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Review Article

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Clinical and Therapeutic Significance of Various Heat Shock Proteins

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Abstract: The purpose of this study was to explore the different roles of heat shock proteins especially in immunity and infections. Heat shock proteins were discovered 56 years ago, and much of the work has focused on the role of these proteins that play in protecting cells from stress. Heat shock proteins are highly conserved class of proteins present in all species from bacteria to humans. Several experimental studies have been successful in pointing to the role of heat shock protein as a clinical biomarker and therapeutic target in a variety of diseases. It will also highlight features of HSP family, and will discuss future implications of HSPs in the diagnosis and prognosis of clinical and therapeutic significance. The development of membrane-interacting drugs that modify specific membrane domains, modulating heat shock response, may also be of significant therapeutic benefit. These proteins function as molecular chaperones, assisting in the refolding of misfolded proteins or their elimination if they become irreversibly damaged. Proteomic studies have identified several different HSPs in various disease types that may be clinical biomarkers or molecular targets for various therapies.

Keywords: Heat shock proteins, Molecular chaperones, Polypeptides, Infectious diseases, Immunity

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1 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 5-10 ^{0}C higher than that optimal for the growth of the cell being studied, and thus these proteins are often called heat shock proteins (HSP).[1] There is now no doubt that HSPs 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.[2] 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.[3] 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.[4] 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.[5] They are a family of proteins that are produced within the human body due to the presence of heat shock 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.[6] 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. The drastic increase in the expression will be transcriptionally regulated within the cells.[7] 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). 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. As the names of these shock proteins suggest these proteins are 60, 70, and 90 kilo daltons 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.[8]

1.1. Heat Shock 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. The proposed function of chaperones is to assist in self-assembly of proteins by inhibiting alternative assembly pathways that produce nonfunctional structures.[9] Chaperone activity merely prevents aggregation and does not necessarily need to be associated with (re)folding of the bound substrate. Hsp70 may not be recycled and cells will be rapidly depleted from Hsp70 chaperone activity.[10] Also, given the complexity of compartmentalization in mammalian cells and the movement of heat shock proteins in and out of different compartments. The 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.[11] 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.[12]

1.2. Events in the Heat-shocked Cell

Many of the molecular events that occur in response to heat shock are also found in cells when they are subjected to other types of stress. Heavy metal poisons, sulfhydryl oxidants, and amino acid analogues all induce proteins that are identical to hsps in chicken cells. It remains to be seen whether events known to regulate gene transcription in sporulating cells are related to those in heat-shocked cells. It could also be interesting to compare hsps to some of the proteins and enzymes that are induced by sporulation. The fact that this response has been highly conserved throughout evolution strongly suggests that it plays an important role in the biological world[12]. The events that regulate heat shock gene expression in prokaryotes differ in several ways from those in eukaryotes. Unlike in eukaryotes, where different heat shock genes are expressed non-coordinately, heat shock genes in prokaryotes form a regulon and appear simultaneously. Second event is, the heat shock transcription factor is an isomer of the sigma subunit, the bacterial RNA polymerase's regulatory element. Under normal growth conditions, this sigma factor is present at low levels. Under normal growth conditions, this sigma factor is present in low concentrations, but levels rapidly increase after heat shock due to much slower protein degradation, enhanced translation of its mRNA, and increased transcription of its gene. In prokaryotes, protein structure manipulations that result in an increase in the amount of poorly folded proteins activate the heat shock regulon. A temperature-sensitive mutant with a defect in the ubiquitin-dependent proteolytic degradation pathway accumulates defective proteins in animal cells. Under non-heat shock conditions, this mutant has higher levels of heat shock proteins. In contrast, the addition of deuterium oxide or glycerol, both of which can stabilise proteins, inhibits and delays heat shock protein induction. Heat shock, in addition to causing improper polypeptide folding, causes plenty of other changes that are dependent on both the severity of the stress and the cell system. These include effects on macromolecular synthesis, cation levels, protein phosphorylation states, metabolic pathways, cytoskeleton networks etc[13].

1.3. Thermotolerance

Based on the findings of structural and functional studies of four major heat shock protein families, it is clear that their role in polypeptide folding and unfolding provides the best model for explaining how the major heat shock proteins function to date[14]. Previous studies in a rat model of human adult respiratory distress syndrome, rats first made thermotolerant via whole body hyperthermia suffered no mortality as compared with 30% mortality observed for the non-heated group[15]. The problem is determining how to improve the termotolerant phenotype in a timely and clinically relevant manner. *In vitro*, the phenotype takes anywhere from 8 to 18 hours from the time of stress response induction to fully develop, which is likely the time required to synthesize and accumulate maximal levels of the stress proteins. Application of the stress response to clinical medicine is more promising in nonemergent situations viz. surgeons found that skin flap survival improves if the flap is first made themotolerant[16]. Another possible application is to make donor transplant organs thermotolerant, potentially increasing the time that the organ can be transplanted or even improving survivability after transplantation. All of the other cellular consequences associated with the acquisition of the thermotolerant phenotype are still unknown. A series of damaging events occur in mammalian tissues, including the cessation of cell division, decreased mitochondrial activity, and increased activity of lysosomal enzymes. Heat-shock protein induction protects cells from many of the effects of thermal damage and leads to thermotolerance. Although there are positive correlations between the amount of heat shock proteins present and the degree of tolerance, expections do occur. As a result, while some heat shock proteins are required, they may not be sufficient for thermotolerance. Furthermore, thermotolerance appears to be important for stress survival. The comparison of two hydra species, Hydra oligactis and Hydra attennata, is a good example of the latter. The former is extremely sensitive to thermal stress and cannot develop thermotolerance, whereas the latter is thermoresistant and can develop thermotolerance. Given the importance of heat shock genes in survival, it is surprising that H. oligactis survives, raising the possibility that heat shock proteins have negative effects[17].

1.4. HSP family

Large number of individual chaperons and co-chaperons that have been identified are divided up into several different classes; HSP60 family, HSP60 family, HSP70 family, HSP90 family, HSP100 family, HSP110 family and the small heat shock proteins (sHSP)[18]. The HSP60 family has been shown to be involved in the development of many diseases, such as adjuvant arthritis in rats, rheumatoid arthritis in humans, insulin-dependent diabetes mellitus in mice, and systemic sclerosis in humans. HSP60 is located in mitochondria. HSP70 is in the cytosol and has family of GRP78 which plays role in helping protein folding assembly and refolding, transporting and blocking protein degradation in endoplasmic reticulum. HSP70 is expressed by physical exercise. HSP90 binds steroid receptors, protein kinases, intermediate filaments, microtubules, and actin microfilaments in a specific manner. HSP90 is an essential component of the glucocorticoid receptor, assembled in a complex of several proteins. HSP100 is located in the cytoplasm and cochaperones with HSP40, HSP70, and HSP90. HSP100 plays a role in refolding the aggregate. The broad ranges of HSPs are organelle-specifically expressed within the body to play physiological roles via interacting with various signal pathways[19].

1.5. HSP and immune responses

Stress create a physiologically dysregulating state of threat in themselves, which includes immune system changes such as a lack of acute immune response to threat, an exaggerated immune response to chronic threat, and the possibility of ongoing dysregulation, which increases vulnerability to both major and minor illness[20]. Stress has behavioural effects that contribute to the sickness behaviours of infected or injured animals in terms of inflammatory and immunological effects. Neurovegetative symptoms such as changes in sleep, appetite, energy level, and sex drive are examples of these behavioural effects. These symptoms are similar to the clinical picture of major depression in humans. These findings led to the development of the cytokine hypothesis of major depression. Future research should provide more insight into the various epidemiological, pathophysiological, and clinical issues as the therapeutic use of cytokines for various medical conditions develops. Over the last decade, clinical research on the role of psychological stress on the expression of Th1/Th2 cytokines has shifted from considering stress's immunosuppressive effects to considering stress's immunomodulatory effects[21]. To fight pathogens, Th1 and Th2 cytokines orchestrate different immune pathways: Th1 cytokines coordinate cellular immune responses, while Th2 cytokines coordinate humoral immune responses. Under stress, one type of immunity may be stimulated while another is suppressed, resulting in immunomodulatory (rather than globally immunosuppressive) effects. Intriguing evidence concerns potential stress-to-inflammatory disease pathways mediated by Th1/Th2 cytokines and cortisol. Future research addressing these issues directly in patient populations will assist researchers in developing biologically plausible alternatives to the immunosuppression model to reveal how psychological stress affects inflammatory conditions[22].

1.6. Antigenicity of HSP

Antibody raised against a heat-shock protein with molecular weight of 105,000 (hsp 105) purified from mouse FM 3A cells cross-reacted to the 42'C-hsp of the same cells. The antibody reacted only weakly to hsp 105 and hsp 42 of human HeLa cells[23]. These results suggested that hsp 105 and 42' C-hsp have the same antigenic determinant, and that 42"C-hsp may have a structure similar to that of hsp 105. Anti-mouse hsp 105 antibody reacted not only to hsp 105 but also to the 42°C-hsp of mouse FM 3A cells. This indicated that hsp 105 and 42°C-hsp have common antigenicity and probably have a similar structure. Hsp 70, hsp 85, and hsp 105 are generally observed in mammalian cells. The first two are well conserved in divergent species from bacteria to humans, but hsp 105 has been found only in mammalian cells. An immunocytochemical study done with mouse kidney cells has shown that hsp 105 is located in the cytoplasm and perinuclear regions of unstressed cells, and some move to nucleus or nucleolus during heat shock. There is much evidence of a correlation between the intracellular accumulation of heat-shock proteins and the thermotolerance of the cells. Thermotolerance develops in cells heat-shocked at 45°C as well as at 42°C, so hsp seems not to have an essential role for the development of thermotolerance in the cells[24].

1.7. HSP in Plants

Molecular analysis indicates that the major classes of HSPs synthesized by plants are homologous to HSPs of other eukaryotes[25]. Several proteins with homology to HSPs, or in some cases HSPs themselves, are also components of unstressed plant cells. The discovery that different proteins of the major HSP families are found in more than one cellular compartment further indicates HSPs play a role in basic biochemical processes. The HSPs and their homologs must perform many essential functions in both normal and stressed cells, but these functions are only beginning to be understood. The current hypothesis that HSP60, HSP70, and HSP90 function to alter the conformation or assembly of other protein structures provides an exciting starting point for further investigations[26]. Detailed analysis of the molecular mechanisms of these processes, and determination of the protein substrates involved, will be important to an understanding of how these processes may protect or allow recovery of the heat-stressed cell. More complete characterization of the HSP genes along with further studies of the intracellular localization and biochemical properties of HSPs will be required. Manipulating HSPs for plant improvement will only be possible when the mechanism of HSP induction and the roles of individual HSPs are better understood.

1.8. HSP in eukaryotes

HSP 70 is present in low concentrations as molecular chaperones in unstressed cell. Concentration of HSPs is increasing rapidly in muscle of young adults during cellular stress (hypothermia, oxidative stress, exercise, changes in pH, the incorporation of new amino acids into proteins, viral infection) [27]. Increase of HSPs leads to significant changes in gene expression leading to remodeling of skeletal muscle. This response is significantly diminished in aged individuals and deficit achieved around 44% in experimental studies. Induction of several hundred and repression of several thousand genes. Heat shock factor 1 (HSF1), the "master regulator" of the HSR, controls only a fraction of heat shock-induced genes and does so by increasing RNA polymerase II release from promoter-proximal pause. However, its scope, extent, and the molecular mechanism of regulation are poorly understood[28].

1.9. *Mechanisms underlying HSP gene transcription*

The heat shock response, which is characterised by increased expression of heat shock proteins (Hsps), is induced when cells and tissues are exposed to extreme conditions that cause acute or chronic stress[29]. Hsps act as molecular chaperones, promoting survival and regulating cellular homeostasis. If severe stress, a signal that causes programmed cell death, known as apoptosis, is activated, providing a finely tuned balance between survival and death. Several non-stressful conditions, in addition to extracellular stimuli, induce Hsps during normal cellular growth and development. Heat shock transcription factors control the increased expression of heat shock genes in response to various stimuli (HSFs). The functional relevance of distinct HSFs is now emerging following the discovery of the HSF family (i.e., murine and human HSF1, 2, and 4, as well as a unique avian HSF3). Heat-induced Hsp expression is mediated by HSF1, an HSF prototype, and HSF3, whereas HSF2 is refractory to classical stressors. Recently developed powerful genetic models have provided evidence for both cooperative and specific functions of HSFs that expand beyond the heat shock response. Heat shock transcription factors control the expression of inducible Hsp (HSFs). Most HSFs acquire DNA binding activity to the heat shock element (HSE) in response to various inducers such as elevated temperatures, oxidants, heavy metals, and bacterial and viral infections, thereby mediating transcription of the heat shock genes and resulting in Hsp accumulation[30].

1.10. HSP and its development

There is a substantial body of literature detailing the organisation and sequence of HSP genes from a variety of organisms, including man, plants, worms, flies, and bacteria[31]. Several investigators involved in research on the cellular stress response have thoroughly reviewed this information. The importance of HSFs as heat shock response regulators is reflected in their high cross-species conservation in evolution. The HSFs are made up of functional modules that demonstrate the transcription factors' complex regulation at both the intra- and intermolecular levels. The most conserved functional domain is the amino-terminal helix-turn-helix DNA binding domain (DBD) of Hsp[32]. Many microorganisms are exposed to extreme temperature differences during their normal life cycle, and HSPs may be used by the organism during the initial stress period. Parasites, in particular, are frequently found in multiple hosts with varying body temperatures. The first evidence of small HSP involvement in normal embryonic development came from a molecular analysis of the small-molecular-weight HSP genes in Drosophila melanogaster. In fact, the expression of the four small HSPs under non-heat-shocked conditions closely parallels the rise in ecdysterone titer in D. melanogaster during early development. A number of recent independent studies have looked into the molecular basis of the dual regulation of small HSP gene expression. The response to heat shock differs dramatically between somatic and germ-line cells in the developing egg chamber of Drosophila. Following heat shock, folicle cells and nurse cells synthesise the normal complement of HSPs, whereas no synthesis occurs in the developing oocyte or even earlier stages of embryogenesis[33].

1.11. HSP in infection of virus

The production of heat shock proteins is a common response of all organisms to a variety of stresses. These include physiological stress, environmental stress, and microorganism infection[34]. A number of viruses have been shown to induce HSP expression in vitro; however, unlike many bacteria and parasites, viruses do not encode HSP genes; thus, HSP expression in cells infected with these viruses represents cellular HSP. Heat shock proteins (HSPs) have recently been identified as conserved compounds that are expressed under stress conditions in both prokaryotic and eukaryotic systems. These proteins perform the function of molecular chaperones. Several studies have found elevated levels of HSPs in patients with infectious diseases, implying that HSPs could serve as promising biomarkers[35]. Hsps also play important roles in antigen presentation, dendritic cell maturation, and lymphocyte activation. As a result, these proteins can be used to create vaccines for bacterial and viral infections. Because viruses usually attract HSP70, HSP70 can have both positive and negative effects in virus-infected plants. HSP70 can promote viral genome replication and

translation, the formation of viral replication complexes, and viral particle propagation from cell to cell and throughout the plant. HSP gene silencing in several virus-host plant systems, as well as comparisons of susceptible and resistant species, have revealed that HSPs70 speed up infection progression. In some host and virus systems, however, an increase in temperature during the process known as thermotherapy limits viral multiplication[36].

1.12. *Application studies of HSP*

A number of studies have shown that the 70 kDa HSP family (Hsp70) and 90 kDa HSP family (Hsp90) are associated with antigenic peptides in the cytosol and mediate their translocation and processing, as role of intracellular HSPs in antigen processing and presentation[37]. Role of extracellular HSPs in innate immune responses - Recently, it was revealed that extracellular HSPs could activate DCs as well as exogenous TLR ligands. Though it has been suggested that extracellular HSPs' pro-inflammatory actions are mediated by contamination with LPS or other microbial chemicals, it is true that TLR activation by HSPs differs from TLR activation by microbial substances in several ways. There is compelling evidence that HSPs play an evolutionary important role and that these proteins are under strict evolutionary control as a balance of benefits and costs. While there is great potential for using HSP expression to detect natural adaptation and stress exposure in natural populations, some challenges and key issues must be addressed. From an ecological standpoint, these critical issues must be addressed in order to fully appreciate the complex responses and adaptations to stress, as well as to improve our understanding of HSPs and other molecular chaperones for stress adaptation and potential use as biomarkers. Role of extracellular HSPs in adaptive immunity - MHC class I peptides are derived from non-APC endogenous proteins. MHC class I, on the other hand, can present peptides derived from exogenous proteins in professional APC, a process known as 'cross-presentation.' Extracellular HSPs may improve cross-presentation of HSP-bound antigens to MHC class I in DCs. The immune response to HSP family proteins and HSP-bound antigens differs. As a result, depending on the tissue and temperature, hyperthermia treatment may have a distinct effect on the immune response, either immunogenic or tolerogenic. Though more research is needed to develop a novel therapeutic strategy, there have been promising advances in the field of immunotherapy[38].

1.13. *HSP in cancer*

Heat shock proteins have been linked to the treatment of both cancer and inflammatory diseases, with approaches that take advantage of these proteins opposing immune properties. It appears that HSP family members Hsp60 and Hsp70 can be processed by antigen-presenting cells and that HSP-derived epitopes then activate regulatory T cells and suppress inflammatory diseases, whether from external sources or induced locally during inflammation[39]. These effects also extend to cancer cells' HSP-rich environments, where elevated HSP concentrations may contribute to the immunosuppressive tumour milieu. HSPs, on the other hand, can be important tumour immunity mediators. Some HSPs can bind tumor-specific peptides and deliver them deep into the antigen-processing pathways of antigen-presenting cells due to their molecular chaperone properties. Heat shock proteins are overexpressed in a wide range of human cancers and are implicated in tumor cell proliferation, differentiation, invasion, metastasis, death, and recognition by the immune system. Several HSP are implicated with the prognosis of specific cancers, most notably Hsp27, whose expression is associated with poor prognosis in gastric, liver, and prostate carcinoma, and osteosarcomas, and Hsp70, which is correlated with poor prognosis in breast, endometrial, uterine cervical, and bladder carcinomas. Increased Hsp expression may also predict the response to some anticancer treatments. Although at the diagnostic level Hsps are not informative, they are effective biomarkers for carcinogenesis in some tissues and signal the degree of differentiation and aggressiveness of certain cancers[40].

1.14. *HSP in COVID*

Health systems worldwide are now facing three major problems: 1) to identify asymptomatic carriers of infection; 2) to give effective home care to symptomatic people; 3) to properly stage hospitalized patients to avoid overwhelming numbers in intensive care units. This last group of patients experience, among other clinical signs, very low pO2 blood concentrations due to the destruction of lung parenchyma and massive activation of both innate and acquired immune responses[41]. A link between Covid-19 and development of autoimmunity has been reported. A possible explanation could be molecular mimicry between SARS-CoV-2 and human proteins. Considering multimodal anti-inflammatory mechanisms of action of anti-Hsp90 treatment and drug repositioning results, it may be hypothesized that Hsp90 inhibition could also be a treatment option for cytokine storm-mediated acute respiratory distress syndrome in Covid-19 patients[42]. Recent research has demonstrated that, during certain pathogen including SARS-CoV-2 infections, NLRP3 is capable of detecting specific ligands, activate caspase-1, and induce the release of various pro-inflammatory cytokines with vital roles against viral infection[43].

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 adaptive and innate immune system against cancer and infectious diseases[44]. In order to shed some light into this paradoxical situation and to formally distinguish how HSPs elicit immune responses, Pramod Srivastava[45] proposed the following four paradigms: 1. Despite 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. 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.[46]

1.16. 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.[47] Protein aggregation in the cell is intimately tied to protein folding and stability. These intrinsic properties of proteins are modified by molecular chaperones. 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.[48] Constitutively expressed Hsps function as molecular chaperones and participate in protein synthesis, protein folding, protein transport, and protein translocalization processes and upon heat shock, prevent irreversible aggregation of proteins.[49] 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.[50]

1.17 *Cell death mechanism of HSP*

The present state of the art of the links between tumour cell death and the immune system will be summarised in this study, with a focus on cell death-related pathways implicated in the generation of an immunological response to dying tumour cells[51]. We anticipate that a detailed molecular understanding of the immunogenicity of cancer cell death will open up new avenues for cancer therapy. Apoptotic cell death is caused by a morphologically homogeneous entity that was previously thought to be non-immunogenic and non-inflammatory. Recent research, however, suggests that apoptosis can be immunogenic in certain circumstances. Some plasma membrane characteristics, in particular, acquired at the preapoptotic stage, can cause immune effectors to recognise and attack preapoptotic tumour cells. Some plasma membrane characteristics, in particular, acquired at the preapoptotic stage, can cause immune effectors to recognise and attack preapoptotic tumour cells. The signals that mediate tumour cell immunogenicity include elements of the DNA damage response. Depending on the cell type and the precise cause of cell death, eukaryotic cells can die via different pathways and with distinct morphological changes. The fate of dying cells can be classified based on phenomenological and ultrastructural changes based on our current understanding of cell death mechanisms. During their agony, dying tumour cells can release proinflammatory cytokines, which can aid in eliciting an immune response. Necrotic cell death is thought to be the type of cell death linked with indiscriminate extracellular release of soluble intracellular contents through the permeabilized plasma membrane. Several components released into the extracellular matrix during necrotic cell death mediate important immunological effects. Interestingly, necrotic cells release HSP as well as uric acid, both of which can cause proinflammatory effects via TLR2 or by activating the NALP3 inflammasome [52].

2 DISCUSSION

The clinical role of stress is a physical, mental or emotional factors that causes bodily or mental tension. On a whole body level, stresses can be induced by environmental, psychological or social situations or by illness, or from a medical procedure [53]. At a cellular level, stress can be induced by a wide variety of conditions including heat shock, cold shock, pH shift, hypoxia, UV light and during wound healing or tissue remodeling [54]. Increased expression of heat shock proteins protects the cell by stabilizing unfolded proteins, giving the cell time to repair or resynthesize damaged proteins. The involvement of cytosolic and ER-resident HSPs in protein folding processes might have general significance in plants. HSPs also play an essential and regulatory role in the innate immune response in plant cells[55]. Genetic and proteomic research has led to the isolation of various subcellular HSPs, which are critical for innate immunity in different plant species. In animals, HSPs such as HSP60, HSP70, HSP90, and Grp94 are able to induce the innate immune response directly and are thus considered as danger- or damage-associated molecular patterns [56]. Future studies will be needed to reveal the possible interactions between HSPs and receptors that trigger innate immunity[57].

3 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.

4 AUTHORS CONTRIBUTION STATEMENT

Maheswara Reddy Mallu conceived and designed the study. Sree Rama Chandra Karthik Kotikalapudi and Renuka Vemparala were responsible for data collection and acquisition of data. Chandana Agaarapu analysed, interpreted the data and wrote the initial manuscript. Siva Reddy Golamari critically revised the manuscript. All the authors read and approved the final version of the manuscript.

5 CONFLICT OF INTERESTS

Conflict of interest declared none

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