The role of heat shock proteins as chaperones on several human diseases

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ABSTRACT

Some heat shock proteins (HSPs), act as molecular chaperones. These and other molecular chaperones that are not HSPs, function in a variety of protein biosynthetic event and protect proteins from the deleterious effects of stressors by stabilizing, and refolding proteins. They assist protein folding, assembly, transport and degradation. Several human diseases such as neurodegeneration, cancer, aging, retinal dystrophy, and inflammation arise from defects HSPs and protein folding. This review demonstrates the chaperones such as properties of HSPs in cellular processes and their implication in different kind of human diseases.

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Molecular chaperones are intracellular proteins that prevent inappropriate intra-and intermolecular interactions of polypeptide chains. Different chaperones associate to form functional complexes (chaperone) and work coordinately to accomplish specific functions during the folding, transport or degradation of particular proteins.[1] This ubiquitous, well conserved protein account for 1-2% of all cellular proteins in most cells and has become an increasingly active subject of research in the past couple of years.[2,3] Heat shock proteins (HSPs) first came to attention due to their specific induction during the cellular response of all organisms to heat shock, but are now known to constitutively and abundantly expressed in the absence of any stress.[4] Therefore, HSPs considered being chaperones, which play a universal role in maintaining cellular homeostasis. Heat shock proteins have been defined by their apparent molecular weight as family: many small HSPs (sHSPs) (5-30 KDa), HSP40, HSP60, HSP70, HSP90, and HSP110, which have been presented in **Table 1** according to their location and cellular function. They, either alone or in cooperation with other chaperones, are involved in cellular processes as disparate as correct folding and assembly of proteins, transport of proteins to specific intracellular locations, protein degradation, and preservation and reconstructing of the cytoskeleton.[5,6] It has been demonstrated several mechanisms where defective chaperones and HSPs proteins have pathogenic consequences. Recently, determined role of these proteins has been implicated in a variety of human diseases such as neurodegenerative, cancer, aging, heart, autoimmune, inflammatory diseases and retinal dystrophy.[7,8] The present review summarizes the vital role of HSPs in the control of disease pathology, arising from their function as molecular chaperones in stabilization, refolding and protection of proteins.

Involvement of HSPs in neurodegenerative diseases. Recent finding indicate that protein misfolding and aggregation cause many neurodegenerative diseases. Among these "proteinopathies" are Alzheimer's, Parkinson, polyglutamine diseases and prion disorders.

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Table 1 - The location and cellular function of heat shock proteins (HSPs) family.

HSPs family	Cellular location	Cellular function
Small HSPs (5-30 KDa)	Ubiquitous	Prevent protein aggregation[39,40]
HSP40	Cytoplasm and nucleus	Co-chaperone partner, regulating protein folding, transport, translational initiation and gene expression[41,42]
HSP60	Mitochondria	Protein assembly[43]
HSP70	Cytoplasm, ribosome and nucleus	Assembly and transport of newly synthesized proteins within cells and removal of denatured proteins[44]
HSP90	Cytoplasm and nucleus	Binds steroid receptors, protein kinases, intermediate filaments, microtubules, and actin microfilaments, in a specific manner. It is an essential component of the glucocorticoid receptor[38,45]
HSP110	Cytoplasm and nucleus	Preventing the aggregation and assisting the refolding of heat-denatured model substrate[46]

Alpha-synuclein is a protein, which is aggregated in Alzheimer and Parkinson's diseases.[9,10] It was first suspected after the isolation of an alpha-synuclein fragment from amyloidal plaques in Alzheimer's disease. Later, 2 different alpha-synuclein mutations were shown to be associated with autosomal-dominant Parkinson's disease. However, the discovery that alpha-synuclein is a major component of Lewry bodies and Lewry neuritis, confirmed its role in Parkinson pathogenesis.[11]

Polyglutamine diseases, which including Huntington disease, spinobulbar muscular atrophy (SBMA), dentatorubral pallidoluysian atrophy, and 5 forms of dominantly inherited spinocerebellar ataxia (SCAs), are a group of inherited neurodegenerative disorders characterized by protein misfolding and aggregation. In their diseases, protein induces a stress response and that specific molecular chaperones assist the handling of misfolded or aggregated polyglutamine protein in neurons. Spinal and bulbar muscular atrophy is one of the groups of human inherited neurodegenerative diseases caused by polyglutamine expansion. In this disorder, receptor protein is aggregates when truncated. Combination of HSP70 and HSP40 was the most effective among the chaperones in reducing aggregate formation in a cultured neuronal cell model of SBMA.[12,13]

Heat shock proteins in retinal disease. The ocular lens is a transparent organ comprised of a highly concentrated and highly ordered matrix of structural proteins, called crystalline, which are probably the longest lived proteins of the body. Alpha-crystalline, is one of the major lens proteins, accounts for approximately 40% of the protein and has been shown to act in a chaperon-like manner.[14] Posttranslational modification of these proteins has been implicated as a possible etiology of human cataracts.[15] The subunit molecular mass of alpha-crystalline, such as sHSPs, is around 20 KDa although the protein exists as a large aggregate of average mass around 800 KDa during chaperone action. The increased immunostaining of HSP60 and HSP27 in the glaucomatous eyes may reflect a role of those proteins as a cellular defense.[16,17]

Heat shock proteins in cardiovascular disease. Enhanced synthesis of HSPs, which act as chaperones, leads to a transient but powerful increase in tolerance to such endangering situations as ischemia, hypoxia, oxidative injury, and endotoxemia in cardiovascular disease. The regulation and function of HSP chaperones and their clinical significance in conditions such as cardiac hypertrophy and cardiac surgery have been reported by different studies.[18,19] In few studies it was evaluated the effects of drugs and agents on HSPs activity and its regulation in cardiovascular system. Dexamethasone activated HSF-1, which induced a 60% increase in HSP72 in adult cardiac myocytes. Also, it has been reported that estrogen and progesterone's regulate HSPs expression.[20] Recently, attention has been focused upon novel approaches using gene-based therapies to treat cardiovascular disease, which HSPs genes will be one of the potential candidates for this therapeutic approach.[21]

Heat shock proteins in cancer. Molecular chaperones participate in essential physiological process, such as

regulation of cell cycle, differentiation, programmed cell death and tumorigenicity. For example, sHSP are transiently expressed during the cell division to differentiation transition and this phenomenon prevents differentiating cells from undergoing apoptosis. Of interest, tumor cells usually express high levels of sHSP, and anticancer drugs, such as cisplatin, trigger the accumulation of sHSP.[22] It was evaluated the effects of agents that bind the molecular chaperone HSP90 on estrogen receptor function in breast cancer.[23] Other authors have evaluated the effect of phytosulfokine (PSK) on the expression of HSPs in human strains at the protein and messenger ribonucleic acid (mRNA) levels. It was observed that PSK suppress the expression of HSP47 and HSP60 in human tumor cell lines.[24] It has been reported that individual HSPs such as HSP27, HSP70 may have diagnostic and prognostic value for different gynecologic malignancies.[25] Also, there are reports regarding the use of HSP-peptide complexes as tumor vaccines for cancer immunotherapy.[26] Taken together, the possible exploitation of the properties of HSPs for development of unique anti-cancer therapies is currently under active investigation.[27]

Heat shock proteins in other diseases. It has been known that different HSPs are expressed in skeletal muscles, namely, sHSPs (including ubiquitin, HSP20, HSP27), HSP70, HSP60 and HSP90.[28-30] It has been reported that HSPs responded in muscle diseases; however, the molecular mechanism of HSP induction, regulation and its role in maintaining the muscle function, are not completely understood.[31,32] There have been a number of reports that suggest the role of HSP60 as an autoantigen in a variety of autoimmune diseases[33,34] such as diabetes and arthritis.[35,36] Furthermore, the involvement of HSP chaperones have been implicated in several other disorders including stroke, myocardial infarction, atherosclerosis, inflammatory syndromes, infections, parasitic diseases, and aging process.[37,38]

In conclusion, molecular HSPs as chaperones are abundant and highly conserved group of proteins, which bind and stabilize proteins at intermediate stages of folding, assembly translocation across membranes and degradation. Despite the obvious importance of stress response, only recently has scrutiny focused on the role of HSP in the control of disease pathology. Stroke, inflammatory syndromes, infectious and parasitic diseases, cardiovascular, neurodegeneration diseases, cancer, and aging are but some examples of conditions in which HSPs chaperones are being scrutinized. Therefore, it would be of great therapeutic benefit to discover compounds that clinically safe yet able to induce HSPs chaperone genes to over express these proteins in patients with mentioned diseases. Consequently, this emerging technology (HSPs chaperones and corresponding genes) holds to promise for a variety of clinical applications including diagnostic markers, prognostic indicators, vaccine development, cancer therapies, and control of autoimmune diseases.

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