https://jsras.rcc.edu.ly/
Vol.3 No.2 (2026), 1-6
Article history:
Received: 10 May. 2026
Accepted: 15 May. 2026
Published: 10 Jun. 2026

Journal of Sustainable Research in Applied Sciences

The Role of Molecular Chaperones and Protein Quality Control Systems in Disease

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DOI: https://doi.org/10.36602/jsras.2026.3.2.1
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Index Terms
Molecular Chaperones, Proteostasis, Protein Quality Control Systems, Diseases.

Abstract
Protein homeostasis, or proteostasis, is essential for cell health as it includes a network of chaperones and degradation mechanisms that control proper protein function. Major chaperones such as Hsp70, Hsp90, Hsp60, and GRP78, prevent protein aggregation, allow correct folding, and aid in the removal of damaged proteins. During stress, specialist systems like ER-associated degradation and unfolded protein responses help to maintain proteostasis across various cell compartments. This article studies how proteostasis failures are linked to neurodegenerative diseases such as Alzheimer's and Parkinson's, where chaperones lead to harmful protein buildup in neurons. Chaperones, on the other hand, increase cancer cell survival by stabilizing dangerous proteins. Thus, chaperones can be both harmful and beneficial, making them promising for therapeutic interventions.

دور المرافقات الجزيئية وأنظمة مراقبة جودة البروتين في الأمراض

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DOI: https://doi.org/10.36602/jsras.2026.3.2.1
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الكلمات المفتاحية
المرافقات الجزيئية، الاستتباب البروتيني، أنظمة مراقبة جودة البروتين، الأمراض.

الملخص
يُعد التوازن البروتيني أو الاستتباب البروتيني Proteostasis أمرًا أساسيًا لصحة الخلايا، إذ يشتمل على شبكة من المرافقات البروتينية (Chaperones) وآليات التحلل التي تتحكم في الأداء السليم للوظائف البروتينية. وتعمل المرافقات الرئيسية مثل Hsp70، وHsp90، وHsp60، وGRP78 على منع تجمع البروتينات، وتتيح طيها بشكل صحيح، وتساعد في التخلص من البروتينات التالفة. وخلال فترات الإجهاد الخلوي، تساعد الأنظمة المتخصصة مثل التحلل المرتبط بالشبكة الإندوبلازمية(ERAD) واستجابات البروتين غير المطوي (UPR) في الحفاظ على التوازن البروتيني عبر مقصورات خلوية متعددة. وتدرس هذه المقالة كيفية ارتباط فشل التوازن البروتيني بالأمراض التنكسية العصبية مثل الزهايمر وباركنسون، حيث يؤدي خلل المرافقات إلى تراكم بروتيني ضار في الخلايا العصبية. ومن ناحية أخرى، تزيد المرافقات البروتينية من فرص بقاء الخلايا السرطانية من خلال تثبيت البروتينات الخطرة. وبذلك، يمكن أن تكون هذه المرافقات ضارة ومفيدة في آن واحد، مما يجعلها أهدافاً واعدة للتدخلات العلاجية المستقبلية.

1. INTRODUCTION

Proteins carry out various functions in biological systems, such as immune regulation, intracellular signaling, structural reinforcement, and enzymatic catalysis, all of which are necessary function components. Correct protein folding is a fundamental cellular priority since its biological activity is entirely dependent on the integrity of its three-dimensional structure. The proteostasis network is a collection of integrated protein quality control mechanisms upon which cells depend in order to maintain a healthy and functional proteome. By incorporating protein synthesis, folding, trafficking, and targeted degradation, this mechanism prevents the accumulation of misfolded or aggregated proteins that could disrupt cellular balance. Changes in proteostasis have been linked to various human illnesses; for example, neurodegenerative disorders, whereas some tumors utilize hyperactive proteostasis pathways to promote uncontrolled proliferation (1).

Molecular chaperones, are essential as regulatory system. They are essential for preventing premature aggregation and encouraging appropriate conformational maturation in families like heat shock proteins (Hsp70, Hsp90, and Hsp60). While Hsp60 and associated chaperonins generate a regulated environment that promotes folding, Hsp70 interacts with exposed hydrophobic areas on unfolded chains. Hsp90 performs a specialized function in preserving the stability and activity of signaling proteins, such as kinases and receptors (2,3). Chaperones function in close coordination with protein degradation systems, namely the ubiquitin-proteasome system (UPS) and autophagy pathways. In the UPS, misfolded proteins are tagged with ubiquitin by the sequential actions of the E1, E2, and E3 enzymes, allowing the proteasome to selectively degrade them. Larger aggregates or damaged organelles are removed by autophagy, in which cellular components are sequestered and transported to lysosomes for degradation (4,5).

The endoplasmic reticulum (ER) has a strong quality control mechanism called ER-associated degradation (ERAD), which identifies, ubiquitinates, and retrotranslocates misfolded proteins to the cytosol for proteasomal destruction. Cells activate the unfolded protein response (UPR) when the ER's folding capacity is surpassed. Through the IRE1, PERK, and ATF6 pathways, this adaptive signaling network lowers total protein synthesis while increasing the expression of chaperones and ER-associated quality control elements. Prolonged ER stress, drives the UPR toward pro-apoptotic signaling pathways, eventually resulting in programmed cell death (6,7), even though it is initially protective. Similarly, mitochondria maintain their proteome through chaperones and specialized proteases and respond to proteotoxic challenges via the mitochondrial unfolded protein response (UPRmt). In the face of oxidative or metabolic stress, this route aids in maintaining mitochondrial function and encourages the expression of stress-mitigating factors (8).

1.1 Proteostasis (Protein Homeostasis)

Protein homeostasis, or proteostasis, is a key biological process that ensures proteins are properly synthesized, folded, maintained, and degraded inside cells. This complex balance is crucial for cellular function, adapting to environmental changes, and avoiding diseases caused by protein misfolding and aggregation. The proteostasis network (PN) is a highly coordinated system made up of molecular chaperones, protein degradation pathways, and regulatory mechanisms that work together to maintain the integrity of the proteome throughout an organism's life (9,10).
The difficulties of managing a large and dynamic proteome are at the heart of proteostasis.

With molecular chaperones serving as key coordinators, the PN oversees protein biogenesis, folding, conformational maintenance, and timely degradation. These chaperones aid in the folding of newly formed polypeptides, prevent misfolding, and guide aberrant proteins toward refolding or degradation. The two primary degradation systems—the ubiquitin-proteasome system (UPS) and the autophagy-lysosomal pathway—work together to eliminate damaged or extra proteins, hence preventing the buildup of hazardous aggregates (11).

Proteostasis is not a static process; rather, it is actively controlled in reaction to cellular stress, ageing, and environmental pressures. As we age, the PN's capacity diminishes, resulting in a decrease in the efficiency of protein folding and degradation. This drop is especially harmful in non-dividing, long-lived cells like neurons, where a lack of proteostasis contributes to the pathophysiology of neurodegenerative diseases like Alzheimer's and Parkinson's. The accumulation of misfolded and aggregated proteins in these circumstances highlights the crucial role of proteostasis in preserving cellular and organismal health (12).

1.2 Main Components of the Proteostasis Network

There are a few essential elements in the proteostasis network that collaborate to preserve protein homeostasis (13):

1. Protein Synthesis / Translation: The mechanism through which proteins are synthesized. It involves ribosomes and related molecules that guarantee the precision of protein synthesis (14).
2. Molecular Chaperones: These proteins help in the proper folding of newly formed proteins, prevent misfolding and aggregation, and aid in the refolding of misfolded proteins. Heat shock proteins (HSPs), including Hsp70 and Hsp90, are among the most significant chaperone families (15).
3. The Ubiquitin-Proteasome System (UPS): the primary method for breaking down proteins that are misfolded or have a short lifespan. It involves attaching ubiquitin chains to proteins, which tells the 26S proteasome to degrade them. The enzymes E1, E2, and E3 are involved in the ubiquitination process (16).

4. Autophagy-Lysosomal Pathway: A catabolic mechanism that includes the lysosomal degradation of cellular components, such as misfolded proteins, protein aggregates, and broken organelles. Two advantages of autophagy include the removal of harmful proteins and the maintenance of cellular health (17). The many types of autophagy include selective autophagy, chaperone-mediated autophagy (CMA), macroautophagy, and microautophagy (18).
5. Stress Response Pathways: In response to cellular stress, these pathways—like the unfolded protein response (UPR) and the heat shock response (HSR)—aid in reestablishing proteostasis by increasing the synthesis of chaperones and other protective proteins (19).

1.3 Molecular Chaperones

Molecular chaperones are a diverse group of proteins that are essential for maintaining cellular protein homeostasis, or proteostasis, by facilitating the proper folding, assembly, and breakdown of other proteins. Newly produced polypeptides are constantly at risk of misfolding and aggregation in the congested and dynamic cellular environment, which can result in loss of function and the creation of toxic species. Molecular chaperones act as surveillance agents, ensuring that proteins achieve and maintain their functional conformations, particularly when subjected to cellular stressors like high temperature, oxidative stress, or exposure to toxins (20)(21).

Chaperones are divided into two families: ATP-dependent and ATP-independent. Through cycles of ATP binding and hydrolysis, ATP-dependent chaperones, such as the Hsp70 and Hsp90 families, actively help client proteins fold and refold by facilitating substrate binding and release. To regulate their activity and direct substrates along pathways for folding, retention, or degradation, these chaperones often collaborate with co-chaperones (22). For example, the Hsp70 system is crucial for maintaining protein quality because it interacts with a wide range of substrates and collaborates with other chaperone systems and degradation machinery to protect the integrity of the proteome (23). On the other hand, ATP-independent chaperones, such as small heat shock proteins (sHsps) like caseins and α-crystallins, mainly work by attaching to partly unfolded proteins and stopping their aggregation, particularly under stress. These chaperones are especially crucial for maintaining clarity and preventing cataract development in tissues with low protein turnover, like the lens of the eye (24).

Molecular chaperones have flexible mechanisms to help proteins fold correctly. They protect non-native proteins from unwanted interactions and guide them to fold properly. Chaperones can also isolate misfolded proteins, help refold them, or mark them for degradation. This process is vital for cell health, as misfolded proteins relate to diseases like Alzheimer's and Parkinson's (25).

1.4 Protein Quality Control (PQC) Systems

They are essential for ensuring the structural and functional integrity of the cellular proteome. These mechanisms guarantee that freshly produced polypeptides fold correctly, remain stable, and are properly trafficked or destroyed if damaged. Proper protein conformation is critical because even modest folding mistakes can impair metabolic processes, signaling networks, and cell survival. PQC, therefore, incorporates processes of protein synthesis, molecular chaperoning, and targeted degradation to protect proteome stability; perturbations in these networks are significantly related to neurological disorders and cancer (26).

Molecular chaperones are essential to the PQC system because they aid newly synthesized or stress-denatured proteins in attaining their functional conformations.

To get rid of proteins that cannot be rescued, these chaperones work in tandem with degradation pathways like the ubiquitin-proteasome system (UPS) and autophagy. These chaperones collaborate with degradation mechanisms such as the ubiquitin-proteasome system (UPS) and autophagy to eliminate proteins that cannot be salvaged. In the UPS route, E1, E2, and E3 enzymes work together to bind ubiquitin molecules to faulty substrates, designating them for proteolysis inside the 26S proteasome (26). Autophagy, which sequesters cellular components into autophagosomes for lysosomal breakdown, clears larger aggregates or damaged organelles (27).

In organelles with significant protein folding needs, such as the endoplasmic reticulum (ER), PQC is especially crucial. ER-associated degradation (ERAD), the ER's own quality control mechanism, identifies misfolded secretory and membrane proteins, retrotranslocates them into the cytoplasm, and marks them for ubiquitin-mediated degradation. The unfolded protein response (UPR) is activated by sensors like IRE1, PERK, and ATF6 when the amount of misfolded protein in the endoplasmic reticulum (ER) exceeds its capacity (7). This response momentarily stops total protein production while simultaneously boosting chaperone expression in an effort to regain equilibrium. If stress persists, the signaling mechanism changes to apoptotic pathways, which causes programmed cell death (28). Similar strategies, such as mitochondrial chaperones and proteases, are used by mitochondria to activate the mitochondrial UPR (UPRmt) in order to mitigate oxidative and proteotoxic stress, hence protecting organelle function (29). Most mitochondrial proteins come from nuclear genes and need to be imported into mitochondria. This process is done by translocases, specifically the TOM and TIM, which help proteins get to the right places in the mitochondria (30).

Mitochondrial chaperones, help newly imported proteins fold correctly, preventing problems. Mitochondrial proteases remove misfolded or damaged proteins to keep only properly folded ones active (31).

The ubiquitin-proteasome system checks the outer mitochondrial membrane for damaged proteins and labels them for degradation to maintain health. The mitochondrial unfolded protein response (UPRmt) is a protective response that helps manage protein stress by refolding misfolded proteins and regulating chaperones and proteases (32).

1.5 Proteostasis Failure and Its Consequences

Changes in the fine balance of protein production and breakdown are the main cause of proteostasis failure. One of the most severe consequences is the accumulation of misfolded proteins, which have the potential to aggregate and generate toxic compounds. For example, misfolded proteins like amyloid-beta and alpha-synuclein have been shown to trigger a cascade of detrimental events in neurodegenerative diseases such as Alzheimer's and Parkinson's (33). By interfering with organelle integrity, mitochondrial activity, and communication routes, these aggregates can impair cellular functions, ultimately resulting in neuronal cell death (34).

Additionally, immune response may be hampered by proteostasis malfunction. According to studies, the unfolded protein response is triggered by endoplasmic reticulum (ER) stress, which is brought about by protein misfolding. Although the UPR is initially helpful, ongoing activation can result in inflammation, which increases the risk of developing autoimmune illnesses and systemic inflammation (35).

Cancer is another area where proteostasis failure has a large impact. Tumor cells employ the proteostasis network to survive situations that would typically cause apoptosis, such as food restriction and hypoxia (36). The overexpression of molecular chaperones, in malignant cells helps to stabilize oncogenic proteins and prevent their degradation (37). As a result, cancer cells are able to maintain their proliferative capacity even in the face of significant cellular stress. As a result, targeting the proteostasis network offers a viable avenue for cancer therapy, and researchers are exploring the potential of small-molecule inhibitors that disrupt chaperone activity as potential treatments (36). In addition to cancer and neurological conditions, proteostasis failure has been associated with metabolic diseases, in which faulty proteins build up and interfere with metabolic functions. The misfolding of proteins critical in insulin signaling is the main way that endoplasmic reticulum stress has been linked to insulin resistance in type 2 diabetes (38).

2. CONCLUSION

In the PQC pathway within cells, chaperones play crucial roles in proteostasis, which involves proper protein folding, protection against protein aggregation, and targeting damaged proteins for degradation through the UPS or autophagy/lysosomal pathway. Dysregulation of the above processes plays an important role in the development of various diseases, wherein neurodegenerative disorders like Alzheimer's disease and Parkinson's disease are associated with the formation of protein aggregates as a defining feature. Therefore, approaches that promote enhanced protein removal by chaperones hold promise as a therapeutic approach to restoring homeostasis and preventing neurodegeneration (1).

However, even though they are known for protecting cells under normal circumstances, there are several molecular chaperones that have a paradoxical role in the field of cancer. It is a fact that tumor cells make use of the chaperone system to help stabilize oncogenic proteins, and also cope with adverse environmental conditions including hypoxia, nutrient deprivation, and drug stress. Some of these chaperones that play an important part include HSP90 and HSP70 since these chaperones have been implicated as key players in cancer cells owing to the fact that they help stabilize and activate a range of oncogenic proteins like mutant p53, AKT, HER2, EGFR, and BCR-ABL (39)(40).

Through the similar principles as other mechanisms leading to oncogenesis, HSP60 has been shown to play a role in cancer development because of its contribution to the preservation of mitochondrial structure, metabolism regulation, and apoptosis inhibition. High levels of HSP60 have been associated with increased tumor stages and metastasis formation along with negative consequences in various cancers, such as colorectal, ovarian, and hepatocellular carcinoma. Also, HSP60 is involved in cancer cell survival due to the interaction with proteins responsible for mitochondrial apoptosis and metabolism regulation. All these facts allow suggesting that HSP60 can be regarded as both a prognostic factor and a possible target of therapy (41).

Yet another chaperone that is known to play an important role in cancer development is ER-resident glucose-regulated protein 78 (GRP78/BiP). During prolonged exposure to ER stress, the concentration of GRP78 increases and it can move from the ER to the surface of the cell, acting as a signal receptor that stimulates survival pathways. Overexpression of GRP78 is considered to be responsible for the increased aggressiveness of tumors, as well as cell proliferation and metastasis, and plays an important role in increasing their resistance to therapy. Additionally, surface-bound GRP78 (csGRP78) is considered to be an extremely promising target for anti-tumor therapy due to selective expression on cancer cells and contribution to drug resistance mechanisms. In recent times, anti-GRP78 monoclonal antibodies, peptides, and nanoparticles were shown to be highly promising tools for cancer-selective inhibition (42)(43).

In general, the dysregulation of chaperone expression is considered one of the characteristics of malignant transformations that facilitate the use of proteins in the maintenance of protein homeostasis by cancer cells. The growing number of studies on the issue has increased interest in the development of chaperone-based approaches to treatment. Currently used techniques include HSP90 inhibitors, HSP70 regulation agents, anti-GRP78 antibodies, peptides, and nanoparticles designed to specifically affect protein homeostasis of tumors. The prospects for further investigation include the development of combinations of the therapy involving chaperones with immunotherapy and precision medicine. In addition, advancements in proteomics, drug discovery powered by artificial intelligence, and the use of targeted nanocarriers will facilitate the introduction of novel approaches to targeting protein chaperones (39)(43).

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