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Review Article

Balancing act: navigating the intricacies of proteostasis

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ABSTRACT

Proteostasis, the intricate balance of protein synthesis, folding, trafficking, and degradation, is a fundamental cellular process crucial for maintaining cellular health and homeostasis. Imbalances in proteostasis are implicated in various diseases, including neurodegenerative disorders, cancer, aging, type 2 diabetes mellitus, cataract, huntington's disease, heart disease, sarcopenia, ischemic disorders, diabetic neuropathy and other metabolic conditions. We delve in to the proteostasis mechanisms and highlight the significance of proteostasis in the context of protein misfolding diseases that have broadened our understanding of proteostasis network. Further, we explore the relevance of proteostasis in cancer, shedding light on the interplay between the ubiquitin-proteasome system and oncoproteins. Furthermore, we also address therapeutic approaches aimed at modulating proteostasis to combat protein misfolding diseases. The mysteries of protein balance continue to captivate researchers, and the evolving landscape of proteostasis research promises insights into novel therapeutic strategies and a deeper understanding of its role in human health. This review offers a comprehensive perspective on the ever-expanding frontiers of proteostasis research, with the hope of inspiring further exploration and innovation in this dynamic field.

Keywords: Cancer, Neurodegenerative diseases, Proteostasis, Therapeutic strategies, Ubiquitin-proteasome system

INTRODUCTION

Proteins play a central and diverse role in the functioning of cells and organisms. They are involved in every biological process and serve various crucial functions, making them essential components of life.[1] From enzymatic activities (metabolism, DNA replication, protein synthesis etc.) to structural support and regulatory functions, proteins are the backbone of biological processes. Proteostasis, which refers to the maintenance of protein stability and function within a cell or organism, is indeed crucial for the survival of every living cell. This is because numerous essential physiological functions depend on well-regulated proteostasis. Proteostasis, also known as protein homeostasis, is a state of maintaining a healthy and balanced proteome within a cell. It is a dynamic process and encompasses a range of processes including protein synthesis, post translational modification, folding, maintenance, quality control and degradation of damaged or unwanted proteins. These processes involve various cellular mechanisms, such as the proteasome, autophagy, lysosome, and cytoplasmic enzymes, which work together to ensure that proteins are properly folded, functional, and appropriately regulated, while also eliminating those that may be damaged or no longer needed.[2] It is a finely tuned and highly coordinated cellular mechanism, governs the health and vitality of living organisms. These processes range from protein synthesis and proper folding to accurate trafficking and regulated degradation of proteins. Proteins rely on specific structures for their function, dictated by the sequence of amino acids in their polypeptide chains. However, most proteins are intricate and require assistance to fold correctly. Molecular chaperones help

proteins fold properly, preventing misfolded states, especially under cellular stress. Errors in folding can lead to loss of function and harmful protein aggregation, disrupting cell balance. Protein folding and chaperone activity are vital for maintaining cellular health and functionality. Proteostasis ensures that proteins are properly folded, transported, and degraded, which, in turn impacts their functionality and stability. Disruptions in proteostasis can lead to various diseases and cellular dysfunction. It consists various cellular pathways and processes that collectively maintain protein homeostasis within the cell. These pathways rely on a multitude of enzymes, molecular chaperones, and specialized proteins to ensure the correct folding and regulation of the cell's proteome. Intracellular proteostasis refers to the maintenance of protein homeostasis within the cell's interior.[3]

It essentially relates to the overall management of protein health and function within the cell, which encompasses all the processes. Both cellular and intracellular proteostasis are interconnected and critical for the cell's survival and the prevention of protein misfolding, aggregation, and the associated detrimental consequences. Intracellular proteostasis involves keeping proteins properly folded, functional, and free from harmful aggregation. This is crucial for the cell's overall health and proper functioning. In the pursuit of unravelling the mysteries of protein balance, we will delve into proteostasis mechanism, uncover novel therapeutic approaches and deepen our comprehension of the role of proteostasis in human health and diseases. Furthermore, discussion of how disturbances in proteostasis and proteotoxicity are associated with various diseases like neurodegenerative disorders and cancer.

PROTEOSTASIS MECHANISMS

An exploration of the complex network of cellular machinery that ensures proper protein folding, trafficking, and degradation. The proteostasis network, also known as the protein homeostasis network, is a complex and highly regulated system within cells responsible for maintaining the proper balance of protein synthesis, folding, trafficking, and degradation (Figure 1).[4] It ensures that proteins achieve and maintain their correct three-dimensional structures and functional states. Various components of the proteostasis network are as follow:

Protein synthesis

Proteins are synthesized in the cell's ribosomes, following the instructions encoded in messenger RNA (mRNA). Nascent polypeptide chains emerge from the ribosome, and they are initially in an unfolded or partially folded state. Excessive synthesis of proteins can lead to proteostasis imbalance. To maintain proteostasis, it is crucial to regulate the biosynthetic flux of proteins.[5] This involves controlling the rate of protein synthesis and ensuring that it matches the capacity of protein folding, quality control, and degradation systems.

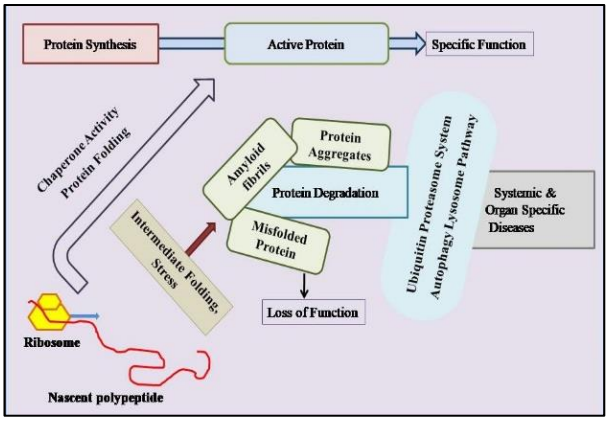

Figure 1: Proteostasis network mechanism and its components.

Molecular chaperones

Molecular chaperones are fundamental components of the proteostasis network, contributing to the maintenance of protein homeostasis. Their role in protein biogenesis and proteostasis is central to maintaining cellular health and preventing proteotoxicity-related diseases. They play a central and essential role in maintaining protein quality control systems within the cell. These specialized proteins are critical for ensuring that newly synthesized polypeptides achieve their correct three-dimensional structures and functional states, particularly in the complex and crowded cellular environment 6. They recognize exposed hydrophobic regions on nascent polypeptides, preventing them from aggregating or misfolding. Members of these chaperone protein families are often referred to as heat-shock proteins or stress proteins (HSPs). Chaperones can be classified based on their molecular weight, and some of the well-known classes include HSP40, HSP60, HSP70, HSP90, HSP100, and small ATP-independent HSPs (sHSPs).[6]

They assist in the correct folding of newly synthesized proteins. When proteins become misfolded or denatured under stress conditions, chaperones aid in refolding them to their functional states. Further, chaperones are classified based on sort of interactions with proteins is holdases, foldases, and disaggregates. Holdases recognize and stabilize partially folded or misfolded proteins, preventing their aggregation without using adenosine triphosphate (ATP). They maintain these proteins in a state conducive to refolding and presenting client proteins to foldases. This plays a central role in the actual process of facilitating the correct folding of client proteins. They provide energy and assistance for the refolding process. Disaggregases are specialized in disaggregating client protein aggregates. They work to break apart protein aggregates, often formed due to stress or misfolding and transfer the partially folded proteins to a holdase and/or

foldase.[7] Chaperones play a role in the assembly of protein complexes and oligomers. They help proteins navigate through the cell to reach their intended destinations. Chaperones can be involved in targeting misfolded or damaged proteins for degradation, preventing their accumulation.

Protein quality control system

The balance between protein synthesis, folding, and degradation is tightly regulated to maintain cellular proteostasis. Post-translational modifications and signaling pathways are involved in regulating protein degradation and quality control. Cells have quality control mechanisms to ensure that only properly folded and functional proteins are allowed to continue their intended cellular functions. Misfolded or damaged proteins can be targeted for degradation through various pathways. The primary objective of protein quality control (PQC) systems is to preserve protein homeostasis. This means that the cell aims to maintain the correct balance and quality of proteins, both in terms of their structure and abundance.[8]

Protein degradation

Proteolysis is a fundamental biological process that regulates protein turnover, quality control, and various cellular functions. The diversity of proteases, from small monomeric enzymes to large proteasomes, allows cells to finely tune the degradation of specific proteins based on their structure, function, and regulatory signals. This process is essential for maintaining protein homeostasis within the cell.

Ubiquitin-proteasome system

The UPS is a highly selective and rapid intracellular protein degradation system that degrades nearly 80% of all cellular proteins. The two discrete and successive steps involved in the degradation of a protein via the ubiquitin-proteasome pathway. In the first step, multiple ubiquitin molecules are covalently attached to the protein substrate. This process is known as ubiquitination or ubiquitylation. Ubiquitination involves the sequential addition of ubiquitin molecules to specific lysine residues on the target protein. The attachment of ubiquitin molecules forms a polyubiquitin chain on the protein substrate, which serves as a recognition signal for targeting the protein for degradation. This step marks the protein for recognition by the proteasome. In the second step, the protein that has been ubiquitinated is recognized by the 26S proteasome complex. The 26S proteasome, ATP-dependent protease complex, recognizes and degrades proteins that are tagged with ubiquitin. During degradation, the protein is unfolded and cleaved into smaller peptide fragments by the proteasome. This results in the release of free and reusable ubiquitin molecules, which can be used for subsequent rounds of ubiquitination. Proteins ubiquitylation is a highly regulated process that is catalyzed in an ATP-dependent manner including the role of ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3). The 26S proteasome, a large protein complex, recognizes and degrades ubiquitinated proteins. The UPS is the major cytosolic proteolytic system in eukaryotes, responsible for the degradation of short-lived regulatory proteins and proteins involved in cell cycle control, transcription, and other critical processes. It operates in multiple cellular compartments, making it an integral part of proteostasis in the nucleus, cytoplasm, and the endoplasmic reticulum.[10]

Autophagy autophagy is another degradation pathway involved in proteostasis. It is responsible for removing damaged organelles and long-lived proteins. It literally means “self-eating” and its three major pathways in eukaryotic cells: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). These pathways share the common goal of targeting cellular components for lysosomal degradation but differ in their mechanisms.[11] Macroautophagy and microautophagy are generally involved in the bulk degradation of cellular components, while CMA is highly selective and degrades specific proteins.[12] Proteins with a CMA-targeting motif are recognized by chaperone proteins and delivered to lysosomes for degradation.

Proteins that undergo minor modifications, such as limited misfolding or the addition of a few ubiquitin molecules, can be recognized and degraded by the proteasome system. In contrast, extensively damaged proteins, which may have undergone significant misfolding or other detrimental changes, tend to form aggregates. These aggregates are composed of multiple protein molecules and may be more complex and insoluble. The proteasome's recognition and degradation mechanisms are less effective at processing these large, insoluble aggregates. Nevertheless, the UPS and Autophagy are strictly interconnected, Autophagy can regulate the activity of the 26S proteasome, a component of the UPS, through a process known as proteaphagy. In proteaphagy, autophagy selectively targets and degrades specific proteasomes. Autophagy activity is controlled by various factors, including E3 ubiquitin ligases and deubiquitinases.[13] These factors participate in different phases of autophagosome formation and fusion with lysosomes. This further highlights the network character of the proteostasis network in a cell. In addition to the proteasome and lysosomes, there are other proteolytic enzymes and systems that are specialized for the clearance of damaged proteins in specific cellular compartments. Specific proteases within the cell are responsible for degrading proteins involved in highly regulated functions. For example, oxidized protein hydrolase (OPH) is involved in the clearance of cytosolic oxidized proteins, working in coordination with the proteasome to remove oxidized proteins from the cytoplasm. Mitochondria, being preferential sites for protein oxidation, have various proteolytic systems

responsible for removing damaged proteins. Examples include Lon protease (LonP) and ClpXP.[14] Cellular stress responses cells have various stress response pathways, including the unfolded protein response (UPR) and the endoplasmic reticulum stress response, which help to mitigate proteotoxic stress. The unfolded protein response (UPR) is a cellular signaling pathway that is activated in response to the accumulation of unfolded or misfolded proteins in the endoplasmic reticulum (ER), an organelle involved in protein synthesis and folding.[15] The UPR is a critical mechanism for maintaining protein homeostasis and cell survival. The ER is responsible for proper protein folding and quality control. When there is an excessive accumulation of unfolded or misfolded proteins in the ER due to various stressors (e.g., nutrient deprivation, changes in calcium levels, viral infection), ER stress occurs. The UPR comprises three major signaling pathways initiated by three ER transmembrane proteins: PERK (PKR-like ER kinase), IRE1 (inositol-requiring enzyme 1), and ATF6 (activating transcription factor 6). These sensors detect ER stress and trigger signaling cascades to restore proteostasis. One of the main responses to UPR activation is a reduction in global protein synthesis to alleviate the burden on the ER. The UPR promotes the expression of ER chaperone proteins that assist in protein folding and refolding, aiding in the clearance of misfolded proteins. If ER stress is severe and prolonged, the UPR can trigger the degradation of misfolded proteins to prevent their accumulation. Depending on the extent of ER stress, the UPR can lead to the activation of inflammatory responses or cell death (apoptosis) to eliminate severely stressed cells. Dysregulation of the UPR has been implicated in various diseases, including neurodegenerative disorders, cancer, diabetes, and metabolic diseases. Modulating the UPR has potential therapeutic implications for managing diseases associated with protein misfolding and ER stress. The UPR is a vital mechanism that allows cells to adapt to ER stress and maintain protein homeostasis. It represents a complex network of signaling pathways aimed at preserving cell health in the face of protein folding challenges 16. Understanding the intricacies of the proteostasis network is crucial for developing therapeutic strategies for diseases linked to protein misfolding and aggregation. The ability to target the proteostasis network, including the modulation of molecular chaperone activity, offers a potential avenue for the development of novel therapeutic interventions in diseases where proteostasis disruption is a contributing factor.

PROTEIN MISFOLDING DISEASE

The ability to maintain protein homeostasis decreases with age. This can result in the accumulation of misfolded or aggregated proteins, a hallmark of many diseases (Table 1). The neurodegenerative diseases are characterized by the misfolding, aggregation, and accumulation of specific proteins in the brain, leading to neuronal dysfunction and cell death. Some neurodegenerative diseases like Alzheimer's, Parkinson's, cystic fibrosis, Parkinson's, Huntington's, amyotrophic lateral sclerosis, tau/β-amyloid (Aβ), α-synuclein respectively.[33] Cystic fibroisis (CF) is a genetic disorder characterized by mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene. CFTR is a protein that regulates the flow of salt and water in and out of cells, particularly in the airway and digestive tract. Mutations in the CFTR gene lead to impaired ion transport, causing thick, sticky mucus to build up in various organs. Alzheimer's disease is characterized by the accumulation of misfolded amyloid-beta (Aβ) and tau proteins in the brain.[18] These aggregates contribute to cognitive decline and neurodegeneration. Parkinson's disease (PD) is involving the aggregation of alpha-synuclein into Lewy bodies in dopaminergic neurons. This leads to motor symptoms and progressive neurodegeneration. Huntington's disease is caused by an expanded polyglutamine repeat in the huntingtin protein. Misfolded huntingtin protein aggregates in neurons, resulting in motor and cognitive impairments. Amyotrophic lateral sclerosis involves the misfolding and aggregation of various proteins, including superoxide dismutase 1 (SOD1) and TDP-43. This results in motor neuron degeneration. Prion diseases is caused by infectious, misfolded proteins called prions. Prions induce the misfolding of normal proteins, leading to the formation of more prions and progressive neurodegeneration. Examples include Creutzfeldt-Jakob disease and mad cow disease 19. Protein aggregation diseases, which can indeed affect tissues beyond the central nervous system and cancer. These diseases, often characterized by the formation of amyloid fibrils and the aggregation of specific proteins, can have systemic effects and manifest in various peripheral tissues. Such diseases include type 2 diabetes, inherited cataracts, heart disease, sarcopenia, ischemic disorders, diabetic neuropathy, sickle cell anemia, some forms of atherosclerosis, hemodialysis-related disorders, and short-chain amyloidosis, among many others.[20] Type 2 diabetes mellitus (T2DM) is a significant global health challenge, with a growing prevalence worldwide.[21] It is characterized by metabolic dysregulation and insulin resistance. Therefore, understanding the molecular mechanisms underlying the pathophysiology of T2DM is key to improving current therapies. Loss of protein homeostasis leads to the accumulation of damaged proteins in cells, which results in tissue dysfunction. The elimination of damaged proteins occurs through the ubiquitin-proteasome system (UPS) and autophagy.

Table 1: Current therapeutic approaches to restore proteostasis in various diseases.

S. no.	Diseases	Therapeutic approaches	References
1	Fungal Infection	Proteasome inhibitors, chaperone-based therapies, autophagy modulator	34
2	Cancer	Proteasome inhibitors, chaperone-based therapies, autophagy modulator, RNA based therapeutics, gene therapy	35, 36
3	Metabolic disorder	Molecular chaperone, autophagy modulator, RNA based therapeutics, proteasome inhibitors, small molecule	37, 38
4	Neurodegenerative	Molecular chaperone, autophagy modulator, RNA based therapeutics, proteasome inhibitors, small molecule, natural products, gene therapy	39

CURRENT THERAPEUTICS APPROACHES

Dysregulation of proteostasis is implicated in various diseases (Table 1), including neurodegenerative disorders like Alzheimer's and Parkinson's disease. Several therapeutic approaches are being explored to restore proteostasis, with a focus on enhancing protein quality control mechanisms.

Proteasome inhibitors

Proteasomes are central to the cell's protein quality control mechanisms. They ensure that proteins are properly folded, functional, and not harmful to the cell. They are highly regulated, and abundant multi-enzyme complexes that acts as the cell's "protein shredder". The proteasome is an essential component of the cell's protein quality control system, and it plays a critical role in maintaining proteostasis by regulating the degradation of various proteins, including those involved in cell cycle regulation and apoptosis. They play a pivotal role in the clearance of misfolded, unfolded, and potentially cytotoxic proteins.[22] Disruption of proteasome function can have severe consequences and is a target for both therapeutic interventions and research into various diseases associated with protein misfolding and aggregation. In cancer cells, mutations or aberrant expression of specific proteins can lead to the production of misfolded or otherwise non-functional proteins. These abnormal proteins are tagged for degradation by the ubiquitin-proteasome system. Cancer cells, due to their altered protein metabolism and genetic changes, often become more reliant on the proteasome for the clearance of abnormal or mutant proteins. Inhibition of proteasomal function in cancer cells can lead to the accumulation of these dysfunctional proteins, causing cellular stress and apoptosis. Proteasome inhibitors are a class of drugs that interfere with the function of the proteasome. It works by blocking the proteasome's activity, leading to the accumulation of misfolded or dysfunctional proteins within the cell.[22] Various preclinical studies have consistently demonstrated that cancer cells are more sensitive to proteasome inhibition compared to normal cells. Proteasome inhibitors interfere with signaling pathways that are crucial for cancer cell survival and proliferation. For example, they can inhibit the activation of the transcription factor NF-κB, which is associated with cell survival and immune evasion. Many cancer types rely on specific oncoproteins for their growth. Proteasome inhibitors can interfere at the p53 level, leading to the stabilization and reactivation of p53 in cancer cells. The stability of the tumor suppressor protein p53 is tightly regulated by the ubiquitin-proteasome system, and specific 26S proteasome inhibitors play a crucial role in modulating this regulation. It can lead to the degradation of these oncoproteins, which is detrimental to cancer cell survival. Inhibition of the proteasome can result in the stabilization of tumor suppressor proteins, which can promote cell cycle arrest and apoptosis.[23] Deregulation of the cell cycle is a common feature of cancer. This can involve the overexpression of certain cyclins, which is frequently observed in various cancer types. Overexpression of cyclins can lead to increased Cdk activity and uncontrolled cell division. Cancer cells, which often have high rates of protein synthesis and unique protein profiles, tend to be more sensitive to proteasome inhibitors compared to normal cells. This heightened sensitivity to proteasome inhibitors is a key factor in the development and use of these drugs in cancer therapy.[24]

There are several proteasome inhibitors used in the treatment of various cancers. Bortezomib (Velcade) is approved for the treatment of multiple myeloma, a type of blood cancer that involves the proliferation of plasma cells in the bone marrow. It is also approved for the treatment of certain other cancers such as mantle cell lymphoma (MCL) in patients who have received at least one prior therapy. MCL is a subtype of non-Hodgkin lymphoma. Bortezomib disrupts the normal proteasomal degradation of proteins within cells, leading to the accumulation of specific proteins and ultimately inducing apoptosis in cancer cells. Carfilzomib (Kyprolis) is approved for the treatment of multiple myeloma in various settings, including in combination with other agents for newly diagnosed multiple myeloma, as well as for the treatment of relapsed or refractory multiple myeloma. Carfilzomib, like bortezomib, is a proteasome inhibitor that disrupts protein degradation in cancer cells, leading to apoptosis.[25] Ixazomib (Ninlaro) is another proteasome inhibitor for the treatment of multiple myeloma in combination with lenalidomide and dexamethasone. It disrupts the proteasome's function,

leading to the accumulation of specific proteins and ultimately inducing apoptosis (cell death) in cancer cells. It is considered an oral proteasome inhibitor, offering the convenience of an oral medication for the treatment of multiple myeloma. Other proteasome inhibitors are Oprozomib, Marizomib, Delanzomib, MG-132 and MLN-2238 with potential in cancer therapy.[26] Proteasome inhibitors represent a significant advancement in cancer therapy, offering new treatment options and improved outcomes for patients with specific malignancies. proteasome inhibitors offer a valuable strategy for disrupting the balance of protein turnover in cancer cells, taking advantage of the unique protein metabolism of malignancies.

Chaperone based therapies

Chaperone-based therapies, also known as chaperone therapies or pharmacological chaperone therapies, are a class of treatments that involve the use of small molecules to correct the misfolding or instability of specific proteins within cells. These therapies are primarily targeted at genetic diseases caused by mutations that lead to the production of misfolded or dysfunctional proteins. Chaperone molecules help these mutant proteins achieve their proper three-dimensional structures, thereby restoring their normal function. Chaperone-based therapies have shown promise in various genetic disorders, particularly in the context of protein misfolding diseases. For neurodegenerative disorders, inhibiting Hsp90 can lead to the degradation of disease-associated proteins, such as huntingtin, mutant forms of the androgen receptor in spinal and bulbar muscular atrophy (SBMA).[27] This approach destabilizes misfolded proteins and promotes their clearance. Chaperone-based therapies represent an exciting area of research and treatment development for certain genetic disorders, especially those characterized by protein misfolding. They hold the potential to address the underlying causes of these diseases and improve the quality of life for affected individuals.

Autophagy modulators

Autophagy modulators are compounds or strategies that can either enhance or inhibit the autophagy process in cells. Autophagy modulators may exhibit a dual role in cancer treatment. They might be beneficial in sensitizing cancer cells to therapy at the early stages of treatment but could be detrimental in promoting treatment resistance in advanced cancers. Different inhibitors that target various components of the PI3K/AKT/mTOR pathway leads to favorable outcomes in various types of cancers. Chloroquine (CQ) and Hydroxychloroquine (HCQ) are among the most well-known autophagy inhibitors and have been studied in clinical trials in combination with other cancer treatments. Bafilomycin A1 is another lysosomotropic agent that inhibits autophagy by preventing the acidification of lysosomes, thereby blocking autophagosome-lysosome fusion. Several evidence demonstrates that BafA1 suppresses the growth of a variety of cancer cells.[28-30] Drugs like bortezomib, which are used in cancer therapy, have been investigated for their potential in HD. Spautin-1 is a compound that promotes the degradation of Beclin-1, a key autophagy protein. By reducing Beclin-1 levels, Spautin-1 inhibits autophagy. Spautin-1 has been studied for its potential for both cancer and neurodegenerative disease research. The restoration of proper autophagy could help clear Aβ, and other protein aggregates associated with the disease. ATG5 and ATG7 Inhibitors are essential autophagy-related proteins. Inhibitors targeting these proteins have been developed to block autophagy at its initiation stages and have been explored in cancer research. Various other compounds are being investigated as autophagy inhibitors in cancer, including specific mTOR inhibitors (e.g., rapamycin), proteasome inhibitors (e.g., bortezomib), and others. Modulating autophagy in diabetes, particularly in type 2 diabetes, preventing the development and progression of diabetes-related complications.[31] Now a days, the development of more specific and targeted autophagy modulators is a growing area of research.

RNA based therapeutics

RNA-based therapeutics are a rapidly evolving field with various types of RNA molecules being explored for their potential in treating a wide range of diseases. These therapeutics leverage the unique properties of RNA to modulate gene expression and cellular processes. Small Interfering RNA (siRNA) molecules are typically double-stranded RNA sequences that can be designed to target specific messenger RNA (mRNA) molecules. When introduced into cells, siRNA binds to complementary mRNA, leading to mRNA degradation and subsequent reduction in the corresponding protein's expression. siRNA-based therapeutics are used to silence the expression of disease-related genes. They hold promise for various conditions, including genetic disorders, viral infections, and certain cancers.[32] MicroRNA (miRNA) are small, endogenous RNA molecules that naturally regulate gene expression. In therapy, synthetic miRNA analogs or miRNA mimics can be used to modulate gene expression by targeting specific mRNA. Conversely, anti-miRNA molecules (antagomirs) can inhibit endogenous miRNA function. miRNA-based therapeutics have potential applications in cancer, cardiovascular diseases, and neurological disorders, among others. Small Activating RNA (saRNA) are designed to upregulate the expression of specific genes. They can be used to increase the production of proteins, such as tumor suppressors, that are otherwise insufficiently expressed in disease. saRNA therapies are being explored for various conditions, including cancer and genetic disorders. Messenger RNA (mRNA) therapies introduce exogenous mRNA encoding a specific protein into cells. This mRNA is then translated into the corresponding protein by the cell's machinery. The success of mRNA vaccines in addressing COVID-19 has highlighted their potential in public health and medicine. Also, mRNA therapies

have potential applications in genetic diseases, cancer immunotherapy, and protein replacement therapies. CRISPR-Cas systems use guide RNA (gRNA) to target specific DNA sequences for gene editing. The gRNA directs the Cas protein to make precise changes in the genome. CRISPR-based therapeutics have revolutionized gene editing and hold promise for treating genetic disorders, cancer, and a wide range of diseases.[33] These RNA-based therapeutics represent a diverse set of strategies for modulating gene expression, protein production, and cellular processes. They have the potential to offer new treatment options for a wide range of diseases and conditions, although challenges remain in terms of delivery, specificity, and safety. Ongoing research and clinical trials are crucial for further developing and optimizing these therapies.

CURRENT AND EXISTING CHALLENGES AND FUTURE OUTLOOK

Understanding proteostasis is not only fundamental to basic biology but also has significant implications for the development of treatments for various diseases, particularly those related to protein misfolding and aggregation. Proteostasis refers to the regulation and maintenance of protein homeostasis in a cell, which is critical for its proper functioning. Imbalances in proteostasis can lead to a variety of diseases, including neurodegenerative disorders, cancer, and autoimmune diseases. The field of proteostasis faces several current and existing challenges, but it also holds promise for future advancements. As cells age, they become less efficient in maintaining proteostasis, leading to the accumulation of misfolded proteins. This is a key factor in many age-related diseases, including Alzheimer's, Parkinson's, Huntington's disease etc. Diseases such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS) involve the aggregation of specific proteins. Understanding the mechanisms behind protein aggregation and developing effective therapies is challenging. Cells have complex mechanisms to ensure protein quality, including chaperones and the ubiquitin-proteasome system. Understanding how these systems function and how they can be modulated to maintain proteostasis is an ongoing challenge.

The crosstalk between the UPS and autophagy highlights the coordinated control of protein degradation processes within the cell. The selective degradation of proteasomes by autophagy, as well as the reciprocal regulation between these pathways, plays a role in maintaining cellular proteostasis and metabolic health. This interplay is an area of active research and may hold promise for therapeutic interventions in conditions related to metabolic dysfunction. Developing drugs that can target specific proteins or cellular pathways to restore proteostasis is a significant challenge. Many potential drug candidates have failed in clinical trials. Autophagy is a cellular process responsible for degrading and recycling damaged proteins and organelles. Dysregulation in autophagy can lead to proteostasis-related diseases. Understanding the intricacies of autophagy and finding ways to modulate it is a challenge. Research into proteostasis is likely to lead to the development of more targeted therapies for proteostasis-related diseases. These therapies might aim to modulate specific proteins or cellular pathways to restore proper protein folding and degradation. Understanding the genetic and environmental factors that influence proteostasis will enable the development of personalized treatments for individuals with proteostasis-related diseases. Proteostasis is a key focus in research on neurodegenerative diseases like Alzheimer's and Parkinson's. Improved understanding of protein misfolding and aggregation will likely lead to novel therapeutic strategies. Research into small molecules and molecular chaperones that can stabilize or refold misfolded proteins is ongoing. These compounds may prove effective in treating a range of diseases. Advanced computational techniques, including machine learning and artificial intelligence, can help in drug discovery and in silico screening of potential proteostasis-modulating compounds. In summary, proteostasis is a complex and evolving field of study with significant implications for human health.

CONCLUSION

Proteostasis, the regulation and maintenance of protein homeostasis within cells, is vital for proper cellular function and overall health. Disruptions in proteostasis are linked to numerous diseases, particularly those characterized by protein misfolding and aggregation, such as neurodegenerative disorders like Alzheimer's, Parkinson's, and Huntington's diseases. As cells age, their ability to maintain proteostasis diminishes, leading to the accumulation of misfolded proteins and increased disease risk. Key components in proteostasis include molecular chaperones and the ubiquitin-proteasome system (UPS), both of which ensure protein quality by facilitating proper folding and degradation of proteins. The interplay between UPS and autophagy, another crucial protein degradation pathway, is essential for maintaining cellular proteostasis and metabolic health. However, understanding and manipulating these complex systems to develop effective therapies remains a significant challenge. One promising area of research is the development of drugs targeting specific proteins or pathways to restore proteostasis. Despite numerous potential candidates, many have failed in clinical trials, highlighting the difficulties in translating basic research into effective treatments. Modulating autophagy, which is responsible for degrading and recycling damaged proteins and organelles, represents another potential therapeutic strategy, though understanding its intricacies is equally challenging. Advancements in proteostasis research are expected to yield more targeted therapies for related diseases. These therapies may focus on modulating protein folding and degradation processes to restore balance. Additionally, understanding the genetic and

environmental factors influencing proteostasis could lead to personalized treatments for affected individuals. In the realm of neurodegenerative diseases, a deeper understanding of protein misfolding and aggregation will likely lead to novel therapeutic strategies. Ongoing research into small molecules and molecular chaperones that stabilize or refold misfolded proteins holds promise for treating a wide range of proteostasis-related conditions. Furthermore, advanced computational techniques, including machine learning and artificial intelligence, are enhancing drug discovery and the in-silico screening of potential proteostasis-modulating compounds. The field of proteostasis is both complex and rapidly evolving, with significant implications for human health. Continued research into the mechanisms regulating protein homeostasis and the development of innovative therapeutic strategies offers hope for combating a variety of diseases linked to proteostasis imbalances.

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