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Featured Article

Nuclear but not mitochondrial-encoded oxidative phosphorylation genes are altered in aging, mild cognitive impairment, and Alzheimer's disease

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Abstract

Introduction: We have comprehensively described the expression profiles of mitochondrial DNA and nuclear DNA genes that encode subunits of the respiratory oxidative phosphorylation (OXPHOS) complexes (I–V) in the hippocampus from young controls, age matched, mild cognitively impaired (MCI), and Alzheimer's disease (AD) subjects.
Methods: Hippocampal tissues from 44 non-AD controls (NC), 10 amnestic MCI, and 18 AD cases were analyzed on Affymetrix Hg-U133 plus 2.0 arrays.
Results: The microarray data revealed significant down regulation in OXPHOS genes in AD, particularly those encoded in the nucleus. In contrast, there was up regulation of the same gene(s) in MCI subjects compared to AD and ND cases. No significant differences were observed in mtDNA genes identified in the array between AD, ND, and MCI subjects except one *mt-ND6*.
Discussion: Our findings suggest that restoration of the expression of nuclear-encoded OXPHOS genes in aging could be a viable strategy for blunting AD progression.
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Keywords: Aging; Alzheimer's disease; Mild cognitively impaired (MCI); Mitochondria; Oxidative phosphorylation-related genes expression; Microarray; Postmortem brains

1. Introduction

Alzheimer's disease (AD) is a progressive, degenerative brain disease and the most common cause of dementia [1,2]. AD is characterized by a gradual decline in cognitive function and the presence of pathologic inclusions including amyloid β (Aβ) plaques and neurofibrillary tangles [1]. The disease is preceded by a presymptomatic stage that can last for years during which time the clinical symptoms are undetectable. An intermediate stage between normal aging and AD has been identified as mild cognitive impairment. This disease state is characterized by problems with memory, language acquisition and processing, critical thinking, and judgment problems that are greater than normal age-related changes [2].

Bioenergetic failure and mitochondrial dysfunction in AD are well documented [2–10]. Several studies using multiple preclinical *in vitro* and *in vivo* AD models have demonstrated a decline in mitochondrial function before the development of AD pathology [2–8]. Mitochondria are key organelles that regulate a multitude of metabolic and signaling pathways including programmed cell death [11–15]. The primary function of mitochondria is to produce ATP through the process of oxidative phosphorylation (OXPHOS), which is regulated through four respiratory multi-subunit enzyme complexes (complexes I–IV) and ATP synthase (complex V), all located in the inner mitochondrial membrane (Fig. 1) [16–18].

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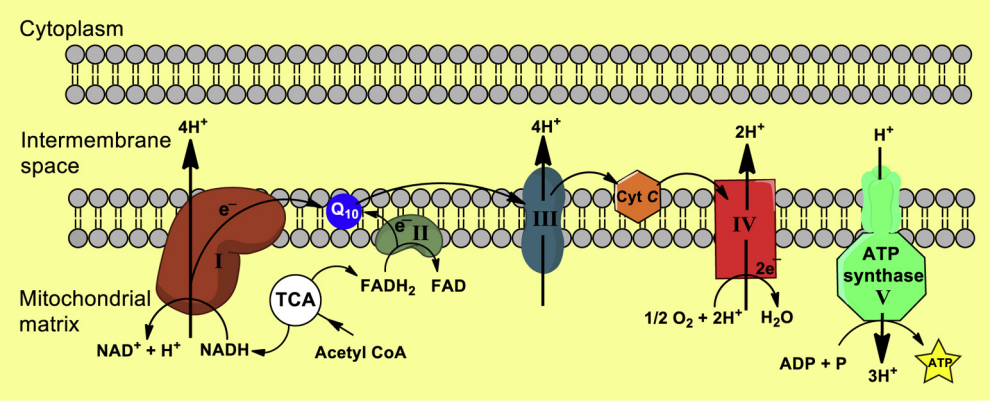

Fig. 1. Mitochondrial oxidative phosphorylation system (OXPHOS) shown: The five respiratory chain complexes with the corresponding electron transport chain numbers (I–V). In the bottom part, these are indicated by the subunits of each respiratory chain complex gene numbers, which were selected by microarray analysis. Among the ~80 polypeptides constituting the electron transport chain, 13 are encoded by mtDNA, and the rest are all encoded by nDNA, synthesized in the cytosol, and translocated to the mitochondria. TCA, trichloroacetic acid; Cyt C, cytochrome C; ADP, adenosine diphosphate; ATP, adenosine triphosphate.

Mammalian mitochondrial DNA (mtDNA) is a maternally inherited, double-stranded circular genome of approximately 16.6 kb [19–21]. It contains 37 genes encoding 13 protein subunits of enzymes involved in oxidative phosphorylation, two ribosomal RNAs, and 22 transfer RNAs necessary for translation of these proteins. The remaining subunits are encoded by the nuclear genome, synthesized in the cytosol, and subsequently imported into mitochondria through protein translocation machineries of the outer and inner membranes [19–21].

A critical role of mitochondrial dysfunction has been hypothesized in both aging and neurodegenerative diseases [2–10]. Numerous studies use animal models based on genetic mutations found in rare early onset familial AD cases that represent <1% of AD patients [1]. Recently, it has been demonstrated that mitochondrial bioenergetic deficits precede AD pathology in the female triple transgenic mouse model of AD (3xTgAD) [4]. Converging lines of evidence indicate that mitochondria are direct targets of Aβ [22–24], and that Aβ is directly responsible for impaired electron transport chain function [22–28]. Accumulation of Aβ in neurons is believed to be an essential step leading to Aβ-mediated mitochondrial dysfunction and contributes to energy failure, neuronal apoptosis, and production of reactive oxygen species (ROS) in AD brain tissue [25–29]. Mitochondrial dysfunction and oxidative damage occur early in the course of disease, before the onset of significant plaque pathology, and act causally in disease pathogenesis [4,30]. Normal aging and AD are both marked by prominent defects in brain metabolism and increased oxidative stress. Although inheritance of certain susceptibility genes increases the risk of the disease, aging is the most prominent risk factor for the non-Mendelian sporadic AD which affects most patients diagnosed for dementia over the age of 60 years [31]. Several studies have provided evidence of neuronal metabolic impairments at the transcript and protein level in AD brain, which was ascribed to the down regulation of mitochondrial-associated genes; in particular, oxidative phosphorylation genes [27,32–37]. Following this line of thought, we present here a microarray-based study that focuses specifically on the role of OXPHOS-related genes in aging and in AD.

It is clear from the literature that the etiology of AD is not completely understood; hence, the use of a wide array of animal and cellular models to address the pathological process of the early onset, dominantly inherited familial form of this disease. Although these model system(s) do feature particular aspects of the disease process, no model has yet fully recapitulated the human disease. There is much evidence that late onset AD overlaps with normal aging in many clinical and pathologic features [38–43]. Therefore, the availability of human postmortem brain tissue is of great importance for biological studies on human brain aging and the progression to disease. These unique tissue specimens make it possible to investigate potential gene expression alterations before, during, and after the onset of AD. In this study, we compared expression profiles of mitochondrial genes (e.g., OXPHOS) from the hippocampus from clinically and pathologically confirmed AD cases, young controls, age-matched controls, and MCI cases.

2. Methods

Frozen unfixed hippocampus was obtained from 44 non-AD controls (age, 20–99 years), 10 amnestic mild cognitively impaired cases, and 18 sporadic AD cases (age, 74–95 years; Table 1) from seven nationally recognized brain banks. Inclusion criteria can be found in Berchtold et al. [38]. Total RNA was extracted from heterogeneous population across hippocampal subfields as described previously [38], and RNA quality was assessed using the Agilent BioAnalyzer (Agilent Technologies, Palo Alto, CA). Average RIN for the samples was 8.29 (SD, 0.775; range, 6.7–9.6), with 93% of the cases (67 of 72) having RIN > 7. There