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Heat shock proteins in pathology: A review

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ABSTRACT

Heat shock proteins of the 70 kDa family (HSPAs/HSP70s) are major molecular chaperones and cytokines of most cells and microbes, extracellular and interstitial fluids, blood, synovial fluids and secretory body fluids like saliva. The induction of human HSPAs plays an important role at cellular level under most stress conditions. HSPAs play a role in numerous physiological and pathological events, including modulation of cytokine release and immunity. Despite their advantageous effects maintaining health of several oral tissues, HSPAs are likely to play a role in the progression of pathological conditions like OLP, OSMF and Carcinogenesis. The review attempts to provide a critical overview of Hsps and their divergent roles in cellular processes particularly in the context of human health and disease.

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1. Introduction

Organisms and cells respond to various stress conditions such as environmental, metabolic, or pathophysiological by selectively upregulating the expression of a group of proteins called the heat shock proteins (HSPs).[1] HSPs were discovered by Ferruccio Ritossa in 1962 when they observed that temperature shock had induced odd puffing patterns in salivary polytene chromosomes in Drosophila melanogaster. HSPs are ubiquitous, highly conserved proteins found in all prokaryotic and eukaryotic species. The term 'heat shock' protein is a misnomer, since in addition to raised temperature, other conditions like oxidative stress, nutritional deficiencies, UV irradiation, chemicals like ethanol, viral infections, and ischemia–perfusion injuries can induce the protein expression.[2]

Heat shock proteins A (HSPAs) have both stimulating and inhibitory epitopes. They either activate or inhibit cytokine and chemokine production of dendritic cells or monocytes and help in the maturation of dendritic cells.[3] Besides the above, extracellular HSPAs modulate neuronal function, and on entering the blood stream, they also possess the ability to act at distant sites of the body as ancestral danger signals.[4] HSPs are detected in neoplasms arising from many tissues and organs such as prostate, adrenal gland, bladder, and oral carcinomas.[5–7] Also recent studies have revealed that HSPs are expressed in cardiovascular diseases, and these studies demonstrated that circulating Hsp60 is elevated in a subpopulation of patients with acute coronary syndromes and levels are associated with early atherosclerosis and serum concentrations of proinflammatory cytokines.[8]

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These proteins can be categorized into several families based on their approximate molecular weights, for example, the Hsp 60 kDa, Hsp 70 kDa, and Hsp 90 kDa families. These proteins while functioning as molecular chaperones participate in protein assembly, stabilization, folding, and translocation of oligomeric proteins, whereas as proteases, such as ubiquitin-dependent proteasomes, mediate the degradation of damaged proteins.[4]

2. Role of HSPs in defense

2.1. *Cytoprotection and mucosal defense*

Important mechanisms for the maintenance of mucosal health are based on the cytoprotective effects of extracellular HSPAs.[9]

Extracellular cytoprotective effects are based on three different mechanisms:

(1) A specific binding of HSPAs on mucosal cell surfaces, leading to surface defense against toxins through the mucosal cell surface proteins.[4]
(2) A more specific adhesion-type binding to sulfoglycolipid structures of mucosal cells preventing bacterial colonization of mucosal surfaces through occupying mucosal binding sites of **HSPA**-related bacterial adhesins.[10]
(3) Surface receptor binding of HSPAs mostly followed by internalization, leading to the decrease of the cells' apoptotic and necrotic liability and release of several cytokines.[11]

2.2. *Immune/inflammatory defense of mucosa*

Besides surface protection, extracellular HSPAs also participate in several immunological mechanisms responsible for mucosal defense. The appearance of intracellular HSPAs on the surface of spontaneously developing tumor cells leads to the lysis of these cells by natural killer (NK) cells. Surface expression of HSPAs on tumor cells is frequently accompanied by HSPA release (via lipid rafts and/or exosomes) leading to the activation of NK cells, Langerhans cells, and dendritic cells that are present in the environment.[12]

Furthermore, cellular or microbial damage (or release) induced extracellular appearance of both uncomplexed ''free'' HSPAs and membrane-bound HSPAs act as ancestral danger signals, which leads to the following:

(1) The release of proinflammatory cytokines from several immune cells like monocytes, dendritic cells, macrophages, and T lymphocytes.
(2) The release of nitric oxide from macrophages.
(3) The activation of NK cells.
(4) The activation of complement via antibody-independent alternative pathway.
(5) The induction of local sIgA responses against microbial HSPA homologues, which blocks adherence and prevents transmucosal invasion of the microbe at issue.[13]

3. Role of HSPs in pathology

3.1. *Periapical inflammation*

HSPAs play a role in the formation of several periapical inflammatory lesions.[14] The expression of HSPAs was increased in lymphocytes and endothelial cells of inflammatory periapical granulation tissues.[14] There was also a tendency toward the increase of HSPA expression in lining epithelium of periapical inflammation-induced radicular and residual cysts comparing to Malassez' epithelial rests of control areas. This may indicate a possible role of HSPAs in the activation and proliferation of lining epithelium.[15] Surprisingly, the Malassez' epithelial rests of control noncystic areas also express a relatively high amount of HSPAs.[14] Furthermore, HSPAs (both microbial and mammalian) stimulate bone resorption, presumably via the induction of proinflammatory cytokines, which are also known activators of osteoclasts.[16] Premised bone resorptive effect is another strong indication of an important role of HSPAs in the progression of periapical lesions.[16]

3.2. *Oral ulcers and wound healing*

The increased HSPA level of mucosal cells has been demonstrated in the case of nonspecific oral ulcerations and gingival wound healing.[17] Although oral tissues have not been particularly investigated, it is very likely that the role of HSPAs in the pathomechanism and healing of oral ulcers and oral wounds is similar to those in relation to gastric ulcers and wound healing of the skin.[10] In the case of gastric ulcers, HSPA is markedly overexpressed in cells located at the ulcer base and their level decreases with healing of ulcer. The extent of HSPA induction in mucosal cells inversely correlates with the severity of newly induced ulcers. Similarly, the level of intracellular HSPAs positively correlates with the efficiency of wound healing of the skin, and the level of HSPAs decreases with the progress of the healing process.[9]

3.3. *Mucosal allergic reactions and autoimmunity*

Overexpression of HSPAs may also play a role in the appearance of atopic-type (Immunoglobulin E (epsilon) mediated) allergic reactions, in autoimmune disorders, and in haptenation-inducing T cell immunity and sensitization. However, it is not yet clear to what extent extracellular HSPAs are involved in such processes in relation to the oral mucosa, which considerably differs from other mucosal surfaces in this relation.[18] Cross-reactivity of specific antibodies against microbial HSPAs with human HSPAs may occur similarly to other types of HSPs.[9,10]

3.4. *Oral lichen planus (OLP)*

The etiology of OLP is unknown.[19,20] Since the onset of OLP is known to exacerbate by large plethora of exogenous agents, recently, the focus has shifted onto a family of molecules, and the HSP as the cellular expression of this antigen was also seen in lichen planus. Both HSP-60 and HSP70 induce the release of

cytokines from the lymphocytes and contribute to the pathogenesis of autoimmune disease and chronic inflammation.[21] Sugerman et al. drew comparisons in HSP staining among OLP, dysplastic OLP, normal oral mucosa, and nonspecific oral ulceration. They noted a full thickness expression of HSP in 94% of their OLP cases.[22]

3.5. *Oral submucous fibrosis (OSMF)*

OSMF is a chronic insidious scarring disease of oral cavity, pharynx, and upper digestive tract, characterized by sunken cheeks with progressive inability to open the mouth due to loss of elasticity and development of vertical fibrous bands in labial and buccal tissues and shrunken uvula.[23] Areca nut chewing is the main causative agent, although various studies revealed that its etiology is multifactorial.[24] Regulation of heat shock protein 70 (HSP70) expression in OSMF is not known much; HSP70 is synthesized in all living organisms on stress situations arising in cells. Expression of HSP70 indicates that stress plays an important role as a predisposing factor in OSMF and its subsequent progression to oral squamous cell carcinoma.[22]

3.6. *Carcinogenesis*

Hsp, such as Hsp70, Hsp27, and Hsp90, inhibit apoptosis by direct physical interaction with apoptotic molecules, and are also overexpressed in several tumor cells.[23] HSP binds to procaspases, inhibiting their activation. The overexpression of Hsp may help the accumulation of hidden mutations in tumors, which can help their further progression to more aggressive types of malignant/metastatic cells.[25]

Depletion of Hsp70 from tumor cells by various methods induces their apoptosis.[25] Inhibition of Hsp90 in tumor cells results in the dimerization-induced activation of death receptors, suggesting that Hsp keeps death proteins in an apoptosis-resistant state by a direct association.[25] Aging and various diseases, such as neurodegenerative diseases, induce the accumulation of damaged/misfolded proteins due to oxidative stress and/or proteotoxic insults. Moreover, chaperone function,[26] HSP induction, and the degradation of damaged proteins are all impaired under these conditions.[27] Tumors undergo facilitated evolution due to the increased proliferation and selection pressure.

4. Conclusion

HSPs play an important role in oral defense under both healthy and pathological conditions; however, their role is somewhat ''Janus-faced,'' exerting both immune-stimulating and immune-regulatory properties. The involvement of Hsp in a multitude of intracellular actions places them as central coordinators in deciding the fate of cell. We need much more comparative investigations on the induction of various Hsp, as well as on their occupancy, to get a full picture of the optimal levels of these proteins. However, from the number of successful clinical studies, it is concluded that, Hsp can be used as novel molecular targets for pharmacological and therapeutic purposes.

Conflicts of interest

The authors have none to declare.

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