Cholesterol Metabolism Orchestrates Epigenetic Remodeling to Facilitate Neuronal Gene Activation During Direct Neuronal Reprogramming

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Abstract

Direct neuronal reprogramming via attenuation of polypyrimidine tract-binding protein 1 (PTBP1) has emerged as a candidate regenerative approach to replace neurons lost in neurodegenerative disorders, offering potential for functional restoration. Although emerging evidence confirm that *PTBP1* deficiency drives transdifferentiation of somatic cells into functional neurons, whether concurrent metabolic remodeling actively instructs this cell fate conversion or merely occurs as a non-functional epiphenomenon remains to be elucidated. Given the brain's status as the most cholesterol-enriched organ, it relies on sterol homeostasis for neuronal architecture synaptic transmission and myelin integrity. We also considered the role of acetyl-CoA as a metabolic intermediate linking cellular bioenergetics to epigenetic regulation. Thus, we investigated the hierarchical relationship between PTBP1-mediated reprogramming and coordinated metabolic-epigenetic remodeling. Then, we used a well-established fibroblast-to-neuron transdifferentiation model and employed an integrated multi-omics approach (metabolomics, transcriptomics, and epigenomics) to map dynamic network changes during *PTBP1* knockdown-induced transdifferentiation. Our findings demonstrate that *PTBP1* knockdown in human dermal fibroblasts effectively drives neuronal conversion. It is accompanied by global transcriptional downregulation of cholesterol biosynthesis pathways and intracellular accumulation of acetyl-CoA. Mechanistically, PTBP1 maintains cholesterol homeostasis by directly mediating the alternative splicing of core cholesterol enzymes and a key transcription factor. The accumulated acetyl-CoA subsequently fuels histone acetylation, driving genome-wide chromatin remodeling. This sequential metabolic-epigenetic cascade is required to activate the neurodevelopmental transcriptional programs essential to neuronal fate specification. Inhibition of cholesterol synthesis by statins enhances transdifferentiation efficiency, whereas mevalonate supplementation reversed this effect, demonstrating a functional requirement of cholesterol metabolic remodeling for *PTBP1*-mediated neuronal transdifferentiation. Multi-omic profiling further corroborates that statin treatment amplifies the open chromatin landscape and reinforces neuron-specific gene expression signatures. Collectively, these findings identify cholesterol metabolism as an instructive node functionally coupling *PTBP1*-mediated neuronal reprogramming to epigenetic remodeling, revealing a hierarchical mechanism wherein metabolic rewiring actively orchestrates the epigenetic and transcriptional execution of cell fate conversion, with direct implications for regenerative therapeutics.

Keywords

PTBP1, Direct Neuronal Reprogramming, Epigenetic Remodeling, Cholesterol Synthesis, Metabolic Rewiring