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Heat Shock Proteins as Guardians of Proteostasis in Non-communicable Diseases

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Abstract
Non-communicable diseases (NCDs) include metabolic syndromes, cardiovascular diseases, and neurodegenerative disorders. Together, these deleterious health conditions pose a significant threat to global health. The precise regulation of proteostasis at the cellular level is essential for the development and advancement of non-communicable disorders. It regulates fundamental processes such as protein synthesis, folding, trafficking, and degradation. Molecular chaperones of the heat shock superfamily play a crucial but often overlooked role in maintaining proteostasis within this intricate biological network. The review focuses on understanding the complex functions of heat shock proteins (HSPs) in preserving cellular homeostasis and their significant involvement in treating NCDs. In this review of existing literature, we investigated the intricate processes via which HSP dysregulation causes proteotoxic stress, hence contributing to the onset of non-communicable diseases. In addition, we explored the potential therapeutic uses of targeting heat shock proteinsto improve the therapeutic outcome of major NCDs. There is a favourable prospect in the fight against NCDs that holds great potential for improving human health. By acquiring a more profound comprehension of the interrelated function of heat shock proteins (HSPs) in maintaining protein homeostasis, substantial advancements can be achieved.

Key Words: Non-communicable diseases (NCDs), Proteostasis, Heat Shock Proteins (HSPs), Metabolic syndrome, Neurodegenerative disorders, Cardiovascular disorders.

I. Introduction

Proteostasis is a vital component of the complex network of biological processes, as it regulates the equilibrium of protein levels(Verma et al., 2021). Proteins are essential for biological processes and must undergo proper folding to carry out their jobs effectively (Adeoye et al., 2023). Managing environmental stress and genetic alterations is a recurring obstacle that requires attention. These problems frequently cause misfolding and malfunction, ultimately leading to the emergence of chronic diseases(Labbadia & Morimoto, 2015). Heat shock proteins (HSPs) are essential for maintaining cellular homeostasis and serve as a critical defence mechanism against diverse stressors (Daniyan et al., 2022). These chaperones, initially identified in connection with heat stress, have a vital function in maintaining the integrity and activity of proteins. Recently, there has been growing interest in the role of Heat Shock Proteins (HSPs) in maintaining cellular homeostasis in chronic diseases, which are also referred to as non-communicable diseases (NCDs)(Dubey et al., 2015). A multitude of diseases, including cancer, neurological disorders, cardiovascular diseases, and metabolic syndromes, are impacted by an intricate interplay of genetics, environmental variables, and personal lifestyle choices(Adeoye et al., 2022). HSPs, or heat shock proteins, have lately been recognised as significant factors in the progression and treatment of non-communicable diseases (NCDs). Therefore, exploring HSPs could lead to the discovery of new therapeutic approaches for these conditions.

The current literature review specifically examines the complex functions of Heat Shock Proteins (HSPs) in protecting against stress and maintaining cellular equilibrium in Non-Communicable Diseases (NCDs). Our goal is to enhance our comprehension of the diverse ways in which HSPs influence disease outcomes and examine new therapy possibilities by conducting a thorough analysis of existing literature and doing in-depth research on the underlying mechanisms. The purpose of this extensive literature search is to acquire additional knowledge about the processes via which HSPs protect cellular balance in non-communicable diseases (NCDs). The objective is to promote additional investigation and advancement in the utilisation of HSPs for the identification and therapy of persistent illnesses.

Overview of Heat Shock Proteins in Non-Communicable Diseases

Heat shock proteins (HSPs) play a crucial role in various physiological activities that are associated with several non-communicable diseases (NCDs). Theseinclude cancer, neurological disorders, cardiovascular illnesses, and metabolic syndromes(Boopathy et al., 2022). These proteins play a vital role in maintaining cellular equilibrium and orchestrating cellular responses to disease-causing factors. ThusHSPs play a remarkable roles in the onset of non-communicable diseases (NCDs). Certain HSPs, like HSP90 and HSP70, have been found to contribute to the growth and survival of tumours by aiding oncogenic proteins and inhibiting apoptotic pathways. However, various Heat Shock Proteins (HSPs), including HSP27 and HSP60, possess the capacity to inhibit tumour growth by impeding the metastasis of cancer cells and rendering them more vulnerable to cell-killing treatments(Yun et al., 2019). The intricate interplay between different HSPs that either facilitate or hinder tumour growth underscores their wide-ranging roles in cancer development and treatment response(Chatterjee & Burns, 2017).

Neurodegenerative diseases, like Alzheimer's and Parkinson's disease, are characterised by the improper folding and buildup of proteins(Adeoye et al., 2022). These processes are controlled by heat shock proteins (HSPs) such as HSP70 and HSP90n(Beretta & Shala, 2022). These chaperones play a crucial role in the process of protein restructuring and breakdown, ensuring the smooth functioning of neurons by preventing the buildup of protein clusters(Gupta et al., 2020). In addition, neuroprotective heat shock proteins (HSPs) like HSP27 and HSPB5 (αB-crystallin) play vital roles in preventing programmed cell death and maintaining the well-being of neurons(Navarro-Zaragoza et al., 2021). These proteins show great potential for therapeutic interventions in neurodegenerative disorders.

HSPs play a crucial role in promoting the health of blood vessels and supporting the proper functioning of the heart, particularly in cardiovascular conditions like atherosclerosis and myocardial infarction(Patnaik et al., 2023). HSP27 and HSP70 play a crucial role in safeguarding endothelial cells from the harmful effects of oxidative stress and inflammation(Bellini et al., 2017). This helps to maintain the optimal functioning of blood vessels and minimise the formation of atherosclerotic plaques. Furthermore, HSPB1 (HSP27) and HSPB6 (HSP20) contribute to the contraction and relaxation of the heart, safeguarding the functionality of heart muscle cells and minimising harm resulting from insufficient blood flow(Ikwegbue et al., 2018).

The cellular responses mediated by HSPs are of utmost importance in understanding the link between metabolic disorders such as obesity and type 2 diabetes(Moin et al., 2021). These responses, particularly in relation to insulin signalling and glucose metabolism, play a critical role. HSP70 and HSP90 play a crucial role in maintaining insulin sensitivity by managing insulin receptor signalling pathways(Esmaeilzadeh et al., 2023). Additionally, HSP27 and HSPB1 provide protection to pancreatic beta-cells, preventing apoptosis and preserving their capacity to secrete insulin.

The functional network of heat shock proteins (HSPs) in non-communicable diseases (NCDs) underscores the diverse and context-specific roles they play in the progression and manifestation of diseases. Understanding the molecular pathways that contribute to HSP-mediated cellular responses holds promise for developing targeted treatment strategies to mitigate the effects of non-communicable diseases (NCDs) and improve patient outcomes(Rowles et al., 2020).

Inventory and Classification of Molecular Chaperones

Hsps were the first known molecular chaperones, and they play an essential part in both the normal and stressed-out processes of cellular proteostasis (Moayed et al., 2020). The correctly folded form of a protein does not contain the hydrophobic patterns that can be found in misfolded forms of the protein(Atkin et al., 2021). Chaperones are able to identify these patterns. Holdases only require binding in order to perform their activity; otherwise, they are able to function independently of ATP(Graff et al., 2020). However, in many instances, the ATP-dependent cycle that enables recurrent binding and release of chaperones is necessary for protein (re)folding (Bolhassani and Agi 2019). This cycle is known as the folding cycle. The latter task is performed by chaperones that are dependent on ATP, and these chaperones require specialized co-chaperones that regulate the ATP cycle (binding, hydrolysis, and release) in order to establish substrate specificity and destination(Hall, 2020). The molecular weight of the initial member that established each family of molecular chaperones served as the inspiration for the names of those families. There are four primary families of chaperones that are found in metazoans. These are the Hsp60s, Hsp70s, Hsp90s, and the small molecular weightHsps (sHsp) (Wu et al., 2017).sHsps typically function as more conventional holdases due to the absence of an ATPase domain in their structures. Oligomeric complexes are very prevalent, and when they do occur, they frequently exist in a dormant form, waiting for an opportunity to respond to a misfolding event. sHsps are activated in response to stress and assist in the re-folding of proteins that have become misfolded. They frequently work in conjunction with other chaperones, such as Hsp70s, to accomplish this task (Lianos et al., 2015).

HSP 70

The Hsp70 family, which includes both heat shock-inducible and constitutively expressed members (such as HSP70-1/HSPA1A and HSC70/HSPA8), performs a variety of functions(Radons, 2016). Some of these include protein synthesis, folding, refolding, disaggregation, membrane translocation, endocytosis, and the degradation of terminally misfolded proteins. These are just some of the many functions that the Hsp70 family is responsible for (Martine andRébé, 2019). This functional diversity is due, in part, to the involvement of a large number of different co-chaperones. The Hsp70 ATPase cycle is typically regulated by a nucleotide exchange factor (NEF), in collaboration with a J-domain protein (DNAJ), and a member of the J-domain protein (DNAJ) family(Mayer &Gierasch, 2019). Humans have been found to have a total of 49 DNAJs, but E. coli only has a total of six. It's probable that the enhanced malleability of Hsp70 machinery has anything to do with this rise in

complexity(Mayer, 2021). After Hsp70s and their co-chaperones have completed their work with a client, they are able to pass that client along to chaperonins and the Hsp90 family (Carra et al., 2017).

HSP60

The heat shock protein HSP60 has a high degree of evolutionary conservation. There are two subfamilies that make up the ATP-dependent Hsp60 family, which is often referred to as the chaperonins or Cpn60(Zhang et al., 2016). Group I HSP60s can be found in prokaryotic mitochondria (as GroEL) as well as eukaryotic mitochondria and chloroplasts. HSP10 serves as a cofactor for these HSP60s (GroES in prokaryote) (Ciocca et al., 2013). Members of Group II, which can also be found in the cytoplasm of archaea, can also be found in the cytoplasm of eukaryotic cells. Eukaryotic chaperonin is a multiprotein complex that can also be referred to as t-complex 1 (TCP1) or chaperonin containing TCP1(Trösch et al., 2015). It is comprised of two rings, each of which contains eight subunits that are distinct from one another but are functionally analogous (CCT). Subunits will bind ATP and then hydrolyze it so that a central folding chamber may be opened and closed. This will allow substrate proteins to be folded (Mymrikov et al., 2011). To keep its double ring shape intact, the HSP60 protein found in eukaryotic cells needs both a cofactor and an interaction with a nucleotide (Chatterjee and Burns, 2017).

In the absence of HSP10 and ATP, the heat shock protein HSP60 exists as a solitary heptamer ring. Combining HSP60 with HSP10 results in the formation of complexes in the shape of footballs, with ATP-dependent mechanisms leading to the formation of double-ring structures between single rings. Even in the absence of HSP10, Group II chaperonins have the potential to benefit from TRiC(Dawood, 2020). GroEL is responsible for the transport of substrates into its lumen, which is then followed by the coupling of the heptamer HSP60 complex with HSP10 on the head region to ATP. Incorrectly folded proteins, on the other hand, can be re-encapsulated in GroEL and sent back to the folding process for further processing. The protein chaperonin is essential to a variety of different cellular activities (Kurop, et al., 2021). According to the findings of a recent piece of research, the correct folding of around ten percent of all newly generated proteins requires TRiC. Chaperonin is a protein that helps prevent proteins from clumping together and aids in the refolding of proteins when they are under stress. HSP60 is absolutely necessary for the proper operation of the respiratory chain that is housed within mitochondria. In response to both exogenous and endogenous stress, HSP60s act as bidirectional regulators of the apoptotic process (Zhang et al., 2021).

HSP90

With the exception of archaea, members of the Hsp90 family have been extremely well conserved throughout the course of evolutionary history. In order to regulate a wide variety of cellular activities, members of the Hsp90 family, including those that are induced (such as HSP90AA1) and those that are constitutively generated (such as HSP90B1), interact with over 20 co-chaperones and adaptors (Mymrikov et al., 2011). Hsp90s have a wide variety of various clients, including protein kinases and steroid hormone receptors, which makes them key regulators of many distinct signaling cascades. There are six distinct human genes that code for heat shock protein 90 (HSP90) (Li et al., 2020). Two of these genes are located in the cytosol (induced expressed HSP90AA and constitutive expressed HSP90AB), two are located in the endoplasmic reticulum (GRP94), and two are located in the mitochondria. There is a lot of structural similarity across different HSP90 homologues, especially in terms of the properties that are conserved(Zuhelke et al., 2018). These domains are located at the beginning, middle, and end of the monomer, respectively. Because of a series of ATP-dependent dynamic conformation alterations, HSP90 is able to assist in the folding process. These modifications are themselves regulated by an abundance of cochaperones. Because it does not contain a nucleotide that is attached to it, HSP90 always assumes a conformation in which the NTD is open, and it forms dimers by utilizing the CTD domain (Bakthisaran et al., 2015). The MD domain of HSP90 is used to load client proteins in an open conformation onto the protein, and the binding of ATP is what drives the NTD dimerization. As a consequence of the hydrolysis of ATP, HSP90 assumes a closed conformation, which allows it to maintain its flexibility. When the ADP is withdrawn from HSP90, the protein goes back to the open form in which it was found. After

the client proteins have been folded and unfolded multiple times, their natural states are reverted to their original form (Leak, 2014). About ten percent of the proteins that make up the human proteome cannot develop without the help of HSP90. Interacting with a wide variety of proteins, such as transcription factors and ubiquitin proteins, in addition to more than sixty percent of the kinase proteins found in the human kinome, is one of the many functions of the heat shock protein HSP90. In addition to their role as protein foldases, members of the heat shock protein 90 (HSP90) family are also important contributors to the maturation of protein structures in their final stages (Zininga et al., 2018). To give one example, in order to keep their structure intact, active oncogenic kinases are dependent on the HSP90 chaperon. Kinase clients are rendered unstable when they are subjected to an HSP90 inhibitor and are subsequently degraded by the proteasome. HSP90 plays a variety of roles in cell survival that originate from its function as a chaperone. These responsibilities include cell signaling and the regulation of the cell cycle. HSP90 is involved in a wide range of processes involving the stability and activity of proteins (Kennedy, et al., 2014).

Large Heat Shock Proteins such as HSP 110 and Grp 170

Large heat shock proteins are common in eukaryotic organisms and include proteins such as HSP110 and Grp170. Grp170 is localized only in the endoplasmic reticulum, in contrast to HSP110, which is ubiquitous throughout the cell and even in the nucleus (ER). They have been demonstrated to be evolutionarily conserved and are therefore commonly grouped with the HSP70 family since they are homologous to that family and have the same structure (Daniyan et al., 2019). Each of these is regularly produced within cells and has the potential to be rapidly triggered in response to various stressors in order to keep proteostasisintact They function as holdases, preventing substrates from adhering to one another. The yeast HSP110 protein controls the degradation of ubiquitin-dependent as well as -independent substrates through its interaction with the 19S component of the 29S proteasome(Kandasamy & Andréasson, 2018). In the meantime, HSP110 participates in the ADPATP exchange as a cochaperon of HSP70. In this role, HSP110 plays the role of the NEF. The HSP-110 cochaperone plays an important part in the HSP70-mediated degradation process and is essential for HSP70's ability to fold proteins in cells. This is due to the fact that HSP70 is dependent on HSP-110 (Milano et al., 2020).

Roles of Heat Shock Proteins in Diabetes Mellitus

Diabetes is a multifaceted condition that encompasses disturbances in insulin function and the control of glucose levels(Owigho et al., 2022). Heat shock proteins (HSPs) are essential for safeguarding and adjusting to the demands of this complex situation. While HSPs have long been acknowledged for their expertise in addressing cellular stress, there has been a surge of interest in their role in diabetes and its related complications. This has opened up fresh avenues for exploring potential treatments(Hooper & Hooper, 2009). The role of HSPs in diabetes is intriguing, as they have a significant impact on the regulation of glucose levels and the body's response to insulin. As an example, we can examine the protein HSP70(Esmaeilzadeh et al., 2023). Key elements in insulin signalling pathways, like insulin receptor substrate-1 (IRS-1), have the ability to interact with it(Sharma et al., 2022). The role of HSP70 in the control of IRS-1 folding and transportation results in improved glucose absorption in tissues and heightened insulin sensitivity(Ernst et al., 2017). Insulin resistance is a common feature of type 2 diabetes, and the malfunction of HSP70 could potentially exacerbate this condition.

Importantly, HSPs have a significant impact on insulin sensitivity and are essential for maintaining the insulin production capacity of pancreatic beta cells. The cells in diabetes undergo prolonged metabolic stress, which results in their dysfunction and eventual death(Zilaee& Shirali, 2016). Heat shock proteins (HSPs), such as HSP27 and HSP70, play a crucial role in safeguarding beta cells from protein misfolding induced by stress. Additionally, they activate pathways that enhance cell survival. The Heat Shock Proteins (HSPs) have a vital function in ensuring the accurate production and release of insulin in response to changes in blood sugar levels.

They function as molecular chaperones, ensuring the proper structure and functionality of crucial proteins in the beta-cells(Nakhjavani et al., 2010).

In addition, diabetes is strongly linked to oxidative stress and inflammation, and HSPs have fascinating connections to both of these processes. This condition is marked by the presence of persistent, mild inflammation and oxidative stress, resulting in tissue damage and a diminished capacity of the body to react to insulin(Bahadoran et al., 2023). Nevertheless, heat shock proteins (HSPs) such as HSP60 and HSP70 possess the capacity to reduce inflammatory responses and combat detrimental reactive oxygen species (ROS) owing to their antioxidant and anti-inflammatory characteristics(Tanju et al., 2009).

Regrettably, diabetes has the potential to cause issues with the function of the endothelium and the development of atherosclerosis in blood vessels(Adeoye et al., 2023). There is a growing body of evidence indicating that heat shock proteins (HSPs) may play a role in the development of these conditions. For instance, HSP27 potentially plays a significant role in promoting the health of endothelial cells, which are vital for the optimal functioning of blood arteries. When heat shock proteins (HSPs) are not functioning optimally in individuals with diabetes, it can result in the decline of vascular health and the progression of heart-related conditions(Batulan et al., 2016).

The Roles of Molecular Chaperones in Neurodegenerative Disorders

Protein aggregates are typically brought on by a malfunction in the cellular machinery that is responsible for protein quality control (PQC) (proteostasis). The molecular chaperones are essential nodes in the PQC network because they support cellular proteostasis by regulating the folding of nascent polypeptides, refolding proteins that have been misfolded, or eliminating aberrant proteins by degrading them through the ubiquitin-proteasome system (UPS) or autophagy (ChakafanaandShonhai, 2021). In the case that a protein does not go through the process of (re)folding or clearance, misfolded forms will begin to accumulate and will eventually merge. Positively, the fact that amyloid deposits in neurodegenerative disorders tend to grow up over time merely suggests that PQC pathways, which can prevent aggregation, are active in younger people(Sharma et al., 2014). The formation of amyloid can be effectively controlled by chaperones due to the fact that they monitor protein folding and prevent it from becoming disordered and clumped together. Amyloids cannot form or spread without first going through a number of critical stages (Li et al., 2019). It is believed that the progressive pathological spread seen in prions and diseases similar to prions is due to the intracellular and intercellular propagation of aggregated material. Prions are infectious agents that can cause disease in humans. Because of their ability to protect growing cells from the harm that can be caused by protein aggregation, researchers are shifting their attention more and more toward molecular chaperones as a potential target for intervention (Barre et al., 2021). As the basic job of chaperones is to facilitate protein folding and guard it from misfolding and aggregation, their role in the prion-like spread of misfolded proteins may appear obvious at first glance. There are, however, other studies that imply the contrary, namely that chaperones actually make the protein more toxic or induce more misfolding than it would be otherwise. However, under certain physiological conditions, chaperones may also interact with the natural form of prion-like proteins (Dawood et al., 2020). Patients with Creutzfeldt-Jakob disease (CJD) and animals that have been infected with prions have an elevated number of genes that belong to the heat shock protein 70 (Hsp70) family. In addition, numerous models have shown that chaperone levels can be altered to affect the course of disease, which further highlights the significance of chaperones for prion disorders. Mice lacking the heat shock factor 1 (HSF1) gene, which is the primary transcription factor responsible for the creation of numerous chaperones, expire around twenty percent more quickly than wild-type animals when they are exposed to prions (Kurop et al., 2020). Prion illness also progressed more quickly when there were lower amounts of Hsp70s in either the cytosol or the endoplasmic reticulum (ER). The evidence pointing in the opposite direction is more circumstantial. This is necessary in order to develop effective therapeutic methods (Zhang et al., 2021).

Functional Network of Heat Shock Proteins in Non-Communicable Diseases

Heat shock proteins (HSPs) play a crucial role in a complex network that impacts various non-communicable diseases (NCDs), such as cancer, neurological disorders, cardiovascular illnesses, and metabolic syndromes(Daniyan et al., 2019). This network showcases the diverse roles of Heat Shock Proteins (HSPs) in regulating cellular processes and responding to disease-causing factors, making them essential contributors to the development of Non-Communicable Diseases (NCDs).HSPs in cancer have two distinct roles, exhibiting both functions that support tumour growth and functions that inhibit tumour growth. Certain Heat Shock Proteins (HSPs), such as HSP90 and HSP70, are present in elevated levels within cancer cells(Albakova et al., 2022). These proteins play a crucial role in supporting the growth and survival of tumours. They assist in folding and stabilising oncoproteins and also prevent cell death pathways. On the other hand, HSP27 and HSP60, among other Heat Shock Proteins (HSPs), possess the capacity to inhibit tumour growth, hinder the dissemination of cancer cells, and enhance the efficacy of chemotherapy by facilitating cell death(Choi et al., 2019). The delicate balance between these contrasting functions determines the overall impact of HSPs on cancer progression and treatment outcomes(Somu et al., 2024).

HSPs play a crucial role in protecting neurons from protein misfolding and aggregation, which are key factors in neurodegenerative diseases like Alzheimer's and Parkinson's disease. HSP70 and HSP90, for instance, play a crucial role in restoring the proper shape of misfolded proteins and identifying damaged proteins for degradation(Rutledge et al., 2022). This helps prevent the buildup of protein clusters and ensures the optimal functioning of neurons. Moreover, heat shock proteins (HSPs) like HSP27 and HSPB5 (αB-crystallin) possess the capacity to inhibit cell death (apoptosis) and promote cell survival pathways, making them potential targets for the treatment of neurodegenerative diseases(Arrigo & Gibert, 2014).

HSPs have a crucial role in safeguarding the well-being of blood vessels and ensuring the proper functioning of the heart in cardiovascular conditions like atherosclerosis and myocardial infarction. HSP27 and HSP70 play a crucial role in protecting endothelial cells from oxidative stress and inflammation, which helps to preserve vascular integrity and minimise the formation of atherosclerotic plaque(Ferns et al., 2006). Furthermore, HSPB1 (HSP27) and HSPB6 (HSP20) play crucial roles in regulating the contraction and relaxation of the heart, monitoring the performance of cardiomyocytes, and protecting against harm resulting from insufficient blood supply(Poznyak et al., 2023).

The functional network of Heat Shock Proteins (HSPs), particularly those related to insulin signalling and glucose metabolism, also plays a significant role in impacting metabolic disorders like obesity and type 2 diabetes(Oliveira de Souza et al., 2021). HSP70 and HSP90 play a crucial role in regulating insulin sensitivity by interacting with insulin receptor substrates and boosting insulin receptor signalling. However, HSP27 and HSPB1 play a crucial role in protecting pancreatic beta-cells from cell death and preserving their capacity to secrete insulin(Edkins et al., 2017). Taken together, the intricate involvement of heat shock proteins (HSPs) in non-communicable diseases (NCDs) highlights their significant contribution to the progression and emergence of these conditions. Scientists are looking to discover novel therapeutic strategies that focus on chaperones involved in HSP-mediated cellular responses. Through a thorough analysis of the molecular mechanisms involved in these reactions, their aim is to alleviate the impact of non-communicable diseases (NCDs) and improve patient outcomes.

Heat Shock Proteins with a high sensitivity and risk of cardiovascular illness

There are many different types of cardiovascular disorders, some of which include hypertension, atherosclerosis, coronary artery disease, arrhythmias, heart failure, and idiopathic LV heart malfunction. Despite the availability of a wide variety of treatments that are proven to be helpful, cardiovascular diseases continue to be a major cause of death and disability on a global scale. In addition, HSP is engaged in both normal cellular physiological activities as well as pathological processes, the most important of which are cardiovascular diseases (Dawood, 2021). HSPs are important immunostimulatory molecules that play a role in both the innate immune response and the adaptive immunological response to sickness. When inflammation takes place, it sets off a chain

reaction of cellular stress events, such as apoptosis, oxidative stress, and shear stress, as well as cellular and humoral immunological responses(Patnaik et al., 2023). These events and responses all have a detrimental impact on the structure and function of the cardiovascular system (Kennedy et al., 2014). HSPs are associated with both beneficial and harmful effects in CVDs. HSPs are initially activated as a response to the presence of stressful stimuli. There is a high level of HSP expression in cardiovascular diseases (CVDs), where these proteins have a cardioprotective effect by preventing cell death(Pockley&Frostegård, 2005). According to the findings of a number of research, there is a connection between the quantity of HSPs that are generated by mild stress and their protective effect against subsequent exposure to stress that is of a more severe kind (Milani et al., 2020). The fact that the overexpression of HSPs has a protective effect in cultured cardiomyocytes, transgenic mice, or intact hearts when it is given by viral vectors provides another evidence that HSPs can protect cardiac function. There is a possibility that atherosclerosis plays a part in the pathophysiology of HSPs as well as immunological responses against them(Dabravolski et al., 2022). One potential trigger for cross-reactive autoimmune responses is the expression of host-protected heat shock protein 60 (hHSP60) on vascular endothelial cells (Li et al., 2019). As a consequence of the great degree of sequence consistency that exists between human and microbial HSPs, it is possible for there to be a cross-reaction to the immune response that is elicited by bacterial HSPs in the course of an infection. Endothelial dysfunction and atherosclerosis are both caused by GroEL because of its high immunogenicity and its ability to cross-react with hHSP60, which is expressed on endothelial cells (Yusof et al., 2021). This kicks off a cascading process of inflammation, which has the effect of accelerating the formation of atherosclerosis. Lesions that initially appeared as fatty streaks have the potential to transform into atherosclerotic plaques if infections and other risk factors for cardiovascular disease continue to be present(Luca et al., 2023). HSPs have been shown to perform a protective role in the arterial wall when exposed to physiological conditions. However, due to the highly conserved nature of their sequences, HSPs that are produced on the surface of vascular endothelial cells have the potential to act as targets for detrimental autoimmunity when the body is affected by disease (Kan and Lin, 2021). The majority of HSPBs are expressed in cardiac and skeletal muscle cells. These HSPBs include HSPB1, HSPB2, HSPB3, HSPB5, HSPB6, HSPB7, and HSPB8(Bartelt-Kirbach et al., 2017). Because of recent discoveries that point to the preventive influence that these kinds of relatives have on the cardiovascular system, the majority of studies regarding cardiovascular disorders center on these sorts of relatives(Luca et al., 2023). HSPB1 is a protein chaperone that performs a variety of roles in the cell. Plaques of human atherosclerosis both secrete less high-sensitivity protein B1 (HSPB1) and have lower levels of HSPB1 in their plasma than healthy persons do. High levels of HSPB2 expression in the heart have been associated to having protective effects against myocardial hypertrophy and ischemia (Chen et al., 2022). Additionally, hypertension is affected by HSP70. An increased level of HSP70 in the circulation and kidney of hypertensive patients is connected to HSP70 genetic polymorphisms and essential hypertension(Rodrigues-Krause et al., 2012). This regulation occurs between chaperones and cochaperones throughout the development of cardiovascular diseases. An accumulation of misfolded proteins can result in a multitude of cardiovascular diseases if there is an imbalance between the processes of protein production, folding, and destruction (Franklin et al., 2005). It is essential to keep in mind that distinct HSP proteins each work in their own unique way to either promote or prevent the development of CVDs and the symptoms that accompany them. As a consequence of this, it is challenging to develop CVD therapeutic techniques based on HSPs due to the delicate balancing act that needs to be conducted between the physiologic and pathologic functions that are associated with them. If the relationship between HSPs and CVDs were better known, then it would be possible to design new therapeutic procedures in a more expedient manner (Wang et al., 2022).

Conclusion, Recommendations and Future Perspectives

Together with its co-chaperones, the Hsp protein family makes up an intricate network of folding machineries. There has been significant development in our comprehension of the mechanical underpinnings of these folding

devices; nonetheless, there are still a number of essential concerns that remain unanswered. It is not known whether the activity of Hsp proteins to aid in protein folding depends on the ability to induce conformational changes in the bound substrates, how the coupling mechanism permits ATP to regulate substrate binding, or to what extent sequence variations within the family translate into variations in the mechanism. However, it is known that Hsp proteins are required for protein folding. When medications are used to study the action of chaperones as possible molecular targets in the process of innovative drug discovery, it is not known to what extent the medications will be selective for the HSps of infected cells while sparing the HSps of healthy cells. This is because it is not known. This underscores the necessity for properly planned experimental trials that compare the expression of heat shock proteins in healthy and infected cells in order to establish the distinct roles that different drugs play in these critically important interactions.

References

[1.] Adeoye B.O., Iyanda, A., Daniyan, M., Adeoye A.D., Olajide, L., Akinnawo, O., Adebola, A., Oluwseun, O., &Olatinwo, M. (2023). Anti-DyslipidaemiaAnd Cardio-Protective Effects Of Nigerian Bitter Honey In Streptozotocin Induced Diabetic Rats. *8*, 10–18. https://doi.org/10.22270/ujpr.v8i2.920

[2.] Adeoye Bayo O., Iyanda A., Daniyan, M., Victor O, E., Adeoye, A., Abijo, A., &Bimbola, A.-A. (2022). Ameliorative effects of Nigerian bitter honey on streptozotocin-induced hepatorenal damage in Wistar rats. *Journal of Krishna Institute of Medical Sciences University*, *11*, 65–76.

[3.] Adeoye A.D., Ayoka A., Akano O.., Abijo, A., Adeoye B.O.,Oyebanjo, O., & Adetunji O. (2022). *Neuroprotective Effects of Garcinia kola ethanol Seed Extract on Haloperidol-Induced Catalepsy in Mice*. *6*, 281–286. https://doi.org/10.26538/tjnpr/v6i2.18

[4.] Al Wakeel, R. A., Saad, M. F., Abdel Azeez, A., Elkhiat, F., &Shukry, M. (2019). Both experimental hypo-and hyper-thyroidism exacerbate the adverse effects of chronic heat stress in broilers. *British poultry science*, *60*(3), 330-339.

[5.] Albakova, Z., Mangasarova, Y., Albakov, A., &Gorenkova, L. (2022). HSP70 and HSP90 in Cancer: Cytosolic, Endoplasmic Reticulum and Mitochondrial Chaperones of Tumorigenesis. *Frontiers in Oncology*, *12*, 829520. https://doi.org/10.3389/fonc.2022.829520

[6.] Arrigo, A.-P., & Gibert, B. (2014). HspB1, HspB5 and HspB4 in Human Cancers: Potent Oncogenic Role of Some of Their Client Proteins. *Cancers*, *6*(1), 333–365. https://doi.org/10.3390/cancers6010333

[7.] Atkin, A. S., Moin, A. S. M., Al-Qaissi, A., Sathyapalan, T., Atkin, S. L., & Butler, A. E. (2021). Plasma heat shock protein response to euglycemia in type 2 diabetes. *BMJ Open Diabetes Research and Care*, *9*(1), e002057. https://doi.org/10.1136/bmjdrc-2020-002057

[8.] Bahadoran, Z., Mirmiran, P., Kashfi, K., & Ghasemi, A. (2023). Vascular nitric oxide resistance in type 2 diabetes. *Cell Death & Disease*, *14*(7), Article 7. https://doi.org/10.1038/s41419-023-05935-5

[9.] Bakthisaran, R., Tangirala, R., & Rao, C. M. (2015). Small heat shock proteins: role in cellular functions and pathology. *Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics*, *1854*(4), 291-319.

[10.] Barre, A., Pichereaux, C., Simplicien, M., Burlet-Schiltz, O., Benoist, H., &Rougé, P. (2021). A proteomic-and bioinformatic-based identification of specific allergens from edible insects: probes for future detection as food ingredients. *Foods*, *10*(2), 280.

[11.] Bartelt-Kirbach, B., Slowik, A., Beyer, C., &Golenhofen, N. (2017). Upregulation and phosphorylation of HspB1/Hsp25 and HspB5/αB-crystallin after transient middle cerebral artery occlusion in rats. *Cell Stress & Chaperones*, *22*(4), 653–663. https://doi.org/10.1007/s12192-017-0794-9

[12.] Batulan, Z., Pulakazhi Venu, V. K., Li, Y., Koumbadinga, G., Alvarez-Olmedo, D. G., Shi, C., & O'Brien, E. R. (2016). Extracellular Release and Signaling by Heat Shock Protein 27: Role in Modifying Vascular Inflammation. *Frontiers in Immunology*, *7*, 285. https://doi.org/10.3389/fimmu.2016.00285

[13.] Bellini, S., Barutta, F., Mastrocola, R., Imperatore, L., Bruno, G., & Gruden, G. (2017). Heat Shock Proteins in Vascular Diabetic Complications: Review and Future Perspective. *International Journal of Molecular Sciences*, *18*(12), 2709. https://doi.org/10.3390/ijms18122709

[14.] Beretta, G., & Shala, A. L. (2022). Impact of Heat Shock Proteins in Neurodegeneration: Possible Therapeutical Targets. *Annals of Neurosciences*, *29*(1), 71–82. https://doi.org/10.1177/09727531211070528

[15.] Bolhassani, A., & Agi, E. (2019). Heat shock proteins in infection. *ClinicaChimica Acta*, *498*, 90-100.

[16.] Boopathy, L. R. A., Jacob-Tomas, S., Alecki, C., & Vera, M. (2022). Mechanisms tailoring the expression of heat shock proteins to proteostasis challenges. *The Journal of Biological Chemistry*, *298*(5). https://doi.org/10.1016/j.jbc.2022.101796

[17.] Carra, S., Alberti, S., Arrigo, P. A., Benesch, J. L., Benjamin, I. J., Boelens, W., ... & Tanguay, R. M. (2017). The growing world of small heat shock proteins: from structure to functions. *Cell Stress and Chaperones*, *22*(4), 601-611.

[18.] Chakafana, G., &Shonhai, A. (2021). The role of non-canonical Hsp70s (Hsp110/Grp170) in cancer. *Cells*, *10*(2), 254.

[19.] Chatterjee, S., & Burns, T. F. (2017). Targeting heat shock proteins in cancer: a promising therapeutic approach. *International journal of molecular sciences*, *18*(9), 1978.

[20.] Chatterjee, S., & Burns, T. F. (2017). Targeting Heat Shock Proteins in Cancer: A Promising Therapeutic Approach. *International Journal of Molecular Sciences*, *18*(9), 1978. https://doi.org/10.3390/ijms18091978

[21.] Chen, Y., Deng, C., Xu, Q., Chen, X., Jiang, F., Zhang, Y., ... & Jiang, J. (2022). Integrated analysis of the metabolome, transcriptome and miRNome reveals crucial roles of auxin and heat shock proteins in the heat stress response of loquat fruit. *Scientia Horticulturae*, *294*, 110764.

[22.] Chiaradia, E., Renzone, G., Scaloni, A., Caputo, M., Costanzi, E., Gambelunghe, A., ... &Buratta, S. (2019). Protein carbonylation in dopaminergic cells exposed to rotenone. *Toxicology Letters*, *309*, 20-32

[23.] Choi, S.-K., Kam, H., Kim, K.-Y., Park, S. I., & Lee, Y.-S. (2019). Targeting Heat Shock Protein 27 in Cancer: A Druggable Target for Cancer Treatment? *Cancers*, *11*(8), 1195. https://doi.org/10.3390/cancers11081195

[24.] Ciocca, D. R., Arrigo, A. P., & Calderwood, S. K. (2013). Heat shock proteins and heat shock factor 1 in carcinogenesis and tumor development: an update. *Archives of toxicology*, *87*(1), 19-48.

[25.] Dabravolski, S. A., Sukhorukov, V. N., Kalmykov, V. A., Orekhov, N. A., Grechko, A. V., & Orekhov, A. N. (2022). Heat Shock Protein 90 as Therapeutic Target for CVDs and Heart Ageing. *International Journal of Molecular Sciences*, *23*(2), 649. https://doi.org/10.3390/ijms23020649

[26.] Daniyan, M. O., Fisusi, F. A., & Adeoye, B.O. (2022). Neurotransmitters and molecular chaperones interactions in cerebral malaria: Is there a missing link? *Frontiers in Molecular Biosciences*, *9*. https://www.frontiersin.org/articles/10.3389/fmolb.2022.965569

[27.] Daniyan, M. O., Przyborski, J. M., &Shonhai, A. (2019). Partners in Mischief: Functional Networks of Heat Shock Proteins of Plasmodium falciparum and Their Influence on Parasite Virulence. *Biomolecules*, *9*(7), 295. https://doi.org/10.3390/biom9070295

[28.] Dawood, M. A., Eweedah, N. M., Elbialy, Z. I., & Abdelhamid, A. I. (2020). Dietary sodium butyrate ameliorated the blood stress biomarkers, heat shock proteins, and immune response of Nile tilapia (Oreochromis niloticus) exposed to heat stress. *Journal of Thermal Biology*, *88*, 102500.

[29.] Duan, Y., Wang, H., Mitchell-Silbaugh, K., Cai, S., Fan, F., Li, Y., ... & Ouyang, K. (2019). Heat shock protein 60 regulates yolk sac erythropoiesis in mice. *Cell death & disease*, *10*(10), 1-12.

[30.] Dubey, A., Prajapati, K. S., Swamy, M., & Pachauri, V. (2015). Heat shock proteins: A therapeutic target worth to consider. *Veterinary World*, *8*(1), 46. https://doi.org/10.14202/vetworld.2015.46-51

[31.] Düzgün, M. B., Theofilatos, K., Georgakilas, A. G., &Pavlopoulou, A. (2019). A Bioinformatic approach for the identification of molecular determinants of resistance/sensitivity to Cancer thermotherapy. *Oxidative medicine and cellular longevity*, *2019*.

[32.] Edkins, A. L., Price, J. T., Pockley, A. G., & Blatch, G. L. (2017). Heat shock proteins as modulators and therapeutic targets of chronic disease: An integrated perspective. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *373*(1738), 20160521. https://doi.org/10.1098/rstb.2016.0521

[33.] Ernst, K., Schmid, J., Beck, M., Hägele, M., Hohwieler, M., Hauff, P., Ückert, A. K., Anastasia, A., Fauler, M., Jank, T., Aktories, K., Popoff, M. R., Schiene-Fischer, C., Kleger, A., Müller, M., Frick, M., & Barth, H. (2017). Hsp70 facilitates trans-membrane transport of bacterial ADP-ribosylating toxins into the cytosol of mammalian cells. *Scientific Reports*, *7*(1), 2724. https://doi.org/10.1038/s41598-017-02882-y

[34.] Esmaeilzadeh, A., Mohammadi, V., Elahi, R., &Rezakhani, N. (2023). The role of heat shock proteins (HSPs) in type 2 diabetes mellitus pathophysiology. *Journal of Diabetes and Its Complications*, *37*(11), 108564. https://doi.org/10.1016/j.jdiacomp.2023.108564

[35.] Ferns, G., Shams, S., & Shafi, S. (2006). Heat shock protein 27: Its potential role in vascular disease. *International Journal of Experimental Pathology*, *87*(4), 253–274. https://doi.org/10.1111/j.1365-2613.2006.00484.x

[36.] Franklin, T. B., Krueger-Naug, A. M., Clarke, D. B., Arrigo, A. P., & Currie, R. W. (2005). The role of heat shock proteins Hsp70 and Hsp27 in cellular protection of the central nervous system. *International Journal of Hyperthermia*, *21*(5), 379-392.

[37.] Graff, A. M. de, Mosedale, D. E., Sharp, T., Dill, K. A., & Grainger, D. J. (2020). Proteostasis is adaptive: Balancing chaperone holdases against foldases. *PLoS Computational Biology*, *16*(12). https://doi.org/10.1371/journal.pcbi.1008460

[38.] Greene, E. S., Emami, N. K., & Dridi, S. (2021). Research Note: Phytobiotics modulate the expression profile of circulating inflammasome and cyto (chemo) kine in whole blood of broilers exposed to cyclic heat stress. *Poultry Science*, *100*(3), 100801.

[39.] Gu, J., Wang, C., Hu, R., Li, Y., Zhang, S., Sun, Y., ... & Liu, C. (2021). Hsp70 chaperones TDP-43 in dynamic, liquid-like phase and prevents it from amyloid aggregation. *Cell Research*, *31*(9), 1024-1027.

[40.] Gupta, A., Bansal, A., & Hashimoto-Torii, K. (2020). HSP70 and HSP90 in neurodegenerative diseases. *Neuroscience Letters*, *716*, 134678. https://doi.org/10.1016/j.neulet.2019.134678

[41.] Hall, D. (2020). On the nature of the optimal form of the holdase-type chaperone stress response. *FEBS Letters*, *594*(1), 43–66. https://doi.org/10.1002/1873-3468.13580

[42.] Haslbeck, M., & Vierling, E. (2015). A first line of stress defense: small heat shock proteins and their function in protein homeostasis. *Journal of molecular biology*, *427*(7), 1537-1548.

[43.] Hooper, P. L., & Hooper, P. L. (2009). Inflammation, heat shock proteins, and type 2 diabetes. *Cell Stress & Chaperones*, *14*(2), 113. https://doi.org/10.1007/s12192-008-0073-x

[44.] Ikwegbue, P. C., Masamba, P., Oyinloye, B. E., &Kappo, A. P. (2018). Roles of Heat Shock Proteins in Apoptosis, Oxidative Stress, Human Inflammatory Diseases, and Cancer. *Pharmaceuticals*, *11*(1), Article 1. https://doi.org/10.3390/ph11010002

[45.] Janowska, M. K., Baughman, H. E., Woods, C. N., &Klevit, R. E. (2019). Mechanisms of small heat shock proteins. *Cold Spring Harbor Perspectives in Biology*, *11*(10), a034025.

[46.] Kan, Y., & Lin, H. X. (2021). Molecular regulation and genetic control of rice thermal response. *The Crop Journal*, *9*(3), 497-505.

[47.] Kan, Y., & Lin, H. X. (2021). Molecular regulation and genetic control of rice thermal response. *The Crop Journal*, *9*(3), 497-505.

[48.] Kandasamy, G., & Andréasson, C. (2018). Hsp70-Hsp110 chaperones deliver ubiquitin-dependent and -independent substrates to the 26S proteasome for proteolysis in yeast. *Journal of Cell Science*, *131*(6), jcs210948. https://doi.org/10.1242/jcs.210948

[49.] Kennedy, D., Jäger, R., Mosser, D. D., & Samali, A. (2014). Regulation of apoptosis by heat shock proteins. *IUBMB life*, *66*(5), 327-338.

[50.] Kurop, M. K., Huyen, C. M., Kelly, J. H., & Blagg, B. S. (2021). The heat shock response and small molecule regulators. *European Journal of Medicinal Chemistry*, *226*, 113846.

[51.] Labbadia, J., & Morimoto, R. I. (2015). The Biology of Proteostasis in Aging and Disease. *Annual Review of Biochemistry*, *84*, 435–464. https://doi.org/10.1146/annurev-biochem-060614-033955

[52.] Leak, R. K. (2014). Heat shock proteins in neurodegenerative disorders and aging. *Journal of cell communication and signaling*, *8*(4), 293-310.

[53.] Li, H. G., Yang, Y., Liu, M., Zhu, Y., Wang, H. L., Feng, C. H., ... & Xia, X. (2022). The in vivo performance of a heat shock transcription factor from Populus euphratica, PeHSFA2, promises a prospective strategy to alleviate heat stress damage in poplar. *Environmental and Experimental Botany*, 104940.

[54.] Li, J., He, X., Deng, Y., & Yang, C. (2019). An update on isolation methods for proteomic studies of extracellular vesicles in biofluids. *Molecules*, *24*(19), 3516.

[55.] Li, X., Yu, H., Liang, L., Bi, Z., Wang, Y., Gao, S., ... & Yang, C. (2020). Myricetin ameliorates bleomycin-induced pulmonary fibrosis in mice by inhibiting TGF-β signaling via targeting HSP90β. *Biochemical Pharmacology*, *178*, 114097.

[56.] Lianos, G. D., Alexiou, G. A., Mangano, A., Mangano, A., Rausei, S., Boni, L., ... &Roukos, D. H. (2015). The role of heat shock proteins in cancer. *Cancer letters*, *360*(2), 114-118.

[57.] Liu, J. Y., Hawsawi, H. B., Sharma, N., Carmichael, D. W., Diehl, B., Thom, M., & Lemieux, L. (2022). Safety of intracranial electroencephalography during functional electromagnetic resonance imaging in humans at 1.5 tesla using a head transmit RF coil: Histopathological and heat-shock immunohistochemistry observations. *NeuroImage*, *254*, 119129.

[58.] Liu, J., Zhao, H., Wang, Y., Shao, Y., Zhang, L., & Xing, M. (2018). Impacts of simultaneous exposure to arsenic (III) and copper (II) on inflammatory response, immune homeostasis, and heat shock response in chicken thymus. *International Immunopharmacology*, *64*, 60-68.

[59.] Lü, X. P., Shao, K. Z., Xu, J. Y., Li, J. L., Ren, W., Chen, J., ... & Zhang, J. L. (2022). A heat shock transcription factor gene (HaHSFA1) from a desert shrub, Haloxylonammodendron, elevates salt tolerance in Arabidopsis thaliana. *Environmental and Experimental Botany*, 104954.

[60.] Luca, A. C., David, S. G., David, A. G., Țarcă, V., Pădureț, I.-A., Mîndru, D. E., Roșu, S. T., Roșu, E. V., Adumitrăchioaiei, H., Bernic, J., Cojocaru, E., &Țarcă, E. (2023). Atherosclerosis from Newborn to Adult—Epidemiology, Pathological Aspects, and Risk Factors. *Life*, *13*(10), 2056. https://doi.org/10.3390/life13102056

[61.] Luo, W., Sun, W., Taldone, T., Rodina, A., &Chiosis, G. (2010). Heat shock protein 90 in neurodegenerative diseases. *Molecular neurodegeneration*, *5*(1), 1-8.

[62.] Majdeddin, M., Braun, U., Lemme, A., Golian, A., Kermanshahi, H., De Smet, S., & Michiels, J. (2020). Guanidinoacetic acid supplementation improves feed conversion in broilers subjected to heat stress associated with muscle creatine loading and arginine sparing. *Poultry science*, *99*(9), 4442-4453.

[63.] Martine, P., &Rébé, C. (2019). Heat shock proteins and inflammasomes. *International journal of molecular sciences*, *20*(18), 4508.

[64.] Mayer, M. P. (2021). The Hsp70-Chaperone Machines in Bacteria. *Frontiers in Molecular Biosciences*, *8*. https://doi.org/10.3389/fmolb.2021.694012

[65.] Mayer, M. P., &Gierasch, L. M. (2019). Recent advances in the structural and mechanistic aspects of Hsp70 molecular chaperones. *Journal of Biological Chemistry*, *294*(6), 2085–2097. https://doi.org/10.1074/jbc.REV118.002810

[66.] McLoughlin, F., Basha, E., Fowler, M. E., Kim, M., Bordowitz, J., Katiyar-Agarwal, S., & Vierling, E. (2016). Class I and II small heat shock proteins together with HSP101 protect protein translation factors during heat stress. *Plant Physiology*, *172*(2), 1221-1236.

[67.] Meng, X., Wang, N., He, H., Tan, Q., Wen, B., Zhang, R., ... & Li, D. (2022). Prunus persica transcription factor PpNAC56 enhances heat resistance in transgenic tomatoes. *Plant Physiology and Biochemistry*, *182*, 194-201.

[68.] Milani, A., Baesi, K., Agi, E., &Bolhassani, A. (2020). Detection of Anti-IgGs against Heat Shock Proteins 27 and 20, HP91 Peptide, and HIV-1 Polypeptides in HIV-Positive and Negative Patients. *Journal of Medical Microbiology and Infectious Diseases*, *8*(3), 113-104.

[69.] Moayed, F., Bezrukavnikov, S., Naqvi, M. M., Groitl, B., Cremers, C. M., Kramer, G., Ghosh, K., Jakob, U., & Tans, S. J. (2020). The Anti-Aggregation Holdase Hsp33 Promotes the Formation of Folded Protein Structures. *Biophysical Journal*, *118*(1), 85–95. https://doi.org/10.1016/j.bpj.2019.10.040

[70.] Mogk, A., Ruger-Herreros, C., &Bukau, B. (2019). Cellular functions and mechanisms of action of small heat shock proteins. *Annual review of microbiology*, *73*, 89-110.

[71.] Moin, A. S. M., Nandakumar, M., Diane, A., Dehbi, M., & Butler, A. E. (2021). The Role of Heat Shock Proteins in Type 1 Diabetes. *Frontiers in Immunology*, *11*, 612584. https://doi.org/10.3389/fimmu.2020.612584

[72.] Mymrikov, E. V., Seit-Nebi, A. S., & Gusev, N. B. (2011). Large potentials of small heat shock proteins. *Physiological reviews*, *91*(4), 1123-1159.

[73.] Nakhjavani, M., Morteza, A., Khajeali, L., Esteghamati, A., Khalilzadeh, O., Asgarani, F., & Outeiro, T. F. (2010). Increased serum HSP70 levels are associated with the duration of diabetes. *Cell Stress & Chaperones*, *15*(6), 959–964. https://doi.org/10.1007/s12192-010-0204-z

[74.] Navarro-Zaragoza, J., Cuenca-Bermejo, L., Almela, P., Laorden, M.-L., & Herrero, M.-T. (2021). Could Small Heat Shock Protein HSP27 Be a First-Line Target for Preventing Protein Aggregation in Parkinson's Disease? *International Journal of Molecular Sciences*, *22*(6), 3038. https://doi.org/10.3390/ijms22063038

[75.] Oliveira de Souza, C., Sun, X., & Oh, D. (2021). Metabolic Functions of G Protein-Coupled Receptors and β-Arrestin-Mediated Signaling Pathways in the Pathophysiology of Type 2 Diabetes and Obesity. *Frontiers in Endocrinology*, *12*. https://www.frontiersin.org/articles/10.3389/fendo.2021.715877

[76.] Owigho O.P, Adeoye B.O., Giebel, H., Fam, S., Adeoye A.D., A., & Saliu, O. (2022). Distribution of diabetes co-morbidities and treatment outcome of hypertension at a tertiary lifestyle medical centre in ile-ife, osun state nigeria: a 5 -year retrospective study. *European journal of pharmaceutical and medical research*, *9*, 21–27.

[77.] Pan, R., He, D., Xu, L., Zhou, M., Li, C., Wu, C., ... & Zhang, W. (2019). Proteomic analysis reveals response of differential wheat (Triticum aestivum L.) genotypes to oxygen deficiency stress. *BMC genomics*, *20*(1), 1-13.

[78.] Park, H. J., Jang, G. Y., Kim, Y. S., Park, J. H., Lee, S. E., Vo, M. C., ... & Park, Y. M. (2019). A novel TLR4 binding protein, 40S ribosomal protein S3, has potential utility as an adjuvant in a dendritic cell-based vaccine. *Journal for immunotherapy of cancer*, *7*(1), 1-13

[79.] Patnaik, S., Nathan, S., Kar, B., Gregoric, I. D., & Li, Y.-P. (2023). The Role of Extracellular Heat Shock Proteins in Cardiovascular Diseases. *Biomedicines*, *11*(6), Article 6. https://doi.org/10.3390/biomedicines11061557

[80.] Pockley, A. G., &Frostegård, J. (2005). Heat shock proteins in cardiovascular disease and the prognostic value of heat shock protein related measurements. *Heart*, *91*(9), 1124–1126. https://doi.org/10.1136/hrt.2004.059220

[81.] Poznyak, A. V., Orekhova, V. A., Sukhorukov, V. N., Khotina, V. A., Popov, M. A., & Orekhov, A. N. (2023). Atheroprotective Aspects of Heat Shock Proteins. *International Journal of Molecular Sciences*, *24*(14), 11750. https://doi.org/10.3390/ijms24141175

[82.] Radons, J. (2016). The human HSP70 family of chaperones: Where do we stand? *Cell Stress & Chaperones*, *21*(3), 379–404. https://doi.org/10.1007/s12192-016-0676-6

[83.] Rodrigues-Krause, J., Krause, M., O'Hagan, C., Vito, G. D., Boreham, C., Murphy, C., Newsholme, P., & Colleran, G. (2012). Divergence of intracellular and extracellular HSP72 in type 2 diabetes: Does fat matter? *Cell Stress & Chaperones*, *17*(3), 293. https://doi.org/10.1007/s12192-011-0319-x

[84.] Rowles, J. E., Keane, K. N., Gomes Heck, T., Cruzat, V., Verdile, G., &Newsholme, P. (2020). Are Heat Shock Proteins an Important Link between Type 2 Diabetes and Alzheimer Disease? *International Journal of Molecular Sciences*, *21*(21), 8204. https://doi.org/10.3390/ijms21218204

[85.] Rutledge, B. S., Choy, W.-Y., &Duennwald, M. L. (2022). Folding or holding?—Hsp70 and Hsp90 chaperoning of misfolded proteins in neurodegenerative disease. *The Journal of Biological Chemistry*, *298*(5), 101905. https://doi.org/10.1016/j.jbc.2022.101905

[86.] Schopfer, F. J., & Khoo, N. K. (2019). Nitro-fatty acid logistics: formation, biodistribution, signaling, and pharmacology. *Trends in Endocrinology & Metabolism*, *30*(8), 505-519.

[87.] Sharma, A., Toepfer, C. N., Ward, T., Wasson, L., Agarwal, R., Conner, D. A., ... & Seidman, C. E. (2018). CRISPR/Cas9-mediated fluorescent tagging of endogenous proteins in human pluripotent stem cells. *Current protocols in human genetics*, *96*(1), 21-11.

[88.] Sharma, E., Borah, P., Kaur, A., Bhatnagar, A., Mohapatra, T., Kapoor, S., & Khurana, J. P. (2021). A comprehensive transcriptome analysis of contrasting rice cultivars highlights the role of auxin and ABA responsive genes in heat stress response. *Genomics*, *113*(3), 1247-1261.

[89.] Sharma, K., Akre, S., Chakole, S., & Wanjari, M. B. (n.d.). Stress-Induced Diabetes: A Review. *Cureus*, *14*(9), e29142. https://doi.org/10.7759/cureus.29142

[90.] Singh, G., Sarkar, N. K., & Grover, A. (2021). Tango between ethylene and HSFA2 settles heat tolerance. *Trends in Plant Science*, *26*(5), 429-432.

[91.] Sluchanko, N. N., Beelen, S., Kulikova, A. A., Weeks, S. D., Antson, A. A., Gusev, N. B., & Strelkov, S. V. (2017). Structural basis for the interaction of a human small heat shock protein with the 14-3-3 universal signaling regulator. *Structure*, *25*(2), 305-316.

[92.] Somu, P., Mohanty, S., Basavegowda, N., Yadav, A. K., Paul, S., & Baek, K.-H. (2024). The Interplay between Heat Shock Proteins and Cancer Pathogenesis: A Novel Strategy for Cancer Therapeutics. *Cancers*, *16*(3), 638. https://doi.org/10.3390/cancers16030638

[93.] Sun, Y., &MacRae, T. H. (2005). The small heat shock proteins and their role in human disease. *The FEBS journal*, *272*(11), 2613-2627.

[94.] Tanju, İ. A., Çekmez, F., Pirgon, O., & Karademir, F. (2009). Diabetic Ketoacidosis Precipitated by Henoch-Schonlein Purpura. *International Journal of Biomedical Science : IJBS*, *5*(2), 189–191. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3614763/

[95.] Taylor, R. P., & Benjamin, I. J. (2005). Small heat shock proteins: a new classification scheme in mammals. *Journal of molecular and cellular cardiology*, *38*(3), 433-444.

[96.] Trösch, R., Mühlhaus, T., Schroda, M., &Willmund, F. (2015). ATP-dependent molecular chaperones in plastids—More complex than expected. *Biochimica et Biophysica Acta (BBA) - Bioenergetics*, *1847*(9), 872–888. https://doi.org/10.1016/j.bbabio.2015.01.002

[97.] Vendredy, L., Adriaenssens, E., & Timmerman, V. (2020). Small heat shock proteins in neurodegenerative diseases. *Cell Stress and Chaperones*, *25*(4), 679-699.

[98.] Verma, K., Verma, M., Chaphalkar, A., & Chakraborty, K. (2021). Recent advances in understanding the role of proteostasis. *Faculty Reviews*, *10*, 72. https://doi.org/10.12703/r/10-72

[99.] Wang, G. Y., Chen, S. Y., Chen, Y. Y., Hong, C. J., Hsu, Y. H., & Yen, G. C. (2021). Protective effect of rosmarinic acid-rich trichodesmakhasianumclarke leaves against ethanol-induced gastric mucosal injury in vitro and in vivo. *Phytomedicine*, *80*, 153382.

[100.] Wang, M. L., Rivlin, M., Graham, J. G., &Beredjiklian, P. K. (2019). Peripheral nerve injury, scarring, and recovery. *Connective tissue research*, *60*(1), 3-9.

[101.] Wang, W., Zheng, H., Wen, J., Xu, K., Xu, Y., Ji, D., ... & Xie, C. (2022). Early signaling events in the heat stress response of Pyropiahaitanensis revealed by phosphoproteomic and lipidomic analyses. *Algal Research*, *67*, 102837.

[102.] Waters, E. R., & Vierling, E. (2020). Plant small heat shock proteins–evolutionary and functional diversity. *New Phytologist*, *227*(1), 24-37.

[103.] Webster, J. M., Darling, A. L., Uversky, V. N., & Blair, L. J. (2019). Small heat shock proteins, big impact on protein aggregation in neurodegenerative disease. *Frontiers in pharmacology*, *10*, 1047.

[104.] Wu, J., Liu, T., Rios, Z., Mei, Q., Lin, X., & Cao, S. (2017). Heat shock proteins and cancer. *Trends in pharmacological sciences*, *38*(3), 226-256.

[105.] Yue, Z., Wang, Y., Zhang, N., Zhang, B., & Niu, Y. (2021). Expression of the Amorphophallus albus heat stress transcription factor AaHsfA1 enhances tolerance to environmental stresses in Arabidopsis. *Industrial Crops and Products*, *174*, 114231.

[106.] Yun, C. W., Kim, H. J., Lim, J. H., & Lee, S. H. (2019). Heat Shock Proteins: Agents of Cancer Development and Therapeutic Targets in Anti-Cancer Therapy. *Cells*, *9*(1), 60. https://doi.org/10.3390/cells9010060

[107.] Yusof, N. A., Charles, J., Wan Mahadi, W. N. S., Abdul Murad, A. M., & Mahadi, N. M. (2021). Characterization of inducible HSP70 genes in an Antarctic yeast, Glaciozyma antarctica PI12, in response to thermal stress. *Microorganisms*, *9*(10), 2069.

[108.] Zhang, G., Cheng, W., Du, L., Xu, C., & Li, J. (2021). Synergy of hypoxia relief and heat shock protein inhibition for phototherapy enhancement. *Journal of Nanobiotechnology*, *19*(1), 1-13.

[109.] Zhang, S., Zhou, H., Yu, F., Bai, C., Zhao, Q., He, J., & Liu, C. (2016). Structural insight into the cooperation of chloroplast chaperonin subunits. *BMC Biology*, *14*, 29. https://doi.org/10.1186/s12915-016-0251-8

[110.] Zhao, D., Qi, X., Zhang, Y., Zhang, R., Wang, C., Sun, T., ... & Lu, Y. (2022). Genome-wide analysis of the heat shock transcription factor gene family in Sorbus pohuashanensis (Hance) Hedl identifies potential candidates for resistance to abiotic stresses. *Plant Physiology and Biochemistry*, *175*, 68-80.

[111.] Zhao, D., Xia, X., Su, J., Wei, M., Wu, Y., & Tao, J. (2019). Overexpression of herbaceous peony HSP70 confers high temperature tolerance. *BMC genomics*, *20*(1), 1-11.

[112.] Zilaee, M., & Shirali, S. (2016). Heat Shock Proteins and Diabetes. *Canadian Journal of Diabetes*, *40*(6), 594–602. https://doi.org/10.1016/j.jcjd.2016.05.016

[113.] Zininga, T., Ramatsui, L., &Shonhai, A. (2018). Heat shock proteins as immunomodulants. *Molecules*, *23*(11), 2846.

[114.] Zuehlke, A. D., Moses, M. A., & Neckers, L. (2018). Heat shock protein 90: its inhibition and function. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *373*(1738), 20160527.