The DNA-RNA-protein-metabolome continuum links TBI and ADRD

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The relationship between environmental threats like traumatic brain injury (TBI) and Alzheimer's disease and related disorders (ADRD) is poorly understood. Our study investigates how repetitive mild TBI (rmTBI) influences tauopathies, focusing on molecular changes and identifying biomarkers. We used the CHIMERA model to induce rmTBI in wild-type and tau transgenic mice. Seven days post-injury, we performed comprehensive molecular analyses, including whole-genome bisulfite sequencing, RNAseq, DART-seq, spatial protein profiling, and spatial metabolomics. Brain function was assessed using resting-state functional MRI (rsfMRI) with graph theory analysis. Results showed that TBI significantly alters DNA methylation, gene expression, RNA methylation, protein profiles, and metabolomics, with more pronounced effects in tau models. We identified unique rsfMRI signatures for each model that corresponded to molecular changes. Mitochondrial function and tau stability emerged as key disrupted processes, primarily driven by epigenetic modifications to DNA and RNA. These changes had downstream effects on the lipidome and glycome, coinciding with rsfMRI-detected functional abnormalities in specific brain regions. Our findings suggest that rmTBI drives tauopathies through complex epigenetic mechanisms, leading to mitochondrial dysfunction and tau destabilization. This culminates in metabolic abnormalities in brain regions showing functional damage. The identified molecular and imaging markers offer potential pathways for therapeutic intervention in ADRD patients with a history of TBI.

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