

TRIM11: A powerful guardian of proteostasis

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Cells have developed protein quality control (PQC) systems to ensure the proper structure and function of proteins. These systems consist of degradation systems and chaperone systems. The degradation systems are responsible for removing misfolded proteins. The chaperone systems prevent protein misfolding and the formation of protein aggregates. Dysfunction of PQC in neurons is closely associated with the accumulation of misfolded proteins, a hallmark of neurodegenerative diseases such as Alzheimer's disease (AD).¹ One prominent feature in AD patients is the formation of tau protein neurofibrillary tangles (NFTs), in which contribute to neuronal death and memory loss. NFTs of tau proteins are also implicated in over 20 other dementias and movement disorders, collectively known as tauopathies,

including progressive supranuclear palsy and Pick's disease. However, the mechanism by which soluble tau proteins convert into insoluble fibrillar aggregates remains poorly understood in these diseases. The ability to manually manipulate and convert insoluble tau aggregates into soluble forms would represent a promising therapeutic approach for all tauopathies. Recently, Zhang et al. found that tripartite motif 11 (TRIM11), which is down-regulated in AD brains, plays a crucial role in maintaining the soluble form of tau protein. TRIM11 acts as both a molecular chaperone and a disaggregase, preventing tau misfolding and dissolving preformed tau fibrils.¹ This study highlights TRIM11 as a promising target for preventing and slowing the progression of AD and other related neurodegenerative disorders.

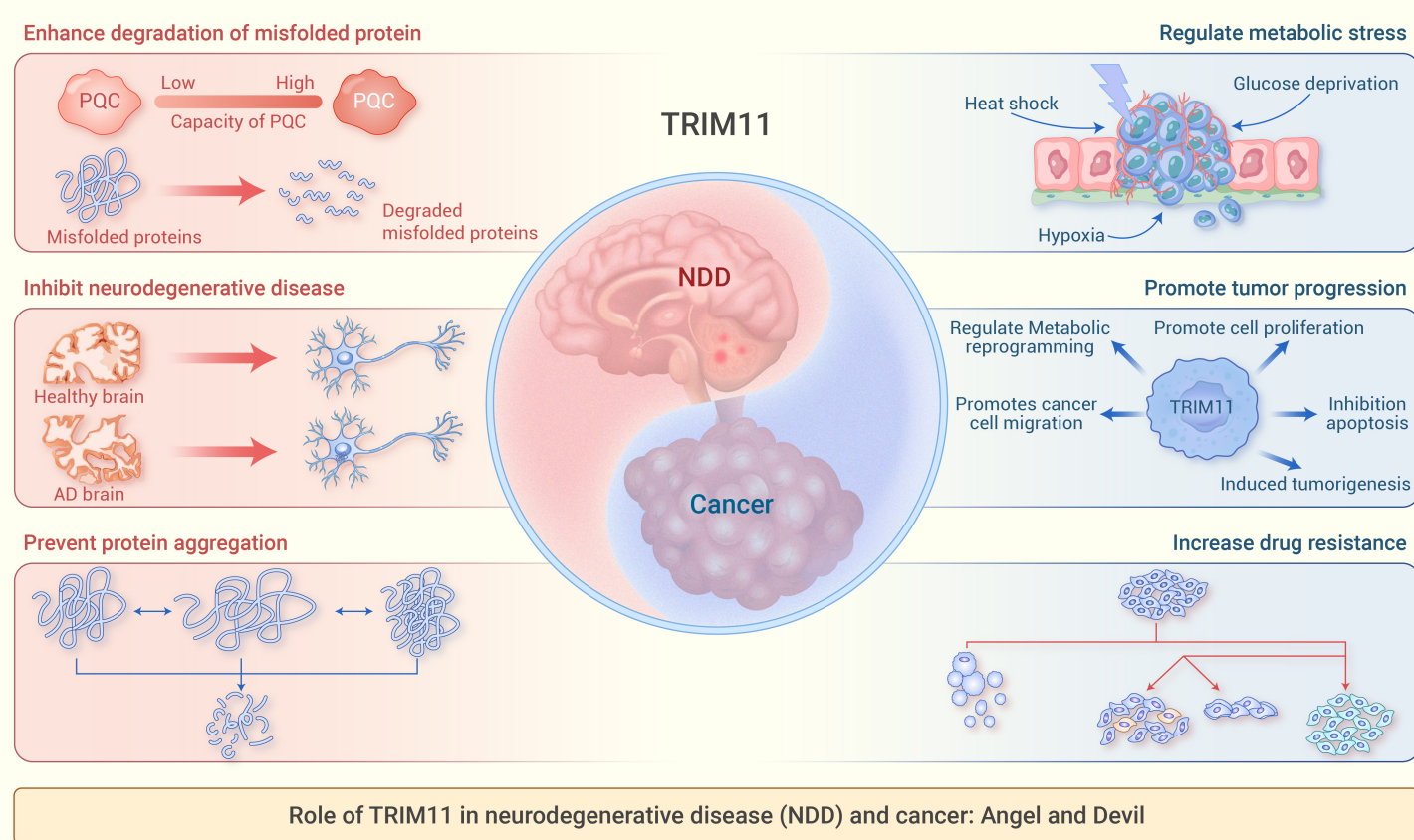


Figure 1. The dual role of TRIM11 in cancer and neurodegenerative diseases.

Increasing evidence highlights the crucial role of tripartite motif (TRIM) family proteins in maintaining cellular proteostasis and regulating protein quality control (PQC). In the study by Santosh Chauhan et al., TRIM16 was found to utilize the NRF2-p62 axis and autophagy to facilitate the safe disposal of misfolded proteins, thus maintaining protein homeostasis and ultimately facilitating tumor growth.² Furthermore, TRIM11 plays a role in promoting the degradation of aberrant and normal regulatory proteins, thereby enhancing overall proteolysis by directly enhancing proteasome activity.³ This dual nature of TRIM11 is evident in its contribution to oncogenic transformation and tumor growth. Therefore, it is crucial to acknowl-

edge the multifaceted role of TRIM11, as it can both protect against neurodegenerative diseases and promote tumor progression (Figure 1).

Tau, a microtubule-associated protein (MAP), plays a role in regulating axonal transport, DNA integrity protection, and the NMDA receptor signaling pathway. However, in AD and primary age-related tauopathy (PART), misfolded tau proteins accumulate and form intracellular aggregates, contributing to cognitive impairment and neuronal dysfunction. Factors such as hyperphosphorylation, acetylation, and overall tau protein regulation can exacerbate tau misfolding and aggregation.¹ Understanding these underlying mechanisms holds promising opportunities for AD treatment. Notably, Zhang

et al. demonstrated that the expression of TRIM11 is down-regulated in the brains of AD patients and plays a crucial role in suppressing tau aggregation.¹ TRIM11 exerts control over tau aggregates through several mechanisms. Firstly, it binds to mutant and hyperphosphorylated tau proteins, promoting their SUMOylation and subsequent proteasomal degradation. This finding aligns with their previous research, which demonstrated that TRIM11 prevents and reverses protein aggregation and rescues a mouse model of Parkinson's disease.⁴ Moreover, TRIM11 acts as a chaperone molecule and a disaggregase, facilitating proper folding of tau proteins, reducing the production of toxic tau protein "seeds", and dissolving existing filamentous tau. Additionally, in HEK293T cells expressing mutant tau protein, TRIM11 promotes the proteasomal degradation of misfolded and excess soluble tau, maintaining a healthy balance of functional tau and reducing the seeding of tau aggregates. Thus, their work suggests that up-regulating the expression of TRIM11 may hold potential as an effective treatment for AD and other neurodegenerative tauopathies.

Previous studies have shown that increased expression of TRIM11 can mitigate α -synuclein fibrillization and restore viability in Parkinson's disease cell models⁴. Similarly, elevated TRIM11 expression provides neuroprotection in models of Huntington's disease and spinocerebellar ataxia type.⁵ Given the crucial role of TRIM11 in clearing misfolded proteins and dissolving amyloid fibrils, up-regulating its expression prevents a viable therapeutic target for neurodegenerative tauopathies. Recently, Zhang et al. confirmed the therapeutic potential of TRIM11 by demonstrating that intracranial delivery of TRIM11 through adeno-associated viruses ameliorated pathology, reduced neuroinflammation, and improved cognitive impairments in multiple animal models of tauopathies. These promising findings shed light on the potential successful treatment of Alzheimer's disease and other neurodegenerative

disorders. However, two major challenges need to be addressed. Firstly, strategies to elevate TRIM11 expression must be developed, such as AAV-mediated gene therapy or small-molecule drugs. Secondly, since high TRIM11 expression is associated with oncogenic transformation and tumor progression, careful control of its localization and expression level is crucial. In conclusion, TRIM11 plays a central role in maintaining cellular proteostasis and emerges as a promising target in both cancer and neurodegenerative diseases. Further investigation is warranted to fully explore its potential in these areas.

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DECLARATION OF INTERESTS

The authors declare no competing interests.