Regulation of JAK/STAT signalling by SOCS in the myocardium

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This editorial refers to ‘SOCS1 gene transfer accelerates the transition to heart failure through the inhibition of the gp130/JAK/STAT pathway’ by A. Cittadini et al., pp. 381–390, this issue.

In the myocardium, cytokines are activated in response to acute and chronic cardiac stresses. Some of them, including the interleukin (IL)-6 family of cytokines, have been implicated in cardioprotection, cardiac hypertrophy, inflammation, and heart failure via activation of the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway (Figure 1).1–3 Much effort has been made to explore the physiological/pathophysiological functions and mechanisms of positive regulation of the JAK/STAT signalling pathway in cardiac disease. Recent research has placed increasing emphasis on the termination of the signals by suppressors of cytokine signalling (SOCS) proteins.4 In the current issue of Cardiovascular Research, Cittadini et al.5 describe a possible role of SOCS1 in the transition from hypertrophy to heart failure in a chronic pressure-overload cardiac rat model. These authors report that SOCS1 is up-regulated in the decompensated phase of pressure overload. Interestingly, enhanced SOCS1 expression in cardiomyocytes through adeno-associated gene transfer accelerates the transition from hypertrophy to failure associated with sustained inhibition of the glycoprotein 130 (gp130) pathway. These findings support an involvement of SOCS1 in the pathogenesis of heart failure.

2. The role of the JAK/STAT pathway in cardiac pathophysiology

In response to cardiac stresses, cardiomyocytes produce the IL-6 family of cytokines, which includes IL-6, cardiотrophin 1, and leukaemia inhibitory factor.1,2 Each cytokine binds to its receptor, followed by the activation of the common receptor subunit, gp130, which then initiates the activation of JAKs. The activated JAKs phosphorylate the receptor cytoplasmic domains, which create docking sites for STAT molecules. Once bound to the receptor, the STAT proteins are phosphorylated by JAKs, followed by dimerization and translocation into the nucleus, where they interact with specific DNA sequences and transcription factors to regulate the transcription of the target genes. It is now known that a large number of cytokines, growth factors, and hormonal factors also activate the JAK/STAT pathway.

Because chronic activation of the JAK/STAT pathway promotes inflammation and may have pathological effects on the heart, negative regulation by the SOCS proteins is therefore crucial for maintaining a well-balanced JAK/STAT signalling.2 SOCS proteins constitute a family of eight-related proteins: CIS (cytokine-inducible SH2-domain containing protein) and SOCS1 to SOCS7, of which SOCS1 and SOCS3 have been characterized most intensively. Each SOCS family member has a central SH2 domain, an amino-terminal domain of variable length and sequence, and a carboxyl-terminal 40-residue SOCS box. The SOCS box interacts with elongin B and elongin C, Cullins and the RING finger-domain-only protein RBX2, forming an E3 ubiquitin ligase complex, which mediates the degradation of bound partners of the SOCS proteins through their SH2 domain.7 In addition, both SOCS1 and SOCS3 can inhibit JAK directly through their kinase inhibitory region (KIR) in the amino-terminal region (Figure 1).

3. Negative regulation of the JAK/STAT pathway by SOCS

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The SOCS proteins were identified as target genes of the JAK/STAT pathway, forming a negative-feedback loop to inhibit signal propagation. They can also be induced by other signalling pathways independent of JAK/STAT signalling. The list of inducers of SOCS proteins in the myocardium is growing; included among them are IL-6 cytokines, interferon (INF) γ, tumour necrosis factor (TNF) α, and angiotensin II. In this context, the study by Cittadini et al. shows that acute mechanical stretch to the isolated perfused hearts induces SOCS1 and SOCS3 through the gp130/JAK/STAT signalling pathway. Other cytokines and growth factors also induce SOCS1 and/or SOCS3 in cardiomyocytes. The induced SOCS1 and SOCS3 suppress the gp130/JAK/STAT signalling through (i) blocking the interaction of STAT with receptors by competition via SH2-domain-mediated binding to JAKs and cytokine receptors, (ii) inhibiting the catalytic activity of JAKs through the KIR, (iii) inducing proteasome-mediated degradation of SOCS-binding partners. The IL-6/gp130/JAK/STAT pathway represents a protective mechanism against pathological stresses by inducing cardioprotective agents including anti-apoptotic genes and ROS scavengers and by up-regulating angiogenic factors. However, the excessive activation of this pathway induces excessive NO production and oxidative stress and contributes to the maladaptive response. COX-2, cyclooxygenase 2; iNOS, inducible nitric oxide synthase; MnSOD, manganese superoxide dismutase; MT, metallothioneins; AGT, angiotensinogen; MMP, matrix metalloproteinase.

Figure 1 Schematic diagram of structure and function of SOCS1 and SOCS3. (A) Domain organization of SOCS1 and SOCS3. All SOCS family proteins contain a central SH2 domain and a carboxy-terminal conserved SOCS box. Both SOCS1 and SOCS3 also have a unique amino-terminal KIR domain. (B) Negative feedback regulation of the IL-6/gp130/JAK/STAT system by SOCS in the myocardium (red arrow). IL-6 family cytokines induce SOCS1 and SOCS3 through the gp130/JAK/STAT signalling pathway. Other cytokines and growth factors also induce SOCS1 and/or SOCS3 in cardiomyocytes. The induced SOCS1 and SOCS3 suppress the gp130/JAK/STAT signalling through (i) blocking the interaction of STATs with receptors by competition via SH2-domain-mediated binding to JAKs and cytokine receptors, (ii) inhibiting the catalytic activity of JAKs through the KIR, (iii) inducing proteasome-mediated degradation of SOCS-binding partners. The IL-6/gp130/JAK/STAT pathway represents a protective mechanism against pathological stresses by inducing cardioprotective agents including anti-apoptotic genes and ROS scavengers and by up-regulating angiogenic factors. However, the excessive activation of this pathway induces excessive NO production and oxidative stress and contributes to the maladaptive response. COX-2, cyclooxygenase 2; iNOS, inducible nitric oxide synthase; MnSOD, manganese superoxide dismutase; MT, metallothioneins; AGT, angiotensinogen; MMP, matrix metalloproteinase.
the onset, of cardiac hypertrophy induced by pressure overload. It should be noted that the endogenous role of SOCS1 in cardiac remodelling remains to be confirmed/determined by a loss-of-function approach.

4. Concluding remarks

The IL-6 family cytokines, gp130/JAK/STAT signalling, and negative-feedback regulation by SOCS proteins are crucial to the pathophysiology of cardiac hypertrophy and heart failure. The importance of JAK/STAT signalling in mediating both protective and harmful effects on cardiomyocytes is well established. The mechanisms of regulating this pathway have been significantly advanced during the past decade since the discovery of the SOCS protein family. Further research is warranted to investigate the roles of SOCS proteins in cardiac disease and their value as therapeutic targets.

Conflict of interest: none declared.

References