Abstract Template

Abstract Title: Dysregulation of the Tip60/HDAC2 epigenetic landscape in the brain is an early event in Alzheimer's disease progression

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Abstract (not more than 300 words)

Cognitive impairment is a debilitating hallmark during pre-clinical stages of Alzheimer's disease (AD) yet causes remain unclear. As histone acetylation homeostasis is critical for early developmental epigenetic gene control, we postulate that its misregulation contributes to cognitive deficits preceding AD pathology. Here, we utilize genome-wide chromatin and transcriptional profiling to show that disruption of Tip60 HAT/HDAC2 epigenetic homeostasis is an early event in the AD *Drosophila* brain and triggers epigenetic alteration of synaptic gene expression well before Aβ plaques form. Repressed genes display genome-wide enhanced HDAC2 binding and reduced Tip60 and histone acetylation enrichment at synaptic genes. Increasing Tip60 in the AD brain protects against disruption of Tip60 HAT/HDAC2 balance and neuroepigenetic alterations and maintains appropriate synaptic gene expression, 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 transcriptional regulatory proteins, act as an additional layer of control in coordinating efficient co-regulated gene transcription. Thus, we asked whether Tip60 utilized this mechanism in its epigenetic control of activity dependent synaptic genes in the brain. Our findings reveal that Tip60 shuttles into the nucleus following extracellular stimulation of rat hippocampal neurons with concomitant enhancement of Tip60 binding and activation of the same synaptic genes we identified as repressed in the *Drosophila* and human AD brain. We show that hippocampal stimulation also mobilizes these same synaptic genes and Tip60 to RNAPII-rich TFs. Strikingly, we find that 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 epigenetic gene control is critical for synaptic gene activation and its disruption is an initial early event in AD progression.

Keywords—Alzheimer's disease, cognitive function, neuroepigenetic, synaptic genes

Professional Biography (100-150 words)

Dr. Felice Elefant is a Professor of Biology at Drexel University and a graduate of the Executive Leadership in Academic Technology, Engineering and Science (ELATES) Program. She received her Ph.D. from Temple University and carried out her post-doctoral training in the field of epigenetics at University of Pennsylvania School of Medicine. She leads a successful National Institutes of Health (NIH) funded research program that focuses on neuroepigenetic mechanisms that govern regulation of higher order brain function. Dr. Elefant has authored over 90 manuscripts, chapters and abstracts and served as an invited speaker at numerous international and national scientific forums. She serves as an editorial board member of repute.



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