Chapter 20
The STAT3 Pathway and Downstream Mechanisms in Cardiac Remodeling: Friend or Foe

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Abstract Multiple in vitro and in vivo studies have shown that the signal transducer and activator of transcription 3 (STAT3) protein regulates key mechanisms in cardiac physiology (exercise, pregnancy) and pathophysiology (pressure overload, ischemia/reperfusion, myocardial infarction (MI), myocarditis, and cardiotoxic agents). STAT3 is activated in various cardiac cell types including cardiomyocytes, endothelial cells, fibroblasts, and cardiac progenitor cells by a multitude of factors including cytokines, growth factors, neurohormones, mechanical load, and ischemia. It acts as a signaling molecule, a transcription factor, and a mitochondrial protein involved in energy production, and it controls autocrine and paracrine pathways. While the majority of data imply rather beneficial roles of STAT3 in the heart, newer studies implicate that this is mainly the case when the expression and activation of STAT3 is precisely regulated. In contrast, continuous uncontrolled activation of STAT3 in cardiomyocytes seems to promote adverse cardiac remodeling processes especially after MI. Here, we provide an overview on STAT3 signaling and summarize the current understanding of the role of STAT3 for cardiac inflammation, metabolism, remodeling, and regeneration based on experimental and clinical studies. Finally, we highlight the consequences of targeting STAT3 for future therapeutic approaches in the setting of cardiac remodeling.

Keywords STAT3 • Cardiac remodeling • gp130–STAT3 signaling • Inflammation • Metabolism • Angiogenesis • Hypertrophy • Sarcomere structure

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Abbreviations

ADMA	Asymmetric dimethylarginine
Bcl-3	B cell lymphoma 3
CCL2	Chemokine ligand 2
CCR2	Chemokine ligand receptor 2
CLC	Cardiotrophin-like cytokine
CNTF	Ciliary neurotrophic factor
CT-1	Cardiotrophin 1
CTGF	Connective tissue growth factor
CVF	Cobra venom factor
ECM	Extracellular matrix
eNOS	Endothelial nitric oxide synthase
EPO	Erythropoietin
ERK	Extracellular signal-regulated kinase
ETC	Electron transport chain
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
gp130	Glycoprotein-130
HK2	Hexokinase 2
IL	Interleukin
JAK	Janus kinase
LIF	Leukemia inhibitory factor
LPS	Lipopolysaccharide
LV	Left ventricle
MBL	Mannose-binding lectin
MHC	Myosin heavy chain
MI	Myocardial infarction
MMP	Matrix metalloproteinase
OSM	Oncostatin M
miRNA	microRNA
NF-κB	Nuclear factor-κB
PAI-1	Plasminogen activator-1
PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3
PKB	Protein kinase B, also known as AKT
PPAR	Peroxisome proliferator-activated receptor
PPCM	Peripartum cardiomyopathy
PIAS	Protein inhibitors of activated STAT
PTPRT	Protein tyrosine phosphatase receptor T
ROS	Reactive oxygen species
SH2	Src homology 2 domain
SHP2	SH2 domain-containing cytoplasmatic protein
SOCS	Suppressor of cytokine signaling
STAT3	Signal transducer and activator of transcription 3

STAT3-KO	STAT3-knockout
TAC	Transverse aortic constriction
TIMP-1	Tissue inhibitor of metalloproteinase-1
TNC	Tenascin C
TNF-α	Tumor necrosis factor-α
TSP-1	Thrombospondin-1
Ube	Ubiquitin-conjugating enzyme
UPS	Ubiquitin–proteasome system
VEGF	Vascular endothelial growth factor

20.1   Introduction

The adult heart experiences numerous insults of physiological (aging, pregnancy, exercise) and pathophysiological [ischemia/reperfusion, myocardial infarction (MI), pressure overload, infections, and cardiotoxic agents] nature, which can induce alterations in the cardiac homeostasis and architecture. These alterations may be adaptive and protective to a certain stress situation or can be maladaptive, thereby inducing, driving, and contributing to heart failure [1].

Recent findings in experimental in vitro and in vivo models implicate important intermediate signal-transduction pathways in the coordination of remodeling processes following cardiac stress stimuli [2]. It is a key issue for the clinical arena to identify both detrimental as well as protective pathways and to transfer this knowledge into clinical practice. In this regard, the STAT3 signaling system has been shown to critically impact on changes in cardiac inflammation, vasculature, extracellular matrix (ECM) composition, energetics and metabolism, and cardiomyocyte survival and architecture [3–13].

As a transcription factor, STAT3 participates in the regulation of numerous genes involved in cell survival, hypertrophic growth, proliferation, angiogenesis and neovascularization, development and regeneration, and anti-oxidative pathways [3, 4, 6–11, 13, 14]. Furthermore, STAT3 has been reported to modulate ECM response to mechanical overload and to influence inflammatory processes [4, 6–8, 10]. While many of these effects of STAT3 are achieved by its own direct transcriptional activity, recent findings identified the novel function of STAT3 to directly interact with mitochondrial function [12], which adds to the complexity of STAT3-mediated regulatory processes.

Altogether, recent studies support the conclusion that STAT3 functions as part of an integrated signaling network in the heart. Here, we provide an overview of established STAT3-related biological mechanisms in cardiac physiology and pathophysiology, we illustrate its particular role in directing cardiac cellular processes that modulate ventricular remodeling, and finally we challenge the question whether STAT3 signaling conducts beneficial or detrimental effects with respect to cardiac function and heart failure.

20.2 Canonical gp130-STAT3 Signaling, a Central Regulatory Circuit in Cardiac Physiology and Pathophysiology

Interleukin (IL)-6-type cytokines such as IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), and cardiotrophin-like cytokine (CLC) are a family of helix bundle cytokines that play a key role in cellular and tissue homeostasis [15, 16]. They are involved in inflammatory and immunologic processes as well as in hematopoiesis, liver and neuronal regeneration, embryonic development, and cardiovascular physiology [16–18].

All IL-6-type cytokines interact with the glycoprotein-130 (gp130) receptor, and upon ligand binding, the homodimerization of gp130 (upon binding of IL-6 and IL-11) or heterodimerization of gp130 with LIF receptor (following binding of LIF, CNTF, CLC, OSM, and CT-1) or OSM receptor (for OSM), respectively, occurs [19–21] leading to the activation of three major downstream pathways: the Janus kinase (JAK)-STAT, the SH2 domain-containing cytoplasmic protein tyrosine phosphatase (SHP2)–extracellular signal-regulated kinase (ERK), and the phosphatidylinositol-3-kinase (PI3K)–protein kinase B (PKB, AKT) pathways [4, 18, 22–26]. The induction of the gp130-JAK-STAT pathway through IL-6-type cytokines leads mainly to activation of STAT3 and to a lesser extent to STAT1 activation [17]. Following dimerization of the gp130 receptor complex, JAK1, JAK2, JAK3, and tyrosine kinase 2 (Tyk2) constitutively connected to the intracytoplasmic membrane-proximal regions of the receptor subunits are catalytically activated and themselves transphosphorylate tyrosine residues in the gp130 receptor intracellular domain [27, 28]. This allows the recruitment of STAT proteins to the gp130 receptor complex via recognition of its phosphotyrosines by the STAT Src homology 2 domains (SH2) resulting in binding of monomeric STAT to the Y-X-X-Q motives and in phosphorylation of STAT proteins at a single carboxy-terminal tyrosine residue at amino acid position 705 (Y705) [29]. The phosphorylated STAT proteins then detach from their receptor and undergo homo- or heterodimerization through reciprocal interactions between the SH2 domain of one monomer and the phosphorylated tyrosine residue of the other [30]. Dimeric STAT proteins translocate in an importin-α-dependent manner to the nucleus, bind to specific DNA elements in the promoters of immediate early target genes, and activate specific gene expression programs.

Ligand-dependent STAT activation is a tightly controlled transient process, lasting for minutes up to several hours, during which nuclear STAT proteins are eventually inactivated by tyrosine dephosphorylation leading to their nuclear export [31]. Additional regulatory mechanisms are known to negatively control STAT activity, that is, gp130 receptors are rapidly internalized upon binding of their ligands and are degraded by the ubiquitin–proteasome pathway [32]. Furthermore, SHP-1/2 can interact with the intracytoplasmic portion of cytokine receptors and dephosphorylate JAK proteins, thereby lowering their activity [33, 34]. In addition, the suppressor of cytokine signaling (SOCS) family represents a specific negative regulatory

feedback element of STAT signaling [35], since, for example, SOCS3 is a direct transcriptional target of STAT3. SOCS1, SOCS3, and SHP-1/2 interact with the kinase domain of various JAK proteins or the cytoplasmic phosphotyrosine residue (phospho-Y759 in humans, phospho-Y757 in mice) of the gp130 receptor resulting in the inhibition of STAT protein phosphorylation, thereby leading to termination of JAK-STAT signaling [36–38]. Additional negative regulators consisting of the group of protein inhibitors of activated STAT (PIAS-1, PIAS-3) inhibit the binding of phosphorylated STAT1 and STAT3 dimers to DNA, thereby reducing the transcriptional activation of STAT target genes. Finally, the protein tyrosine phosphatase receptor T (PTPRT) specifically dephosphorylates the Y705 residue of STAT3 and thereby regulates target gene expression but also cellular localization of STAT3 [39]. Importantly, the activation state of STAT3 seems to play a major role whether IL-6-gp130 signaling acts in a more anti-inflammatory or a more proinflammatory manner.

Not only is gp130-STAT3 signaling tightly controlled, but also activation of the other gp130-triggered signaling pathways is regulated to avoid unlimited cytokine signaling from the gp130 receptor with possible detrimental effects. For example, SHP2 limits gp130-SHP2-ERK signaling [18, 40, 41]. In addition, SOCS3 competes with SHP2 for binding to phosphorylated Y757 of the gp130 receptor, thereby limiting gp130-SHP2-ERK signaling and STAT activation [18, 40, 41]. Thus, simultaneous activation of SHP2-ERK and STAT maintains a balanced gp130 signaling, which appears crucial for beneficial responses mediated by this receptor system [40, 42]. Indeed, mice with a systemic deletion of all STAT-binding sites at the C terminus of the gp130 receptor, *gp130$^{\Delta STAT}$*, are characterized by impaired induction of the STAT1 and STAT3 activation and sustained activity of the SHP2-ERK pathway, which is associated with impaired intestinal wound healing and immune response and reduced life spans [18, 40, 41]. In contrast, *gp130^{Y757F}* mice harboring a phenylalanine substitution at Y757 (Y757F) abolish binding of SHP2 and SOCS3 leading to a prolonged and continuous activation of STAT1 and STAT3 in response to IL-6 and IL-11 without activation of ERK or AKT signaling. As a consequence, *gp130^{Y757F}* mice spontaneously develop gastric adenomas, splenomegaly, and an exaggerated immune response [18, 40, 41]. Moreover, mice with a cardiomyocyte-specific Y757F mutation (*αMHC-Cre$^{tg/-}$*; *gp130$^{fl/Y757F}$*) display a high inflammatory reaction and LV rupture rate with increased mortality after MI [10].

Albeit an unrestricted high activation of gp130-STAT3 signaling seems to be detrimental in many organ systems including the heart, activation of STAT3 is absolutely required for many protective mechanisms in the heart including compensatory hypertrophy, cardiomyocyte protection, and wound healing after MI [4, 24, 43, 44].

In conclusion, it seems that a well-controlled and balanced activation of IL-6-type cytokine gp130-STAT3 signaling is beneficial for most organs including the heart, but sustained and prolonged gp130-STAT3 appears to be detrimental and is responsible for enhanced inflammation and high mortality, for example, after MI [10].

20.3   STAT3 in Cardiac Inflammation

STAT3 was initially described as a DNA-binding protein that recognizes the IL-6-responsive element in the promoter of the α_2-macroglobulin gene whose gene product belongs to the acute-phase response of the liver [45, 46]. Further evidences for STAT3 being a mediator of inflammation include the discovery of overlapping DNA-binding sites for STAT3 and the proinflammatory nuclear factor-κB (NF-κB) in the promoter of acute-phase proteins and the finding that it is activated by most proinflammatory agents, such as IL-6-type cytokines [47, 48]. Experiments with IL-6-knockout and cardiac-specific transgenic mice reveal its role in mediating cardiac inflammation after burn injury in combination with sepsis [49].

To ensure resolution of inflammation, the infiltration of inflammatory cells and the expression of proinflammatory cytokines in response to injury are balanced by the production of the anti-inflammatory cytokine IL-10 [50]. In an ischemia/reperfusion model, IL-10 is shown to be induced in the myocardium with concomitant downregulation of IL-6 mRNA expression [51, 52]. Furthermore, IL-10 suppresses the inflammatory response by inhibiting the expression of several cytokines such as IL-1, IL-6, IL-12, and TNF-α in activated macrophages and dendritic cells and mediates its effects indirectly through activation of STAT3 [52–54]. Hereafter, the induced STAT3 activates the expression of other genes, which in turn are required for a selective control of the transcription of inflammatory genes [53]. One of those intermediate genes might be *B cell lymphoma (Bcl-3)*, whose gene product blocks TNF expression after IL-10-mediated STAT3 activation in human macrophages [54].

Interestingly, infiltrating CD5-positive T cells have been identified as a predominant source of reperfusion-dependent IL-10 production, which express the cytokine upon induction by IL-6 [52, 55]. Another proinflammatory cytokine, tumor necrosis-α (TNF-α), is as well able to induce IL-10 synthesis by monocytes [55].

20.3.1   STAT3 and Inflammation Following Myocardial Ischemia

STAT3 is rapidly and transiently activated in response to myocardial ischemia per se or by reperfusion following ischemia. Mice harboring a cardiomyocyte-restricted deletion of STAT3 (*αMHC-Cre*[tg/-]; *STAT3*^{fl/fl}: STAT3-KO) display increased cardiac injury and lower survival rates after MI mainly caused by adverse remodeling suggesting that STAT3 is needed for protective mechanisms after ischemia [7]. Likewise, mice lacking the gp130 receptor and therefore having reduced STAT3 activation in the acute phase after infarction show increased mortality rates [10]. However, not only lack of STAT3 activation but also sustained uncontrolled cardiac activation of STAT3 after MI as it is present in mice carrying the mutation of *gp130*[Y757F] only in cardiomyocytes (*αMHC-Cre*[tg/-]; *gp130*[fl/Y757F] mice) leads to lower survival rates post-MI. The high mortality under unrestricted gp130-STAT3 activation derives mainly from enhanced and prolonged ventricular inflammation and high rupture rates [10].

In search for adverse downstream effectors of STAT3 signaling in infarcted *αMHC-Cre*[tg/-]; *gp130*[fl/Y757F] left ventricles (LVs), the mannose-binding lectin (MBL)/ lectin complement activation has been identified as a mediator of inflammation by hyperactivated STAT3 whose relevance is supported by the finding that attenuation of complement activation by the C3 antagonist cobra venom factor (CVF) reduces cardiac inflammation and improves cardiac function and survival in infarcted *αMHC-Cre*[tg/-]; *gp130*[fl/Y757F] mice [10]. In addition, a murine SOCS3-knockout model, in which STAT3 is continuously activated because the negative feedback loop of the gp130-STAT3 signaling in cardiomyocytes is abolished, develops lethal cardiac arrhythmias and heart failure in response to pressure overload, supporting the hypothesis that too much of STAT3 activation seems to be harmful for the heart [56]. However, it seems that STAT3 not simply promotes inflammation, it can also act as a mediator of anti-inflammatory effects since it has been shown that in ischemia/reperfusion injury, the cardioprotective effects and the attenuation of myocardial inflammation by recombinant IL-10 given were lost if STAT3 activation was inhibited [57]. Likewise, intravenous administration of exogenous IL-11 evokes activation of STAT3 in cardiomyocytes in vivo and attenuates cardiac fibrosis and suppresses the expression of proinflammatory cytokines like IL-6 and TNF-α in a STAT3-dependent manner supporting the anti-inflammatory properties of activated STAT3 [58]. Here it is important to note that a majority of cytokine expression in the ischemic heart seems to derive from non-myocyte cells [59, 60].

Taken together, STAT3 plays an important role for protective mechanisms in the ischemic heart and after ischemia/reperfusion; however, the genetic and pharmacological dissection of gp130-mediated signaling indicates that only a well-controlled and balanced STAT3 activation is protective in the ischemic heart. Moreover, it seems specifically important in which cell type STAT3 is activated under ischemic condition, a feature that may explain the somehow contrary roles of STAT3 with regard to cardiac inflammation under ischemic conditions.

20.3.2   STAT3 and Myocarditis

It seems that STAT3 acts as a protective factor in viral myocarditis since cardiac-specific overexpression of SOCS3 increases the susceptibility to viral infection of the myocardium [61]. Further evidences for STAT3 regulating cardiac inflammation in responses to pathogens derive from STAT3-KO mice, which display a significantly higher TNF-α secretion and cardiac apoptosis rate in response to lipopolysaccharide (LPS)-induced inflammation [11].

With regard to cardiac inflammation, the question whether STAT3 is a friend or a foe cannot be answered in general. STAT3-mediated responses depend on the abundance of the particular cytokines, which activate the gp130-STAT3 signaling cascade, and on the cell type where these cytokines and the receptor system are expressed and activated in order to be either pro- or anti-inflammatory. Furthermore, the activation status of STAT3 is of major importance for the behaviors as a friend

or a foe, since too much STAT3 activation after MI or cardiac deletion of STAT3 during LPS-mediated inflammation could be detrimental. Thus, the key issue seems to be a balanced and well-controlled activation of STAT3 in all cells affected by inflammatory processes in the heart.

20.4 STAT3 in Angiogenesis and Extracellular Matrix Composition

One of the earliest evidence of a potential role of STAT3 in angiogenesis was derived from observations showing that granulocyte-macrophage colony-stimulating factor (GM-CSF) via activated STAT3 contributes to vessel formation [62].

However, genetic analysis in mice with an endothelial-specific deficiency of STAT3 (*Tie2-Cre^{tg/-}*; *STAT3^{fl/fl}*), where STAT3 is depleted at E8 in angioblasts, showed that these mice survive into adulthood without major vascular defects implicating that endothelial STAT3 is optional for vessel formation during development [63].

While it seems that STAT3 is not directly required for vessel formation by endothelial cells, it has been shown that STAT3 acts as a transcription factor for angiogenic mediators such as vascular endothelial growth factor (VEGF) and as a suppressor of angiostatic genes [64]. The mechanisms of vascular formation in the postnatal heart involve both auto- and paracrine circuits where specifically secreted paracrine factors from cardiomyocytes seem to play a pivotal role for cardiac angiogenesis [65]. Indeed, it has been shown that STAT3 participates in the upregulation of VEGF and VE-cadherin expression in cardiomyocytes [64, 66], a feature that is in line with the observation that STAT3 acts as a paracrine mediator in cardiomyocytes for vascular growth as, for example, demonstrated in mice with cardiomyocyte-specific overexpression of STAT3 (*αMHC-STAT3tg*) that displays increased myocardial capillary density [64, 67].

In contrast to *αMHC-STAT3tg* mice, the STAT3-KO (*αMHC-Cre^{tg/-}*; *STAT3^{fl/fl}*) in cardiomyocytes leads to a rarification of cardiac capillaries, an enhanced fibrosis, and the development of an age-dependent heart failure suggesting a crucial role of STAT3 in controlling paracrine mechanisms involved in postnatal angiogenesis [7, 11]. Surprisingly, STAT3-KO mice show no differences in the expression of VEGF or VEGF receptors. However, they display an increase in the expression of antiangiogenic factors, which are able to inhibit endogenous VEGF activity or release such as connective tissue growth factor (CTGF) and thrombospondin-1 (TSP-1) [7, 68, 69]. Other potent antiangiogenic factors are as well upregulated like tissue inhibitor of metalloproteinase-1 (TIMP-1), tenascin C (TNC), and plasminogen activator-1 (PAI-1), which act by promoting apoptosis of endothelial cells or alter ECM composition [7, 8, 70, 71]. In this regard, supernatants of STAT3-KO cardiomyocytes are able to repress the proliferation of endothelial cells [7]. Additionally, TIMP-1 is well known to enhance fibrosis by inhibition of matrix-degrading enzymes such as matrix metalloproteinases (MMPs) [72]. This regulatory alteration may explain the

age-dependent increase in interstitial fibrosis and enhanced deposition of collagens of STAT3-KO mice, indicating impaired ECM homeostasis [7, 11]. Thus, deterioration of angiogenesis in the aging myocardium of STAT3-KO mice is caused at least in part by altered structural and regulatory components of the matrix scaffold of the vascular bed and by enhanced collagen accumulation [7, 73]. Additionally, disturbance of ECM homeostasis may cause insufficient migration of angiogenic cells such as endothelial cell precursors or blood-derived primitive stem cells to the side of injured myocardium and thereby reduces the neoangiogenic capacity [74].

Moreover, STAT3 is involved in angiogenesis under pathophysiological conditions like MI. In this regard, activated STAT3 induces angiogenesis in the ischemic preconditioned infarcted myocardium [75]. In a STAT3-dependent manner, granulocyte colony-stimulating factor (G-CSF) is involved in cardiac remodeling after MI by increasing the number of endothelial cells in the border zone of the infarcted myocardium. This observation is diminished in dominant-negative STAT3 transgenic mice, suggesting that the enhanced vascularization is mediated STAT3-dependently in cardiomyocytes [76].

Furthermore, in *αMHC-Cre*$^{tg/-}$; *gp130*$^{fl/Y757F}$ with a continuous activation of STAT3 in cardiomyocytes, the prolonged activation of STAT3 contributes to a higher capillary density in the nonischemic myocardium in the subacute phase after MI [10]. But the increase in capillarization is not sufficient to improve the outcome after MI. In fact, the high vessel density in the border zone of infarcted *αMHC-Cre*$^{tg/-}$; *gp130*$^{fl/Y757F}$ mice may weaken the tissue or may promote further inflammation and thereby even contribute to adverse effects such as LV rupture and dilatation of the scar. During elimination of necrotic tissue and digestion of collagens in the border zone and later in the infarct scar, the adverse remodeling is mediated by MMPs released from inflammatory cells. In fact, in *αMHC-Cre*$^{tg/-}$; *gp130*$^{fl/Y757F}$ mice, MMP-1 and MMP-13 expression is upregulated, but is not counterbalanced by upregulated expression of their inhibitors such as TIMP-1 [10].

Additionally, STAT3 signaling influences the fate of cardiac stem or progenitor cells by the modulation of paracrine circuits in the heart or the direct induction of differentiation of stem cells. In this context, STAT3 activation (mediated by LIF stimulation) is able to directly induce endothelial differentiation of cardiac Sca-1$^+$ stem cells contributing to neovascularization during cardiac remodeling [77, 78]. Moreover, cardiomyocyte-specific deficiency of STAT3 alters the cardiac microenvironment by the release of STAT3-dependent paracrine factors such as erythropoietin (EPO). The depletion of EPO within the cardiac microenvironment attenuates the endothelial differentiation of an endogenous cardiac progenitor cell population by arresting their chemokine ligand 2 (CCL2)/chemokine ligand receptor 2 (CCR2) system, which as a consequence impairs the vasculogenic regeneration of the heart [79]. Interestingly, the endothelial differentiation seems to be VEGF independent [79]. These aspects suggest a potential positive role of STAT3 signaling for the fate of cardiac stem or progenitor cells contributing to the homeostasis of the heart, especially after cardiac injury, and harbor an endogenous source for the generation of new capillaries and vessels. The formation of new vessels could contribute to the preservation of the cardiac function.

Finally, STAT3 seems to play a key role in the regulation of cardiac angiogenesis during pregnancy-induced adaptive processes such as physiological hypertrophy of the maternal heart. In fact, cardiac-restricted deletion of STAT3 leads to peripartum cardiomyopathy (PPCM) with a massive loss of cardiac microvessels as the major phenotype [9]. This pathologic decrease in blood vessels is mainly caused by unbalanced oxidative stress in cardiomyocytes that promotes the release of activated cathepsin D, which subsequently cleaves the nursing hormone prolactin in the angiostatic factor 16 kDa prolactin. It is important to note that STAT3 expression and activation is downregulated in cardiac tissue of patients with PPCM suggesting that STAT3 activation is also crucial for cardioprotection from pregnancy-related stress in humans.

Conclusively, these data suggest that STAT3 plays an important role in protecting the vasculature as well as inducing neoangiogenesis in the heart under physiological and pathophysiological conditions by controlling paracrine circuits.

The proangiogenic features of STAT3 seem to involve paracrine mechanisms in cardiomyocytes and non-myocytes including the expression and regulation of VEGF, which indicate that activation of STAT3 controls vessel growth in vivo. In addition, STAT3 seems important to suppress the expression of antiangiogenic factors such as CTGF, TSP-1, and TIMP-1 and the generation of angiostatic peptides such as 16 kDa prolactin. Especially in cardiac adaptation processes in response to physiological stress (pregnancy) or in response to injury, STAT3 is essential for the formation and preservation of blood vessels and ultimately for the maintenance of the cardiac function. However, too much proangiogenic activity induced by a continuous activation of STAT3, for example, in the infarcted heart may be detrimental since enhanced vessel formation in the border zone of the infarcted LV may weaken the tissue and promote inflammation, ventricular rupture, and scar dilatation. Therefore, a precise regulation of STAT3 expression and activity is also necessary for beneficial cardiac angiogenesis.

20.5   STAT3 and Heart Metabolism

It is inevitable for the cardiac muscle to consistently produce high amounts of ATP to meet the demand of energy required to maintain cardiac pump function. There is ample evidence that derangements in myocardial fuel selection and energetics occur in heart failure; however, causes and consequences of these defects remain poorly understood [80]. With its important role as a mediator of cardiac vessel growth, STAT3 is important to provide the pipes to transport energy and oxygen to the cardiac muscle. Apart from its role in angiogenesis, distinct forms of STAT3 actions have been implied in the direct modulation of substrate metabolism and energy generation. However, so far data are derived from liver and from tumor biology, while effects on the role of STAT3 on cardiac energy generation are less elaborated.

STAT3 has been shown to act as a master metabolic regulator in STAT3-dependent cancer cell lines where it enhances aerobic glycolysis and downregulates

mitochondrial activity [81]. For instance, in human breast cancer cells, IL-6 enhances glycolysis by STAT3-mediated upregulation of the glycolytic enzymes hexokinase 2 (HK2) and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), a result that could be confirmed in mouse embryonic fibroblast and links inflammation to alterations in cancer metabolism [82, 83]. In liver, a link between STAT3 signaling and modulation of glycolysis has been suggested since hepatocyte-specific STAT3 deletion results in hepatic insulin resistance [84]. In the heart of a transgenic mouse model with a cardiac-specific overexpression of peroxisome proliferator-activated receptor (PPAR)-α, insulin-induced STAT3 activation measured as phosphorylation at Y705 is diminished and therefore associated with an elevated oxidation of fatty acids and downregulation of genes involved in glycolysis [85].

With regard to substrate use, there is a major difference between cancer cells which strongly rely on glucose oxidation as their preferred way of energy generation and striated muscle cells which mostly favor fatty acids as the substrate for ATP production. In this context, STAT3 was attributed to mediate leptin-induced lipid oxidation in skeletal muscle, while the effect of STAT3 on cardiac fatty acid oxidation has yet to be investigated [86].

However, it is known that with the development of heart failure, the cardiac muscle switches from fatty acid utilization to glucose oxidation as the preferred substrate for energy generation [87]. Whether this switch is protective as it adapts the heart to different energy demands or contributes to the development of heart failure is a matter of debate and not really understood. A contribution of STAT3 in the regulation of genes involved in cardiac substrate utilization has not been evaluated yet. However, a direct function of STAT3 in mitochondrial ATP production in the heart and in cardiomyocytes has recently been demonstrated [12]. In fact, evidence has been presented that STAT3 is present in mitochondria of B cells and cardiomyocytes, where it binds to complex I and II of the electron transport chain (ETC) [12, 88]. This direct protein–protein interaction of STAT3 with ETC components requires phosphorylation at S727 but seems to be independent from Y705 phosphorylation or DNA binding. Deletion of STAT3 in this model leads to a drastic reduction in complex I and II activities, a lower membrane potential and ATP production, and an increase in the production of reactive oxygen species (ROS) [12]. The mitochondrial localization of STAT3 could recently be confirmed, and additionally a Tom20-mediated import of the protein was described [88]. Genetic deletion as well as pharmacologic inhibition of STAT3 phosphorylation at both sites, Y705 and S727, leads to a decreased ADP-stimulated respiration in the presence of complex I substrates [88]. No effect of STAT3 on complex II, complex IV, or uncoupled respiration was detected in cardiomyocyte mitochondria [88].

Also, an interaction between the mitochondrial protein cyclophilin D that is part of the mitochondrial permeability transition pore complex and STAT3 is reported, and STAT3 deletion or inhibition is found to increase the susceptibility of pore opening [88]. Interestingly, mice overexpressing a transgenic STAT3 protein with a mitochondrial target sequence but a mutated DNA-binding site in cardiomyocytes also display reduced complex I and II activities. However, this reduction is, unlike in the STAT3-deficient situation, not associated with augmented ROS, or decreased

ATP production and cardiac function and left ventricular dimensions are comparable to wild-type mice at 1 year of age [89]. Mitochondria from these transgenic mice are protected against ischemia-induced ROS production via complex I and show diminished cytochrome c release in response to ischemic insult [89]. It therefore seems likely that mitochondrial-targeted STAT3 on top of the endogenous protein protects against ischemic damage by partially inhibiting electron flow through complex I [89].

In the aforedescribed studies, the effect of mitochondrial-located STAT3 on cellular respiration at the level of the ETC is attributed to direct interactions of STAT3 and ETC proteins. However, to generate sufficient amounts of ATP required for maximal myocardial performance, nearly equimolar amounts of STAT3 and complex I and II proteins would be necessary. Using different proteomic approaches, it was shown that the ratio of STAT3 to complex I/II is ~10^{-5} [90]. From these experiments it can be concluded that direct regulation of cellular respiration by protein–protein interaction of STAT3 and respiratory chain proteins is not feasible and that the observed modulations in ATP production by STAT3 might rather be due to regulation of the expression of mitochondrial genes [90].

Taken together, STAT3 plays an important role in the heart and in cardiac cells for upstream processes like transport of nutrition and oxygen, while little is known about the role of STAT3 in cardiac fuel selection and substrate oxidation. However, strong evidence exists that STAT3 is essential to mediate ATP production in mitochondria via the ETC. However, the exact mechanisms by which STAT3 influences ATP generation especially at the level of complex I and II are controversially discussed. Additional studies are therefore necessary to decipher the contribution of disrupted metabolism in adverse structural remodeling of the myocardium in general and to determine the role of STAT3 in this context.

20.6   STAT3 in Hypertrophy and Sarcomere Composition

The role of the JAK-STAT pathway for the development of cardiac hypertrophy and a putative therapeutic utility still remains a matter of debate. While early studies demonstrated that under massive STAT3 overexpression (*αMHC-STAT3^{tg}*), mice develop spontaneous concentric cardiac hypertrophy [67], the role of physiological expression and activation of STAT3 for cardiac hypertrophy was until recently unclear [10]. Some studies have favored a decisive contribution of STAT3 to the development of cardiac hypertrophy, particularly in response to certain pathophysiological stimuli, such as MI and ischemia/reperfusion [7], pressure overload, and hormones [91]. In this regard, upregulation of STAT3 signaling in response to MI may contribute to an adaptive component of remodeling processes in an effort to maintain function and forward flow in the acute phase. However, prolonged and unbalanced activation of JAK-STAT3 signaling appears detrimental after MI due to enhanced inflammation and left ventricular instability with increased rupture rate as mentioned above in the *αMHC-Cre$^{tg/-}$*; *gp130$^{fl/Y757F}$* mice [10].

Further evidence for the involvement of STAT3 signaling in cardiomyocyte hypertrophy is provided by in vitro experiments using the activator of gp130 receptor signaling, LIF, which induces cell growth in cardiomyocytes, a feature that is prevented by concomitant overexpression of SOCS3 [38]. However, LIF mainly induces a distinct type of cell growth that is marked by thinning of the width and elongation of the length, a phenotype that is considered as an eccentric cell growth, rather than a concentric hypertrophy. A link between STAT3 and the ubiquitin–proteasome system (UPS) was identified in a microRNA-dependent manner. In this circuit, STAT3 negatively regulates the expression of miR-199a on the transcriptional level, which in turn fine-tunes the expression of at least two ubiquitin-conjugating enzymes, the Ube2i and Ube2g, on the posttranscriptional level [5]. Under circumstances of low STAT3 expression, for example, as it occurs in the end-stage failing heart [92], the expression of miR-199a is upregulated with a subsequent impairment of the UPS. Consequently, this leads to disturbed homeostasis of certain sarcomeric proteins, such as α- and β-MHC proteins, a severe derangement of the sarcomere ultrastructure, and an eccentric type of cardiomyocyte growth—a phenotype that corresponds to the architecture of the cardiomyocyte syncytium in dilated cardiomyopathy. Moreover, the derailed UPS activity and protein turnover also result in alteration of the cardiomyocyte secretome with accumulation of the endogenous endothelial nitric oxide synthase (eNOS) inhibitor asymmetric dimethylarginine (ADMA), which in a paracrine fashion impairs endothelial function of adjacent vessels [5].

Conclusively, STAT3 regulates sarcomere composition, cardiomyocyte growth, and hypertrophy and thus determines the transition from adaptive to maladaptive remodeling depending on the extent, time point, and duration of signaling activity. While under certain conditions a transiently enhanced STAT3 activity may promote adaptive concentric hypertrophy, prolonged STAT3 activation or deficiency result in ventricular instability or eccentric ventricular dilatation, respectively. Notably the STAT3-related processes with regard to regulation of sarcomeric gene composition via microRNAs and the UPS are not restricted exclusively to the cardiomyocyte itself but may also impact via release of metabolites such as ADMA in a paracrine manner on the non-myocyte compartment especially the myocardial vasculature.

20.7   Conclusion

In conclusion, STAT3 is involved in multiple biological mechanisms in the developing, the adult, and the injured heart. A timely regulated STAT3 activation appears cardioprotective by positively modulating anti-oxidative defense, angiogenesis, eventually metabolism and energy production, hypertrophy, and survival, as reported in previous studies [7, 8, 11, 12, 67, 93]. However, upregulation and sustained activation of STAT3 promotes ventricular inflammation and rupture after ischemic insults resulting in high mortality. These antithetic effects clearly demonstrate that a precise regulation of STAT3 expression and activity is required for beneficial effects of STAT3 in the heart.

This double-faced nature of STAT3 may offer an explanation for discrepancies existing between experimental findings that demonstrated mainly beneficial effects of gp130-STAT3 signaling for the cardiovascular system and clinical studies which found that high serum levels of gp130 ligands, that is, IL-6, predict a poor outcome in patients after MI or with heart failure [94–96]. Based on the data summarized in this report, it could be speculated that high IL-6 serum levels in patients indicate a high and continuous activation state of STAT3 which has been shown to be detrimental especially after MI. Therefore, it should be explored whether there is a link between high IL-6 serum levels, activation state of cardiac STAT3, and poor prognosis in patients after MI. If this is the case, targeting STAT3 by small molecule inhibitors as currently tested in cancer therapy [97] might be a novel therapy option in these patients. In turn, in other scenarios such as heart failure due to myocarditis, peripartum cardiomyopathy, or heart failure due to cardiotoxic treatment strategies, therapies that enhance STAT3 activation may be beneficial and promote healing and regeneration. Taken together, in most cardiac physiological and pathophysiological situations, balanced STAT3 expression and activation is essential for cardioprotection and behaves as a friend, but an unbalanced STAT3 activation can turn a friend into a foe. Therefore, therapeutic success of targeting STAT3 in positive or negative ways will require the possibility to precisely control the activation status of STAT3.

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