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Interplay of Proteostasis and Ribostasis in Neurodegeneration: Insights into Common Mechanisms

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Abstract

Neurodegenerative diseases represent a significant and growing global health burden, characterized by progressive loss of neuronal function and cell death. While the exact etiology of these disorders remains elusive, emerging evidence suggests that disruptions in proteostasis and ribostasis play pivotal roles in their pathogenesis. Proteostasis refers to the maintenance of protein homeostasis, ensuring proper protein folding, degradation, and clearance, while ribostasis involves the regulation of RNA dynamics, including synthesis, processing, and degradation. In this article, we explore the intricate interplay between proteostasis and ribostasis in neurodegenerative processes, shedding light on common mechanisms underlying disease progression. We discuss how perturbations in protein and RNA metabolism contribute to neuronal dysfunction and demise, and highlight potential therapeutic strategies aimed at restoring proteostasis and ribostasis to mitigate neurodegenerative pathology.

Keywords: Neurodegeneration; proteostasis; ribostasis; protein homeostasis; RNA dynamics; cellular mechanisms.

Introduction

Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease, are characterized by progressive neuronal loss and dysfunction, leading to devastating clinical outcomes. Despite intensive research efforts, effective disease-modifying therapies remain elusive, underscoring the urgent need to elucidate the underlying pathogenic mechanisms. Recent studies have implicated disturbances in proteostasis and ribostasis – essential cellular processes governing protein and RNA dynamics – in the pathogenesis of neurodegeneration [1]. Understanding the interplay between these two pathways offers valuable insights into the common mechanisms driving neuronal demise and holds promise for the development of novel therapeutic interventions. Disturbances in protein homeostasis (proteostasis) and inflammation are prominent features of both normal aging and several age-related neurodegenerative conditions. While the proteostasis network plays a crucial role in preserving the functionality of intracellular and extracellular proteins, inflammation represents a biological response to various detrimental stimuli [2]. Cellular stressors can inflict damage upon proteins, exacerbating misfolding and eventually overwhelming the degradation machinery. Particularly in postmitotic neurons, which possess limited regenerative capabilities, the regulation of proteostasis is of paramount importance. Maintaining a delicate balance between protein synthesis, unfolding, refolding, and degradation is essential for preserving cellular functions within the central nervous system (CNS). Dysfunctions in proteostasis can incite inflammatory responses in glial cells, thereby instigating a cascade of events leading to further disturbances in proteostasis. In this review, we delve into the mechanisms underlying proteostasis and inflammatory responses, highlighting their pivotal roles in the pathological manifestations of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Additionally, we examine the intricate interplay between proteostatic stress and excessive immune activation, which fuels inflammation and exacerbates proteostatic dysfunction.

Proteostasis and Ribostasis: Fundamental Processes in Cellular Homeostasis

Proteostasis encompasses a network of cellular pathways responsible for maintaining protein homeostasis, including protein synthesis, folding, trafficking, and degradation. Disruptions in proteostasis can lead to the accumulation of misfolded or aggregated proteins, triggering cellular stress responses and compromising neuronal function. Similarly, ribostasis regulates RNA metabolism, encompassing processes such as transcription, splicing, translation, and RNA degradation [3]. Dysregulation of ribostasis can result in aberrant RNA processing and impaired protein synthesis, contributing to neuronal dysfunction and degeneration.

Interplay between Proteostasis and Ribostasis in Neurodegeneration

Emerging evidence suggests intricate crosstalk between proteostasis and ribostasis in the pathogenesis of neurodegenerative diseases. Dysfunctional proteins implicated in neurodegeneration, such as amyloid-beta, tau, alpha-synuclein, and TDP-43, disrupt both proteostasis and ribostasis pathways. Aberrant RNA processing and translation contribute to the accumulation of misfolded proteins, while impaired protein clearance mechanisms exacerbate ribostasis dysregulation [4]. Furthermore, alterations in RNA-binding proteins and ribonucleoprotein complexes disrupt proteostasis by impairing protein quality control mechanisms. This bidirectional interplay between proteostasis and ribostasis creates a feedforward loop that amplifies neurodegenerative pathology.

Inflammation Induces Oxidative Stress

Inflammatory Response: Inflammation is a natural defense mechanism of the body against harmful stimuli, such as pathogens,

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tissue injury, or irritants.

Oxidative Stress: Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses.

Interplay between Inflammation and Oxidative Stress: Inflammatory responses can trigger the production of ROS by various immune cells, including neutrophils, macrophages, and microglia [5].

Reactive Oxygen Species (ROS): ROS are highly reactive molecules containing oxygen, such as superoxide radicals, hydrogen peroxide, and hydroxyl radicals. They can cause damage to lipids, proteins, and DNA within cells.

Sources of ROS in Inflammation: ROS production can occur through multiple pathways during inflammation, including the activation of NADPH oxidase, the release of ROS from mitochondria, and the activity of inflammatory enzymes like myeloperoxidase.

Consequences of Oxidative Stress: Excessive ROS production can lead to oxidative damage to cellular components, including lipid peroxidation, protein oxidation, DNA damage, and mitochondrial dysfunction [6].

Amplification Loop: Oxidative stress can further exacerbate inflammation by activating redox-sensitive transcription factors such as NF-κB, which induce the expression of pro-inflammatory cytokines, creating a positive feedback loop.

Role in Disease Pathogenesis: Chronic inflammation and oxidative stress are implicated in the pathogenesis of various diseases, including neurodegenerative disorders, cardiovascular diseases, cancer, and autoimmune diseases.

Therapeutic Implications: Targeting oxidative stress pathways may represent a potential therapeutic strategy for mitigating inflammation-associated diseases. Antioxidant therapies, lifestyle modifications, and anti-inflammatory agents could be beneficial in reducing oxidative stress and inflammation.

Therapeutic Strategies Targeting Proteostasis and Ribostasis

Restoring proteostasis and ribostasis represents a promising therapeutic approach for mitigating neurodegenerative diseases. Pharmacological interventions targeting protein degradation pathways, such as the ubiquitin-proteasome system and autophagy-lysosomal pathway, aim to enhance protein clearance and alleviate proteostatic stress. Similarly, modulating RNA metabolism through small molecules or RNA-targeted therapies holds potential for restoring ribostasis and ameliorating neurodegenerative pathology [7-11]. Additionally, lifestyle interventions, including diet and exercise, have been shown to influence proteostasis and ribostasis, highlighting the importance of holistic approaches in disease management.

Conclusion

The interplay between proteostasis and ribostasis plays a central role in the pathogenesis of neurodegenerative diseases, contributing to neuronal dysfunction and demise. Understanding the complex interactions between these pathways provides valuable insights into the common mechanisms underlying disease progression. Therapeutic strategies aimed at restoring proteostasis and ribostasis hold promise for slowing or halting the progression of neurodegeneration, offering hope for the development of effective treatments for these devastating disorders. Continued research into the molecular mechanisms governing proteostasis and ribostasis will pave the way for innovative therapeutic interventions to combat neurodegenerative diseases.

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