A HOLISTIC APPROACH TO PHYSIOLOGY

FROM CELLULAR STRESS TO CARDIOVASCULAR ADAPTATION

Editor
ERSİN BEYAZCICEK

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A HOLISTIC APPROACH TO PHYSIOLOGY: FROM CELLULAR STRESS TO CARDIOVASCULAR ADAPTATION

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PREFACE

In today's scientific world, the boundaries of physiology are expanding from molecular mechanisms at the cellular level to the holistic evaluation of systemic responses at the organismal level. This book, titled 'A Holistic Approach to Physiology: From Cellular Stress to Cardiovascular Adaptation,' aims to address the multi-layered structure of physiological processes in the light of modern scientific knowledge.

The main motivation for the preparation of the book is to gain a deeper understanding of the effects of stress responses initiated at the cellular level on the overall health of the organism and to explain the role of these processes in the pathophysiology of diseases. Many topics, ranging from the molecular basis of cellular stress to mitochondrial dysfunctions, from oxidative damage to protein quality, and from inflammatory processes to cardiovascular adaptations, are comprehensively covered with the support of current scientific literature.

I would like to thank all authors and researchers who contributed to the creation of this book for their scientific rigour and devoted work. I would also like to express my sincere gratitude to Gözde Yücel, who contributed to the page layout and technical aspects of the book, and to BIDGE Publications for their assistance with the publication process.

In this era of continuous evolution of science, I hope that this book, which combines the basic principles of physiology with current research, will be a useful reference source for researchers, faculty members, graduate students, and professionals working in the field of medicine.

Assoc. Prof. Dr. Ersin BEYAZCICEK

Editor

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CELLULAR STRESS: MECHANISMS AND RESPONSES

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Introduction

Cellular stress refers to the effects of physical, chemical, and biological factors that disrupt the balance of fundamental biological processes in organisms, thereby affecting cellular functioning (Iqbal et al., 2024). These stressors can cause damage to basic biomolecules, such as deoxyribonucleic acid (DNA), proteins, and lipids, within the cell, leading to loss of function and potential cell death. The cellular stress response is a collection of molecular mechanisms initiated by the cell to defend and repair itself to survive these damages (Calakos & Caffall, 2024).

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Free radicals are chemical structures containing at least one unpaired electron in their outer orbit. Unpaired electron generally gives them high reactivity. The most common free radicals and reactive molecules in biological systems are derived from oxygen (reactive oxygen species, ROS) and nitrogen (reactive nitrogen species, RNS). ROS or RNS are formed during electron transfer reactions by losing or accepting electrons (Halliwell & Gutteridge, 2015). ROS are essential players in cellular proliferation, differentiation, migration, apoptosis, and necrosis. Low to moderate levels of ROS and RNS are necessary for maintaining various critical physiological functions, redox homeostasis, and regulating key transcription factors. In contrast, excessive ROS formation is responsible for disrupted redox homeostasis. This leads to oxidative stress and ROS-mediated damage to all essential biomolecules, including DNA, proteins, and membranes (Liguori et al., 2018).

Recent studies have revealed that the cellular stress response plays an important role not only as a survival mechanism but also in various disease processes (such as cancer, neurodegenerative diseases, and heart diseases) (Jomova et al., 2023). Therefore, a detailed understanding of the stress response process is crucial for the development of new approaches to treating and managing these diseases.

This section focuses on the biological foundations and molecular mechanisms of cellular stress, the functions of stress proteins, and the role of the stress response in disease processes.

2. Basic Concepts of Cellular Stress

2.1. Types of Stressors

Cellular stressors can be classified into three main categories according to their sources: physical, chemical, and biological stressors (Figure 1).

Physical stressors, such as heat, cold, and mechanical pressure, can cause deformation in cell membranes and internal structures, thereby disrupting cellular processes. For example, high temperatures can cause proteins to fold incorrectly, while mechanical stress can affect the cell skeleton(Rahmati, Silva, Reseland, A. Heyward, & Haugen, 2020).

Chemical stressors, including toxic chemicals, heavy metals, and reactive oxygen species (ROS), can damage biomolecules within the cell, leading to oxidative stress (Fichman, Rowland, Oliver, & Mittler, 2023; Gómez-González, Latorre, Arroyo, & Trepat, 2020).

Biological stressors, such as viruses, bacteria, and other pathogens, can cause the production of foreign proteins in cells and activate the immune system (Jurcau, 2021).

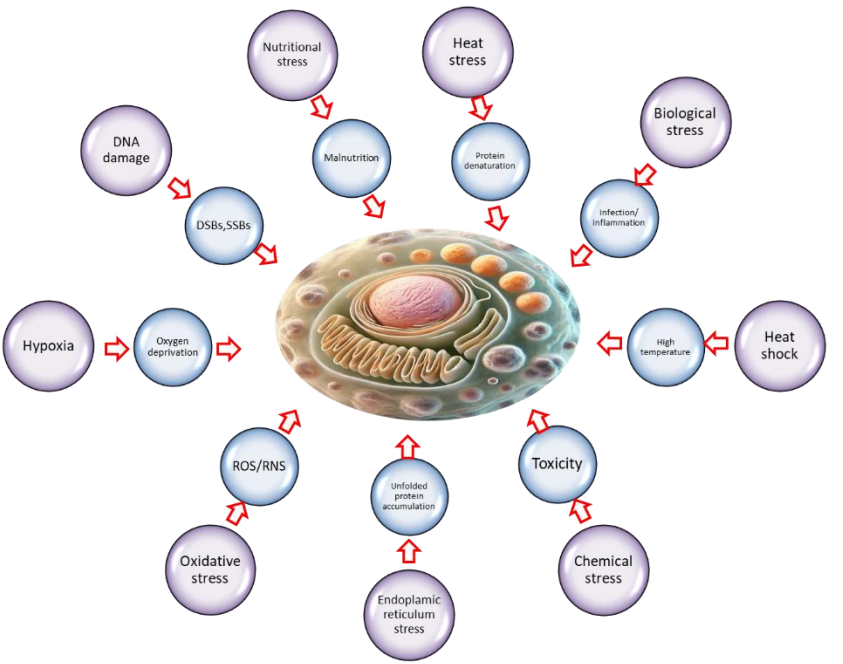


Figure 1. Schematic representation of the effects of various stress factors on cells.

2.2. Homeostasis and Signal Transduction Pathways

Cells must maintain homeostasis to respond effectively to stress. Homeostasis encompasses the biological processes necessary to maintain intracellular biochemical balance, and when exposed to stress, cells attempt to correct this situation using signaling pathways. For example, signaling pathways such as nuclear factor kappa B (NF-κB) and jun N-terminal kinase (JNK) are among the primary pathways that initiate the cellular stress response. Through these pathways, stress is detected, and the expression of specific genes is increased, leading to the production of protective proteins (Su et al., 2024).

Signal transduction pathways comprise a series of enzymes that activate or inhibit one another, amplifying and regulating signals. In the mitogen-activated protein kinase (MAPK) pathway, Raf (MAP kinase kinase kinase) activates MEK (MAPKK), which in turn activates ERK (MAPK). MAPKK, also known as mitogen-activated protein kinase kinase, activates MAPK by phosphorylating it. MAPKK regulates the MAPK signaling pathway by receiving signals from outside the cell. In this process, MAPKK receives signals from the MAPKKK enzyme and activates MAPK independently. Each step of activation can lead to the phosphorylation of multiple downstream proteins. In response to cellular stress, the p38 MAPK pathway is activated, leading to the increased expression of inflammatory response proteins, such as tumor necrosis factor α (TNF-α), and plays a role in the cell's response to stress and inflammation (Cuadrado & Nebreda, 2010).

3. Effects of Various Types of Stress

Cellular stress types cause different biochemical and physiological changes in cells. Physical, chemical, and biological stress types cause damage to cell structure and function. Each

triggers different signaling pathways that activate cells' survival, adaptation, and defense mechanisms.

3.1. Effects of Physical Stress

Physical stress occurs when external factors, such as high temperatures, mechanical damage, radiation, hypoxia (oxygen deficiency), or osmotic pressure, affect cells. High temperatures induce heat shock, causing cells to synthesize heat shock proteins (HSPs). HSPs prevent the denaturation of cellular proteins and protect proteins, thereby ensuring cell survival. Physical stress factors such as radiation cause DNA damage, triggering DNA repair mechanisms and increasing the risk of cancer. Cold stress can cause changes in the cellular membrane structure and lead to a decrease in metabolic rate, slowing down biochemical reactions (Singh, Shin, Ju, et al., 2024).

3.2 Effects of Chemical Stress

Chemical stress occurs when various chemical agents damage cells. Chemicals such as heavy metals, toxins, environmental pollutants, and reactive oxygen species (ROS) can cause oxidative damage to cellular structures, particularly to essential biomolecules like proteins, lipids, and DNA. Chemical stress leads to oxidative stress and inflammation, triggering the activation of antioxidant systems. Prolonged oxidative stress is associated with aging, cancer, and neurodegenerative diseases (Dossena & Marino, 2021).

3.3 Effects of Biological Stress

Biological stress is triggered by pathogens such as viruses, bacteria, and parasites, as well as inflammation, autoimmune responses, and internal biological processes that disrupt cellular functions. When pathogens attack cells, the immune system activates antimicrobial responses. Additionally, biological stress often triggers

the release of pro-inflammatory cytokines, which in turn activate inflammatory responses in cells and can lead to chronic inflammation (Dhabhar, 2024; Medzhitov, 2021). Pathogens such as viruses or bacteria can stimulate the immune system, leading to excessive cytokine production. This condition is known as a 'cytokine storm' and can result in uncontrolled inflammation, organ failure, and even death. Serious consequences of this condition have been observed during the COVID-19 pandemic (Amegashie et al., 2024). In summary, biological stress, particularly infections caused by pathogens such as viruses and bacteria, can cause significant damage at the cellular level. Excessive immune system reactions can lead to serious health issues such as autoimmune diseases and cancer. Therefore, early diagnosis and effective treatment of infections are crucial.

4. Molecular Mechanisms of Stress Response

The molecular mechanisms of stress response involve adaptive responses to stress conditions in cells. In this process, cells respond through various signal transduction pathways and regulatory molecules. These mechanisms are detailed below.

4.1. Signal Transduction Pathways

The cellular stress response is regulated through signal transduction pathways, which trigger cellular repair and protection processes. These processes occur through the MAPK pathway, the NF-κB pathway, and the phosphoinositide 3-kinase and serine/threonine kinase (PI3K/AKT) pathway.

Mitogen-activated protein kinase (MAPK) pathway: The MAPK pathway plays a central role in cellular growth, differentiation, and stress response. This pathway enables the detection of stress factors and the interaction of signals with the nucleus (Batt et al., 2024). It allows cells to respond to various

external stimuli (physical, chemical, and biological stress factors) and internal stress conditions. The MAPK pathway regulates essential cellular processes, including cell growth, differentiation, apoptosis, and inflammation. The MAPK pathway functions as a phosphorylation cascade that progresses through the sequential activation of different MAPK subtypes (Mordente, Ryder, & Bekker-Jensen, 2024). There are three main MAPK pathways (Figure 2). The first is the extracellular signal-regulated kinase (ERK1/2) pathway (Zurawska et al., 2024). Growth factors and mitogens typically activate the ERK1/2 pathway and promotes cell proliferation. Under cellular stress, ERK plays a crucial role in supporting survival and proliferation mechanisms.

The second is the p38 MAPK pathway. This pathway plays a specific role in the stress response and is typically activated by stress factors, including oxidative stress, cytokines, and UV radiation. p38 regulates inflammatory responses and triggers apoptotic mechanisms (Zurawska et al., 2024). The third is the c-Jun N-terminal kinase (JNK) pathway. This pathway is activated by various stress factors, particularly DNA damage and oxidative stress. JNK initiates a stress response that promotes apoptosis and inflammation and is associated with pathological conditions such as cancer and neurodegenerative diseases (Yan, He, Lv, Yang, & Yuan, 2024). These pathways activate transcription factors in response to cellular stress, regulating the expression of specific genes and thereby initiating cellular adaptation, repair, or apoptosis mechanisms. The MAPK pathway integrates different signaling pathways in response to cellular stress, initiating adaptive or damage-repair responses. Various stress signals, including oxidative stress, inflammatory cytokines, hypoxia, and DNA damage, activate the MAPK pathway, triggering cellular stress responses through this pathway. These responses often aim to alleviate the stress condition or regulate cell death. The ERK1/2 pathway protects cells under low-level stress,

ensuring cell survival and adaptation. The JNK and p38 MAPK pathways support apoptotic responses under high stress, facilitating the clearance of damaged cells. In particular, the p38 pathway regulates cytokine production, managing inflammatory responses and supporting immune system responses.

Nuclear factor kappa B (NF-kB) pathway: NF-kB is a transcription factor that becomes active, particularly in inflammatory stress conditions. This pathway activates protective responses in cells against stress-induced damage. The NF-κB signaling pathway is a crucial cellular signaling mechanism that plays a pivotal role in regulating various biological processes, including immune responses, inflammatory reactions, cell survival, proliferation, and differentiation (S. Wang, Liu, Wang, & Zhang, 2009). Acting as an immediate response mechanism, it can rapidly respond to a wide variety of external stimuli, including cytokines, pathogens, free radicals, and other stress signals. The NF-κB pathway can be activated by multiple signals, including TNF-α, interleukin 1 (IL-1), lipopolysaccharides (LPS), viral infections, and other stress conditions. When inactive, NF-κB binds to the inhibitory protein IκB in the cytoplasm. Upon activation by the aforementioned signals, the IκB kinase (IKK) complex is activated, resulting in the phosphorylation of IκB and its subsequent degradation through the ubiquitin-proteasome pathway. The degradation of IκB releases NF-κB, allowing it to translocate to the nucleus, bind to κB sites on DNA, and activate the transcription of specific genes (Moynagh, 2005). The termination of NF-κB signaling involves newly synthesized IκBα, which can enter the nucleus, bind to NF-κB, and return it to the cytoplasm, thereby inactivating NF-κB. Proper control of the NF-κB signaling pathway is crucial for maintaining normal cellular functions and preventing the development of disorders such as cancer, autoimmune diseases, and chronic inflammatory diseases (Karin, Cao, Greten, & Li, 2002). This

underscores its importance as a primary target for pharmaceutical interventions.

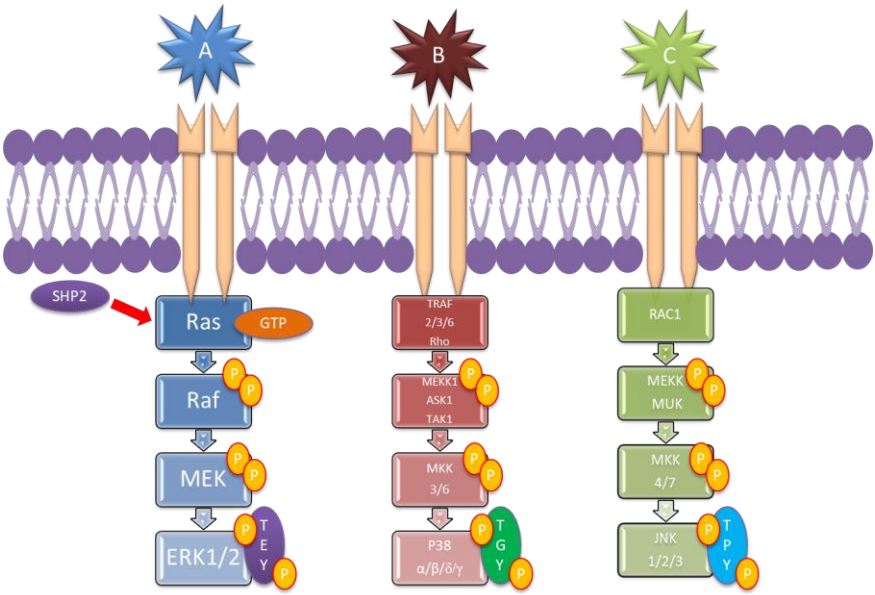


Figure.2. MAPK sinyal yollarının temsili gösterimi. (A) ERK1/2 yolu. (B) p38 α, β, δ ve γ yolakları. (C) JNK 1, 2 ve 3 yolakları (Soares-Silva, Diniz, Gomes, & Bahia, 2016).

Phosphoinositide 3-kinase (PI3K) and serine/threonine kinase (PI3K/AKT) pathway: The PI3K/AKT signaling pathway is a crucial signaling pathway that plays a pivotal role in cellular stress responses, regulating cell growth, survival, metabolism, and apoptosis (Iqbal et al., 2024). When cells are under stress, this pathway sends important signals to protect the cell, enable adaptation, or eliminate damaged cells. Activation of the PI3K/AKT pathway supports protective responses against various stress factors, including oxidative stress, DNA damage, and hypoxia. The PI3K/AKT pathway transmits signals through a phosphorylation cascade initiated by cell surface receptors (Figure 3). This pathway is primarily regulated by the phosphoinositide 3-kinase (PI3K) and

serine/threonine kinase (AKT) enzymes. When growth factor receptors on the cell membrane (e.g., IGF-1 or EGF) are activated, PI3K is activated, followed by AKT activation via phosphoinositide molecules. Activated AKT phosphorylates various target proteins within the cell and regulates different cellular functions. The PI3K/AKT pathway regulates cell growth and protein synthesis processes. AKT promotes cell growth by activating the mTOR (mammalian target of rapamycin) pathway. AKT inhibits apoptotic signals, thereby preventing the cell from dying. This mechanism contributes to the survival of cells under stress. The PI3K/AKT pathway regulates cellular glucose and energy metabolism (Bae, Hallis, & Kwak, 2024). In an energy-sensitive environment, this pathway activates metabolic pathways such as glycolysis. In cellular stress conditions, the PI3K/AKT pathway triggers DNA repair mechanisms to help repair cellular damage.

The PI3K/AKT pathway plays a crucial role in forming an important adaptation mechanism, particularly by supporting protective responses during cellular stress. This pathway prevents cell death by suppressing apoptotic signals, thereby increasing cell survival rates under stress. AKT reduces the formation of reactive oxygen species (ROS) in the cell by supporting antioxidant defence mechanisms. In the absence of energy, PI3K/AKT optimizes cellular metabolism to ensure cell survival. The PI3K/AKT pathway contributes to the control of cellular damage by regulating inflammation and cytokine signals (Shiau et al., 2022).

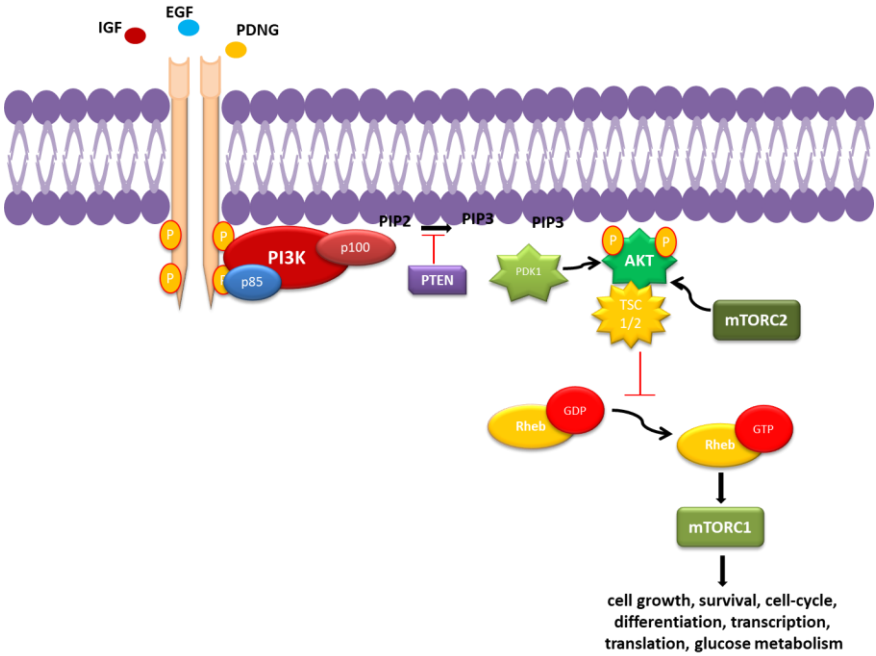


Figure 3. Representative representation of the PI3K/AKT pathway

4.2 The Role of Transcription Factors

Transcription factors (TFs) regulate gene expression under cellular stress, thereby managing processes such as adaptation, survival, repair, and death. These proteins initiate or suppress the transcription of target genes in response to various stress signals, thereby helping the cell adapt to stress factors (Fischer & Sammons, 2024). Different transcription factors play key roles in responding to specific types of stress (oxidative stress, hypoxia, thermal stress, etc.). The main transcription factors that become active under cellular stress are summarised below.

Nuclear factor erythroid 2-related factor 2 (Nrf2: Regulates the cell's antioxidant defense mechanisms under oxidative stress conditions (Figure 4). Nrf2 protects the cell against oxidative

damage by increasing the expression of antioxidant genes (Iqbal et al., 2024).

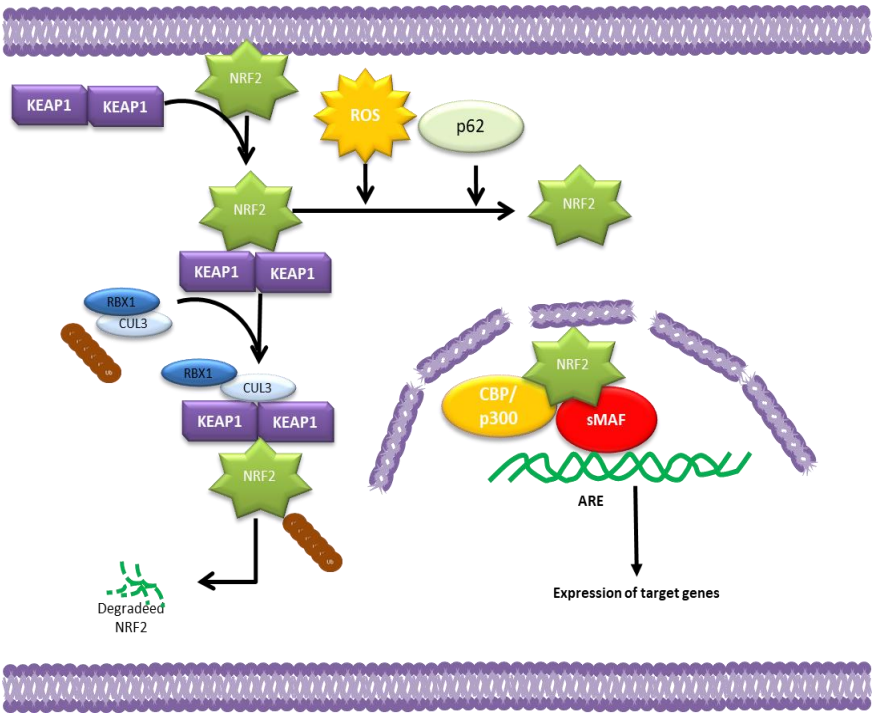


Figure 4. Schematic representation of transcription factor Nrf2 function (ARE: antioxidant response element) (Bae et al., 2024).

Hypoxia-inducible factor 1 (HIF-1): Activates under hypoxic conditions and regulates cellular adaptation in situations where oxygen levels are low (Figure 5). HIF-1 facilitates the transcription of genes that support energy metabolism and processes such as angiogenesis(Bae et al., 2024).

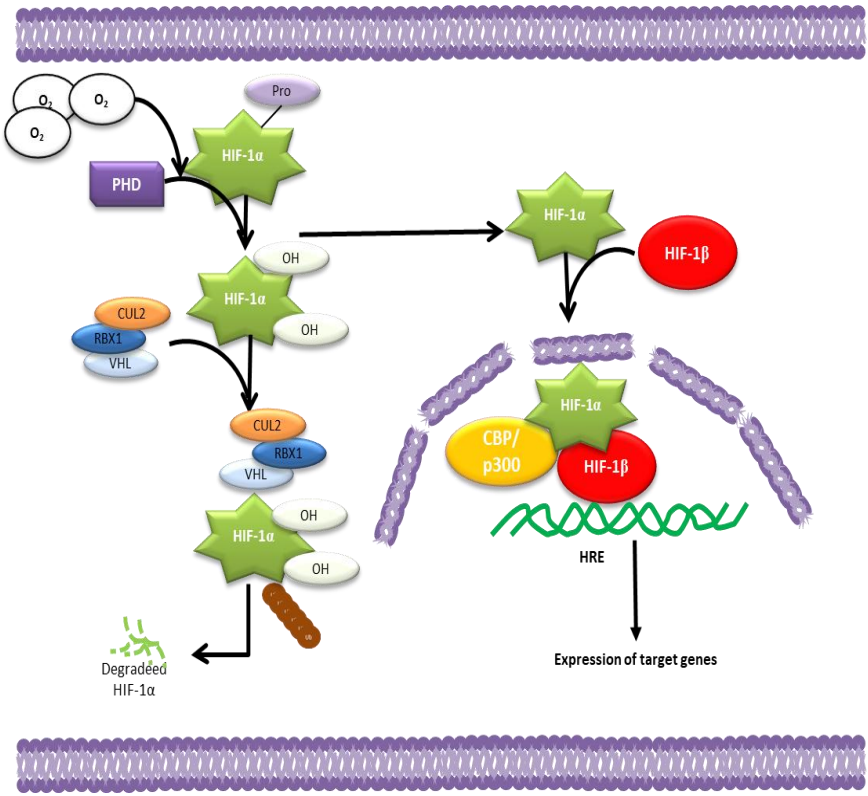
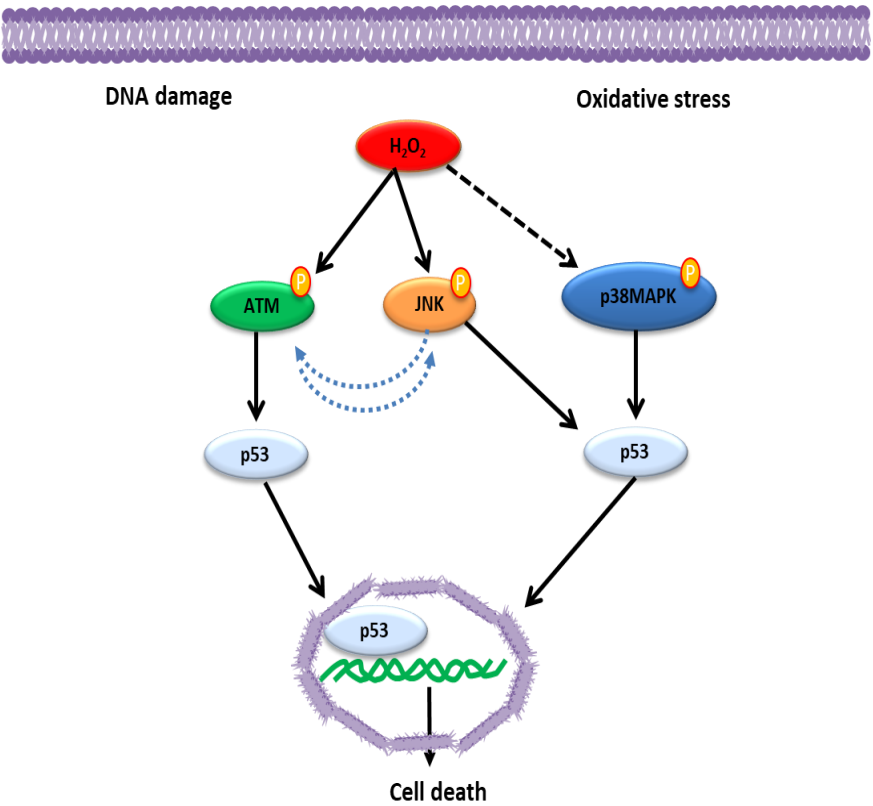


Figure 5. Schematic representation of HIF function (HRE: Hypoxia response element) (Bae et al., 2024).

p53: It activates in stressful situations such as DNA damage, stopping the cell cycle and initiating repair processes (Figure 6). When the damage cannot be repaired, it regulates cell death by initiating apoptosis (Fischer & Sammons, 2024).

Activator Protein 1 (AP-1): Activate under various stress signals (oxidative stress, UV radiation, inflammation) and control the expression of genes that regulate cell growth, differentiation, and apoptosis (Figure 7).



Figuer 6. Schematic representation of p53 function (Shi, van Soest, Polderman, Burgering, & Dansen, 2021).

In summary, transcription factors such as Nrf2 provide a protective response against oxidative stress by increasing the production of antioxidant enzymes. p53 and AP-1 respond to DNA damage and other serious cellular damage by arresting the cell cycle or initiating apoptosis. HIF-1 regulates cellular metabolism and angiogenesis under hypoxic conditions.

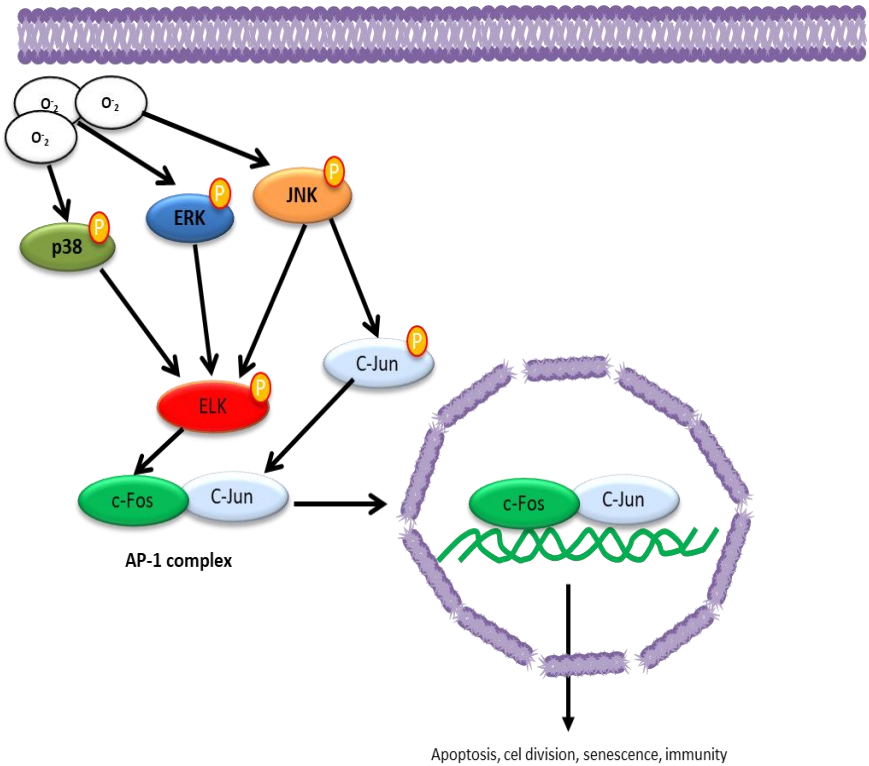


Figure 7. Representative demonstration of activation of the AP-1 transcription factor by oxidants (Averill-Bates, 2024).

4.3. Post-translational Modifications

Post-translational modifications (PTMs) enable cells to adapt to stress conditions by regulating the functions, stability, localization, and roles of proteins in cellular signaling processes (Sheng, Xia, Yang, & Hu, 2023; H. Zhou et al., 2024). These modifications occur after proteins are synthesized and enable cells to respond quickly to environmental changes. The main types of post-translational modifications (PTMs) that play a crucial role in cellular stress include phosphorylation, ubiquitination, acetylation, methylation, SUMOylation, and nitrosylation (Figure 8).

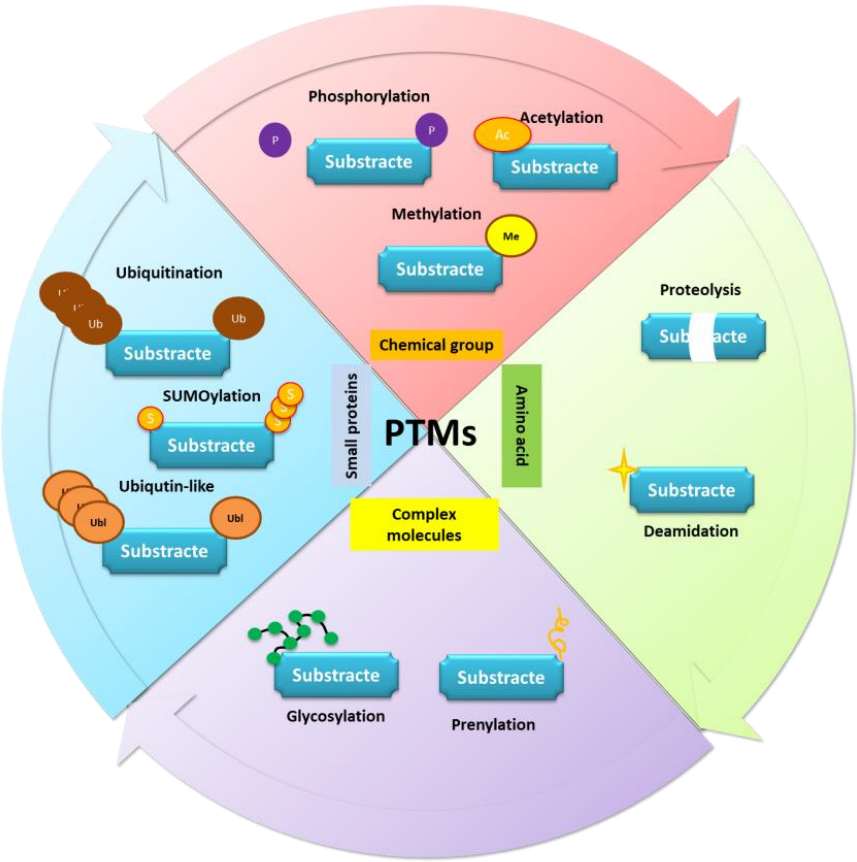


Figure 8. Post-translational modifications of proteins (Salas-Lloret & González-Prieto, 2022)

Phosphorylation: Protein phosphorylation provides a rapid signal transduction mechanism, particularly in the cellular stress response. Phosphorylation regulated by kinases modulates processes such as stress response and cell survival by altering protein activity (Yoo, 2024).

Ubiquitination: The addition of ubiquitin and ubiquitin-like proteins regulates protein degradation via the proteasome. The

degradation of damaged proteins in the cell is critical, especially in situations such as oxidative and thermal stress (Sheng et al., 2023).

Acetylation and Methylation: These modifications, which typically occur on histone proteins, regulate gene expression and help cells adapt to stress conditions (Sheng et al., 2023).

SUMOylation: The addition of a small ubiquitin-like modifier (SUMO) protein plays a role in protein nuclear transport, the cell cycle, and DNA repair. It typically protects against DNA damage during cellular stress (H. Zhou et al., 2024).

Nitrosylation: Nitrosylation, which occurs under oxidative stress conditions, affects the structure and function of proteins, helping the cell respond to reactive oxygen species (H. Zhou et al., 2024).

5. Stress Proteins and Their Functions

Stress proteins (SPs) are proteins that are synthesized at increased levels when cells are exposed to intracellular or extracellular stressors (Wan, Song, Li, & He, 2020). They exert protective effects against cellular stress. Stress proteins include heat shock proteins (HSPs) and RNA chaperone proteins (RNPs). These proteins primarily function in the ER (Hebert & Molinari, 2007). SPs trigger signaling cascades to neutralize and eliminate both intracellular (e.g., pathogen invasion) and extracellular (e.g., starvation, stimulation by cytokines, chemokines, or hormones) stressors (Wan et al., 2020). Responses triggered by SPs can activate pathways that support cell survival or, under certain conditions, initiate cell death (i.e., apoptosis, necrosis, pyroptosis, or autophagic cell death) to eliminate damaged cells and protect a specific organ or tissue. It is widely known that dysregulation of stress proteins is associated with various human diseases, including cardiovascular diseases, neurodegenerative diseases (e.g., Parkinson's disease,

Alzheimer's disease), stroke, human cancers, and infectious diseases (Baena-Lopez, Wang, & Wendler, 2024).

5.1. Chaperones

Chaperones are proteins that ensure the correct folding of proteins in cells, their functionalization, and the maintenance of proteostasis (protein homeostasis). These proteins protect the cell by preventing proteins from misfolding or forming aggregates under cellular stress conditions. Various types of chaperones, which can function either ATP-dependent or ATP-independent, contribute to maintaining cellular health, especially under stress conditions. Chaperones work to ensure that newly synthesized or denatured proteins achieve the appropriate three-dimensional structure. In this process, chaperones interact with temporary bonds that convert substrate proteins into misfolded forms and enable them to refold (Balchin, Hayer-Hartl, & Hartl, 2020). Most chaperones, especially ATP-dependent ones, facilitate protein folding by providing energy through ATP hydrolysis and become reusable. Among chaperone proteins are members of the HSP family (e.g., HSP70, HSP90, HSP60), which assist in maintaining proteostasis during stress responses and under normal physiological conditions (Balchin et al., 2020). Chaperones are highly activated under cellular stress conditions (e.g., heat shock, oxidative stress, hypoxia) and contribute to preventing protein aggregation, unfolding misfolded proteins, and maintaining proteostasis in collaboration with the proteasome system. During the stress response, chaperones target oxidized or damaged proteins, protecting the cell from potentially toxic effects. For example, chaperones such as HSP70 and HSP90 bind to proteins damaged by stress, refolding them or marking them for degradation by the proteasome (Assaye & Gizaw, 2022).

5.1.1. Heat Shock Proteins (HSP)

Italian scientist Ritossa discovered that raising the incubation temperature of Drosophila larvae resulted in increased gene transcription of certain unknown proteins. He named these proteins HSP (Ritossa, 1962). Studies have shown that there are many types of HSP (Wan et al., 2020). HSPs are classified into subclasses based on their molecular weight, including HSP100, HSP90, HSP70, HSP60, HSP40, and some small HSPs (15–40 kDa) (Carra et al., 2017; X. Wang, Chen, Zhou, & Zhang, 2014). HSP expression is rapidly induced when cells are exposed to starvation, hyperthermia, hypoxia or hyperoxia, pathogens, chemicals, or UV radiation (Figure 9). HSPs function to ensure proper protein folding and to repair or degrade denatured proteins. HSPs play a crucial role in regulating cell survival, differentiation, and cell death. Accumulating evidence suggests that some HSPs are involved not only in innate cellular immunity but also in antigen presentation during the adaptive immune response (Murshid, Gong, & Calderwood, 2012). HSPs also serve as potential biomarkers for certain diseases. Elevated HSP70 levels in plasma have been associated with heart failure, and high HSP27 levels in human peripheral blood mononuclear cells have been linked to coronary artery disease (CAD) (Timofeev, Kiselev, Dzhioeva, & Drapkina, 2023).

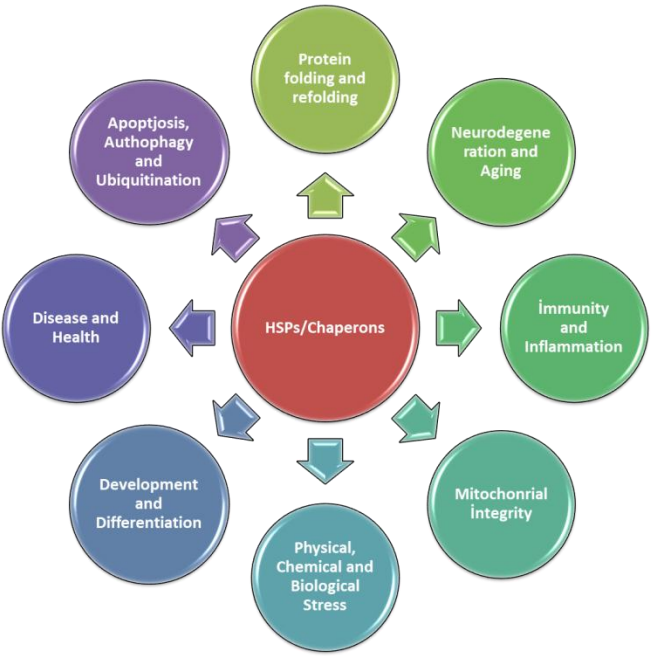


Figure 9: Representative illustration of HSPs and associated functions.

Small heat shock proteins (sHSPs): sHSPs are chaperone proteins weighing 15–40 kDa that play a crucial role in protein folding and the cellular stress response (Castelli et al., 2024). These proteins function through an ATP-independent mechanism, preventing protein aggregation under stress conditions and protecting cellular health. sHSPs play a critical role in the cellular stress response, with increased expression under conditions such as oxidative stress, heat shock, and inflammation. Small HSPs are notable for their low molecular weight and structurally possess an 'alpha-crystallin' region, which is a conserved region critical for protein-protein interactions (Carra et al., 2017). sHSPs are ATP-independent chaperone proteins that interact with proteins prone to denaturation under stress, stabilizing them (Figure 10). These proteins assist cells in targeting damaged or misfolded proteins for

degradation during the post-stress recovery process and maintain proteostasis (Dabbaghizadeh & Tanguay, 2020). Small HSPs increase their expression in response to environmental stress factors such as oxidative stress, hypoxia, and heat shock. These proteins protect the cell by binding to damaged proteins and preventing misfolded proteins from forming aggregates. sHSPs facilitate the refolding of proteins by larger chaperone proteins by causing the proteins they bind to dissolve (Vendredy, Adriaenssens, & Timmerman, 2020).

Additionally, sHSPs play a role in signal transduction pathways in the cellular stress response and are particularly involved in regulating the apoptosis process (Gu, Fan, & Yu, 2023). Small HSPs exhibit protective effects in stress-related conditions such as neurodegenerative diseases, cardiovascular disorders, and cancer (Gu et al., 2023). For example, sHSPs have been observed to provide protection against ischemia and reduce the effects of oxidative stress in the cardiovascular system (Timofeev et al., 2023). hey also help reduce protein aggregates and protect cell health in neurodegenerative diseases such as Alzheimer's and Parkinson's (Singh, Shin, Ju, et al., 2024).

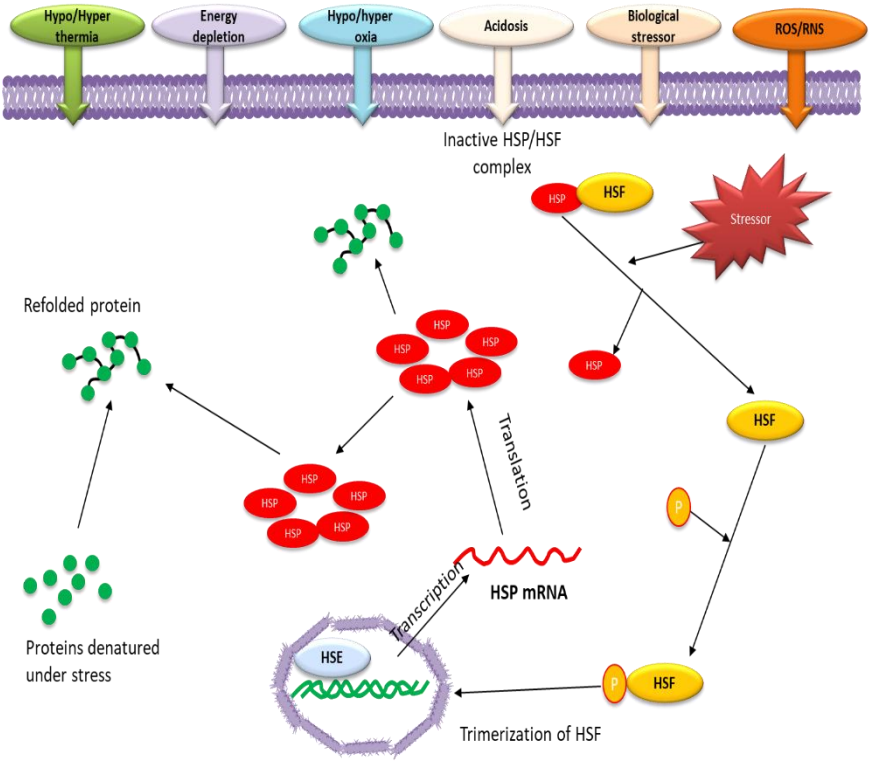


Figure 10. Molecular mechanism of heat shock protein (Rovelli et al., 2020).

Heat Shock Protein 60 (HSP60): HSP60 is a vital chaperone protein found in cells, particularly in the mitochondria, which regulates protein folding. HSP60 plays an important role in the cellular stress response, maintaining the stability of mitochondrial proteins, facilitating their folding, and contributing to the maintenance of cellular homeostasis. HSP60 functions as a chaperone protein located in the mitochondria and operates through an ATP-dependent mechanism. This protein ensures the proper folding of other proteins while refolding misfolded or damaged proteins, thereby contributing to the continuation of mitochondrial functions (Bahr, Katuri, Liang, & Bai, 2022). HSP60 becomes active as a regulatory protein in the mitochondrial stress response during

cellular stress conditions. It helps cells adapt to conditions such as oxidative stress, inflammation, and hypoxia (Singh, Shin, Han, et al., 2024). In cells exposed to mitochondrial stress, HSP60 levels increase, contributing to the repair of mitochondrial damage and the protection of functional proteins (Kumar et al., 2022). HSP60 also protects cells by influencing the regulation of cytokines during the inflammatory process and plays a role in the inflammatory response (Singh, Shin, Han, et al., 2024). The role of HSP60 in stress-related conditions such as neurodegenerative diseases, cardiovascular diseases, and cancer is being investigated (Bahr et al., 2022). For example, in Alzheimer's disease, HSP60 has been shown to help preserve mitochondrial function and reduce protein aggregates (Koszła & Sołek, 2024). In cancer cells, the overexpression of HSP60 supports the cellular stress response and contributes to the survival of tumor cells (Kumar et al., 2022).

Heat Shock Protein 70 (HSP70): HSP70 represents an important family of chaperone proteins produced in cells in response to stress. HSP70 proteins help cells survive and maintain their functions under stressful conditions. These proteins play a crucial role in tasks such as maintaining cellular homeostasis, facilitating proper protein folding, and preventing the formation of protein aggregates. The HSP70 family is a highly conserved group of proteins found in both the cytosol and organelle-specific compartments of eukaryotic cells. Various stress factors, such as heat, oxidative stress, infection, toxins, and UV radiation, increase HSP70 expression (Timofeev et al., 2023). HSP70 ensures the proper folding of proteins, refolds denatured proteins, and mediates protein degradation. HSP70 operates via an ATP-dependent mechanism; when ATP binds, it releases its substrate, and when ADP binds, it tightly binds the substrate, preventing its denaturation or aggregation (Castelli et al., 2024). HSP70 plays a crucial role, particularly under stressful cellular conditions. Proteins that are

misfolded or denatured under stress are stabilized by binding to HSP70 and are refolded (W. Wang, Liu, Liu, & Hendrickson, 2021).

Additionally, HSP70 proteins are involved in regulating cellular quality control mechanisms, such as the dissolution of protein aggregates and their degradation via autophagy (Mahto, Bhattacharya, & Bhattacharya, 2024). HSP70 has been shown to have protective effects against various stressors, including oxidative stress and inflammation. For example, under oxidative stress conditions, HSP70 protects the cell by supporting cellular antioxidant mechanisms and contributes to the repair of damage (Singh, Shin, Han, et al., 2024). Additionally, the protective role of HSP70 in conditions such as cancer, neurodegenerative diseases, and aging is being intensively studied. Especially in neurodegenerative diseases, it has been shown that HSP70 reduces cellular toxicity by accelerating the degradation of misfolded proteins (Rai, 2024).

Heat Shock Protein 90 (HSP90): HSP90 is a highly conserved chaperone protein family that performs critical functions in cells. HSP90 proteins play an important role in ensuring the proper folding, activation, and stability of proteins in cells. Especially under stress conditions, HSP90 expression increases, contributing to the maintenance of cellular homeostasis. The HSP90 family consists of conserved chaperone proteins found in the cytosol, endoplasmic reticulum, and mitochondria. HSP90 operates via an ATP-dependent mechanism and plays a key role in ensuring the proper folding, functionalization, and stability of co-bound proteins (Castelli et al., 2024). The functions of HSP90 are of critical importance for numerous co-factors, including kinases, transcription factors, and cell cycle regulatory proteins (Chiosis, Digwal, Trepel, & Neckers, 2023). Therefore, a decrease in HSP90 activity or functional impairment can lead to cellular stress and disease. HSP90 becomes active to prevent protein denaturation, regulate the degradation of misfolded proteins, and mitigate the effects of stress when cells are

under stress. In the cellular stress response, HSP90 protects against factors such as oxidative stress, inflammation, and DNA damage (Rai, 2024). HSP90 plays an important protective role in these processes by both directly regulating protein folding and modulating antioxidant and inflammatory signaling pathways (Chiosis et al., 2023). The function of HSP90 is being intensively studied, particularly in conditions such as cancer, neurodegenerative diseases, and cardiovascular diseases (Rai, 2024). In cancer cells, the overexpression of HSP90 enables cancer cells to survive under stress conditions, while in neurodegenerative diseases, HSP90 reduces cellular toxicity by preventing the accumulation of protein aggregates (Rai, 2024).

Heat Shock Protein 100 (HSP100): HSP100 is a member of the large heat shock protein family and has a molecular weight of approximately 100 kDa or greater. These proteins play an important role in protein disaggregation and refolding processes, particularly under conditions of intracellular stress (Koszła & Sołek, 2024). HSP100 proteins protect cells under stressful conditions by maintaining cellular homeostasis and regulating protein quality. HSP100 proteins are found in a wide range of organisms, from bacteria to eukaryotes, and play a critical role in maintaining cellular proteostasis. These proteins function in an ATP-dependent manner and facilitate the dissolution of protein complexes that require high energy consumption (Koszła & Sołek, 2024). Members of the HSP100 family typically contain an AAA+ (ATPase Associated with diverse cellular Activities) domain, which enables ATP hydrolysis and directs mechanical energy toward the dissolution of unfolded or misfolded proteins (Morey & Houry, 2024). HSP100 proteins dissolve misfolded or aggregated proteins, allowing other chaperones to refold them. HSP100 significantly contributes to the maintenance of protein homeostasis under cellular stress conditions (e.g., oxidative stress, heat shock, hypoxia). With their ability to

reverse protein aggregation, HSP100 proteins help proteins regain their functionality, thereby reducing cellular stress (Singh, Shin, Ju, et al., 2024). HSP100 proteins are also associated with aging, neurodegenerative diseases, and certain types of cancer. In neurodegenerative diseases, in particular, HSP100's function of dissolving protein aggregates supports long-term cellular functionality and preserves cellular health (Koszła & Sołek, 2024).

5.2. Proteasomes

Proteasomes are large protein complexes that play a critical role in cellular protein degradation and protein quality control. In particular, the 26S proteasome plays an important role in maintaining cellular proteostasis by degrading misfolded or damaged proteins within the cell. This process protects the cell from toxic protein accumulation caused by stress and helps regulate various cellular processes (Kandel, Jung, & Neal, 2024). Proteasomes are complex structures with proteolytic activity that facilitate the degradation of faulty or old proteins within the cell (Feng et al., 2024). The 26S proteasome is the best-known structure. The 26S proteasome consists of two main components: the 20S core proteasome complex and the 19S regulatory complex. The 20S core complex possesses proteolytic activity and breaks down target proteins into small peptides. The 19S regulatory complex recognizes ubiquitin-labeled proteins, unfolds them from their folded states, and directs them to the 20S core (Figure 11). These processes are ATP-dependent and facilitate the degradation of proteins within the proteasome (Mao, 2021).

Proteasomes function in a pathway known as the ubiquitin-proteasome system (UPS). Ubiquitin-labeled proteins are recognized by proteasomes and degraded, which is critical for maintaining cellular proteostasis. Proteasomes also play a role in the cell cycle, gene expression, and cellular response mechanisms (Feng et al.,

2024). Proteasomes play an important role in the stress response by clearing the increased load of damaged or misfolded proteins under cellular stress conditions. Stress factors such as heat shock, oxidative stress, and infection disrupt the protein balance within the cell, leading to the activation of proteasomes. Proteasomes protect the cell by breaking down toxic protein aggregates that accumulate during stress, thereby contributing to the maintenance of cellular homeostasis (Korovila et al., 2017). In particular, dysfunction of the proteasome system in neurodegenerative diseases can lead to the increased accumulation of toxic proteins within the cell, resulting in harmful effects such as cell death. Therefore, proteasomes are being investigated as potential therapeutic targets in many diseases, including Alzheimer's, Parkinson's, and Huntington's diseases (Abramovich, Kleczko, Masto, & Frydman, 2024; Fernández-Cruz & Reynaud, 2021; Höhn, Tramutola, & Cascella, 2020).

Proteasomes are critical for maintaining protein balance in cells, clearing misfolded or damaged proteins, and regulating cellular processes. Additionally, the most important proteasomes and their functions, which play a role in many important biological processes such as regulating cellular responses (e.g., cell cycle, apoptosis) and immune responses, are summarised below.

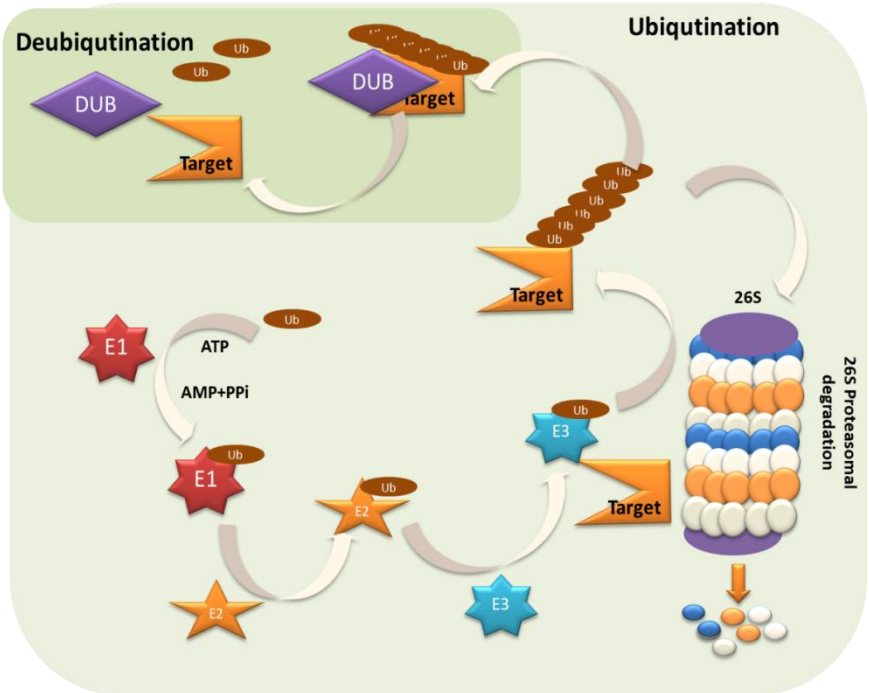


Figure 11. Protein proteasomal degradation via the ubiquitin-proteasome system (UPS) and the counteracting pathway by DUBs. UPS requires a series of processes involving the enzymes E1, E2 and E3. The result of ubiquitination is degradation of the target protein (DUB: Deubiquitinating enzymes; E1: Ubiquitin-activating enzyme; E2: Ubiquitin-conjugating enzyme; E3: Ubiquitin-protein ligase enzyme) (Choi & Baek, 2022)

26S Proteasome: Structure and Function: The 26S proteasome works with the 20S core protease complex and one or two 19S regulatory complexes through an ATP-dependent mechanism. It degrades ubiquitin-labeled proteins. Through this function, it maintains protein homeostasis by degrading misfolded and damaged proteins (Feng et al., 2024). Under cellular stress conditions, particularly oxidative or thermal stress, it rapidly degrades accumulated toxic proteins, thereby protecting the cell from potential damage caused by protein accumulation (Mao, 2021)

20S Proteasome: Structure and Function: The 20S proteasome forms the core structure of the 26S proteasome and consists of 28 subunits arranged in four rings. It can function without energy requirements and operates independently of ubiquitin. It targets and degrades proteins that are difficult to fold under conditions such as oxidative stress. Under oxidative stress, it supports cellular health by clearing damaged proteins that accumulate in the cell. By degrading proteins without requiring the ATP-dependent 26S proteasome system, it conserves energy and maintains proteostasis under stress conditions (Pepelnjak et al., 2024).

Immunoproteasome: The immunoproteasome functions as a special variant of the 20S proteasome and is activated by cytokine signals (e.g., IFN-γ). This proteasome is particularly involved in the antigen-processing process and functions as part of the immune system (Nie et al., 2024). When activated under immune system-stimulating conditions such as infection or inflammation, it provides the peptides necessary to fight pathogens. By appropriately degrading harmful proteins within the cell to support the immune response, it enhances the adaptive immune system (Inholz et al., 2024).

Thymoproteasome: Thymoproteasome is a subtype of immunoproteasome and is found only in the thymus organ. This structure plays a crucial role in the production of peptides specifically used in antigen presentation for T-cell development. By regulating antigen presentation during T-cell training in the thymus, it contributes to the immune system's development of self-tolerance. This function supports immune tolerance and helps prevent autoimmune reactions (Mishto, Takala, Bonfanti, & Liepe, 2024).

Proteasomes are large and complex structures that play an important role in the degradation and regulation of proteins in cells,

particularly by providing a specific and regulated mechanism for protein degradation. This mechanism is summarised below.

Start of the degradation process: In order for a protein to be recognised by the proteasome, it must first be 'labeled.' This is usually achieved by adding a small group of proteins called ubiquitin to the lysine residue of the protein. Ubiquitin acts as a marker, combining serine and lysine in its structure (Kandel et al., 2024).

Ubiquitination: Ubiquitin is added to the target protein using specific enzyme chains (E1, E2, E3 enzymes). This process is known as 'ubiquitination.' Proteins are labeled with ubiquitin molecules through the action of the E1 (activation), E2 (conjugation), and E3 (ligase) enzymes. E3 ligase enzymes select target proteins and label them with a ubiquitin chain—this process of ubiquitination chains the protein, preparing it for degradation (Kandel et al., 2024).

Proteasome Binding: The ubiquitin-labeled protein binds to the proteasome, where it is recognized. The proteasome consists of two main components: a central core (the 20S form) and surrounding regulatory complexes (the 19S form). The ubiquitin-labeled protein binds to the 19S regulatory complex (Pepelnjak et al., 2024).

Role of the Regulatory Complex: The 19S regulatory complex recognizes ubiquitin-labeled proteins, unfolds them through ATP hydrolysis, and facilitates the subsequent degradation process. This complex monitors whether proteins are of the appropriate size and whether they are ready for degradation (Pepelnjak et al., 2024).

Protein Degradation: The target protein is directed to the 20S core of the proteasome, where it is broken down into peptides. There are three proteolytic activities in the 20S core complex, which break down the protein into short peptides (Qiu, Chen, Li, & Zhuang, 2022).

Post-degradation: The short peptides formed after the degradation process are released for use in other cellular processes, converted into amino acids for use in cellular restructuring, or secreted outside the cell. This process is critically important for maintaining intracellular protein balance (Qiu et al., 2022).

Ubiquitin Recycling: During the degradation process, ubiquitin molecules are recycled and reused during protein degradation. This recycling ensures the continuity of the ubiquitin pool within the cell and maintains the proteasome system's efficiency (Thomas, Salcedo-Tacuma, & Smith, 2023).

5.3. Autophagy Proteins

Autophagy is a process in which the cell recycles its own damaged organelles, misfolded proteins, and various cellular waste products by breaking them down through lysosomal activity. Autophagy proteins involved in this process play various roles from the initiation of the autophagic pathway to lysosomal degradation (Figure 12). The structural properties and functions of autophagy proteins are crucial for maintaining cellular health, particularly under stress conditions.

Autophagy-Related (ATG) proteins: ATG proteins are essential for initiating the autophagy process and forming autophagosomes. The ATG1/ULK1 complex activates the signaling pathways that initiate autophagy, and the ATG8 protein family facilitates the expansion of the autophagosome membrane. The ATG12-ATG5-ATG16L1 complex regulates the closure of the autophagosome and the targeting of target proteins to the closed membrane. Under cellular stress conditions, ATG proteins protect cell health by accelerating the autophagic degradation of accumulated toxic proteins and damaged organelles. In particular, they initiate autophagy processes under conditions of oxidative

stress and nutrient deprivation to maintain intracellular homeostasis (Nishimura & Tooze, 2020).

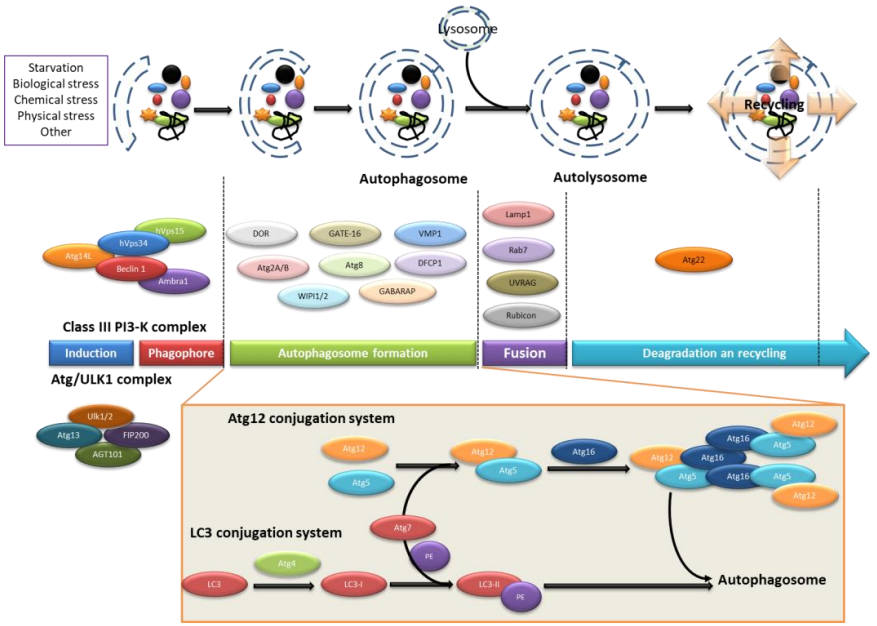


Figure 12. Function and mechanisms of autophagy (Y. Li, Liu, Wu, & Li, 2020; Neutel, Hendrickx, Martinet, De Meyer, & Guns, 2020).

Microtubule-associated protein 1A/1B-light chain 3 (LC3): LC3 is an important protein involved in the formation of the autophagosome membrane. The LC3-I form binds to lipids during the autophagy process, converting to the LC3-II form and attaching to the autophagosome membrane. This conversion is an important step in the formation and expansion of autophagic structures. LC3-II is used as a biomarker for evaluating autophagy flow and accelerates autophagy under cellular stress conditions to clear toxic proteins. By protecting the cell against oxidative and nutritional stress, it plays a crucial role in aging and disease processes (Yu & Klionsky, 2022).

Beclin-1: Beclin-1 is one of the key proteins that initiates the formation of autophagic structures and is part of the PI3K class III complex. This complex plays an important role in the nucleation of the autophagic membrane. Beclin-1 acts as a central protein in the regulation of the autophagy process. Beclin-1 triggers autophagy, particularly under conditions such as oxidative stress and nutrient deprivation, thereby protecting cell health. Through its interaction with the anti-apoptotic Bcl-2 protein, it regulates the balance between autophagy and apoptosis (Kaur & Changotra, 2020; Tran et al., 2024).

p62/SQSTM1: p62 is an important adaptor protein in autophagy processes and directs ubiquitin-labeled proteins into the autophagosome. During autophagy, p62 interacts with LC3-II to incorporate labeled proteins into the autophagosome. It protects cell health by facilitating the degradation of misfolded proteins and damaged organelles that accumulate under stress conditions. Especially under oxidative stress, autophagy mediated by p62 prevents the accumulation of toxic proteins in the cell (Chen et al., 2020; Lin et al., 2023).

Mammalian Target of Rapamycin (mTOR): mTOR is a central kinase that regulates cellular growth and autophagy processes. It suppresses autophagy processes depending on the availability of nutrients; however, under stress conditions, mTOR inactivation triggers autophagy. With this regulatory role, it controls the initiation of autophagy processes (Saxton & Sabatini, 2017). Under cellular stress conditions (e.g., nutrient deprivation or oxidative stress), mTOR is inhibited, activating autophagy. This allows the cell to conserve energy and increase its chances of survival (Ballesteros-Álvarez & Andersen, 2021).

6. Endoplasmic Reticulum Stress and Unfolded Protein Response (UPR)

Endoplasmic reticulum (ER) stress is a type of cellular stress caused by the accumulation of proteins that are not properly folded or are misfolded within the cell. This condition can lead to the disruption of intracellular balance and toxic effects that may contribute to various diseases. In response to ER stress, the cell initiates a defense mechanism called the Unfolded Protein Response (UPR). The UPR is a signaling pathway that activates various pathways to reduce the protein load in the ER and restore cellular homeostasis (Hetz & Papa, 2018).

6.1 Sources of ER Stress

Many factors contribute to the onset of ER stress (Hetz, Zhang, & Kaufman, 2020; Ron & Walter, 2007; M. Wang & Kaufman, 2016):

- **Protein Folding Defects:** Incorrect folding of proteins usually occurs as a result of genetic mutations, misfolding, or environmental factors. Unfolded proteins accumulate in the ER, creating a stressful situation.
- **Calcium Deficiency:** The ER plays a role in cellular calcium storage and regulation. A decrease in calcium levels can disrupt ER function and trigger a stress response. Calcium is essential for protein folding and maintaining cellular functions.
- **Inflammatory Cytokines:** Cytokines such as IL-6 and TNF-alpha can trigger inflammatory conditions that cause ER stress. These cytokines can negatively affect cellular functions, thereby increasing ER stress.

- **Metabolic Changes**: Disorders in sugar and lipid metabolism can lead to increased ER stress. Conditions such as obesity and diabetes, in particular, can affect ER function and lead to such stress conditions.
- **Chemical and Physical Stresses**: Physical stress factors such as alcohol consumption, exposure to toxic substances, or temperature changes can affect the normal function of the ER and trigger a stress response.

6.2 UPR Mechanism

The basic UPR pathways in mammals, first discovered in yeast, consist of the main signaling cascades IRE1α, PERK, and ATF6α3, which are initiated by ER transmembrane protein sensors. These signal-transducing proteins contain ER luminal domains that detect misfolded protein peptides and cytosolic domains that interact with signaling molecules as scaffolds to protect cells from ER stress under physiological conditions via translational or transcriptional apparatus (Hetz et al., 2020).

- **PERK Pathway (Protein Kinase RNA-like Endoplasmic Reticulum Kinase)**: PERK detects ER stress and phosphorylates the eIF2α (eukaryotic translation initiation factor 2 alpha) protein. This phosphorylation helps cells conserve energy and resources under stressful conditions by reducing overall protein synthesis. As a result, the production of specialized mRNA for the synthesis of folded proteins is increased (Ron & Walter, 2007).
- **IRE1 Pathway (Inositol-Requiring Enzyme 1)**: IRE1 detects the presence of unfolded proteins in the ER. IRE1 triggers the UPR by processing mRNAs and activating the transcription factor XBP1 (X-box binding protein 1).

Activated XBP1 increases the expression of UPR genes, thereby enhancing protein folding capacity (Hetz & Papa, 2018).

- **ATF6 Pathway (Activating Transcription Factor 6)**: ATF6 detects ER stress and migrates from the ER membrane into the nucleus. In the nucleus, ATF6 promotes cellular adaptation processes by increasing the expression of target genes. These genes are involved in managing ER stress and improving the protein folding process (Hetz et al., 2020).

6.3. The Role of UPR in Cellular Stress

UPR functions as an adaptive response mechanism to reduce cellular stress. However, if ER stress persists for an extended period and at high intensity, UPR can activate apoptotic pathways, leading to cell death. This dual effect demonstrates that the UPR has both a survival function and, when necessary, a cell elimination function (Figure 13). This response mechanism is associated with many diseases, including diabetes, neurodegenerative diseases, cancer, and cardiovascular diseases (M. Wang & Kaufman, 2016).

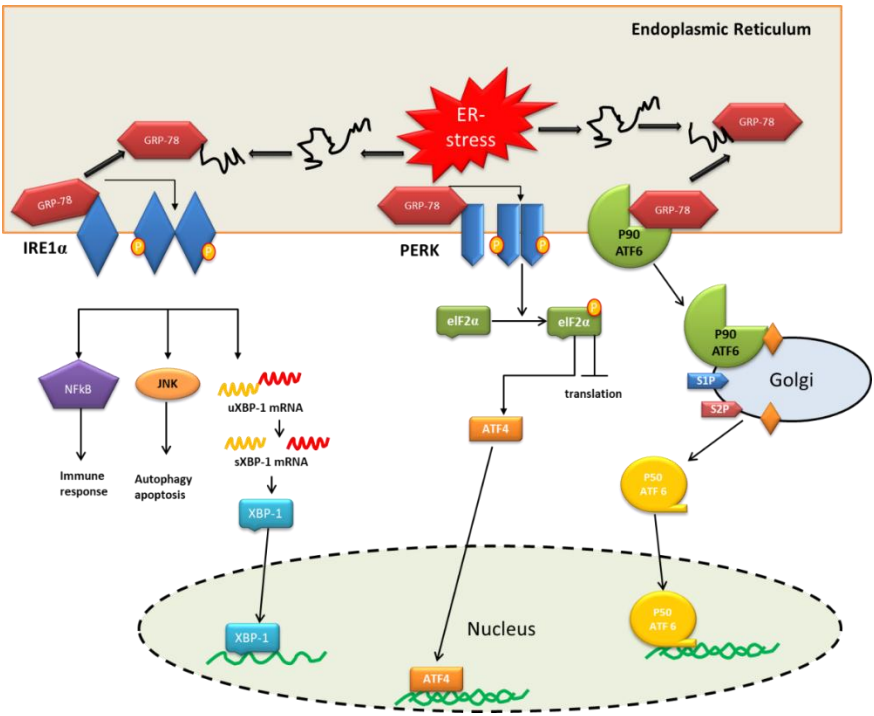


Figure 13. Three major pathways recognize ER stress and induce the unfolded protein response through activation of the transcription factors XBP-1, ATF4, and ATF6 (Lukas et al., 2019).

7. Mitochondrial Stress and Oxidative Stress

Mitochondrial stress and oxidative stress are related to mitochondria and ROS, which are fundamental components of cellular metabolism. These types of stress contribute to the disruption of cellular balance and the development of various diseases. Mitochondrial stress arises from mitochondrial dysfunction, while oxidative stress occurs when ROS production exceeds cellular antioxidant defenses. Both types of stress are associated with aging, cancer, neurodegenerative diseases, and metabolic disorders (Figure 14).

Mitochondrial stress is characterized by the disruption of cellular processes, including energy production, calcium balance, reactive oxygen species (ROS) production, and mitochondrial apoptosis. This condition may be caused by factors such as mitochondrial DNA mutations, decreased protein quality, energy metabolism disorders, and calcium irregularities. The cell detects mitochondrial stress and activates mechanisms to maintain mitochondrial quality and eliminate damaged mitochondria. The cellular response to mitochondrial stress encompasses processes such as mitochondrial fusion and fission, mitophagy, and the mitochondrial unfolded protein response (UPRmt), all of which work together to maintain mitochondrial quality. In particular, UPRmt increases the production of proteins necessary for the proper functioning of mitochondria under stress (Shpilka & Haynes, 2018).

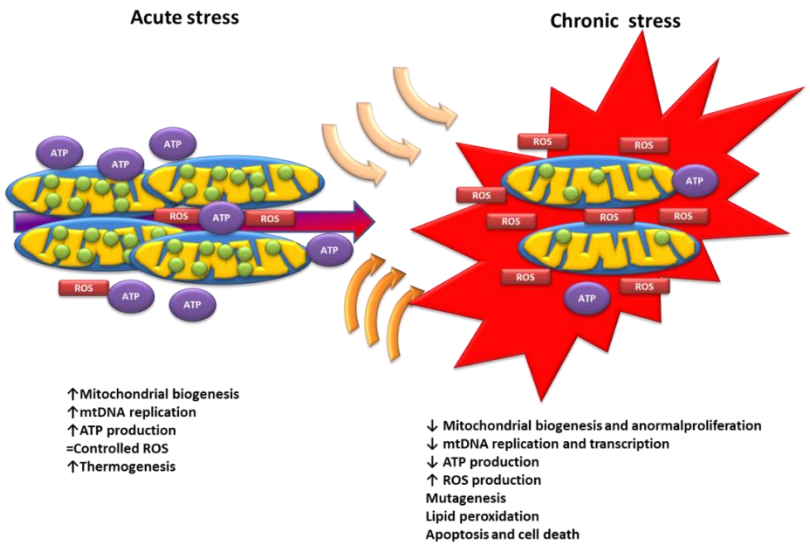


Figure 14. Mitochondrial stress response under acute or chronic stress (Manoli et al., 2007).

Oxidative stress occurs when excessive amounts of reactive oxygen species (ROS) are generated inside the cell, leading to

damage to cellular biomolecules, including DNA, proteins, and lipids. ROS occurs as a by-product of normal metabolic processes, but this production can be increased by various factors (environmental toxins, radiation, inflammation, etc.). Oxidative stress develops when the cell's antioxidant defense mechanisms are inadequate, leading to oxidative modifications of proteins, DNA damage, and lipid peroxidation. The cell activates enzymatic defense mechanisms, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, as well as antioxidant molecules like glutathione, to cope with oxidative stress (Sies, Berndt, & Jones, 2017).

Mitochondrial stress and oxidative stress trigger adaptive and apoptotic processes in the cell and function to maintain cellular balance or eliminate the cell when necessary. Especially in prolonged stress situations, mitochondrial dysfunction and excessive accumulation of reactive oxygen species (ROS) can lead to cell death by activating the cellular apoptosis pathway. Effective control of these stressors is critical in slowing down aging and disease processes. Interactions, such as mitochondrial stress leading to oxidative stress or oxidative stress exacerbating mitochondrial dysfunction, can increase cellular stress (Pickles, Vigié, & Youle, 2018).

7.1. Mitochondrial Dysfunction and Stress Response

Mitochondrial stress is often associated with excessive ROS production. ROS are by-products formed during normal metabolic processes of cells. Mitochondrial dysfunction causes excessive accumulation of these ROS and can lead to the following consequences (Pickles et al., 2018; Shpilka & Haynes, 2018; Sies et al., 2017):

Mitochondrial dysfunction leads to decreased energy production, resulting in reduced ATP (adenosine triphosphate)

production. Lack of energy leads to impairment of cellular functions and initiation of cell death processes.

Increased oxidative stress: Excessive ROS production can cause cellular damage, including lipid peroxidation, DNA damage, and protein oxidation. Oxidative stress can lead to impaired cellular functions and various diseases.

7.2. Effects of Oxidative Stress

Oxidative stress leads to various damages in cellular components (Pickles et al., 2018; Shpilka & Haynes, 2018; Sies et al., 2017):

- **Lipid peroxidation**: oxidative stress causes oxidation of lipids in the cell membrane. This can affect cellular functions by disrupting the integrity of the membrane.
- **DNA damage**: oxidative stress can cause mutations and damage to DNA. Such damage can predispose to the development of genetic diseases such as cancer.
- **Protein oxidation**: oxidation of proteins disrupts their structure and function. Oxidized proteins can lead to impaired cellular function and loss of proteostasis (protein balance).

7.3 Mechanisms of the Mitochondrial Stress Response

The mitochondrial stress response involves adaptive mechanisms that cells implement in response to mitochondrial dysfunction. These response mechanisms aim to regulate protein folding, energy production, and oxidative stress, enabling mitochondria to maintain their function. In particular, processes such as UPRmt, mitophagy, mitochondrial fusion and fission, and the control of ROS (reactive oxygen species) are involved in the mitochondrial stress response (Figure 15).

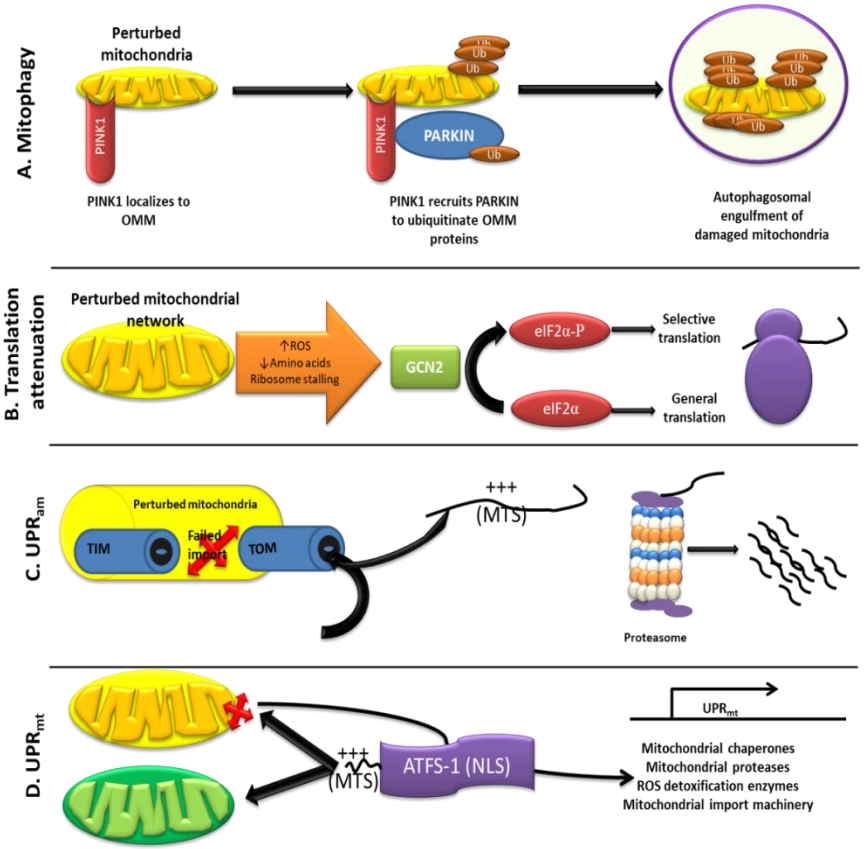


Figure 15. Mitochondrial stress response pathways. (A) Mitophagy; stabilization of PINK1 kinase in damaged mitochondria, activation of ubiquitin ligase Parkin and autophagosome (B) Activation of kinase GCN2 in mitochondrial dysfunction, phosphorylating eIF2α and reducing mitochondrial dysfunction. (C) UPR increase in the cytosol and stimulation of proteasome activity by UPRam. (D) UPRmt regulation by competing organelle targeting sequences in the transcription factor ATFS-1 (Melber & Haynes, 2018).

The mitochondrial unfolded protein response (UPRmt) is a cellular response mechanism against the accumulation of unfolded or damaged proteins in mitochondria. UPRmt ensures that these proteins are folded adequately through the action of chaperones. In

this process, mitochondrial protein homeostasis is maintained by activating transcription factors such as ATF5. This response supports the functionality of mitochondria by preserving the quality of mitochondrial proteins (Torres, Fleischhart, & Inestrosa, 2024).

Mitophagy is the destruction of damaged mitochondria through autophagy. PINK1 and Parkin proteins accumulate on the surface of mitochondria, enabling the recognition of damaged mitochondria and trigger the degradation of these organelles in the lysosome. Mitophagy maintains mitochondrial quality and increases cellular energy efficiency (Pickles et al., 2018).

Mitochondrial fusion and fission allow mitochondria to fuse and fission with each other to maintain their integrity and functionality. This process enables damaged mitochondria to fuse with healthy ones, thereby stabilizing the distribution of mitochondrial DNA. Dynamin-related protein 1 (Drp1) and mitofusins (Mfn1, Mfn2) play critical roles in this process (Preminger & Schuldiner, 2024).

ROS control and antioxidant defense mechanisms: Mitochondria produce ROS as a by-product of cellular respiration. In case of increased ROS production, the cell activates antioxidant defense systems (SOD, catalase, glutathione peroxidase, etc.). These defense mechanisms help protect the integrity of the mitochondrial membrane (Yamashita et al., 2024).

Regulation of energy metabolism: Mitochondria are the main source of ATP production, and energy metabolism is reorganized under mitochondrial stress. Energy sensors such as AMPK (AMP-activated protein kinase) maintain cellular energy balance by suppressing protein synthesis to reduce energy expenditure in mitochondrial stress states (Huang et al., 2024).

8. Regulation of Stress Response and Homeostasis

Regulation of the stress response and homeostasis is related to the ability of cells to maintain equilibrium in the face of environmental and cellular stresses. Under stress, cells attempt to maintain homeostasis through mechanisms such as rerouting energy sources, protein folding, and eliminating damaged organelles. Various regulatory mechanisms, including signaling pathways, chaperones, autophagy, and antioxidant mechanisms, are involved in these processes. Effective regulation of the stress response is critical for cell health and longevity.

8.1. Positive and Negative Feedback Loops

Positive and negative feedback loops are mechanisms that play important roles in regulating cellular stress responses. These loops maintain homeostasis by optimizing the ability of cells to sense stress signals and adjust their responses accordingly. With positive feedback loops, the cell can accelerate or amplify a response, while with negative feedback loops, it limits the response and prevents overreactions. In stressed cells, these feedback loops regulate processes such as protein folding, ROS production, and antioxidant defense.

Positive feedback is a cycle in which the product of a biological process reinforces itself, making it stronger. Under conditions of cellular stress, positive feedback accelerates the cellular response and enhances the effect of a specific signal. The accumulation of reactive oxygen species (ROS) in mitochondria is an important indicator of cellular stress. ROS can trigger the production of more ROS through positive feedback. This leads to an increased oxidative stress response in the cell and may eventually lead to cellular damage (Schieber & Chandel, 2014). During inflammation, the production of inflammatory cytokines (e.g., TNF-α) further triggers its own production, strengthening the

inflammatory response through positive feedback. Although this process is effective against infection under acute stress, it can cause tissue damage if it becomes chronic (Medzhitov, 2021). In cells under stress, the production of HSPs increases, which promotes protein folding. HSPs promote the production of other HSPs by reinforcing the stress response through positive feedback. Thus, the cell can maintain protein homeostasis more effectively (Reinle, Mogk, & Bukau, 2022).

Negative feedback is when the products of the process stop or slow down that process. In the cellular stress response, negative feedback prevents the stress response from becoming excessive and maintains homeostasis. These loops are critical for maintaining cellular balance. Cells produce antioxidant enzymes (e.g., glutathione peroxidase and superoxide dismutase) to reduce ROS levels. These antioxidants limit the oxidative stress response through negative feedback by reducing ROS levels. This process prevents ROS from causing cellular damage and protects cell health (Sies & Jones, 2020). p53 protein plays an important role in responding to cellular stresses such as DNA damage. p53 arrests the cell cycle or initiates apoptosis under stressful conditions. However, there is also the protein Mdm2, which limits p53 activity through negative feedback. This feedback loop prevents over-activation of p53, preventing healthy cells from entering apoptosis (Levine, 2020). In ER stress, the unfolded protein response (UPR) is activated. The UPR initially improves protein folding but limits the response to excess protein folding through negative feedback. UPR components such as IRE1 help maintain protein homeostasis in the cell by limiting the response under extreme stress conditions (Hetz & Saxena, 2017).

8.2. Epigenetic Regulation

Epigenetic regulation is of great importance in cellular stress response as a mechanism that controls gene expression without altering the DNA sequence. The impact of stress on epigenetic regulation often involves regulatory elements such as DNA methylation, histone modifications, and miRNAs. By increasing or decreasing the expression of genes that control the stress response, these mechanisms prepare the cell to adapt to stress and enable long-term cellular responses.

DNA methylation is a type of chemical modification that usually occurs at CpG sites and often represses gene expression. DNA methylation profiles can change under cellular stress. Decreased methylation in the promoter regions of stress-related genes activates these genes and accelerates the stress response (McCaw, Stevenson, & Lancaster, 2020). Chemical modifications of histone proteins (such as acetylation, methylation, and phosphorylation) control gene expression by loosening or tightening the chromatin structure. Under stress conditions, histone modifications ensure that genes involved in the stress response are easily expressed. Increased histone acetylation causes chromatin to become more open and related genes to become more active (N. Wang, Hu, & Wang, 2024).

MicroRNAs (miRNAs) target mRNAs, causing their degradation or repression of translation. During cellular stress, the expression of certain miRNAs is altered, and these miRNAs control the expression of stress-related genes. Increased expression of miR-21 under oxidative stress protects the cell by suppressing the expression of pro-inflammatory genes (Yi, 2024).

Under cellular stress, epigenetic mechanisms enhance the cell's adaptive ability by re-regulating the expression of stress-related genes. While these changes temporarily regulate gene

expression in the short term, in the long term they form epigenetic memory and make the cell more resistant to subsequent stress conditions (Rossnerova et al., 2020). Oxidative stress causes various modifications in DNA and histone proteins, which increases the expression of genes that typically stimulate antioxidant responses. Epigenetic activation of antioxidant enzymes such as SOD and catalase protects the cell against oxidative damage (Adam et al., 2024).

Stress signals such as inflammatory cytokines regulate the expression of inflammation-related genes through epigenetic changes. This may lead to the persistence of epigenetic changes in chronic inflammation, which may increase the persistence of inflammation and cause tissue damage (Klimczak & Śliwińska, 2024).

Under metabolic stress conditions, epigenetic regulation targets genes regulating energy metabolism. DNA methylation and histone modifications in genes related to energy metabolism are adjusted according to the energy needs of the cell and allow cells to maintain energy balance under stress (Rath, Hawsawi, Alzahrani, & Khan, 2024).

9. Relationship of Cellular Stress Response to Diseases

Cellular stress plays an important role in the pathogenesis of many diseases. The cellular stress response is closely associated with conditions that cause or exacerbate diseases. This response mechanism protects cells from harmful external stimuli, but in situations of prolonged or extreme stress, these defense pathways can become inadequate and lead to cell damage, contributing to disease development. Inadequacy or misdirection of the cellular stress response underlies a variety of chronic diseases, such as cardiovascular disease, cancer, neurodegenerative diseases, diabetes, and autoimmune diseases.

9.1. The Role of Cellular Stress in Cancer Diseases

Cellular stress has an important role in cancer development. Oxidative stress contributes to cancer formation by causing DNA damage (Bae et al., 2024; Dhabhar, 2024; Feng et al., 2024; Iqbal et al., 2024; Mahto et al., 2024; Yi, 2024; H. Zhou et al., 2024). Cellular stress factors such as protein misfolding, mitochondrial dysfunction, and inflammation lead to disruption of intracellular homeostasis and the creation of a microenvironment that promotes tumor development. Cancer cells adapt to these stressors, facilitating their survival and proliferation.

The accumulation of free radicals (ROS) leads to DNA and protein damage at the cellular level. This damage leads to genetic instability, one of the fundamental mechanisms of cancer. When DNA repair mechanisms fail due to oxidative stress, mutations accumulate, and the formation of cancer cells becomes easier (D. Li et al., 2024). Similarly, the misfolding of proteins in ER stress leads to the accumulation of toxic aggregates inside the cell. This activates the UPR (unfolded protein response) mechanism as an adaptive response in cancer cells (Koszła & Sołek, 2024; Torres et al., 2024). UPR activation helps cancer cells meet increased protein synthesis requirements and survive under stress (Kandel et al., 2024).

Cancer cells reprogram their metabolism to meet their energy needs under mitochondrial stress (Preminger & Schuldiner, 2024; Torres et al., 2024; Yamashita et al., 2024). This adaptation, known as the Warburg effect, enables cancer cells to become glycolysis-dependent and proliferate rapidly by increasing anaerobic respiration (Barba, Carrillo-Bosch, & Seoane, 2024). At the same time, cellular stress factors promote the development of cancer in the tumor microenvironment by triggering the inflammation process. Cancer cells utilize inflammatory signals to evade the immune system and establish a self-protective microenvironment. In these stressful

conditions, cancer cells develop resistance by inhibiting autophagy and apoptosis to survive. Autophagy, in particular, allows cancer cells to survive under stress and adapt to conditions such as nutrient scarcity (Dhabhar, 2024; Iqbal et al., 2024; D. Li et al., 2024).

9.2. The Role of Cellular Stress in Neurodegenerative Diseases

Cellular stress plays a central role in the development of neurodegenerative diseases (such as Alzheimer's, Parkinson's, and Huntington's). Brain cells are particularly susceptible to oxidative stress, protein misfolding and mitochondrial dysfunctions. These conditions lead to protein aggregation in neurons, a lack of intracellular energy, and ultimately, neuronal loss. In most neurodegenerative diseases, the cellular stress response may be overstimulated or impaired. Stress-induced inflammation, protein toxicity and oxidative damage accelerate disease progression (Jomova et al., 2023; Kandel et al., 2024; Koszła & Sołek, 2024; Rai, 2024).

Since the brain is a high oxygen-consuming organ, it is highly susceptible to oxidative stress. Accumulation of free radicals and inadequate antioxidant mechanisms lead to neuronal damage and contribute to neuronal loss, especially in Alzheimer's and Parkinson's disease. Similarly, protein misfolding increases ER stress, especially in Alzheimer's and Huntington's diseases (Abramovich et al., 2024; Rai, 2024). Misfolded proteins lead to the formation of toxic aggregates within the cell, which triggers the UPR mechanism (Abramovich et al., 2024). However, prolonged activation of this mechanism can lead to cell death. In addition, mitochondrial stress affects cellular energy production and produces oxidative phosphorylation disorders (Bae et al., 2024; Torres et al., 2024; Yamashita et al., 2024). In Parkinson's disease, loss of mitochondrial function in particular, accelerates the death of dopaminergic neurons and increases disease symptoms (Rai, 2024).

At the same time, cellular stress conditions lead to the overactivation of specialized immune cells in the brain, known as microglia. This overactivation can trigger chronic inflammation. This, in turn, contributes to the progression of neurodegenerative diseases (Huo et al., 2021).

Neurons rely on autophagy to clear protein aggregates and damaged organelles. In Alzheimer's and Parkinson's diseases, autophagy mechanisms are impaired, leading to the accumulation of toxic proteins and an increased risk of cell death. The accumulation of abnormal proteins (for example, beta-amyloid and tau proteins) creates cellular stress. Cells activate stress responses to clear these abnormal proteins; however, these mechanisms can be impaired over time (Abramovich et al., 2024; Rai, 2024).

9.3. The Role of Cellular Stress in Cardiovascular Diseases

Cellular stress plays an important role in the development and progression of cardiovascular diseases (Jomova et al., 2023; Nie et al., 2024; Patel & Keyes, 2023; Timofeev et al., 2023; van Doorn et al., 2024). Stress factors such as oxidative stress, inflammation, mitochondrial dysfunction and ER stress can cause damage to cardiovascular tissues and trigger the development of diseases such as hypertension, atherosclerosis, and myocardial infarction. The response of cardiomyocytes and vascular cells to these stressors determines the course of the disease. Chronic cellular stress can cause structural and functional disorders in the cardiovascular system, while acute stress can increase the risk of sudden heart attack.

Oxidative stress triggers the onset of atherosclerosis by leading to low-density lipoprotein (LDL) oxidation (Jomova et al., 2023; Nie et al., 2024; Qiu et al., 2022). Oxidized LDL contributes to the formation of plaque in the blood vessels, impeding blood flow, and is associated with hypertension. This leads to atherosclerosis and

an increased risk of heart attack. Cellular stress triggers an inflammatory response, leading to atherosclerosis. Inflammation causes endothelial dysfunction in vascular cells, which contributes to the development of atherosclerosis. Increased inflammation in the heart vessels accelerates the progression of coronary artery disease. At the same time, myocytes can become dysfunctional when they experience mitochondrial stress due to their high energy requirements. Mitochondrial stress reduces ATP production and affects the contractile strength of the heart, increasing the risk of heart failure. Furthermore, mitochondrial damage leads to the accumulation of reactive oxygen species (ROS) in the heart, increasing the oxidative stress burden. Since protein synthesis occurs rapidly in cardiac cells, they are also susceptible to ER stress. ER stress caused by protein misfolding increases the risk of cardiomyopathy, which can lead to heart failure. Long-term ER stress adversely affects cardiac function by causing cell death and tissue damage (Kandel et al., 2024).

9.4. The Role of Cellular Stress in Autoimmune Diseases

Cellular stress has an influential role in the onset and progression of autoimmune diseases. Oxidative damage, inflammation, and protein misfolding due to cellular stress can cause the immune system to react against its own cells. In autoimmune diseases, as cells attempt to adapt to external stressors, autoantigens are released and recognized by the immune system, triggering a mistargeted immune response in the body. This leads immune cells to attack their own tissues and organs, and cellular stress-related mechanisms may become chronic in autoimmune diseases (Dhabhar, 2024).

At the cellular level, oxidative stress triggers inflammation by causing damage to DNA, proteins, and lipids as a result of accumulation of free radicals. Chronic oxidative stress can increase

tissue damage characteristic of autoimmune diseases and cause the immune system to attack these tissues (F. Zhou et al., 2023). Similarly, ER stress leads to protein misfolding and the release of autoantigens, one of the main causes of autoimmune diseases. ER stress contributes to the misdirection of the immune system by triggering autoantigens, especially in diseases such as rheumatoid arthritis and lupus (Kandel et al., 2024). Furthermore, mitochondrial stress may increase the autoimmune response by disrupting intracellular energy balance. Apoptosis caused by mitochondrial stress leads to the emergence of autoantigens that trigger autoimmune diseases. Antigenic materials released by apoptosis are recognized by the immune system and generate an incorrectly targeted immune response (Mihaylova et al., 2024; Poznyak et al., 2024). Chronic inflammation caused by cellular stress leads to an imbalance of the immune system in autoimmune diseases. Inflammatory signals cause hyperactivity of immune cells and damage to healthy tissues. This process is particularly seen in diseases such as Hashimoto's thyroiditis, type 1 diabetes, and multiple sclerosis (Morshed & Davies, 2019). Cellular stress causes gene expression changes in the immune system by leading to epigenetic modifications. Increased or decreased activation of some genes, especially under stress, is among the factors that trigger autoimmune responses of immune cells (Olichwier et al., 2024; N. Wang et al., 2024; Yi, 2024).

9.5. The Role of Cellular Stress in Metabolic Diseases

Cellular stress plays an important role in the development and progression of metabolic diseases. Cellular stress factors such as oxidative stress, inflammation, ER stress and mitochondrial dysfunction are particularly influential in the pathogenesis of diseases such as diabetes, obesity, fatty liver disease, and metabolic syndrome. These stress factors in cells disrupt energy balance and metabolic processes, negatively affect cellular functions and lead to

metabolic imbalances such as insulin resistance, lipid accumulation and inflammatory responses (Agbaje, Zachariah, Bamsa, Odili, & Tuomainen, 2023; Blagov et al., 2024; "A Brief Review on Diabetes Mellitus: Short Communication," 2024; Kumar et al., 2022; Rath et al., 2024).

Oxidative stress targets cellular structures with RO accumulation and disrupts insulin signaling pathways. Increased oxidative stress, especially in skeletal muscle, liver, and adipose tissue, contributes to the development of T2DM by triggering insulin resistance (Blagov et al., 2024; "A Brief Review on Diabetes Mellitus: Short Communication," 2024; Klimczak & Śliwińska, 2024). Cellular stress also contributes to the pathogenesis of metabolic diseases through epigenetic modifications. Epigenetic changes such as DNA methylation, histone modifications, and regulation of miRNAs can lead to changes in the expression of genes that affect metabolic processes (Klimczak & Śliwińska, 2024; Rath et al., 2024; Yi, 2024). In addition to these changes, lipid accumulation in cells may increase under ER stress, and this is associated with fatty liver disease and obesity. Chronic ER stress increases the risk of inflammation and cell death in these organs (Feng et al., 2024). Similarly, chronic inflammation contributes to metabolic diseases by impairing adipose tissue function. Activation of inflammatory signaling pathways in adipose tissue reduces insulin sensitivity and leads to inappropriate storage of lipids. This has a particularly important role in obesity and metabolic syndrome (Blagov et al., 2024; "A Brief Review on Diabetes Mellitus: Short Communication," 2024; Klimczak & Śliwińska, 2024). At the same time, UPR is activated due to ER stress, leading to changes in lipid metabolism. Mitochondrial stress leads to a decrease in energy production and disruption of metabolic balance. This is particularly seen in metabolic diseases such as obesity and diabetes. Since mitochondrial dysfunction reduces ATP production in cells, it leads

to disruptions in metabolic processes and triggers diseases (Blagov et al., 2024; "A Brief Review on Diabetes Mellitus: Short Communication," 2024; Rath et al., 2024).

10. Conclusion

The stress responses of cells are directly linked to the fundamental dynamics of life. These responses provide protection against environmental changes and internal threats while also playing a critical role in maintaining cellular homeostasis. The mechanisms discussed in this chapter provide an important foundation for understanding the effects of stress on cells and how these effects shape health.

Stress responses, particularly the effects of mitochondrial and endoplasmic reticulum stress, are of great importance for their impact on the energy production and protein folding processes of cells. Oxidative stress is the underlying mechanism underlying many pathologies such as aging, cancer, neurodegenerative diseases, and heart disease. Cells develop various adaptive responses to survive under these stress conditions. However, disruption or over-activation of stress responses can lead to disease progression and loss of cellular function.

The association of stress responses with various diseases, such as cancer, neurodegenerative diseases, and metabolic disorders has been studied. Cancer cells gain a survival advantage by manipulating stress responses, while neurodegenerative diseases are characterized by abnormal protein accumulations and the effects of oxidative stress. Heart disease is directly related to the adverse effects of cellular stress on vascular health. In this context, targeting stress responses may help to develop new therapeutic strategies.

The aging process affects the efficiency of stress responses, leading to reduced cellular function. Low-stress tolerance, chronic

inflammation, and impairment of molecular stress resistance mechanisms may lead to increased health problems in older individuals. Therefore, enhancing stress responses with aging may be an important goal for promoting healthy aging.

Further research on the mechanisms of stress responses will help us better understand the roles of these processes in pathological conditions. Furthermore, studying the genetic, epigenetic, and environmental factors that regulate cellular stress responses may allow individuals to become more resilient to disease by optimizing their stress responses.

In conclusion, cellular stress responses are critical elements that determine the balance between health and disease. Advances in this field offer important opportunities for both basic science and clinical applications. Research is expected to provide new perspectives on how to optimize these responses and which strategies will be effective in preventing or treating diseases.

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CARDIOPROTECTIVE ROLE OF *Viburnum opulus* IN MYOCARDIAL INFARCTION: MODULATION OF OXIDATIVE STRESS, INFLAMMATORY PATHWAYS, AND ENDOGENOUS PEPTIDE SYSTEMS

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1. Introduction

Cardiovascular diseases, particularly ischaemic heart disease and myocardial infarction (MI) are leading causes of global mortality and encompass all conditions that impair cardiac structure and function. According to the World Health Organization (WHO), approximately 17.9–18 million cardiovascular-related deaths occur worldwide each year, highlighting the significant public health burden of ischaemic heart disease. Myocardial infarction (MI) is the most common cause of heart failure in ischaemic heart disease (Minicucci, Azevedo, Polegato, Paiva, & Zornoff, 2011). The

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mortality rate of MI, which is one of the important diseases that threaten people's lives, is increasing rapidly. It imposes a serious economic burden on families and society and has become an important public health problem (Deckert, Winkler, Meisinger, Heier, & Becher, 2014). Risk factors for cardiovascular diseases can be divided into environmental and non-environmental factors. Environmental factors include smoking, obesity, stress, unhealthy diet, and sedentary life, while non-environmental factors include diseases such as hypertension, diabetes, hypercholesterolaemia, dyslipidaemia (Aniza, Nurmawati, Hanizah, & Ahmad Taufik, 2016). Despite advances in reperfusion therapy and medical management, MI survivors remain at high risk for complications such as heart failure, arrhythmias, and reinfarction. This has spurred interest in adjunct therapies that can limit myocardial injury and promote cardiac repair.

MI, also known as heart attack in public, is typically caused by acute thrombosis following plaque rupture in a coronary artery, leading to cessation of blood flow and irreversible necrosis of cardiac muscle. Symptoms of MI include chest pain radiating to the left arm or left side of the neck, shortness of breath, sweating, nausea, vomiting, abnormal heartbeat, anxiety, fatigue and other factors (Lu et al., 2015), and approximately 64% of people with MI do not experience chest pain, so-called ‘silent’ MI (Valensi, Lorgis, & Cottin, 2011). MI is classified into several types: type 1 (spontaneous MI due to a primary coronary event), type 2 (MI secondary to an imbalance in myocardial oxygen supply and demand), type 3 (sudden cardiac death attributed to MI), and types 4 and 5 (MI associated with percutaneous coronary intervention and coronary artery bypass grafting, respectively) (Thygesen et al., 2018).

Among the numerous biomarkers associated with myocardial injury, cardiac troponin I (cTn-I) and creatine kinase-MB (CK-MB)

are widely recognized indicators of cardiomyocyte necrosis and are routinely used in the clinical diagnosis of myocardial infarction (Beyazcicek & Beyazcicek, 2023a, 2023b; Gök & Beyazçiçek, 2024). Elevated levels of atrial natriuretic peptide (ANP) (Della Corte, Pacinella, Todaro, Pecoraro, & Tuttolomondo, 2023; Kacprzak, Brzeczek, & Zielinska, 2021) and B-type natriuretic peptide (BNP), secreted in response to ventricular wall stress, serve both as markers of cardiac dysfunction and as endogenous cardioprotective mediators due to their vasodilatory, natriuretic, and anti-fibrotic properties (Naidoo & de Vasconcellos, 2023; Sangaralingham, Kuhn, Cannone, Chen, & Burnett Jr, 2022). However, neprilysin, a metalloprotease enzyme, degrades these beneficial peptides, limiting their therapeutic potential during cardiac stress (Bernelin et al., 2019) (Vodovar et al., 2015). Additionally, vasoactive peptides such as bradykinin (Obtułowicz, 2016) and adrenomedullin (ADM) are similarly regulated by neprilysin, and their modulation significantly influences vascular tone and myocardial function (Hamid, Baxter, & therapeutics, 2005; H. K. Wong, Cheung, & Cheung, 2012). Oxidative stress also plays a central role in myocardial infarction, characterized by an imbalance between total oxidant status (TOS) and total antioxidant status (TAS). The oxidative stress index (OSI), defined as the ratio of TOS to TAS, offers a comprehensive assessment of redox imbalance and correlates with the extent of myocardial damage (Aksoy, Baş, Bağcı, Savaş, & Özaydın, 2022). Therefore, therapeutic strategies that aim to mitigate oxidative stress and preserve the activity of endogenous cardioprotective peptides, particularly through targeting regulatory enzymes such as neprilysin, have garnered increasing scientific attention in recent years.

Given this context, *Viburnum opulus* (commonly known as guelder rose or “gilaburu” in Turkey), with its traditional medicinal use and rich phytochemical composition, has emerged as a

promising candidate for cardioprotection. Owing to its abundance of bioactive compounds and historical applications in the treatment of cardiovascular and inflammatory conditions, *V. opulus* warrants investigation for its potential role in modulating oxidative damage and peptide-regulating pathways involved in myocardial injury (Mazur et al., 2021; Zakłos-Szyda et al., 2019).

Given its traditional medicinal use and rich phytochemical profile, *Viburnum opulus* (commonly known as guelder rose or "gilaburu" in Turkey) (Kajszczak, Zakłos-Szyda, & Podsędek, 2020) has gained attention as a potential cardioprotective agent (Mazur et al., 2021; Zakłos-Szyda et al., 2019). This deciduous shrub, native to Europe and parts of Asia and North Africa, bears bright red berries that are rich in potassium and bioactive compounds such as iridoids, flavonoids, anthocyanins, and various phenolic acids (Kajszczak et al., 2020). Historically, various parts of the plant—fruits, bark, leaves, and flowers—have been used to manage ailments including hypertension, cardiac disorders, gastrointestinal issues, and inflammatory diseases (Mazur et al., 2021). The fruit juice, often fermented in Anatolian regions to reduce its bitterness, is traditionally consumed for its diuretic and circulatory benefits (Kajszczak et al., 2020). Given its documented antioxidant, anti-inflammatory, and vasorelaxant properties, *V. opulus* offers a compelling profile for investigation in cardiovascular contexts.

Therefore, this review study investigated the potential of *V. opulus* to reduce myocardial damage, particularly by modulating oxidative stress and vasoactive peptide systems such as neprilysin and natriuretic peptides.

2. Pathophysiology of MI

Myocardial infarction is characterized by the irreversible death of heart muscle due to prolonged ischemia. The immediate cause is typically an occlusive thrombus in a coronary artery at the

site of an atherosclerotic plaque rupture or erosion. This leads to an acute cessation of blood supply to the downstream myocardium. Within minutes of coronary occlusion, affected cardiomyocytes lose contractile function (Fathima, Science, & Technology, 2021). Prolonged ischemia (20–30 minutes or more) causes cells to undergo necrosis (Tygesen, Alpert, & Jaffe, 2018)– the sarcolemmal membrane ruptures, releasing cardiac troponins, creatine kinase-MB (CK-MB), and other biomarkers into the bloodstream (Reddy, Khaliq, & Henning, 2015).

The cascade of events in MI begins with myocardial ischemia, which deprives cardiomyocytes of oxygen and substrates. Within minutes, energy depletion and ion pump failure lead to cytosolic calcium overload and acidosis. These disturbances trigger hypercontracture and activation of degradative enzymes, initiating cell death. The ischemic zone accumulates reactive oxygen species (ROS) from mitochondrial dysfunction and xanthine oxidase activation, as well as reactive nitrogen species (RNS), especially upon reperfusion (Andreadou et al., 2020). Oxidative stress damages membranes (lipid peroxidation) and proteins, exacerbating cardiomyocyte necrosis and apoptosis. Necrotic cells release intracellular contents, provoking an intense inflammatory response. Neutrophils and macrophages infiltrate the infarcted myocardium to clear debris but also release proteases and additional ROS, potentially extending injury. Over days to weeks, the infarct undergoes granulation and scar formation (Ferrari et al., 2004; Xu et al., 2019).

Inflammation is also one of the central component of MI pathophysiology. Necrotic myocardial cells release damage-associated molecular patterns that trigger complement activation and cytokine release (TNF-α, IL-1, IL-6) (N. G. J. C. P. Frangogiannis, 2015; N. G. J. C. r. Frangogiannis, 2012). Neutrophils are recruited to the infarct within hours, peaking at 1–3 days post-MI. They

phagocytose debris and secrete proteolytic enzymes (matrix metalloproteinases, elastases) and additional ROS, which can inadvertently extend the injury into border zones (Francisco & Del Re, 2023; Valikeserlis, Athanasiou, & Stakos, 2021). By 3–7 days, macrophages become the dominant leukocytes in the infarct, clearing dead cells and orchestrating tissue repair. While necessary for healing, excessive or prolonged inflammation may thin the infarct wall and increase the risk of complications like ventricular rupture (Francisco & Del Re, 2023).

Surviving myocardium remodels: initially, compensatory neurohormonal activation (sympathetic drive, renin-angiotensin-aldosterone system [RAAS]) maintains cardiac output, but chronically these pathways induce hypertrophy, fibrosis, and chamber dilation that can progress to heart failure (Hartupee & Mann, 2017).

In the light of this information, it can be said that, MI pathophysiology encompasses: ischemic injury (energy failure, Ca^{+2} overload, necrosis), oxidative stress and reperfusion injury, robust inflammation, and remodeling and heart failure progression. Each of these stages presents potential therapeutic targets. Limiting oxidative stress and inflammation has been a key strategy to reduce infarct size in experimental studies. Likewise, blocking maladaptive remodeling through RAAS inhibition or β-blockade is standard post-MI care. Recently, augmentation of endogenous cardioprotective pathways (like the natriuretic peptide system) has gained attention in both acute and chronic settings.

3. Role of Cardiac Biomarkers in Cardiac Injury

The heart is not only an pump but also an endocrine organ. In response to myocardial stretch or stress, the heart secretes natriuretic peptides which act to restore homeostasis. Atrial natriuretic peptide (ANP) was the first to be discovered, originating

predominantly from atrial granules. B-type natriuretic peptide (BNP), initially found in brain extracts, is secreted mainly by ventricular myocytes (especially when ventricular wall tension rises). A third member, C-type natriuretic peptide (CNP), is expressed mostly in endothelium and the nervous system. In the context of MI and heart failure, ANP and BNP have overlapping actions via the guanylyl cyclase-A (GC-A) receptor, while CNP acts on GC-B receptors (Volpe, Battistoni, & Rubattu, 2019).

3.1. Creatine Kinase-MB (CK-MB)

Creatine kinase (CK) is an enzyme that catalyzes the reversible conversion of creatine and ATP into creatine phosphate and ADP (Aujla, Zubair, & Patel, 2024). It is a dimeric enzyme located in both the mitochondria and cytosol of muscle cells, composed of two subunits: M and B. There are three isoenzymes: CK-BB (CK1), CK-MB (CK2), and CK-MM (CK3). CK-MM is the predominant isoform found in most tissues, while CK-BB is primarily present in the brain, kidneys, and gastrointestinal tract. CK-MB is found in the heart, skeletal muscle, small intestine, diaphragm, uterus, tongue, and prostate (Bojinca, Bojinca, Balanescu, & Balanescu, 2018). Approximately 20% of myocardial CK exists in the CK-MB form, making it a specific and valuable cardiac biomarker for the diagnosis of myocardial infarction (MI). In contrast, CK-MB comprises only about 5% of skeletal muscle CK, which reduces its specificity in MI diagnosis, especially during trauma or inflammation when its levels may also rise. Another limitation of CK-MB is its high molecular weight, which makes it less sensitive in detecting minor myocardial injuries. CK-MB levels begin to rise 4–9 hours after myocardial injury, peak at around 24 hours, and return to normal within 48–72 hours (Aydin et al., 2019). However, numerous non-cardiac conditions—such as certain cancers, pulmonary embolism, inflammation, endocrine disorders, renal failure, strenuous exercise, trauma, and various medical

interventions—may cause false-positive CK-MB elevations. Therefore, these factors must be considered when using CK-MB as a biomarker for MI diagnosis (Aydin et al., 2019). The analysis of cardiac biomarkers plays a critical role in early diagnosis, risk assessment, clinical reliability, and cost-effectiveness.

3.2. Cardiac Troponin-I (cTn-I)

Cardiac troponin I (cTnI) is the inhibitory component of the troponin complex, which regulates cardiac muscle contraction. It is encoded by a unique cardiac-specific gene and has an amino acid sequence distinct from skeletal muscle troponin I isoforms. Notably, cTnI contains a unique N-terminal peptide with phosphorylation sites that modulate its interaction with actin and tropomyosin (S. Wong, Feng, Jin, & cardiology, 2019). This cardiac isoform is expressed exclusively in heart muscle (after early infancy), which underlies its high tissue specificity as a biomarker for myocardial injury (Giannitsis, Mueller, & Katus, 2019). During myocardial infarction, damage to myocardial cells leads to the release of cTnI into the bloodstream in a characteristic kinetic pattern. Levels typically begin to rise within 3–4 hours of symptom onset. They reach peak concentrations at approximately 18–24 hours post-infarction, reflecting the bulk release of troponin from necrotic heart muscle. Thereafter, cTnI levels decline gradually over several days as the protein continues to leak from the injured myocardium. In many cases, cTnI can remain elevated for about 5–7 days (or longer in large MIs), which means a troponin test may detect an infarction even days after the acute event. This prolonged elevation is diagnostically useful, though it can complicate the assessment of reinfarction shortly after an initial MI (Kristensen et al., 2024). With its high sensitivity and specificity, cTnI serves as the cornerstone biomarker for diagnosing acute myocardial infarction. Because the cardiac isoform of troponin I is not present in adult skeletal muscle, even tiny increases in cTnI are highly specific for cardiac muscle

injury. Modern high-sensitivity cTnI assays can detect very low troponin concentrations, allowing the identification of even minor myocardial damage and enabling earlier diagnosis of MI (often within the first hours of presentation) (Cao et al., 2019). The sensitivity of these assays is so high that a normal cTnI level measured a few hours after chest pain onset effectively rules out MI in most cases (Azar, Sarkis, & Giannitsis, 2021). The specificity of cTnI for myocardial tissue injury is excellent; however, an elevated troponin by itself is not specific for a heart attack cause. In other words, cTnI can be released due to cardiac injury from non-coronary causes as well. Clinicians therefore interpret a positive troponin in context, distinguishing acute coronary syndromes from other conditions that also elevate cTnI (Cao et al., 2019). In addition to its diagnostic utility, cTnI offers valuable prognostic insights in acute coronary syndromes and various other clinical conditions. In acute MI and unstable angina (ACS), the magnitude of troponin elevation correlates with the extent of myocardial damage and risk of adverse outcomes. Patients with higher cTnI levels tend to have larger infarcts and face increased risks of complications such as heart failure, arrhythmias, and mortality (Lippi, Cervellin, Sanchis-Gomar, & Circulation, 2020). Troponin measurements are thus integral to risk stratification in ACS, guiding decisions about the urgency of interventions (for example, high troponin concentrations may prompt early invasive management). Importantly, cTnI is also a valuable prognostic indicator in non-ischemic conditions. Any elevation of cTnI signifies myocardial stress or injury, so it often portends worse outcomes even when the cause is not a heart attack . For instance, patients with heart failure who have chronically elevated troponin levels are at higher risk of disease progression and death (Steiro et al., 2024). Similarly, in conditions like pulmonary embolism, sepsis, or myocarditis, the presence of an elevated cTnI identifies patients with greater risk of shock, arrhythmias, or

mortality due to underlying cardiac strain (Lippi et al., 2020). Thus, cardiac troponin I serves not only as a definitive diagnostic marker for myocardial infarction but also as a general gauge of cardiac risk across a broad spectrum of acute and chronic medical conditions.

3.3. Natriuretic Peptides (ANP/BNP)

Among the key neurohormonal responses to MI are changes in natriuretic peptides (NPs) and their catabolic enzyme, neprilysin. Atrial natriuretic peptide (ANP) and B-type (brain) natriuretic peptide (BNP) are cardiac hormones released primarily by atrial myocytes (ANP) and ventricular myocytes (BNP) in response to stretch, volume overload, or neurohormonal stimulation (Nakagawa & Saito, 2022).

3.4. Physiological actions of ANP/BNP

Binding of ANP or BNP to GC-coupled receptors (NRP-A, NRP-B) on target cells (such as kidney tubular cells, vascular smooth muscle cells, adrenal gland, endothelium, and cardiomyocytes) triggers the production of the second messenger cyclic GMP (cGMP) (Volpe et al., 2019).

Downstream effects of this signaling include:

- **Vasodilation:** cGMP causes relaxation of vascular smooth muscle, reducing systemic vascular resistance and afterload (Volpe et al., 2019).
- **Natriuresis and diuresis:** In the kidneys, ANP/BNP increase glomerular filtration rate (by afferent arteriolar dilation and efferent constriction) and inhibit sodium reabsorption in the collecting ducts, promoting salt and water excretion. This reduces blood volume and preload (Matsumoto et al., 2022; Nishikimi & Nakagawa, 2022).

- **RAAS and sympathetic inhibition:** Natriuretic peptides directly suppress renin and aldosterone secretion. They also decrease sympathetic outflow and inhibit norepinephrine release. The net effect is blunting of vasoconstrictive and sodium-retentive mechanisms (Afsar, Afsar, Caliskan, & Lentine, 2024; Al-Kuraishy, Al-Gareeb, Alexiou, Batiha, & Science, 2022).
- **Anti-hypertrophic and anti-fibrotic effects:** In the heart, NP signaling antagonizes pro-hypertrophic pathways and fibrosis. Natriuretic peptides (NPs) exert infarct-limiting and anti-remodeling effects in acute myocardial infarction, potentially by inhibiting TGF-β1 and NF-κB signaling, while activating GATA transcription factors. Their cardioprotective actions may also involve pathways such as heme oxygenase-1 and PPAR-γ (Krylatov et al., 2021).

Given these effects, it is not surprising that higher endogenous NP levels correlate with better outcomes in heart failure up to a point – though very high levels indicate severe disease, the NPs are part of a compensatory response. After an MI, ANP and BNP secretion surges (Nishikimi & Nakagawa, 2022) (especially if the infarct is large and causes elevated intracardiac pressures). Initially, this helps reduce cardiac load and limit damage (Shinde, Juwarwala, Modi, & Chandarana, 2023). However, NPs are short-lived hormones (Brignone et al., 2021), tightly regulated by clearance mechanisms. One major clearance route is via the natriuretic peptide clearance receptor (NPR-C) present in many tissues which binds and internalizes NPs. The other route is enzymatic degradation chiefly by neprilysin (NEP) (Nakagawa & Saito, 2022).

3.5. Neprilysin

Neprilysin is a zinc-dependent endopeptidase on cell surfaces (especially renal brush border, lung, vascular endothelium,

and also in cardiomyocytes). Neprilysin (NEP), also known as neutral endopeptidase, is a membrane-bound metalloprotease widely expressed in the heart, kidneys, lungs, and vasculature (Pavo, Prausmüller, Bartko, Goliasch, & Hülsmann, 2020). NEP's substrate spectrum is broad – it degrades natriuretic peptides (preferring CNP > ANP > BNP in vitro) as well as other vasoactive and neuropeptides (Nakagawa & Saito, 2022). For instance, NEP breaks down bradykinin (a vasodilator that also has cardioprotective, anti-fibrotic effects), adrenomedullin (a vasodilator and inotrope), endothelin-1 (a vasoconstrictor, interestingly producing vasodilatory fragments), substance P and neuropeptide Y (neurotransmitters), Angiotensin II and even beta-amyloid in the brain (D. J. J. N. R. C. Campbell, 2017; Nakagawa & Saito, 2022). By virtue of this broad activity, NEP serves as a key modulator of cardiovascular homeostasis, balancing the actions of multiple peptide systems. In the setting of MI or heart failure, where levels of ANP/BNP, bradykinin, and other peptides rise, NEP is responsible for degrading these potentially beneficial mediators. The net result of NEP upregulation is often detrimental (Pavo et al., 2020): it blunts natriuresis and vasodilation (through NP and bradykinin breakdown) and may even increase angiotensin II (by degrading Ang-(1–7), which normally opposes Ang II). Elevated NEP activity has been observed in chronic heart failure, and NEP expression in cardiac tissue can be induced by hemodynamic stress, indicating its role in disease progression (Pavo et al., 2020).

Therapeutic targeting of NEP/NP: Recognition of the NP system's protective effects led to the development of drugs that enhance NP signaling. Initial attempts using recombinant ANP/BNP had limited success due to hypotension and short half-life issues. A more effective strategy has been neprilysin inhibition (Von Lueder et al., 2013). By inhibiting NEP, endogenous natriuretic peptides are not broken down as quickly, thus prolonging their action. However, NEP inhibition alone can cause accumulation of other substrates

(like bradykinin or even amyloid peptides), so in practice it was combined with RAAS inhibition to yield balanced effects. The ARNI (angiotensin receptor–neprilysin inhibitor) sacubitril/valsartan showed in the PARADIGM-HF trial that it significantly reduced cardiovascular death and heart failure hospitalization in chronic HFrEF compared to an ACE inhibitör (Pavo et al., 2020). Mechanistically, ARNI therapy increased circulating ANP/BNP levels (as expected with NEP blocked) and enhanced cGMP signaling, while also providing RAAS blockade. This dual action translated into reduced cardiac fibrosis and hypertrophy in patients (Pavo et al., 2020). In experimental acute MI, enhancing NP signaling appears beneficial as well: for instance, infusion of ANP in patients with acute MI reduced infarct size (Kasama, Furuya, Toyama, Ichikawa, & Kurabayashi, 2008), and ARNI therapy initiated after MI in animal models improved left ventricular remodeling and even reduced the risk of cardiac rupture by mitigating matrix metalloproteinase activation (Kasama et al., 2008). These findings underscore that robust natriuretic peptide activity can be cardioprotective, whereas unchecked neprilysin activity may be detrimental after MI. Therefore, therapies that modulate the NP–NEP axis are of great interest.

In summary, the neprilysin-natriuretic peptide axis is a critical moderator of cardiovascular injury and repair. High natriuretic peptide activity helps to counteract the harmful consequences of MI (reducing wall stress, inhibiting fibrosis), whereas heightened neprilysin activity can negate these benefits. Therapeutically, tipping the balance in favor of NPs (either by providing exogenous peptides or blocking their degradation) is a proven strategy to improve cardiac outcomes. This interplay provides a mechanistic backdrop for evaluating new cardioprotective interventions – including natural compounds – on parameters such as NP levels or NEP activity in the setting of MI.

3.6. Adrenomedullin (ADM)

Adrenomedullin (ADM) is a multifunctional peptide involved in cardiovascular homeostasis, initially discovered in pheochromocytoma tissue. Synthesized primarily in vascular endothelial and smooth muscle cells, ADM exerts potent vasodilatory effects and plays a key role in regulating vascular tone, fluid balance, and endothelial barrier function. It is upregulated in response to cardiovascular stress, such as myocardial infarction, heart failure, or sepsis. ADM mediates its effects via the calcitonin receptor-like receptor (CLR) complexed with receptor activity-modifying proteins (RAMPs), activating cAMP-dependent pathways (Nishikimi & Nakagawa, 2018).

In myocardial infarction, elevated ADM levels are associated with improved hemodynamics due to its vasodilatory and natriuretic actions, which reduce preload and afterload. Additionally, ADM possesses anti-apoptotic and anti-inflammatory properties, potentially limiting infarct size and mitigating adverse cardiac remodeling. Clinically, ADM concentrations correlate with disease severity and prognosis in heart failure and acute coronary syndromes. As such, it is not only a marker of cardiovascular stress but also a promising therapeutic target in conditions involving myocardial injury and endothelial dysfunction (Voors et al., 2019).

3.7. Bradykinin

Bradykinin is a vasoactive nonapeptide that plays a pivotal role in cardiovascular physiology and pathophysiology. Generated from kininogen through the action of kallikreins, bradykinin exerts its effects via B1 and B2 receptors, leading to vasodilation, increased vascular permeability, and stimulation of nitric oxide (NO) and prostacyclin release. In the context of myocardial infarction, bradykinin contributes to cardioprotection by enhancing coronary blood flow, reducing inflammation, and limiting ischemia-

reperfusion injury (Mohammadi, Shafie, Ghomashi, Abdolizadeh, & Sadeghpour, 2024).

The cardioprotective effects of bradykinin are largely attributed to its ability to activate endothelial nitric oxide synthase (eNOS) and inhibit apoptotic signaling pathways in cardiomyocytes (Ancion et al., 2019). Moreover, its interaction with the renin-angiotensin-aldosterone system (RAAS) and natriuretic peptide pathways underscores its importance in maintaining cardiovascular homeostasis. However, bradykinin is rapidly degraded by enzymes such as angiotensin-converting enzyme (ACE) and neprilysin (D. J. J. F. i. m. Campbell, 2018). Consequently, medications that inhibit these enzymes—such as ACE inhibitors or neprilysin inhibitors—can potentiate bradykinin's beneficial effects, a mechanism partly responsible for the improved outcomes observed in patients treated with these agents following MI.

4. Natural Cardioprotective Strategies

Alongside pharmaceutical approaches, there is growing interest in natural compounds and medicinal plants as cardioprotective agents. Many bioactive phytochemicals (flavonoids, phenolics, etc.) exert antioxidant, anti-inflammatory, or vasodilatory effects that could theoretically mitigate myocardial injury. Indeed, oxidative stress is a major instigator of cardiac damage in MI (Hosseini et al., 2023), and numerous plant-derived antioxidants have shown cardioprotective effects in preclinical models. For example, polyphenols like resveratrol, quercetin, and kaempferol have demonstrated reduction in infarct size and improvement in cardiac function in animal studies, via mechanisms such as free radical scavenging, enhancement of endogenous antioxidant enzymes, and inhibition of apoptosis (Cebova & Pechanova, 2020). Moreover, certain medicinal herbs can modulate key pathways: Sanguisorba minor, a herb with potent antioxidant

activity (Cristina, Ramona, Ioana, & Petru, 2021), was recently shown to attenuate isoprenaline-induced MI in rats by mitigating oxidative stress – treated rats had lower lipid peroxidation (malondialdehyde, MDA) and higher superoxide dismutase levels, correlating with reduced troponin release and histologic injury (Hosseini et al., 2023). These findings encourage the exploration of traditional remedies as complementary cardioprotective agents.

4.1. Viburnum opulus

Viburnum opulus L. (Caprifoliaceae) (known as guelder rose or European cranberrybush) is one such candidate with a rich ethnomedicinal history and promising pharmacologic profile. *V. opulus* is a deciduous shrub native to Europe and Western Asia, whose red berries and bark have been used in folk medicine for various ailments (Sagdic, Ozturk, Yapar, & Yetim, 2014). Traditional uses of *V. opulus* fruit preparations include treatment of hypertension, heart ailments, coughs, inflammatory conditions, kidney stones, and gynecological cramps (Kajszczak, Kowalska-Baron, & Podsędek, 2021). In Turkish folk practice, a tart juice made from *V. opulus* berries (gilaburu) is consumed for kidney health and as a general health tonic. Modern phytochemical analyses reveal that *V. opulus* fruits are rich in phenolic compounds (especially phenolic acids like chlorogenic acid and neochlorogenic acid, as well as flavonoids and anthocyanins), vitamin C, organic acids, and iridoid glycosides. These constituents confer a variety of biological activities: antioxidant and free radical scavenging properties are particularly pronounced, but anti-inflammatory, anti-obesity, anti-diabetic, anti-carcinogenic, and even osteogenic effects have also been documented in experimental settings. Given its multifaceted bioactivity and traditional use in cardiovascular disorders (e.g. as a blood pressure-lowering folk remedy) (Kajszczak et al., 2020), *V. opulus* has gained attention as a potential cardioprotective natural agent.

4.2. Bioactive Properties of *Viburnum opulus*

Beyond its ethnobotanical applications, *Viburnum opulus* exhibits a complex phytochemical profile that underpins its potential pharmacological benefits. The most commonly utilized parts—its fruits and bark—contain a broad spectrum of bioactive compounds.

Phytochemical analyses have revealed a diverse array of secondary metabolites in *V. opulus* extracts:

- **Phenolic acids:** notably chlorogenic acid, neochlorogenic acid, and p-coumaric acid derivatives, which are abundant in the fruit. Chlorogenic acid (5-caffeoylquinic acid) in particular is present in high concentration (in one analysis, ~30 mg per gram of dried fruit extract). These compounds are potent antioxidants (Perova et al., 2014; Sedat Velioglu, Ekici, Poyrazoglu, & Technology, 2006).
- **Flavonoids:** Flavonoids are among the most prominent bioactive compounds found in *Viburnum opulus* fruits. These include quercetin, kaempferol, and various anthocyanins, which contribute not only to the plant's distinctive red pigmentation but also to its potent antioxidant capacity (Goławska, Łukasik, Chojnacki, & Chrzanowski, 2023). Flavonoids help neutralize free radicals, reduce lipid peroxidation, and modulate inflammatory pathways. Their vasoprotective effects—such as enhancing endothelial nitric oxide production and inhibiting platelet aggregation—may contribute significantly to the cardioprotective potential of *V. opulus* (Kajszczak et al., 2020; Liu, Bai, Zhao, & Huang, 2022).
- **Iridoids:** Iridoids and their glycoside derivatives, including monotropein and loganic acid, are

characteristic constituents of V. opulus, particularly in the bark. These compounds have demonstrated anti-spasmodic, anti-inflammatory, and hepatoprotective effects in various models. Their modulatory action on cytokine expression and smooth muscle relaxation may contribute to the plant's traditional use in treating cramps, hypertension, and urogenital complaints (Dienaitė, Pukalskienė, Pereira, Matias, & Venskutonis, 2020; Kajszczak et al., 2020; Perova et al., 2014).

- **Triterpenes and sterols:** Triterpenes and phytosterols are also present in *V. opulus*, contributing to its anti-inflammatory and lipid-regulating properties. Compounds such as ursolic acid—a pentacyclic triterpene—have been shown to exhibit vasorelaxant, antioxidant, and cardioprotective effects. Together, these lipid-soluble constituents add to the broad pharmacological potential of V. opulus, particularly in metabolic and vascular disorders (Woźniak, Skąpska, & Marszałek, 2015).

- **Vitamins and Organic acids:** *V. opulus* fruits are rich in organic acids, such as malic, citric, and ascorbic acids. These contribute to the sour taste of the berries and enhance their antioxidant potential. Vitamin C (ascorbic acid) not only acts synergistically with phenolics in neutralizing oxidative stress but also supports immune function and vascular health, adding to the overall therapeutic value of the fruit (Dienaitė et al., 2020).

4.3 Biological Activities of *Viburnum opulus*

Because of this rich phytochemistry, *V. opulus* exhibits a spectrum of biological activities.

- **Antioxidant activity:** Perhaps the most documented property. *V. opulus* fruit extracts have high free radical scavenging capacity in DPPH and ABTS assays, and strong reducing power in FRAP assays (Kajszczak et al., 2020). The berry extract's antioxidant potency has been compared favorably to known antioxidants; one study highlighted that *V. opulus* juice contained different phenolic compounds contributing to its exceptional antioxidant profile (Kraujalytė, Venskutonis, Pukalskas, Česonienė, & Daubaras, 2013). The branch and leaf extracts also show antioxidant effects, but the fruits generally have the highest phenolic content. Antioxidant components identified include chlorogenic acid, as well as unique iridoids (Polka, Podsędek, & Koziołkiewicz, 2019). By quenching ROS and RNS, these extracts protect cells from oxidative damage. For example, *V. opulus* fruit phenolics protected liver cells from free fatty acid-induced oxidative stress in vitro (Kajszczak et al., 2020).
- **Anti-inflammatory activity:** *V. opulus* extracts have been shown to reduce inflammation markers in various models. The fruit extract suppressed neutrophil infiltration and inflammatory mediator expression in an acetic acid-induced colitis model in rats (Akat, Almaghrebi, & Herbs, 2025; Gülada et al., 2024). Additionally, *V. opulus* fractions inhibited pro-inflammatory enzymes (like COX-2, iNOS) and cytokines in cell culture studies, aligning with traditional use for inflammatory conditions (Bidian et al., 2022).
- **Vasorelaxant and endothelial-protective effects:** A remarkable pharmacological finding is that *V. opulus* fruit

extracts induce relaxation of blood vessels. Bujor et al. **(2019)** demonstrated that *V. opulus* fruit extract produced endothelium-dependent vasodilation in rat aortic rings precontracted with phenylephrine (with an EC_50 ~6.3 µg/mL, indicating potent effect) . This vasorelaxation was largely abolished by removing the endothelium or inhibiting nitric oxide synthase, indicating that it works by boosting endothelial nitric oxide (NO) production (Bujor et al., 2019). Indeed, *V. opulus* was found to inhibit arginase in the vascular tissue. Arginase competes with endothelial nitric oxide synthase (eNOS) for the substrate L-arginine; by inhibiting arginase, more L-arginine is available for NO production. Thus, *V. opulus* enhances NO-mediated vasodilation. The high chlorogenic acid content is thought to be a major contributor to this effect, given that chlorogenic acid and related phenolics can inhibit arginase and have endothelium-dependent vasodilatory actions in other studies. Improved endothelial function not only lowers blood pressure but also protects against atherosclerosis and thrombosis. Traditional use of *V. opulus* for hypertension finds pharmacological justification in these findings (Bujor et al., 2019).

- **Antispasmodic activity:** The bark of *V. opulus* (cramp bark) has been used to relieve muscle spasms, menstrual cramps, and even threatened miscarriage in folkloric medicine. It contains viburnine (an alkaloid) and various polyphenols that have relaxant effects on smooth muscle, possibly through calcium channel antagonism or other pathways. While this is more relevant to uterine cramps, it might also confer some vasodilatory or anti-arrhythmic

benefit in the heart by calming hyperactive muscle tissue (Kajszczak et al., 2020).

- **Metabolic effects:** *V. opulus* has shown anti-diabetic and anti-obesity potential. In diabetic rat models, its extracts improved blood glucose control and insulin sensitivity (likely via polyphenols enhancing insulin signaling or inhibiting carbohydrate-digesting enzymes) (Kajszczak et al., 2020). There is also evidence of lipid-lowering effects and protection against hepatic steatosis in cell models. These properties could indirectly benefit cardiovascular health, given the link between metabolic syndrome and heart disease (Pietrzyk, Zakłos-Szyda, Redzynia, & Podsędek, 2021).
- **Cytoprotective and anti-apoptotic effects:** Beyond antioxidant activity, *V. opulus* fruit extracts have demonstrated cytoprotective effects in various cell lines under stress (Kajszczak et al., 2020). For example, they reduced chemically induced apoptosis in pancreatic beta cells and protected endothelial cells from oxidative injury. The mechanisms may involve activation of survival pathways like Nrf2 (antioxidant response element) and inhibition of caspases (Zakłos-Szyda et al., 2019).
- **Other activities:** Antimicrobial (especially against Gram-positive bacteria) and antiviral activities have been noted for *V. opulus* extracts (Česonienė, Daubaras, Kraujalytė, Venskutonis, & Šarkinas, 2014), though these are less relevant to cardioprotection. Anti-ulcer effects (due to tannins and flavonoids) and diuretic effects (from the organic acids and potassium content) have also been

reported, which complement its use in urinary and digestive issues (Golikova, 2023).

Crucially, many of these activities converge on pathways that are highly pertinent in MI. Oxidative stress and inflammation are central to myocardial injury; *V. opulus*'s ability to neutralize ROS and dampen inflammatory responses suggests a direct cardioprotective capacity. Its endothelium-enhancing effect implies it could improve coronary blood flow and reduce afterload, benefiting an ischemic heart. Moreover, by inhibiting arginase and possibly neprilysin, *V. opulus* may modulate key regulators of vascular tone and cardiac remodeling.

In the context of neprilysin and natriuretic peptides, it's worth noting that *V. opulus* has components that affect similar pathways. For instance, bradykinin is degraded by neprilysin; *V. opulus*'s polyphenols might slow bradykinin breakdown indirectly by inhibiting NEP or ACE (some flavonoids are mild ACE inhibitors). Additionally, *V. opulus*'s known diuretic effect from traditional use could be through NP-like action or RAAS suppression.

V. opulus is a nutraceutical powerhouse with multiple bioactivities beneficial to cardiovascular health. Its antioxidant and vasodilatory capabilities stand out as particularly relevant to protecting the heart from ischemic injury.

4.4. Potential Cardioprotective Mechanisms of *Viburnum opulus*

Myocardial infarction (MI) initiates a cascade of tissue injury driven by ischemia, oxidative stress, and inflammation. *V. opulus* (European cranberrybush) has attracted interest as a cardioprotective adjunct in this context due to its rich phytochemical profile (R Vasanthi, ShriShriMal, & K Das, 2012). The fruits of V. opulus are abundant in antioxidants (phenolic compounds such as flavonoids

and anthocyanins, vitamin C, and others) that have documented bioactivity. These constituents underpin the plant's traditional use in cardiovascular ailments and suggest multiple mechanisms by which V. opulus could mitigate cardiac damage in MI.

Antioxidant Effects: A key protective mechanism of V. opulus is the attenuation of oxidative stress during MI (R Vasanthi et al., 2012). Acute ischemia and subsequent reperfusion lead to excessive generation of reactive oxygen species in the heart, which in turn cause lipid peroxidation of membranes, protein oxidation, and DNA damage in cardiomyocytes (Perrelli, Pagliaro, & Penna, 2011). V. opulus extracts display strong free-radical-scavenging activity (Juhnevica-Radenkova et al., 2024; Kraujalytė et al., 2013), directly neutralizing ROS (Eken et al., 2017) and bolstering the heart's own antioxidant defenses. In experimental models, treatment with V. opulus has been shown to preserve or boost levels of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants like reduced glutathione. Correspondingly, markers of oxidative injury (e.g. malondialdehyde, a byproduct of lipid peroxidation, and protein carbonyls) are significantly reduced with V. opulus treatment (Eken et al., 2017). The observed alterations in TAS, TOS, and OSI levels suggest that V. opulus may contribute to the restoration of redox homeostasis in infarcted cardiac tissue. This potential antioxidative effect could play a role in limiting oxidative damage and supporting cardiomyocyte integrity during myocardial infarction.

Anti-Inflammatory Effects: The findings suggest that V. opulus may exert anti-inflammatory effects, which could play a supportive role in reducing myocardial injury and enhancing cardioprotection in the context of infarction. The initial tissue necrosis in MI triggers a robust inflammatory response – immune cells infiltrate the damaged myocardium and release pro-

inflammatory cytokines (such as tumor necrosis factor-α and interleukin-6) that can extend the injury and hinder healing (Saparov et al., 2017). Bioactive compounds from V. opulus help dampen this excessive inflammation. Research indicates that V. opulus extracts can interfere with inflammatory signaling pathways (for example, by down-regulating NF-κB activation), leading to lower levels of cytokines and chemokines (Kajszczak et al., 2020). The modulation of inflammatory responses by V. opulus could play a role in minimizing secondary myocardial injury and supporting tissue preservation and repair processes.

Enzyme Modulation and Biomarker Regulation: Another intriguing mechanism is the modulation of enzymes involved in cardiac stress signaling and remodeling. One example is neprilysin, a metalloprotease that degrades protective natriuretic peptides like B-type natriuretic peptide (BNP) (Pavo et al., 2020). BNP is released by cardiac tissue under stress and acts to reduce cardiac workload through vasodilation and diuresis (Nakagawa & Saito, 2022) (Matsumoto et al., 2022; Nishikimi & Nakagawa, 2022). In the post-MI setting, inhibiting neprilysin (and thereby sustaining BNP levels) is known to improve outcomes – this is the rationale behind neprilysin inhibitor drugs used in heart failure. V. opulus may influence this axis (Pavo et al., 2020). Its phytochemicals could potentially inhibit neprilysin or otherwise enhance natriuretic peptide activity, helping to maintain higher BNP availability (Von Lueder et al., 2013). This would augment the heart's compensatory responses, improving hemodynamics and limiting adverse ventricular remodeling after MI. Additionally, V. opulus impacts the classic biomarkers of myocardial injury. The analysis of cardiac biomarkers plays a critical role in the early diagnosis of myocardial infarction (MI), risk stratification, clinical reliability, and the reduction of healthcare costs. Delays in the accurate diagnosis of MI can hinder the timely evaluation of underlying comorbid conditions.

In recent years, protein-based molecules known as cardiac troponins (including TnC, TnI, and TnT) have largely replaced traditional cardiac enzymes in clinical diagnostics due to their superior specificity and sensitivity for myocardial injury (Aydin et al., 2019).

Among the bioactive compounds studied for their cardioprotective properties, resveratrol—a non-flavonoid polyphenol—has emerged as a promising nutraceutical with potential applications in the prevention and treatment of cardiovascular diseases (Çıracı & Kalafat, 2021). Studies have demonstrated that resveratrol administration significantly reduces the serum levels of cardiac injury markers such as cTn-I, cTn-T, creatine kinase (CK), creatine kinase-MB (CK-MB), and lactate dehydrogenase (LDH), thereby mitigating myocardial damage (Zhang, Jia, Wei, Yao, & Jiang, 2024).

V. opulus (VO), a plant known for its rich phytochemical profile, naturally contains trans-resveratrol, a stilbenoid compound with well-documented anti-cancer, anti-inflammatory, antioxidant, vasodilatory, and cardioprotective properties. Given this composition, V. opulus is thought to exert beneficial effects on cardiovascular health by enhancing antioxidant defenses, suppressing inflammatory responses, and preserving myocardial cell integrity (Dönmez, Kadakal, & Quarterly, 2024). Therefore, the cardioprotective potential of V. opulus may be partially attributed to its trans-resveratrol content, which reinforces its relevance as a therapeutic candidate in the context of myocardial infarction and related cardiovascular pathologies.

Building upon this evidence, the cardioprotective effects of V. opulus in myocardial infarction appear to stem from a multifaceted mechanism involving antioxidant, anti-inflammatory, and enzyme-modulating actions. By neutralizing ROS and restoring the endogenous antioxidant capacity, V. opulus mitigates oxidative

tissue injury. Simultaneously, its anti-inflammatory properties help to suppress acute inflammatory cascades, thereby minimizing secondary damage to the myocardium. Moreover, modulation of key enzymes and hormonal mediators—such as neprilysin and brain natriuretic peptide (BNP)—suggests that V. opulus contributes to the preservation of cardiac function and structural integrity following infarction. These converging pathways collectively reduce myocardial cell death and improve overall cardiac performance in experimental post-MI models. Although clinical evidence remains limited, the favorable outcomes observed in preclinical studies provide compelling justification for further investigation into the therapeutic potential of V. opulus as an adjunctive strategy in the management of myocardial infarction.

5. Conclusion

Myocardial infarction remains a challenging clinical entity where timely reperfusion is life-saving but not sufficient to avert long-term cardiac dysfunction in many patients. There is a clear need for adjunct therapies that can reduce myocardial injury and improve healing. *Viburnum opulus*, with its abundant polyphenols and traditional use in cardiovascular and inflammatory disorders, offers a compelling natural intervention to fill this gap. Through this literature review, we have outlined how *V. opulus* can counteract key pathological processes of MI: it scavenges harmful oxidants, dampens excessive inflammation, supports endothelial and ventricular function, and importantly, may modulate the neprilysin–natriuretic peptide axis to favor cardioprotection.

Emphasizing neprilysin and natriuretic peptide regulation provides a novel perspective on *V. opulus*'s benefits. Modern heart failure therapy has validated that enhancing natriuretic peptides (and inhibiting their degradation) leads to better outcomes. The possibility that a natural substance like *V. opulus* could augment this

same pathway is intriguing. Early evidence suggests *V. opulus*-treated hearts experience a more balanced neurohormonal state after MI, with lower neprilysin and more effective natriuretic peptide signaling, akin to a physiological ARNI effect. This might translate into less fluid overload, lower cardiac filling pressures, and reduced remodeling – outcomes that are highly desirable in post-MI care.

It is important to note that while preclinical results are promising, clinical data in humans are still lacking. Future research should prioritize: (1) isolating and identifying the specific compounds in *V. opulus* responsible for neprilysin inhibition or NP preservation, (2) confirming these effects in *in vivo* models of MI (including possibly large animal models) and in *in vitro* assays of NEP activity, and (3) conducting pilot clinical studies or trials in post-MI or heart failure patients to assess safety, optimal dosing, and efficacy of *V. opulus* (for example, as an extract capsule or functional beverage). Additionally, gene expression studies on infarcted myocardium could clarify how *V. opulus* influences pathways like Nrf2, NF-κB, and TGF-β (which drives fibrosis).

From a practical standpoint, *V. opulus* as a therapeutic agent could be integrated with existing treatments. Its use does not preclude standard care; in fact, it may complement β-blockers, ACE inhibitors, and ARNI by providing antioxidative and endothelial benefits that those drugs do not directly address. For patients who prefer natural or dietary supplements, *V. opulus* could be an attractive option, provided it is administered in a standardized, evidence-based manner.

In conclusion, *V. opulus* exemplifies the potential of nutraceuticals in cardioprotection. Its multi-targeted actions – especially the enhancement of intrinsic cardioprotective systems like natriuretic peptides and the mitigation of maladaptive enzymes like neprilysin – highlight a sophisticated mechanism of benefit that

modern pharmacology seeks to achieve. As research continues to unravel its molecular effects, *V. opulus* may well transition from folk remedy to a scientifically endorsed adjunct in the prevention and management of myocardial infarction and its sequelae. Harnessing such natural cardioprotective strategies, alongside conventional therapy, moves us closer to the goal of minimizing myocardial injury and improving the quality of life for patients after MI.

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CARDIOVASCULAR ADAPTATIONS TO EXERCISE IN THE LIGHT OF SCIENTIFIC FACTS

ALI GOK[1]

Introduction

It is widely recognized that cardiovascular disease (CVD) represents a significant global health burden (Beyazcicek, Beyazcicek, Kubur, & Gok, 2024; Gök & Beyazçiçek, 2024). A substantial body of research has identified physical inactivity as a primary and independent risk factor for poor cardiovascular health. In addition, a robust correlation has been demonstrated between physical inactivity and the presence of numerous risk factors that contribute to the development of cardiovascular disease (CVD) (Isath et al., 2023). The primary function of the cardiovascular system is to supply tissues with essential nutrients, particularly oxygen, and to facilitate the removal of waste products, such as carbon dioxide, from these tissues (Uzun, 2016).

The cardiovascular system undergoes significant adaptations in response to life circumstances, and these changes are essential for

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enhancing overall performance and cardiovascular health. An understanding of these adaptations is necessary to comprehend the body's response to prolonged physical activity. Endurance exercise imposes persistent demands on the cardiovascular system. The body is designed to enhance cardiovascular health by increasing the efficiency of the heart and blood vessels through physiological changes over time.

Regular exercise has been shown to have positive effects on the autonomic nervous system, increasing parasympathetic tone and decreasing sympathetic activity. These changes have been associated with lower blood pressure and heart rate in both normotensive and hypertensive individuals (Zada, Naseri, & Zalmai, 2024). For example, in middle-aged men participating in a 33-year aerobic exercise program, no increase in resting blood pressure was observed. Long-term exercise training can slow the age-related decline in maximum oxygen uptake (VO2max). A decline in VO2max of only 5.8-6.8% per decade has been observed in exercising men (Kasch et al., 1999). This represents a substantial enhancement in comparison to the deterioration observed in individuals who do not engage in physical activity, which typically exhibits a decline of 10% or more per decade.

Cardiovascular adaptations during and after exercise are complex physiological processes involving multiple systems in the body. These adaptations are critical for increasing cardiovascular efficiency, improving overall health, and reducing the risk of cardiovascular disease. Primary adaptations can be categorized as follows: acute responses during exercise and chronic adaptations resulting from regular physical activity.

Regular exercise, when performed against a workload of certain intensity, has been shown to induce long-term adaptations in the cardiovascular system and the entire body. The anticipated

chronic responses encompass cardiac hypertrophy, bradycardia, augmented stroke volume, elevated maximum oxygen consumption, skeletal muscle hypertrophy, increased skeletal muscle capillary density, augmented blood volume, elevated hemoglobin levels, alterations in blood pressure, and diminished recovery time. The effects of these responses on the heart are described as "sports heart" and are all physiological adaptations. As previously mentioned, these characteristics are relinquished upon the cessation of physical activity (Yıldız, 2023).

The recovery period, known as the period after exercise when cardiovascular adaptations are most pronounced, is the process of the body returning to its normal state for rest and restoration. During this period, microdamages in the muscles are repaired, energy stores are replenished, and the level of inflammation in the body decreases. At the same time, heart rate and respiration rate return to normal. This process allows the cardiovascular system to prepare for the next exercise and prevents health problems that can occur after excessive exercise.

Exercise is among the most potent physiological stressors in the human body, inducing both acute and chronic adaptations in the cardiovascular system. In the contemporary medical paradigm, physical inactivity is acknowledged as a significant modifiable risk factor for cardiovascular disease (Sun, Zhang, & Shi, 2024). In response to elevated metabolic demands, the cardiovascular system exhibits a notable degree of adaptability. Evidence of this adaptability includes an augmentation in cardiac output during periods of physical exertion, reaching an approximate increase of 6 liters per minute (Ainab et al., 2025). Regular exercise has been demonstrated to induce beneficial alterations in cardiovascular structure, function, and regulation, manifesting at both the structural and molecular levels (Crisafulli, Piepoli, Thijssen, & Bassareo, 2020). A substantial body of research has demonstrated the efficacy

of exercise in reducing cardiovascular dysfunction, even in specific conditions such as hemodialysis (Özdemir & Barğı, 2025).

This section discusses exercise-induced cardiovascular adaptations, with a particular focus on the physiological changes occurring in the cardiovascular system. A comprehensive review of the acute and chronic effects of exercise on the cardiovascular system, as well as the underlying molecular mechanisms and their importance in clinical practice, is provided in this study, based on the available scientific literature.

Exercise and Acute Cardiovascular Changes

During physical activity, the cardiovascular system undergoes changes to meet the increased metabolic demands associated with sudden physiological responses. During exercise, heart rate increases compared to resting levels. This increase allows the heart to pump more blood. Stroke volume also increases during exercise, enabling more blood to be pumped to the body. This results in greater delivery of oxygen and nutrients to the tissues. These adaptations are the mechanisms by which the cardiovascular system alters its structure and function to meet the increased demands of the body during exercise.

The relationship between cardiac output and metabolic demand

The most salient response of the cardiovascular system during acute exercise is a substantial increase in cardiac output to meet metabolic demands. In healthy individuals, a direct correlation has been observed between the augmentation of oxygen uptake and the escalation of cardiac output. This relationship is characterized by an approximate 6 L/min increase in cardiac output for every 1 L/min increase in oxygen uptake. The regulation in question is subject to the influence of numerous factors, including central command,

exercise pressure, reflex arcs, and arterial baroreceptors (Ainab et al., 2025). The augmentation in cardiac output that occurs during periods of physical exertion is accomplished by a concurrent rise in both heart rate and stroke volume. The cardiac response is characterized by different contributions of heart rate and stroke volume, which vary according to the intensity of physical effort. Research conducted on highly trained individuals has demonstrated that maximal heart rate and myocardial work capacity do not impose limitations on maximal exercise capacity. Conversely, cardiac contractility and left ventricular filling have the capacity to restrict cardiac output by diminishing stroke volume (Banks & Skrinjar, 2014).

During periods of physical exertion, the cardiovascular system undergoes a pronounced response, aiming to accommodate the augmented metabolic demands of active muscles. This response is accompanied by an increase in heart rate (HR), stroke volume (SV), and cardiac output (Meixner & Herbert, 2021; Nobrega et al., 2014). Heart rate can increase significantly during high-intensity activities, often exceeding 180 beats per minute. Stroke volume may also increase due to increased myocardial contractility and venous return from muscle pump action (Green, Hopman, Padilla, Laughlin, & Thijssen, 2017; Nobrega et al., 2014). These changes are mediated by autonomic nervous system adjustments that primarily promote vasodilation in active muscle groups while redirecting blood flow by constricting peripheral vessels through sympathetic activation. (Nobrega et al., 2014).

Furthermore, the augmented cardiac output during physical exertion is crucial for the delivery of oxygen and nutrients to active muscles while concurrently facilitating the removal of metabolic waste products, including carbon dioxide and lactic acid (Green et al., 2017; Nobrega et al., 2014). The body's capacity to adapt to these demands is reflected in the heart's ability to pump a greater volume

of blood with each contraction. This phenomenon is known as increased stroke volume. This phenomenon is particularly evident in athletes engaged in endurance training (Buliuolis, Ežerskis, & Poderienė, 2018; Pier & Antonio, 2020). This adaptation is frequently accompanied by a decrease in resting heart rate, indicating improved cardiovascular efficiency (Nealen, 2016).

Hemodynamic Changes and Vascular Adaptations

Hemodynamic alterations that transpire during periods of physical exertion result in pivotal adaptations within the vascular system. The hemodynamic stimuli engendered by exercise, particularly in the context of stress reduction and environmental stress, exert a direct effect on vascular structure and function [6]. These stimuli induce protective hemodynamic stimuli in the endothelium and contribute to adaptations in vascular function and structure. The hemodynamic responses in the endothelium against atherosclerosis are generated by blood flow patterns and endothelial shear stress during acute exercise. These responses serve as the foundation for vascular function and structural adaptations. It has been demonstrated that structural adaptations in arterial lumen dimensions following prolonged exercise reduce the acute functional vasodilation requirement. This reduction can be attributed to increased endothelial shear stress during repeated exercise bouts (Sakellariou et al., 2021).

Subsequent to the culmination of an exercise session, the cardiovascular system commences a recovery phase, during which heart rate and blood pressure progressively revert to baseline levels. The recovery process is influenced by a number of factors, including the intensity and duration of the exercise, the individual's fitness level, and the type of exercise performed (Romero, Minson, & Halliwill, 2017). It has been demonstrated that individuals with elevated levels of aerobic fitness demonstrate accelerated heart rate

recovery (HRR), a phenomenon that is correlated with enhanced cardiovascular health and diminished mortality risk (Kline et al., 2013; Tricot et al., 2021). An enhanced heart rate recovery (HRR) has been identified as a marker of augmented autonomic regulatory capacity and cardiovascular flexibility, thereby facilitating a more efficient recovery process (Kline et al., 2013; Romero et al., 2017).

A multifaceted relationship exists between exercise intensity, cardiovascular function, and physiological responses during the acute cardiovascular adaptations to exercise. The heart rate (HR) is influenced by a variety of factors, including metabolic demands as well as non-metabolic factors. The correlation between exercise rate (ER) and heart rate (HR) provides a fundamental understanding of this complex relationship. This distinction enables the analysis of metabolic and non-metabolic demands during physical activity, thereby providing a novel approach to estimating oxygen consumption (Baig, 2014).

Cardiovascular adaptations differ according to the type of exercise. Aerobic exercises increase oxygen consumption by increasing the work of the heart and lungs. These exercises strengthen the cardiovascular system by increasing heart rate and stroke volume. Anaerobic exercises, on the other hand, are short-term, intense activities that aim to increase muscle strength. In these exercises, the cardiovascular system adapts to work quickly and pumps more oxygen into the body to regulate blood pressure.

The investigation of cardiovascular adaptations resulting from prolonged aerobic exercise, with a focus on cardiac structure in athletes, demonstrates the potential of aerobic training to induce substantial changes in cardiac output and stroke volume. It is imperative to comprehend the physiological adaptations that ensue from protracted physical exertion to fully grasp the subject matter (Lee & Oh, 2016).

Acute exercise is defined by transient alterations in cardiac output and heart rate, which are observed during and for a brief period following each exercise session. Prolonged physical exertion has been demonstrated to result in favorable remodeling of the heart, a phenomenon referred to as "athletic heart syndrome." This topic will be addressed in subsequent sections.

Exercise and Chronic Cardiovascular Adaptations

The documented correlation between physical activity and long-term cardiovascular adaptations is well-established in the scientific literature. The intensity and duration of exercise have been demonstrated to exert a substantial influence on the magnitude of cardiovascular adaptations.

High-intensity intermittent exercise has been shown to be more effective than moderate-intensity continuous exercise in improving cardiovascular fitness and function in people with cardiovascular disease (Abell, Glasziou, & Hoffmann, 2017; Wisløff et al., 2007). However, even moderate-intensity exercise can provide significant cardiovascular benefits (Gaesser, 2007).

Structural Cardiac Adaptations

Chronic adaptations to regular exercise training result in significant structural and functional changes in the cardiovascular system. These adaptations include increased left ventricular mass, improved endothelial function, and increased vascular compliance (Kelsey Pinckard, Kedryn K Baskin, & Kristin I Stanford, 2019; Sakellariou et al., 2021). Although this effect is similar in aerobic and anaerobic sports, it is more pronounced in some anaerobic sports, such as wrestling. Studies with wrestlers aged 12-14 years show the early structural effects of chronic exercise. Significant increases in interventricular septum, left ventricular diastolic diameter, aortic root, and left atrial diameter were found in children

who wrestled compared to sedentary children. These findings suggest that exercise can cause echocardiographically identifiable changes even in childhood (Otağ & Otağ, 2011).

It has been shown that regular aerobic exercise can reduce arterial stiffness and improve the overall health of the vascular system, which is of great importance for the prevention of atherosclerosis and other cardiovascular diseases (Ogita, 2013). The mechanisms underlying these adaptations involve a combination of hemodynamic stimuli, such as increased stress on the endothelium that promotes the release of nitric oxide and other vasodilator factors (Ogita, 2013; Sakellariou et al., 2021).

Molecular and Cellular Adaptations

Exercise-induced cardiovascular adaptations involve complex regulatory mechanisms. For example, the neuropeptide α-calcitonin gene-related peptide (αCGRP) has been recognized as an important mediator of the advantageous effects of physical activity on the cardiovascular system (Skaria & Vogel, 2022). Furthermore, exercise-induced changes in gene expression and signaling pathways within the nucleus tractus solitarii (NTS), a major hub for cardiovascular regulation, play an important role in exercise-related antihypertensive outcomes (Waki et al., 2013).

Exercise-induced or physiological cardiac growth contrasts with growth elicited by pathological stimuli such as hypertension. Comparison of the molecular and cellular basis of physiological and pathological cardiac growth has revealed phenotype-specific signaling pathways and transcriptional regulatory programs. Cardiovascular adaptations to exercise are mediated by complex signaling pathways at the molecular level. These signaling pathways include the insulin-like growth factor 1/PI3K/Akt pathway. Exercise elicits coordinated multi-organ responses, including skeletal muscle, vasculature, heart, and lung. In the short term, cardiac output

increases to meet the demand of strenuous exercise. Prolonged exercise triggers cardiac remodeling, including growth and adaptive molecular and cellular reprogramming. Signaling pathways such as the insulin-like growth factor 1/PI3K/Akt pathway mediate many of these responses (Vega, Konhilas, Kelly, & Leinwand, 2017).

Cardioprotective mechanisms of exercise include induction of heat shock proteins, increased cardiac antioxidant capacity, expression of endoplasmic reticulum stress proteins, anatomical and physiological changes in coronary arteries, changes in nitric oxide production, adaptive changes in cardiac mitochondria, increased autophagy and improved function of sarcolemmal and/or mitochondrial ATP-sensitive potassium channels. (Golbidi & Laher, 2011).

Metabolic Adaptations and Energy Production

Prolonged exercise causes a number of structural and functional modifications within the cardiovascular system (Hastings et al., 2022; Wilson, Ellison, & Cable, 2016). These modifications include increases in heart chamber size, myocardial cell hypertrophy, and overall cardiac mass (Wilson et al., 2016). At the cellular and molecular levels, exercise induces adaptations characterized by enhanced mitochondrial biogenesis and increased fatty acid oxidation (K. Pinckard, K. K. Baskin, & K. I. Stanford, 2019; Wilson et al., 2016).

Metabolic changes play an important role in cardiovascular adaptation to exercise. Regular exercise leads to adaptations in many tissues in the body, especially adipose tissue and skeletal muscle. As a result, athletes' endurance capacity and sports performance increase. Adipose tissue undergoes significant changes with exercise. The browning of white adipose tissue, characterized by an increase in the number and activity of mitochondria, has a positive effect on sports performance by increasing total brown adipose

tissue. Exercise also increases energy production and oxygen utilization capacity. While an increase in oxidative stress can be observed alongside increased mitochondrial activity, during prolonged exercise the body's antioxidant defense system is activated, thus minimizing the negative effects of oxidative stress (Badem & Dikmen, 2024).

In addition, exercise training causes favorable changes in blood lipid profiles, including a decrease in low-density lipoprotein (LDL) cholesterol and an increase in high-density lipoprotein (HDL) cholesterol (Ogita, 2013; Kelsey Pinckard et al., 2019). These lipid changes contribute to a reduced risk of coronary heart disease and other cardiovascular diseases. Furthermore, regular physical activity has been associated with improved glucose metabolism and insulin sensitivity, further reducing cardiovascular risk factors, especially in populations with metabolic disorders such as diabetes (Okada et al., 2010).

In mammalian species, heart size increases in proportion to body size, increased metabolic demand, and the need to supply large amounts of blood volume (Shave, Howatson, Dickson, & Young, 2017). This exercise-induced cardiac remodeling has also been clearly seen in human endurance athletes and has been termed the "athlete's heart" (La Gerche, Roberts, & Claessen, 2014).

Literature reviews on the relationship between exercise and heart volume provide important insights into the effects of exercise on cardiac structure and function by providing an in-depth review of important studies and findings in this field. The effects of long-term aerobic exercise on cardiac structure, left ventricular stroke volume, and cardiac output were examined. The study showed significant differences between regular exercisers and the control group in terms of various measurements of the left ventricle. In particular, it has been emphasized that prolonged aerobic exercise leads to an

improvement in cardiac structure, the so-called 'athletic heart,' which is distinguishable from pathological manifestations. These findings suggest that exercise positively affects heart volume and function (Lee & Oh, 2016).

On the other hand, a study examined the effects of exercise on left ventricular systolic and diastolic cardiac function in sedentary women. In this study comparing step aerobics and core exercises, the effectiveness of exercise types in improving left ventricular function and reducing cardiovascular risk factors was determined. This study makes an important contribution to understanding the effects of different types of exercise on heart volume and function (Cicek et al., 2017).

Adaptation of the cardiovascular system to exercise is also influenced by genetic and environmental factors. For example, individual responses to exercise training can vary considerably depending on genetic predisposition, which affects cardiovascular structure and function (Papadakis et al., 2012). Furthermore, factors such as age, gender, and ethnicity may also play a role in how the cardiovascular system adapts to exercise, highlighting the importance of personalized exercise prescriptions in clinical settings (Islam, Khalsa, Vyas, & Rahimian, 2021).

Exercise-induced cardiovascular adaptations have been shown to exert protective effects against a range of cardiovascular diseases, including coronary artery disease, heart failure, and anthracycline-induced cardiotoxicity (Kang et al., 2021; Thijssen, Redington, George, Hopman, & Jones, 2018). However, the capacity to adapt to exercise is known to decline with age, a phenomenon that can be attributed to the disruption of signaling pathways involved in adaptive homeostasis (Davies, 2018).

Cardiovascular Adaptations in Special Populations

The cardiovascular effects of exercise in children and adolescents show different characteristics compared to adults. Studies on 12-14 year-old children participating in wrestling have shown that physical exertion can lead to echocardiographically identifiable changes even in this age group. These findings suggest that even in childhood, exercise can cause measurable adaptations in the cardiovascular system (Otağ & Otağ, 2011).

Cardiovascular effects of exercise in hemodialysis patients demonstrate the therapeutic value of exercise in special populations. Hemodialysis is a life-saving treatment for patients with chronic renal failure; however, it can also cause health complications, including cardiovascular dysfunction. Cardiovascular dysfunction during hemodialysis can typically be attributed to factors such as fluid imbalance, electrolyte imbalances, and oxidative stress. Exercise approaches to address these complications include aerobic exercises, home programs, and resistance exercise training. A review of the existing literature shows that aerobic exercise regimens are particularly effective in reducing cardiovascular complications in individuals undergoing hemodialysis. Improved heart rate regulation, increased blood flow, and cardiovascular endurance are observed following exercise training. (Özdemir & Bargı, 2025).

In acute disease states such as COVID-19 infection, more thought needs to be given to the cardiovascular effects of exercise. In the post-acute period, physiotherapy and rehabilitation may be useful in coping with potential respiratory, functional, and emotional losses resulting from prolonged mechanical ventilation and prolonged stay in intensive care after COVID-19 infection (İnce, Yağlı, Sağlam, & Kütükcü, 2020).

Effects of Exercise on Platelet Functions and Coagulation

The important function of platelets in the development of atherosclerosis and cardiovascular diseases has significantly driven researchers to investigate the effect of physical exercise on platelets. It has been shown that acute, vigorous exercise can cause hyperreactivity in platelets. This phenomenon may be related to exercise-induced oxidative stress and the thromboxane A2 pathway. Acute exercise has been shown to cause an increase in collagen-induced platelet secretion concomitant with a decrease in plasma total antioxidant status. Studies suggest that acute exercise produces a transient activator effect on platelet function, which is closely related to changes in antioxidant capacity. It has been shown that even short-term training programs can increase antioxidant defenses in plasma, and this may be concomitant with a decrease in platelet sensitivity. In experimental animals in the short-term training group, plasma total antioxidant status levels were found to increase, and ADP-induced platelet ATP secretion was found to decrease. A significant negative correlation was found between these two parameters (Fiçicilar, 2004).

Exercise, Endothelial Function and Vascular Health

Endothelial function is considered a valuable marker of cardiovascular health, as it indicates the body's ability to maintain homeostasis of vascular tone. The demonstration of the positive effects of 8 weeks of knee extension exercise on endothelial function demonstrates the direct effects of exercise on vascular health (Crisafulli et al., 2020).

Exercise produces direct effects on the vasculature through the impact of hemodynamic forces on the endothelium, leading to functional and structural adaptations that reduce cardiovascular risk. These adaptations are facilitated by blood flow patterns and endothelial shear stress during exercise. Observation of structural

adaptations in arterial lumen dimensions following prolonged exercise demonstrated a reduction in the acute need for functional vasodilation during repeated bouts of exercise, which may be attributable to an increase in endothelial shear stress. In contrast, inner wall thickness is influenced by systemic factors, including transmural pressure, which is modulated by overall changes in blood pressure during periods of exercise (Sakellariou et al., 2021).

Cardiovascular Adaptations for Performance and Conditioning

As demonstrated in the extant literature, the isoforms of the lactate/proton co-transporter (MCT1 and MCT4) located in the plasma membranes of skeletal muscle have been shown to play a role in both muscle pH and lactate regulation. The present study hypothesizes that the expression of sarcolemmal MCT isoforms may play an important role in exercise performance. Acute exercise has been demonstrated to induce alterations in human MCT content within the first 24 hours following the onset of exercise, while chronic exercise exerts a distinct effect on MCT1 and MCT4 content, independent of initial conditioning levels. Intensity has been identified as the most significant factor in regulating exercise-induced changes in MCT content. The regulation of these proteins is of critical importance for the cardiovascular system's adaptation to metabolic demands (Bayrak, Patlar, & Bulut, 2024).

In a study investigating the effects of isometric preconditioning contraction protocols on jump performance, the researchers sought to contribute to our understanding of the acute adaptive capacity of the cardiovascular system. The effect of preconditioning contractions involving isometric leg press exercises performed following a traditional warm-up routine on acute performance outcomes was found to be heterogeneous (Kaçoğlu & Yıldırım, 2017).

In recent years, the hypothesis has been proposed that mitochondrial stress may provide short-term metabolic benefits and induce a hormetic effect, thereby offering long-term benefits in terms of increased stress resistance and lifespan. This response, termed mitohormesis, has been shown to enhance an organism's resistance to stress factors, thereby facilitating adaptation. This mechanism constitutes the molecular basis for the long-term protective effects of exercise on the cardiovascular system. Depending on the type, intensity, and duration of exercise, specific physiological changes occur in the body. The efficacy of these changes in enhancing the adaptive capacity of the cardiovascular system has been demonstrated (Badem & Dikmen, 2024).

These literature reviews synthesize extant research, offering an exhaustive examination of the relationship between physical activity and cardiac volume. Each study employs a distinct approach to examining the effects of exercise on heart health, thereby contributing to the expansion of the extant body of knowledge in this field.

Prospective Observations

The effects of exercise on the cardiovascular system involve complex and multidimensional adaptations at both acute and chronic levels. The precise regulation of cardiac output in response to metabolic demand during acute exercise demonstrates the extraordinary adaptive capacity of the cardiovascular system (Ainab et al., 2025). The effects of chronic exercise at structural, functional, and molecular levels demonstrate the therapeutic value of exercise in the prevention and treatment of cardiovascular diseases (Golbidi & Laher, 2011; Özdemir & Bargı, 2025).

The effects of chronic exercise at structural, functional, and molecular levels demonstrate the therapeutic value of exercise in the prevention and treatment of cardiovascular diseases (Özdemir &

Bargı, 2025). The cardiovascular adaptations evident in children and adolescents from a young age underscore the significance of cultivating habitual exercise routines from an early age, a practice that research has identified as critical to promoting cardiovascular well-being and reducing the risk of adverse health consequences over time (Otağ & Otağ, 2011).

Subsequent research, delving into the molecular underpinnings of cardiovascular adaptations to exercise with greater precision, is anticipated to facilitate the development of personalized exercise prescriptions. A more profound comprehension of recently identified mechanisms, such as mitohormesis, is imperative [36]; it possesses the potential to unlock new ways to enhance the cardioprotective benefits of exercise. Furthermore, the enhancement of the quality and standardization of online information regarding exercise in cardiovascular disease is becoming increasingly imperative (Cimen, 2025).

Conclusion

In summary, cardiovascular adaptations during and after exercise are imperative for enhancing physical performance and overall health. The relationship between exercise and cardiovascular adaptations is characterized by a complex interaction of acute responses and chronic changes that enhance cardiovascular efficiency, reduce disease risk, and improve overall health. During periods of acute exercise, there is a notable increase in heart rate, stroke volume, and cardiac output. Conversely, the recovery phase is marked by a return to baseline levels, which are influenced by the individual's fitness level and the intensity of the exercise. Chronic adaptations encompass structural changes in the heart and blood vessels, enhanced endothelial function, and favorable alterations in lipid profiles. Collectively, these adaptations contribute to a diminished risk of cardiovascular disease. There is substantial

evidence supporting the cardiovascular benefits of regular physical activity, and numerous studies emphasize the importance of exercise as a non-pharmacological intervention for preventing and managing cardiovascular diseases. Future research should continue to explore the underlying mechanisms of these adaptations and identify the most appropriate exercise methods to optimize cardiovascular health in different populations.

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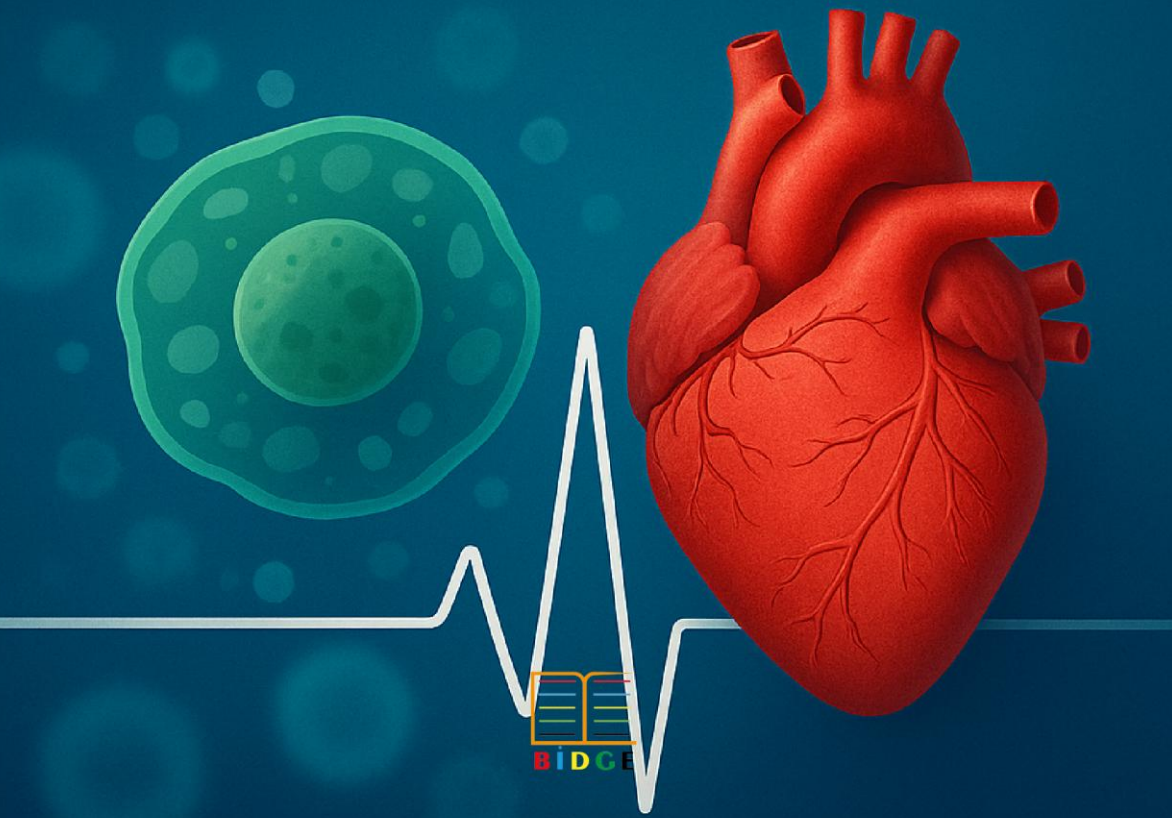
A HOLISTIC APPROACH TO PHYSIOLOGY

FROM CELLULAR STRESS TO CARDIOVASCULAR ADAPTATION



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