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Review

Are mitochondria critical in the pathogenesis of Alzheimer's disease?

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Abstract

This review summarizes recent findings that suggest a causal connection between mitochondrial abnormalities and sporadic Alzheimer's disease (AD). Genetic causes of AD are known only for a small proportion of familial AD patients, but for a majority of sporadic AD patients, genetic causal factors are still unknown. Currently, there are no early detectable biomarkers for sporadic AD, and there is a lack of understanding of the pathophysiology of the disease. Findings from recent genetic studies of AD pathogenesis suggest that mitochondrial defects may play an important role in sporadic AD progression, and that mitochondrial abnormalities and oxidative damage may play a significant role in the progression of familial AD. Findings from biochemical studies, in vitro studies, gene expression studies, and animal model studies of AD are reviewed, and the possible contribution of mitochondrial mutations to late-onset sporadic AD is discussed.
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Contents

Abbreviations: AD, Alzheimer's disease; mtDNA, mitochondrial DNA; Aβ, beta amyloid; ETC, electron transport chain; ATP, adenosine triphosphate; 8-OHG, 8-hydroxyguanosine; APP, amyloid precursor protein; ROS, reactive oxygen species; Cybrids, cytoplasmic hybrids; ABAD, Aβ binding alcohol dehydrogenase; KGDHC, alpha-ketoglutarate dehydrogenase; KMV, alpha-keto-beta-methyl-*n*-valeric acid; TCA, tricarboxyclic acid; YAC, yeast artificial chromosome

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1. Introduction

Alzheimer's disease (AD) is a late-onset, progressive, age-dependent neurodegenerative disorder, characterized clinically by the impairment of cognitive functions and changes in behavior and personality [121,146,147]. AD is associated with the presence of intracellular neurofibrillary tangles and extracellular beta amyloid (Aβ) plaques, a loss of neuronal subpopulations, synaptophysin immunoreactivity of presynaptic terminals, cholinergic fibers, and the proliferation of reactive astrocytes and microglia [55,144,145].

AD occurs in both familial and sporadic forms. Familial AD can be caused by mutations in the amyloid precursor protein, presenilin 1, and presenilin 2 [45,121]. Early-onset familial AD (autosomal dominantly inherited) accounts for a small fraction (2–3%) of AD cases, whereas sporadic AD represents the majority of AD cases [Rudy Tanzi, personal communication]. A major risk factor in sporadic AD is the ApoE genotype. Several epidemiological studies have reported that patients with the E4 allele are associated with an increased risk of developing both late-onset familial and sporadic AD [106,115,119]. In the majority of late-onset AD patients, the causal factors are still unknown. Recently, however, several reports suggest that mitochondrial defects play a role in late-onset sporadic AD [34,53,63,72,141]. This paper reviews research that suggests a causal connection between mitochondrial abnormalities and sporadic AD.

2. Mitochondria

Mitochondria, which are cytoplasmic organelles, are thought to have arisen about 1.5 billion years ago from a symbiotic association between a glycolytic proto-eukaryotic cell and an oxidative bacterium [155]. Several features that reflect an endo-symbiotic origin are their double-membrane structure, and the circular mitochondrial genome of modern mitochondria with mitochondria-specific transcription, translation, and protein assembly systems. Mitochondria have adapted to their new intracellular environment by reducing their genome size to about 16,500 base pairs. This reduction has increased their replication rate and, thus, ensures the transmission of the mitochondrial genome to two daughter cells [155]. This improved transmission is assumed to be accomplished by the deletion of nonessential genes and the transfer of many essential genes to the nucleus where the proteins are transcribed into mRNA, translated on cytoplasmic ribosomes, and selectively imported back into the mitochondrion [118].

2.1. Mitochondrial genome

The mammalian mitochondrial DNA consists of a 16.5 kb double-stranded circular DNA molecule [62,117,127]. Each mitochondrion contains from two to ten copies of mtDNA. Thus, on average, each cell contains several thousands of copies of mtDNA [126]. The mtDNA contains 13 polypeptide genes, all of which encode essential components of the electron transport chain (ETC). The mtDNA also encodes the 12S and 16S rRNA genes and the 22 tRNA genes required for mitochondrial protein synthesis [117,126,155]. All of the 13 polypeptide genes in a mitochondrion are involved in producing components of the mitochondrial complexes.

mtDNA encodes seven subunits (ND1, 2, 3, 4, 4L, 5, and 6) of the 43 subunits constituting complex I, one (cytochrome *b*) of 11 subunits of complex III, three (COX1, COX2, and COX3) of 13 subunits of complex IV, and two (ATPase 6 and ATPase 8) of 17 subunits of complex V. Nuclear genes encode the remaining mitochondrial proteins, the metabolic enzymes, the DNA and RNA polymerases, the ribosomal proteins, and the mtDNA regulatory factors, such as mitochondrial transcription factor A [62,155]. mtDNA replication of the heavy (outer) and light (inner) strands occurs from separate sites (O_H and O_L) and is under nuclear control [117]. mtDNA transcripts serve as primers that initiate the replication of the heavy strand [117]. DNA polymerase is responsible for mtDNA replication and is stimulated by the binding of mitochondrial, single-stranded binding proteins to the exposed, single-stranded mtDNA [117].

2.2. Mitochondrial inheritance

Mitochondria are transmitted through the cytoplasm of an oocyte at fertilization and, therefore, are maternally inherited [117,155]. However, in rare instances, paternal inheritance and a recombination of mtDNA have been reported [40,120]. Mitochondria contain no protective histones and have a mutation rate that is 17 times greater

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