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The Role of Heat Shock Proteins in Oxidative Stress

Oksidatif Streste Isı Şoku Proteinlerinin Rolü

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Abstract

Oxidative stress is at the forefront of these changes that develop during inflammation, which is at the core of diseases. Oxidative stress occurs due to both the excessive release of oxidation products as a result of metabolic activity and a deficiency in the antioxidant system. Oxidative stress, which has recently become a focus of scientific interest, plays a role in the pathogenesis of many diseases. While increased oxidative stress triggers inflammation, a reduction in oxidative stress contributes to the healing process of the disease. Therefore, oxidative stress is beneficial both in understanding diseases and in monitoring various treatment processes. Various biomarkers are used to monitor oxidative stress during inflammation. Heat shock proteins, whose use is gaining momentum in current research, are protein groups that are released during cell injury due to increased intracellular oxidation-induced temperature. Heat shock proteins are responsible for cell development, cycle, metabolism, signaling, proliferation, apoptosis, differentiation, and, in particular, the proper folding of proteins. These proteins are also called stress proteins because they increase under various stress conditions that cause inflammation, such as infection, dehydration, toxicity, starvation, and physical and chemical factors. Heat shock proteins are classified into different groups based on their function and molecular structure. In this research, the structure, types, functions and possible contributions of heat shock proteins to scientific studies were discussed.

Keywords; Cell İnjury, heat shock proteins, oxidative stress, reactive oxygen species

Özet

Hastalıkların temelinde yatan inflamasyon sırasında gelişen bu değişimlerin başında oksidatif stres gelir. Oksidatif stres, hem metabolik aktivite sonucu oksidasyon ürünlerinin aşırı salınımı hem de antioksidan sistemdeki eksiklik nedeniyle ortaya çıkar. Son zamanlarda bilimsel ilgi odağı haline gelen oksidatif stres, birçok hastalığın patogenezinde rol oynar. Artan oksidatif stres inflamasyonu tetiklerken, oksidatif stresin azalması hastalığın iyileşme sürecine katkıda bulunur. Bu nedenle oksidatif stres, hem hastalıkların anlaşılmasında hem de çeşitli

tedavi süreçlerinin izlenmesinde faydalıdır. İnflamasyon sırasında oksidatif stresi izlemek için çeşitli biyobelirteçler kullanılır. Güncel araştırmalarda kullanımı giderek artan ısı şoku proteinleri, hücre içi oksidasyon kaynaklı sıcaklığın artması nedeniyle hücre hasarı sırasında salınan protein gruplarıdır. Isı şoku proteinleri, hücre gelişimi, döngüsü, metabolizması, sinyal iletimi, çoğalması, apoptozu, farklılaşması ve özellikle proteinlerin düzgün katlanmasından sorumludur. Bu proteinler, enfeksiyon, dehidratasyon, toksisite, açlık ve fiziksel ve kimyasal faktörler gibi iltihaplanmaya neden olan çeşitli stres koşullarında artış gösterdikleri için stres proteinleri olarak da adlandırılır. Isı şoku proteinleri, işlevlerine ve moleküler yapılarına göre farklı gruplara ayrılır. Bu araştırmada, ısı şoku proteinlerinin yapısı, türleri, işlevleri ve bilimsel çalışmalara olası katkıları tartışılmıştır.

Anahtar Kelimeler: Hücre zedelenmesi, ısı şoku proteinleri, oksidatif stres, reaktif oksijen türleri

Introduction

Cell damage is the basis of diseases, and oxidative stress has a cyclic relationship with cell damage. Oxidative stress: The energy required for the survival of living organisms is provided by the burning of nutrients with oxygen. A large portion of the oxygen used for energy production in the mitochondria of aerobic organisms is converted to water through electron transport reactions. A small portion of the oxygen that cannot be converted to water is reduced during metabolism to form reactive oxygen species. Reactive intermediates released during energy production have unpaired electrons in their outermost orbitals. These structures, which are unstable due to the lack of electrons in their outer orbitals, are also considered free radicals. These short-lived, small, and high-energy free radicals tend to stabilize by binding to stable macromolecules in their environment. These oxidation products, released during the normal metabolic processes of living organisms, are compensated by the organism's antioxidant system. Oxidative stress is the disruption of the balance between oxidation products and the antioxidants that control them, either due to increased oxidation or a deficiency in the antioxidant mechanism, in favor of oxidants (Jakubczyk et al. 2020; Pisoschi & Pop, 2015; Sies et al. 2017).

2. Reactive Oxygen Species (ROS)

Reactive oxygen species (ROS), a product of normal metabolic processes, are produced by the activation of many enzymes involved in cell energy production, particularly neutrophil myeloperoxidase (MPO), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and xanthine oxidase (XOD). These cellular metabolic products have beneficial effects in relatively small amounts. Free radicals contribute to cellular responses, activate various warning mechanisms, and facilitate biological processes through numerous enzymatic reactions. However, excessive free radical production in the body, which cannot be compensated by antioxidants, binds to important cellular components such as carbohydrates, proteins, lipids, and nucleic acids. Free radicals attach to these macromolecules, disrupting their structure and function, leading to cell injury. Oxidative stress, which is crucial for cell injury, the basis of diseases, also plays a key role in the pathogenesis of many diseases. Oxidative stress is implicated in the pathophysiology of many diseases, particularly cancer, diabetes, cardiovascular, neurological, toxic, and infectious diseases. For these reasons, oxidative stress biomarkers are utilized in the diagnosis and monitoring of many diseases (Çenesiz, 2020; Jomova et al. 2023; Adwas et al. 2019; Sies et al. 2017).

Oxidative stress in the body arises from endogenous and exogenous sources. Endogenous factors include infection, aging, exercise, chronic diseases, immunological factors, and inadequate or unbalanced nutrition. Environmental factors such as air pollution, cigarette smoke, ozone, phytochemicals, solvents, metallic cations, ultraviolet rays, ionizing radiation, pesticides, drugs, chemotherapeutics, food residues, and toxic agents constitute exogenous causes of oxidative stress (García-Caparrós et al. 2021; Adwas et al. 2019). In these etiologies, where there is an increase in oxidation products and a deficiency in the antioxidant system, free radicals are released due to oxidative respiration in the mitochondria. These free radicals consist of reactive oxygen and nitrogen derivatives. Reactive oxygen species are mainly hydrogen peroxide (H2O2), superoxide anion radical (O2-), hydroxyl radicals (HO-), singlet oxygen (O2), hypochlorous acid (HOCl), peroxyl radical (POO-), alkyl radical (R), perhydroxyl radical (HO2-), ozone (O3), alkoxyl radical (RO-) and organic peroxide radical (RCOO-). Reactive nitrogen molecules are nitric oxide (NO-) and peroxynitrite (ONOO-) (García-Caparrós et al. 2021; Puppel et al. 2015; Lushchak & Lushchak, 2021).

Antioxidant System

Oxidation products released as a result of cellular activity are maintained at a healthy threshold by antioxidants to maintain organismal homeostasis. Some of these antioxidants are endogenously present in the living body, while others are exogenously obtained. Endogenous intracellular enzyme systems are more effective in defending against reactive oxidation products. The primary intracellular antioxidant enzyme systems are glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and catalase (CAT) (Pisoschi & Pop, 2015; Ma et al. 2017).

Antioxidants can be either endogenous or exogenous, and among these, endogenous agents are enzymatic and non-enzymatic. GSH-Px, which acts in the presence of selenium, eliminates hydrogen peroxide in the cellular mitochondria. SODs, which exist in the varieties SOD1 (Cu/Zn SOD), SOD2 (Mn SOD), and SOD3, enable the conversion of superoxide ions produced by NADPH into hydrogen and oxygen peroxide through oxidation. CAT, another antioxidant enzyme that plays a key role in detoxification, prevents the formation of hydrogen peroxide. In addition to these antioxidants, there are also non-enzymatic antioxidants. Non-enzymatic antioxidants primarily include glutathione (GSH), vitamin A (β-carotene), vitamin E (α-tocopherol), and vitamin C (ascorbic acid). Of these, GSH protects cells against oxidative stress during intracellular redox states. Vitamin A scavenges singlet oxygen, peroxide, and superoxide radicals from reactive oxygen species. Vitamin E protects the cell against peroxyl radicals generated by the oxidation of polyunsaturated fatty acids found in the phospholipids of the cell membrane and some membrane organelles. Vitamin C exerts an antioxidant effect by reducing H2O2, OH-, and HOCl produced by neutrophils (Pisoschi & Pop, 2015; Adwas et al. 2019; Moussa et al. 2019).

Oxidative stress, which plays a role in the etiology and pathogenesis of many diseases, also provides benefits in the diagnosis, treatment, and monitoring of these diseases. Oxidative stress is indispensable for both disease diagnosis and solution-oriented studies such as disease prevention and treatment. Oxidative stress, which holds a crucial place in today's scientific studies, utilizes various biomarkers representing oxidants or antioxidants and their metabolites (Frijhoff et al. 2015; Demirci-Çekiç et al. 2022).

Heat Shock Proteins (HSP)

Heat shock proteins are a group of proteins that increase when cells are exposed to high temperatures to eliminate proteotoxic damage. They are also called stress proteins because they increase under various stress conditions, such as inflammation, infection, dehydration, starvation, hypoxia, ultraviolet light, toxicity, and oxidation. They are also considered components of the stress response. They are responsible for cell development, cycle, metabolism, signaling, proliferation, apoptosis, differentiation, and, in particular, proper protein folding. Because HSPs do not denature under stress due to their hydrogen bonds, strong hydrophobic interactions, and bipolar helical stability, they play an integral role in cellular protection, protecting proteins from stress and preventing cell damage. Although heat shock proteins have been classified differently, they are generally grouped as small HSP types (p20, α-A and B crystallin, cvHSP, HSP27, HSPB2, HSPB3, HSPB8, HSPB9), HSP40, HSP60, HSP70, HSP90, HSP100, and HSP110, according to their functions and molecular weights. However, HSP27, HSP60, HSP70, and HSP90 are used as oxidative stress biomarkers in current studies (Hu et al. 2022; Jee, 2016; Park & Seo, 2015; Öztürk et al. 2009).

Heat Shock Protein-27 (HSP27)

HSP27, a small HSP, has a molecular weight of 27 kDa and consists of three domains: the N-terminal, the C-terminal, and α-crystallin, which is approximately 80 amino acids long. HSP27 functions independently of ATP and is produced under conditions of infection, heat, and oxidative stress, even in cases of ATP deficiency. In the event of cell injury resulting from oxidation, the amount of ATP in the cell drops significantly, and ATP-independent chaperones are immediately activated to prevent protein degeneration. HSP27, one of the most important of these, contributes significantly to cell protection by stimulating other heat shock proteins (Garrido et al. 2006; Vidyasagar et al. 2012).

HSP27 expression begins before cell differentiation and declines with cell proliferation and differentiation. For this reason, HSP27 is also called a pre-differentiation marker. HSP27 acts as an antioxidant during oxidative stress, reducing reactive oxygen species (ROS) and intracellular iron levels and increasing intracellular glutathione levels. It also exerts cytoprotective effects by undertaking functions such as apoptosis and cytoskeletal regulation. As the stress condition within the cell begins to improve, ATP levels begin to rise, and ATP-

dependent chaperones such as HSP70 and HSP90 are recruited to facilitate protein refolding and transport. HSP27 is involved in various mechanisms beyond its chaperone function. HSP27, which is involved in critical processes such as cytoskeletal dynamics, apoptosis, autophagy, and reactive oxygen species reduction within the cell, interacts with anti-inflammatory signaling pathways outside the cell. The HSP27 protein is overexpressed in cancer cells, but it causes the cells to acquire drug resistance (Wang et al. 2014; Garrido et al. 2003; Concannon et al. 2003).

Heat Shock Protein-60 (HSP60)

HSP60, a mitochondrial matrix protein, is important in mitochondrial damage because it is a chaperonin responsible for protein folding within mitochondria. It plays crucial roles in the synthesis, proper folding, and transport of mitochondrial proteins from the cytoplasm to the mitochondrial matrix. The HSP60 (60kDa) protein can be found in the mitochondria and cytoplasm within the cell, and can also be secreted extracellularly. While HSP60 is primarily found in mitochondria, it can also be found on the cell surface, in the extracellular space, in the endoplasmic reticulum, and in cytoplasmic granules and vesicles. In mammals, HSP60 consists of two components: mitochondrial (mt-HSP60) and cytosolic (T-complex polypeptide-1). mt-HSP60 exists in a dynamic equilibrium between monomers, heptamers, and quaternary decamers. At low concentrations, it dissociates into monomeric structures and, in the presence of mt-HSP10, a cofactor of mt-HSP60, and ATP, it assembles into quadruplex decamers. Cytosolic HSP60 forms a hetero-oligomeric ring structure and facilitates the folding of cytoskeletal proteins such as actin and tubulin (Habich & Burkart, 2007; Tkáčová, J., & Angelovičová, 2012).

In the cell, it helps proteins achieve the correct conformation together with its co-chaperone, HSP10. The HSP60/HSP10 complex performs its protein-coating function in an ATP-dependent manner. In the absence of ATP and protein substrate, the HSP60 protein exists in a double-ring form called the “APO conformation.” In the presence of ATP, HSP10 proteins bind to HSP60 to form a functional complex. After the protein substrate and ATP are removed from the medium, the HSP10 proteins bind to HSP60 to form a functional complex. After the protein substrate and ATP are removed from the medium, the HSP10 proteins dissociate from HSP60, and HSP60 returns to its initial Apo conformation. In addition to its chaperone function, the HSP60 protein also plays a role in immune responses. It activates T lymphocytes, leading

to the stimulation and maturation of dendritic cells. HSP60 proteins released extracellularly serve as endogenous signals during central nervous system injuries by activating microglia via TLR4 receptors (Malik & Lone, 2021; Grundtman et al. 2011; Berestoviy et al. 2021).

Heat Shock Protein-70 (HSP70)

HSP70, with a mass of 70 kDa, can be found in various compartments within the cell, such as the nucleus, cytosol, endoplasmic reticulum, and mitochondria, as well as extracellularly. HSP70 expression can be altered by the effects of various molecules, such as intracellular pH, calcium, cyclic AMP, and extracellular protein kinase C-1, 4, and 5 triphosphate. The HSP70 family is an ATP-dependent chaperone protein and consists of five different members found in the cytosol (HSP70/HSC70), mitochondria (HSP75), and endoplasmic reticulum, as well as inducible and constitutive forms. Almost all members of this family have the same structure, a 45 kDa N-terminal ATPase domain and a 25 kDa C-terminal substrate-binding domain. The C-terminal substrate-binding domain is further divided into β-sandwich and C-terminal α-helical subdomains (Pulur et al. 2017; Hassan et al. 2019; Mayer & Bukau, 2005).

HSP70's most important function is to prevent protein denaturation under heat stress, thereby exhibiting thermotolerance. This is because cells under stress have difficulty performing normal physiological processes such as substance transport, DNA replication, protein synthesis, or transport. Under various stress conditions, such as heat stress, HSP70 expression increases significantly, helping cells perform their normal activities. HSP70 also plays important roles in signal transduction, cell division, cell differentiation, and programmed cell death. Furthermore, HSP70 plays a significant role in tumor formation, aging, viral infections, neurodegenerative and autoimmune diseases by regulating DNA replication, substance transport, protein synthesis, cell regulation, and apoptosis. The HSP70 protein utilizes ATP energy within the cell to ensure the folding of newly synthesized proteins or the refolding of misfolded proteins into the correct conformation. This protein is found in the cytoplasm, endoplasmic reticulum, and mitochondria within the cell, and is also secreted extracellularly. Thus, in addition to its chaperone function, the HSP70 protein plays roles in various mechanisms both inside and outside the cell. It is involved in the delivery of proteins to various organelles within the cell, protein transport across the cell membrane, and apoptosis regulation. Extracellular HSP70 proteins interact with glial cells and neurons and play a role in

the activation of microglia. Furthermore, HSP70 proteins located in synapses are involved in the regulation of synaptic transmission and the endocytosis/exocytosis process (Qu et al., 2015; Kiang & Tsokos, 1998; Mayer & Bukau, 2005; Beere & Green, 2001).

Heat Shock Protein-90 (HSP90)

HSP90, with a mass of 90 kDa, is abundant in eukaryotic cells. HSP90 is an ATP-dependent chaperone protein with a flexible dimeric structure. Each monomer consists of three domains: the N-terminal domain, the M-domain bound to the N-domain, and the C-terminal domain bound to the M-domain. ATP binds to the N-terminal domain, and the hydrolyzing pocket, with its ATPase activity, is located in this region. The M-domain is the region with which certain proteins or chaperones interact. The C-terminal domain regulates HSP90 dimerization. HSP90 has two main cytoplasmic forms: HSP90α (inducible form) and HSP90β (constitutive form). However, recent studies have indicated the existence of new isoforms of HSP90. These are HSP90N, which is associated with cellular transformation; Grp94 (Glucose-related protein 94) located in the endoplasmic reticulum; HSP75/TRAP1, found in the mitochondrial matrix; and Tumor necrosis factor receptor-associated protein (Pearl & Prodromou, 2006; Wandinger et al., 2008; Li & Buchner, 2013).

HSP90α plays a role in cell growth and cell cycle regulation, while HSP90β plays a role in early embryonic development, germ cell maturation, cytoskeletal stabilization, cellular transformation, signal transduction, and long-term cell adaptation. The most important difference between these two isoforms is that the α form dimerizes more readily than the β form, and that the α form is less expressed in most cells than the β form. Biochemically distinguishing HSP90 isoforms is quite difficult, and studies have used HSP90 α/β, a mixture of the α and β forms of HSP90 (Pires & Khole, 2009; Sreedhar et al., 2004). While it constitutes 1-2% of total cellular proteins under non-stressful conditions, this proportion increases to 4-6% in many disease states such as cancer, viral infections, inflammation, or other stress conditions, preventing stress-related deterioration in the cell. HSP90 (90 kDa) proteins are involved in the correct folding of newly synthesized or misfolded proteins, thus preventing protein aggregation under stress conditions. HSP90 proteins utilize ATP or GTP energy in their chaperone function. HSP90 proteins are found in the cytoplasm, endoplasmic reticulum, and mitochondria of the cell (Sreedhar et al., 2004; Li & Buchner, 2013). HSP90 proteins play a critical role in cell signaling pathways by participating in the folding of molecules such as steroid hormone

receptors and protein kinases. HSP90 proteins interact with cytoskeletal elements such as actin, tubulin, and microtubules, protecting these molecules under stress conditions and thus maintaining the cytoskeleton. HSP90 proteins, located in the endoplasmic reticulum, are responsible for calcium homeostasis and protein processing. Mitochondrial HSP90 proteins protect against reactive oxygen species and prevent mitochondrial apoptosis (Wandinger et al., 2008; Sreedhar et al., 2004; Prodromu, 2016).

Heat Shock Proteins in Current Studies

With oxidative stress being the subject of numerous studies, oxidative stress biomarkers are also gaining importance. Recent studies are using different biomarkers that better indicate oxidative damage. Heat shock proteins have also demonstrated remarkable success in the detection of oxidative stress and have become frequently preferred in current studies. In some studies, Yusuf et al. (2018) examined HSP 70 expression in colorectal cancer studies and suggested that it may contribute to carcinopathogenesis. Hrudka et al. (2021) stated that HSP27, HSP70, and HSP110 expression may guide the prognosis of colorectal cancer. Tremosini et al. (2012) confirmed the clinical usefulness of HSP70 in the diagnosis of hepatocellular carcinoma. Giaginis et al. (2009) reported that HSP27, HSP60, and HSP90 are critical for the management of gastric adenocarcinoma patients and correlated them as clinicopathological diagnostic parameters. They also stated that HSP90 expression could be an independent prognostic biomarker in gastric adenocarcinoma patients. Hamelin et al. (2011) identified and validated HSP60 as a potential serum marker for colorectal cancer. Wilhelmus et al. (2006) reported that some HSP types have a role in the pathogenesis of Alzheimer's disease. Uztimur et al. (2025) reported that HSP27 expression in the brain tissue of cattle with T. annulata has a role in the pathogenesis of the disease. Sönmez et al. (2017) evaluated the antioxidant properties and the healing effect of vinpocetine on tissue damage due to testicular torsion by using HSP70 expression. Oyagbemi et al. (2018) used HSP70 as an oxidative stress biomarker in their study demonstrating the ameliorative effect of quercetin on sodium fluoride-induced hypertension. Indharty et al. (2020) reported that curcumin protects brain cells from apoptosis by increasing HSP70 expression in traumatic brain injury. Öztürk et al. (2023) reported that thymoquinone attenuates doxorubicin-induced lung injury via HSP 90. Glaessgen et al. (2008) stated that monitoring HSP27, HSP60 and HSP70 may be effective in the prognosis of prostate cancer. Dong et al. (2013) clarified that increased expression of HSP70 is closely related to the severity

of COPD and smoking status. Sharma et al. (2010) monitored the neuroprotective effect of Cerebrolysin in heat stress-induced brain damage through HSP27 expression. Karapınar et al. (2017) used HSP70 expression as an oxidation marker in sheep naturally infected with capripox. Dörtbudak et al. (2025) used HSP27 as an oxidative stress biomarker in diabetic gastropathy studies. Dörtbudak et al. (2025) used HSP27 as an oxidative stress biomarker in LPS-induced experimental sepsis studies. Dörtbudak et al. (2025) used HSP27 as an oxidative stress biomarker in 5-FU-induced various organ toxicities.

Conclusion

From the past to the present, diseases have negatively impacted living organisms' standard of living. Therefore, scientists dedicated to the welfare of living beings have focused on combating diseases and developing ways to prevent them. Cell damage is at the root of diseases, and clarifying the causes and subsequent events is essential to combating them. A series of studies have proven the crucial role of oxidation in cell deterioration. This phenomenon, also known as oxidative stress, is a cornerstone in understanding diseases and has become an option for their resolution. Therefore, oxidative stress, which has been the subject of considerable attention for some time, is indispensable in current studies and remains relevant. The importance of oxidative stress, as well as the biomarkers that enable its monitoring, are of interest to scientists. Because oxidative stress has a proven role in disease pathogenesis, its elimination is possible through manipulation. For these reasons, the presence and regulation of oxidative stress are achieved through biomarkers. To date, numerous oxidative stress biomarkers have guided research using various diagnostic methods. The scope of these biomarkers is currently being studied. Among these biomarkers, heat shock proteins have become a new trend in monitoring oxidative stress. Heat shock proteins, as indicators of oxidative stress-related damage in the cell, provide a significant advantage for studies conducted in this area. This review aims to illuminate the general properties and mechanisms of heat shock proteins, a biomarker that allows monitoring oxidative stress, which plays a role in the pathophysiology of many diseases, and to illuminate their place in current research.

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