Cardiotrophin-1 in Heart Failure

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Cardiotrophin-1 (CT-1) is a 201 amino acid member of the interleukin (IL)-6 cytokine superfamily, which includes leukemia inhibitory factor (LIF), ciliary neurotrophic factor, IL-11, and oncostatin M. Cardiotrophin-1 was discovered by Pennica el al via expression cloning of mouse embryoid bodies, using a cardiac myocyte hypertrophy screen to identify positive clones. CT-1 has hypertrophic and cardioprotective properties and acts through LIF receptor β/glycoprotein 130 (gp130)-coupled signaling pathways. The LIF receptor binds CT-1, and then gp130 associates with the ligand-receptor complex and transduces the proximal signal. CT-1 intracellular signaling pathways include extracellular signal regulated kinases (ERK), mitogen activated protein (MAP) kinases, the janus kinase (JAK)/signal transducers and activators of transcription (STAT) system, and PI3-kinase/Akt. Downstream mediators of CT-1’s cellular effects include multiple ERK-coupled transcription factors, STAT-3, nuclear factor-(JAK)/signal transducers and activators of transcription (STAT), and PI3-kinase/Akt. CT-1’s biological properties. Mice with genetic ablation of CT-1 immediately became a candidate for the molecular basis of pathological hypertrophy and remodeling in dilated cardiomyopathy phenotypes. The cardiac myocyte protective effects were also appreciated early in the investigation of CT-1’s biological properties. Mice with genetic ablation of gp130 have hypoplastic hearts, which suggests a role for CT-1 or other IL-6-type cytokines in normal cardiac development. However, mice with ventricular myocyte-restricted knockout of gp130 using a ventricular myosin light chain 2 promoter that drives a Cre/lox recombination/knockout system from early in development have no cardiac abnormalities at birth, indicating that the hypoplastic heart phenotype of generalized gp130 knockout mice is likely secondary to hematologic or other noncardiac effects. Instead, cardiac myocyte-restricted knockout of gp130 in adult mice leads to left ventricular dilatation, myocyte apoptosis, and failure when the left ventricle is subjected to increased wall stress, highlighting the cardioprotective effects of gp130 signaling.

The tissue expression of CT-1 is not confined to the fetal or adult heart. CT-1 is also expressed in adult skeletal muscle, ovary, colon, prostate, and testis and in fetal kidney and lung. When administered to mice intraperitoneally, CT-1 stimulates growth in the liver, kidney, and spleen and causes increases in platelet and red cell counts. CT-1 also has potent neuroprotective properties. Therefore, CT-1 likely has multiple, diverse biological functions.

Mechanical stretch of cardiac myocytes increases the expression of CT-1 and activates the JAK/STAT pathway, providing a link from the biological properties of CT-1 to its potential role in remodeling in response to hemodynamic overload. Cardiac fibroblasts are major producers of CT-1, and non-myocytic production of CT-1 is probably important in the hypertrophic process. Myocardial gene expression of CT-1 is increased in heart failure animal models, and in humans with chronic heart failure, circulating levels of CT-1 are increased. Importantly, in animal models, CT-1 expression precedes the development of pathological hypertrophy. In model systems, norepinephrine markedly increases the expression of CT-1 in cardiac myocytes in vitro and in vivo, via a cAMP response element in the 5′ flanking region of the CT-1 gene. IL-6 superfamily cytokines induce at least some aspects of the myocardial fetal gene program that is a marker of pathological hypertrophy in both animal models and humans, and which likely plays a role in the development of the contractile dysfunction that accompanies pathological hypertrophy. Fetal gene induction in the failing human heart is under partial β2-adrenergic control, and so β-adrenergic stimulation of CT-1 gene expression is a candidate for the molecular mechanism of adrenergically-driven pathological remodeling in the failing human heart. CT-1 also engages in cross-talk with other mediators of hypertrophy, including angiotensin II and endothelin-1. In fact, the data of Sano et al suggest that substantial amounts of the cardiac hypertrophy produced by angiotensin II and endothelin-1 is mediated through increased expression of IL-6, LIF, and CT-1 in cardiac fibroblasts. Thus, myocardial CT-1 expression is a classic example of a cardiac compensatory mechanism that can be helpful or harmful. CT-1 signaling is anti-apoptotic and promotes hypertrophy, either of which may be beneficial, at least early in settings of hemodynamic overload. However, CT-1 also seems to play a role in the induction of the type of pathological hypertrophy and remodeling that is known to have an adverse effect on the natural history of left ventricular systolic dysfunction and chronic heart failure.

In the current issue of Circulation, Zolk and colleagues report that chronically failing human left ventricles removed from subjects with either idiopathic dilated...
or ischemic cardiomyopathy express increased amounts of CT-1 mRNA (by 142%) and protein (by 68%). In view of the previously described elevated circulating levels in patients with chronic heart failure, the increased CT-1 expression in animal models, and the transmyocardial step-up of CT-1 in the human heart, these new findings are not surprising. In isolation, the obvious implication of this finding is that CT-1 is contributing to ventricular chamber hypertrophy and remodeling, as well as to protection against apoptosis in dilated cardiomyopathies. However, Zolk et al. also measured protein abundance of several key components of the CT-1 signal transduction systems. Levels of gp130 protein were decreased by 34% while cognate mRNA abundance was increased by 91%, suggesting that gp130 protein turnover was increased by ligand-dependent internalization and degradation, with synthesis not keeping pace. In the study by Zolk et al., protein abundance of LIF receptor and suppressor of cytokine signaling (SOCS)-3, the latter an endogenous JAK inhibitor and suppressor of cytokine signaling, were not altered in the myopathic ventricles.

In their interpretation of these findings, the authors speculate that desensitization of gp130 signaling “might contribute to deterioration of contractile function” in chronic heart failure by promoting apoptosis and ventricular dilatation as occurred in left ventricular pressure-overloaded cardiac myocyte-restricted gp130 knockout mice. However, Zolk et al. did not assess the status of any downstream effectors of gp130, such as tyrosine phosphorylation of STAT-3, and so it is not clear whether the discordant changes in CT-1 and gp130 would produce a net increase or decrease in CT-1 signaling. Neither is it clear whether, if present, decreased CT-1/gp130 signaling would be harmful. If the net effect of increased gp130 signaling is harmful within the context of an established dilated cardiomyopathy phenotype, as suggested by recent observations in cultured heart cells and a transgenic model investigating LIF activation of ERK5, then a reduction in signaling would be adaptive. Moreover, since different intracellular signaling pathways likely mediate the hypertrophic (JAK/STAT23 and/or ERK522 pathways) and anti-apoptotic (ERK1/2 pathways23) effects of CT-1, traffic through these respective signaling systems also depends on other cross-regulating influences. Thus, at present it is uncertain whether these newly described changes in the CT-1 signaling pathway constitute an adaptive or maladaptive response by the hypertrophied, failing human heart.

Work such as the study by Zolk et al. performed in explanted failing and nonfailing human hearts has provided valuable information and often novel insights into the pathobiology of chronic heart failure. Despite obvious limitations, which include being able to investigate only end stage disease and exposure of experimental material to multiple drugs and other potentially confounding variables, the phenotype of advanced dilated cardiomyopathy produces such overwhelming changes in gene expression and functional or structural biology that findings made in explanted human hearts have typically been reliable and reproducible. The major salutary features of this model can be appreciated in the article by Zolk et al. These are 1) confirmation of work previously performed in model systems and extension to the human setting (ie, increased CT-1 protein expression in failing myocardium), and 2) generation of new hypotheses, in this case that desensitization of CT-1 signaling maladaptively complicates a favorable, protective mechanism. Our experience has been that the greatest value of explanted human heart work is in hypothesis generation as a prelude to prospective studies in animal models and humans. As has been the case for therapeutic manipulation of other compensatory mechanisms in the failing heart, clinical investigation is ultimately required to determine whether a change observed in explanted failing hearts is adaptive or maladaptive. Thus, the question of the correct interpretation of the changes in CT-1/gp130 reported by Zolk et al. will only be definitively answered by clinical trials that measure the efficacy and safety of yet to be developed modulators of CT-1 signaling and are conducted in patients with chronic heart failure.

References


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