Editorial

Human heart failure: our current STATus of knowledge

Vanessa P.M. van Empel, Leon J. De Windt*
Hubrecht Laboratory, Royal Netherlands Academy of Sciences and Arts, Uppsalalaan 8, 3584 CT Utrecht, The Netherlands

Received 21 November 2002; accepted 25 November 2002

See article by Ng et al. [10] (pages 333–346) in this issue.

Is this a dagger which I see before me ... or art Thou but a dagger of the mind ... From Shakespeare’s Macbeth (II, I, 33).

1. gp130/STAT signaling and human heart failure

Cardiac muscle hypertrophy involves the exuberant growth of individual myofibers triggered by increased mechanical load (as in chronic hypertensive disease) or decreased mechanical performance (as observed in ischemic damage) and constitutes an independent clinical risk factor for heart failure development [1,2]. Consequently, elucidating the molecular circuitry controlling the initiation and maintenance of cardiac remodeling is the focus of intense research in modern cardiovascular biology. Integrative approaches have identified dozens of ligands, receptors, cytoplasmic signal amplifiers and transcriptional effectors of myocyte hypertrophy in the last decade [3]. Nevertheless, the challenge remains to identify those common disease-provoking and -sustaining pathways, given the variability in genetic susceptibility and environmental disparities of general human populations, to allow rational design of novel therapeutic targets, which may eradicate the burden that heart failure places on the health care system in industrialized countries.

Cytokines are renowned as essential mediators of normal and pathological immune responses. Whereas heart failure was conventionally viewed as an hemodynamic disorder by clinicians, modern studies have revealed that excessive elaboration of organ-restricted ligands may play a much more intimate role in cardiac disease progression as previously suspected [1]. In addition to the well-documented, noxious function of ‘classical’ ligands as neurohormones and the locally produced renin–angiotensin axis, pro-inflammatory cytokines are clearly locally hyperactivated during human heart failure [4–7]. gp130 has been identified as a signal transducing receptor for the interleukin-6 (IL-6) family of cytokines [IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF) and cardiotrophin-1 (CT-1)] and displays a broad expression pattern, including the heart. Ligand binding to its cognate receptor induces heterodimerization with gp130, leading to activation of Janus kinase (JAK) and tyrosine phosphorylation of gp130 itself. This event in turn evokes the activation of a cascade of signal transduction pathways, involving STAT (signal transducer and activator of transcription), Ras-MAPK (mitogen activated protein kinase) and PI3K (phosphatidylinositol kinase) -Akt pathways, the activation of each depends upon distinct regions of gp130 (Fig. 1) [8].

Studies from the immune biology field have provided evidence that JAKs and STATs play essential roles in cytokine function [9]. Three members of the JAK family, JAK1, JAK2, and Tyk2, associate with and are activated by the gp130 receptor following cytokine binding, which in their turn phosphorylate the latent, cytoplasmic transcription factor STAT, allowing it to bind to its responsive element in target genes (Fig. 1) [8].

An overwhelming body of cell culture and small animal-based studies indicates that cytokines operating through the gp130 pathway are intimately involved in the development of cardiac myocyte hypertrophy and apoptosis, two phenomena closely associated with the development of human heart failure [4–7]. Notwithstanding this evidence in experimental systems, any demonstration that the gp130/JAK/STAT signaling axis is activated in the diseased human heart would fortify these experimental conclusions. The study of Ng et al. [10] in this issue of Cardiovascular Research for the first time demonstrates consistent tyrosine phosphorylation status of STAT1, 3, 5 and 6 in ventricular biopsies of explanted human hearts with dilated cardiomyopathy (DCM), and increased STAT1 and STAT5 in...
transplant material of ischemic heart disease (IHD). Given the limitations of the source (human transplant material), the quality of their Western blot data is admirable. The differential activation pattern of STAT isoforms in DCM and IHD is consistent with the notion that cardiac remodeling is not associated with global activation of signal transducers, but rather characterized by select activation of discrete pathways, depending on heart failure etiology and original insult. The correlation between previously reported elevated cytokine levels in heart tissue and circulating plasma during end-stage failure [4–6], and their findings of differential STAT activation in human DCM/IHD material, reinforces the authors to speculate on anti-cytokine treatment in human heart failure [10].

Does the gp130 receptor/JAK/STAT axis truly represents a previously unnoticed therapeutic target, or is the involvement of this pathway in failure progression more complex and as a therapeutic device but an imaginary dagger, one that exists only in our mind?

2. Cardiac signaling: the good, the bad and where STAT may fit in

Ng et al. [10] make the logical inference from their findings of persistent activation of several STAT isoforms in chronic heart failure that inhibition of cytokine signaling might prove beneficial in preventing aspects of decompensated hypertrophy and heart failure. However, it is becoming increasingly clear that qualitatively distinct forms of hypertrophy signals exist in parallel, both during initial and later stages of cardiac remodeling, and some signals, including those for cell survival itself, are beneficial and may prevent/delay the transition to decompensation. The most compelling evidence in support of latter view stems from a study using mice with ventricular chamber-restricted deletion of the gp130 receptor, of all genes. These animals have a normal cardiac structure and function and a normal life span in the absence of environmental stress, but in response to aortic pressure overload these mice display...
rapid onset of dilated cardiomyopathy and massive induction of myocyte apoptosis versus the control mice that exhibit ‘compensatory’ hypertrophy [11]. The unequivocal, genetic evidence from this study indicates that myocyte apoptosis, at least in this experimental setting, is a crucial phenomenon in the transition between the early phases of hypertrophy and heart failure, and, consequently, stimulation of gp130-dependent signals may result to be protective in the setting of heart failure following biomechanical stress [11].

In further support of this concept, several genetic models now exist of hypertrophy that is well tolerated or even beneficial. The mitogen-activated protein kinase (MAPK) superfamily culminates in three subfamilies of terminal effector kinases: extracellular signal-regulated protein kinase (ERK1/2 and ERK5), c-jun NH2-terminal kinase (JNK), and p38MAPK. Specific activation of ERK1/2 by a kinase that lies upstream caused concentric hypertrophy without decompensation accompanied by marked resistance to apoptotic cell death [12]. Likewise, the PI3K/Akt pathway can promote cardiac myocyte growth that is perhaps more physiological and associated with cardioprotection in cell culture and in mice [13]. And finally, selective activation of STAT3α itself in the murine heart causes concentric hypertrophy with marked resistance against doxorubicin-induced cardiomyopathy [14], which may be the result of its documented potential to upregulate notorious cytoprotectors as Bcl-XL, VEGF and manganese superoxide dismutase (MnSOD) [15].

By sharp contrast, a catastrophic cardiomyopathy is evoked by selective activation of either the p38MAPK [16] or ERK5-terminal branch of MAPK [17], and the Ca2+-dependent transducers calcineurin [18] and Ca2+-calmodulin dependent protein kinase (CamK) [19] in transgenic mice, thus incriminating these effectors more so than e.g. ERK1/2 MAPK, PI3K-Akt or JAK-STAT signaling as targets for drug development in heart failure. Therefore, accurate assessment of who is ‘good’ and who is ‘bad’ in ventricular remodelling now seems more relevant than ever in the present era of new molecular phenotypes.

Is this then the final verdict on the gp130/JAK/STAT signaling axis? Should we promote cytokine signals rather than inhibit them as a treatment to heart failure? Not quite, this pathway comprises yet a third level of complexity.  

3. gp130 signaling: inherent negative feedback signals

Regulation of the JAK signaling pathway takes place at several levels, including receptor internalization, dephosphorylation by protein phosphatases, degradation by the proteasome pathway, and by a recently discovered family of cytokine-inducible inhibitors of cytokine signaling. This suppressor of cytokine signaling (SOCS) family (also referred to as cytokine-inducible SH2 protein [CIS] or STAT-induced STAT inhibitor [SSI] family) consist of eight members (CIS and SOCS1–7). Functionally, CIS and SOCS1–3 proteins interact with cytokine receptors and/or JAKs, thereby inhibiting activation of kinases and STATs.

SOCS3, the intrinsic inhibitor of JAK, was recently shown to display a biphasic induction in response to pressure overload stimuli in the mouse, and its induction was closely correlated with STAT3 phosphorylation, as well as other parameters of hypertrophy, suggesting that cardiac gp130/JAK/STAT signaling is precisely controlled by this endogenous suppressor. This notion is further reinforced by the fact that viral-mediated gene transfer of SOCS3 to ventricular cardiomyocytes completely suppressed both hypertrophy and antiapoptotic phenotypes induced by LIF [14].

The group of Bogoyevitch [10] compared the general phosphotyrosine status between control and IHD/DCM human hearts and noted marked phosphorylation of several high molecular mass proteins in failure samples, consistent in size of (cytokine) receptors. This change in receptor tyrosine phosphorylation correlates well with their noted upregulation of STAT phosphorylation, suggesting that upstream controlling pathways, rather than an absence of intrinsic STAT inhibitors such as SOCS, may predominate the activation of STAT. This delicate balance between upstream (receptor) and downstream (SOCS) regulators of the pathway should become a future experimental goal in the form of an identification of the specific tyrosine-hyperphosphorylated receptor(s) and an assessment of SOCS expression levels during the progression to failure.

Perhaps the most intriguing observation of the study of Ng et al. [10], at least from a mechanistic point of view, was the identification of STAT3β, not STAT3α, as the hyperphosphorylated STAT3 isoform in end-stage failure material. These α and β isoforms are spliceforms from the single STAT3 gene, with β being a C-terminal truncation of STAT3α. Importantly, earlier, non-cardiac studies have demonstrated that STAT3β is able to bind STAT consensus binding sites in regulatory DNA of STAT-responsive genes, yet failed to activate transcription, suggesting that the STAT3β isoform, highly activated in the failing human heart, may function in a dominant negative fashion toward other STAT members [20]. Although latter contention remains to be thoroughly investigated in the cardiac setting, it is tempting to speculate that a STAT3β pro-death pathway may be preferentially activated at the final stages of heart failure progression. Whether activation of inhibitory STAT3β constitutes a determinant in the transition to decompensation, and what the molecular mechanism underlies the obviate switch from STAT3α to 3β activation, remains to be explored.

All in all, this particular study provides a platform for in depth studies to define the precise involvement of the gp130/JAK/STAT axis in regulating heart failure. As for the Cardiovascular Scientist, our attitude toward this pathway and its role in disease development is reminiscent
to Shakespeare’s legacy, but unlike MacBeth, we should embrace, not fight, our disheartenments and use this momentum as an opportunity to contemplate our future actions, before making the tragic decision to slay the noble king Duncan.

Acknowledgements

We thank L.G. de Windt and M. Lazaar for editorial assistance. Vanessa P.M. van Empel is supported by the Dr Dekker MD/PhD program of the Netherlands Heart Foundation (NHS 2001-D012). Leon J. De Windt is supported by a Young Investigator’s Award in Cardiology from the Bekales Foundation, grant 902-16-275 from the Netherlands Foundation for Scientific Research (NWO) and the Royal Netherlands Academy of Arts and Sciences (KNAW).

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