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CRISPR-Cas9 Epigenetic Reprogramming of Microglia: A Novel Therapeutic Strategy for Alzheimer's Disease Modulation

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Abstract

Alzheimer's disease (AD) pathogenesis is increasingly linked to microglial dysfunction and neuroinflammation. While genetic editing approaches have shown promise, epigenetic modulation of microglial phenotype transitions remains unexplored. This study introduces a novel CRISPR-dCas9-based epigenetic editing platform targeting the *TREM2* and *CX3CR1* loci to induce M2-like anti-inflammatory microglial states in APP/PS1 transgenic mice. Using adeno-associated virus serotype 9 (AAV9) delivery vectors crossing the blood-brain barrier, we demonstrate sustained transcriptional upregulation of phagocytic pathways and suppression of pro-inflammatory cytokine cascades. Our findings reveal a 40% reduction in amyloid-beta plaque burden and significant restoration of synaptic density at 12-week post-intervention. Single-cell RNA sequencing confirmed stable epigenetic remodeling across microglial subpopulations without off-target genomic integration. This work establishes epigenetic reprogramming as a viable disease-modifying therapy for neurodegenerative disorders.

Keywords: CRISPR-dCas9, epigenetic editing, microglia reprogramming, Alzheimer's disease, neuroinflammation, AAV9 delivery

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