Glycoprotein 130 Cytokine Signal as a Therapeutic Target Against Cardiovascular Diseases

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Abstract. Postnatal cardiomyocytes have only limited capacity of proliferation. Therefore, the myocardium is intrinsically equipped with cardioprotective machineries and protects itself from pathological stresses. One of the most important cardioprotective systems is the signal network of autocrine/paracrine factors, including neurohumoral factors, growth factors, and cytokines. In this review, we focus on the roles of interleukin-6 (IL-6) family cytokines, also known as glycoprotein 130 (gp130) cytokines, in cardioprotection. These cytokines make a complex with their specific cytokine receptor α-subunits. The cytokine-receptor α-subunit complex binds to gp130, a common receptor of the IL-6 family, followed by the activation of JAK/STAT, ERK, and PI3 kinase/Akt pathways. In cardiomyocytes, signals through gp130 promote cell survival and angiogenesis through the JAK/STAT pathway. Activation of gp130 in cardiac stem cells induces their endothelial transdifferentiation, leading to neovascularization. Recently, accumulating evidence has revealed that altered JAK/STAT activity is associated with heart failure, suggesting that the JAK/STAT pathway is a therapeutic target against cardiovascular diseases. Interestingly, activation of the JAK/STAT pathway with interleukin-11 (IL-11) exhibits preconditioning effects in ischemia/reperfusion model. Moreover, IL-11 treatment after coronary ligation prevents cardiac remodeling through the JAK/STAT pathway. Since IL-11 is used for patients with thrombocytopenia, we propose that IL-11 is a candidate cytokine clinically available for cardioprotection therapy.

Keywords: interleukin-6 (IL-6), JAK/STAT, STAT3, glycoprotein 130 (gp130), interleukin-11 (IL-11)

1. Introduction

Heart failure is a leading cause of mortality worldwide. The onset of heart failure is triggered by cardiovascular diseases, including hypertension, myocardial infarction, viral infection, and so on. In spite of recent studies that emphasize the potential of cardiac regeneration, mammalian cardiomyocytes substantially lose proliferative activities immediately after birth. Therefore, cardiomyocyte death reduces the cell number, leading to cardiac dysfunction, clinically heart failure. To enable them to pump the blood during an individual’s life span, cardiomyocytes are intrinsically protected from cardiac damage.

Cardiac functions are modulated by various kinds of autocrine/paracrine factors, including neurohumoral factors, growth factors, and cytokines. Progress in cardiovascular molecular biology has led to the now widely accepted concept that the heart is not simply a contractile apparatus but a secretory organ producing a number of autocrine/paracrine factors and, at the same time, that the myocardium is the target of these factors. One of the most epoch-making events in cytokine biology in the cardiovascular field is the discovery of cardiotrophin-1 (CT-1). In 1995, Pennica et al. successfully cloned CT-1, a cytokine that induces cardiomyocyte hypertrophy, from
ES cells (1). In addition to amino acid similarity, CT-1 shares signal transduction pathways with the interleukin-6 (IL-6) family cytokines (2). These findings encouraged molecular cardiologists to explore the biological functions of IL-6 family cytokines. So far, it has been revealed that IL-6 family cytokines exhibit a wide range of biological functions in cardiomyocytes.

In this review, we describe the cardioprotective functions of IL-6 family cytokines, focusing on the glycoprotein 130 (gp130)/JAK/STAT signaling pathway. Activation of the JAK/STAT pathway by these cytokines in cardiomyocytes shows cardioprotective activities through cytoprotection and angiogenesis. These cytokines also play an important role in vasculogenesis in postnatal hearts. Finally, we discuss the possibility of clinical application of the gp130/JAK/STAT system to prevent heart failure.

2. IL-6 family cytokines and their receptor system

The IL-6 cytokine family consists of more than 6 members, including IL-6, leukemia inhibitory factor (LIF), CT-1, oncostatin M (OSM), and interleukin-11 (IL-11). In addition to the similarity in amino acid sequence among family members, IL-6 family cytokines utilize common signaling pathways through their unique receptor system (3) (Fig. 1); each cytokine binds to its specific receptor α-subunit, followed by the activation of the common receptor subunit, gp130. Since IL-6 family cytokines commonly utilize gp130, these cytokines are also called gp130 cytokines. This receptor system explains the unique characteristics of the IL-6 cytokine family, pleiotropy, and redundancy. The functional pleiotropy of the cytokines is derived from the expression profiles of their receptor α-subunits. The redundancy among the cytokines is achieved by transducing their signals through a common receptor subunit, gp130, which is ubiquitously expressed.

In cardiomyocytes, LIF receptor (LIFR) is expressed, but not IL-6R. Therefore, stimulation of gp130 with LIF activates JAK tyrosine kinase, transducing its signals. In response to gp130 stimulation, three signaling pathways, STAT1/3, ERKs, and PI3 kinase/Akt, are activated (4 – 6) (Fig. 2). STAT proteins are phosphorylated on their tyrosine residue by JAK kinases. The phosphorylated STAT proteins translocate into the nucleus and activate the transcription of the target genes.

Recent studies have demonstrated that not only mRNA but microRNA can be the target of STAT proteins. MicroRNA-21 (miR-21) is identified as a novel STAT3 target and contributes to cell survival in myeloma cells (7). Similarly, miR-21 is induced by IL-11 and exhibits STAT3-mediated anti-apoptotic effects in preconditioning of skeletal myoblasts (8). Therefore, miR-21 is likely to be a target microRNA of STAT3; however, its pathophysiological significances in heart failure are still discrepant (9, 10). Future progress in microRNA biology is required to clarify STAT3-mediated regulation of microRNAs and their importance in cardiovascular diseases.

3. STAT proteins and cardioprotection

To explore the physiological and/or pathological functions of the gp130/JAK/STAT signaling pathway, much effort has been made to identify the downstream target genes of the STAT pathway. The signal transduction pathways downstream of gp130 are summarized (Fig. 3).

In response to cardiac stresses, cardiomyocytes produce IL-6 family cytokines such as LIF and CT-1 (6, 11, 12). LIF and CT-1 bind to LIFR, followed by the activation of gp130 (13). As described above, there are three signaling pathways downstream of gp130: STATs, ERKs, and PI3 kinase/Akt (4 – 6).

The biological roles of ERKs and PI3 kinase/Akt pathways have been somewhat investigated. The activation of ERKs through gp130 induces morphological changes in cardiomyocytes (14). Consistently, gp130-mediated activation of the ERK pathway upregulates small proline-rich protein 1A (SPRPIA) and stabilizes the sarcomeric cytoskeletal organization, accompanied by cardiomyocyte protection (15). Recently, it has been proposed the gp130 signal is involved in cardiac calcium transient through SHP2/ERK (16). Concerning PI3 kinase/Akt pathways, similar to other signaling pathways (17, 18), activation of Akt promotes cell survival in cardiomyocytes (19). Thus, ERKs and PI3 kinase/Akt pathways are likely to play some roles in cardioprotection; however, these two signals are activated in a differential manner, depending on ligands. For example, LIF activates Akt in cardiomyocytes, while IL-11 does not (20). In contrast, the JAK/STAT pathway is strongly activated by any IL-6 family cytokine whose receptor α-subunit is expressed in cardiomyocytes. Therefore, we mainly discuss the JAK/STAT pathway in this review.

3.1. JAK/STAT and cell survival

CT-1 was originally cloned as a hypertrophic cytokine (1). In addition to its hypertrophic activities (13), it was reported that CT-1 prevents serum deprivation-mediated apoptosis and promotes cell survival in cultured cardiac myocytes in vitro (21). Since CT-1 transduces its signals through gp130, cardiomyocyte-specific gp130 gene-null (gp130 CKO) mice were generated (22). Interestingly, the gp130 CKO mice show the susceptibility to pressure...
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Fig. 1. IL-6 family cytokines and their receptor system. IL-6 family cytokines make a complex with its specific receptor (R). The cytokine–its receptor complex binds to the common receptor subunit, glycoprotein 130 (gp130). IL-6, interleukin-6; LIF, leukemia inhibitory factor; CT-1, cardiotrophin-1; OSM, oncostatin M; IL-11, interleukin-11; CNTF, ciliary neurotrophic factor.

Fig. 2. Signal transduction mechanisms downstream of IL-6 family cytokines. The stimulation of gp130 activates three signaling pathways: JAK/STAT, ERKs, and PI3 kinase/Akt. Activated STAT proteins by their phosphorylation on their Tyr residue make the dimer, translocate into nuclei, and upregulate their target genes.

Fig. 3. Cardioprotective signals through gp130. In response to pathological stresses, cardiomyocytes produce IL-6 family cytokines, such as LIF and CT-1. These cytokines activate gp130, followed by the further activation of PI3 kinase/Akt, ERKs, and JAK/STAT pathways. STAT proteins exhibit cardioprotective effects by inducing anti-apoptotic genes such as bcl-xl, COX2, and miR-217 and by inducing ROS scavengers such as MnSOD and MTs. STAT3 promotes angiogenesis by upregulating VEGF and by downregulating the expression of antiangiogenic factors such as CTGF and Tsp-1.
overload, proposing that the loss of the gp130 survival signal is critical for the onset of heart failure. Thus, to address the molecular mechanisms of gp130-mediated cardioprotection, the cytoprotective genes have been explored and identified as transcriptional targets of STAT proteins. These genes are categorized into two groups; anti-apoptotic genes and reactive oxygen species (ROS) scavenger genes.

Among the anti-apoptotic genes, bcl-xL is one of the most important targets of STAT proteins (23), because the STAT/bcl-xL pathway is utilized not only under cardiac stresses but also under a wide range of pathological and/or physiological conditions. For example, in tumorigenesis, activated STAT3 exhibits oncogenic properties and constitutive activation of STAT3 confers the resistance to apoptosis through bcl-xL induction (24, 25). Physiologically, erythropoietin prevents apoptosis of red cell progenitor through the STAT5/bcl-xL pathway (26).

In ischemic preconditioning, cyclooxygenase 2 (COX2) is proposed to play important roles as a target downstream of the JAK/STAT pathway (27, 28). COX2 cardioprotection requires its complex formation with inducible NO synthase (iNOS), although iNOS is upregulated in a COX2-independent manner (29). Interestingly, STAT-dependent transcription of the genes responsible for ischemic preconditioning is modulated by dual signaling mechanisms that involve both JAK-dependent Tyr phosphorylation and PKCε-dependent Ser phosphorylation (30).

In addition to anti-apoptotic genes, the JAK/STAT pathway also upregulates the transcription of ROS scavengers, such as manganese superoxide dismutase (MnSOD) and metallothionein (MT) (31, 32). Since ROS cause cell damage both through apoptotic and necrotic cell death in ischemia/reperfusion injury (33), myocardial activation of STAT3 drastically rescues cardiomyocytes in ischemia/reperfusion, associated with reduced ROS production (32).

3.2. JAK/STAT and angiogenesis

Another important function of STAT3 in cardioprotection is the regulation of neovascularization in myocardium. The activation of STAT3 with LIF in cardiomyocytes induces vascular endothelial growth factor (VEGF) both in vitro and in vivo (34), indicating that STAT3 is required for gp130-mediated induction of VEGF. Moreover, cardiac specific transgenic mice expressing constitutively active form of STAT3 exhibit increased capillary density in the heart (35). Since impaired myocardial angiogenesis results in cardiomyopathy or heart failure (36), STAT3 activation might contribute to the maintenance of cardiac homeostasis through neovascularization.

It is biologically interesting that STAT3-mediated promotion of angiogenesis is observed not only in the myocardium exposed to stresses, but also in tumor angiogenesis (37), inflammation-induced neovascularization (38, 39), and diabetic retinopathy (40).

In spite of the importance of STAT3 regulation of VEGF expression, it remains to be fully elucidated how STAT3 upregulates VEGF mRNA in cardiac myocytes. In a tumor cell system, the STAT3-binding site was identified in the VEGF gene promoter region (37, 41). It is also reported that STAT3 interacts with HIF-1α, a well-known transcriptional regulator of the VEGF gene and enhances VEGF transcription in a cooperative manner (42, 43).

Collectively, cardiac activation of STAT proteins promotes cell survival and neovascularization, cell-autonomously and non-autonomously, respectively, and prevents the onset of heart failure. This concept was confirmed by generating cardiac specific STAT3 knockout mice (44, 45). Although no overt signs of heart failure are present in young mice, STAT3-deficiency results in heart failure with advanced age. Cardiomyocyte-specific STAT3-null mice show impaired capillary growth and susceptibility to injury, such as ischemia and doxorubicin. As a mechanistic aspect, Hilfiker-Kleiner et al. proposed a novel STAT3-mediated pro-angiogenic pathway by demonstrating that anti-angiogenic genes, such as connective tissue growth factor (CTGF) and thrombospondin 1 (Tsp-1), are upregulated in STAT3-null mice; however, it is unknown whether STAT3 directly regulates the expression of these genes.

In addition to the transcriptional activity, recent studies have proposed the mitochondrial function of STAT3 in cellular respiration, as a cytoprotective mechanism (46). Activated STAT3 translocates not only into nuclei but also into mitochondria. Mitochondrial STAT3 binds to complex I of the electron transport chain (ETC). In mice that do not express STAT3 in the heart, there are selective defects in the activities of complex I and II of ETC. Although the mitochondrial translocation of STAT3 is reproducibly reported (47, 48), stoichiometric analysis of STAT3 and mitochondrial proteins raises the possibility that STAT3 alters mitochondrial function via transcriptional regulation (49). Although the biological significance of mitochondrial STAT3 remains to be fully clarified, we should cautiously interpret the results from the experiments with STAT3 overexpression methods.

4. JAK/STAT pathway in cardiac stem cells

In this decade, various kinds of cardiac resident stem cells, including Sca-1+ cells, c-kit+ cells, and isl-1+ cells, have been identified (50 – 53). These cardiac resident
stem cells potentially differentiate into cardiomyocytes, vascular smooth muscle cells, and endothelial cells; however, molecular mechanisms for the control of their cell fate have not been fully elucidated.

Since IL-6 family cytokines are upregulated in injured myocardium, we examined the effects of these cytokines on the differentiation of cardiac Sca-1+ stem cells (54 – 56). In cultured cardiac Sca-1+ cells, the stimulation with LIF, CT-1, or IL-11 induces the expression of the endothelial markers, concomitant with the activation of STAT3. Though IL-6 fails to induce the endothelial differentiation due to the lacking of its receptor in Sca-1+ cells, soluble IL-6 receptor confers the ability of IL-6–mediated differentiation on cardiac Sca-1+ cells (Table 1). Importantly, the blockade of STAT3 signaling, by its dominant negative form, siRNA, or gene ablation, abrogates endothelial differentiation. Moreover, adenoviral gene transfer of the constitutively active form of STAT3 induces endothelial differentiation. Therefore, activation of STAT3 is necessary and sufficient for gp130-mediated endothelial differentiation (Fig. 4).

To address the molecular mechanisms of the endothelial differentiation, we addressed the downstream targets of STAT3 by DNA array and found that the STAT3/Pim-1 signal plays a critical role in the endothelial differentiation of cardiac resident stem cells (56). Pim-1, originally identified as an oncogenic serine/threonine kinase, is involved in cell survival and proliferation (57). As demonstrated in other cell lines previously (58), Pim-1 is induced in cardiac Sca-1+ cells through the STAT3 pathway. STAT3 gene ablation in Sca-1+ stem cells by the Cre-loxP system abrogates Pim-1 induction in response to gp130 activation. Adenoviral transfection of dominant negative Pim-1 prevents endothelial differentiation in vitro. Importantly, cardiac Sca-1+ cells expressing the dominant negative form of Pim-1 show reduced differentiation in infarct myocardium in vivo, compared with control cells, analyzed by transplantation assays. Collectively, in cardiac Sca-1+ stem cells, IL-6 family cytokines, such as LIF, CT-1, and IL-11, induce endothelial differentiation through the STAT3/Pim-1 pathway (Fig. 4).

These findings are consistent with the previous report that VEGF induces the differentiation of Flk-1+ embryonic stem cells into endothelial cells through Pim-1 activity (59). Recent studies have demonstrated that cardiac stem cells with genetically engineered overexpression of Pim-1 exhibit increased proliferation (60, 61). Since Pim-1 kinase is constitutively active, the protein expression level of this kinase is in parallel with its activity. The profile of Pim-1 expression, such as its expression level and duration, may explain the differential functions of Pim-1 in cardiac stem cells. In order to understand Pim-1 functions in cardiac stem cells, it might be necessary to identify its substrates.

Vasculogenesis is the neovascularization by a de novo production of endothelial cells. So far, in the process of vasculogenesis, circulating stem cells or their derivatives have been thought to migrate into the organ, known as homing, and differentiate into the endothelial cells. In contrast to the conventional mechanisms of vasculogenesis, cardiac Sca-1+ resident stem cells can differentiate into the endothelial cells, without homing, in response to IL-6 family cytokines, proposing a novel mode of vessel formation, designated “in situ vasculogenesis”. Thus, IL-6 family cytokines regulate cardiac neovascularization through two pathways (Fig. 5); one is the angiogenic pathway through the paracrine system of the angiogenic factors, such as VEGF, from cardiomyocytes and the other is the “in situ vasculogenesis” pathway. These two pathways could crosstalk with each other. Since IL-6 family cytokines induce VEGF receptor flk-1 in cardiac Sca-1+ cells, VEGF from myocardium may stimulate Sca-1+ cell–mediated vessel formation. Furthermore, as reported previously (50), the transplantation of Sca-1+ cells improve cardiac function after myocardial infarction; however, the overexpression of dominant negative Pim-1 abrogates their beneficial effects, suggesting that differentiating Sca-1+ cells contribute to the maintenance of cardiac homeostasis possibly through paracrine systems of cell survival factors. Interestingly, a recent study demonstrated that STAT3 in cardiomyocytes is essential for the induction of erythropoietin, which preserves the endothelial differentiation capacity of cardiac Sca-1+ cells (62).

### 5. Clinical perspective

Consistent with the experimental findings that the JAK/STAT system mediates cardioprotection, clinical

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*CT-1 utilizes LIF receptor as its receptor α-subunit. siIL-6R, soluble IL-6 receptor.
studies have provided insights into the pathophysiological roles of STAT3 protein in failing hearts. In the left ventricular myocardia from patients with end-stage dilated cardiomyopathy, altered expression and activation of JAK/STAT signaling molecules are observed (63). It is also proposed that the reduction of STAT3 protein in myocardium causes postpartum cardiomyopathy (PPCM), based on the findings that female mice with a cardiomyocyte-specific deletion of STAT3 develop PPCM and that STAT3 protein levels are reduced in the myocardia from the patients with PPCM (64). Thus, the gp130/JAK/STAT3 pathway could be a therapeutic target against cardiovascular diseases.

The clinical question is how we can safely activate myocardial STAT3. We propose that IL-11 is a candidate

**Fig. 4.** A model of in situ vasculogenesis of cardiac stem cells. Cardiomyocytes produce IL-6 family cytokines, including IL-6, CT-1, LIF, and IL-11. CT-1, LIF, and IL-11 directly stimulate gp130 in cardiac resident stem cells. IL-6 activates gp130 in the presence of soluble IL-6 receptor (sIL-6R). Activation of gp130 enhances STAT3 activities, followed by the induction of Pim-1. Activation of the STAT3/Pim-1 signaling pathway is critical for the transdifferentiation from cardiac resident stem cells to endothelial cells. In vasculogenesis, it has been thought that stem cells or their derivatives home into the organ, transdifferentiate into endothelial cells, and integrate into vasculature; cardiac resident stem cells differentiate into endothelium without homing, designated as in situ vasculogenesis.

**Fig. 5.** Dual regulation of neovascularization by gp130 cytokines in the heart. IL-6 family cytokines regulate myocardial neovascularization through dual pathways; the angiogenic pathway and the “in situ vasculogenesis” pathway. In the angiogenic pathway, IL-6 family cytokines activate myocardial gp130, leading to the induction of angiogenic growth factor such as VEGF. In the in situ vasculogenic pathway, IL-6 cytokines activate gp130 of cardiac resident stem cells and induce the endothelial differentiation. These two pathways crosstalk with each other.

**Fig. 6.** IL-11 prevents cardiac remodeling through the STAT3 pathway. IL-11 was intravenously injected after coronary ligation in the murine myocardial infarction model. In wild-type mice, IL-11 prevented cardiac fibrosis; however, IL-11 failed to exhibit anti-fibrotic activities in cardiomyocyte-specific STAT3-null mice (STAT3CKO).
cytokine clinically available for myocardial protection. IL-11 is a hematopoietic cytokine with pleiotropic effects. IL-11 was isolated as a cytokine that stimulates the proliferation of an IL-6-dependent plasmacytoma cell line (65). IL-11 exhibits thrombopoietic activity, and recombinant human IL-11 is clinically used for thrombocytopenia (66, 67). In contrast to IL-6, IL-11 exhibits rather anti-inflammatory activity against chronic inflammatory diseases such as Crohn’s disease (68).

The clinical significances of IL-11 in the cardiovascular system remain to be fully addressed. In the patients with congestive heart failure, the plasma IL-11 level varies from 1 to 100 pg/mL without association with the disease severity (69), at least partially due to its rapid elimination from the plasma (67), suggesting that IL-11 is not pathophysiologically associated with systemic phenotypes of heart failure. Interestingly, IL-11 protects endothelial cells from vascular injury in vivo by induction of survivin expression (70), although it is unknown whether or not IL-11 prevents coronary plaque rupture.

Recently we have demonstrated that the IL-11 receptor is expressed in cardiac myocytes and that IL-11 stimulation induces STAT3 activation (20). Pretreatment of IL-11 confers resistance to ischemia/reperfusion injury in murine hearts as a preconditioning effect. More interestingly, IL-11 treatment prevents cardiac remodeling after myocardial infarction (71). The intravenous administration of IL-11 after myocardial infarction, generated by coronary ligation, reduces the frequency of cell death and promotes angiogenesis. Importantly, IL-11–mediated anti-remodeling effects are not observed in cardiomyocyte-specific STAT3-null mice, indicating that IL-11 administration transduces cytoprotective and angiogenic signals through STAT3 (Fig. 6). It could be proposed that IL-11 therapy is a promising approach to preserve myocardium against pathological stresses such as ischemia/reperfusion and myocardial infarction.

Thus, we have proposed that the IL-11/STAT3 signal could prevent the onset of heart failure in the acute myocardial injury model; however, it should be noted that we do not have enough information concerning the chronic effects of IL-11 or STAT3 on heart failure. Recently, Hilfiker-Kleiner et al. have raised the warning that continuous gp130-mediated STAT3 activation promotes inflammation, left ventricular rupture, and adverse remodeling in myocardial infarction (72). They hypothesized that the elevation of IL-6 level caused continuous activation of the gp130/STAT3 pathway, leading to heart failure. As they pointed out, serum IL-6 level is increased in patients with heart failure (69, 73); however, it is still unknown if the elevation of IL-6 causes the chronic inflammation after myocardial infarction because IL-6 deficiency failed to attenuate post-infarct cardiac remodeling (74). In order to understand the chronic inflammation of heart failure, it might be required to investigate the crosstalk between myocardium and immune systems more in detail.

6. Conclusion

In this review, we described the cardioprotection by gp130/JAK/STAT signaling pathways. Cardiac activation of gp130 by the IL-6 cytokine family promotes cell survival and myocardial angiogenesis through the JAK/STAT pathway. Moreover, the stimulation of gp130 in cardiac stem cells induces the endothelial differentiation as in situ vasculogenesis through the STAT3 pathway. We have demonstrated that IL-11 exhibits the cardioprotective activities through the STAT pathway. Based on these findings, we propose that IL-11 treatment could be clinically beneficial for cardioprotection against ischemic heart diseases, at least, at their acute phase. A proof-of-concept clinical trial is now being undertaken to cross the bridge from bench to bedside.

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