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Heat Shock Proteins: Unveiling Their Impact on Cardiovascular Disorders

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Abstract

Heat shock proteins (HSPs) were discovered in the early 1960s as important intracellular proteinaceous components that aid in stress physiology and reprogram cellular responses to allow the organism to survive. HSPs were discovered in extracellular spaces in the early 1990s and were shown to activate gamma-delta T-lymphocytes. Subsequent research linked them to a variety of diseases, including autoimmune disorders, diabetes, cancer, hepatic, pancreatic, and renal illnesses, and cachexia. In recent years, there has been a lot of excitement and enthusiasm surrounding the idea of HSP-targeted new molecular therapies.

Keywords: Heat shock proteins; Illnesses; Molecular therapies; Cardiovascular disorders; Inflammatory; Tumour

Introduction

Heat shock proteins (HSPs) were discovered in Drosophila in 1962 as temperature-sensitive proteins. Similar compounds were later discovered in several species, including humans [1]. HSPs were primarily researched in humans as intracellular components, assisting other proteins in maintaining their structure and function under stress circumstances such as physiological stress, mechanical stress, environmental stress (heat, cold, UV radiation), and infections [2,3]. The role of extracellular HSPs in health and illness is not fully known and requires additional research. This review examines this rapidly increasing field of study and covers current viewpoints and gaps in knowledge regarding the function of extracellular HSPs in diverse disease states, with a focus on cardiovascular illnesses.

When cells are subjected to different stressors, they develop a family of polypeptides known as stress proteins, or HSPs. The production of HSPs is a fundamental and well-preserved cellular response observed in plants, animals, and humans [4-7]. HSPs were assumed to be restricted to the intracellular region until 1989, when HighTower and Guidon discovered HSP70 (HSPAI) in an external media [8]. For numerous years, this first discovery was dismissed as an artefact and received little attention. However, as more information became available, interest in extracelluar HSPs grew by 2000. First, HSP70 was shown to be released during tissue necrosis and macrophage activation [9]. Furthermore, HSP60 (HSPD 1), a typically intracellular protein, was found in extracellular areas in several illness situations, and anti-HSP 60 antibodies were found in the blood [10-12]. HSPs can be released from the intracellular to the extracellular environment by three mechanisms: (a) translocation across plasma membranes, (b) release associated with lipid vesicles, and (c) passive release following necrosis.

Function in non-cardiac disorders

Under normal conditions, HSP production amounts for less than 10% of total protein content; however, during periods of stress, this figure can rise to 15% or higher. Cancer, diabetes, chronic inflammatory and immunological illnesses, trauma, and diseases affecting the cardiovascular, renal, hepatic, and pulmonary systems are among the clinical conditions linked with Ec-HSPs. Hsp70 levels in the plasma have been found to be elevated during pregnancy, after strenuous activity, and after acute illnesses. A higher Hsp70 level associated with increased survival in severely sick patients [13]. Several investigations have shown that Hsp70 has an immune-regulating role. Hsp70 has also been demonstrated to activate macrophages, monocytes, dendritic cells, and natural killer cells. Cancer cells produce significant quantities of Hsp70 at various phases of tumour development and during treatment, and hence Hsp70 has been linked to tumour cell proliferation and apoptosis resistance. Hsp70 has been linked to cancer cell motility, migration, and metastasis. HSPs also suppress apoptosis and boost antioxidant defence. Human Epidermal Growth Factor Receptor-2 (HER2) influences downstream signal proteins throughout cell growth; its mutation or overexpression leads to cancer and metastasis. Hsp90 is related with HER2 activity [14]. Extracellular Hsp70 and Hsp90 produced by tumours increased catabolism, resulting in muscle loss and systemic inflammation. Elevated circulating Hsp70 and 90 levels have been linked to cancer-induced muscle wasting in mice, and they have been linked to the pathological grade and stage of cancer [15]. Increased levels have also been seen in cancer patients who have lost weight. Hsp90 serum levels have been shown to be elevated in rheumatoid arthritis patients, and they have been demonstrated to activate macrophages. Hsp90 levels were shown to be elevated in the serum of patients with systemic lupus erythematosus. Hsp60 was found in the saliva and serum of people with type 2 diabetes, however Hsp70 was found in diabetic ketoacidosis. Hsp70 can worsen alcohol- or H. pylori-associated gastritis while also strengthening the gastric defence system. Raised Hsp27 levels have been linked to inflammatory bowel disease, hepatic dysfunction, and pancreatitis. Hsp70 and Hsp40 were overexpressed in various cellular models of spinal and bulbar muscular atrophy, a kind of motor neuron disease; they prevented the buildup of aberrant polyglutamine proteins and thereby decreased cell death [16]. Recent study on Alzheimer's disease and Parkinson's disease, two major neurodegenerative illnesses, verified the protective effect of HSPs, which impact protein folding and transfer misfolded proteins to the ubiquitin-proteasome system for degradation [17].

Cardiovascular diseases

Cellular stressors are rapidly being recognised as causing an

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accumulation of misfolded proteins during the development of cardiac hypertrophy, heart failure, and ischemia-reperfusion damage. Currie et colleagues. observed in 1988 that higher Hsp70 levels are related with greater recovery from ischemia injury in rats [18]. Cardiac dysfunction can arise when the compensatory systems are overburdened. Increasing data suggests that modulating the activity of chaperones and related molecules might improve heart protection. Only in the last few years has it been demonstrated that the major HSPs (Hsp70 and Hsp90) and co-chaperones (CHIP and BAG-3) play a critical role in preserving cardiac integrity under stress. Their significance in myocardial ischemia and heart failure is also gradually becoming obvious, however the specific mechanism is unknown [19]. Targeting the protein quality control system in heart failure, as in Alzheimer's disease and other neurodegenerative disorders, is a unique therapeutic strategy. Several significant observations on HSPs and their impact on heart failure corroborate this. Myocardial infarction, heart failure, genetic mutations, and ageing can all result in misfolded proteins. Misfolded proteins are harmful to cardiomyocytes (direct impact), resulting in proteinopathy and heart failure. Ec-HSP can influence apoptosis as well as cardiomyocyte contractile performance in heart failure patients.

Acute coronary syndromes

In the pathophysiology of ischemia-reperfusion damage, increased reactive oxygen species and the formation of oxidative stress are critical. Several studies have found a link between HSPs and oxidative stress. Overall, HSPs are thought to be cardioprotective and aid in damage healing. Following coronary artery bypass surgery, any aortic cross-clamping procedure, or in the presence of ischemia, Hsp70 expression is increased in the myocardium. Hsp70 is also released during ischemic preconditioning and exercise. Surprisingly, individuals with greater levels of Hsp70 in their blood had lower rates of post-operative atrial fibrillation [20].

Hypertension

Hsp70 levels are higher in the blood and kidneys of hypertensive individuals. HSPs can cause renal inflammation and hypertension in animals. Hsp70 peptide sequences prevent and treat salt-induced hypertension. Autoimmune reactivity against Hsp70 may contribute to the development of essential hypertension. Hsp70 genetic polymorphisms are linked to essential hypertension. Ec-HSP has also been linked to hypertension-related hypertrophy and fibrosis.

Chronic atrial fibrillation

When atrial cardiomyocytes are stressed, proteostasis is disrupted and remodelling occurs, resulting in chronic atrial fibrillation. HSP27 is raised in the early stages of atrial fibrillation as a protective mechanism; when the persistent stage is reached, its levels are depleted. Hsp60, Hsp10, and Hsp75/mortalin expression has been found to be upregulated in those with persistent atrial fibrillation. According to certain research, changes in Hsp60 expression are related with varying degrees of atrial myolysis in various phases of atrial fibrillation.

Discussion

Recently, promising in vitro results have uncovered new paths for HSP-driven therapies. Because Hsp70 protects tissue from ischemia reperfusion damage, therapies to boost specific HSPs are more likely to be effective in acute ischemic syndromes than in chronic disease states. Ec-HSPs can protect the heart against a variety of myocardial assaults. In a mouse investigation, extracellular Hsp25 decreased doxorubicin-induced cardiotoxicity. Because of its ability to induce HSF1, Hsp72, and Hsp70 mRNA, geranyl-geranyl-acetone (GGA) has recently been postulated as a possible cardioprotective drug. Hsp70 increases heart failure in animals with DCM or pressure-overloaded ventricles, suggesting that overexpression may exacerbate chronic diseases. Hsp-inhibitors (17-AA and 17-DMAG) have also been demonstrated to attenuate inflammatory responses in atherosclerosis.

Conclusion

Under normal circumstances, intracellular HSPs function as molecular chaperones, folding, assembling, localising, secreting, and translocating cellular proteins. Mechanical stress, environmental stress (heat, cold, UV radiation), and infections all significantly increase their expression. Extracellular HSP detection is a new area of research. Despite early doubts about their significance, it is generally accepted that these molecules are not artefacts but rather represent unique biological events. Ec-HSPs appear to have a main function in signalling or cellular communication. Intracellular HSPs primarily function as chaperones. Ec-HSPs are elevated in common cardiac diseases such as cardiac hypertrophy, heart failure, and reperfusion damage. The evidence supporting the function of extracellular Hsp70, Hsp90, and BAG-3 in the aetiology of heart failure and other chronic cardiac illnesses is shaky at best, with some contradictory findings; nonetheless, a cardioprotective impact has been identified. Existing information gaps concerning this intriguing biological phenomena require additional investigation.

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Conflict of Interest

Author declares no conflict of interest.

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