

 <p>ISSN NO. 2320-5407</p>	<p>Journal Homepage: -www.journalijar.com</p> <h2>INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)</h2> <p>Article DOI:10.21474/IJAR01/12539 DOI URL: http://dx.doi.org/10.21474/IJAR01/12539</p>	 <p>INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR) ISSN 2320-5407 Journal Homepage: http://www.journalijar.com Journal DOI:10.21474/IJAR01</p>
---	---	---

RESEARCH ARTICLE

CLINICAL AND THERAPEUTIC SIGNIFICANCE OF HEAT SHOCK PROTEINS

Sreeja Nannapaneni¹, Gnana Sri Deepika Vusthepalli¹, Pavan Santhosh Gupta Vusthepalli¹, Kusuma Naredla¹, Kavya Gowd Aitha¹ and Suryanarayana Veeravilli²

1. Department of Biotechnology, Koneru Lakshmaiah Education Foundation, Guntur, Andhra Pradesh, India
2. Department of Humanities and Basic Sciences, Aditya Engineering College, Surampalem, Andhra Pradesh, India.

Manuscript Info

Manuscript History

Received: 23 December 2020
Final Accepted: 25 January 2021
Published: February 2021

Key words:-

Heat Shock Proteins, Molecular Chaperones, Polypeptides, Infectious Diseases, Homeostasis, HSP.

Abstract

Multiple experimental investigations have been successful in suggesting the role of heat shock protein as a clinical biomarker and therapeutic target in several diseases. All living cells, from the simplest prokaryote to the most complex multicellular organism, contain heat shock proteins-molecular chaperones that are responsible for management of unfolded polypeptides within the cell. In view of the fundamental role of heat shock proteins in maintenance of protein homeostasis, it seems likely that malfunctions associated with members of heat shock protein families would have pathological effects. Such effects might be minimal under normal physiological conditions, but could be exacerbated at times. This review provides an overview of the cell biology and immunology of heat shock proteins focusing predominantly on immunological responses to heat shock proteins in a range of immune-mediated diseases and in infectious diseases.

Copy Right, IJAR, 2021,. All rights reserved.

Introduction:-

All cells contain groups of highly conserved proteins that increase rapidly in concentration when the cells are exposed to environmental heat shock. The most studied heat shock is temperature 5-10⁰C higher than that optimal for the growth of the cell being studied, and thus these proteins are often called heat shock proteins (HSP)[1]. There is now no doubt that heat shock proteins have a profound immunoregulatory effect on the host's immune system. This knowledge has successfully been harnessed to generate a number of important clinical trials. HSP is mediated via a number of distinct mechanisms and it appears that different cell types utilize distinct mechanisms of release.

Despite these cell type differences in the mechanism of release, HSP exocytosis, both basally and in response to cellular heat shock, is a highly conserved response. HSP were considered for many years to be intracellular proteins that were upregulated in response to physiological heat shock. Intracellular HSP have many important functions: as protein-folding machines, or chaperones; the protection of cells in response to heat shock; and the protection of cells against apoptosis. HSP have since been found to be present outside of the cell, and much research also now focuses on the importance of extracellular HSP and their effects on immune responses. Cytosolic heat shock proteins and endoplasmic reticulum resident chaperones or HSP control the folding and prevent the aggregation of proteins[2]. Tumor-derived HSPs, released by dying cells or purified from tumor cells, induce protective anti-tumoral immune responses. This property of HSPs is related to their ability to chaperone tumor-derived peptides and to be internalized, in a receptor-dependent manner, by antigen-presenting cells.

Corresponding Author:-Suryanarayana Veeravilli

Address:-Department of Humanities and Basic Sciences, Aditya Engineering College, Surampalem, Andhra Pradesh, India.

Heat Shock Proteins :

They are a family of proteins that are produced within the human body due to the presence of heat shock conditions and their ability to protect the various different cells from heat but they are now also known to protect the cells from various other conditions such as the exposure to cold, tissue remodeling, UV light, and even the healing of a wound. These proteins are responsible for performing chaperone functions by stabilizing the new proteins to make sure that they have the proper folding or they may even help by refolding the proteins that have been damaged due to heat shock[3]. These proteins are vital to protect our cells from heat shock conditions and they can be found in almost every living organism that is present in the modern world. Heat Shock Proteins are further internally divided into various different groups depending on their molecular weights. To give you a vague example let's look into a few HSP types such as HSP60, HSP70 and HSP90[4-6]. As the names of these shock proteins suggest these proteins are 60, 70, and 90 kilodaltons respectively. Although it may seem that these proteins are only formed due to triggers caused by heat shock within the body this is not completely true. HSP can also be formed due to non-heat shock conditions in which they will be monitoring the proteins of the cells[7].

HSP as Molecular chaperones:

To assist polypeptide folding *in vivo*, a set of proteins, called molecular chaperones, exist whose function is to ensure that polypeptides will either fold or be transported properly. In biochemical terms, a molecular chaperone is defined as "a protein that prevents improper interactions between potentially complementary surfaces and disrupts any improper liaisons that may occur. The proposed function of chaperones is to assist in self-assembly of proteins by inhibiting alternative assembly pathways that produce nonfunctional structures. Chaperone activity merely prevents aggregation and does not necessarily need to be associated with (re)folding of the bound substrate[8].

Hsp70 may not be recycled and cells will be rapidly depleted from Hsp70 chaperone activity[9]. Also, given the complexity of compartmentalization in mammalian cells and the movement of heat shock proteins in and out of different compartments. Function of heat shock proteins, in particular Hsp70, in mammalian cells is that they indeed act as chaperones to prevent irreversible aggregates and assist in either the folding or degradation of their client proteins. Function of heat shock proteins, in particular Hsp70, in mammalian cells is that they indeed act as chaperones to prevent irreversible aggregates and assist in either the folding or degradation of their proteins[10-13]. The heat shock response is triggered primarily by non-native proteins accumulating in a heat shocked cell and results in increased expression of heat shock proteins (Hsps), i.e., of chaperones capable of participating in the refolding or elimination of non-native proteins[14]. Best known is the transcriptional part of this response that is mediated predominantly by heat shock factor 1[15].

Heat shock Proteins and Immunity:

Due to their high degree of conservation and their relative broad substrate binding capacity, at first sight a specific stimulation of the immune system appeared quite unusual. However, during the last decade evidence has accumulated that HSPs are potent activators of the adoptive and innate immune system against cancer and infectious diseases[16]. In order to shed some light into this paradoxical situation and to formally distinguish how HSPs elicit immune responses, Pramod Srivastava proposed the following four paradigms: 1. Despite of the high degree of sequence homology within different HSP families, some variable regions exist that might function as classical species specific, foreign antigens for the host's immune system. 2. Due to their heat shock inducibility and their capacity to transport proteins across membranes, HSPs might be immunogenic because they are expressed in a tissue-specific manner and only in distinct cellular and subcellular compartments[17]. 3. An immune response might also be initiated by molecular mimicry between HSP epitopes and classical non-self antigens. 4. HSP by themselves are not immunogenic but might act as carriers for foreign antigens and thus HSP-chaperoned peptides might be responsible for the initiation of a specific immune response. It became obvious that for cancer immunity pattern 1, 2, and 4 are relevant, whereas pattern 3 seems to play a role in autoimmune and infectious diseases[18].

Role of Heat shock Proteins in Infections:

Protein aggregation is an unwanted side reaction *in vitro* that often causes technical problems in pharmaceutical and biotechnological processes. *In vivo*, protein aggregation can have detrimental effects, since it is critically involved in a variety of potentially lethal diseases. Folding intermediates are more prone to aggregate than the unfolded state, because in the unfolded state the hydrophobic side chains are scattered relatively randomly in many small hydrophobic regions. Protein aggregation in the cell is intimately tied to protein folding and stability[19]. These intrinsic properties of proteins are modified by molecular chaperones[20]. Accumulation of abnormally folded proteins as a result of a variety of heat shock situations, including hyperthermia, viral infection, ischemia, anoxia,

oxidative heat shock, and exposure to heavy metals, triggers the heat shock response, which results in the expression of heat shock proteins (Hsps) in many cellular systems[21]. Constitutively expressed Hsps function as molecular chaperones and participate in protein synthesis, protein folding, protein transport, and protein translocation processes and upon heat shock, prevent irreversible aggregation of proteins. Despite all cellular protection mechanisms, protein aggregation plays an increasing role in health with age, especially in the light of the increasing life span in Western civilizations. Many important facets of protein folding diseases have been analyzed in recent years. While a number of key aspects still remain to be addressed on the molecular level, chances are high that it will be possible to successfully establish therapeutic concepts for these increasingly important diseases. Recently, an antibody has been generated that interacts with oligomeric, but not with monomeric or fibrillar forms of polyglutamine repeat proteins, A β -peptide, α -synuclein, and prion protein.

Alzheimer's Disease:

In Alzheimer's disease, A β peptides (A β 42 and A β 40) are the principal components of extracellular amyloid plaques[22]. These aggregation-prone peptides are generated in the secretory pathway by the sequential action of β - and γ - secretase on the transmembrane A β precursor protein. Two chaperones in the cytosol of mammalian cells, Hsp72 and Hsp28, are synthesized at high levels only after heat shock or other forms of metabolic heat shock. Consequently, expression of both Hsp72 and Hsp28 is often diagnostic of the cell having initiated a heat shock response[23]. Previous studies suggested that heat shock induced expression of Hsp72 and Hsp28 is selectively impaired in ScN2a cells. Notwithstanding that the roles and mechanisms of action of chaperones in AD are still incompletely understood, there is already enough evidence to encourage the development of therapeutic strategies targeting them, either to block their activity in case they promote disease progression or to boost their performance when they are protective. The latter is an example of positive chaperonotherapy, which also includes chaperone replacement via gene or protein administration. On the contrary, if a chaperone is found to help the disease, it has to be blocked or eliminated, which constitute modalities of negative chaperonotherapy.

Parkinson's Disease:

The etiologies of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, polyglutamine diseases, or prion diseases may be diverse; however, aberrations in protein folding, processing, and/or degradation are common features of these entities, implying a role of quality control systems, such as molecular chaperones and the ubiquitin- proteasome pathway[24]. There is substantial evidence for a causal role of protein misfolding in the pathogenic process coming from neuropathology, genetics, animal modeling, and biophysics. The presence of protein aggregates in all neurodegenerative diseases gave rise to the hypothesis that protein aggregates, be it intracellular or extracellular deposits, may perturb the cellular homeostasis and disintegrate neuronal function. So far, the precise mechanism of their neuroprotective potential is poorly understood. Conceptually, chaperones may maintain or convert proteins in a nontoxic conformation and/or enhance the sequestration or degradation of toxic species. Surprisingly, overexpression of chaperones suppressed α -synuclein- and polyglutamine induced toxicity in animal models without affecting the number or morphology of aggregates[25]. Recent in vitro studies with polyglutamine expansion proteins indicated that Hsp70 and Hsp40 act on early intermediates in the aggregation process. By using fluorescence resonance energy transfer (FRET), Hsp70 and Hsp40 interfere with an intramolecular conformational change of a soluble pathogenic polyglutamine fragment, thereby preventing the binding and inactivation of transcription factors. Atomic force microscopy indicated that Hsp70 and Hsp40 cooperatively modulate protein aggregation by partitioning monomeric conformations, attenuating the formation of spherical and annular oligomers and facilitating formation of fibrillar and amorphous aggregates.

Conclusion:-

A number of reports in the last few years have described research aimed at elucidating the role of heat shock proteins, molecular chaperones in particular, in the pathogenesis of neurodegenerative disorders. The findings begin to shed light on the molecular mechanism of protein aggregation and deposition, and of the ensuing cell death. The results also begin to elucidate the role of molecular chaperones in pathogenesis. This is a fascinating area of research with great clinical implications. During the last decade, our knowledge of neurologic diseases has been enriched by the demonstration of the prion-like character of tens of pathologies, starting from the release from initially pathologic cells to infection of adjacent cells. Since molecular chaperones play an important role in these events, novel drugs that target HSPs in the assembly of extracellular particles and their extra- and intracellular transport will be necessary.

Conflict Of Interests:

The authors declare that there is no conflict of interests exist among them regarding the publication of this paper.

References:-

1. Sørensen JG, Kristensen TN, Loeschke V. The evolutionary and ecological role of heat shock proteins. *Ecology letters*. 2003 Nov;6(11):1025-37.
2. Park CJ, Seo YS. Heat shock proteins: a review of the molecular chaperones for plant immunity. *The plant pathology journal*. 2015 Dec;31(4):323.
3. Tutar L, Tutar Y. Heat shock proteins; an overview. *Current Pharmaceutical Biotechnology*. 2010 Feb 1;11(2):216-22.
4. Haslbeck M, Vierling E. A first line of stress defense: small heat shock proteins and their function in protein homeostasis. *Journal of molecular biology*. 2015 Apr 10;427(7):1537-48.
5. Lee DG, Ahsan N, Lee SH, Kang KY, Bahk JD, Lee IJ, Lee BH. A proteomic approach in analyzing heat-responsive proteins in rice leaves. *Proteomics*. 2007 Sep;7(18):3369-83.
6. Pulford DJ, Vazquez SF, Frost DF, Fraser-Smith E, Dobbie P, Rosenvold K. The intracellular distribution of small heat shock proteins in post-mortem beef is determined by ultimate pH. *Meat Science*. 2008 Aug 1;79(4):623-30.
7. Narberhaus F. α -Crystallin-type heat shock proteins: socializing minichaperones in the context of a multichaperone network. *Microbiology and Molecular Biology Reviews*. 2002 Mar 1;66(1):64-93.
8. Gottesman S, Wickner S, Maurizi MR. Protein quality control: triage by chaperones and proteases. *Genes & development*. 1997 Apr 1;11(7):815-23.
9. Kampinga HH, Kanon B, Salomons FA, Kabakov AE, Patterson C. Overexpression of the cochaperone CHIP enhances Hsp70-dependent folding activity in mammalian cells. *Molecular and cellular biology*. 2003 Jul 15;23(14):4948-58.
10. Snoeckx LH, Cornelussen RN, Van Nieuwenhoven FA, Reneman RS, Van der Vusse GJ. Heat shock proteins and cardiovascular pathophysiology. *Physiological Reviews*. 2001 Jan 10;81(4):1461-97.
11. Javid B, MacAry PA, Lehner PJ. Structure and function: heat shock proteins and adaptive immunity. *The Journal of Immunology*. 2007 Aug 15;179(4):2035-40.
12. Kim HP, Morse D, Choi AM. Heat-shock proteins: new keys to the development of cytoprotective therapies. *Expert opinion on therapeutic targets*. 2006 Oct 1;10(5):759-69.
13. Treweek TM, Meehan S, Ecroyd H, Carver JA. Small heat-shock proteins: important players in regulating cellular proteostasis. *Cellular and molecular life sciences*. 2015 Feb;72(3):429-51.
14. Imai J, Yashiroda H, Maruya M, Yahara I, Tanaka K. Proteasomes and molecular chaperones: cellular machinery responsible for folding and destruction of unfolded proteins. *Cell Cycle*. 2003 Nov 28;2(6):584-8.
15. Barna J, Csermely P, Vellai T. Roles of heat shock factor 1 beyond the heat shock response. *Cellular and Molecular Life Sciences*. 2018 Aug;75(16):2897-916.
16. Kumar V, Sharma A. Neutrophils: Cinderella of innate immune system. *International immunopharmacology*. 2010 Nov 1;10(11):1325-34.
17. Jolly C, Morimoto RI. Role of the heat shock response and molecular chaperones in oncogenesis and cell death. *Journal of the National Cancer Institute*. 2000 Oct 4;92(19):1564-72.
18. Elenkov IJ, Chrousos GP. Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. *Trends in Endocrinology & Metabolism*. 1999 Nov 1;10(9):359-68.
19. Jayaprakash NG, Surolia A. Role of glycosylation in nucleating protein folding and stability. *Biochemical Journal*. 2017 Jul 15;474(14):2333-47.
20. Walter S, Buchner J. Molecular chaperones—cellular machines for protein folding. *Angewandte Chemie International Edition*. 2002 Apr 2;41(7):1098-113.
21. Neuer A, Spandorfer SD, Giraldo P, Dieterle S, Rosenwaks Z, Witkin SS. The role of heat shock proteins in reproduction. *Human Reproduction Update*. 2000 Mar 1;6(2):149-59.
22. Gu L, Guo Z. Alzheimer's A β 42 and A β 40 peptides form interlaced amyloid fibrils. *Journal of neurochemistry*. 2013 Aug;126(3):305-11.
23. Tatzelt J, Zuo J, Voellmy R, Scott M, Hartl U, Prusiner SB, Welch WJ. Scrapie prions selectively modify the stress response in neuroblastoma cells. *Proceedings of the National Academy of Sciences*. 1995 Mar 28;92(7):2944-8.
24. Winklhofer KF, Tatzelt J, Haass C. The two faces of protein misfolding: gain- and loss- of- function in neurodegenerative diseases. *The EMBO journal*. 2008 Jan 23;27(2):336-49.
25. Hands SL, Wyttenbach A. Neurotoxic protein oligomerisation associated with polyglutamine diseases. *Acta neuropathologica*. 2010 Oct 1;120(4):419-37.