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The CSI Chemistry Department Presents

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Histone post-translational modifications in ALS/FTD: New opportunities in neurodegenerative disease

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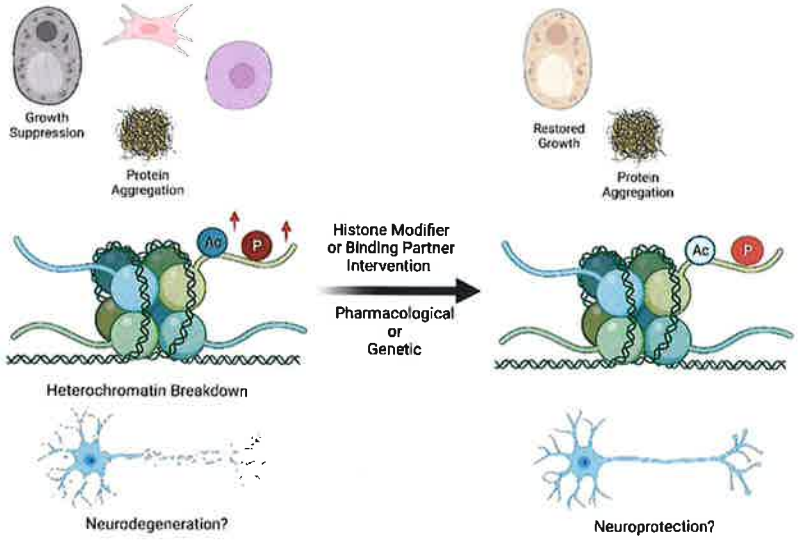
An aging population has led to a drastic increase in the prevalence of neurodegenerative diseases. Among these, frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) impact different neuronal types causing motor and behavioral symptoms, respectively. Bearing significant overlap in disease mechanisms, these two disorders comprise two ends of a disease continuum. Several genes have been linked to ALS/FTD pathology, including FUS, TDP-43, and C9orf 72. A hallmark of ALS/FTD is the cytoplasmic mislocalization and aggregation of the FUS, TDP-43, and c9orf72 proteins.

As genetics alone fails to explain the etiology of ALS/FTD, recent work has explored epigenetic mechanisms in this context. Epigenetic channels include the post-translational modification (PTM) of histones. DNA wraps around the core histone proteins H2A,H2B, H3, and H4, which can undergo acetylation, phosphorylation, and mono-, di-, or trimethylation among many other modifications on specific residues. We reveal unique histone PTM landscape aberrations are connected to distinct ALS/FTD proteinopathies in yeast models. Several of these findings are recapitulated in human cellular disease models. Furthermore, we show that chemical and genetic manipulation of proteins that install and remove histone PTMs leads improved cell survival in yeast models, highlighting epigenetic mechanisms as a potential target for therapeutic development in neurodegeneration.



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