REVIEW ARTICLE

LIF and the heart: *Just Another Brick in the Wall?* *

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ABSTRACT. Multiple studies have shown that the cytokine leukemia inhibitory factor (LIF) is protective of the myocardium in the acute stress of ischemia-reperfusion. All three major intracellular signaling pathways that are activated by LIF in cardiac myocytes have been linked to actions that protect against oxidative stress and cell death, either at the level of the mitochondrion or via nuclear transcription. In addition, LIF has been shown to contribute to post-myocardial infarction cardiac repair and regeneration, by stimulating the homing of bone marrow-derived cardiac progenitors to the injured myocardium, the differentiation of resident cardiac stem cells into endothelial cells, and neovascularization. Whether LIF offers protection to the heart under chronic stress such as hypertension-induced cardiac remodeling and heart failure is not known. However, mice with cardiac myocyte restricted knockout of STAT3, a principal transcription factor activated by LIF, develop heart failure with age, and cardiac STAT3 levels are reported to be decreased in heart failure patients. In addition, endogenously produced LIF has been implicated in the cholinergic transdiffrentiation that may serve to attenuate sympathetic overdrive in heart failure and in the peri-infarct region of the heart after myocardial infarction. Surprisingly, therapeutic strategies to exploit the beneficial actions of LIF on the injured myocardium have received scant attention. Nor is it established whether the purported so-called adverse effects of LIF observed in isolated cardiac myocytes have physiological relevance *in vivo*. Here we present an overview of the actions of LIF in the heart with the goal of stimulating further research into the translational potential of this pleiotropic cytokine.

Key words: cytokine, cardiac remodeling, heart failure, cholinergic transdifferentiation, GP130, JAK STAT signaling

Leukemia inhibitory factor (LIF) was so named based on the ability of this cytokine to inhibit differentiation of M1 leukemic myeloid cells into macrophages [1, 2]. However, the name is unfortunate given the pleiotropic nature of LIF. Over the last four-plus decades, multiple studies have shown that LIF may either stimulate proliferation or induce differentiation depending upon the cell type or its stage of development, and have highlighted the impact that this cytokine has on a wide range of cell types. The importance of LIF stretches from early embryonic life where it is crucial for blastocyst implantation, as well as embryonic stem (ES) cell self-renewal and differentiation, to adult animals were LIF exerts critical effects on skeletal muscle, vessels, bone, neurons, as well as the endocrine, reproductive, and immune systems [1, 3]. LIF is a critical modulator of tissue repair, inflammation, and skeletal muscle regeneration, as well as cachexia, and influences both physiological and pathological (notably certain cancers) processes. Here we focus exclusively on the impact that LIF has on the stressed or injured myocardium. The reader is referred to several recent excellent reviews for further information on the broad range of actions LIF has in other physiological and pathological contexts [1-6].

LIF is one of the IL-6 family cytokines that belong to the long-chain four-helix bundle cytokine superfamily and signal, at least, in part through the transmembrane protein gp130 [1, 2, 6, 7]. LIF signals through a heterodimer of gp130 with a related protein, the LIF receptor (LIFR). There are several forms of LIF [2], but the best studied is a secreted and variably glycosylated protein (34-63 kDa) possessing the ability to induce a wide range of paracrine and autocrine effects that can be contradictory depending upon the cell type and context, such as proliferation and survival *versus* differentiation and apoptosis. This pluripotency in function may be due, in part, to the integration of the different signaling pathways that can be induced once LIF is combined with its receptor gp130-LIFR. A particular signaling pathway may be dominant when LIF acts on a certain cell type, but less prominent in a different cell type. Another potential explanation is the differential ability of LIF-activated transcription factors, such as STAT3 and STAT1, to access different promoters in different cell types depending on chromatin organization [1]. Beginning in the early 1990s, the role of LIF in the heart has been explored. In this review, we discuss the reparative role that LIF has in the wounded heart and strategies that may be used to exploit that role.

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LIF SIGNALING IN THE HEART: THE WALL OF PROTECTION

Signaling events

LIF is a member of the IL-6 cytokine family that signals through a shared gp130 receptor and thus produces overlapping but distinctive biological actions from the other family members. For LIF, signal induction occurs when this cytokine binds LIFR and evokes its dimerization with gp130 [7]. Several studies have implicated the downstream signaling events in the formation of a "wall of protection" against acute stress in cardiac myocytes. In 1996, Kunisada *et al*. demonstrated that LIF activates JAK-STAT and MAPK pathways in both *in vitro* and *in vivo* studies of cardiac myocytes [8]. In subsequent studies, the phosphoinositide 3-kinase (PI3K)/AKT emerged as another protective signaling pathway downstream of gp130-LIFR

[9-14]. Each of these pathways exerts its own way of ensuring cardiac myocyte protection, and together increases the likelihood of cardiac myocyte survival and endurance. Divergence of LIF signaling is basically attributed to the presence of two motifs (YXXQ and YXXV) on the intracellular regions of both gp130 and LIFR that allow for recruitment and activation of different molecules [7]. These binding motifs are phosphorylated by the JAK tyrosine kinases that are constitutively associated with the receptors and activated by transautophosphorylation that occurs upon gp130-LIFR dimerization [7] (*figure 1*).

LIFR and gp130 have three and four YXXQ motifs, respectively, that serve as docking sites to recruit STAT3 or, in the case of the more membrane-distal sites, both STAT3 and STAT1 via interaction with their SH2 domains [7, 16]. These transcription factors are, in turn, phosphorylated by the associated JAKs on a specific tyrosine residue that
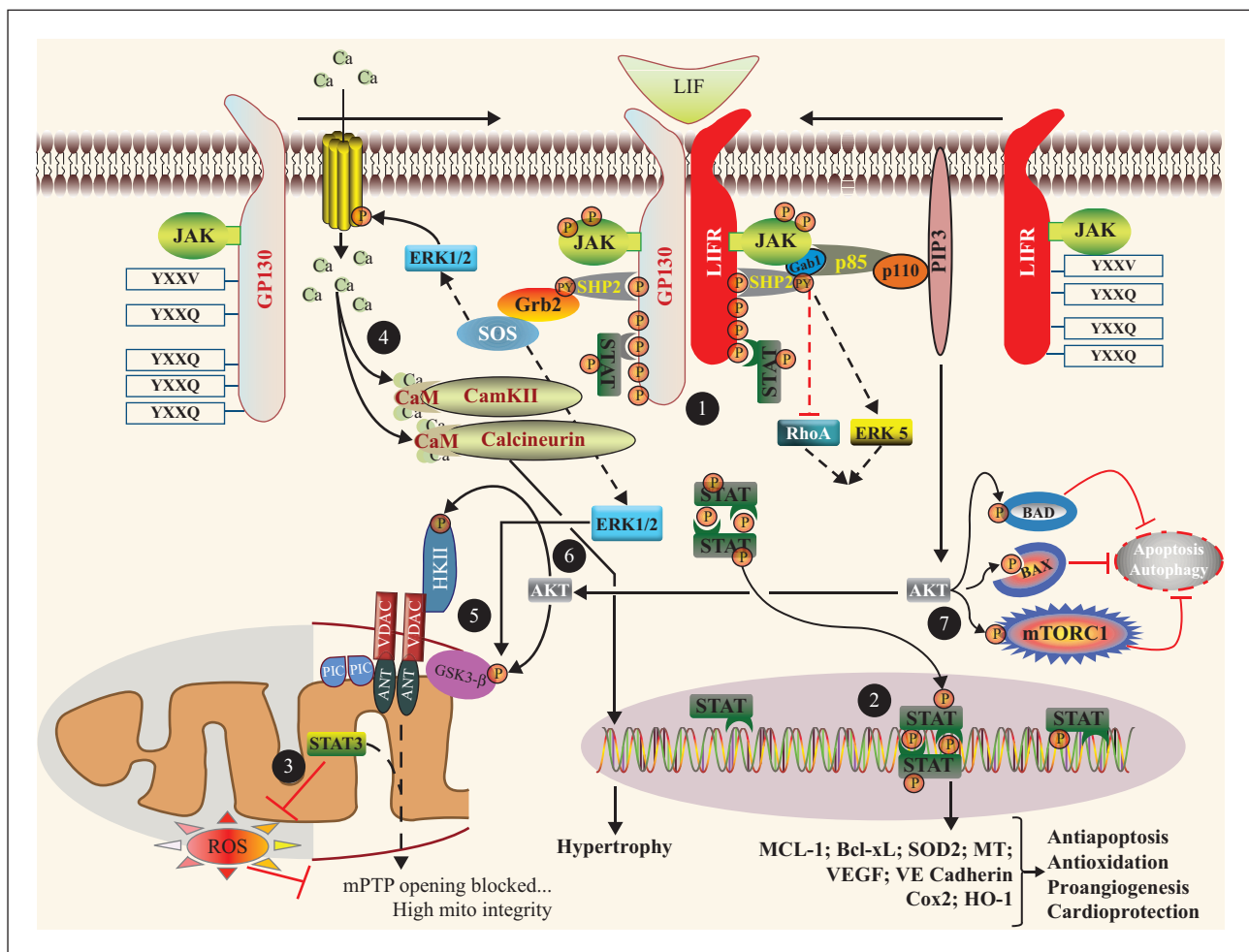

Figure 1

LIF evokes both genomic and nongenomic events to protect cardiac myocytes. **(1)** LIF induces dimerization of gp130 and LIFR, which in turn activates the associated JAK tyrosine kinases. The JAKs phosphorylate recruitment sites for STAT1 and STAT3 (YXXQ), and a scaffold protein SHP2 (YXXV) linked to ERK1/2, ERK5, and PI3K/AKT activation. Each of these signaling pathways is linked to cellular protection and/or cell growth. **(2)** STAT3 (and to a lesser extent STAT1) induces expression of anti-apoptotic, anti-oxidative stress, and pro-angiogenic genes (e.g., metallothioneins (MT); MCL-1; Bcl-xL; SOD2; VEGF; VE Cadherin; Cox2; HO-1). **(3)** Evidence for a nongenomic role for STAT3 in optimizing mitochondrial respiration and limiting ROS formation has recently been described. **(4)** ERK1/2 couples to cell growth via an impact on transcription factors (not shown) and intracellular increases in Ca^{2+}. The latter activates calmodulin (CaM) and the serine/threonine phosphatase calcineurin, which in turn activates gene transcription (via NFAT) or derepresses pathological cardiac gene expression via Ca^{2+}/calmodulin-dependent protein kinases II (CamKII). **(5)** ERK1/2 has protective effects on mitochondria via phosphorylation and inhibition of GSK3-β, which prevents opening of the mitochondrial permeability transition pore (mPTP). The exact identity of the mPTP is not known, but involves a voltage-dependent anion channel (VDAC), mitochondrial phosphate carrier (PIC), and adenine nucleotide translocase (ANT). **(6)** The phosphoinositide 3-kinase-Akt signaling network also inhibits opening of the mPTP via GSK3-β or mitochondrial hexokinase II (HKII) phosphorylation. **(7)** AKT inhibits apoptosis and autophagy via phosphorylation of mTOR complex 1 (mTORC1), BAD, and BAX. AKT activation is linked to protective gene expression as well. See text and References 7 and 15 for additional details.

induces formation of parallel STAT dimers. In the canonical scheme, the dimers translocate to the nucleus and bind specific promoter elements to induce gene transcription [17-23]. Both STAT3 and STAT1 are phosphorylated as well in response to LIF, on a specific serine residue within their C-terminal transactivation domain (TAD), which serves to further enhance transcriptional activity at least in part by aiding the recruitment of the cofactor p300 [17]. For both STAT3 and STAT1 there is evidence, in non-cardiac cells, that serine phosphorylation alone is linked to increased gene expression, perhaps even a profile of genes distinct from those activated by the canonical pathway [24, 25].

Once phosphorylated, YXXV becomes a docking site for SHP2. On one hand, SHP2 serves as a scaffold protein after being tyrosine phosphorylated by the JAKs, and on the other hand contributes to gp130-LIFR signaling termination as a result of its phosphatase activity [26-29]. In the former capacity, SHP2 interacts with Gab1 (Grb2-associated binder-1) or Grb2 (growth factor receptor bound protein 2), which triggers signaling cascades leading to different types of ERK (ERK1/2 and ERK5) activation that are also involved in cellular protection (*figure 1*) [30-35]. The last identified major pathway activated by LIF is PI3K/AKT. Details of its activation have not been defined with great clarity, which is not surprising since this pathway is activated by various types of agonists and receptors, either directly or via cross-talk with other signaling pathways. Oh *et al.* showed that PI3K is activated by direct interaction with JAK1 post-LIF stimulation [9]. Others have reported that this interaction is part of a larger, multi-protein complex centered on Gab1 recruitment to SHP2 and linking JAK1, STAT3, Gab1, and SHP2 to the regulatory subunit of PI3K, p85. Downstream of PI3K, AKT activation sets in motion a diversity of events important in maintaining cellular homeostasis and survival [7].

Evidence that LIF is cardioprotective

Both the MAPK/ERK1/2 and PI3K/AKT pathways that are activated by LIF are associated with short-term protection of cardiac myocytes against acute ischemia/reperfusion (I/R) injury, which does not require gene transcription [33]. This has been ascribed to inhibition of opening of the mitochondrial permeability transition pore (mPTP) in response to increases in intracellular Ca^{2+} and reactive oxygen species (ROS), mainly by phosphorylating two targets on the mitochondrial outer membrane, hexokinase II (HKII) and glycogen synthase kinase 3 β (GSK3-β) (*figure 1*) [11, 13, 31, 32]. This inhibition allows the cell to cope better with oxidative stress and prevents cell death via apoptosis or necrosis. In addition, AKT increases the phosphorylated-to-total protein ratios of BAD and BAX, as well as Bcl-2 levels and mTORC1 activity promoting anti-apoptotic and anti-autophagic actions that support cell survival. Interestingly, evidence has emerged that STAT3 and AKT constitute a mutual transactivation circuit in cardiac myocytes [36].

Two STATs (STAT1 and STAT3) dominate LIF signaling in the heart. These STATs form homodimers or heterodimers with each other [19]. Overall, evidence has linked STAT3 – in some instances activated by LIF – to protection of cardiac myocytes via the upregulation of anti-apoptotic

(Bcl-xL and MCL-1 [37, 38]), antioxidant (MnSOD and metallothioneins; 39-41], pro-angiogenic (VEGF and VE cadherin [40, 42]), and cardioprotective (Cox2 and HO-1) proteins [38]. In a few instances, STAT1 has been implicated in the upregulation of some of these proteins as well; although, overall evidence has linked STAT1 (independent of LIF) to induction of a pro-apoptotic gene expression profile in cardiac myocytes [43].

In addition to the delayed transcriptional effects, recent studies have revealed an important non-transcriptional, short-term role of STAT3 in mitochondria. The presence of STAT3 seems to be responsible somehow for full activity of complexes I and II thus modulating the electron transport chain and limiting excessive ROS production in response to injury [44, 45]. These interesting observations are poorly understood and are currently under investigation.

The protective effects of LIF on cardiac myocytes have been best studied in response to acute cardiac insults generated by I/R. Nelson *et al.* examined the impact of LIF on acute ischemic injury in rabbit hearts and showed a significant increase in percentage recovery with LIF-pretreatment that correlated with an increase in myocardial MnSOD, a powerful ROS scavenger [41]. Sun *et al.* showed that the flavonoid compound luteolin exerts a pro-survival and anti-inflammatory effect, and promotes recovery following I/R injuring in diabetic rats, mainly by up-regulating cytokines such as LIF [46]. A similar conclusion was made by Miyamoto *et al.* who tested the direct effect of LIF on neonatal rat ventricular cardiac myocytes exposed to oxidative stress [13]. It is worth mentioning that many studies emphasized the importance of PI3K/AKT, as a cardioprotective signaling pathway downstream of LIF activation [10, 47, 48].

LIF would seem to have other beneficial actions on other cell types that are reparative in the infarcted myocardium. In the mouse infarcted myocardium, LIF was shown to contribute to homing of bone marrow-derived cardiac progenitors, as well as differentiation of resident cardiac stem cells into endothelial cells [49-52]. Increased circulating LIF in a mouse MI model not only protected against cardiac myocyte death, but enhanced neovascularization, and enticed bone marrow cells to the heart and their differentiation into cardiac myocytes [47].

Based on the signaling pathways activated by LIF, we can deduce why this cytokine promotes cardioprotection and ensures cellular stability in both acute and, likely, chronic stress. Evidence suggests that these pathways are involved in the launch of the adaptive compensatory mechanism to maintain normal cardiac output in response to hypertension, which is overviewed in the following paragraph. Identifying the potential targets that undermine delivery of this cardioprotective program, and under which conditions, has not yet been achieved, but promises great therapeutic potential. A summary of diverse studies demonstrating the protective effects of LIF on cardiac myocytes is provided in *table 1*.

LIF ON DUTY: A BIGGER HEART WHEN NEEDED?

Adaptive cardiac remodeling in response to pressure overload is a normal compensatory mechanism acquired by the heart in early phases of remodeling in order to

Table 1
Evidence that LIF is protective of cardiac myocytes

Action	Model	Signaling Pathway
LIF enhanced BMP2-induced signaling and bcl-xL expression in DOX-injured cells [53].	NRVM	ERK1/2
LIF improved survival of cardiac myocytes, enhanced recruitment of BMC and their differentiation to cardiac myocytes, and induced neovascularization [47].	*In vivo* mouse MI	ND
LIF protected against peroxide-induced mitochondrial depolarization [13].	NRVM	AKT-induced HKII phosphorylation
In vivo treatment with LIF protected against ischemia/reperfusion contractile dysfunction and injury [41].	Isolated perfused rabbit heart	Attributed to increase in SOD2
PHLPP-1 knockdown enhanced LIF cardioprotection [11].	NRVM and isolated mouse heart	Increased AKT activation and mitochondrial HKII
LIF induced Bcl-xL and protected against serum starvation-induced cell death [37].	NRVM	STAT1
LIF protected against hypoxia/reoxygenation-induced death via SOD2 upregulation [39].	NRVM	STAT3
LIF protected against DOX-induced apoptosis [10].	NRVM	AKT-induced BAD phosphorylation and reduction of caspase-9 activity

BMC, bone marrow cells; DOX, doxorubicin; HKII, hexokinase II; NRVM, neonatal rat ventricular myocytes; ND, not determined; PHLPP-1, PH domain leucine-rich repeat protein phosphatase-1.

maintain normal cardiac performance. The importance of this cardioprotective reversible phase drove scientists to understand better the underlying signaling pathways in order to find pharmacological targets that regulate this phase as well as to prevent progression into maladaptive remodeling leading to heart failure. We named this phase the "window of opportunity" (WOP; *figure 2*). WOP is characterized by cardiac hypertrophy, whereby the individual cardiac myocytes increase in size to accommodate the increased ventricular wall stress associated with hypertension. Others have termed the cardiac hypertrophy that occurs in this situation maladaptive as it is accompanied by a re-expression of fetal genes and is not well controlled or in harmony with other remodeling changes occurring in the heart at the same time [54, 55]. Hypertension-induced cardiac hypertrophy is also associated with a diminution in the contractile ability of heart (due to changes both within and outside the cardiac myocyte) that may eventually prove detrimental to heart function. This growth of cardiac myocytes is clearly distinguishable from the physiological or beneficial hypertrophy that occurs with exercise [54, 55]. However, there are aspects of this early cardiac hypertrophic remodeling seen in hypertension that are clearly beneficial to the heart, and which are related to a reduction in ventricular wall stress and increased energy producing capacity of cardiac myocytes.

The contribution of LIF to either maladaptive or physiological cardiac hypertrophy is unclear. Certainly, the three major signaling pathways linked to gp130/LIFR activation have been shown to induce cardiac hypertrophy (on their own or in response to their activation by various agonists and experimental/mechanical manipulations) both in cultured cells as well as *in vivo* [55-57]. Some studies dealing with gp130 signaling in cardiac myocytes have reported the importance of STAT3 signaling, while others emphasized the role of MAPK/ERK and PI3K pathways in cardiac hypertrophy [34, 35, 58-68]. Culture condi-

tions that slightly bias the outcome by favoring growth, the specificity of inhibitors, and the relevance of overexpressing transgenic mouse models are just a few of the shortcomings associated with these studies that make a definitive assessment of their importance to pathological or physiological cardiac hypertrophy impossible. Whether LIF (or the gp130 cytokines for that matter) makes a relevant contribution to cardiac myocyte growth is unclear. Reports on cultured neonatal rat ventricular myocytes showed that upon LIF stimulation, tyrosine phosphorylated SHP2 is linked to MEK5/ERK5 activation via Gab1 recruitment, which, in turn, leads to a unique, hypertrophic phenotype of longitudinal elongation of cardiac myocytes such as is seen in the volume-overloaded heart [34, 35, 68]. However, *in vitro* studies are generally reductionistic by design and eliminate many factors that may counterbalance a cellular process *in vivo*. Our laboratory explored whether chronic LIF administration in normal healthy mice would lead to cardiac hypertrophy when the heart does not actually need growth [69]. We found that LIF improved cardiac performance, but did not cause hypertrophy. However, this may not be the case in the hypertensive heart. LIF is upregulated in the hypertrophied adult heart in response to hemodynamic overload [70]. Moreover, hearts with cardiac myocyte-restricted gp130 knockout fail to hypertrophy in response to pressure overload [71].

The contribution of LIF signaling to contractile dysfunction is unclear as well. An interesting observation documented downregulation of the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) gene and protein expression in neonatal rat cardiac myocytes in response to LIF [72, 73], suggesting a possible detrimental effect of LIF on cardiac performance as would occur in heart failure. In contrast, Murata *et al.* reported an increase in intracellular Ca^{2+} concentrations $[Ca^{2+}]_I$ of cardiac myocytes due to increased L-type Ca^{2+} current ($I_{Ca,L}$) [74]. The
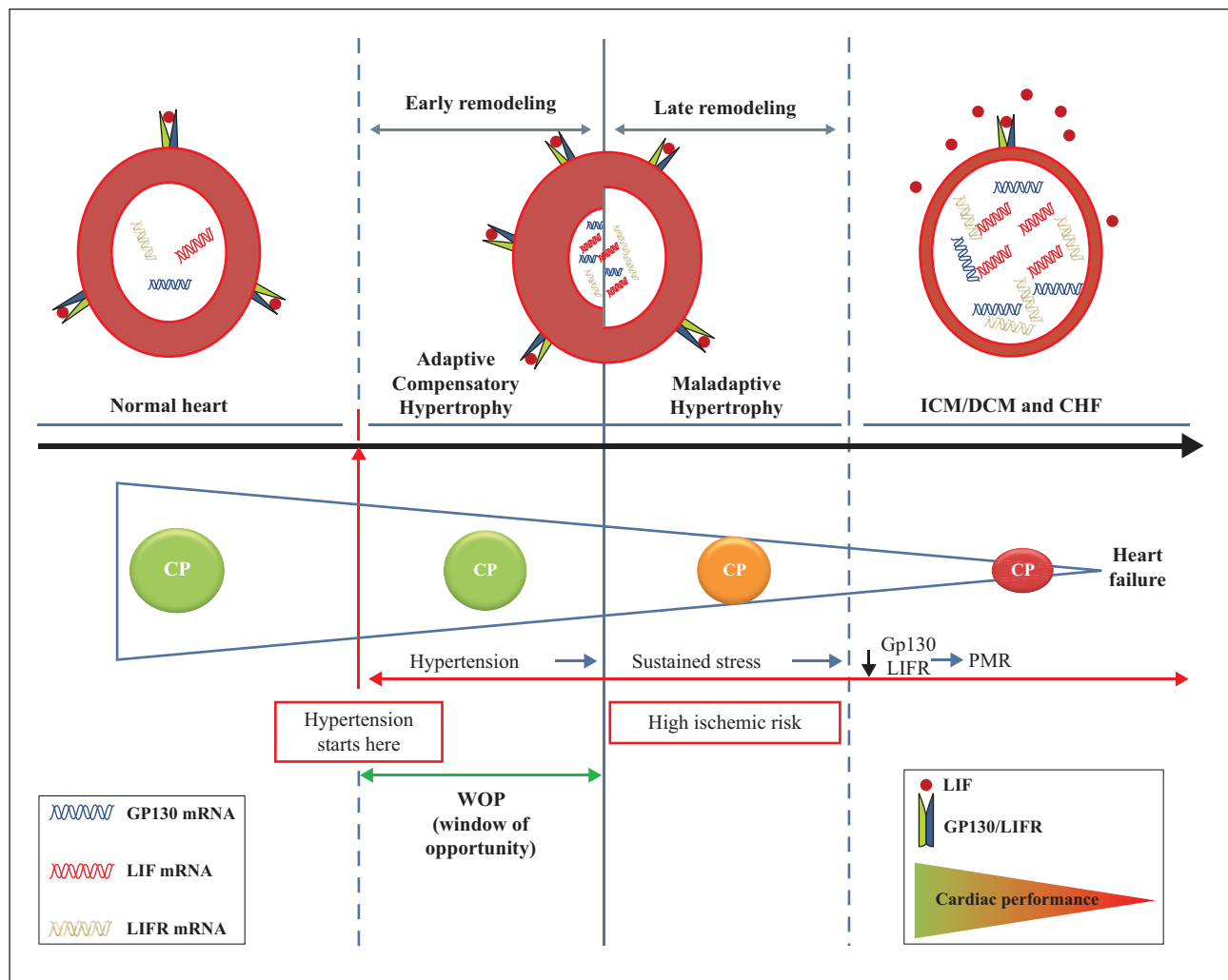
Figure 2

Defining the role of LIF in chronic stress on the heart. In response to increased blood pressure (hypertension), the heart undergoes hypertrophy. Initially, this increase in cardiac muscle mass is beneficial as it reduces wall stress (early remodeling). In time, the remodeling proves ineffective or harmful to survival of the cardiac myocytes. Inadequate vascularization, increased sympathetic drive or wall stress can predispose the heart to myocardial infarction that can further compromise its ability to pump blood. The wall of the ventricles may eventually thin and the heart dilates (late remodeling). Heart failure and further diminution of cardiac performance (CP) is the outcome. Identification of the protective mechanisms of the heart that are activated early against chronic stress could lead to therapeutic interventions to prevent the progressive maladaptive remodeling (PMR) and heart failure (window of opportunity, WOP). LIF (and STAT3) may contribute to protection of the heart against chronic stress. Evidence suggests however, that receptor levels for LIF decease with the development of heart failure, while levels of this cytokine are actually increased. ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; CHF, congestive heart failure.

resultant calmodulin kinase and calcineurin activation in LIF-treated cardiac myocytes was linked to hypertrophy and was fully inhibited with a specific MAPK inhibitor, PD98059 [74, 75]. A separate study suggested that LIF-induced ERK1/2 activation leads to phosphorylation of a serine residue within the $Ca_v1.2$ subunit of the L-type Ca^{2+} channel, thereby increasing Ca^{2+} influx and $[Ca^{2+}]_I$ [76]. Another study involving the disruption of SHP2-GP130 interaction also implicated the MEK/ERK pathway in LIF-induced calcium increases in cardiac myocytes [77]. Finally, LIF was reported to reduce contractile function, induce insulin resistance, and induce changes in energy metabolism and gene expression consistent with energy conserving adaptations at the expense of mitochondrial oxidative phosphorylation, as reported for some stages or types of cardiac hypertrophy and heart failure [78-80]. However again, these studies were carried out using cultures of neonatal rat ventricular myocytes and their physiological relevance has not yet been established.

WHEN THE WALL FALLS: LIF AND HEART FAILURE

Gp130 plays a critical role in development of the heart during early embryonic life. Embryos lacking this receptor display lethality during mid- to late-gestational age, with a cardiac muscle defect associated with cardiomyocyte degeneration [81]. Of the IL-6 type cytokines that signal through gp130, only CT-1 and LIF have been shown to promote *in vitro* neonatal (rat and mouse) cardiac ventricular myocyte growth and survival [82].

Post-natal gp130 cardiac myocyte-restricted knockout (KO) mice are viable without any sign of morphological defect during embryonic life or adulthood [71]. However, under biomechanical stress induced by pressure overload, these KO animals exhibit no adaptive hypertrophic response and are more prone to cardiac dysfunction characterized by dilating cardiomyopathy and massive cardiomyocyte apoptosis [71]. These findings indicate that gp130 is a necessary detriment to heart failure

development. Consistent with this conclusion is the observation that long-standing hypertension in the spontaneously hypertensive rat (SHR) is associated with a reduction in the heart of LIFR expression, and gp130/LIFR signaling that correlates with cardiac myocyte loss and transition from adaptive hypertrophy to heart failure [83]. Conflicting findings have been reported from human heart failure biopsies on whether dilated and/or ischemic cardiomyopathies are associated with decreases in gp130 or LIFR [19].

These findings highlight the importance of gp130 signaling as a chronic stress response pathway that promotes cellular survival and limits cardiac remodeling into heart failure. Unlike with acute stress, the protective signaling events linked to gp130/LIFR in chronic stress are not defined, but likely revolve around STAT3, as mice with post-natal deletion of STAT3 in cardiac myocytes are prone to developing heart failure with age [84].

Reduced levels of gp130 and/or LIFR, as well as their downstream signaling components, under chronic stress may diminish cardioprotective LIF signaling. Yet with various degrees of heart failure, LIF is significantly elevated in both the plasma and the failing ventricles - like a futile cry for help [83, 85-88]. Sustained stress induced by either pressure overload or ischemic-induced volume overload may progressively lead to loss of the LIF wall of protection thereby contributing to the transition from adaptive/maladaptive remodeling to dilated cardiomyopathy and heart failure (*figure 2*). Direct evidence supporting this hypothesis awaits discovery.

AND THE BEAT GOES DOWN: LIF AND CHOLINERGIC TRANSDIFFRENTIATION IN HEART FAILURE

In the 70s, Patterson *et al.* first documented the influence of non-neuronal cells on neurotransmitter synthesis of dissociated sympathetic neurons from rats [89-91]. It was clear that sympathetic neurons had undergone a transdifferentiation process characterized by a 100- to 1000-fold increase in acetylcholine levels [91]. In separate studies, Fukada *et al.* purified a factor from cultured rat heart cells that they named cholinergic differentiation factor (CDF) due to its ability to induce neurotransmitter switching from norepinephrine to acetylcholine in cultured sympathetic neurons [92, 93]. Remarkably, CDF was later confirmed to be LIF [94]. Moreover, similar studies with either rat sweat gland extracts or recombinant LIF induced the cholinergic switch in cultured rat sympathetic neurons [95, 96]. Two early studies documented that cholinergic switching may occur *in vivo*. Cholinergic switching was significant in the pancreas of LIF-overexpressing mice, and natural after-birth cholinergic transdifferentiation of noradrenergic sympathetic axons of the sweat glands from the rat footpad was inhibited with gp130 sympathetic-restricted gene knock-out [97]. Surprisingly, cholinergic switching occurs in the heart under pathological conditions. In a recent study, Kanazawa *et al.* used a Dahl, salt-sensitive rat to provoke heart failure under chronic, salt-induced hypertension [98]. As a result, LIF was highly upregulated in the ventricles of the failing heart and this was accompanied by a reduction in norepinephrine synthesis. This phenomenon was further tested in two other models: (A)

mice overexpressing heart-specific LIF, which exhibited cardiac sympathetic nervous system (SNS) to parasympathetic nervous system (PNS) neurotransmitter-switching and (B) conditional SNS-targeted gp130 knockout mice, which prevented heart failure-induced cholinergic transdifferentiation in response to transverse aortic constriction (TAC)-induced pressure overload. Furthermore, primary stellate ganglion neurons failed to undergo neurotransmitter switching when cultured in a medium of failing cardiac myocytes that had been pretreated with siRNA to downregulate LIF [98]. Neuronal rejuvenation was also identified in autopsied patients with CHF [98]. Recent evidence suggests that besides upregulating PNS genes and downregulating genes involved in noradrenergic signaling in sympathetic neurons, the gp130 cytokines induce the degradation of the rate-limiting enzyme in catecholamine synthesis, tyrosine hydroxylase [99].

Cholinergic transdifferentiation may be beneficial in the pathophysiological condition of heart failure. To maintain cardiac output, a neurohumoral compensatory mechanism of enhanced sympathetic drive to the failing heart occurs. Ironically, an increased SNS drive on the heart in the long run is detrimental, and causes cardiomyocyte toxicity. Increasing PNS tone and reducing SNS drive may represent an endogenous protective mechanism of cardiac myocytes. Cholinergic transdifferentiation is likely to be important in the infarcted myocardium as well [99].

EXPLOITING THE THERAPEUTICAL BENEFITS OF LIF IN THE HEART

Any therapeutic strategy using LIF to protect the heart is complicated by the link between LIF and cachexia and certain cancers. For MI, a targeted approach delivering LIF specifically to the injured myocardium might involve genetically reprograming stem or progenitor cells that home to the heart to secrete LIF (once reaching the heart) or constructing acellular support matrices that slowly release LIF while reducing wall tension [100]. In heart failure where signaling components may be downregulated, increasing responsiveness of cardiac myocytes to LIF poses significant hurdles. For this situation, understanding the role and regulation of STAT3 in chronic stress may lead to novel therapeutic approaches that tap into the cardioprotective aspects of LIF.

SUMMARY AND CONCLUSION

Evidence over the last decade has clearly established the beneficial actions that LIF has in preventing injury to the myocardium and facilitating repair to the injured heart in the setting of ischemia/reperfusion. The importance of LIF in the chronically stressed heart is largely unexplored. However, LIF has been implicated in cholinergic transdifferentiation that may offer some relief to the sympathetically-stressed cardiac muscle in the hypertrophied and failing heart, as well as post-MI. LIF may also hold promise in preventing excessive collagen deposition and extracellular matrix remodeling of the heart as seen in the infarcted, hypertensive, and aged heart [101]. The next decade should witness the development of targeted

strategies to exploit the beneficial actions of LIF on the heart while offsetting any potential adverse effects of this remarkable cytokine.

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