Exploring the interaction between microglial dysfunction and mitochondrial impairment in Alzheimer's disease

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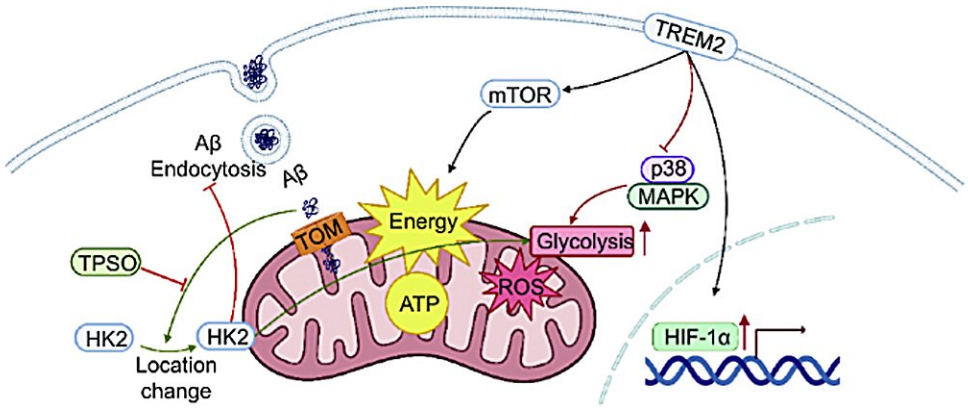

Abnormal microglial energy metabolism in AD. Translocation of Aβ into microglial mitochondria by the outer membrane translocase (TOM) impairs mitochondrial function and inhibits phagocytosis. TREM2 promotes gene expression of the transcription factor HIF1α and mTOR signaling, but inhibits p38/MAPK signaling and glycolysis in microglia. TPSO inhibits the activation of the glycolytic pathway and the reduction of Aβ endocytosis caused by HK2 localization in microglial mitochondria. Credit: Aging Research, Tsinghua University Press

Alzheimer's disease (AD) is marked by severe neurodegeneration and cognitive decline, presenting significant challenges for its prevention and treatment. Traditional hypotheses have focused on amyloid-beta plaques

and Tau pathology, but recent findings point to a significant role for microglial dysfunction and mitochondrial impairment. Given these challenges, there is a pressing need for deeper research into the mechanisms underlying AD.

A team from the Laboratory of Aging Neuroscience and Neuropharmacology at China Pharmaceutical University and Chungnam National University published a review in the journal *Aging Research*. This research explores the interaction between microglial dysfunction and mitochondrial impairment in AD, offering new insights into the disease's progression.

The study reveals that microglia, the primary immune cells in the central nervous system, play a crucial role in AD progression. Under normal conditions, microglia maintain neuronal homeostasis and clear metabolic byproducts. However, in AD, mitochondrial dysfunction leads to abnormal microglial activity, resulting in neuroinflammation and neuronal loss.

The researchers emphasize the importance of maintaining mitochondrial homeostasis for proper microglial function. They highlight how metabolic disturbances and energy dysregulation in microglia significantly contribute to AD development.

Additionally, the study explores mechanisms underlying microglial activation and its effects on neuronal health, focusing on the interplay between inflammatory pathways and mitochondrial dynamics. These findings suggest that targeting microglial mitochondria could be a promising therapeutic strategy to mitigate AD progression, providing a new direction for developing treatments that address the disease's root causes.

Dr. Jian Sima, senior author of the study, states, "Our findings highlight

the intricate relationship between microglial activity and mitochondrial function in AD. By understanding this connection, we can develop targeted therapies that address the root causes of microglial dysfunction, potentially slowing or even halting disease progression."

This research underscores the potential of targeting microglial mitochondria as a therapeutic strategy for AD. By restoring mitochondrial function in microglia, it may be possible to reduce neuroinflammation and neuronal loss, thereby improving cognitive function in AD patients. These findings pave the way for developing novel treatments that could significantly impact how we approach Alzheimer's therapy in the future.

More information: Qiudan Luo et al, The interaction between microglial dysfunction and mitochondrial impairment in Alzheimer's disease, *Aging Research* (2024). DOI: 10.26599/AGR.2023.9340020

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