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Microbial Heat Shock Proteins: Roles Other than Just Stress Proteins †

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Abstract: Heat Shock Proteins are so named stress proteins or stress molecules due to their secretion triggered by stress encountered by living beings. Although their primary documented role has been maintaining and regulating protein conformations to reduce effects of aberrant conditions faced by the host, heat shock proteins have been found to have therapeutic effects in treatments of many diseases and conditions. Those derived from certain bacteria, in particular, have been found to have high immunomodulatory potential and are being considered as adjuvants and immune-stimulators in immunocompromised individuals. Extensive research has been done establishing their role as potential vaccine antigens or epitopes targeted in cancer therapies. Certain neuropathies and assumed incurable auto immune diseases have also seen light in terms of therapeusis mediated by heat shock proteins. This review focuses on giving an extensive study about multiple moonlighting roles of heat shock proteins derived from microorganisms, at molecular level, which are being used to immunize and treat diseases in many mammalian species, including humans.

Keywords: HSP; immunomodulator; therapeusis; stress proteins

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1. Introduction

All life forms experience stress and release certain biomolecules or peptides/proteins which act as signalling agents and mediate to initiate mechanisms that can alleviate the stressed conditions and their deleterious effects. Heat Shock proteins are such biomolecules which are released in the cell cytosol when exposed to unfavourable and stressed conditions. Cells tend to protect themselves by increasing their HSP expression so that no abnormal protein folding occurs or molecular conformation alteration occurs in the course of stress conditions. This review capitulates moonlighting properties of heat shock proteins i.e., different roles played by these proteins and their application to therapeusis of certain disorders and diseases.

2. Moonlighting Roles of Heat Shock Proteins

2.1. Disease Induction

Heat shock proteins are conserved proteins which normally function as chaperones in the cell and gets released in stress conditions. However, under certain stress conditions, HSP also act as endogenous harmful signals for the immune system as they activate innate and adaptive immune responses. Their further immunogenic activity is mediated by binding to CD14 and TLR molecules [9].

Overexpressed HSP60 has been reported in various inflammatory diseases like Crohn's disease affected intestinal cells, juvenile dermatomyositis (JDM) affected myocytes and in synovial fluid and tissues of patients affected with Rheumatoid arthritis (RA)

and juvenile idiopathic arthritis (JIA). In cases of atopic dermatitis, HSP find a pivotal role to play in development of the disease [6]. HSP60, once secreted, stimulate CD3+T-cells. These reactive cells then produce high levels of Interferon-γ and lesser amounts of IL-10. HSP 60 is recognised by proinflammatory T-cells and is secreted in copious amounts by sensitised T-cells. Stimulation with HSP60 has also been seen to induce CD4+ $CD25^{bright}$ T cells which then express FOXP3 in healthy as well as diseased host bodies, thus confirming role of HSP in induction of the disease [4].

2.2. Pathogen Survival

A microbial pathogen encounters a number of changes as it enters the host from the environment, some of which can be stress-inducing. Alterations in factors like temperature, pH, and pO2 [5] and organic host defence systems like phagocytosis, specialised phagocytes [23] are some of these. In order to defend itself against the host, pathogen activates HSP and other evasion mechanisms. HSP GroEL and DnaK are allegedly overexpressed in S. Typhimurium. When utilised as an infectious agent, such strains of S. Typhimurium were extremely virulent, but its mutant with the *hsp* gene removed was extremely vulnerable to being killed by activated macrophages [2]. Bacteria can overexpress immunodominance of HSP too. This type of expression is most common in intracellular pathogens while other pathogens can survive in macrophages in absence of increased HSP synthesis. Thus, it gets established that pathogen survival varies with the extent of HSP expression.

2.3. Molecular Mimicry

Due to their highly conserved nature, HSPs from many organisms show homology with HSPs of other organisms. This property makes it difficult for the immune system to distinguish between host and microbial HSP. As a result of this molecular mimicry, cross-reactivity occurs between HSP of the microbe and HSP secreted by stressed host cells, leading to cellular dysfunction. Development of many disorders like atherosclerosis can be attributed to molecular mimicry as the stressed endothelial cells show enhanced expression of HSP resulting in a severe progressive form of disease [7]. HSP60 is the most common Hsp encountered in such disorders.

3. Therapeusis by HSPs

3.1. Autoimmune Diseases

Autoimmune diseases usually take up a chronic course. The activation of immunoregulatory mechanisms by HSPs is known to suppress these autoimmune disorders. In particular, microbial HSPs like HSP60 from *Mycobacterium tuberculosis* has been reported to suppress induction of arthritis. Not only arthritis, inflammatory diseases like collagen induced arthritis, atherosclerosis and insulin-dependent diabetes mellitus are a few to name which were suppressed by immunising patients using whole proteins or synthetic peptides of HSP. Due to a loss of immunological tolerance to self-antigens, auto-immune disorders are characterised by a strong immune response that results in severe chronic inflammation. Their current therapies are traditional corticosteroids and chemical that causes inflammation targeting, which are all known to weaken the immune system and encourage negative side effects. However, thanks to developing technologies, HSP has been attempted as an alternate and safer form of treatment sfor regulating autoimmune diseases. Several pre-clinical studies demonstrate that drug-induced HSP production in the cell has the potential to downregulate inflammation. Additional research demonstrates that inflammation can be suppressed actively by full-length HSP vaccination or their conserved peptides throughout evolution [11].

3.2. Neuropathy Treatment

Certain HSP molecules are integral parts of normal neuronal and axonal functioning. Not only do they maintain neuronal integrity and functioning, they also support the cytoskeleton microtubules, interact with intermediate filament proteins but also aid in muscle contraction [3]. Such vital contributions have been extensively studied and therapy against neuropathies includes administration of HSP co-inducers like Arimoclomol and Celastrol which increase the production of HSP in affected motor neurons. In addition to these, the basic chaperoning function of heat shock proteins also comes into play when considering therapies for neuronal disorders. Due to some abnormal protein or abnormal aggregate formation, neuronal function can be hampered leading to neuropathology in disorders like Dementia, prion diseases, hereditary neuropathies and Parkinson's disease. HSPs like HSPBI and HSPB8 have been found to be crucial in causing degradation of protein aggregates, thus facilitating efficient neuronal conduction and impulse transmission [10].

3.3. Increased Organ Perfusion

Not only is organ perfusion crucial for homeostasis, it is also important for internal organ health and normal systemic functioning. But any percentage of reduction in cellular/tissue/organ perfusion can lead to serious disorders such as Chronic Heart Failure, Peripheral Arterial Disease, Parkinson's and Alzheimer's diseases and other motor and cognitive impairments. These impairments are commonly manifested as thickened endothelia of blood vessels. HSPs have been reported to cause reduced intimal hyperplasia, particularly by Hsp27 [1]. Hsp70 has also been reported to inhibit Angiotensin II and reduce vascular hypertrophy [12]. HSP 90 also keeps vascular hyperplasia in check by upstreaming hypoxia inducible factor-1 [8].

4. Conclusions

This review concludes that Heat Shock Proteins are those biomolecules which not only act as saviours from stress for the host cells or bodies but also possess many other roles i.e., moonlighting roles. These moonlighting roles are confined not only to human cells but also help pathogens to survive in infections but also act as signalling molecules in inflammation. It also concludes that HSP, on the basis of their normal chaperoning and conformation-maintaining properties, can be used in treating chronic, debilitating and even hereditary diseases and disorders which have not found specific treatments till now. Hence, there is a scope for many more pivotal roles for HSP to play in modern medicine, therapeusis and diagnosis.

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