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REVIEW ARTICLE

Heat Shock Proteins, A Short Review

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ABSTRACT

Proteins play an important role in all physiological processes is a known fact. A newer class of proteins, known as heat shock proteins (HSPS), has been recently discovered to be associated with various bodily functions including folding and aggregation of other proteins, transport of proteins and a role in pathogenesis of cancer, as pro-survival or anti-apoptotic properties. In the recent past, a number of drugs have been developed with pro as well as anti hsp activities for the management of a certain diseases. Example being Efungumab which acts against hsp90 and has been approved for the management of invasive candidiasis. Similarly, methylene blue, a dye, is under trials for the treatment of alzheimer's disease. If proved to be safe and effective, these new classes of drugs may be a turning point in the management of difficult disease.

KEYWORDS

Apoptosis, Geldanamycin, Efungumab, Apatorsen, Methylene blue

INTRODUCTION

Stressful conditions trigger certain defence mechanisms, including those at molecular levels. This was first seen in Drosophilia and was reported in 1974.[1] Heat Shock Proteins (HSPs), also known as Stress-induced Proteins or Stress Proteins, are one such class of proteins that are produced in the body in response to stress, under the control of Heat Shock Factors (HSFs), although some are constitutively expressed. The stress may be heat, cold, UV radiation, infections, inflammation, heavy metal exposure or else. HSPs are produced by all organisms and are ubiquitously present. The primary involvement of these proteins is in the folding and stabilization of other proteins, and thus they play an intimate role in the aggregation of various other proteins.[2] Besides action on protein folding, these HSPs also possess pro- and anti-apoptotic properties, making them suitable targets for drug development. The HSP families are classified according to their molecular weight.[3] Table 1 describes in brief the classification as well as a few functions of these proteins.

In the recent past, various drug have been developed which act in line or against the HSPs but a still in their infancy. Besides drugs, the HSPs are also employed as diagnostic tools in various cancers. These are referenced in Table 2.

The flip side is the new set of adverse effects which are seen with these class of drugs. In patients with H.pylori infection which is implicated in the development of gastric carcinoma, it was observed that HSPs contributed to the progression of H. pylori-associated gastric carcinogenesis as well as led to the aggravation of gastric inflammation.[33]

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Table 1: Functions of Heat Shock Proteins

Family	Function
HSP90 (constitutive, induced)[4 - 8]	- Regulatory interactions with signalling proteins - Protein synthesis, folding and degradation - Stabilization of misfolded proteins - Binding of estrogen, progesterone, androgen, and aldosterone [5] - Delivery of antigens to APCs [6] - Cancer cells: enhances growth, supresses senescence, provides resistance to stress induced apoptosis. [7] - Cardioprotective: binds to NO synthase and Guanylate cyclase, cause vascular relaxation [8]
HSP70 (constitutive) [6, 9 - 12]	- Protein folding, membrane transport of proteins [9] - Anti-apoptotic [10] - Delivery of antigens to APCs [6] - In sympathetic neurons: [11] • HSP 72 – inhibits degradation of Tau protein, heat shock inducible • HSC 70 - promotes degradation of Tau protein Low levels – associated with insulin resistance [12]
HSP60 (constitutive)	- In the mitochondria, replication and transcription of DNA, pro-survival. [13] - In the cytosol, complexes and inhibits maturation and activation of Caspase 3 – Anti apoptotic [14] - At the surface and extracellularly, stimulates immune response [15]
HSP40	- Protein folding, co-chaperon for HSP70 [16] - HSP40-70 complex – modulate accumulation of polyglutamine proteins [17]
HSP27 (β1) (induced)	- Anti-apoptotic, prevents proteolysis by inhibiting liberation of cytochrome c from mitochondria[18]
Small HSPs	- Stabilization of misfolded proteins[19]

Table 2: Drugs acting via HSPs

Family	Drug	Disease
Against HSP90	Geldanamycin (derivative, 17-allylamine,17-demethoxigeldanamycin)	Malaria[20] Huntington's disease[21] Cacncers[22,23]
	Efungumab	Invasive Candidiasis[24]

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Against HSP70	Triptolide	Pancreatic cancer[25] Mesothelioma[26]
	Methylene blue (inhibits ATPase activity of HSP72)	Alzheimer's disease[27]
Pro-HSP60	Bortezomib[28]	Malignancies, increases expression of HSP60 on malignant cells and thus enhances immune response against tumour cells
Against HSP40	Quercetin (inhibits HSP 40 and 27)	Parkinson's disease[29] Cancer[30]
Against HSP27	Apatorsen (antisense oligonucleotide)	Cancer[31]
	Diagnostic tool[32]	Increased levels - Renal injury and fibrosis, Cancers of breast, lung, liver, prostate, rectal, osteosarcoma, leukaemia, cerebral and cardiac ischemia
		Reduced levels – oesophageal cancer
		Anti-HSP27 IgA – Gynaecological malignancies

Autoimmune disease: Since these are highly conserved in nature, they are the initiators as well as the targets of autoimmune attack. Molecular mimicry and cross presentation of antigens are the phenomena of their involvement in autoimmunity. Their roles have been implicated in atherosclerosis, uveitis, lupus and Behcet's disease. [34]

Atherosclerosis: Risk factors for atherosclerosis including infection, oxidative stress, biomechanical stress, all lead to the overproduction of HSPs through the activation of heat shock transcription factor 1 which may lead to worsening of atherosclerosis.[35]

The anti-apoptotic property may lead to a poor prognosis and resistance to therapy in cancer which the anti-apoptotic activity may be therapeutically advantageous.[36]

Insomnia or sleep deprivation can lead to an increased level of HSPs acting as a neuroprotective response, emphasizing on the role of adequate sleep in disease prevention.[37]

CONCLUSION

Harms and benefits are two sides of the same coin, as is the case with heat shock proteins. Despite their presence ubiquitously, a small rise or fall in their levels can have a different specific new set of adverse implications. However, despite the availability of information, further research in needed in order to develop newer drugs which may prove beneficial in the treatment of difficult, incurable diseases.

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