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Short Commentary

On the Substrate of Memory: Engram and Mitoengram

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Introduction

Mitochondria hold great therapeutic promise for a range of age-related diseases and disorders owing to their aptitude to orchestrate a myriad of signaling cascades that govern tissue maintenance and repair [1]. Age-associated mitochondrial dysfunction undermines these cell and organismal homeostasis-maintaining roles [1-4]. As such, the evolutionary mitochondrial mechanisms that define cell phenotype are both less efficient and less effective in the geriatric population notably in organs, tissues and cells with elevated metabolic demands [5,6]. Although mitochondria have long been considered solely from the vantage point of metabolic requirements for transitions between stem cell states, increasing evidence dispel this reductive notion and suggests that mitochondria heavily impact stem cell identity and fate decisions [7,8]. Indeed, we and other researchers have found that altered mitochondrial dynamics and inheritance represent a critical source of cellular memory in various empirical models [9-13].

Over the past century, the accepted view of memory is rooted in two substantial theories; the Engram Theory [14], which describes a sparse ensemble of select neuronal cells that undergo persistent biophysical and/or biochemical changes (i.e., engram) to store and recall memories, and the Hebbian Theory [15] which postulated that the emergence of the engram cell collective is linked to the augmented synaptic connectivity, a mechanism that has been empirically confirmed [16-21]. This conceptualization of memory as a functional pattern of cellular interconnections does broadly harmonize with insights arising from startling observations that memory can also be stored in only a minor subset of individual non-neuronal cells in the context of both naturally-occurring and synthetic cellular memory [9,12]. Though direct functional involvement of mitochondrial bioenergetics in memory, such as through mitochondrial cannabinoid receptor CB1 of hippocampal neurons [22] or mitoflash (i.e., local and transient ROS burst) [23], and more recently, through cytochrome c oxidase subunit 4 (Cox4) [24], is known now, the enduring physicochemical changes of mitochondria and connectivity patterns of mitochondrial networks underlying the transgenerational inheritance of cellular memory, or mitoengram [12], has not been previously explored in the traditional research setting of cell engram.

Mitochondria represent an important therapeutic target with tremendous translation potential. Understanding how the mitochondrial mechanisms of memory storage and retrieval is a crucial step in understanding how to better treat the dementing illnesses affecting our rapidly expanding geriatric population. From single cells to organs, memory traces can have enabling and constraining functional effects with profound structural, dynamical and regulatory ramifications, including in clinical settings [25-27]. As the complex molecular and physiological manifestations of both chronological and/or replicative aging accrue and compound, and as the lifetime-transient cellular experiences continue to amass, it is completely conceivable that the cell capacity to record, store, retrieve or erase memories declines with the decline of the underlying mitochondrial substrate.

Intriguing questions thus emerge: might we near a point where we can make on-demand healthy cellular memories if we hold a better comprehension of specific physiological and pathological states of mitochondrial function and architecture? Can the gain of mitochondrial insights into cellular memory lead to novel approaches to enhance maintenance and repair of aged or diseased tissues? Furthermore, with this very rudimentary understanding and significant knowledge gaps, what are the state-of-the-art technological toolbox that can enable us to address these queries? The discovery of mitoengram [12] is important not only because it reveals a previously undescribed mechanism underlying the cellular memory dependence on mitochondria, but also because it defines mitochondria as a universal unit of cognitive information, beyond the brain cell engram, and raises tantalizing possibilities for the next-generation of molecular and cellular cognition therapeutics [28].

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