

Thiamine Pyrophosphokinase-1 Deficiency Inducing Metabolic Reprogramming In Microglia Exacerbates Amyloid-β Pathology

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Microglial TPK preserves oxidative metabolism and neuroprotective function; its loss drives maladaptive metabolic reprogramming that worsens amyloid pathology, while its restoration offers a promising therapeutic strategy in Alzheimer’s disease.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
The shift in microglial energy metabolism from oxidative phosphorylation (OXPHOS) toward glycolysis represents a key driver of Alzheimer’s disease (AD) pathogenesis, contributing to microglial dysfunction. However, the molecular mechanisms underlying OXPHOS impairment in microglia remain poorly understood. Thiamine pyrophosphokinase-1 (TPK), a central enzyme that catalyzes the conversion of thiamine to its active form, thiamine diphosphate—an essential cofactor in OXPHOS—may play a critical role in this process.	We examined TPK expression in microglia from postmortem human AD brains and APP/PS1 mice. Cultured microglia were treated with amyloid-β or pro-inflammatory stimuli. Microglia-specific Tpk knockout APP/PS1 mice were generated and analyzed using transcriptomic profiling, functional assays—including phagocytosis and motility—and histology to assess metabolic and behavioral changes. In vivo dynamics were monitored via two-photon microscopy. Additionally, we employed CRISPR/Cas9-mediated genome editing to enhance TPK expression in microglia.	Suppression of microglial TPK, observed in both human AD and APP/PS1 mice, triggered a pathogenic cascade. Tpk deficiency induced metabolic reprogramming characterized by lipid droplet accumulation, energy shortfall, and impaired phagocytosis, collectively disrupting microglial homeostasis. These alterations manifested as hyperdynamic but ineffective process motility, leading to diminished plaque coverage. Genetically, microglial Tpk knockout (mcKO) exacerbated Aβ deposition and synaptic loss in APP/PS1 mice, whereas microglial Tpk overexpression (mcOE) enhanced plaque coverage and alleviated these pathologies. Together, these findings identify TPK as a critical regulator and a promising therapeutic target.	TPK acts as a pivotal metabolic safeguard for microglial homeostasis. Its loss compromises metabolic fitness and neuroprotective functions, thereby accelerating AD progression. Our results nominate TPK as a compelling therapeutic target for restoring microglial function in AD.	1.Marschallinger, J, et al., Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. Nature neuroscience 23, 194-208 (2020). 2.Baik, S, et al., A Breakdown in Metabolic Reprogramming Causes Microglia Dysfunction 303 in Alzheimer's Disease. Cell metabolism 30, 493-507.e496 (2019). 3.Chen, Z, et al., Decoding Alzheimer's disease from perturbed cerebral glucose 324 metabolism: implications for diagnostic and therapeutic strategies. Progress in neurobiology 108, 21-43 (2013).
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