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

RESEARCH ARTICLE

International Conference on Recent Advances in Biotechnology, Biomolecules and Pharmacy RABBP – 2020 (Organized in Virtual Mode due to COVID-19 Pandemic) during 17th to 19th December 2020 at KL University, Vijayawada, Andhra Pradesh, India.

BIOLOGICAL ROLES OF VARIOUS STRESS PROTEINS AND THEIR CLINICAL IMPLICATIONS

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Manuscript Info

Key words:-
Stress Proteins, Molecular Chaperones, Infectious Diseases, Immunological Responses, Heat Shock, Homeostasis

Abstract

All living cells, from the simplest prokaryote to the most complex multicellular organism, contain stress proteins-molecular chaperones that are responsible for management of unfolded polypeptides within the cell. Unfolded polypeptides are generated during protein synthesis, and also as a result of breakdown associated with protein turnover. Interaction of polypeptides with the chaperone proteins plays an essential role in their folding and assembly into functionally mature oligomers and regulates trafficking between intracellular compartments. Particularly high levels of molecular chaperones are required to maintain protein homeostasis in cells subjected to stress conditions-such as heat shock, nutrient deprivation, malignant transformation, and anoxia-when intracellular proteins are destabilized, or when a major alteration is required in overall cell protein composition. In view of the fundamental role of stress proteins in maintenance of protein homeostasis, it seems likely that malfunctions associated with members of stress 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 stress proteins focusing predominantly on immunological responses to stress proteins in a range of immune-mediated diseases and in infectious diseases.

Introduction:-

All cells contain groups of highly conserved proteins that increase rapidly in concentration when the cells are exposed to environmental stresses. The most studied stress is temperature 5-10^{0}C higher than that optimal for the growth of the cell being studied, and thus these proteins are often called heat shock proteins (or 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

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number of distinct mechanisms and it appears that different cell types utilize distinct mechanisms of release[2]. Despite these cell type differences in the mechanism of release, HSP exocytosis, both basally and in response to cellular stress, is a highly conserved response. The Heat shock proteins (HSP) were considered for many years to be intracellular proteins that were upregulated in response to physiological stress[3]. Intracellular HSP have many important functions: as protein-folding machines, or chaperones; the protection of cells in response to stress; and the protection of cells against apoptosis[4]. 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. Recently, heat shock proteins (Hsp) have been found to modulate macrophage function[5]. In addition, Hsp that appear in circulation after stress as the result of cell lysis or secretion activate the response of macrophages. A better understanding of the role of Hsp in macrophage function may provide new directions in the development of therapeutic approaches for the treatment of inflammation, injury and other immune diseases[6]. Cytosolic heat shock proteins and endoplasmic reticulum resident chaperones or HSP control the folding and prevent the aggregation of proteins. Tumor-derived HSPs, released by dying cells or purified from tumor cells, induce protective anti-tumoral immune responses[7]. 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.

Heat Shock Proteins

They are a family of proteins that are produced within the human body due to the presence of stressful conditions. They were first discovered due to 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[8]. 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 stress. The drastic increase in the expression will be transcriptionally regulated within the cells. The upregulation of the Heat Shock Proteins plays a vital role to the heat shock response which is induced to the Heat Shock Factor (HSF)[9]. These proteins are vital to protect our cells form stressful 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 lets look into a few HSP types such as HSP60, HSP70 and HSP90. 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 stress within the body this is not completely true. HSP can also be formed due to non-stressful conditions in which they will be monitoring the proteins of the cells[10]. We can consider monitoring as recycling old protein cells or help newly created protein cells to fold properly. There are various HSP available within a living organism and all of them tend to have their own applications. Heat shock response and the acute inflammatory response (APR) are both key homeostatic mechanisms for resisting extracellular insult[11-13]. There is evolving understanding regarding the relationship between these two responses. Activation of the HSR exerts some pro-inflammatory effects when HSP are released during cell insult and such extracellular HSP induce cytokine release in inflammatory and immune modulating cells. However, the intracellular mediators of the HSR including the transcription factor heat shock factor 1 (HSF1) and the HSP have profoundly anti-inflammatory effects. HSF1 can be induced by the elevated temperatures encountered in inflamed tissues and in fever as well as by anti-inflammatory prostaglandins[14]. Such activated HSF1 represses cytokine release both directly by inhibiting nuclear factor of interleukin 6 (NF-IL6) and indirectly when elevated HSP inhibit the potent inflammatory factor NF-kB[15]. Reciprocal effects are observed on activation of the APR which leads to inhibition of HSF1 through stimulation of inactivating phosphorylation events involving the mitogen activated kinase (MAPK) pathways. Activation of the HSR thus constitutes a feedback regulatory mechanism for the APR and limits the lethal over stimulation of cytokine release which may occur during infection[16]. However, in order for rapid activation of the APR, mechanisms also exist for HSF1 repression, permitting controlled activation of the response during infection.

Cold Shock Protein

These are also a group of proteins that are produced due to presence of stressful conditions within the cells however it will more be focused upon the phenomenon in which the cells are exposed to the cold. Many micro-organisms manufacture these cold shock proteins within their body due to a fast downshift in the temperature[17]. This phenomenon in which there is a fast downshift in temperature is known as cold shock. One of the most prominent responses of the microorganisms to cold shock is induction of cold shock proteins. All the three groups of microorganisms, i. e. psychrophiles, pedophiles and thermopiles, synthesize cold shock proteins to counteract the effect of temperature downshift[18]. The cold-shock response and cold shock proteins have been studied in detail

using *E. coli* and *Bacillus subtitles* as model system. The first cold-shock protein, CspA, was reported from *E.coli* and its homologues have been reported from a number of gram positive and gram-negative bacteria, but not from archaea and cyan bacteria. The CspA family of E. coli consists of nine homologous proteins, CspA to CspI, but among them only CspA, CspB, CspG and CspIis cold-shock inducible. Survival and tolerance at cold temperatures, the differentially expressed cellular proteins, and cholera toxin (CTX) production were evaluated in Vibrio cholera O1[19].

Stress Proteins 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[20]. The proposed function of chaperones is to assist inself-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. Hsp chaperone-like activities in living mammalian cells after stress, one requires a system that allows examination of HSP functions in different cellular compartments in relation to thermotolerance[21]. This system must be thermo responsive, which means heat-sensitive, and it must allow recovery after heat shock. In cells, active refolding of unfolded proteins during heat shock may not be very productive because when the substrate is released from the chaperone, it will immediately unfold again. In addition, Hsp70 may not be recycled and cells will be rapidly depleted from Hsp70 chaperone activity[22]. 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. The heat shock response is triggered primarily by non-native proteins accumulating in a stressed 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[23-25]. Best known is the transcriptional part of this response that is mediated predominantly by heat shock factor 1 (HSF1). HSF1 activity is regulated at different levels by Hsps and co-chaperones and is modulated further by a number of mechanisms involving other stress regulated aspects of cell metabolism. In all eukaryotic cells, the endoplasmic reticulum (ER) is an intracellular organelle where folding and assembly occurs for proteins destined to the extracellular space, plasma membrane, and the exo/endocytic compartments[26]. The ER has evolved highly specific signalling pathways called the unfolded protein response (UPR) to cope with the accumulation of unfolded or misfolded proteins[27]. Elucidation of the molecular mechanisms by which accumulation of unfolded proteins in the ER transmits a signal to the cytoplasm and nucleus has led to major new insights into the diverse cellular and physiological processes that are regulated by the UPR[28]. Over the past 10 years, tremendous progress has been made in identifying the components that regulate the UPR upon accumulation of unfolded protein in the ER lumen. However, little is known regarding the physiological roles of the different UPR pathways in maintaining cell homeostasis and in disease pathogenesis[29].

Stress 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[30]. 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[31]: 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 stress 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. 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 be play a role in autoimmune and infectious diseases.

Role of Stress 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. These intrinsic properties of proteins are modified by molecular chaperones[32]. Accumulation of abnormally folded proteins as a result of a variety of stress situations, including hyperthermia, viral infection, ischemia, anoxia, oxidative stress, and exposure to heavy metals, triggers the heat shock response, which results in the expression of heat shock proteins (Hsps) in many cellular systems. Constitutively expressed Hsps function as molecular chaperones and participate in protein synthesis, protein folding, protein transport, and protein translocalization processes and upon stress, prevent irreversible aggregation of proteins[33]. 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, Aβ-peptide, α-synuclein, and prion protein.

Role of Chaperones in 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[34]. 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[35]. Surprisingly, overexpression of chaperones suppressed α-synuclein- and polyglutamine induced toxicity in animal models without affecting the number or morphology of aggregates. 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[36]. 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.

Role of Chaperones in Alzheimer's Disease

In Alzheimer's disease, Aβ peptides (Aβ42 and Aβ40) are the principal components of extracellular amyloid plaques. These aggregation-prone peptides are generated in the secretory pathway by the sequential action of β-and γ- secretase on the transmembrane Aβ 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 stress. Consequently, expression of both Hsp72 and Hsp28 is often diagnostic of the cell having initiated a stress response. Previous studies suggested that stress induced expression of Hsp72 and Hsp28 is selectively impaired in ScN2a cells[37]. 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[38].

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.

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