo- or heterodimerization through reciprocal interactions between the SH2 domain of one monomer and the phosphorylated tyrosine residue of the other [22]. Dimeric STAT proteins eventually translocate to the nucleus, bind to specific DNA elements in the promoters of downstream target genes, and activate transcription (Fig. 1).

Ligand-dependent STAT activation is a tightly controlled transient process, lasting for minutes up to several hours in which nucleic STAT proteins are eventually inactivated by tyrosine dephosphorylation followed by their return to the cytoplasm [45]. There are further regulatory mechanisms that normally serve to decrease STAT activity on different levels of the signal transduction pathway. In the first instance, growth factor receptors, such as gp130, are rapidly internalized upon binding of the correspondent ligand and degraded by the ubiquitin proteasome pathway [49]. Additionally, the Src homology domain-containing tyrosine phosphatases 1/2 (SHP-1/2) can interact with the intracytoplasmic portion of cytokine receptors and dephosphorylate JAK proteins thereby lowering their activity [25, 31]. The suppressor of cytokine signaling (SOCS) (also referred to as cytokine-inducible SH2 protein (CIS)) family represents a specific negative regulatory feedback element of STAT signaling and its upstream kinases (Fig. 1) [131]. Expression of some of its members is transcriptionally upregulated by STAT proteins assigning activated STATs a role in the negative regulation of their own phosphorylation state (Fig. 1). Comparable to SHP-1/2, SOCS-1 and SOCS-3 interact with the kinase domain of various JAK proteins or the cytoplasmic phosphotyrosine residue (phospho-Tyr759) of the respective receptor resulting in the inhibition of STAT protein phosphorylation [84, 168, 169]. In addition to SHPs and SOCSs, the group of protein inhibitors of activated STAT (PIAS-1, -3) is capable of inhibiting the binding of dimerized phosphorylated STAT1 and STAT3 to DNA, thereby averting the transcriptional activation of STAT target genes. Consequently, the relative levels of STAT and PIAS determine STAT3-induced gene expression. Only recently was the protein tyrosine phosphatase (PTP) receptor T (PTPRT) found to specifically dephosphorylate the Y705 residue of STAT3 and thereby regulate its target gene expression and its cellular localization [173]. Importantly, the activation state of STAT3 seems to play a major role whether IL-6-gp130 signaling acts in a more anti-inflammatory or a more pro-inflammatory manner. For example in macrophages lacking the SOCS3 gene or carrying a mutation of the SOCS3-binding site in gp130, the lipopolysaccharide (LPS) induced production of tumor necrosis factor alpha (TNFα) is suppressed by IL-6, while in wildtype macrophages IL-6 stimulation represses STAT3 activation and results in enhanced TNFα production [170].

Taken together, IL-6 cytokines are defined by the use of a common receptor subunit gp130. All IL-6 cytokines are able to activate STAT3; however, the overall strength of STAT3 signaling is largely influenced by inhibitory pathways on each level of the gp130-JAK/STAT cascade – from the membrane receptor to the nucleus (Fig. 1).

The gp130-STAT3 signaling cascade is altered in the failing human heart: cause or consequence?

The recognition of the key role of gp130-dependent signaling in the development of the heart and the regulation of cardiac physiology, especially the strong influence of the JAK/STAT pathway on cardiac angiogenesis and cardiomyocyte hypertrophy founded a sustained focus of research on the homeostasis and dysregulation of the gp130 system in human cardiac pathophysiology. Meanwhile numerous studies have investigated the expression of IL-6 type cytokines, the corresponding receptors and activated downstream mediators in the framework of different cardiac diseases and their progression towards heart failure.

Furthermore, cumulative data of recent clinical and experimental studies indicate distinct changes in the expression pattern of circulating IL-6 type cytokines in patients with cardiac hypertrophy and chronic heart failure [57, 73, 148, 149].

Changes in systemic levels of the IL-6 type family of cytokines

For almost a decade it has been known that the serum level of IL-6 is a strong independent predictor for the morbidity and mortality of patients with heart failure after myocardial infarction and of other etiologies [15, 89, 105, 118, 119, 148]. Likewise, measurement of the soluble gp130 receptor (sgp130) serum levels has been suggested to identify patients at high risk for heart failure progression in addition to established prognostic markers such as B-type natriuretic peptides and atrial natriuretic peptide [44]. In line with this notion, patients with dilative or hypertrophic cardiomyopathy and chronic heart failure have increased plasma concentrations of IL-6 and sgp130, with elevated ratios of IL-6 to sgp130 protein level [21, 145]. It is also known that plasma levels of IL-6 and of soluble gp130 correlate with the severity of left ventricular dysfunction [6, 44, 57, 162]. Moreover, systemic levels of IL-6 and sgp130 were shown to be even higher in hypertrophic cardiomyopathy compared to dilated cardiomyopathy [21]. In acute coronary syndromes the elevated serum levels of IL-6 and sIL-6R positively correlate with early inflammatory parameters and classical risk factors such as body mass index, blood pressure and lipid levels [17]. In this regard, it has been speculated that circulating IL-6 may contribute to the progression of the disease by enhancing thrombotic complications of chronic heart failure [23]. Interestingly, it was recently found that an IL-6 promoter polymorphism (174 G→C) is associated with a higher risk of coronary heart disease and death after acute coronary syndromes [3, 60]. In addition, it has been shown that peripheral levels of additional IL-6 type cytokines such as LIF significantly increase in association with the severity of chronic heart failure [57]. Likewise, the level of circulating CT-1 was found to be a predictor of death or heart failure following acute myocardial infarction [73]. Most importantly, the studies in humans revealed a significant correlation between CT-1 expression, LV end-diastolic dimensions, and the severity of left ventricular systolic dysfunction [137]. CNTF could not be detected in the plasma of patients with moderate heart failure [91]; no additional data on systemic CNTF levels are available to date.

Changes in myocardial expression of the IL-6 type family of cytokines

Intriguingly, not only systemic levels of IL-6 type cytokines and sgp130 are elevated in cardiovascular disease but also the local gp130-STAT3 signaling cascade is altered at every level in the failing human heart [28, 67, 68, 113, 175]. For instance, it is known that both CT-1 and LIF are increasingly expressed in the failing left ventricular myocardium. While the heart had previously been recognized as a source of circulating CT-1 in humans [5], during the last years several investigations uncovered its regulation in cardiac pathophysiology. In principle, hemodynamic overload seems to be a sufficient stimulus for the upregulation of LIF and CT-1 expression in the adult human heart. Indeed, the release of CT-1 was found to be stimulated by ventricular stretch [109]. Comparable to systemic levels, the increase in local myocardial CT-1 in hypertensive patients [40, 86, 126] as well as in patients with dilative cardiomyopathy is furthermore significantly correlated with the left ventricular mass index, suggesting that CT-1 might play a role in structural left ventricular remodeling in these patients [149]. On the other hand myocardial levels of IL-6 and LIF receptor appear to be reduced in patients with dilative cardiomyopathy [28, 67]. Interestingly, while the gp130 receptor was found to be hyperphosphorylated [113], gp130 protein expression is not altered [113] or even diminished in the failing left ventricular myocardium [175]. Expression and phosphorylation levels of STAT3 [52, 113], the major downstream signaling molecule of IL-6, as well as phosphorylation of its upstream activators JAK2 and TYK1 is severely reduced in failing hearts of different etiology [113]. Not much information is available to date on the expression state of SOCS proteins, negative regulators of gp130-JAK/STAT signaling, in human failing hearts. One report shows that terminally failing human hearts display increased SOCS-1 and reduced SOCS-3 protein levels [113].

Taken together, circulating IL-6 cytokines positively correlate with the progression of heart failure and the local IL-6-gp130-STAT3 signaling cascade in human failing hearts is dysregulated at all levels. These observations raised the possibility that the gp130 signaling system may actively contribute to the development of heart failure in patients. However, studies in human myocardial tissue could not ascribe distinct roles to individual cytokines of the IL-6 type family in the framework of cardiac pathophysiology. Therefore, the question whether impaired IL-6 cytokine signaling constitutes cause or consequence is still open.

In the following paragraphs we summarize data from experimental analysis concerning individual components of the gp130 signaling system to shed light on their potential role in the pathophysiology of heart failure.

Interleukin-6 and its potential role in the heart

Experimental data show that IL-6 expression in the heart is upregulated during hypoxia/ischemia [59, 120] and in the progression of pathological, maladaptive hypertrophy following myocardial infarction, pressure overload and congestive heart failure [8, 20, 70, 122, 166]. A wide range of factors upregulates cardiac IL-6 ex-

pression, including the inflammatory cytokines IL-1β and TNFα [94], LPS [153], the neurohormones norepinephrine [20] and Ang II [122], and intracellular reactive oxygen species [59, 123]. In contrast, IL-6 release is obviously not enhanced in physiological, adaptive exercise-induced cardiac hypertrophy [61].

IL-6 is produced by both cardiac fibroblasts and myocytes in the human heart [1, 2] and exerts direct influences on cardiomyocytes and cardiac fibroblasts, respectively. In that, IL-6 is known to reduce cardiomyocyte contractility in vitro, partly via induction of iNOS expression and by decreasing intracellular Ca^{2+} transients, most probably due to the downregulation of sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2) in cardiomyocytes [152]. IL-6 is involved in the induction of abnormal collagen deposition by cardiac fibroblasts in vitro in response to Ang II and norepinephrine stimulation which, besides the development of eccentric hypertrophy, constitutes a characteristic feature of maladaptive remodeling of the left ventricle [20, 124]. Furthermore, transgenic mice over-expressing IL-6 display accelerated myocardial injury during viral myocarditis [138].

Despite substantial effects of IL-6 on cardiac cells in vitro and in vivo, mice with a systemic deficiency of IL-6 do not differ from wildtypes concerning their cardiac phenotype and physiology. Moreover, infarct size, cardiac function and survival following myocardial infarction are comparable in both IL-6 knockout mice and wildtypes, most likely because other members of the IL-6 family such as LIF may act in a compensatory manner to activate the JAK/STAT pathway in the absence of IL-6 [37]. However, IL-6 seems to be an integral part of the protective effects of ischemic preconditioning of the myocardium, as IL-6 knockout mice show larger infarct sizes after myocardial infarction with previous coronary occlusion/reperfusion [26]. In this setting, IL-6 is obviously indispensable for the activation of the JAK/STAT pathway and downstream activated protective genes such as inducible NO synthetase (iNOS) and COX-2 in cardiomyocytes. IL-6-induced upregulation of anti-apoptotic Bcl-2 and downregulation of proapoptotic Bax may play additional roles in cardiomyocyte protection from apoptosis following ischemic preconditioning [46]. Interestingly, while administration of IL-6 after myocardial ischemia/reperfusion (I/R) in mice does not exert any specific effect, infusion of an IL-6/soluble IL-6 receptor complex was proven to inhibit cardiomyocyte apoptosis and limit infarct size after I/R, suggesting a rather protective role of IL-6 in the ischemic heart in vivo [93]. The finding that IL-6 apparently only generates a protective signal in combination with its own soluble receptor might be due to the low endogenous expression level of the IL-6 receptor on cardiomyocytes [121], which may also explain difficulties in experimental analysis in cardiomyocytes in vitro. Thus, the effects of IL-6 on survival or death of cardiomyocytes, modulation of cardiac contractility, alterations of vascular endothelium, local oxidative stress, and remodeling (summarized in Table 1), are difficult to define and the causal meaning of IL-6 for the development of heart failure is therefore still elusive [101]. Whether the net effects of IL-6 in the heart are rather beneficial and relevant in cardioprotection or predominantly detrimental in terms of sustaining cardiac inflammation and promoting left ventricular failure is still an open question [69].

Leukemia inhibitory factor and its potential role in the heart

During embryonic development, LIF plays a key part in the modulation of cardiogenesis as it influences commitment and differentiation of cardiomyocytes from the mesoderm and controls maintenance of their phenotype [7, 33].

The LIF receptor and its ligand are also abundantly expressed in postnatal murine cardiomyocytes [2, 77] and in vitro data show that LIF confers both hypertrophic and cytoprotective responses in adult cardiomyocytes [154]. LIF stimulation increases cardiomyocyte growth and promotes a fetal gene expression pattern (upregulated c-fos, β-MHC and ANF) [77, 92]. Characteristically, LIF induces myocardial hypertrophy with a predominant increase in myocardial cell length by addition of new sarcomeric units in series without concomitant increase in cell width, clearly distinguishing it from alpha-adrenergic hypertrophic responses mediated by G protein coupled receptors [75, 163].

Albeit STAT3-dependent signaling was initially found to be responsible for the promotion of cardiomyocyte hypertrophy under stimulation with LIF [79] it appears now that the MEK/ERK/p90(RSK) cascade certainly holds distinct predominance compared with JAK/STAT and PI3-K pathways in LIF-induced gp130-mediated cardiac hypertrophy [76, 77, 92]. More specifically, it has been found that Gab1-SHP2 interaction leading to activation of ERK5 plays a crucial role in the characteristic gp130-dependent longitudinal elongation of cardiomyocytes in the hypertrophic response to LIF-stimulation [98]. However, there is some evidence that maximal stimulation of the MAPK pathways by LIF requires the co-activation of PI3-K/Akt signaling, especially the PI3-K/Akt/PKB-p70 S6 kinase pathway [55], which may thus be a modulator of LIF-induced hypertrophic signaling [102]. It was also demonstrated that LIF-induced cardiac hypertrophy critically involves activation of calcineurin and calmodulin kinases II and IV through an increase in L-type Ca^{2+} current with subsequent enhanced Ca^{2+} influx in cardiomyocytes [71]. The Raf-1/MEK/ERK pathway is possibly involved in the modulation of this activation [97]. LIF concomitantly

activates c-Jun N-terminal protein kinase (JNK) in cardiomyocytes, which suppresses the development of myocyte hypertrophy, thereby constituting a negative regulator within the MAPK family [100].

The JAK/STAT pathway seems to be largely responsible for the transduction of LIF-induced cytoprotective signals in cardiomyocytes [168]. For instance, LIF significantly suppresses the increase of hypoxia/reoxygenation-induced reactive oxygen species (ROS) in a STAT3-dependent manner and thereby diminishes cardiomyocyte injury and apoptosis following ischemia [154]. This protective pathway involves the increased expression of manganese superoxide dismutase (MnSOD), a gene transcriptionally regulated by STAT3 in cardiomyocytes [99]. LIF was also shown to attenuate myocardial inflammation by diminishing cardiac TNFα production following administration of bacterial lipopolysaccharide (LPS) [11]; the downstream signaling pathways involved in this protection are not known.

In vivo studies showed that the overexpression of LIF in acute experimental myocardial infarction leads to significant compensatory cardiomyocyte hypertrophy, an increased number of cardiomyocytes in cell cycle and attenuation of cardiomyocyte apoptosis, reflected in preserved left ventricular function and geometry as compared with wildtype animals [12, 176]. Apart from promoting survival and stimulating hypertrophic responses in cardiomyocytes [75, 168], LIF also stimulates cardiac fibroblast growth and proliferation [147] and seems to be involved in wound healing after myocardial infarction [35, 134, 176]. Interestingly, LIF stimulation reduces collagen production and matrix metalloproteinase (MMP) activity in cardiac fibroblasts and inhibits cardiac fibroblast differentiation into myofibroblasts. This downregulation of several key components of the remodeling process suggests that LIF may play a role in preventing excessive extracellular matrix production following acute myocardial injury [155]. Indeed, overexpression of LIF in vivo was shown to limit infarct size, to induce neovascularization and to decrease fibrosis in both the infarct and its border zone after experimental myocardial infarction in rats [176]. Interestingly, it has been supposed that LIF might also be one of the cardioprotective factors in the early inflammatory reaction after ischemia. In that, tissue-infiltrating macrophages activated by myocardial degradation products may constitute the primary source of LIF release [146].

However, it was also reported that LIF induces contractile dysfunction and an increase in anaerobic energy metabolism in isolated cardiomyocytes, in part mediated by reduced expression of components of the adenosine triphosphate synthase complex and insulin-like growth factor-binding proteins 1 and 6 [32]. Furthermore, there is accumulating evidence for interference of the renin-angiotensin system (RAS) with the activation of STAT3 by LIF in the heart. Though Ang II itself is known to activate STATs and induce hypertrophy in cardiomyocytes it was demonstrated that Ang II pretreatment inhibited LIF-induced phosphorylation of STAT3 and thereby attenuated the cytoprotective effects of LIF in cardiomyocytes; this inhibitory effect could be blocked by an Ang II type I (AT I) receptor antagonist [16, 142]. Deduced from findings for IL-6-induced STAT3 phosphorylation, the inhibitory effects of Ang II might be mediated by MAPKK1 or one of its downstream intermediates [14]. Additionally, Ang II was found to increase LIF, IL-6 and CT-1 expression in cardiac fibroblasts and these cytokines, particularly LIF and CT-1, in turn activate gp130-linked downstream signaling [122]. Indeed, studies in rat models of hypertension revealed that LIF as well as IL-6 and CT-1 seem to be involved in Ang II-dependent left ventricular hypertrophy [80, 122, 123]. This partially negative and partially complementary crosstalk between Ang II and IL-6 type cytokines may contribute to the modulation of myocardial hypertrophy and drive the remodeling process either in an adaptive or maladaptive manner. An overview of cardiotrophic effects of LIF is provided in Table 1.

Cardiotrophin-1 and its potential role in the heart

CT-1 was initially identified in an in vitro model system for cardiac muscle hypertrophy (reviewed by Pennica [110]). In the adult heart an increase in CT-1 expression in cardiomyocytes and fibroblasts of both infarcted and non-infarcted myocardium was detected after myocardial infarction in rats [4]. Studies of ventricular remodeling in hypertensive rats and rabbits showed that expression of CT-1 mRNA is increased already in the early stage of ventricular hypertrophy [63], remains elevated after hypertrophy has been established and in that correlates with its degree [68]. Interestingly, it was demonstrated that CT-1 mRNA and protein along with gp130 expression significantly increases at the transition from left ventricular hypertrophy to congestive heart failure [136].

Similar to LIF, CT-1 activates the major gp130 downstream signaling cascades JAK/STAT, MEK/ERK, and PI3K/Akt [34, 65]. In cardiomyocytes the antiapoptotic effects of CT-1 are predominantly transmitted via MAPK and necessarily require activation of the MEK1/2-ERK1/2 pathway [87, 171]. Interestingly, studies of ischemia/reperfusion injury in rats revealed that activation of ERK1/2 by CT-1 protects cardiomyocytes from apoptosis both when added prior to ischemia or at the time of reoxygenation [18]. Additionally, the survival promoting effects of CT-1 involve p38 MAPK and PI3K/Akt signaling [19, 24, 87] and require activation of NF-kappa B, while they are largely independent from

Table 1 Effects of IL-6 type cytokines in cardiac (patho)physiology

	Cardiomyocytes	Vasculature	ECM modulation	Others
IL-6	induction of iNOS and COX-2 downregulation of SERCA2 decreased intracellular Ca^{2+} transients reduction of contractility upregulation of antiapoptotic Bcl-2 downregulation of proapoptotic Bax cytoprotection in combination with sIL-6R after AMI		increased collagen production by cardiac fibroblasts in response to Ang II and NE	increased susceptibility to viral infection protective effects in ischemic preconditioning
CT-1	protection against ischemic stress by inactivation of proapoptotic BAD and induction of protective heat shock proteins (HSP) hypertrophy with addition of new sarcomeric units in series proliferation contractile dysfunction		promotes fibroblast proliferation and migration induction of collagen synthesis	
LIF	cardiomyocyte differentiation during embryonic development hypertrophy with induction of fetal cardiac gene program cell elongation with addition of new sarcomeric units in series increased Ca^{2+} influx through hightened L-type Ca^{2+} current upregulation of MnSOD expression suppression of hypoxia-induced ROS production cytoprotection, antiapoptotic effects contractile dysfunction increase in anaerobic energy metabolism	induction of myocardial neovascularization	promotes fibroblast proliferation reduction of collagen production and MMP activity in cardiac fibroblasts inhibition of cardiac fibroblast transition to myofibroblasts attenuation of ECM production/fibrosis	attenuation of LPS-induced inflammation amelioration of LV-function and geometry following AMI improved wound healing and limitation of infarct size after AMI involvement in Ang II-induced LV hypertrophy
OSM	cytoprotection enhanced production of TIMP-1 and PAI-1	upregulation of bFGF and MCP-1 expression in endothelial cells promotes endothelial cell proliferation and migration angiogenesis mediated by VEGF	release of CXCL1/5 from cardiac fibroblasts enhanced production of TIMP-1 and PAI-1 promotes fibroblast survival and proliferation increase in ECM production in vivo	
CNTF	reduces obesity-associated hypertrophy in leptin-deficient mice			
IL-11				atrial flutter/fibrillation, enlarged atrial dimensions sodium-retaining effects

STAT3 [24, 83, 116, 127]. One of the key events by which the PI3K/Akt pathway mediates CT-1-induced survival signaling seems to be the phosphorylation of the pro-apoptotic factor Bad [81]. Furthermore, CT-1 can induce expression of protective heat shock proteins (hsp70 and hsp90) in cardiac cells [116]. It has been demonstrated that by this means CT-1-treated cardiomyocytes are protected against subsequent exposure to severe thermal or ischemic stress [132].

Comparable to LIF, CT-1 induces myocardial hypertrophy with a predominant increase in myocardial cell length by addition of new sarcomeric units in series without concomitant increase in cell width [163]. Despite years of intensive research, the exact mechanisms mediating CT-1-induced cardiomyocyte hypertrophy are still not entirely clarified. Originally, activation of the JAK/STAT3 axis has been assigned the key role in the generation of a cardiac hypertrophic phenotype in response to CT-1 stimulation [88, 116, 127, 140]. While it appears quite certain that CT-1-induced cardiac hypertrophy is independent of PI3-K/Akt signaling [140], recent findings indicate that the major pathway responsible for the hypertrophic responses to CT-1 is probably not the JAK/STAT3 pathway or the MEK1-ERK1/2 pathway, but signal transduction via the MEK5-ERK5 pathway [134]. However, it has also been reported that the hypertrophic effects of CT-1 in cardiac cells are at least in part dependent on hsp56 induction downstream of JAK/STAT, MEK/ERK and PI3-K/Akt [65]. On the other hand, inhibition of STAT3 phosphorylation by

ERK1/2 is described to negatively regulate CT-1-induced hypertrophic responses in cardiomyocytes thereby representing an autoregulative element in CT-1 downstream signaling [85, 140].

In numerous experimental studies CT-1 acts as a potent cardiac survival factor, and promotes cardiomyocyte proliferation and hypertrophy in vitro and in vivo [63, 66, 115, 127]. In addition, CT-1 induces fibroblast proliferation, migration and collagen synthesis [34, 36, 70]. In the rat model of chronic myocardial ischemia CT-1 plays an important role in postischemic myocardial tissue repair and scar formation [reviewed by 35]. On the one hand these features confer an adaptive role of CT-1, as the transplantation of skeletal myoblasts transgenic for CT-1 would indicate, since these myoblasts retard the transition from compensatory hypertrophy to heart failure in Dahl salt-sensitive hypertensive rats [141]. On the other hand long-term exposure to CT-1 induces contractile dysfunction in cardiomyocytes in which structural changes due to dedifferentiation of cardiomyocytes and reduction of intracellular Ca^{2+}-handling proteins such as calsequestrin may play an important role [174].

Despite the multifarious biologic effects of CT-1 on cardiac physiology, mice deficient for CT-1 do not show a significantly altered phenotype of the heart. Especially infarct sizes after ischemia/reperfusion injury are not different in CT-1 knockout mice compared to wildtypes [42]. This observation implicates that CT-1 might be redundant in the setting of ischemic injury of the heart.

In summary, augmented CT-1 appears to constitute an important mediator during ventricular remodeling after myocardial infarction (Table 1). However, whether CT-1 confers a beneficial effect by promoting cardiomyocyte survival and hypertrophy and wound healing or contributes to maladaptive processes including eccentric hypertrophy, dilation, left ventricular dysfunction, and heart failure still remains to be elucidated.

Oncostatin M and its potential role in the heart

OSM, an inflammatory mediator mainly produced by activated macrophages, leukocytes, and T-lymphocytes stimulates a variety of mediators implicated in wound repair and seems to have distinct functions in the regulation of connective tissue production and extracellular matrix turnover during inflammatory processes.

After cardiac ischemia/reperfusion injury OSM expression shows an early upregulation with infiltrated leukocytes, macrophages, and endothelial cells constituting the main sources of OSM production [82]. Among the known effects of OSM are the upregulation of bFGF and MCP-1 expression in endothelial cells, the induction of endothelial cell proliferation [133] and the enhancement of endothelial cell migratory properties in vitro [133, 160]. In contrast to LIF and IL-6 [114, 151], OSM shows potent angiogenic activity on human microvascular endothelial cells in vivo via induction of VEGF [30], requiring COX-2 as a cofactor [114]. While LIF and CT-1 have been shown to enhance VEGF expression in mouse and rat cardiac myocytes, OSM has been found to be mainly responsible for this ligand-specific regulation of proangiogenic signaling through the gp130 pathway in the human system [159]. This selective stimulation of VEGF by gp130 ligands is obviously reflected by a distinct receptor expression pattern as the OSM receptor is abundantly expressed on isolated human cardiomyocytes, whereas the IL-6 receptor and LIF receptor show a more sparse distribution [159]. As OSM is produced by activated T lymphocytes, monocytes and neutrophils [41], it might play a crucial role in the revascularization following myocardial ischemia and inflammation.

Recent studies revealed that OSM induces the release of the potent neutrophil chemoattractants CXCL1 (KC chemokine) and CXCL5 (LIX) in murine cardiac fibroblasts dependent on the activation of JAK/STAT, MAPK and PI3K signaling pathways [82]. OSM also increases the production of tissue inhibitor of metalloproteinases 1 (TIMP-1) and plasminogen activator inhibitor 1 (PAI-1) in human cardiomyocytes and fibroblasts, possibly via an ERK1/2 and p38 MAPK-dependent pathway. Thereby OSM exerts direct inhibitory effects on matrix metalloproteinases and the protease urokinase-type PA (u-PA), which in turn are essential for matrix degradation and extracellular proteolysis [158]. As OSM additionally protects fibroblasts from apoptosis and stimulates their proliferation, partly dependent on MAPK [62], as well as extracellular matrix/collagen production in vivo, one can conclude that it has rather profibrotic properties [9, 125]. The fibrogenic activity suggests that OSM functions downstream of inflammation in the tissue repair cascade and induces the fibro-proliferative phase in postischemic repair processes. Interestingly, unlike other IL-6 type cytokines, OSM specifically binds to collagen types I, III, IV, and VI, thereby regulating its own bioavailability at sites of tissue repair [130]. Obviously OSM also seems to exert protective effects on cardiomyocytes and has been postulated to be one of the cardioactive paracrine factors of transplanted embryonic stem cell-derived cardiomyocytes and myoblasts that promote survival of surrounding myocardium (Table 1) [27].

Regarding the effects described above, OSM conceivably plays a role in the modulation of postischemic inflammation in the heart as well as in cardiac remodeling, angiogenesis and repair processes after myocardial ischemia (Table 1) [43].

Ciliary neurotrophic factor and its potential role in the heart

CNTF was initially isolated and purified from bovine cardiac tissue and described as a neurotrophic factor that promotes the survival of cholinergic parasympathetic ciliary neurons [157].

The expression and regulation of CNTF in cardiovascular physiology as well as its possible implications in the pathophysiology of cardiac hypertrophy and heart failure are largely unknown. Furthermore, CNTF has not been recognized to have cardiac activity so far. Therefore, the relevance and the character of this cytokine of the IL-6 type family in cardiac survival pathways are still obscure. However, it emerged that CNTF gene expression is upregulated in viable left ventricular myocardium at a late time point (6 weeks) during postischemic heart failure in rats [144], whereas previous data revealed that there is no upregulation of myocardial CNTF during pressure overload [108]. This suggests a possible role for CNTF especially in postischemic remodeling processes and the transition to heart failure, albeit it is unclear whether CNTF plays a causal role, is part of a compensatory mechanism, or solely constitutes an epiphenomenon.

Interestingly, it was recently reported that CNTF receptors are present on the sarcolemma of murine cardiomyocytes. Furthermore, administration of CNTF to leptin-deficient mice reduced obesity-associated cardiac hypertrophy (Table 1) and, along with leptin, activated the STAT3 and ERK1/2 pathway in leptin-deficient and leptin-resistant cultured murine cardiomyocytes [117]. Therefore, CNTF might act in parallel to leptin in the hypothalamus, and this previously unknown negative feedback loop in obesity-associated cardiac hypertrophy might have therapeutic implications for patients with obesity-related cardiovascular disease and other causes of LVH.

Interleukin-11 and its potential role in the heart

It has been shown that human cardiac cells are able to secrete IL-11 in vitro [1]. The physiological relevance of IL-11 in cardiac physiology is still unknown; indeed, hardly any data exist concerning the regulation of IL-11 expression in the heart and its implications in cardiac hypertrophy and failure.

Employed as an adjuvant therapy to alleviate side effects of chemotherapy, IL-11 has been associated with increased frequency of atrial flutter/fibrillation in elderly patients (Table 1) [164]. Administration of IL-11 reproduced this effect in experiments with old rats and revealed reduced atrial refractoriness and increased atrial dimensions in treated animals [164]. This age-dependent atrial remodeling was ascribed to increased sodium retention as the effects of IL-11 could be reversed by sodium-restricted diet [164]. Further effects of IL-11 on the heart remain to be elucidated, especially whether IL-11-dependent mechanisms also affect the ventricle and which intracellular signaling pathways might be involved in its effects.

Cardiac gp130 receptor signaling is essential throughout life

The heart is among the first organs formed during development. Embryos homozygous deficient for gp130 die between 12.5 days postcoitum and term [172]. Besides other defects, gp130 knockout embryos display hypoplastic ventricular myocardium without septal and trabecular defects. The subcellular ultrastructures in gp130 knockout cardiomyocytes appear normal. Furthermore, the gp130 ligands LIF and CT-1 can be detected in the heart tube. Both cytokines are known to promote cardiomyocyte survival and induce cardiomyocyte growth [128]. These data suggest an essential role of the gp130 receptor system for embryonic and fetal cardiomyocyte survival and growth.

In order to circumvent embryonic and fetal lethality mice with conditional knockouts or cell-type restricted over-expression of specific genes have been used to study the role of gp130 in adult organs. In this regard, heart specific over-expression or knockout is achieved by driving the gene of interest under a cardiomyocyte specific promoter such as the alpha-myosin heavy chain (α-MHC) or the myosin light chain 2 (mlc-2v) promoter.

Despite a slightly increased activation state of downstream signaling molecules STAT3 and ERK1/2 mice with cardiomyocyte specific over-expression 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 [143]. Mice lacking the gp130 receptor in cardiomyocytes (gp130-CKO) are not different from wildtypes at younger age (up to 6 months) [56]. We studied the role of gp130 in the heart of older gp130-CKO mice (up to 12 months). Similar to Hirota et al. [56] our investigations revealed that gp130-CKO mice (αMHC-Cre$^{tg/-}$; gp130$^{flox/flox}$: gp130-CKO) do not develop cardiac dysfunction or increased mortality in the first 6 months of age (Fig. 2). However, beyond the age of 8 months we observed increased mortality in gp130-CKO mice (Fig. 2). Postnatal growth, exercise or infections are distinct forms of stress that the adult heart endures throughout life. It has been demonstrated that regular exercise exerts protection against inflammatory myocardial reactions and is associated with elevated levels of anti-inflammatory cytokines such as IL-6 [111]. In this setting a protective role of IL-6-gp130 signaling to suppress oxidative stress and the production of pro-inflammatory cytokines, i. e. tumor necrosis factor alpha

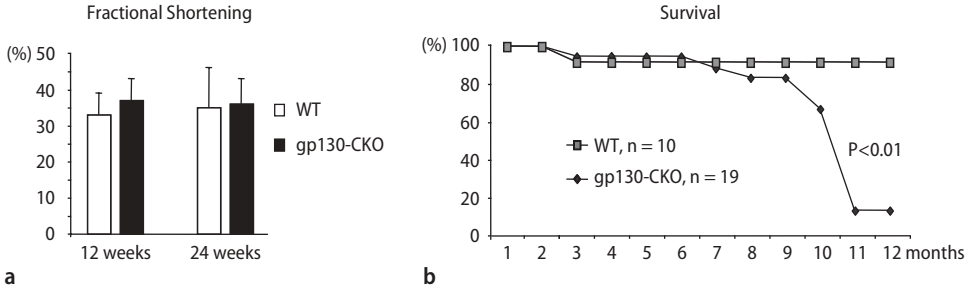

Fig. 2 gp130-KO (αMHC-Cre$^{tg/-}$; gp130$^{flox/flox}$) were generated by breeding gp130-floxed mice [16] with mice expressing the Cre-recombinase under the α-MHC-promoter ((αMHC-Cre$^{tg/-}$) [41]. Male gp130-KO and wildtype siblings (WT: gp130$^{flox/flox}$) were kept under standard conditions for 12 months. **A** Shows fractional shortening (%FS) measured by echocardiography in WT and gp130-KO males at 12 and 24 weeks of age (n = 5 to 6 mice per genotype and time point). **B** Kaplan-Meier curves depicting long-term survival of WT (n = 10) and gp130-KO male mice (n = 19) ($P < 0.01$ by log-rank test)

(TNFα) has been hypothesized [111]. In addition, exercise-induced production and release of IL-6 from myofibers may contribute to abrogate an atherogenic lipid profile, which is often associated with chronic cardiac diseases [111]. However, there is little information so far how gp130 signaling protects the heart from so called "physiological" forms of stress.

Nevertheless, the premature death of gp130-CKO mice suggests 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 to be required for cardiac protection in aging mice.

Gp130 receptor signaling is indispensable for cardioprotection against pathophysiological stress

In the myocardium, activation of gp130 signaling and release of IL-6 type cytokines (e. g. IL-6, LIF and CT-1) occurs within minutes after infarction or ischemia/reperfusion and levels remain elevated up to 7 days post infarction [104].

The pathophysiological relevance of gp130 signaling pathways in the development of heart failure was clearly demonstrated by means of different genetic approaches such as a mouse model with cardiomyocyte-specific deletion of gp130 [56]. While presenting with normal cardiac function and structure under basal conditions, these mice are strikingly less resistant to acute pressure overload induced by thoracic aortic constriction (TAC) in which they display rapid onset of cardiac dysfunction in the framework of dilated cardiomyopathy and massive induction of cardiomyocyte apoptosis compared to control mice that exhibit compensatory hypertrophy [56]. Comparably, transgenic overexpression of a dominant negative form of the gp130 receptor results in attenuation of TAC induced cardiac hypertrophy and reduction of concomitant STAT3 activation [150]. Opposite to gp130 deficiency, continuous activation of gp130 in the heart, achieved by combined overexpression of both IL-6 and the IL-6 receptor, leads to ventricular hypertrophy [58]. These experimental data clearly demonstrate that gp130 receptor signaling is required for compensatory hypertrophy and cardioprotection during episodes of pressure overload.

Activation of JAK/STAT signaling: Beneficial or detrimental for the heart?

Representing the major downstream signaling axis of the gp130 receptor, the JAK/STAT pathway is also activated under various stress conditions such as pressure overload, hypoxia and in acute myocardial infarction [9, 38, 46]. In that, the JAK/STAT signaling pathway seems to hold an important role in the promotion of cardiomyocyte survival and adaptive hypertrophy downstream of gp130. For instance, the importance of the JAK2/STAT3 signaling axis for compensatory left ventricular remodeling is illustrated by the fact that pharmacological inhibition of JAK2 is sufficient to block the development of concentric hypertrophy during pressure overload [10]. Gp130-mediated STAT3 activation also seems to play a major role in preservation of cell survival during virally conditioned myocardial inflammation as both SOCS-3 transgenic mice and cardiac-specific gp130-knockout mice show an increase in susceptibility to viral infection of cardiomyocytes [165].

However, it has also been reported that the JAK/STAT-axis is involved in unfavorable changes after infarction, such as alteration of gene activity that may underlie early diastolic dysfunction (i.e. 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 [29]. This specific gene activation pattern of post-infarction remodeling might reflect a linkage of the JAK/STAT pathway with the Ang II autocrine loop as a strong binding activity of STAT proteins to the angiotensinogen gene promoter could be ob-

served in post-infarction non-ischemic myocardium. Moreover, JAK2 was also described to constitute a coordinating point in relaying Ang II and hypoxia/reoxygenation-triggered signals leading to enhanced susceptibility of cardiomyocytes to apoptotic cell death by upregulation of Bax protein and an increase in Caspase-1 and Caspase-3 activity.

Though JAK2 simultaneously initiates the phosphorylation of cardioprotective pathway components such as S6 ribosomal protein and HSP27, the overall effect of JAK2 activation after myocardial infarction was found to be proapoptotic [90]. In myocardial tissue, however, it is difficult to distinguish which receptor system is responsible for the activation of JAK/STAT signaling and the time and degree of activation as well as the cell types may matter. In this case, a mutation on the gp130 receptor abrogating specifically JAK/STAT activation will provide more insights about the precise role of gp130-JAK/STAT signaling in the pathophysiology of the heart.

STAT3, a master gene of cardioprotection in almost every situation

Mice with a systemic knockout of STAT3 die at E6.5–7.5 [135] prior to heart formation. Experimental studies with embryonic stem cells, however, revealed an important role of STAT3 for initial stages of cardiomyogenesis [33].

Similar to gp130-KO mice, mice with a cardiomyocyte-specific knockout of STAT3 (αMHC-Cre$^{tg/-}$; STAT3$^{flox/flox}$: STAT3-CKO) do not develop gross cardiac abnormalities concerning function and hypertrophy at young age [51, 64]. However, already young STAT3-KO mice (at 3 months of age) display small morphological changes including a modest increase in interstitial fibrosis and a decrease in myocardial capillary density [51]. Moreover, adult STAT3-CKO mice display increased expression of genes well known to inhibit angiogenesis and/or alter ECM composition (reviewed by Hilfiker-Kleiner et al. [53]). In line with a pro-angiogenic role of STAT3 mice with cardiomyocyte-specific overexpression of STAT3 (α-MHC-STAT3^{tg}) present increased capillary density accompanied by enhanced expression of the pro-angiogenic factors VEGF and VE-cadherin [107]. In addition, these mice develop a concentric hypertrophy with preserved cardiac function [107]. Apart from its role in processes regulating cardiac vasculature, growth and ECM homeostasis, there are evidences that STAT3 is required for protection of the heart from infections since STAT3-CKO mice exhibit an increased susceptibility to bacterial infection [64]. Ultimately, the lack of cardiomyocyte STAT3 leads to age related severe heart failure and death [51, 64].

We recently showed that STAT3 is activated in the normal heart during pregnancy and in the early postpartum phase [52]. We reported that pregnancy-induced hypertrophy, the proportional growth of the cardiac vasculature and cardiac function were normal in STAT3-KO females suggesting that STAT3 is not essential in physiological adaptive processes in the heart during pregnancy [52]. However, we showed that STAT3-CKO mice develop a postpartum cardiomyopathy [52]. Hereby we unraveled a mechanism in which cardiomyocyte activity of STAT3 is essential to protect the maternal heart from postpartum oxidative stress and the subsequent cleavage of prolactin into a pro-apoptotic and anti-angiogenic subform which ultimately results in postpartum heart failure [52].

Numerous studies in STAT3-CKO mice confirm that cardiomyocyte STAT3 protein provides protection in response to a wide array of pathophysiological stresses. In this regard, STAT3 is necessary for cardioprotective effects such as preservation of left ventricular functional reserve and perfused capillary density, reduced apoptotic cell death and limited infarct size induced by ischemic preconditioning and various pharmacological preconditioning programs [129]. It is important to mention that STAT proteins play an important role not only for late preconditioning by transcriptionally upregulating cytoprotective genes [106], but also (especially STAT3 and STAT5) for early protective effects of preconditioning which apparently do not involve protein synthesis [167]. A strong protective effect in conditions involving ischemia is further supported by the enhanced susceptibility of STAT3-CKO mice to myocardial ischemia/reperfusion injury and infarction [51]. In this setting, STAT3 deficiency causes enhanced cardiomyocyte apoptosis, increased infarct size, and reduced cardiac function and survival [51]. Likewise, the uniform reaction of the STAT3-CKO heart to doxorubicin treatment and endotoxin (lipopolysaccharide)-induced myocardial inflammation consists in a marked fibrosis and increased cardiomyocyte apoptosis compared to wildtype counterparts [64]. Vice versa, cardiac-specific over-expression of STAT3 attenuates doxorubicin-induced cardiomyocyte apoptosis and subsequent congestive heart failure, indicating that STAT3 can protect the heart from cardiotoxic agents [40]. Furthermore, it was recently reported that the activation of STAT3 by G-CSF delivery in a hamster model of dilated cardiomyopathy is jointly responsible for improved survival, cardiac function and remodeling in these animals via a reduction in autophagy, an increase in cardiomyocyte size, and a reduction in myocardial fibrosis [95].

Thus, the inactivation of STAT3, by deletion of STAT3 itself or resulting from the loss of gp130 mediated activation, appears to be a key event in the diminuation of cardioprotection in response to numerous physiological and pathophysiological stress situations of the heart throughout life.

Table 2 Abbreviations

Abbreviation	Definition
α-MHC	Myosin heavy chain, alpha
AMI	Acute myocardial infarction
ANF	Atrial natriuretic factor
Ang II	Angiotensin type II
Bad	Bcl-associated death promoter
Bax	Bcl2-associated X protein
Bcl-2	B-cell CLL/lymphoma 2
β-MHC	Myosin heavy chain, beta
bFGF	Basic fibroblast growth factor
c-fos	Homologous to Finkel-Biskis-Jinkins (FBJ) murine osteosarcoma virus oncogene
CIS	Cytokine-inducible SH2 protein
(C)KO	(Cardiomyocyte-specific) knockout
CLC	Cardiotrophin-like cytokine
CNTF	Ciliary neurotrophic factor
COX-2	Cyclooxygenase type II
Cre	cyclization recombinase
CT-1	Cardiotrophin-1
CXCL1/5	Chemokine, CXC motif, ligand 1/5
ECM	Extracellular matrix
ERK	Extracellular signal-regulated kinase
Gab1	GRB2-associated binding protein 1
G-CSF	Granulocyte colony stimulating factor
(s)gp130	(soluble) Glycoprotein 130
HSP	Heat shock protein
I/R	ischemia/reperfusion
IL-11	Interleukin-11
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
iNOS	Inducible Nitric oxide synthase
JAK	Janus kinase
JNK	c-Jun N-terminal protein kinase
Kv4.2	potassium voltage-gated channel, Shal-related family, member 2
LIF	Leukemia inhibitory factor
LIFR, OSMR	LIF, OSM receptor
LPS	Lipopolysaccharide
LV	Left ventricle, left ventricular
LVH	Left-ventricular hypertrophy
MAPK	Mitogen-activated protein kinase
MAPKK	MAPK kinase
MCP-1	Monocyte chemoattractant protein 1
MEK	MAPK/ERK kinase
MMP	Matrix metalloproteinase
MnSOD	Manganese superoxide dismutase
NE	Norepinephrine
NF-κB	Nuclear factor kappa B
OSM	Oncostatin M
PAI-1	Plasminogen activator inhibitor 1
PI3K	Phosphatidylinositol-3 kinase
PIAS-1/3	Protein inhibitors of activated STAT1/3
PKB	Protein kinase B
PTP(RT)	Protein tyrosine phosphatase (receptor T)
RAS	renin-angiotensin system
ROS	Reactive oxygen species
RSK	Ribosomal protein S6 kinase
SERCA2	Sarcoplasmic reticulum Ca^{2+} ATPase
SHP-1/2	Src-homology tyrosine phosphatase 1/2
sIL-6R	soluble Interleukin-6 receptor
SOCS-1/3	Suppressor of cytokine signaling 1/3
STAT	Signal transducer and activator of transcription
TAC	thoracic aortic constriction
TIMP-1	Tissue inhibitor of metalloproteinases 1
TNFα	Tumor necrosis factor alpha
Tyk1/2	Tyrosine kinase 1/2
VEGF	Vascular endothelial growth factor

SOCS proteins, endogenous negative regulators of gp130-STAT signaling in the heart

It has been reported that SOCS3, a negative regulator of gp130-JAK/STAT signaling, shows biphasic induction in response to pressure overload in the myocardium and directly modulates stress-induced gp130 cytokine receptor signaling as the key molecular switch for a negative feedback circuit for both cardiomyocyte compensatory hypertrophy and survival [168]. SOCS proteins are also upregulated after myocardial ischemia, but little is known about their role in cardioprotection and remodeling after myocardial infarction.

One report emphasizes a positive role of SOCS3 in prevention of early post-ischemic myocardial dysfunction by modulating TNFα induced IL-6-gp130-STAT3 activity. This report shows that deficiency of TNFα receptor-1 prevented TNFα mediated cardiac dysfunction and was associated with reduced IL-6 levels, attenuated STAT3 phosphorylation and upregulated SOCS3 [156]. An early protective role of SOCS proteins in attenuated IL-6-STAT3 signaling was supported by the observation that early infarct size (determined 3 h post infarction) was smaller in IL-6 knockout mice; however, this difference was not present 24 h after myocardial infarction [37]. Furthermore, CT-1 mediated protection of the murine heart against LPS induced left ventricular dysfunction and dilation was in part ascribed to the activation of SOCS1 [139].

A rather detrimental role of SOCS proteins has emerged in myocarditis models. Gp130-mediated stimulation of cardiomyocytes has a cytoprotective effect against virus infection in culture that can be attenuated by SOCS3. Moreover, despite an intact IFN-mediated antiviral response transgenic mice with cardiomyocyte specific over-expression of SOCS3 display a marked increase in susceptibility to viral infection [165]. Similarly cardiomyocyte specific transgenic expression of SOCS1 inhibits enterovirus-induced signaling of JAK/STAT, with accompanying increase in viral replication, cardiomyopathy, and mortality in coxsackie virus-infected mice [170]. Thus, gp130-JAK/STAT signaling appears to play an important role in preserving adult cardiomyocytes until specific immune responses begin to clear the virus.

Taken together, SOCS proteins seem to be important in the pathophysiology of the heart and a better understanding of their role in cardiac diseases of different etiologies is required.

Conclusions

The IL-6-gp130-JAK/STAT pathway plays an important role in adaptation and maladaption of the heart in response to multiple forms of physiological and pathophysiological stress, supporting the view that this receptor system is a key modulator in the transition of cardiac hypertrophy to heart failure [37, 38, 56, 77, 107].

The major task of future research in the gp130 system is to discover the pathways that promote adaptive hypertrophy, maintain physiological cardiomyocyte function and protect cardiomyocytes from detrimental influences such as hypoxia. In addition, these pathways will have to prove beneficial for extra cellular matrix remodeling, cardiac angiogenesis and wound healing. The challenge is to distinguish these important pathways from the multitude of activated extra- and intracellular signaling cascades that in many cases might solely represent epiphenomena and to understand their timely regulation. In this regard, better understanding of the individual function of IL-6 cytokines in different forms of cardiac stress is indispensable with the aim that these factors might not only serve as biomarkers but may eventually become valuable therapeutic targets.

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Declaration We confirm that all animal studies performed in our lab were in compliance with the *Guide for the Care and Use of Laboratory Animals* as published by the US National Institutes of Health and were approved by the local animal care committees.

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ERRATUM

When we published this article in our July edition of this journal [Basic Res Cardiol 102(4):279–297 (2007)], the references within the text were mixed up by a technical error, so that the coherence between text and reference list was destroyed.

Therefore, this article is corrected and republished [Basic Res Cardiol 102(5):393–411 (2007)].

The publisher apologises for any inconvenience caused by this mistake.