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Review

The dual role of heat shock protein 60 in Cardiac diseases: From mitochondrial chaperone to extracellular immunomodulator — A review and future perspectives

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ABSTRACT

The abundance of mitochondria in cardiac cells is vital, as they are extremely important for adenosine triphosphate (ATP) synthesis, maintaining redox balance, regulating calcium homeostasis, and facilitating lipid synthesis.

One of the most abundant proteins in the mitochondria is the heat shock protein 60 (Hsp60), a chaperone that plays a crucial role in the translocation and folding of mitochondrial proteins.

As a stress protein, Hsp60 increases when the heart muscle is under pressure, such as during a heart attack or heart failure. Recently, our research group has demonstrated that Hsp60 can be released under stress conditions in small and large vesicles or freely in the cell culture medium.

In this review, we have analysed the published literature to determine whether Hsp60 may function as a damage-associated molecular pattern (DAMP) protein capable of interacting with Toll-like receptors (TLRs) to modulate immune responses, and we hypothesised that Hsp60 released in small extracellular vesicles may act as an immunomodulator.

1. Introduction

Heat Shock Protein 60 (Hsp60) is a stress-responsive chaperone widely expressed in normal and non-stressed cells, with functions that depend on its cellular localization. Initially identified within mitochondria, Hsp60 is essential for maintaining mitochondrial protein homeostasis. In eukaryotes, its Adenosine-Triphosphate (ATP) -dependent double-ring structure requires the cofactor Heat Shock Protein 10 (Hsp10) [1,2]. Nearly half of all mitochondrial matrix proteins interact with the Hsp60/Hsp10 complex, and nineteen co-immunoprecipitating partners account for more than 60% of mitochondrial protein mass. Impaired folding of these proteins—due to mutations in the chaperonins or their interactors—may contribute to metabolic and neurological disorders. Consistent with this broad interactome, Hsp60 participates in major mitochondrial metabolic pathways, including oxidative phosphorylation, the tricarboxylic acid cycle, and fatty acid oxidation [3].

Beyond mitochondria, Hsp60 is also detected in the cytosol, plasma membrane, extracellular space, and bloodstream. In these extramitochondrial locations, it influences diverse processes such as cell division, apoptosis, migration, and immunological responses. In the heart, Hsp60 is abundantly expressed in healthy cardiomyocytes and is upregulated by heat stress, suggesting a protective role in myocardial physiology [4].

Since Hsp60 can be released into the circulation inside small and large extracellular vesicles (EVs) [5], vesicles can be engineered to overexpress Hsp60 [6] and Hsp60-derived peptides have demonstrated immunomodulatory effects in clinical studies on rheumatoid arthritis and infectious diseases [7], we hypothesize that Hsp60 may also serve as a damage indicator and key immunomodulator in cardiac disorders. Its compartment-specific localization supports the potential use of Hsp60-bearing vesicles as a therapeutic strategy to modulate inflammation and regulate immune responses in heart disease.

What is actually new in our mini-review compared to the published literature is that we combine Hsp60 with EVs, damage-associated molecular pattern (DAMP) signaling and cardiac disease into one hypothesis. We propose a new role as a DAMP of the vesicles associated Hsp60

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and we compare the activities of free and vesicles-associated Hsp60. In particular, we hypothesize that the vesicle-released Hsp60 may be an immunomodulatory driver, not just a biomarker, and we suggest a structured multi-model experimental roadmap to demonstrate our hypothesis.

2. Extracellular Hsp60 may act as an immunomodulator in injured cardiac tissue

The localization of Hsps in cardiac tissue, such as Hsp60 and the associated Hsp10, is similar to their localization in other tissues. Hsp60 has been found inside mitochondria, in the cytoplasm of cardiac cells [8], on the outer membrane, within exosomes [9], and finally in the blood [10]. Most of the Hsp60 in cardiac cells is located inside mitochondria, whereas the cytoplasm contains only 20–40% of the protein.

In its cytosolic localization, Hsp60 is frequently associated with Bcl-2-associated X protein (Bax) and apoptosis [11]. The expression levels of Hsp60 are typically so low that researchers have used heat shock to detect the localization of this protein. For example, in studies involving rats exposed to 42 ± 1 °C for 0 (control), 20, 80, and 100 min, researchers detected high levels of both Hsp60 and Hsp10 after 100 min, exhibiting a punctate distribution typical of mitochondrial localization [12].

The mechanism through which Hsp60 is released into the extracellular space, either inside EVs or freely in the interstitial space, is not well understood and is widely debated (Fig. 1). Hsp60 may be released as a free protein because of cell lysis, but transport mediated by exocytosis cannot be excluded. Recently, we demonstrated the release of Hsp60 in the culture medium inside small and large vesicles by immortalized muscle cell lines [5]. We also showed that induced expression of high levels of Hsp60 can enhance its localization and its distribution inside mitochondria, in the cytoplasm, and inside EVs [6]. Table 1 compares vesicles-associated and free Hsp60 and their mechanisms of release, receptor engagement, biological activity, immunomodulatory effects and potential translational relevance.

Released in EVs or freely in the serum, Hsp60 may play both pro-inflammatory and anti-inflammatory roles depending on its interactions with cell-surface receptors, including Toll-like Receptors (TLRs) (Fig. 2). It may also bind to other proteins during an immune response to assist in their presentation to lymphocytes [13].

Mechanisms which lead to the incorporation of Hsp60 into EVs may determine the real role of the protein in inflammation and immunity. The Endosomal Sorting Complex Required for Transport (ESCRT)-dependent pathways are thought to contribute to Hsp60 loading into intraluminal vesicles during multivesicular body formation, potentially via recognition of ubiquitinated cargo or adaptor-mediated recruitment [14]. In parallel, lipid raft microdomains enriched in cholesterol and sphingolipids may facilitate Hsp60 partitioning into membrane regions that bud into micro-vesicles or exosomes [15]. Mitochondrial stress signaling, including mitochondrial unfolded protein response and

Table 1
– Comparison between vesicle-associated Hsp60 and Free (Soluble) Hsp60.

Feature	Vesicle-Associated Hsp60	Free (Soluble) Hsp60
Mechanisms of release	Actively packaged into extracellular vesicles (exosomes, microvesicles) during cellular stress; regulated secretion via exocytosis; mitochondrial stress-induced trafficking to vesicles	Passive release from damaged/necrotic cells; leakage during apoptosis; possible non-vesicular secretion; mitochondrial rupture
Stability in extracellular space	High stability due to vesicle membrane protection; resistant to proteases	Lower stability; susceptible to degradation and dilution
Target cell delivery	Vesicle uptake via endocytosis, membrane fusion, or receptor-mediated internalization	Diffusion-dependent; receptor engagement only at cell surface
Receptor engagement	Multivalent presentation of Hsp60; enhanced clustering of TLR2/TLR4; possible cooperation with vesicle lipids and proteins	Direct binding to TLR2/TLR4, CD14, scavenger receptors; lower avidity
Signaling efficiency	Potentially stronger and sustained signaling due to concentrated delivery	Transient signaling depending on local concentration
Biological activity	Targeted intercellular communication; long-range delivery; coordinated signaling cargo	DAMP signal indicating tissue injury; localized inflammatory trigger
Immunomodulatory effects	May induce macrophage activation, dendritic cell maturation, cytokine cascades; possible immune programming via vesicle cargo	Induces TNF-α, IL-1β, IL-6 release; activates NF-κB; promotes innate immune activation
Translational relevance	High: drug delivery platform, engineered EV therapy, targeted immunomodulation	Moderate: biomarker and anti-inflammatory target
Experimental accessibility	Requires EV isolation and characterization	Easily measurable in serum
Kinetics after myocardial injury	Likely delayed and sustained release	Rapid increase after cell damage
Specificity for active signaling	High — indicates regulated secretion	Low — may reflect passive leakage

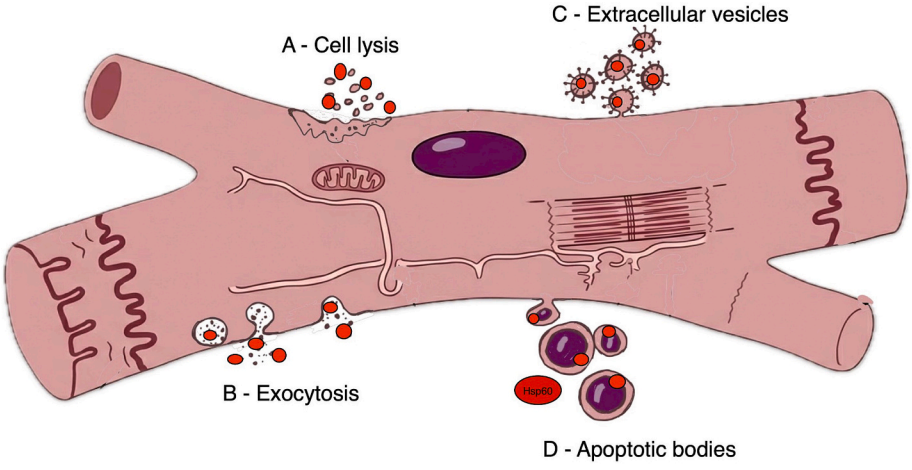

Fig. 1. Mechanisms through which HSP60 is released. Hsp60 can be released by cell lysis (A), exocytosis (B), inside extracellular vesiscles (C), or inside apoptotic bodies (D).

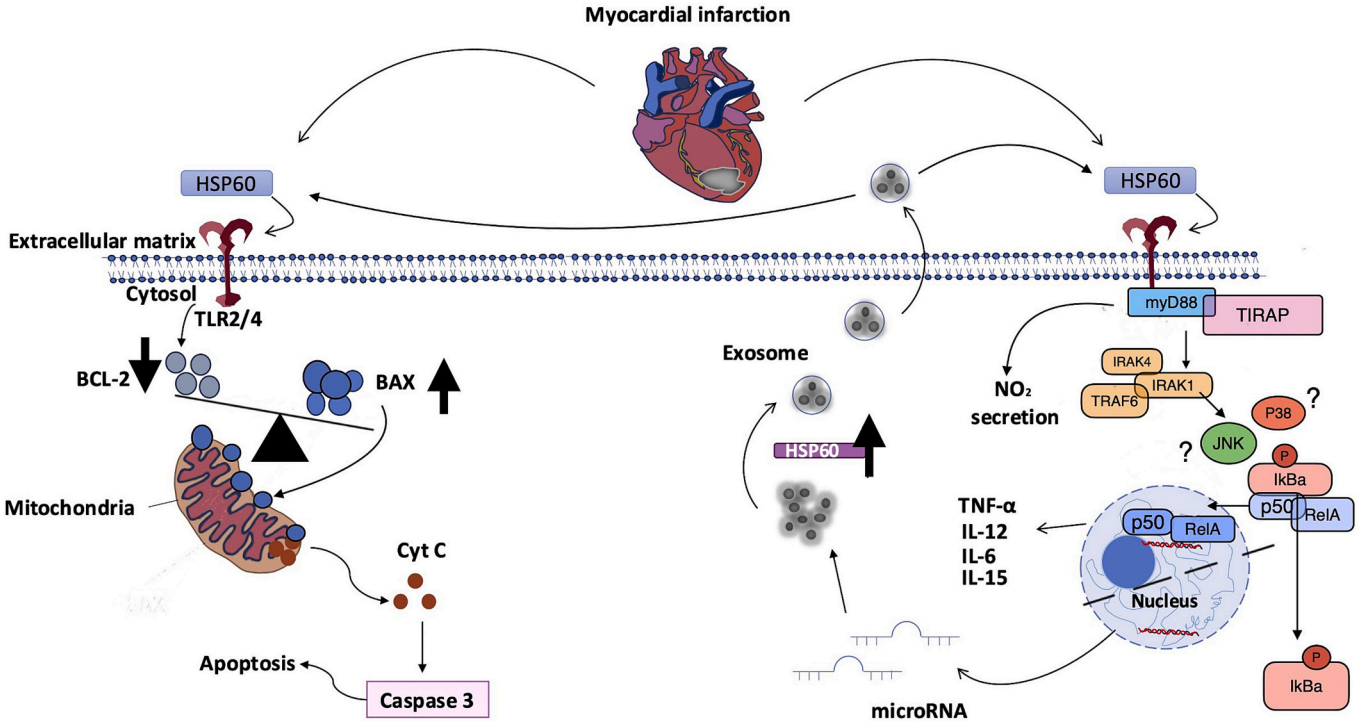

Fig. 2. Schematic representation of HSP60-mediated signaling pathways during myocardial infarction. Ischemic injury promotes extracellular release of HSP60, which binds Toll-like receptors TLR2/4 on the cell membrane. This interaction triggers two major downstream pathways. On the left, TLR2/4 activation disrupts the BCL-2/BAX balance, promoting BAX translocation to mitochondria, mitochondrial outer membrane permeabilization, cytochrome *c* (Cyt c) release, and subsequent activation of caspase-3, ultimately leading to apoptosis. On the right, TLR2/4 stimulation activates the NF-κB signaling pathway, resulting in nuclear translocation of NF-κB and transcription of pro-inflammatory mediators, including TNF-α, IL-6, IL-12, and IL-15, as well as NO_2 secretion. In addition, HSP60 and microRNAs are packaged into exosomes and released into the extracellular space, contributing to amplification of inflammatory signaling and propagation of myocardial injury.

increased Reactive Oxygen Species (ROS), can promote Hsp60 relocalization from mitochondria to the cytosol and its subsequent packaging into EVs. Post-translational modifications—particularly ubiquitination, but also acetylation or phosphorylation—may further regulate Hsp60 trafficking by modulating protein–protein interactions and recognition by sorting machinery [16]. Together, these observations support the existence of selective sorting mechanisms in which stress-induced redistribution, lipid domain association, and ESCRT-related recognition cooperate to preferentially enrich Hsp60 within specific EVs subpopulations.

These mechanisms and the possibility of specific EVs subpopulations let us hypothesize that Hsp60 may be released into the extracellular space under pathological conditions, where it may act as a DAMP protein. Supporting our hypothesis, we found studies demonstrating that the localization of Hsp60 on the cell surface activates the innate immune system, inducing the release of tumor necrosis factor-α (TNF-α). This was observed in a coronary artery ligation model in rats with heart failure, where increased myocyte apoptosis was also noted [46]. Human Hsp60, acting as an immunomodulator, elicited a rapid release of nitric oxide (NO), TNF-α, interleukin-1β (IL-1β), IL-6, IL-12, and IL-15 from macrophages. It can also upregulate costimulatory molecules of major histocompatibility complex class I (MHC-I) and II (MHC-II), Cluster of Differentiation 86 (CD86), and CD40, promoting the maturation of dendritic cells (DCs) and enhancing the antigen-presenting capacity of antigen-presenting cells (APCs) [47].

Moreover, it has been suggested that Hsp60 may act as a ligand for TLR 2 and 4, modulating the immune response and inducing the release of TNF-α, IL-6, and IL-8 [17]. Besides activation of TLR-4 and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway in injured cardiac tissue leads to apoptosis and impaired contractility of the cardiac tissue [18].

Taking into account the literature summarised in this paragraph, we can hypothesize that, as a DAMP, this chaperonin may interact with TLRs on immune cells, leading to a systemic inflammatory response. (Fig. 2).

3. HSP60 and cardiac diseases

Cardiac diseases encompass unstable angina, myocardial infarction (MI), heart failure (HF), arrhythmias, valve disease, hypertension, and congenital or inherited cardiac disorders. Although no studies have specifically examined Hsp60 in unstable angina, several investigations have assessed its expression and function in MI, HF, and arrhythmias. Fig. 3 summarizes Hsp60 expression in these conditions.

Hsp60 is recognized as a marker of MI in both humans and animal models. Multiple studies report elevated Hsp60 levels in the bloodstream of patients and animals with MI, heart failure, or coronary artery disease. In a Chinese cohort, Hsp60 levels increased on both day 1 and day 7 post-MI [19]. Similarly, in C57BL/6 mice with induced MI, Hsp60 was overexpressed intracellularly and released into the interstitial cardiac space [20].

The expression of Hsp60 in MI is not merely a reaction to a hypoxic environment but is finely regulated by cardiac-related micro-RNAs (miRs). Researchers demonstrated the overexpression of miR-1 after the induction of MI and the simultaneous downregulation of Hsp60 [21]. Carvedilol, a nonselective β-adrenergic receptor (β-AR) antagonist, was shown to reduce miR-1 expression and restore Hsp60 levels in response to tissue damage, confirming earlier findings in ischemia–reperfusion injury. Carvedilol's cardioprotective effect is linked to its inhibition of miR-1, thereby preventing apoptosis and increasing Hsp60 in ischemic cardiomyocytes [22,23].

In atrial fibrillation (AF), a common arrhythmia associated with HF, Hsp depletion contributes to proteostasis dysfunction and electropathological remodeling [24,25]. Instead, other studies show increased

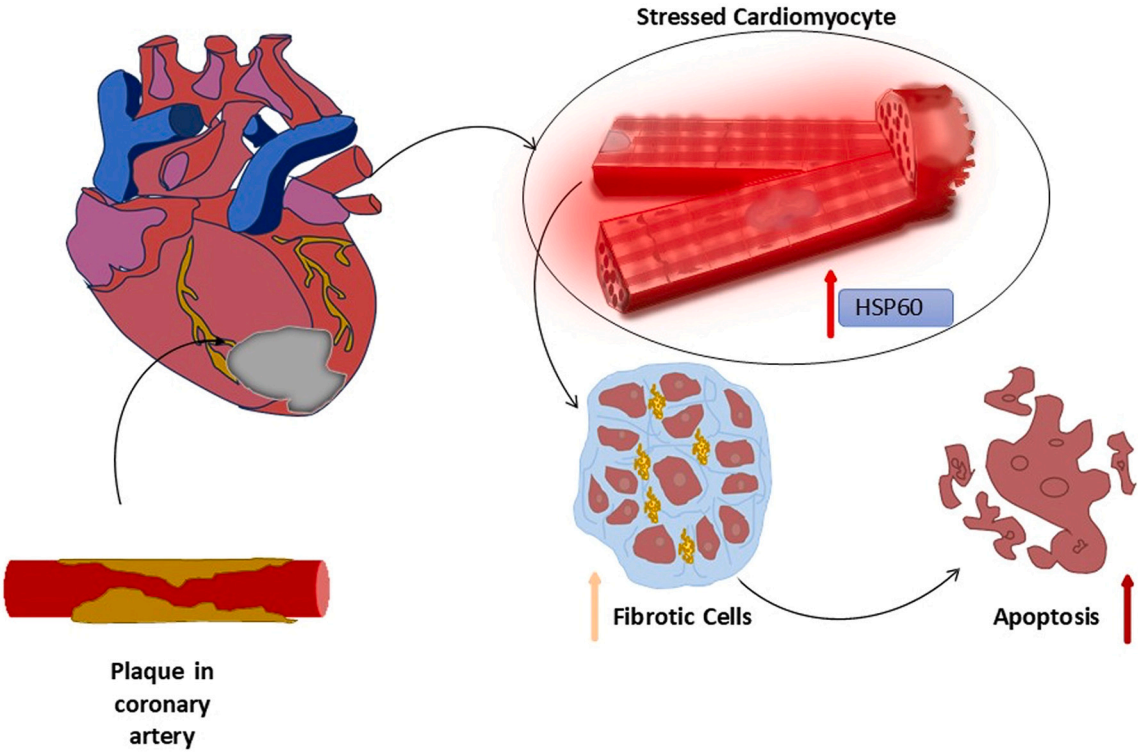

Fig. 3. Hypothetical roles of Hsp60 in myocardial infarction (MI). Coronary artery plaque formation promotes myocardial ischemia, leading to cardiomyocyte stress and increased HSP60 expression and release. Elevated HSP60 levels are associated with structural damage of cardiomyocytes and activation of fibrotic remodeling, characterized by the accumulation of fibrotic cells within the myocardial tissue. This process contributes to progressive cellular dysfunction and ultimately promotes apoptotic cell death. Overall, HSP60 upregulation links coronary plaque instability and myocardial injury to fibrosis and apoptosis.

Hsp60 and Hsp10 expression in atrial tissue from AF patients [26,27], and variations in Hsp60 expression correlate with differing levels of atrial myolysis throughout AF progression [28].

Hsp60 also contributes to atherosclerosis and HF. During it, Hsp60 redistributes to the surface of the heart muscle before being released into the bloodstream [29], and high circulating Hsp60 is associated with increased apoptosis and worsened cardiac function [29,30]. Extracellular Hsp60 affects distant organs by interacting with endothelial and vascular wall cells and high extracellular concentrations can accelerate pathological remodeling by inducing cardiomyocyte death [29,31].

Mechanistically, extracellular Hsp60 activates TLR4 and the myeloid differentiaion factor 88 (MyD88) in cardiomyocytes, increasing cytokine production through the TLR4-MyD88-p38/NF-κB pathway and upregulating TLR2 and TLR4 via the TLR4-MyD88-JNK/NF-κB pathway. They showed that the expression of TLR2 and TLR4 is induced by extracellular Hsp60, regardless of whether it is endogenous (produced by the ischaemic myocardium) or exogenous. The release of Hsp60 from cardiomyocytes during myocardial ischaemia increases the production of inflammatory cytokines via the TLR4-MyD88-p38/NF-κB pathway and increases the expression of TLR2 and TLR4 via the TLR4-MyD88-JNK/NF-κB pathway [32]. Hsp60-induced cytokine release depends on MyD88, p38, JNK, and NF-κB activation. TLR4 signaling via adaptor-inducing interferon-β (TRIF) and MyD88 includes Toll/Interleukin-1 receptor/Resistance protein (TIR) homology domains [33].

Intracellular Hsp60 protects cardiomyocytes from apoptosis when localized to the cytosol or mitochondria. In contrast, its translocation to the plasma membrane is linked to apoptotic signaling. Hsp60 interacts with multiple apoptosis-related proteins, including procaspase-3, survivin, cyclophilin D, p53, Bcl-XL, Bak, and Bax. It suppresses apoptosis by inhibiting Bax and Bak, but under cellular stress mitochondrial Hsp60 may promote apoptosis by facilitating procaspase-3 activation. Reduced Hsp60 expression is associated with decreased Bcl-2, increased Bax, and enhanced apoptosis [22,34,48] (Fig. 2).

Adult cardiomyocytes release ubiquitinated Hsp60 in exosomes under stress, although other studies found no change in exosomal Hsp60 levels under various conditions [9,35].

Regional differences in cardiac Hsp60 expression have been described. The upper left ventricle shows increased levels of several proteins, including Hsp60—an observation relevant to acute MI, which most severely affects this region—whereas the right ventricle shows no comparable increase [36].

A study investigated the effects of recurrent exposure to high temperatures through quick hot water baths as a mean of reducing total blood pressure, minimizing heart remodeling, and enhancing mechanical performance in patients with hypertension-induced cardiac hypertrophy. HSPs, including HSP90, HSP70, and HSP60, were measured in left ventricle (LV) tissue samples due to their sensitivity to elevated temperatures, which lead to increased expression [37]. Certain research findings indicate a correlation between modifications in Hsp60 expression and variances in atrial myolysis throughout different phases of AF [28]. Trandopril was shown to have benefits in left ventricular dysfunction following acute myocardial infarction in an animal experiment by preventing the reduction in mitochondrial activity, lowering reactive oxygen species formation, and altering Hsp60 synthesis [38].

Loss of Hsp60 has severe cardiac consequences. In mice, Hsp60 deletion in mature cardiomyocytes leads to dilated cardiomyopathy (DCM), chamber dilation, ventricular dysfunction, early mortality, and increased lung-to-body weight ratio due to disrupted mitochondrial proteostasis [39].

In a study by Knowlton et al., the levels of several HSPs in patients with ischemic cardiomyopathy, DCM, and a control group were examined. According to the study, DCM patients had twice the levels of Hsp27 and Hsp60 compared to the control group [40]. In another study, Niizeki T et al. discovered a relationship between Hsp60 levels and the prognosis and severity of congestive heart failure in 112 patients. Additionally, they observed that elevated Hsp60 levels were associated with

an increased risk of progressive heart failure. In this study, they claimed that individuals with chronic heart failure had significantly higher levels of Hsp60 than those in a control group. The study also found that, compared to the control group, patients with chronic heart failure had higher serum levels of Hsp60, with this increase being even more pronounced in patients with a higher New York Heart Association (NYHA) functional class. This increase was particularly notable for patients with severe chronic heart failure assigned to NYHA functional class IV [41].

All these data demonstrate that Hsp60 overexpression and its release into the blood are closely related to the severity of cardiac diseases.

Also the co-chaperon Hsp10 may have a role in ischemic pathologies, cardiac disfunction and cardiomyopathies. Hsps reduce the apoptotic effect of unfolded proteins, during stresses like ischemia and heart failure [42]. Moreover, an increase in the levels of Hsp10 in cardiomyocytes preserve the mitochondrial function and prevent apoptosis to occur during ischemia and reperfusion injury. In these circumstances the release of the cytochrome *c*, reduction in the activation of caspase-3 and mitochondrial ATP preservation occur. The administration of an exogenous Hsp10 induces the increase of the mitochondrial ATP after hypoxia/reperfusion, suggesting a direct role in the myocardium protection [43].A direct correlation between Hsp10 and cardiometabolic syndromes has been highlighted in a paper published in 2021, where the authors suggest an adaptive role of Hsp10 in the cardiac metabolic stress [44]. Anyway, Hsp10 even if it is co-localized with Hsp60 in the mitochondrion, it has never been identified in exosomes or extracellular vesicles. For this reason, Hsp10 has been considered until now only a possible biomarker or therapeutic target.

4. Possible experimental approaches suggested

This section of the paper is meant to integrate current knowledge with future experimental directions, spanning in vitro systems, organoids, animal models, and clinical approaches. In particular, this list of experimental approaches has been added to the paper to let the reader think about the mechanistic and casual links between Hsp60, DAMP signaling and heart disease, starting from the most simple in vitro stimulation of cultured cardiomyocytes to the more complex evaluation of Hsp60 levels in acute MI or transcatheter aortic valve replacement (TAVI) patients.

A first approach can be to induce the release of Hsp60 by H_2O_2 stressed rat cardiac precursors cells (CPCs) isolated from rat ventricles treated with collagenase I [45], collect the condition medium (CM) and treat murine bone-marrow-derived macrophages (BMDMs) in a separate well. Stressed CPCs should release Hsp60 in the medium, within extracellular vesicles or freely available in the medium. If the CM induces the release of pro-inflammatory cytokines such as TNFα, IL-6, IL-1β and the activation of the NF-κ B gene, to determine whether it is indeed Hsp60 that binds to the TLR2/TLR4 receptors of the BMDMs and induces inflammation, it is possible to add an anti-Hsp60 antibody to inhibit the interaction between this chaperone and the TLR2/TLR4 receptors. If the antibody is able to inhibit this interaction, then inflammatory cytokines will not be released.

A second approach may be to validate Hsp60 release and signaling in human tissue models. The hypothesis is that human myocardial tissue under ischaemic stress releases Hsp60 and activates local innate responses. As obtaining human myocardial tissue is very difficult, it is possible to use organoids derived from CPCs obtained from human cardiac tissue during heart transplantation surgery or from human induced pluripotent stem cells (hiPSCs). Organoids may undergo oxygen/glucose deprivation for a defined period, followed by reoxygenation to mimic controlled ischaemia. Release of Hsp60 and interaction with TLR2/TLR4 receptors may be evaluated by treatment with neutralizing anti-Hsp60 antibodies and TLR2/TLR4 antagonists. This ex vivo approach has the advantage of testing human tissue and determining whether Hsp60 release and TLR receptor interactions are dependent on native cell-cell architecture.

A third approach may be the use of the well-known mouse MI model with Hsp60 neutralization or TLR2/TLR4 genetic loss. In this model it is possible to test whether blocking extracellular Hsp60 or TLRs receptors reduces infarct size and promotes remodeling after MI (positive or negative effect). The hypothesis is that neutralizing extracellular Hsp60 (or deleting TLRs) reduces post-MI inflammation and improves function. Animals usually used are C57BL/6 mice (with a balanced number of males and females) or TLR2/TLR4 knockout mice, aged 8–12 weeks. Hsp60 can be neutralized injecting systemic doses of anti-Hsp60 antibody starting immediately after MI and continuing until the end of the experiment. Anti-Hsp60 or TLR2/TLR4 deficiency should reduce inflammatory cytokines, reduce infarct size and improve LVEF vs MI + vehicle.

The final approach may involve a human translational observational study measuring serum Hsp60 and inflammatory cytokines in patients with acute myocardial infarction, correlating these with infarct size, or in TAVI patients before and after aortic valve replacement. In this model, it is possible to test only the pro-inflammatory activity of the circulating Hsp60 protein. The hypothesis is that higher circulating Hsp60 levels acutely predict larger infarct size and worse remodeling.

A study may be considered complete and comprehensive only if at least two of these models are used.

5. Future perspectives

The expression of Hsp60 in cardiac tissue appears closely linked to HF, particularly in response to cardiac stress. Several cardiac disorders, including MI and HF, show elevated Hsp60 levels, supporting its potential role as a biomarker of stress and injury in the heart.

Recent findings highlight increased Hsp60 expression in heart disease and its interaction with TLRs. These observations suggest that Hsp60 may function as a DAMP, activating signaling cascades that regulate inflammation and promote the synthesis and release of cytokines such as IL-6. The significance of Hsp60 in cardiac homeostasis is further underscored by evidence that cardiac-specific m-RNAs modulate its expression, linking it to heart failure progression and structural remodeling.

Future studies should explore therapeutic strategies aimed at modulating mitochondrial function and Hsp60 levels to mitigate cardiac disease. The precise mechanisms by which Hsp60 is released into the bloodstream—either freely or within extracellular vesicles—remain to be clarified. Similarly, the molecular interactions between extracellular Hsp60 or Hsp60-containing vesicles and TLR2 or TLR4 require further investigation. Determining whether Hsp60 can consistently act as a DAMP and how it influences cytokine synthesis and release will be crucial.

Our review suggests a new integration pathway, connecting mitochondrial stress, vesicle release and immune activation. The new proposed pathway starts with a mitochondrial stress, which induces Hsp60 relocation into extracellular vesicle. This exosomal Hsp60 may activate TLR receptors inducing inflammation and consequently cardiac remodeling. In summary, the relationship between mitochondrial activity, cardiomyocyte structure, and Hsp60 forms a complex network essential for maintaining cardiac health. Advancing our understanding of this network may enable the development of new therapeutic approaches and improve outcomes following cardiac interventions. A deeper comprehension of the processes described in this article will be fundamental to identifying effective strategies for treating heart disease.

CRediT authorship contribution statement

Vahid Saqagandomabadi: Writing – original draft. **Adelaide Carista:** Writing – original draft. **Stefano Burgio:** Writing – review & editing. **Francesco Cappello:** Supervision, Funding acquisition. **Valentina Di Felice:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Instatext, in order to check the english grammar of the text, and Chatgpt to search for correlations and new papers, to check for the consecutio temporis of the text and to make a more clear text. After using this tools, the authors reviewed, edited and deeply modified the content as needed and take full responsibility for the content of the published article.

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

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