Targeting m^{6}A-RNA Methylation Mitigates Alzheimer's Pathology and Cognitive Decline

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and the accumulation of pathological protein aggregates, including hyperphosphorylated tau (pTau) and amyloid beta (Aβ). Emerging evidence implicates dysregulated RNA modifications, particularly N6-methyladenosine (m^{6}A), in the progression of AD pathology. This study investigates the relationship between m^{6}A levels and AD pathology and evaluates the therapeutic potential of targeting m^{6}A through regulation of the m^{6}A writer enzyme, METTL3, in AD models. Immunohistochemical analyses revealed significantly elevated m^{6}A levels in post-mortem brain tissues from AD patients compared to age-matched controls, with a positive correlation to increased pTau217 and Aβ accumulation. These findings were recapitulated in the humanized P301S tau transgenic mouse model of AD (PS19), which similarly exhibited elevated brain m^{6}A levels associated with pathological markers. Treatment of PS19 mice with the METTL3 inhibitor STM2457 reduced m^{6}A accumulation and mitigated tau pathology, indicating a potential therapeutic effect. Behavioral assessments, including the Morris Water Maze, demonstrated that STM2457-treated PS19 mice showed significantly improved spatial learning and memory compared to untreated littermate controls, with performance approaching that of wild-type mice. These findings identify m^{6}A as a critical contributor to AD pathology and suggest that pharmacological inhibition of METTL3 may offer a promising therapeutic strategy for ameliorating cognitive deficits in Alzheimer's disease.

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