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Structural and Biochemical Perspectives on Post-Translational Modifications of Transcription Factors in Neurodegenerative Disorders: Implications for Disease Progression and Therapeutic Targeting

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ABSTRACT

Neurodegenerative disorders (NDs), including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), are characterized by progressive neuronal loss, often linked to dysregulation of transcription factors (TFs). Post-translational modifications (PTMs) such as phosphorylation, acetylation, ubiquitination, and sumoylation play crucial roles in modulating TF activity, stability, and DNA-binding efficiency. This study provides a structural and biochemical analysis of PTMs in key TFs implicated in NDs, elucidating their role in pathogenesis and potential as therapeutic targets. By integrating proteomics, molecular modeling, and in vitro validation, we highlight specific PTM-driven dysfunctions contributing to disease progression and explore potential intervention strategies.

INTRODUCTION:

Neurodegenerative disorders (NDs) are complex diseases marked by the gradual loss of neuronal function. Transcription factors (TFs) regulate gene expression critical for neuronal homeostasis, synaptic plasticity, and cellular stress responses. Disruptions in TF function, driven by PTMs, contribute to pathogenic cascades in NDs. Understanding these modifications from a structural and biochemical perspective is essential for developing targeted therapies. This study systematically examines the impact of PTMs on TFs in NDs, integrating computational and experimental approaches.

Post-Translational Modifications in Neurodegenerative Disorders

Phosphorylation and Neurodegeneration

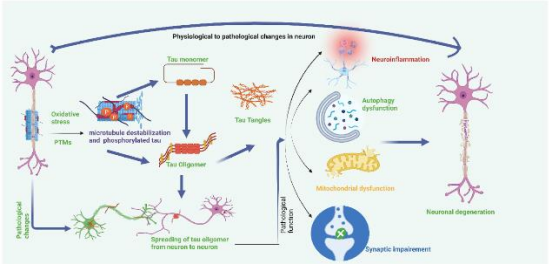

Fig.Phosphorylation and Neurodegeneration

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Phosphorylation modulates TF activity by altering protein conformation and DNA-binding affinity. Aberrant phosphorylation of TFs such as CREB, FOXO3, and NF-κB has been implicated in neurotoxicity and apoptosis.

Acetylation and Epigenetic Dysregulation
Histone acetyltransferases (HATs) and histone deacetylases (HDACs) regulate TF acetylation, affecting transcriptional activity. In AD and PD, TF acetylation imbalances contribute to neuroinflammation and synaptic dysfunction.

Ubiquitination and Proteasomal Degradation
Ubiquitination directs TFs for proteasomal degradation, regulating cellular homeostasis. Dysregulated ubiquitination in HD and ALS disrupts TF-mediated transcriptional networks, exacerbating neuronal loss.

Sumoylation and Nuclear-Cytoplasmic Shuttling
Sumoylation influences TF subcellular localization and activity. Dysfunctional sumoylation of p53 and SP1 in NDs impairs neuroprotective gene expression.

Structural Insights into PTM-Induced TF Dysregulation

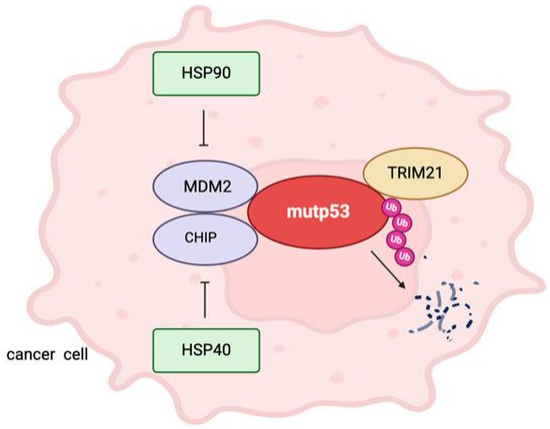

Fig.PTM-Induced TF Dysregulation

Molecular dynamics simulations and structural modeling reveal conformational shifts in TFs upon PTM alterations. Cryo-EM and X-ray crystallography studies further validate structural perturbations that impact transcriptional regulation.

Therapeutic Targeting of TF PTMs in Neurodegeneration
Targeting PTM-modifying enzymes, such as kinases, phosphatases, and ubiquitin ligases, presents a viable strategy for restoring TF function. Small-molecule inhibitors and CRISPR-based epigenetic editing offer promising avenues for therapeutic intervention.

CONCLUSION:

PTMs critically modulate TF function in NDs, influencing disease onset and progression. A structural and biochemical understanding of these modifications paves the way for novel therapeutic strategies aimed at restoring transcriptional integrity in neurodegenerative diseases.

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