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Heat-shock protein 27 (HSP27) not just a biomarker of cardiac and renal diseases

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Abstract

Heat-shock proteins (HSPs) are a large family of conserved chaperone proteins which provide cell protection from various forms of stress including inflammation, hypoxia, ischaemia, and apoptosis. Heat-shock protein 27 (HSP27) is a member of a small molecular weight HSP family and it has recently been connected with cardiac and renal disorders. Several studies stated that HSP27 can be a reliable predictor of cardiac events in patients with chronic heart failure. Moreover, there is a strong inverse relationship between HSP27 level and atherosclerosis. Interestingly, the HSP27 level in atherosclerosis plaques was significantly lower compared to healthy arteries. Additionally, HSP27 was linked with atrial fibrillation (AF) and acute chest pain. Various studies also reported HSP27's usefulness in renal disorders. HSP27 seems to be an independent predictor of not only cardiovascular mortality but also sudden cardiac death (SCD) among haemodialysed (HD) patients. Collaterally HSP27 was proposed as a marker of chronic kidney disease, contrast-induced acute kidney injury (AKI) as well as AKI associated with liver ischaemia-reperfusion injury. Observations from studies conducted to date suggest that HSP27 may be a valuable marker for cardiovascular and nephrological diseases and even a possible therapeutic target. However, to fully understand the role of HSP27 in these diseases, further studies are required.

Keywords: heat-shock protein 27; atherosclerosis; acute kidney injury; atrial ibrillation

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Introduction

Heat-shock proteins (HSPs) are a family of proteins found in all cells of organisms, and they play a crucial role in protecting cells against various forms of stress. The activation of HSPs can be found not only due to elevated temperature but also other stressors such as inflammation, hypoxia, ischaemia, nutritional deficiencies or toxins. They help in maintaining the proper folding of other cellular proteins, prevent protein aggregation, control the cell cycle, assist in the repair of damaged proteins, and protect cells from oxidative stress as well as apoptosis [1–4]. The effect of HSP27 on tissues affected by stress or trauma is shown in Figure 1.

Depending on the molecular weight of HSPs, they are classified into different families. Heat-shock protein 27 (HSP27) is a member of the small molecular weight HSP family. It is considered to be one of the most important low molecular weight HSPs and is partially produced in cardiomyocytes, endothelial cells, and renal medulla [5–8]. Several commercial assays are commonly used to measure serum HSP27. Most of these assays are enzyme-linked immunosorbent assays (ELISAs) that utilize antibodies against HSP27. Although

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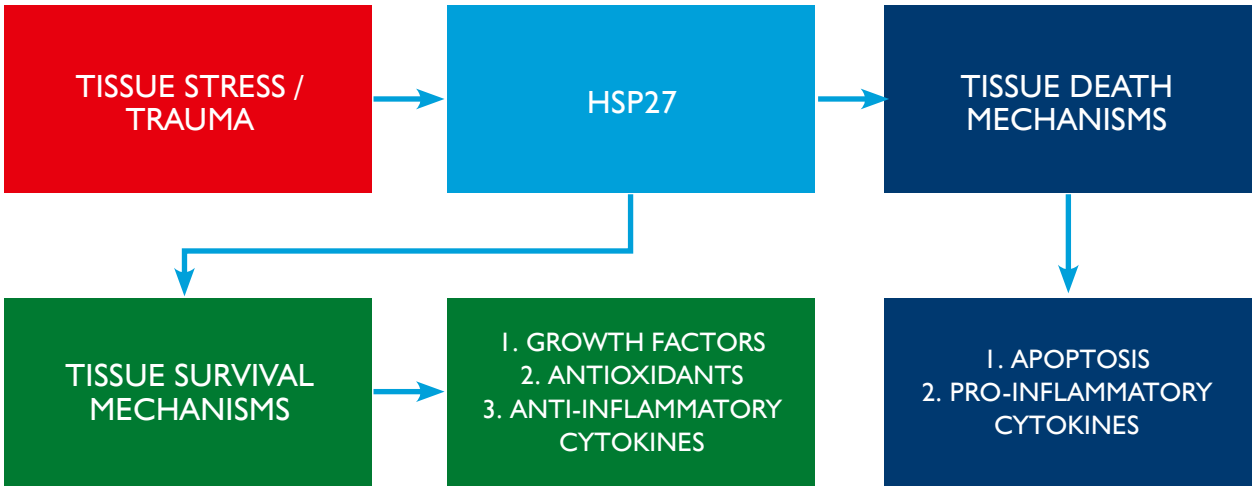

Figure 1. Presents the simplified HSP27 effects on the tissues influenced by stress or trauma

this technique offers valuable information on protein concentrations and can be extremely sensitive, it also has some well-known limitations. It is worth noting that results from commercial clinical HSP27 ELISAs may vary due to differences in antibodies and calibrators used, resulting in considerable measurement variability. Additionally, this technique involves protein horseradish peroxidase (HRP) enzymes that serve as amplifiers. These enzymes are sensitive to reaction conditions such as time, temperature, and pH, which restrict the universal application of the enzyme-based amplification technique leading to false positive results [9]. Liquid chromatography-tandem mass spectrometry-based targeted proteomics serves as an alternative technique. It enables the quantification of the proteins with high quantitative accuracy, reproducibility, and a broad dynamic range [10]. HSP27 was previously related to neurodegenerative diseases [11], however recently there has been a growing interest in linking it with cardiac and renal diseases [5–8, 12].

HSP27 and cardiac diseases

HSP27 has seemed to exert a cardioprotective effect and has been emerging as a potential biomarker and a therapeutic target of cardiovascular disorders [5, 7, 12, 13].

There was a recent study suggesting that HSP27 may be a useful biomarker of cardiovascular death related to chronic heart failure (HF) or sudden HF hospitalization [14]. Chronic HF is a condition in which, as a result of cardiac dysfunction, there is a reduction in the minute capacity of the heart in relation to the metabolic demands of the tissues of the body [15]. Traxler et al. included 134 patients with chronic HF in the study. During a follow-up 33% of patients experienced cardiac events. Statistical analysis showed that HSP27 levels above the median stated for increased risk of an event even after adjustment for factors such as age, gender, aetiology, smoking status and others. According to Traxler, increased levels of HSP27 are due to the myocardium's response to ischaemia-reperfusion injury with the use of Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4). This study proved that HSP27 can be a strong independent predictor of cardiac events in patients with chronic HF [14].

Atherosclerosis is a common condition involving the accumulation of lipids and extracellular matrix material as plaques in the arteries. Over time, it can lead to narrowing and stiffening of the arteries, reducing the blood flow, and consequently causing cardiovascular diseases [16–18]. Martin-Ventura et al. stated that HSP27, among other differentially secreted proteins, can be characterized as a potential biomarker of atherosclerosis. They suggested that HSP27 expression was decreased in atherosclerotic plaques as a result of its degradation by proteolysis contrary to healthy arteries [17]. According to Wick, the observation of high HSP27 expression in the normal-appearing area adjacent to the atherosclerotic plaque may suggest that the inflammatory processes are particularly active in this region. Consequently, there can be a decrease in HSP27 expression toward the atherosclerotic core due to inversely increased proteolytic activity in this region of the plaque [18]. Similar findings were stated in the study by Park et al. Additionally, their study showed a significant increase in serum HSP27 antigen concentrations in patients with acute coronary syndro-

me (ACS) which were not related to cardiovascular disease risk factors [19]. Jaroszyński et al. stated the strong inverse association between serum values of HSP27 and carotid atherosclerosis. Increased serum HSP27 levels mitigated the progression of atherosclerosis and induced a transformation in plaques towards a more stable morphology [12]. These studies proved that HSP27 can be used in clinical practice not only as a strong predictor but also as a possible therapeutic target of atherosclerosis.

Talkhi et al. [8] in their study aimed to characterize the variables associated with serum anti-HSP27 antibody titres which can become a potential biomarker of inflammation in patients with cardiovascular disease (CVD), and consequently improve strategies for managing CVD. Authors revealed that factors associated with anti-HSP27 were, among others, pro-oxidant--antioxidant balance (PAB), physical activity level (PAL), platelet distribution width (PDW), systolic blood pressure (SBP), age, red cell distribution width (RDW), neutrophils to lymphocytes ratio (NLR), platelet count (PLT), glucose, cholesterol, red blood cells (RBC). Of the above factors, PAB presented the strongest correlation and serum anti-HSP27 antibody titre prediction.

Interestingly Shams et al. [20] showed that IgG anti-HSP27 antibodies levels were increased in patients with acute chest pain. This growth was strongly associated with only age and hypertension as cardiovascular risk factors and weakly with diabetes in patients with acute coronary syndrome (ACS). Moreover, some studies have suggested that following ischaemia-reperfusion accident HSP27 level is increased in cardiac myocytes [21, 22].

The most common cardiac arrhythmia, which tends to grow more enduring as time progresses, is atrial fibrillation (AF). Because AF provokes myocyte stress and structural cell changes, Brundel et al. [23] aimed to characterize if and which HSPs may protect cells from myolysis and consequently prevent AF progression. In their study on the HL-1 cell model for AF increased level of HSP27 alone was responsible for attenuating myolysis. Furthermore, they extended their results to human AF, which showed a highly increased expression of HSP27 in the atrial appendages of patients with paroxysmal AF. In addition, Marion et al. in their study investigated the role of HSP27 in AF staging, however, no significant association was observed between HSP level and AF stages or AF recurrence. Nonetheless, serum samples taken from patients who experienced AF recurrence within a year after pulmonary vein isolation (PVI) exhibited elevated levels of HSP27. This implied that HSP27 could serve as a predictive marker for AF recurrence following ablative therapy [24]. Additionally, in patients who underwent arrhythmia surgery, HSP27 can also be a predictor of AF recurrence according to van Marion et al. [25]. Lastly, Kargari et al. [26] found that obese patients had significantly higher levels of HSP27 anti-body titres than the nonobese group, which could potentially suggest that HSP27 can be a risk biomarker of cardiovascular diseases.

There are only a few studies that examined the possible HSP27's usefulness in treating cardiovascular diseases. In the study from 1999, Dillmann proposed a model where HSP27 could provide a protective effect against simulated ischaemia. The author suggested a model in which proteins that have not yet achieved their final folding state bind to the exterior of large oligomeric small heat shock protein complexes, which act as a sheltered environment. Once ischaemia is resolved, these proteins can be released, allowing them to attain their final folding state and resume their normal activity in cells that have recovered from ischaemic injury [27]. Additionally, Brundel et al. noticed that increased HSP27 expression protects myocytes from tachy-pacing-induced myolysis. The HSP response, which is temporarily activated in patients with AF, appears to diminish over time, losing its capacity to prevent structural changes like myolysis and consequently may contribute to the progression of AF. That is why future research is needed to evaluate the therapeutic potential of drugs that may enhance the HSP response in treating AF [23]. Despite these promising results, HSP27's application in treating other cardiovascular diseases remains underdeveloped. Therapeutic protocols aimed at improving conditions such as atherosclerosis, ischaemic heart disease, cardiac arrhythmias, and cardiomyopathies are required to fully understand the usefulness of HSP27.

HSP27 and renal diseases

Results of various studies suggest the utility of HSP27 in the diagnosis and treatment of kidney diseases.

Jaroszyński et al. evaluated the predictive value of HSP27 in mortality and factors associated with HSP27 in a group of haemodialysed (HD) patients. 202 HD patients and 42 controls were enrolled on the study. The main discovery was that there was no discernible difference in serum HSP27 between HD patients and controls. Moreover, decreased levels of HSP27 emerged as a standalone predictor of cardiovascular mortality and sudden cardiac death (SCD), among HD patients [12]. Additionally, Jaroszyński et al. [28] in the other study revealed a significant connection between low HSP27 levels and widened spatial QRS-T angle, which reflects increased heterogeneity of myocardial action potential. The spatial QRS-T angle is the angle between the vectors of ventricular depolarization and repolarization. It is considered to be the strong,

ECG-derived predictor for cardiac events and SCD in the general population and the high clinical risk group of patients, including HD patients [28, 29].

Lebherz-Eichinger et al. [30] have shown in their article from 2012 that patients with chronic kidney disease (CKD) had increased HSP27 levels both in serum and in the urine. They also suggested that it could be an easily obtainable potential marker of the course of CKD, and consequently treatment response. Elevated serum HSP27 level was noticed in pre-dialysis patients which is in agreement with the study from Musiał et al. [31]. Their study was conducted on the paediatric population suffering from CKD and undergoing chronic dialysis. The results have shown that children with CKD are more prone to HSP27 malfunction with HD as the exacerbating factor [31].

The common cause of hospital-acquired acute kidney injury (AKI) is contrast-induced AKI associated with the use of iodine-based radiographic contrast media. The underlying mechanisms of the development of contrast-induced AKI include ischaemia reperfusion injury, among others [32–35]. Elevated levels of HSP27 are typically found within the renal medulla as a reaction to hypoxia and oxidative stress. It seems that HSP27 may exhibit a protective effect against contrast-induced AKI. Previously conducted studies have suggested that HSP27 averts damage and reestablishes the regular functioning of kidney cells after an episode of reperfusion injury [5, 36, 37]. Jaroszyński et al. [38] conducted a study which revealed that low HSP27 level is a reliable and independent predictor of contrast-induced AKI in patients submitted to percutaneous coronary interventions (PCI).

Moreover, it was demonstrated in animal models that overexpression of HSP27 can protect liver cells from injury and AKI associated with liver ischaemia-reperfusion injury in vivo [39]. In addition, Guo et al. revealed HSP27 overexpression in the renal tissues from animal models after acute ischaemic kidney damage. The HSP27 peak level was observed after 6 hours post-reperfusion [40].

Conclusions

The present summary emphasizes some of the recent data on the usefulness of HSP27. HSP27 has been emerging as a reliable biomarker of cardiac disorders, such as atherosclerosis or AF. Moreover, it has seemed to be an independent predictor of cardiovascular mortality and SCD among HD patients, a potential marker of CKD course as well as protect the renal tissue from the development of contrast-induced AKI. Taking it into account HSP27 may become a likely therapeutic target, especially of atherosclerosis in the near future. Nevertheless, further studies on a larger number of subjects are required to expand our knowledge about this remarkable and promising protein.

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