Redox Biology 34 (2020) 101555

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Insights of heat shock protein 22 in the cardiac protection against ischemic oxidative stress

Wenqian Wu[a,b], Lo Lai[a], Mingxing Xie[b], Hongyu Qiu[a,*]

[a] Center of Molecular and Translational Medicine, Institution of Biomedical Science, Georgia State University, Atlanta, GA, 30303, USA
[b] Department of Ultrasound, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China

ARTICLE INFO

Keywords:
Hsp22
Myocardial ischemia
Mitochondria
Oxidative stress
iNOS

ABSTRACT

The acute and chronic myocardial ischemia results in oxidative stress that impairs myocardial contractility and eventually leads to heart failure. However, the underlying regulatory molecular mechanisms are not fully understood. The heat shock protein 22 (Hsp22), a small-molecular-weight protein preferentially expressed in the heart, was found to be dramatically increased in the cardiac oxidative stress conditions in both human and animal models after the acute and chronic ischemia. Overexpression of Hsp22 largely protects the heart against ischemic damage. Mechanistically, overexpression of Hsp22 attenuates hypoxia-induced oxidative phosphorylation in mitochondrial and the high rate of superoxide production. Short term gene delivery of Hsp22 reduces the infarct size caused by the ischemia/reperfusion, providing a clinical therapeutic potential. This review discusses the new progress of the studies on Hsp22 by focusing on its protective effect against the excessive cardiac oxidative stress, including its adaptive induction in myocardium upon the oxidative stress, its protective role in myocardial ischemia/reperfusion, its regulation in mitochondrial oxidative phosphorylation and the underlying molecular signaling pathways promoting cell survival. This information will increase our understanding of the molecular regulation of cardiac adaption under the oxidative stress and the potential therapeutic relevance.

1. Introduction

Oxidative and reductive stress are dual dynamic phases experienced by the cells undergoing adaptation towards endogenous or exogenous noxious stimulus. Under physiological conditions, a redox balance exists; when the production of reactive molecules exceeds the capacity for their clearance, a redox imbalance occurs and oxidative stress ensues in which reactive oxygen species (ROS) are enhanced and exert toxic effects on cells [1,2]. Mitochondrial malfunction is the common denominator arising from excessive oxidative stress [3].

The heart is one of the organs that heavily relies on the mitochondrial function, and is also sensitive to the ROS. Evidences suggest that oxidative stress plays a key role in many aspects of cardiovascular diseases, particularly in coronary artery disease (CAD) which is the leading cause of death in the United States [4,5]. CAD-induced acute and chronic myocardial ischemia result in myocardial hypoxia that leads to oxidative stress in cardiomyocytes, which subsequently impairs myocardial contractility and eventually leads to heart failure (HF) [4,5]. During myocardial oxidative stress, the generation of ROS is enhanced and the defense mechanisms of myocytes are also altered to protect from cardiac injury [6]. Although the recent treatments with reperfusion therapies reduced the mortality of CAD, they do not prevent the cardiomyocyte damage caused by the lethal ischemia, and the treatment itself may also induce a “reperfusion injury” particularly in the early stage of the reperfusion [2,6]. Promoting the resistance or tolerance of the cardiomyocytes to oxidative stress caused by ischemia is a promising strategy to prevent the irreversible myocardial damage and to improve the restoration of cardiac function after reperfusion, thus, becoming an area of active research. Emerging evidence indicates that a small heat shock protein 22 (Hsp22) represents a candidate for such an approach [7–10].

Hsp22, also called H11 Kinase, is composed of 196 amino acids [11,12], and it belongs to the α-crystallin family of chaperones, in which where the α-crystallin domain is located next to the C-terminus [13]. Hsp22 was found to be predominantly expressed in skeletal and cardiac muscle [12,14] and was also found in specific tumors, such as melanoma [15], breast cancer [16], gastric cancer [17], and glioblastoma [18]. Previous studies indicate that Hsp22 is a stress-

* Corresponding author. Center of Molecular and Translational Medicine, Institution of Biomedical Science, Georgia State University Petit Research Center, Room 588, 100 Piedmont Ave, Atlanta, GA, 30303, USA.
E-mail address: hqiu@gsu.edu (H. Qiu).

https://doi.org/10.1016/j.redox.2020.101555
Received 26 March 2020; Received in revised form 16 April 2020; Accepted 23 April 2020
Available online 25 April 2020

associated protein in the heart since it was found to be induced in various conditions of myocardial ischemic stress both in animal models and in patients [19,20]. Overexpression of Hsp22 protects cardiomyocytes against hydrogen peroxide (H_2O_2)-induced oxidative stress and cell death *in vitro* [8,10,21,22]. In addition, a cardiac-specific overexpression of Hsp22 in a transgenic (TG) mouse significantly protects the heart against myocardial ischemic injury *in vivo* [8]. Reciprocally, the knockdown of Hsp22 increases stress-induced cardiomyocytes death and accelerates the transition into heart failure [9]. These data together indicate that Hsp22 has the capability to prevent oxidative myocardial damage and the development of heart failure. In addition, gene delivery of Hsp22 results in a pre–empty protection against the myocardial ischemia [21], implying a therapeutic potential of this protein in the CAD. Our studies in the past years also discovered novel molecular mechanisms by which Hsp22 regulates the pro-survival signaling pathways in the heart [8,9,23]. These results illustrate a previously undescribed cardiac response to oxidative stress and a novel mode of regulation in mitochondrial function.

In this review, we brought new sights in the studies of Hsp22 in the cardiac oxidative stress including the induction of Hsp22 in the adaptive myocardium in response to oxidative stress, the role of Hsp22 in cardiac protection against myocardial oxidative stress caused by ischemia/reperfusion, its regulation in mitochondrial oxidative phosphorylation and the underlying molecular signaling pathways. The summarized information further increases our knowledge of the endogenous adaption to myocardial injury induced by ischemic stress and opens novel therapeutic possibilities for ischemic heart disease.

2. Hsp22 is a stress-associated protein stimulated in the adaptive myocardium in response to oxygen deprivation

It is wide-accepted that severe reduction of coronary blood flow causes cardiac myocyte death and subsequently leads to a permanent loss of the contractile function. However, because of a limited capacity for cell regeneration, the cardiac tissue, when submitted to ischemic stress, may activate endogenous mechanisms of cell survival, resulting in physiological conditions of adaptation to ischemia, among which there are three commonest adaptions known as myocardial stunning, hibernation and ischemic preconditioning (IPC) [24]. These conditions result from a switch in gene and protein expression, which sustains cardiac cell survival in a context of oxygen deprivation and during the stress of reperfusion [24]. Understanding how the molecular adaptation of the cardiac myocyte sustains its survival in these conditions might help to define novel mechanisms of endogenous myocardial salvage in maintaining cellular viability and contractile function of the ischemic hearts.

Both stunning and hibernating myocardium can remain viable and retain their inotropic capacity with reperfusion. While “stunned” myocardium refers to a condition with a transient reversible myocardial contractile dysfunction induced by acute ischemia wherein the blood supply is almost restored by reperfusion [25,26], “hibernating” myocardium is a chronic post-ischemic myocardial contractile dysfunction due to an imbalance between a reduced coronary blood flow at rest and an increased myocardial demand [27,28]. The molecular mechanisms of maintaining the cardiac cell viability in these ischemic territories had been tested, and it was found that most of the genes that were upregulated in stunning or hibernating myocardium are involved in different mechanisms of cell survival, including cytoprotection, stress response and resistance to apoptosis [29,30]. Interestingly, previous studies from human and animal models indicated that Hsp22 was significantly increased in the myocardium after the acute and chronic ischemia. Specifically, Hsp22 was found to be induced only in the stunning and hibernating myocardium but not in the normal myocardium [19,20]. These data indicate that Hsp22 is a stress-associated protein that can be stimulated in an adaptive myocardium in response to oxygen deprivation. Thus, induction of this protein may provide cytoprotective effects, promoting cell survival and preventing irreversible ischemic damage in stunning and hibernating myocardium.

In addition to these two post-ischemic adaptive conditions, myocardial IPC represents a protection against irreversible damage conferred by brief and repetitive episodes of occlusion/reperfusion preceding a longer episode of potentially lethal ischemia [31]. Since IPC represents the most powerful mechanism to reduce infarct size after ischemia, it was considered as a “gold standard” of cardiac cell survival [31]. Two major types of IPCs have been widely recognized: a first window of IPC (FWOP) confers protection for 1–2 h after ischemia [32,33], whereas a second window of IPC (SWOP) [34,35] confers protection during the 24–72 h that follow the IPC stimulus. Although the molecular mechanisms of IPCs are still a matter of intense investigation, studies have revealed a few signaling pathways that are involved in the protection of IPCs. For example, it has been shown that the protection afforded by FWOP is initiated by the release of adenosine, which promotes the opening of the mitochondrial ATP-sensitive potassium channel (KATP channel), and thereby increasing the uptake of K^+ inside the mitochondria [36]. This opening of the KATP channels hyperpolarizes the mitochondria and results in the release of free radicals, which in turn activates specific kinases, including protein kinase C (PKC) and tyrosine kinases, that adapts the heart to a preconditioned state. The mechanism leading to the SWOP is different which may involve the activation of specific transcription factors that trans-activate genes encoding cytoprotective molecules, including heat-shock proteins, anti-oxidant enzymes, cyclooxygenase-2 and the inducible isoform of nitric oxide synthase (iNOS) [36,37].

Multiple studies have been indicated that Hsp22 may play an important role in cardiac protection as that caused by the IPC [8,21]. First, hearts from the TG mice with a cardiac specific overexpression of Hsp22 showed a reduction in infarct size after coronary artery occlusion and reperfusion, which was equivalent to the reduction of infarct size observed in mice submitted to SWOP [8]. Importantly, SWOP does not induce additional protection on these TG mice [8], indicating that Hsp22 may mediate a substituted protective mechanism of SWOP. Secondly, there is also a great similarity at the molecular level. Overexpression of Hsp22 in a cardiac-specific TG mouse model is accompanied by an upregulation of iNOS expression, which is a common end-effector of SWOP [8]. Thirdly, short-term overexpression of Hsp22 in the swine heart by an Hsp22 adenovirus reduces the infarct size after ischemia/reperfusion and upregulates iNOS in the myocardium when compared to the remote area [21]. Such a reduction of infarct size and an increase in iNOS are quantitatively comparable to those found in different models of SWOP [21,36].

In summary, Hsp22 can be stimulated in a myocardium with an adaption to oxidative stress caused by ischemia in stunning and hibernating conditions but not in normal myocardium. Overexpression of Hsp22 can induce the cardiac protection with an equivalence to SWOP in terms of the physiological efficiency and molecular alteration. These together indicate that Hsp22 acts as a potential mediator in cardiac protection against ischemic injury.

3. Hsp22 protects the heart against ischemia by regulating mitochondrial oxidative phosphorylation via an induction of iNOS

Although ROS is generally considered as a key player that induces oxidative stress, it participates not only in the pathological roles in the heart diseases but also in the physiological function that may regulate survival of the cardiomyocytes [38,39]. ROS could be produced from multiple intercellular sources, i.e., the mitochondrial respiratory chain, nicotinamide adenine dinucleotide phosphate (NADPH) and xanthine oxidase. *In vitro* studies have been shown that overexpression of Hsp22 in isolated cardiomyocytes reduces H_2O_2-mediated apoptosis by 60% [8,10,21,22]. In addition, with the mitochondria isolated from the TG mouse heart, the results demonstrated that Hsp22 overexpression attenuates the oxidative phosphorylation and ROS production induced by

anoxia [22]. Such characteristics replicate those conferred by IPC, further support that Hsp22 acts as a potential mediator protecting the mitochondrial function during ischemia. It has been also shown that the deletion of Hsp22 impairs mitochondrial respiration [9] and results in a deterioration of cardiac function under stress [9]. These data together indicate that Hsp22 plays an essential role in preventing excessive ROS production through the reduction of mitochondrial oxidative phosphorylation in the stressed heart. Paradoxically, studies also showed that, in the normoxia condition, overexpression of Hsp22 stimulates the oxidative phosphorylation and increases the ROS production which may be associated with the increased activity and expression of NADPH oxidase (NOX), such as Nox2, and the enhanced activity of xanthine oxidase in the myocardium [40]. These data indicate that the role of Hsp22 in the physiological condition differs from that under the oxidative stress in the heart. These opposite observations further support the concept that Hsp22 is a stress-associated protein in the heart that plays a distinct protective effect under the oxidative stress.

In addition, several studies revealed a significant correlation between the Hsp22 and the expression of iNOS. Both *in vitro* and *in vivo* studies have been shown that overexpression of Hsp22 dose-responsively induced the expression of iNOS in cardiomyocyte and in the TG mouse hearts [8,21]. Reciprocally, the deletion of Hsp22 reduces the iNOS expression in cardiomyocytes in the response to the cardiac stress [9]. Importantly, evidences indicate that Hsp22-mediated cardiac protection relies on the induction of iNOS [8,9,21]. First, the *in vitro* experiments in cardiomyocytes showed that Hsp22-conferred cytoprotection was abolished by the iNOS inhibitor [8,21]. Secondly, it was shown the NO syntheses inhibitor L-NNA abolished the reduction in infarct size observed in animals treated with Hsp22 [21]. These results were also reproduced in the TG mouse model with a cardiac-specific overexpression of Hsp22, by which pre-treatment of TG mice with L-NNA abolished the reduction of the infarct size when compared to non-treated TG mice [21]. These data further imply that iNOS is the major mediator of Hsp22-conferred cardioprotection. It is notable that these findings are important since cardioprotection by NO donors has been limited so far, the observed protective effects of iNOS induced by Hsp22 imply that stimulating the formation of NO from endogenous iNOS inside the cardiac myocytes might have better biological efficiency than that provided by NO donors.

4. Hsp22 mediated-cytoprotection depends on its mitochondrial translocation with iNOS

A mitochondrial localization of Hsp22 has been reported in *Drosophila*, where it is associated with increased respiration, resistance against oxidative stress, and prolonged lifespan [41,42]. The subcellular distribution of Hsp22 was also characterized previously in the mammalian heart, which is predominantly located in the inner membrane of mitochondria [23]. Importantly, it has been also shown that the mammalian Hsp22 translocates to the mitochondria of myocytes through its N-terminal domain which contributes to the cytoprotection of Hsp22 [23].

Additionally, the recent observation showed that mitochondrial translocation of Hsp22 itself determines the mitochondrial localization of iNOS, since overexpression of the Hsp22 N-terminal mutant, which fails to translocate to the mitochondria, reduces the level of iNOS in the mitochondrial compartment, even it is still capable of increasing total iNOS expression in cardiomyocytes [23]. These findings suggest the possibility of a co-translocation mechanism for both Hsp22 and iNOS.

Importantly, the study further showed that the mitochondrial translocation of iNOS and Hsp22 was necessary for the cytoprotective effects of Hsp22 [23]. N-terminal truncation of Hsp22 blocked its mitochondrial translocation, impaired regulation of oxidative phosphorylation, preventing mitochondrial bioenergetics function, and subsequently increased cell death [23]. However, despite the importance of the mitochondrial translocation of Hsp22 in cardiac protection, the mechanisms underlying this process remain unknown.

5. Hsp22 induces iNOS in cardiomyocyte via a pro-survival signaling

Several studies have shown that Hsp22 represents a novel cardiac protective mechanism combining stress-induced adaption of both nuclear gene expression and mitochondrial respiration. For example, it showed recently that the Hsp22 TG mouse exhibited an increase in phosphorylation of mitochondrial signal transducer and activator of transcription 3 (STAT3) on S727 when compared to WT [9]. Reciprocally, silencing Hsp22 in isolated neonatal rat cardiomyocytes attenuated STAT3 activation, indicating that Hsp22 is necessary to activate STAT3 [9]. Further study showed that this activation was mediated by the production of interleukin-6 (IL-6) via the transcription factor nuclear factor-κB (NFκB) [9]. In addition to its transcriptional function, Hsp22 also mediated STAT3 translocation to the mitochondria where it increases oxidative phosphorylation [9]. Both mitochondrial STAT3 translocation and respiration were significantly decreased in Hsp22 knockout mice [9]. Therefore, Hsp22 represents an undescribed activator of mitochondrial functions of STAT3 in response to cardiac stress.

In addition, it was found in the *in vitro* studies with isolated myocytes that overexpression of Hsp22 was accompanied by a significant increase in phosphoinositide 3-kinases (PI3K) activity, phospho-Akt, Smad 1/5/8 phosphorylation and [(3)H] phenylalanine incorporation. In pull-down experiments, Hsp22 increased both the association of aurora-like kinase (Alk3) and the bone morphogenetic protein receptor, type II (BMPR-II) together, and their interaction with the transforming growth factor-beta-activated kinase (TAK)1, a “non-canonical” mediator of the BMP receptor signaling. TAK1 inhibition prevented Hsp22-mediated activation of Akt [10].

Furthermore, an AAA-associated protein named valosin-containing protein (VCP) was also identified as a novel player in cardiac protection conferred by Hsp22. It has been found that VCP was markedly increased in the Hsp22 TG mouse, which also co-localized and interacted with Hsp22 and Akt, predominated in the nuclear fraction of adult mouse cardiac myocytes [43]. Importantly, VCP expression was highly associated with the expression of iNOS in the cardiomyocytes [43]. These data indicate that VCP acts as a downstream target of Hsp22 and may work with Hsp22 and Akt to constitute a complex that regulates the iNOS expression.

These results together indicate that Hsp22 mediates a concomitant activation of several survival kinases which creates an important cross-talk among these molecules. It is notable that Hsp22 not only binds to the multiple survival kinases, as a chaperon protein, it is also responsible for the subcellular redistribution of other proteins [8,23]. Hsp22 clearly predominately accumulates at the periphery of the organelles, such as, within the perinuclear compartment and inner membrane of mitochondria [8,23]. This distinct distribution of Hsp22 provides a fundamental basis for its role in chaperoning the other proteins into nuclear or mitochondria. In addition, Hsp22 was also found to be involved in the metabolic switch that characterizes the ischemic heart through promoting the activity of 5′ AMP-activated protein kinase (AMPK), which subsequently stimulates the glucose uptake and glycolysis to compensate for the lack of aerobic ATP production in ischemic heart [7,8]. Furthermore, studies also showed that Hsp22 enhanced the expression and activity and a subcellular redistribution of the proteasome, which was responsible for the cardiac cell hypertrophy [44]. However, the effects of the enhanced proteasome activity by Hsp22 in the ischemic heart remain largely unknown.

As summarized in Fig. 1, the results indicate that Hsp22 promotes the peri-nuclear accumulation of Akt and VCP, resulting in the activation of the transcription factor NF-kB and STAT3, which in turn induces the expression of iNOS and promotes the survival of the cardiomyocytes. On the other hand, Hsp22 promotes the translocation of STAT3

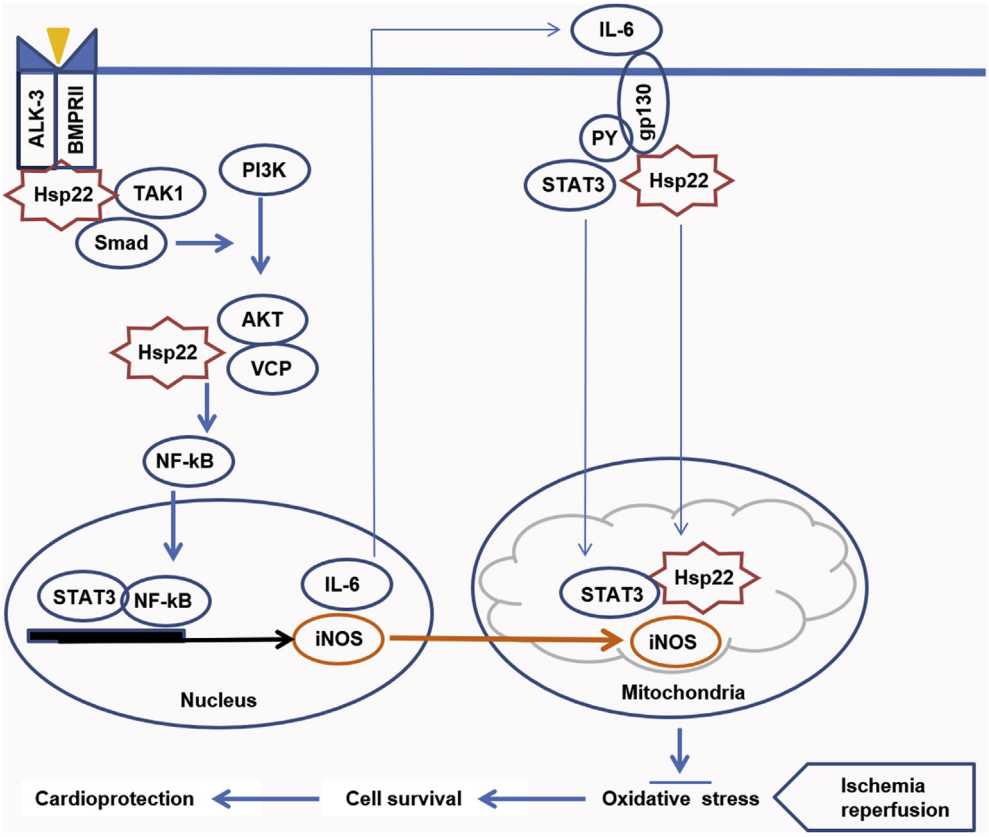

Fig. 1. The scheme of the summary of the molecular signaling mediated by Hsp22 in cardiac protection.

and iNOS to the mitochondria, where it regulates mitochondrial respiration and the ROS production (Fig. 1).

6. Future directions

The information summarized in this review provides the new progresses in the studies of Hsp22 in the heart, it also raised a few important future research interests:

First, the clinical translational potential. Pre-emptive conditioning of the ischemic heart by Hsp22 is an attractive clinical approach to prevent ischemic damage in patients at risk of suffering from subsequent ischemic stress. Patients with unstable angina, or with severe and repetitive ischemic episodes, and patients scheduled for surgical revascularization could benefit from pre-emptive effects of Hsp22 and its downstream targets. Although animal experimental studies have revealed the potential of Hsp22 in reducing ischemic injury in the heart [8,21], its clinical therapeutic effect in ischemic patients still needs to be tested. Many systems of cardiac gene delivery have been reported in pre-clinical animal models, however, use gene delivery for the treatment of cardiovascular disease in clinical is still challenging and the efficiency remains uncertain. Thus, activating endogenous Hsp22 and its medicated survival pathways will be an efficient alternative strategy for the clinical applications in conditions of CAD. To explore this possibility, a better understanding of the mechanisms that induce the endogenous Hsp22/iNOS in the stressed heart becomes extremely important. There are serval aspects remain unclear and need future investigations, such as: how to stimulate endogenous Hsp22 in cardiomyocyte in the stressed heart and how to control the iNOS increase at a moderate level as what was found during the SWOP [45] and in Hsp22 TG mouse [8,21] as well as in the animal models with Hsp22 gene-delivery [8,21]. Since this moderate increase of iNOS (at 2 to 3-fold) has been demonstrated to be beneficial and to be able to avoid the potential toxicity caused by excessive iNOS. It is also important to determine the mechanism mediating the mitochondrial translocation of Hsp22 and iNOS and their subsequent downstream targets and effects in the cardiac mitochondria.

Secondly, the potential diurnal effect of Hsp22 in cardiac protection. Although the diurnal variations in the onset of myocardial infarction are well established, the underlying mechanisms remain largely unknown and the potential role of Hsp22 in this event is unclear. The study has revealed a profound time-of-day-dependence toleration in myocardial ischemia/reperfusion and indicated that Akt and/or GSK-3β are the potential mediators [46]. Considering the well-known interaction between Hsp22 and Akt [8], and their roles in the cardiac protection, we believe that further investigating the potential diurnal effect of Hsp22 in the heart will provide novel insights regarding the etiology and treatment of ischemia-induced cardiac dysfunction.

Thirdly, the potential chronic effects of Hsp22 in the heart. Although many evidences have shown that the activation of the novel signaling conferred by Hsp22 is a promising strategy for the cardiac protection against acute ischemia injury, it is also noticed that the role of the increased Hsp22 in the unstressed condition is still controversial. While Hsp22 overexpression in *Drosophila* has been considered to be responsible to an increased resistance against oxidative stress and a prolonged life span [47,48], a recent report in a mouse model showed a conflict result indicating that long-term chronic overexpression of Hsp22 in the heart may increase the oxidative phosphorylation and mitochondrial ROS production, which ultimately increases senescence and reduces lifespan [40]. Understanding the controversial results and clarifying the chronic impacts of the increased Hsp22 in the heart will help to improve the safety of the treatment and prevents the potential chronic toxicological risk in the heart.

Finally, the role of Hsp22 in the aging heart. It has been shown that Hsp22 is not only upregulated by oxidative stress, it is also upregulated during aging in *Drosophila* [49]. This age-dependent

expression of Hsp22 was found to be influenced by histone methylation and acetylation as well as the production of hydrogen sulfide in *Drosophila* [49]. However, the role of Hsp22 in the aging heart remains unclear in mammals. In addition, it is unknown whether there is a sex-dependent expression of Hsp22 in the heart. Further determining the potential age- and sex-dependent expression of Hsp22 in the heart and exploring their roles will provide new insights in understanding the age-related heart diseases and the gender difference observed in these diseases.

Author contributions

W.Q, L.L, M.X and H.Q wrote this manuscript and approved the submission.

Declaration of competing interest

None.

Acknowledgements

This work is partially supported by NIH grants HL115195-01 (H.Q.), HL137962 (H.Q.), and HL 142291(H.Q. &. G.Q.).

References

[1] M.S. Cooke, et al., Oxidative DNA damage: mechanisms, mutation, and disease, Faseb. J. 17 (10) (2003) 1195–1214.
[2] J.L. Zweier, M.A. Talukder, The role of oxidants and free radicals in reperfusion injury, Cardiovasc. Res. 70 (2) (2006) 181–190.
[3] F. Singh, et al., Reductive stress impairs myoblasts mitochondrial function and triggers mitochondrial hormesis, Biochim. Biophys. Acta 1853 (7) (2015) 1574–1585.
[4] M. Hori, K. Nishida, Oxidative stress and left ventricular remodelling after myocardial infarction, Cardiovasc. Res. 81 (3) (2009) 457–464.
[5] M.K. Misra, et al., Oxidative stress and ischemic myocardial syndromes, Med. Sci. Monit. 15 (10) (2009) RA209–219.
[6] H. Bugger, K. Pfeil, Mitochondrial ROS in myocardial ischemia reperfusion and remodeling, Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1866 (7) (2020) 165768.
[7] C. Depre, et al., H11 kinase is a novel mediator of myocardial hypertrophy in vivo, Circ. Res. 91 (11) (2002) 1007–1014.
[8] C. Depre, et al., H11 kinase prevents myocardial infarction by preemptive preconditioning of the heart, Circ. Res. 98 (2) (2006) 280–288.
[9] H. Qiu, et al., H11 kinase/heat shock protein 22 deletion impairs both nuclear and mitochondrial functions of STAT3 and accelerates the transition into heart failure on cardiac overload, Circulation 124 (4) (2011) 406–415.
[10] X. Sui, et al., Activation of the bone morphogenetic protein receptor by H11kinase/Hsp22 promotes cardiac cell growth and survival, Circ. Res. 104 (7) (2009) 887–895.
[11] R. Benndorf, et al., HSP22, a new member of the small heat shock protein superfamily, interacts with mimic of phosphorylated HSP27 ((3D)HSP27), J. Biol. Chem. 276 (29) (2001) 26753–26761.
[12] G. Kappe, et al., Characterization of two novel human small heat shock proteins: protein kinase-related HspB8 and testis-specific HspB9, Biochim. Biophys. Acta 1520 (1) (2001) 1–6.
[13] Z. Hu, et al., Structure, function, property, and role in neurologic diseases and other diseases of the sHsp22, J. Neurosci. Res. 85 (10) (2007) 2071–2079.
[14] T.K. Chowdary, et al., Mammalian Hsp22 is a heat-inducible small heat-shock protein with chaperone-like activity, Biochem. J. 381 (Pt 2) (2004) 379–387.
[15] C.C. Smith, et al., A novel human gene similar to the protein kinase (PK) coding domain of the large subunit of herpes simplex virus type 2 ribonucleotide reductase (ICP10) codes for a serine-threonine PK and is expressed in melanoma cells, J. Biol. Chem. 275 (33) (2000) 25690–25699.
[16] A.H. Charpentier, et al., Effects of estrogen on global gene expression: identification of novel targets of estrogen action, Canc. Res. 60 (21) (2000) 5977–5983.
[17] X.S. Li, et al., Heat shock protein 22 overexpression is associated with the progression and prognosis in gastric cancer, J. Canc. Res. Clin. Oncol. 140 (8) (2014) 1305–1313.
[18] S. Modem, et al., Hsp22 (HspB8/H11) knockdown induces Sam68 expression and stimulates proliferation of glioblastoma cells, J. Cell. Physiol. 226 (11) (2011) 2747–2751.
[19] C. Depre, et al., Program of cell survival underlying human and experimental hibernating myocardium, Circ. Res. 95 (4) (2004) 433–440.
[20] C. Depre, et al., Gene program for cardiac cell survival induced by transient ischemia in conscious pigs, Proc. Natl. Acad. Sci. U. S. A. 98 (16) (2001) 9336–9341.
[21] L. Chen, et al., Preemptive conditioning of the swine heart by H11 kinase/Hsp22 provides cardiac protection through inducible nitric oxide synthase, Am. J. Physiol. Heart Circ. Physiol. 300 (4) (2011) H1303–H1310.
[22] L. Laure, et al., Cardiac H11 kinase/Hsp22 stimulates oxidative phosphorylation and modulates mitochondrial reactive oxygen species production: involvement of a nitric oxide-dependent mechanism, Free Radic. Biol. Med. 52 (11–12) (2012) 2168–2176.
[23] E. Rashed, et al., Heat shock protein 22 (Hsp22) regulates oxidative phosphorylation upon its mitochondrial translocation with the inducible nitric oxide synthase in mammalian heart, PLoS One 10 (3) (2015) e0119537.
[24] E. Rashed, C. Depre, Cardiac cell survival and reversibility of myocardial ischemia, Arch. Mal. Coeur. Vaiss. 99 (12) (2006) 1236–1243.
[25] G.R. Heyndrickx, et al., Regional myocardial functional and electrophysiological alterations after brief coronary artery occlusion in conscious dogs, J. Clin. Invest. 56 (1975) 978–985.
[26] E. Braunwald, R.A. Kloner, The stunned myocardium: prolonged, postischemic ventricular dysfunction, Circulation 66 (1982) 1146–1149.
[27] S.H. Rahimtoola, A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina, Circulation 72 (1985) V123–V135.
[28] S. Rahimtoola, The hibernating myocardium, Am. Heart J. 117 (1989) 211–221.
[29] G. Gross, et al., Beneficial actoins of superoxide dismutase and catalase in stunned myocardium of dogs, Am. J. Physiol. 250 (1986) H372–H377.
[30] K. Przylenk, R. Kloner, Superoxide dismutase plus catalase improves contractile function in the canine model of the “stunned” myocardium, Circ. Res. 58 (1986) 148–156.
[31] D.J. Hausenloy, D.M. Yellon, Ischaemic conditioning and reperfusion injury, Nat. Rev. Cardiol. 13 (4) (2016) 193–209.
[32] C.E. Murry, et al., Myocardial protection is lost before contractile function recovers from ischemic preconditioning, Am. J. Physiol. 260 (1991) 1796–1804.
[33] D.M. Yellon, J.M. Downey, Preconditioning the myocardium: from cellular physiology to clinical cardiology, Physiol. Rev. 83 (4) (2003) 1113–1151.
[34] M.S. Marber, et al., Cardiac stress protein elevation 24 hours after brief ischemia or heat stress is associated with resistance to myocardial infarction, Circulation 88 (1993) 1264–1272.
[35] T. Kuzuya, et al., Delayed effects of sublethal ischemia on the acquisition of tolerance to ischemia, Circ. Res. 72 (1993) 1293–1299.
[36] R. Bolli, Preconditioning: a paradigm shift in the biology of myocardial ischemia, Am. J. Physiol. Heart Circ. Physiol. 292 (1) (2007) H19–H27.
[37] R. Bolli, Cardioprotective function of inducible nitric oxide synthase and role of nitric oxide in myocardial ischemia and preconditioning: an overview of a decade of research, J. Mol. Cell. Cardiol. 33 (11) (2001) 1897–1918.
[38] G.A. Kurian, et al., The role of oxidative stress in myocardial ischemia and reperfusion injury and remodeling: revisited, Oxid. Med. Cell. Longev. 2016 (2016) 1656450.
[39] J.O. Lundberg, M.T. Gladwin, E. Weitzberg, Strategies to increase nitric oxide signalling in cardiovascular disease, Nat. Rev. Drug Discov. 14 (9) (2015) 623–641.
[40] D. Morin, et al., Hsp22 overexpression induces myocardial hypertrophy, senescence and reduced life span through enhanced oxidative stress, Free Radic. Biol. Med. 137 (2019) 194–200.
[41] G. Morrow, et al., Decreased lifespan in the absence of expression of the mitochondrial small heat shock protein Hsp22 in Drosophila, J. Biol. Chem. 279 (42) (2004) 43382–43385.
[42] H.J. Kim, et al., Gene expression profiling implicates OXPHOS complexes in lifespan extension of flies over-expressing a small mitochondrial chaperone, Hsp22, Exp. Gerontol. 45 (7–8) (2010) 611–620.
[43] P. Lizano, et al., The valosin-containing protein promotes cardiac survival through the inducible isoform of nitric oxide synthase, Cardiovasc. Res. 99 (4) (2013) 685–693.
[44] N. Hedhli, et al., Proteasome activation during cardiac hypertrophy by the chaperone H11 Kinase/Hsp22, Cardiovasc. Res. 77 (3) (2008) 497–505.
[45] Y. Wang, et al., Ischemic preconditioning upregulates inducible nitric oxide synthase in cardiac myocyte, J. Mol. Cell. Cardiol. 34 (1) (2002) 5–15.
[46] D.J. Durgan, et al., Short communication: ischemia/reperfusion tolerance is time-of-day-dependent: mediation by the cardiomyocyte circadian clock, Circ. Res. 106 (3) (2010) 546–550.
[47] G. Morrow, R.M. Tanguay, Drosophila melanogaster Hsp22: a mitochondrial small heat shock protein influencing the aging process, Front. Genet. 6 (2015) 1026.
[48] G. Morrow, M. Le Pecheur, R.M. Tanguay, Drosophila melanogaster mitochondrial Hsp22: a role in resistance to oxidative stress, aging and the mitochondrial unfolding protein response, Biogerontology 17 (1) (2016) 61–70.
[49] V. Shilova, et al., Age-dependent expression profiles of two adaptogenic systems and thermotolerance in Drosophila melanogaster, Cell Stress Chaperones 25 (2) (2020) 305–315.