RESEARCH ARTICLE SUMMARY

AGING

Boosting neuronal activity-driven mitochondrial DNA transcription improves cognition in aged mice

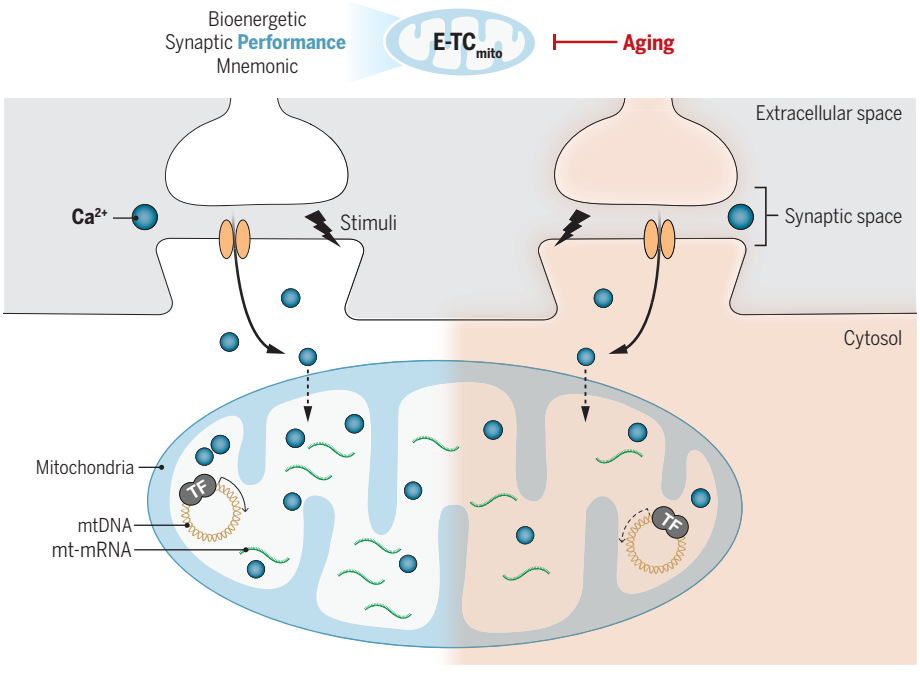
Wenwen Li†, Jiarui Li†, Jing Li, Chen Wei, Tal Laviv, Meiyi Dong, Jingran Lin, Mariah Calubag, Lesley A Colgan, Kai Jin, Bing Zhou, Ying Shen, Haohong Li, Yihui Cui, Zhihua Gao, Tao Li, Hailan Hu, Ryohei Yasuda, Huan Ma*

INTRODUCTION: The dynamic coordination of energy and mass in the brain is essential for understanding cognitive function and its evolution with age. Mitochondria, the cell's energy hubs, contain their own genome (mtDNA), which encodes key components of oxidative phosphorylation (OXPHOS) that produces adenosine triphosphate to power neuronal and synaptic functions. However, how mitochondrial gene expression is regulated during information processing in the brain remains unclear. This question becomes particularly important with aging, as mtDNA levels in neurons decrease, coinciding with a decline in synaptic and neuronal functions.

RATIONALE: This study aims to investigate whether neuronal and synaptic excitation regulates mitochondrial gene expression in a transcription-dependent manner. If excitation-dependent mitochondrial gene transcription coupling (E-TC$_{mito}$) exists, what are the underlying mechanisms, and how does the regulation of this process, triggered by mental activity, affect brain functions such as synaptic transmission and memory? Given the decline in both synaptic function and mitochondrial integrity with advancing age, understanding E-TC$_{mito}$ could provide insights into the complex interplay between these key elements implicated in cognitive aging.

RESULTS: We demonstrate that neuronal and synaptic activity enhances mtDNA expression in excitatory neurons, a process mediated by activity-dependent mitochondrial calcium influx ([Ca^{2+}]$_{mito}$) and transcriptional control mechanisms involving mitochondrial Ca^{2+}-calmodulin–dependent protein kinase II (CaMKII$_{mito}$) and Ca^{2+}/cAMP response element–binding protein (CREB$_{mito}$). Specifically, neuronal activation induces the phosphorylation of the mitochondrial calcium uniporter (MCU) through CaMKII$_{mito}$ in an activity-dependent manner, thereby feedforward-regulating [Ca^{2+}]$_{mito}$. In turn, this activity-dependent process phosphorylates the transcription factor (TF) CREB$_{mito}$ to control mtDNA transcription and expression. Thus, E-TC$_{mito}$ repurposes molecules traditionally associated with excitation-transcription coupling in the nucleus (E-TC$_{nuc}$) to regulate mitochondrial DNA transcription, which can be specifically recruited in dendritic areas closely linked to synaptic activation. In both in vitro and in vivo models, blocking E-TC$_{mito}$ impaired activity-driven mtDNA expression and profoundly disrupted neuronal energy reserves, reducing the capacity to meet synaptic demands. This regulatory mechanism provides crucial feedback control to maintain synaptic resilience against activity challenges and plays an integral role in memory processes. Aged mice exhibited diminished activity-dependent mitochondrial calcium signaling and mtDNA expression, suggesting an age-related decline in E-TC$_{mito}$. Notably, expressing a constitutively active form of CREB$_{mito}$ in aged mice restored activity-dependent mtDNA expression, increased neuronal energy reserves, and enhanced memory performance, suggesting a potential strategy to mitigate age-related cognitive decline.

CONCLUSION: This study uncovers the critical role of E-TC$_{mito}$ in regulating mitochondrial gene expression in response to neuronal and synaptic activity and mental experiences, showing that E-TC$_{mito}$ functions differently from classic excitation-transcription coupling in the nucleus (E-TC$_{nuc}$). It highlights how age-dependent E-TC$_{mito}$ sustains neuronal energy reserves, maintains synaptic resilience, and supports memory by regulating mitochondria in an activity-driven manner. These findings suggest that targeting E-TC$_{mito}$ could offer a therapeutic approach to counteract age-related cognitive decline, opening valuable avenues for future research into brain aging and neurodegenerative diseases. ■



Linking mitochondrial gene transcription with mental activity through age-dependent E-TC$_{mito}$. During information processing, neuronal and synaptic excitation triggers mtDNA expression through mitochondrial calcium signaling, thereby sustaining synaptic transmission and memory functions. This use-dependent mitochondrial plasticity diminishes with age, contributing to age-related neurological deficits. Enhancing this process in aged animals has shown prospective benefits in mitigating memory decline, positioning it as a strategic target for combating cognitive aging.

The list of author affiliations is available in the full article online.
*Corresponding author. Email: mah@zju.edu.cn
†These authors contributed equally to this work.
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