RESTORING NEUROEPIGENETIC HOMEOSTASIS IN THE ALZHEIMER'S DISEASE BRAIN PROMOTES COGNITIVE FUNCTION

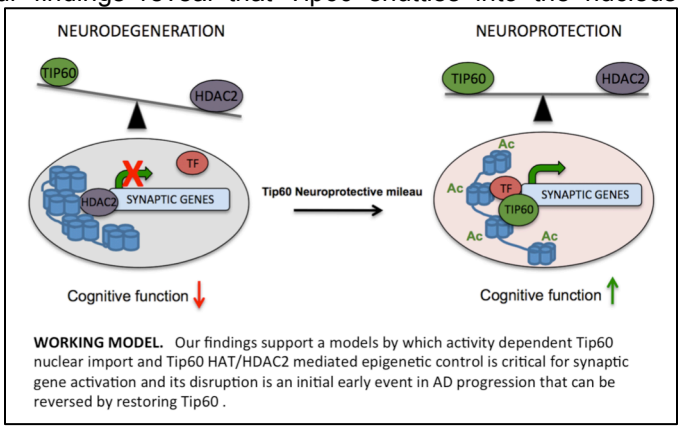
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Cognitive impairment is a debilitating hallmark during pre-clinical stages of Alzheimer's disease (AD) yet causes remain unclear[1]. As histone acetylation homeostasis is critical for early developmental epigenetic gene control, we postulated that its misregulation contributes to cognitive deficits preceding AD pathology. Here, we show that disruption of Tip60 HAT/HDAC2 homeostasis occurs early in the AD *Drosophila* brain and triggers epigenetic repression of a group of synaptic genes well before Aβ plaques form. Repressed genes display enhanced HDAC2 binding and reduced Tip60 and histone acetylation enrichment. Increasing Tip60 in the AD brain restores Tip60 HAT/HDAC2 balance, reverses neuroepigenetic alterations to activate synaptic genes, and reinstates brain morphology and cognition. Importantly, levels of Tip60, neuroepigenetic acetylation marks and activation of these same synaptic genes are significantly reduced in hippocampus from AD patients.

Genomic reorganization of transcription factories (TFs), characterized as specialized nuclear subcompartments enriched in hyperphosphorylated RNAPII and transcriptional regulatory proteins, act as an additional layer of control in coordinating efficient co-regulated gene transcription[2]. Thus, we asked whether Tip60 utilized this mechanism in its epigenetic control of activity dependent co-regulated synaptic genes in the brain. Our findings reveal that Tip60 shuttles into the nucleus following extracellular stimulation of rat hippocampal neurons[3] with concomitant enhancement of Tip60 binding and activation of the same synaptic genes we identified as repressed in the *Drosophila* and human AD brain. Multicolor 3D DNA fluorescent *in situ* hybridization reveals that hippocampal stimulation also mobilizes these same synaptic genes and Tip60 to RNAPII-rich TFs. Consistent with these findings, we show Tip60 is excluded from the nucleus in human AD hippocampal tissue. Our results support a model by which activity dependent Tip60 nuclear import and Tip60 HAT/HDAC2 mediated epigenetic control is critical for synaptic gene activation and its disruption may be an initial early event in AD progression.



WORKING MODEL. Our findings support a models by which activity dependent Tip60 nuclear import and Tip60 HAT/HDAC2 mediated epigenetic control is critical for synaptic gene activation and its disruption is an initial early event in AD progression that can be reversed by restoring Tip60 .

References

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