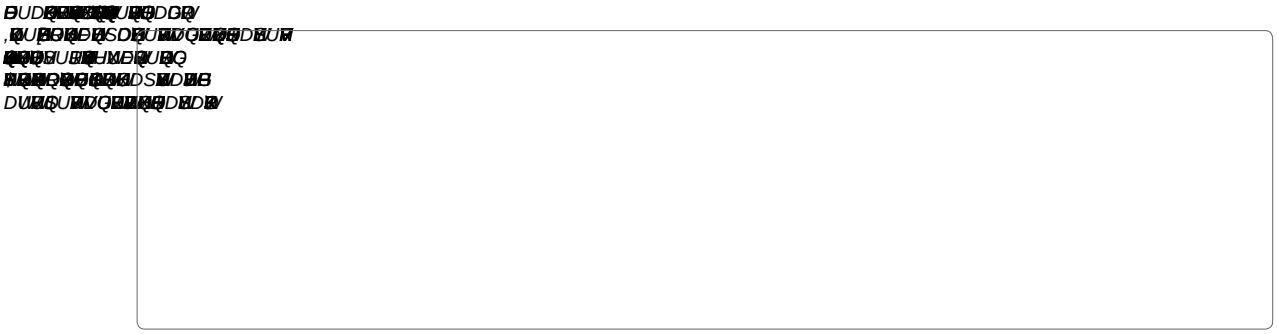
Interplay of Proteostasis and Ribostasis in Neurodegeneration: Insights into Common Mechanisms



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

Int oduction

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 e orts, e ective 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 o ers 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 in ammation 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, in ammation represents a biological response to various detrimental stimuli [2]. Cellular stressors can in ict 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 in ammatory 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 in ammatory 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 in ammation and exacerbates proteostatic dysfunction.

P oteostasis andR ibostasis: Fundamental P ocesses in Cellula Homeostasis

Proteostasis encompasses a network of cellular pathways responsible for maintaining protein homeostasis, including protein synthesis, folding, tra cking, 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.

Inte play between P oteostasis and R ibostasis in Neu odegene ation

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. is bidirectional interplay between proteostasis and ribostasis creates a feedforward loop that ampli es neurodegenerative pathology.

Inflammation Induces Oxidative St ess

Inflammato yR esponse: In ammation is a natural defense mechanism of the body against harmful stimuli, such as pathogens,

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tissue injury, or irritants.