The role of heat shock proteins in the pathogenesis of heart failure (Review)

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Abstract. The influence of heat shock proteins (HSPs) on protein quality control systems in cardiomyocytes is currently under investigation. The effect of HSPs on the regulated cell death of cardiomyocytes (CMCs) is of great importance, since they play a major role in the implementation of compensatory and adaptive mechanisms in the event of cardiac damage. HSPs mediate a number of mechanisms that activate the apoptotic cascade, playing both pro- and anti-apoptotic roles depending on their location in the cell. Another type of cell death, autophagy, can in some cases lead to cell death, while in other situations it acts as a cell survival mechanism. The present review considered the characteristics of the expression of HSPs of different molecular weights in CMCs in myocardial damage caused by heart failure, as well as their role in the realization of certain types of regulated cell death.

Contents

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1. Introduction

The reliability of cellular protein composition is important for proper cellular function in various tissues, especially in the myocardium, as cardiac myocytes (CMCs) are terminally differentiated cells with very limited regenerative potential (1). At the same time, the metabolic demands of the heart require a tight control of protein quality (2). Cellular stress in the myocardium, which occurs during ischemia (3), hypertension (4) and metabolic disorders including diabetes mellitus (DM) (5), can disrupt protein homeostasis and cause abnormal folding of cellular proteins. Intracellular accumulation of toxic, misfolded proteins and their aggregates may contribute to the development of heart failure (6). Cells have an innate mechanism for detecting protein misfolding, which they can use to repair or remove these proteins. This mechanism is called 'protein quality control' and involves three main pathways (Fig. 1) (7,8). First, misfolded proteins are exposed to heat shock proteins (HSPs), which are characterized as molecular chaperones. If the chaperone system fails to refold denatured proteins, they are ubiquitinated by an activated second system and delivered to the proteasome mechanism for subsequent degradation. When these systems are disrupted or overloaded, such ubiquitinated proteins accumulate in agresomes, perinuclear structures which are ultimately utilized by autophagy, the third mechanism (9-12).

HSPs are a family of conserved proteins that can contribute to proper protein folding, maintain protein stability and act as molecular chaperones to regulate cellular metabolism, tissue composition and other processes (13). HSPs are also called stress-induced proteins because of their ability to stabilize and repair proteins during their synthesis in the cell under the action of unfavorable agents on the cell (14,15). Meanwhile, they are also involved in the modulation of inflammatory response, oxidative stress and metabolism (16-18).

The effect of HSPs on the regulated cell death of CMCs is of great interest, as they contribute significantly to the implementation of compensatory and adaptive mechanisms, such as in the case of cardiac damage (19-21). HSPs mediate a number of activation mechanisms of the apoptotic cascade, playing both pro- and anti-apoptotic roles depending on their

cellular localization (22). In some cases, autophagy can lead to cell death, while in other cases it acts as a mechanism for their survival (23,24).

Despite the availability of numerous data, concerning the role of HSPs and factors involved in programmed cell death in response to pathological agents, there is currently no clear idea of their role in the pathogenesis of heart failure caused by various types of cardiovascular pathology.

2. The role of HSPs in the structural and metabolic changes of CMCs in various types of cardiovascular pathology

HSPs and inflammation. HSPs are involved in inflammation, which mediates various pathological processes in the myocardium. Schroder and Tschopp (16) and other scientists paid special attention to the role of HSPs in the formation of intracellular platforms; inflammasomes, which are activated by 'danger' signals and induce inflammatory caspases, mainly caspase-1, which contributes to the production of pro-inflammatory cytokine IL-1β (25,26). A number of other cytokines from the family of pro-inflammatory mediators are also related to these processes (27). TNF is associated with the induction of necrosis, cell damage and tearing of membrane molecules, membrane modularity (28,29). Some members of the HSP family support inflammasome activation, while others inhibit it. In particular, HSP60 (Fig. 2) is required for the phosphorylation and nuclear localization of NF-kB after stimulation by IL-1β in microglia (30). Knockdown of the HSP60 gene leads to inhibition of phosphorylation of the p65 NF-kB subunit and consequently to suppression of NF-kB nuclear translocation. Presumably, HSP60 promotes p65 phosphorylation (31). This activation of the NF-kB pathway leads to the overexpression of both pro-IL-1β and nucleotide-binding oligomerization domain-containing protein 3 (NLRP3), corresponding to the 'priming' step of NLRP3 inflammasome activation (32). HSP60 also induces mitochondrial damage, as evidenced by a decrease in their membrane potential after HSP60 overexpression and treatment with IL-1β. This is accompanied by an increase in reactive oxygen species (ROS) production, which contributes to oxidative stress, which in turn activates the NLRP3 inflammasome (33).

HSPs and platelets, thrombosis. Platelets serve as regulators of hemostasis. Upon interaction with extracellular matrix proteins, such as collagen, platelets are activated, leading to shape change, secretion, filopodia formation and ultimately aggregation (34-36). Platelet aggregation is largely mediated by activation of the platelet integrin αIIbβ3, which undergoes conformational changes in response to stimulation of soluble fibrinogen binding (37,38). The role of HSPs in the activation of thrombus formation is of great interest, particularly in relation to the problem of preventing coronary artery thrombosis.

Rigg *et al* (39) demonstrated the role of HSP70 in the modulation of integrin activation. The regulation of integrin and platelet conformational changes by molecular chaperones together with thiol isomerases has been suggested. The study demonstrated the importance of intracellular HSP70 in the regulation of integrin activation and platelet secretion, but the involvement of extracellular HSP70 in the modulation of platelet integrin activity and thrombus formation should also be considered (39). Activated HSP70 can be translocated to the cell surface and secreted by exosomes. In the extracellular space, HSP70 is able to bind Toll-like and other receptors on monocytes, macrophages, dendritic cells, followed by activation of NFκB/MAP kinase pathways, initiating an inflammatory response in tissues (40-42).

HSP and arterial hypertension (including in combination with DM). In a recent study by Blagonravov *et al* (43), it was found that the production of HSPs can either increase or decrease under the action of various stress factors. In particular, the expression of HSP60 in CMCs of left ventricular (LV) myocardium decreased both during hemodynamic overload of the LV caused by hypertension and during metabolic disturbances in the myocardium associated with DM. Moreover, the combination of hypertension and DM was not associated with a synergistic negative effect on this process. On the contrary, a slightly less pronounced inhibition of HSP60 production was observed. Suppression of HSP60 synthesis is most likely to be associated with energy deprivation due to LV overload and/or insulin-dependent DM, since this protein is ATP-dependent.

HSPs and metabolic syndrome. Metabolic syndrome is a risk factor for the development of heart failure and DM. The features of the metabolic syndrome are systemic inflammation and oxidative stress, which can enhance the expression and release of HSP (44). HSPs play a role in cell signaling and regulation of cell metabolism in conditions of insulin resistance (45). In obesity, an uncontrolled inflammatory reaction and a disorder of the body's defense system play an important role in inhibiting the signaling cascade of insulin receptors and, as a consequence, a disorder of systemic metabolic homeostasis (41). Regulation of HSP expression at the gene level is an important aspect of HSP72 activity in metabolic syndrome. Overexpression of HSP72 leads to an increase in the number of mitochondria in cells, the oxidative capacity and the sensitivity of cells to insulin (44,45). Similarly, lack of HSP72 expression results in mitochondrial dysfunction and insulin resistance (46,47). In addition to increasing HSP72 levels and consequently the ability to improve mitochondrial quality control, exercise also contributes to an increase in the expression of peroxisome proliferator-activated receptor γ-coactivator 1-α (PGC1a) (48). PGC1a is the major transcriptional coactivator for mitochondrial formation (49). The upstream regulatory elements of the PPARGC1A gene were found to contain the heat shock element (HSE) binding sequence (50). This HSE sequence provides a docking site for the primary HSP transcription factor, heat shock factor 1 (HSF1) (51). Numerous HSF1 gene activation and knockdown experiments have convincingly demonstrated that HSF1 is the master regulator of mitochondrial biogenesis, enzymatic function and whole-body metabolism (48). These data illustrate a coordination of HSF1 downstream targets (HSP1 and PGC1a) in the regulation of mitochondrial biogenesis, quality control and enzymatic function in metabolic demand and/or chronic disease (52).

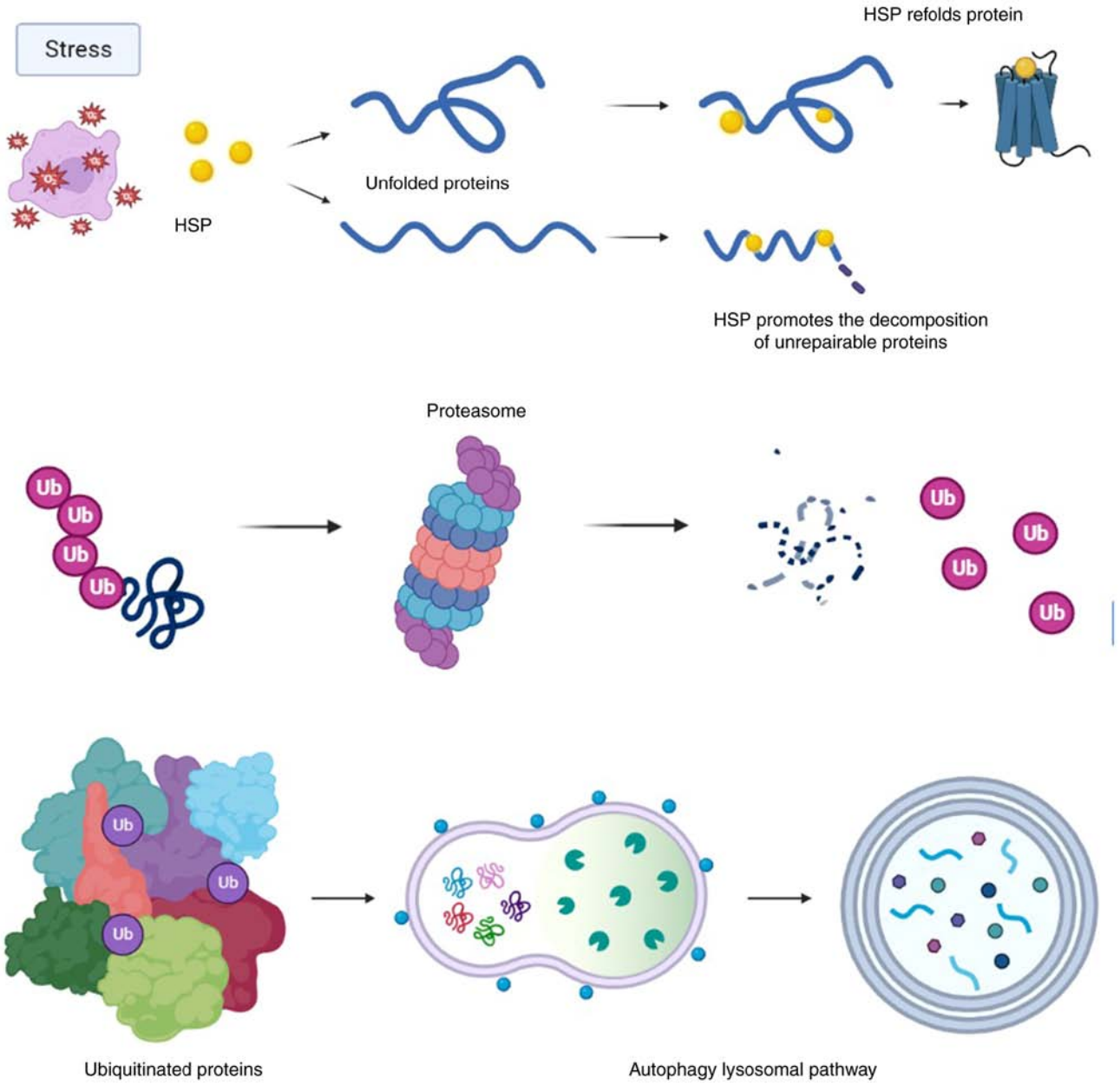

Figure 1. The PQC three main pathways. This system can be targeted to restore cell self-renewal, enhancing the survival of CMCs. PQC, protein quality control; CMCs, cardiomyocytes; HSP heat shock protein.

HSPs and myocardial ischemia. Elevated blood levels of HSPs have been found in patients with coronary artery disease (CAD), although the source of these proteins is still controversial (53). In general, the expression of HSPs appears to be increased in response to ischemia and their dysregulated production contributes to the development of cardiovascular disease (54-57).

Extracellular HSP70 has been found to be an independent predictive marker of mortality in patients with progressive heart failure or sudden cardiac death (58-60). Its role in the development of hypertension-induced cardiac hypertrophy and myocardial fibrosis has also been demonstrated (61-63). It is also notable that HSP70 is a ligand for damage-associated molecular pattern receptors, which can induce inflammation in the myocardium (64,65).

The properties of extracellular HSP90 have been demonstrated in a study by Ranek *et al* (6) in the context of progressive LV hypertrophy. In pathological cardiac hypertrophy, LV mass increases in parallel with extracellular matrix deposition, followed by fibrosis and heart failure (66-68). The main mediator of this process is TGF-β, which is secreted by CMCs and acts on collagen-secreting fibroblasts (69-71). Extracellular HSP90 appears to play some role in stabilizing the signal of TGF-β by influencing the cascade of processes mediating TGF-β induction (72-74). Inhibition of extracellular HSP90 reduces collagen production and stimulation of the canonical TGF-ß pathway (54,74). Since fibrosis is one of the major factors influencing the pathogenesis of a number of chronic cardiac diseases, including CAD and heart failure, targeting extracellular HSP90 can be considered an important point of application for therapeutic intervention with functions different from those characteristics of the intracellular pool of this particular HSP.

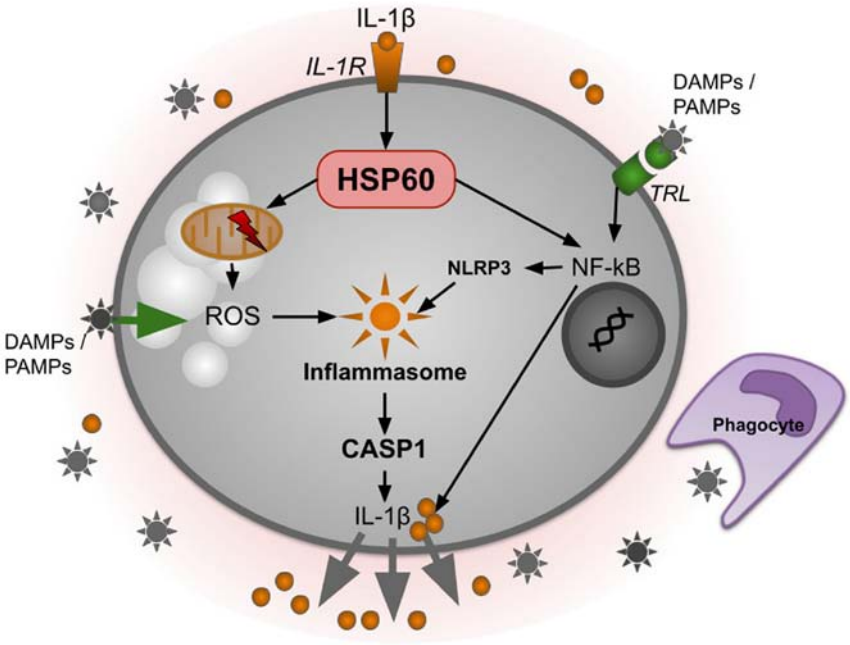

Figure 2. The mechanism of HSP60 regulation endogenous IL-1β by stimulating NLRP3 inflammasome activation. HSP heat shock protein NLRP3, nucleotide-binding oligomerization domain-containing protein 3; ROS, reactive oxygen species; DAMPs, damage-associated molecular pattern receptors; PAMPs, pathogen associated molecular patterns; CASP, caspase.

3. Features of the induction of small ATP-independent HSPs in myocardial damage

Small HSPs are ATP-independent proteins and represent the first line of defense in preventing intracellular protein aggregation under cellular stress when denaturation is highly activated (75,76). At the same time, high molecular weight HSPs, such as HSP60, HSP70 and HSP90, bind unfolded or misfolded proteins and promote their refolding using the energy of ATP hydrolysis (77-79). Therefore, under cellular stress and energy deprivation, ATP-independent small HSPs are able to rapidly and metabolically prevent protein aggregation, maintain denaturing proteins in a folded state and inhibit the denaturation process until ATP-dependent HSPs complete the refolding process (80-82). If proper folding does not occur, small HSPs contribute to the clearance of denatured proteins by directing them to the pathway of degradation mechanisms (Fig. 3) (83-85).

Currently, the role of HSPs in inflammation and their antioxidant capacity are of considerable interest, especially in the aspect of modulating the progression of atherosclerosis by altering its inflammatory mechanisms (86-88).

HSPs are also activated in response to the appearance of oxidized low-density lipoproteins and mediate an anti-inflammatory mechanism through the release of pro-inflammatory IL-10 as well as through the activation of NFκB (89-91). The intracellular function of the HSP27 chaperone is regulated by phosphorylation and dephosphorylation in large aggregates that modulate the assembly of an ATP-independent network. As a chaperone, HSP27 is involved in DNA stabilization, supports antioxidant responses and also acts as an anti-apoptotic factor (92-94). Extracellular release of HSP27 from tissues where blood vessels are affected by atherosclerosis may result from cellular injury or occur in association with secretory lysosomes or exosomes. In its extracellular location, HSP27 binds to a variety of cell membrane receptors on endothelial and immunocompetent cells, including CD91, CD40, CD36, CD14, scavenger receptor A (SR-A) and Toll-like receptors (TLRs) (95,96). The recombinant receptor HSP27 induces TLR-mediated NFκB activation with secretion of both pro- and anti-inflammatory cytokines (55). According to the available data, HSP27 provides protection against the progression of atherosclerosis (22,97).

In a recently published study by Sklifasovskaya and Blagonravov (98), the results of assessment of HSP10 and HSP27 expression in rat LV myocardium in hypertension, DM and their combination were presented. In case of combination of hemodynamic overload and DM, small HSPs showed different expression levels in CMCs. This may be due to activation of different pathways of cell protection and damage. In particular, HSP27 expression increased only in arterial hypertension (AH) of longer duration, while the increase in HSP10 expression was observed in combined pathology. Thus, the levels of ATP-independent HSP10 and HSP27 increase in certain types of myocardial alterations associated with energy deficit. Expression of HSP10 and HSP27 in CMCs changed inversely in AH of different duration, insulin-dependent DM and their combination. Protein HSP27 may play a more important role in cardioprotection in long-term hypertension and protein HSP10 in the case of the combination of AH and DM (98).

Induction of mitochondrial (mt) ROS during hyperglycemia is a key event responsible for endothelial activation and damage (99). HSP22 has been shown to protect vascular endothelium from hyperglycemia-induced damage by reducing mtROS production (100-103). Yu *et al* (101) performed a series of studies using a high fat diet and a streptozotocin model to induce DM. They also exposed human umbilical vein

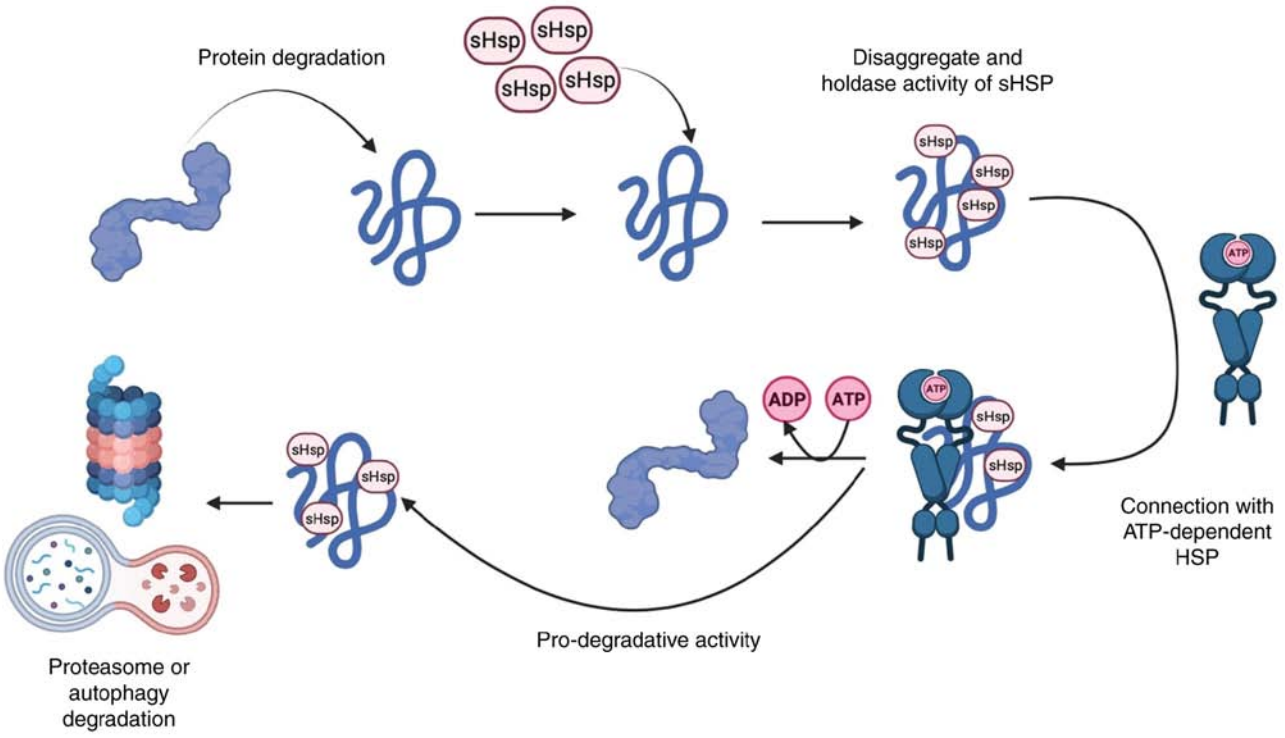

Figure 3. Role of sHSPs and ATP-dependent HSPs in the PQC regulation. sHSP, small HSP; HSP heat shock protein; PQC, protein quality control.

endothelial cells to a high concentration of glucose after overexpressing or silencing HSP22 to investigate the role of the latter. It was found that HSP22 significantly reduced endothelial cell activation and vascular lesions by inhibiting endothelial adhesion, suppressing mtROS-mediated endothelial activation and injury, abolishing a hyperglycemia-induced increase in mtROS and also reducing cytokine secretion. In addition, HSP22 attenuated mtROS and mitochondrial dysfunction in hyperglycemia-stimulated endothelial cells (101).

4. The role of HSPs in regulated cell death

The role of HSPs in autophagy. An important role in the process of autophagy is its regulation by HSPs (104-106). During heat shock, HSP production and autophagy activation are reactions aimed at maintaining the quality of cellular proteins and they complement each other under cellular stress (107,108). Heat stress can lead to protein aggregation and contribute to the development of dysfunction of individual elements of the intracellular environment (10,109-111). Insufficient autophagy or partial degradation of damaged organelles leads to the generation of ROS and the loss of the major functions of lysosomes, resulting in cell death (112-114). In addition, inhibition of autophagy has been observed during the development of myocardial hypertrophy in response to deletion of the Atg5 gene in mouse CMCs (115).

In the case of cardiovascular pathology, cellular stress may also be due to cardiac overload associated with increased resistance to cardiac output caused by hypertension or aortic stenosis. An increase in the autophagic flux of CMCs occurs in association with their hypertrophy (116,117). Myocardial ischemia is associated with a transient increase in autophagic flux, which, however, decreases over time and falls below normal baseline levels (19,118-120). In a model of acute focal LV ischemia, it was shown that the content of Beclin-1 in the CMC cytoplasm was significantly increased on day 1 and later, on days 3 and 5, it gradually decreased but remained above the control level (20). In ischemia, the intensification of CMC autophagy is aimed at replenishing metabolic substrates and removing damaged organelles (121-123). Nutrient depletion stimulates AMP-activated protein kinase, which in turn inhibits mTOR, thereby removing the main inhibitory factor in this process (124-126). In this context, autophagy is considered to be an adaptive response to ischemic injury with cardioprotective effects. Thus, targeted activation of autophagy may be a potential therapeutic approach to heat stress-induced cardiovascular dysfunction (23).

A study showed that HSPB6 regulates the ubiquitination and proteasomal degradation of BECN1. This effect appears to be mediated by a direct interaction of HSPB6 with BECN1 (127). These ideas concerning the role of HSPB6 in autophagy were generated in the context of the description of a novel human mutation in the gene encoding HSPB6 (HSPB6S10F) identified in patients with dilated cardiomyopathy (DCM) (128,129). Negative effects of HSPB6S10F were associated with autophagy dysregulation. It is known that constitutive autophagy in the heart under basal conditions is a homeostatic mechanism aimed at maintaining myocyte size, structure and function of the heart (130). It has also been found that the activity of autophagy was significantly reduced in CMCs with the mutation of the HSPB6S10F gene, as evidenced by the decreased number of autophagosomes and inhibition of autophagic flux. Under these conditions, the rate of CMC apoptosis increases and hypertrophic remodeling develops, ultimately contributing to the progression of heart failure (127). Similar negative effects were associated with a decrease in the interaction of

mutant HSPB6S10F with Beclin1 (BECN1), leading to BECN1 ubiquitation and its degradation by the proteasome. As a result, autophagy flux is significantly suppressed and CMC apoptosis is enhanced. Conversely, overexpression of wild-type HSPB6 (HSPB6 WT) contributed to increased BECN1 levels and also competitively repressed BECN1 binding to Bcl2, thereby stimulating autophagy (127). These data reveal a novel regulatory mechanism by which HSPB6 promotes cell survival through its interaction with BECN1.

Depending on the specific cellular conditions, autophagy can both protect cells from death and act as a means of cellular self-destruction (131,132). The protective mechanism of autophagy is implemented as follows: Organelles and/or parts of the cytoplasm are engulfed by double-membrane autophagic vacuoles, resulting in the physiological utilization of old or damaged organelles (133,134). This provides cells with metabolic substrates to meet energy demands during cellular stress (135,136). However, the accumulation of these vacuoles and further activation of the autophagic pathway represents an alternative mechanism of cell death by atrophy and functional collapse (type II cell death) (137-139). Autophagy can also activate apoptotic (type I) or necrotic (type III) cell death programs by activating common regulators such as Bcl-2 family proteins (140,141).

In a recently published study by Blagonravov *et al* (142), the role of BECN1-dependent autophagy was evaluated in hypertension, DM and their combination. The activation of Bax and Bcl-2 was also examined. It was shown that chronic hypertensive overload of the LV is associated with a decrease in the rate of CMC autophagy. In isolated DM and its combination with hypertension, the opposite effect was observed, which was manifested as a significant increase in the basal level of BECN1-dependent autophagy. In the light of the concept of protein quality control, this phenomenon can be considered as a mechanism for the survival of damaged cells. In hypertension and isolated DM, there is an induction of the apoptotic cascade in LV CMCs, as indicated by an increase in Bax expression and a decrease in the Bcl-2/Bax ratio. At the same time, in the combined pathology, the level of Bax does not increase as significantly as in the other groups, but it remains higher than in the control group. The level of Bcl-2 was also significantly increased and the Bcl-2/Bax ratio tended to increase, but remained below the control. This indicates a decrease of the apoptotic cascade in the comorbid pathology compared to isolated hypertension and DM (142,143).

According to the results obtained by Blagonravov *et al* (43), it is possible to reveal the role of HSP60 and its co-chaperone expression in DM. In particular, the level of BECN1 was increased in the DM group relative to HSP60/HSP10 and in the combined hypertension and DM group, the HSP60/HSP10 chaperone complex and BECN1 protein were expressed at the same level.

This fact indicates that the activation of these proteins plays a maladaptive role in the activity of CMCs, which can serve as an important marker for assessing the progression of vascular damage in this type of pathology. A decrease in the expression of the HSP60/HSP10 complex relative to Bax was also found in all the pathological models studied, while this difference was less pronounced in the combined hypertension with DM group (43,98,143).

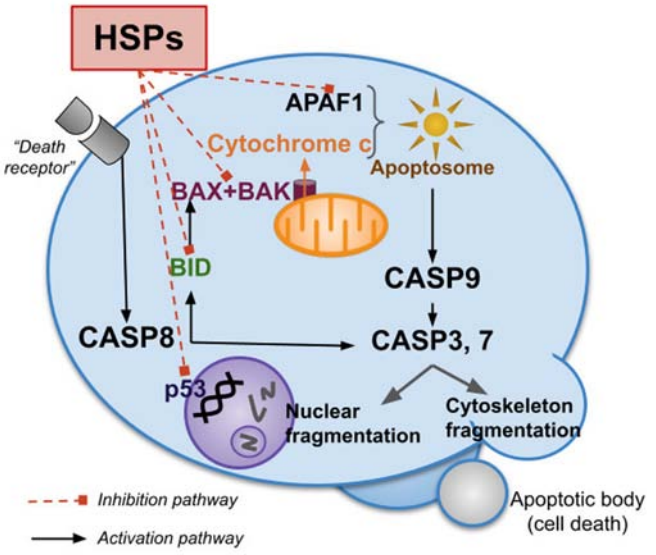

Figure 4. The role of HSPs in suppression of pro-apoptotic factors and inhibition of the apoptotic protease cascade. HSP heat shock protein; CASP, caspase; Apaf1, apoptotic protease activating factor 1.

Thus, a decrease in the production of HSP60 can be considered as one of the pathophysiological mechanisms of LV myocardial damage caused by hypertension and/or DM. In the mentioned study, the expression of HSP27 in LV myocardium was also evaluated. In the group with longer duration of hypertension (SHR rats aged 57 weeks), the ratio of Bax and Bcl-2 was the most pronounced, while the level of HSP27 was also the highest in all groups, which may indicate the activation of protein defense mechanisms directed to Bax binding (43,98,143).

It can be concluded that the role of HSP in autophagy regulation and modulation of the apoptotic cascade requires further investigation.

The role of HSP in apoptosis. Apoptosis, or programmed cell death, is characterized by the activation of the caspase cascade: 'Initiator' caspases induce a chain reaction of specific 'effector' caspases (144-146). These, in turn, are cleaved and thus activate each other. There are two main pathways of initiator caspase activation (147,148). The extrinsic pathway is associated with 'death receptors' on the cell surface, while the intrinsic pathway is induced by pro-apoptotic factors such as cytochrome c released from mitochondria. Cytochrome c, which binds to apoptotic protease activating factor 1 (Apaf-1) and pro-caspase-9, forms an apoptosome that stimulates the activation of caspase-9, which then activates the 'effector' caspase-3 and initiates the apoptotic protease cascade (149,150).

HSPs have a wide range of functions in apoptotic processes. Most of them are aimed at their suppression (151,152). Notably, the same cellular stress signals that induce apoptosis also stimulate HSP synthesis and release. However, when HSP production is increased, apoptosis is inhibited due to the suppression of pro-apoptotic factors such as p53, Bax, Bid, Akt, Apaf-1 and other members of the Bcl-2 family (Fig. 4). HSPs promote cell survival by protecting cells from changes in cellular redox homeostasis and stabilizing the cytoskeleton (152). In addition, HSPs can directly inhibit several steps

of the apoptotic pathway (153). HSPs also inhibit the release of pro-apoptotic molecules from mitochondria, thereby reducing caspase activation (151,154-156).

During the execution of the apoptotic cascade and under ATP deprivation, HSP60 protects mitochondrial proteins, facilitates their folding and prevents their degradation (157,158). In particular, when the Hsp60 gene is deleted in CMCs of young mice, HSP60-dependent mitochondrial proteins are degraded by LONP1 and mitochondrial dysfunction develops, which is one of the mechanisms of DCM and heart failure (159). Cytosolic HSP60 co-localizes with Bax and plays an anti-apoptotic role in cardiac myocytes. Loss of cytosolic HSP60 induces mitochondrial Bax translocation, cytochrome c release and caspase-3 activation, leading to apoptotic cell death (30). In addition, hypoxia triggers apoptosis by inducing dissociation of the HSP60-Bax complex through translocation of cytosolic HSP60 to the membrane and Bax to the mitochondria (160).

It is also worth considering the possibility of increasing the level of Bcl-2 in cells and reducing the activation of the apoptotic cascade by HSPB1. Tian *et al* (161) showed that HSP27 can attenuate oxidative stress-induced apoptosis in endothelial cells by increasing the level of Bcl-2 and decreasing the content of cleaved caspase-3 and Bax. In addition, under ER stress, HSP27 promotes ERK-mediated phosphorylation and Bim degradation by inhibiting the mechanisms of the intrinsic pathway of apoptosis initiation (162). HSP27 can also directly bind to cytochrome c in the cytosol, inhibiting apoptosome formation and interfering with downstream caspase activation. HSP27 can also suppress apoptosis by inhibiting mitochondrial Smac release and subsequent activation of the descending caspase cascade (161). The anti-apoptotic properties of HSP27 are attributed to its direct interaction with caspase-3. HSP27 binds to the pro-domain of caspase-3 and inhibits its proteolytic activation (161,163).

The role of HSP70 in the initiation of the apoptotic cascade has also been demonstrated in a model of myocardial ischemia/reperfusion injury (164-166). Overexpression of HSP70 in the myocardium and endothelium has a cardio-protective effect and increases myocardial injury tolerance. These mechanisms are associated with inhibition of apoptosis and oxidative stress and improvement of endothelial function (60,167). Myocardial HSP70 activates mitochondrial superoxide dismutase Mn-SOD and inhibits nuclear translocation of phosphorylated eukaryotic elongation factor 2 and apoptosis inducing factor, resulting in improvement of mitochondrial function and suppression of apoptosis (168,169). In addition, an increase in mitochondrial aldehyde dehydrogenase 2 activity triggers the accumulation of 4-hydroxynonenal during ischemic myocardial injury, which initiates pro-apoptotic signaling by reducing HSP70 and activating the JNK/p53 pathway. This mechanism ultimately contributes to the development of heart failure, whereas the aforementioned process can be reversed by overexpression of HSP70 (170). It has also been shown that intracellular HSP70 has a cardioprotective effect, whereas extracellular HSP70 appears to be pro-apoptotic (171).

Thus, cytosolic HSPs protect the myocardium from ischemia/reperfusion injury by inhibiting the activation of the apoptotic cascade in CMCs. In particular, the intracellular or extracellular location of HSPs is very important for their function in myocardial infarction or ischemia-reperfusion. Intracellular HSPs have cardio-protective properties, whereas extracellular HSPs exhibit cardio-toxic effects during ischemia-reperfusion.

5. Conclusions and perspectives

HSPs are an important component of the protein quality control system in the cell, both under normal and pathological conditions. They ensure the correct assembly of a number of intracellular proteins and regulate a significant part of the synthesis processes. Insufficient or excessive production of HSPs leads to disruption of cell homeostasis and may also contribute to the activation of cellular stress. This can result in endoplasmic reticulum damage, mitochondrial dysregulation and modulation of regulated (programmed) cell death, including apoptosis and autophagic flux.

Numerous studies (6,21,41,43,44,56-64) confirm a significant increase or decrease in myocardial HSP production in a variety of cardiac diseases, heat stress and metabolic disorders. Recently, the possibility of inducing HSPs to protect myocardial cells during oxidative stress caused by energy deprivation has been widely discussed. This approach is considered as a therapeutic method in the treatment of cardiovascular diseases of various origins, including DM.

Understanding the mechanisms of action of HSPs in the cardiovascular system can serve as a basis for the development of new methods of pharmacotherapy of cardiac pathology.

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Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Authors' contributions

AS and MB conceived the study and wrote the original draft. SS, SC, AR, KA, DP, VG and EA participated in writing and editing the manuscript. SS and EA edited the manuscript. All the authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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