Chapter 12
HSF and Heart Diseases

Jie Yuan and Yunzeng Zou

Abstract In the heart, HSF1 has a wide range of expression in many kinds of cells, including cardiac myocytes, fibroblasts, and endothelial cells, which governs the activation of heat shock proteins and plays a protective role against different pathological stimuli. HSF1 is activated by phosphorylation and transferred into the nucleus. HSPs also regulate HSF1 activity. HSF1 activity is required to maintain redox state and attenuate oxidative damage in the heart under normal physiological conditions. HSF1 protects against ischemia/reperfusion injury and myocardial infarction by inhibiting oxidative stress and cardiomyocyte apoptosis. HSF1 ameliorated death of cardiomyocytes and cardiac fibrosis and thereby prevented cardiac dysfunction as well as hypertrophy induced by chronic pressure overload. HSF1 promotes cardiac angiogenesis during chronic pressure overload, leading to the maintenance of cardiac adaptation. In atherosclerosis, however, HSF1 is activated and highly expressed in atherosclerotic lesions and that proinflammatory cytokine stimulation and disturbed mechanical stress to the vessel are primarily responsible for HSF1 activation in smooth muscle cells. In the failing hearts, HSF1 is increased, but nuclear translocation of the HSF1 is markedly reduced in the viable myocardium upon the pathological stresses. Thus, cardiac protective HSP induction is impaired in the failing heart.

Keywords HSF1 • Activation • Myocardial infarction • Ischemia/reperfusion injury • Cardiac pathologic hypertrophy • Atherosclerosis • Heart failure

12.1 Introduction

The heart is a muscular organ in humans and other animals, which functions as a pump in the circulatory system to provide a continuous circulation of blood throughout the body. By means of this circulation, the heart can provide sufficient oxygenated blood containing nutrients and metabolites, meet metabolic needs, and preserve a constant internal milieu. Its two essential characteristics are contractility

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and rhythmicity. In the regulation of these, the nervous system and neurohumoral effects modulate relationships between venous returns, outflow resistance, frequency of contraction, and inotropic state. There are also intrinsic cardiac autoregulatory mechanisms.

Ischemic heart disease (IHD) accounts for the most of the global heart disease burden, which occurs when the heart is not sufficiently supplied with blood causing damage to the heart muscle. Common IHDs develop when coronary blood supply to myocardium is reduced, either in terms of absolute flow rate (low-flow or no-flow ischemia) or relative to increased tissue demand (demand ischemia). Atherosclerosis, myocardial infarction (MI), ischemia, and reperfusion are major causes for IHD. In addition, pathological cardiac hypertrophy is accompanied with a variable degree of myocardial ischemia. Obviously, IHDs are actually a result of imbalance between myocardial blood supply and oxygen. Long-standing IHDs will lead to heart failure. In fact, heart failure is a complex disorder that leads to disturbance of the normal pumping of blood to the peripheral organs to meet the metabolic demands of the body, which is the final outcome of various cardiovascular diseases such as hypertension, ischemic heart disease, myocarditis, valvular insufficiency, or cardiomyopathy.

12.2 Protein Metabolism and Signaling in Heart Cells

12.2.1 HSF1 and HSF2 in the Heart

At present, four different HSFs (HSF1, HSF2, HSF3, and HSF4) have been identified in vertebrates. HSF1, HSF2, and HSF4 are expressed in the human tissues (Nakai et al. 1997). HSF1 is primarily involved in the stress response and has been found to be a "multifaceted factor" involving in various pathogenesis. In the heart, HSF1 has a wide range of expression in many kinds of cells, including cardiac myocytes, fibroblasts, and endothelial cells, which governs the activation of heat shock proteins (HSPs). HSPs act to ensure the proper protein folding, as well as to prevent protein misfolding and assist in protein refolding to the correct state. Expression of HSPs is mainly regulated by HSF1 at the transcriptional level. In cardiomyocytes, knockout of HSF1 has no effect on basal levels of HSP72 and HSP27, but results in loss of the stress-induced increase in these proteins. In fibroblasts, knockout of HSF1 is associated with loss of both basal expression and stress-mediated induction of HSP72 and HSP27 (Xiao et al. 1999).

Unlike HSF1, HSF2 is not activated by classical stress stimuli, but plays a role in embryogenesis. HSF2 is present in two isoforms (HSF2-α and HSF2-β) (Fiorenza et al. 1995). Both HSF1 and HSF2 are strongly expressed in the developing heart. HSF2 DNA-binding activity is transiently induced after cardiac looping when chambers maturate and valves are formed (Eriksson et al. 2000). HSF2 expression and activation have no temporal or spatial correlation with heat shock gene expression, which indicates that HSF2 activation is associated with specific stages of heart

formation but is not involved in the regulation of inducible heat shock gene expression (Eriksson et al. 2000). The HSF2-α form is transcriptionally more active than the HSF2-β form (Snoeckx et al. 2001). Interestingly, HSF2 operates additionally to HSF1. When both heat shock factors are activated by hemin treatment and heat shock, respectively, transcription of the hsp70 gene is more potent than after activation of HSF1 alone (Tani et al. 1997).

12.2.2 Control of HSF1 Activation

In the nonstressed state, HSF1 exists as a latent monomer in the cytoplasm, with repressed DNA-binding and transcriptional activity (Fig. 12.1). Upon activation, HSF1 undergoes rapid and reversible relocalization within seconds into specific subnuclear structures, termed stress granules (Jolly et al. 1999), which include a monomer-to-trimer transition, nuclear accumulation, and transcriptional activation. First, serine residue 230 of HSF1 in the cytosol is phosphorylated, and then the transcription factor is transferred into the nucleus, where HSF1 trimers bind with high affinity to the heat shock element (HSE) that consist of multiple contiguous invert repeats of the pentamer sequence nGAAn located in the promoter region of target genes (Holmberg et al. 2001; Westerheide and Morimoto 2005). Upon recovery from stress such as heat shock, HSF1 rapidly dissipates from these stress granules to a diffuse nucleoplasmic distribution, typical of unstressed cells (Jolly et al. 1999). There are several phosphorylation sites in HSF1 (Fig. 12.1). Inducible serine 230 phosphorylation positively contributes to the transcriptional competence of HSF1, which is necessary to exert primarily the function of the HSF1 after heat shock stress (Holmberg et al. 2002). However, constitutive residues (serine 303, serine307, or serine363) repress the transcriptional activation of HSF1 (Kline and Morimoto 1997). In stress granules, HSF1 undergoes posttranslational modification by covalent conjugation of a small ubiquitin-like modifier 1 (SUMO-1) protein to lysine 298 preceded by phosphorylation of serine 303 (Chi and Karliner 2004). Negative regulators of HSF1-driven transcription also include the mitogen-activated protein kinase ERK and c-Jun NH2-terminal kinase (Dai et al. 2000). These kinases recognize their substrates via a small domain (D domain) in which phosphorylation of serine 363 appears to be the major target leading to reduced transcriptional activity (Dai et al. 2000). Additionally, phosphorylation on Ser303 in HSF1 by glycogen synthase kinase 3β (GSK3β) reportedly has a negative regulatory effect on HSF1 activation (Chu et al. 1996; Xavier et al. 2000). Substitution of this serine residue with alanine, such as in the HSF1 S303A mutant, results in increased transcriptional activity (Lepore et al. 2001). HSF1 knockout is associated with a chronic increase in tumor necrosis factor-α (TNF-α) levels and increased susceptibility to endotoxin (Xiao et al. 1999). The promoter for TNF-α contains an HSF1 binding site that represses transcription, and thus, loss of this repressor results in sustained expression of TNF-α (Singh et al. 2002). However, TNF-α transiently inhibits activation of HSF1 via TNF-R1, and activation of phosphatase HSF1-heat shock element DNA binding is not sufficient to elicit

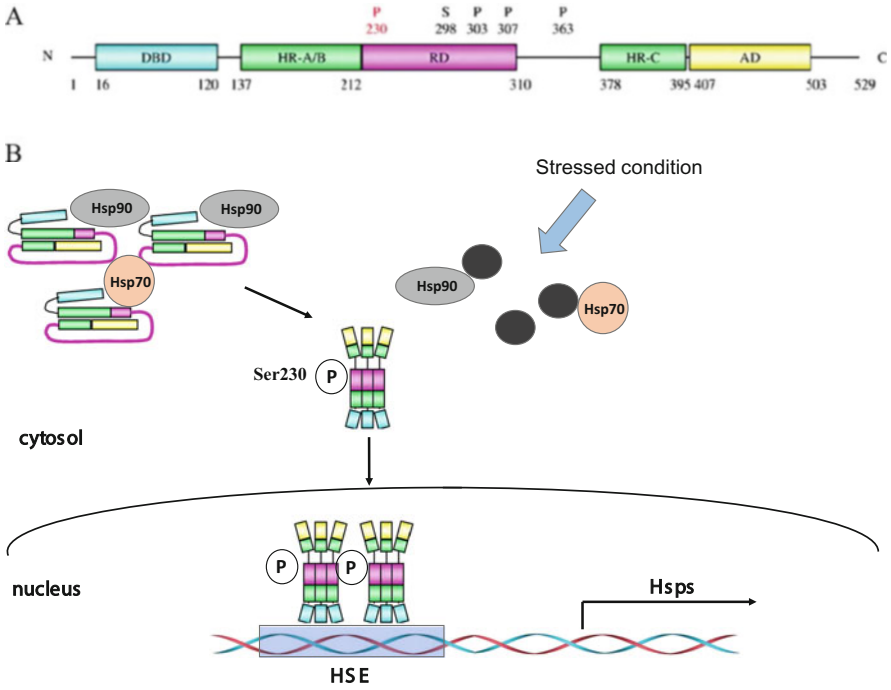

Fig. 12.1 Schematic representation to show the potential regulatory mechanism of HSF1. (**A**) Structure of HSF1. DBD indicates DNA-binding domain; HR, hydrophobic repeat; RD, regulatory domain; AD, transcriptional activation domain; P, phosphorylated site (the activating site is indicated in *red*); S, sumoylated site. (**B**) Under nonstressful conditions, HSF1 exists as a monomer whose transcriptional activity is repressed with HSP70 and HSP90 chaperones that interact with the activation domain of HSF1 and thereby block its activation potential. Under stressed condition, HSP70 and HSP90 switch to interactions with denatured proteins, releasing HSF1 and activation domain. Phosphorylation of the activating site (Ser230) is enhanced, thereby promoting the transcriptional activity of the trimerized HSF1. (Toko et al. 2008)

maximal transcription of the HSP genes, so it is necessary for HSF1 to be modified by phosphorylation and sumoylation to increase its transcriptional activity (Knowlton 2006). Therefore, phosphorylation is key to both activation and inhibition of HSF1, and dephosphorylation mediated by TNF-α can lead to inactivation.

HSPs also regulate HSF1 activity. Under nonstressful conditions, the proteins composed of HSP90, HSP40, heat shock cognate protein (HSC70), and carboxy-terminus of HSC70-interacting protein (CHIP) form a complex with HSF1 (Neef et al. 2011). The formation of this protein complex including HSF1 prevents the translocation of HSF1 from the cytosol to the nucleus and thus suppresses the activation of HSF1. Upon exposure to stress, HSF1 dissociates from the HSP90 protein complex and is translocated into the nucleus, where it binds to the heat shock element in the promoter region of various molecular chaperone genes for their expression (Guo et al. 2001).

12.2.3 Regulatory Role of HSF1 in the Heart

In cardiomyocytes, HSF1 can induce transcription of synapse-associated protein 97 (SAP97) through a SIRT1 (a deacetylase and longevity factor)-dependent interaction with HSEs (Ting et al. 2011). As a linker protein, SAP97 creates the scaffold complex that anchors several channels in the plasma membrane (Kim and Sheng 1996; Gardoni et al. 2007). Therefore, the increase in SAP97 through activation of HSF1 results in stabilization of voltage-dependent K^+ channels ($K_v1.5$ channels) and activation of both I_{Kur} and I_{to} in the cardiomyocytes and modification of responses to adrenergic signaling in the heart, influencing the shape and duration of action potentials in both atrial and ventricular myocytes (Ting et al. 2011).

In vascular smooth muscle cells, reduction of HSF1 amplifies the inflammatory response to angiotensin II (Chen and Currie 2006). HSF1 is primarily known as the transcription factor for the FasL, which has heat shock elements (HSE) in its promoter and is upregulated by HSF1 (Cooper et al. 2010). Activation of both NFκB and AP-1 increases with reduction in HSF1. HSF1 blocks the activation and recruitment of SP1 and AP-1 (Chen et al. 2004; Cooper et al. 2010). HSF1 has also been reported to block transcription of IL-1β by binding its transcription factor and to block expression of c*fos* and c*fms* (Xiao et al. 1999; Xie et al. 2002, 2003), which may explain the increased activation of AP-1 with loss of HSF1.

HSF1 activity is required to maintain redox state and attenuate oxidative damage in the heart under normal physiological conditions. Constitutive expression of HSP chaperones requires HSF1 activity. HSF1-dependent function is linked directly to a major antioxidative pathway through effects on the activity of glucose-6-phosphate dehydrogenase (G6PD). HSF1 deficiency reduces cardiac expression of Hsp25, αB-crystallin, and Hsp70, but not Hsp60 and Hsp90. Consistent with the downregulation of Hsp25, for example, a significantly lower glutathione (GSH)/glutathione disulfide (GSSG) ratio was associated with the decreased activity, but not protein content of G6PD. That such HSF1-dependent requirements are directly and functionally linked to maintain redox homeostasis and antioxidative defenses at normal states (Yan et al. 2002).

12.2.4 Heat Shock Paradox

Induction of the heat shock response with increased expression of the heat shock proteins is well established as a protective response (Currie and Karmazyn 1990). However, when an inflammatory stimulus precedes heat shock, there is an unexpected increase in injury, known as the heat shock paradox (Buchman et al. 1993; Wizorek et al. 2004). Adult cardiac myocytes would exhibit the heat shock paradox. HSF1 was a critical element for injury, and HSP60 is increased as part of the heat shock paradox despite the overall protective effects of the expression of heat shock

proteins (HSPs). Using TNF-α as the inflammatory stimulus followed by heat shock causes more apoptotic injury than any of the other treatments, although HS prior to TNF is protective. TNF/HS can cause a marked increase in NFκB activity. Overall, the heat shock paradox reflects a disassembly of the balance between HSPs and NFκB, viability and apoptosis, and health and inflammation (Kobba et al. 2011).

12.3 Ischemic Heart Disease and HSF

Ischemic heart disease (IHD) or myocardial ischemia is one of the leading causes of mortality all over the world. Myocardial ischemia develops when coronary blood supply to myocardium is reduced. HSF1, as a transcription factor that modulates the cytoprotective response, plays a significantly protective role in cardiac ischemic injury, including apoptosis, fibrosis, and angiogenesis. There is a complex interaction among HSF1, heat shock proteins, NFκB, and TNF-α. This interaction may produce fine-tuning of the inflammatory response. AP-1 activation is also modulated by HSF1.

12.3.1 HSF1 and Myocardial Infarction

HSF1, the transcription factor for heat shock proteins, is expressed in hearts, which has been found to play protective roles in ischemia/reperfusion injury and myocardial infarction. Hearts of the transgenic mice overexpressing a constitutively active form of HSF1 or inducible Hsp70 were more resistant to ischemia/reperfusion injury (Marber et al. 1995; Zou et al. 2003), as indicated by faster recovery of ST-segment elevation in ECG, smaller infarct size, and less apoptosis of cardiomyocytes. In the heart with acute myocardial infarction (MI), HSP72 is rapidly expressed to afford tolerance against myocardial injury under ischemic conditions (Hutter et al. 1994). Therefore, an increase in HSP72 after MI is beneficial for reducing the myocardial damage generated during the development of heart failure. HSP72 expression is predominantly regulated by HSF1.

The main therapeutic intervention after myocardial infarction is to reestablish the coronary blood flow supply. However, restoration of flow is accompanied by detrimental manifestation known as reperfusion injury (Verma et al. 2002). Normally, the reperfusion injury is triggered by a large burst of oxidant molecules accompanying with the inflammatory process. Intracellular reactive oxygen species (ROS), which is accumulated in the oxidative stress, induces myocardial damages. However, oxidative stress also initiates a counterregulatory pathway through the activation of cytoprotective mediators. Oxidative injury leads to activation of HSF1, a transcription factor that modulates the cytoprotective response through gene expression of HSPs (Knowlton and Sun 2001), in terms of translocation to the nucleus and accumulation of HSP70 and HSP90 expression in the ischemic-

reperfused heart (Nishizawa et al. 1999; Costa et al. 2009). Specifically, HSP70 is rapidly induced in response to ischemia and directly protects against myocardial damage, improves metabolic recovery, and reduces infarct size in hearts of transgenic mice (Marber et al. 1995; Suzuki et al. 1997; Lepore et al. 2001; Okubo et al. 2001).

HSF1 activation during ischemia may be induced by multiple cellular stress responses. A decrease in the concentration of high-energy phosphate compounds may be sufficient to activate HSF1 (Benjamin et al. 1992). Intracellular acidosis may also serve as an additional stimulus. Alterations in redox state have been documented to activate cardiac HSF1 DNA binding (Paroo et al. 2002) and activate HSF1 acutely during ischemia/reperfusion (Nishizawa et al. 1999). The δ isoform of CaMKII ($Ca2^{+}$/calmodulin-dependent protein kinase II), predominantly expressed in the heart, serves as antiapoptotic effect of cardiomyocyte triggered by oxidant stress, I/R injury, hypoxia, and Ang II stimulation via phosphorylation of HSF1 and subsequent induction of HSP72 (Peng et al. 2010). Granulocyte colony-stimulating factor (G-CSF) can induce cardioprotection against ischemia/reperfusion (I/R) through enhanced transcriptional activity of HSF1 and increase the association of HSF1 with signal transducer and activator of transcription 3 (Stat3), which contributed to the antiapoptotic effects on cardiomyocytes (Ma et al. 2012). In cardiomyocytes, protein kinase C (PKC) isoforms are involved in cardioprotection (Liu et al. 1999; Fryer et al. 2001). PKC-α not only increases the expression of HSP70 but also protects against simulated ischemia/reperfusion. An increase in PKC-α expression results in an increase in HSP70 gene transcription, but this transcriptional activation is HSF1 independent (Coaxum et al. 2007). Peroxisome proliferator-activated receptor-γ ligands, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), exert cardioprotective effects and attenuate myocardial reperfusion injury by enhancing DNA binding of HSF1 and upregulating the expression of the cardioprotective HSP70 (Zingarelli et al. 2007). It appears that a common consequence of stimuli that activate HSF1 is an increase in the concentrations of unfolded proteins within the cell, which may provide a common stimulus for induction of HSP gene expression (Williams and Benjamin 2000).

Negative regulation of HSF1 may be due to several mechanisms during unstressed conditions. In reperfusion injury, poly(ADP-ribose) polymerase (PARP), a chromatin-associated nuclear enzyme that is activated by stranded DNA nicks and breaks in damaged cells (Lautier et al. 1993), is a repressing factor of HSF1 activation and HSP70 expression (Zingarelli et al. 2004). Another negative regulator of HSF1-mediated transcription is glycogen synthase kinase 3β (GSK3β), which also impairs HSF1 DNA binding (Xavier et al. 2000).

Ischemic and reperfusion activate cardiac myocyte apoptosis, which is an important feature in the progression of ischemic heart disease. HSF1 has critical antiapoptotic features not only in tumors but also in heart cells. HSF1 protects cardiomyocyte from apoptosis under oxidative stress via activation of Akt/protein kinase B, downregulation of intracellular ROS generation, and inhibition of inactivation of Jun N-terminal kinase and caspase 3 (Zou et al. 2003). Apoptosis signal-regulating kinase-1 (ASK1) can affect the inhibitory effects of HSF1 on ROS

generation, JNK activity, and cardiomyocyte injury (Zhang et al. 2011). High-mobility group box 1 (HMGB1) is secreted by active inflammatory cells or impaired tissue cells under stress conditions (Rauvala and Rouhiainen 2010). Once released, extracellular HMGB1 participates in cardiac ischemia/reperfusion responses (Andrassy et al. 2008). HSF1 can effectively inhibit H_2O_2-induced cardiomyocyte death via negatively regulating HMGB1 expression at the early stage of oxidative stress and prevention of HMGB1 translocation at the late stage, which was associated with HSP27 and HSP90 upregulated by HSF1 overexpression (Yu et al. 2012). Ischemia/reperfusion (I/R) injury will stimulate extracellular and endogenous tumor necrosis factor-α (TNF-α) level and induce cardiomyocyte damages (Al-Shudiefat et al. 2013). HSF1 attenuated TNF-α-induced cardiomyocyte death via suppression of NFκB pathway, which not only inhibits activation of RelA at the early stage but also prevents its translocation from the cytoplasm to the nucleus afterward (Wu et al. 2013).

An increased oxidative stress caused by HSF1 deficiency has a detrimental effect on critical molecular targets such as adenine nucleotide translocator 1 (ANT1) and defines such functional consequences at the level of mitochondrial permeability transition pore (MPTP) opening in vivo (Yan et al. 2002). Moreover, Mehlen et al. have found that HSP27 protects cells from death through its conserved ability to raise the pool of reduced glutathione (GSH), which decreases the intracellular ROS level, and HSP25 plays a crucial role in the heart for cellular redox homeostasis (Mehlen et al. 1996). Therefore, HSF1 may downregulate ROS by inducing small HSPs such as HSP27 and HSP25.

12.3.2 HSF1 and Cardiac Pathologic Hypertrophy

Cardiac hypertrophy is one of the key causes of heart failure. The Framingham Heart Study revealed that cardiac hypertrophy is an independent risk factor for heart failure, arrhythmia, myocardial infarction, and sudden death (Levy et al. 1990; Haider et al. 1998). Cardiac hypertrophy is an adaptive response to increased wall stress. At the beginning, cardiac hypertrophy has beneficial effects to maintain cardiac output by reducing wall stress, which is called "adaptive hypertrophy" (Ruwhof and van der Laarse 2000); however, long-term stresses induce systolic dysfunction, leading to "maladaptive hypertrophy" or "pathologic hypertrophy" in the chronic phase, resulting in heart failure (Katz 1990). On the other hand, regular exercise can also induce cardiac hypertrophy without causing systolic or diastolic dysfunction, which is called "physiologic hypertrophy" (Pluim et al. 2000). Maladaptive hypertrophy is actually a result of imbalance between myocardial blood supply and oxygen demand, accompanying with cardiac fibrosis and cellular apoptosis.

HSF1 was first identified as a critical transcription factor that regulates cardiac hypertrophy in 2006. In the high-throughput DNA chip analysis, this study found *HSP* genes (*Hsp70* and *Hsp27*) were markedly upregulated in physiologic cardiac

hypertrophy. Accordingly, HSF1, which regulates HSP gene expression, is activated only in the heart of physiologic hypertrophy but not in chronic pressure overload-induced cardiac hypertrophy (Sakamoto et al. 2006). Constitutive activation of HSF1 in the heart (Nakai et al. 2000) significantly ameliorated death of cardiomyocytes and cardiac fibrosis and thereby prevented cardiac dysfunction as well as hypertrophy induced by chronic pressure overload (which is thought to induce pathologic cardiac hypertrophy). Conversely, when heterozygous HSF1$^{\pm}$ mice (Inouye et al. 2004) were forced to exercise (which is thought to induce physiologic cardiac hypertrophy), significant systolic dysfunction occurred. Likewise, cardiac function was significantly impaired from the early phase of pressure overload, when HSF1 activation was inhibited. Therefore, HSF1 is a key molecule for preservation of systolic function during the development of cardiac hypertrophy under both pathologic and physiologic conditions, which plays a critical role in the transition between adaptive and maladaptive hypertrophy.

Accumulation and aggregation of unfolded proteins are associated with an increase of protein synthesis in hypertrophied hearts and induce cardiomyocyte death that eventually leads to systolic dysfunction (Okada et al. 2005). Thus, the protective effects of HSF1 may be attributable to the functions of HSPs in protein folding and degradation (Toko et al. 2008). In addition to such well-known functions, accumulating evidence indicates that different HSPs directly act on the cell death machinery and inhibit the signaling pathway for cell death at various points (Sreedhar and Csermely 2004). For example, Hsp27 binds to cytochrome c and prevents it from binding to Apaf-1 (Bruey et al. 2000), whereas Hsp70 prevents Apaf-1 from recruiting procaspase-9 (Beere et al. 2000), thereby inhibiting apoptotic cell death. It is conceivable that sustained activation of HSF1 prevents the onset of cardiac dysfunction in hypertrophic hearts through the mechanisms involving a direct action of HSPs on the cell death machinery as well as their functions in protein degradation (Toko et al. 2008).

The production of autocrine/paracrine factors such as angiotensin II and endothelin 1 is increased by pathologic stimuli and plays a critical role in inducing pathologic cardiac hypertrophy. These factors bind to G protein-coupled receptors, leading to dissociation of the Gαq subunit and activation of downstream signaling molecules, which include negative regulators of HSF1 such as ERK and JNK. Accordingly, this signaling pathway may induce pathologic cardiac hypertrophy partly via the inactivation of HSF1 (Toko et al. 2008), although there is a conflicting report that angiotensin II does not influence the activity of HSF1 (Nishizawa et al. 2002).

For cardiac angiogenesis crucially involved in the adaptive mechanism of cardiac hypertrophy, HSF1 promotes cardiac angiogenesis through suppression of p53 and subsequent upregulation of HIF-1 in endothelial cells during chronic pressure overload, leading to the maintenance of cardiac adaptation (Zou et al. 2011).

12.3.3 HSF1 and Atherosclerosis

Atherosclerosis is an inflammatory- and immune-mediated disease, in which HSPs were repeatedly implicated to be crucial (Xu 2002). Several families of HSPs have been demonstrated to be expressed at high levels in atherosclerotic lesions (Berberian et al. 1990; Kleindienst et al. 1993; Rocnik et al. 2000; Kanwar et al. 2001). These highly expressed HSPs in lesions could promote disease progression via evoking proinflammatory and autoimmune responses (Xu 2002). Accordingly, there is an increased HSF1 activity in atherosclerotic lesions in vivo. In atherosclerotic lesions, HSF1 but not HSF2 is mainly localized in the nuclei, and the molecular weight of HSF1 from lesional extracts was larger than that of normal vessels, indicating that HSF1 in lesions was phosphorylated and activated (Metzler et al. 2003). Usually, HSF1 proteins in cultured cells do not markedly change in response to stress, e.g., heat shock or mechanical stress. However, protein levels of HSF1 in atherosclerotic lesions were much higher compared to normal vessels, suggesting different mechanisms of HSF1 activation and regulation of HSP expression in vivo from in vitro cultured cells (Metzler et al. 2003). Therefore, in vivo microenvironment of the vessel wall is of importance in regulation of HSF1 production and activation.

It is believed that Low-Density Lipoprotein (LDL) and oxidized LDL are important in the development of atherosclerosis. Oxidized LDL possesses several proatherogenic properties, including interactions with several receptors, leading to the engorgement of cells with lipids, inhibition of endothelium-dependent vascular relaxation, cytotoxicity to proliferating cells, and stimulation of chemoattractant secretion (Witztum and Steinberg 2001). In vitro, Triglyceride-Rich Lipoprotein (TRLP), oxidized TRLP, LDL, and oxidized LDL do not activate HSF1. However, oxidized LDL and oxidized TRLP may exert their role in HSF1 activation in vivo via stimulating cells producing a panel of cytokines (Niemann-Jonsson et al. 2000). TNF-α, which is present in high concentrations in atherosclerotic lesions (Hansson et al. 2002), can activate HSF1 in smooth muscle cells (SMCs), supporting the role of cytokines in HSF1 activation in atherosclerotic lesions.

Mechanical stretch is a crucial factor in the pathogenesis of atherosclerosis. Using an in vitro mechanical stress model, it has been found that we provide mechanical forces that can evoke rapid activation of HSF1 in SMCs, followed by elevated HSP70 protein levels (Metzler et al. 2003). Interestingly, SMC lines stably expressing dominant negative Rac (Rac N17) abolished HSP protein production and HSF1 activation induced by mechanical forces, whereas a significant reduction of HSF1 activities was seen in Ras N17-transfected cell lines (Xu et al. 2000). Therefore, mechanical stretch-induced HSF1 activation was regulated by Rac/Ras GTP-binding proteins (Xu et al. 2000) that may be primarily responsible for HSF1 activation seen in atherosclerotic lesions.

In summary, risk factors for atherosclerosis, such as biomechanical stress and cytokines induced by hypercholesterolemia, directly stimulate cells of the arterial wall to express high levels of HSF1, which leads to increased expression of HSPs.

Pathologically, overstimulation by the risk factors results in cell death, which releases intracellular HSPs into intercellular spaces to form soluble HSPs that lead to proinflammatory and autoimmune responses (Metzler et al. 2003).

12.4 Heart Failure and HSF

Heart failure is the final common endpoint of various heart diseases, leading to cardiovascular death. Heart failure is also considered as a chronic state of inflammation and stress on the heart tissue. It is generally accepted that heat shock (HS) provides myocardial protection of cardiac mechanical function and metabolism via the enhanced HSF1 activation and synthesis of several HSPs (Yellon et al. 1992).

In the failing hearts, both HSF1 and HSF2, the transcription factors controlling HSP expression, are increased. But nuclear translocation of the HSF1 was markedly reduced in the viable myocardium upon the pathological stresses. HSF1 in the cytosolic fraction and the HSP90 chaperone complex containing HSF1, a repressor of HSF1, were increased, whereas that of HSF1 in the nuclear fraction was reduced. So an increase in the multichaperone complex, especially the HSF1-HSP90 interaction, is associated with attenuation of HSF1 translocation into the nucleus (Marunouchi et al. 2013a). On the other hand, reduced levels of phosphorylated GSK3β (inactive) lead to an increase in the amount of the active GSK3β enzyme for the phosphorylation of HSF1 Ser303, and the activation of HSF1 can be impaired via the increased phosphorylation of the Ser303. Accordingly, cardiac protective HSP72 induction is impaired in the failing heart (Marunouchi et al. 2013b).

HSP72 is a ubiquitous protective protein that is well established as cardioprotective in heart failure. Although HSF1 is increased in the failing heart, HSF72 is not increased accordingly, which shows the activation of HSF1 is suppressed. Because there is no increased phosphorylation of serine 230 or serine 303/307 in HSF1, which is thought to regulate its activity, and electrophoretic mobility shift assay (EMSA) showed no increase in HSF-binding activity with heart failure (Wang et al. 2010). In contrast, HSP60 levels are upregulated in the failing heart. HSP60 on the surface of cardiac myocytes from failing hearts was associated with apoptosis, which may be deleterious (Lin et al. 2007). The increase in HSP60 expression in heart failure is potentially driven by NFκB activation not by activation of HSF1 from the inflammatory state of heart failure (Wang et al. 2010).

There are several different phosphorylation sites for HSF1 activation in response stress. There was no difference in phosphorylation of serine 303/307 between the control and congestive heart failure (CHF). Phosphorylation at serine 230 can increase activation of HSF1, but in failing hearts, there is no significant change in phosphorylation at this site (Holmberg et al. 2001). Other phosphorylation sites are likely involved in the regulation of HSF1 activation, which remains verification (Guettouche et al. 2005).

It is conceivable that sustained activation of HSF1 prevents the onset of cardiac dysfunction in hypertrophic hearts through the mechanisms involving a direct action of HSPs on the cell death machinery as well as their functions in protein degradation.

12.5 Future Perspectives

The past several years have seen a lot of studies of the protective role of HSF in cardiovascular disease during the response to various stressors. These studies could lead to a new strategy for prevention and treatment of cardiovascular diseases such as hypertension, ischemic heart disease, and atherosclerosis. However, the mechanisms underlying the activation of HSF, including its regulation by phosphorylation, sumoylation, and acetylation, remain fully understood. Because there have been many reports that induction of HSF1 and HSPs has a beneficial effect in animal models of cardiovascular disease, activation of HSF1 and HSPs could be a novel therapeutic strategy for various cardiovascular diseases. In the failing heart, the induction of HSP72 was decreased in spite of an increase in HSF1 because of the HSF1-HSP90 interaction associated with attenuation of HSF1 translocation into the nucleus. This suggests the complex regulatory roles of HSF1 and other HSPs in the protection of the heart upon the stress. However, the signal transduction pathways leading to full activation of the various *HSP* genes in the human heart and blood vessels are still incompletely understood. Knowledge of these pathways could lead to the development of well-directed synthetic drugs activating *HSP* genes for patients with cardiovascular disease and provide novel therapeutic strategies.

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