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Review Article

Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease

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ABSTRACT

Alzheimer disease (AD) and Parkinson disease (PD) are the two most common age-related neurodegenerative diseases characterized by prominent neurodegeneration in selective neural systems. Although a small fraction of AD and PD cases exhibit evidence of heritability, among which many genes have been identified, the majority are sporadic without known causes. Molecular mechanisms underlying neurodegeneration and pathogenesis of these diseases remain elusive. Convincing evidence demonstrates oxidative stress as a prominent feature in AD and PD and links oxidative stress to the development of neuronal death and neural dysfunction, which suggests a key pathogenic role for oxidative stress in both AD and PD. Notably, mitochondrial dysfunction is also a prominent feature in these diseases, which is likely to be of critical importance in the genesis and amplification of reactive oxygen species and the pathophysiology of these diseases. In this review, we focus on changes in mitochondrial DNA and mitochondrial dynamics, two aspects critical to the maintenance of mitochondrial homeostasis and function, in relationship with oxidative stress in the pathogenesis of AD and PD.

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Abbreviations: AD, Alzheimer disease; Aβ, amyloid-β; APP, amyloid-β protein precursor; ADDL, Aβ-derived diffusible ligand; ApoE4, apolipoprotein E; COX, cytochrome *c* oxidase; DLP1, aka Drp1, dynamin-like protein 1; ETC, electron transport chain; LHON, Leber's hereditary optic neuropathy; LRRK2 or PARK8, leucine-rich repeat kinase 2; MMP, mitochondrial membrane potential; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyradine; mtDNA, mitochondrial DNA; Mfn, mitofusin; MERRF, myoclonic epilepsy with red ragged fibers syndrome; OPA-1, optic atrophy protein 1; OMM, outer mitochondrial membrane; OXPHOS, oxidative phosphorylation; PD, Parkinson disease; PS, presenilin; PINK1 or PARK6, PTEN-induced putative kinase; ROS, reactive oxygen species; SNP, single-nucleotide polymorphism; SOD, superoxide dismutase

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Introduction

Free radicals are made continuously in eukaryotic cells and must be balanced by antioxidant defense to maintain the redox homeostasis. Imbalance between harmful reactive oxygen species (ROS)[1] and antioxidant defenses causes oxidative stress, which results in oxidative damage. In the brain, when redox balance is lost, oxidative stress causes serious damage that leads to neuronal loss, in congruence with neurodegenerative diseases. ROS, for example, can cause nucleic acid breakage, enzyme inactivation, polysaccharide depolymerization, lipid peroxidation, and a host of other destructive processes. In general, ROS damage all biomolecules, ultimately leading to cell death if in overabundance.

Among all the organelles and enzymes that can generate ROS within the cell, mitochondria are the major sites responsible for more than 90% of the ROS generation. This ROS production can occur when electrons leak out of the electron transport chain (ETC) and react with dioxygen (O_2). Indeed, between 1 and 5% of all O_2 used in complexes I and III of the ETC escapes as superoxide. In response, superoxide dismutases (SOD) in the mitochondria (Mn-SOD or SOD2) and cytosol (Cu-Zn-SOD or SOD1) catalyze a reaction changing superoxide to diatomic oxygen and hydrogen peroxide. Glutathione peroxidases and catalase, in turn, act as additional antioxidant defenses by converting hydrogen peroxide to water. Hydrogen peroxide, however, is not a radical; thus it can cross membranes and rapidly propagate throughout the cell. Nevertheless, it can react with Fe^{2+} and other transition metal ions to form the highly dangerous hydroxyl radical, which is the most reactive species and is capable of initiating autocatalytic radical chain reactions [1].

As the sources of the majority of energy production and endogenous ROS production, mitochondria play a key role in the functioning and survival of neurons in the brain, the most energy-intensive organ in the human body. Notably, the long-lived, energy-demanding neurons have very limited glycolysis, thus making them highly dependent on aerobic OXPHOS for energy [2]. Additionally, as postmitotic cells with polyunsaturated fatty acid enriched in their membranes, neurons are sensitive to ROS buildup. Likewise, normal mitochondrial dynamics is important for maintaining polarity in highly polarized neurons [3]. Consequently, dysfunction in mitochondria seems to promote oxidative stress, aging, and neurodegeneration [4,5]. In fact, mitochondrial dysfunction and oxidative stress constitute the most prominent features found in Alzheimer disease (AD) and Parkinson disease (PD) [6–9]. Whereas defects in almost all aspects of mitochondrial function have been implicated in these neurodegenerative diseases, in this review, we focus on changes in mitochondrial DNA (mtDNA) and mitochondrial dynamics, two aspects critical to the maintenance of mitochondrial homeostasis and function, in relationship with oxidative stress in the pathogenesis of AD and PD.

Mitochondrial DNA and oxidative stress

Reflecting the ancient symbiotic eubacteria origin, mitochondria contain multiple copies of their own DNA, which is a circular double-stranded molecule critical to the maintenance of a functionally competent organelle. Human mtDNA contains genes encoding 12 S and 16 S rRNAs and 22 tRNAs necessary for mitochondrial protein synthesis and 13 polypeptide components of the ETC [10]. mtDNA can be replicated independent of the cell cycle, although loss of mtDNA inhibits G1- to S-phase progression by activating an established checkpoint kinase [11]. mtDNA molecules exist in multiple copies within each cell, which creates the possibility of coexistence of mutant and wild-type copies, a condition called heteroplasmy. It is suggested that a minimum critical load of mutant mtDNA must be met before cell dysfunction or clinical signs become apparent and this pathogenic threshold can be lower in tissues that are highly dependent on oxidative metabolism than in those that can rely on glycolysis [10].

It is worth noting that mtDNA has a relatively short half-life [12] and genes coded by mtDNA have few to no noncoding sequences between one another. Coupled with constant ROS exposure, lack of protection by histone, and limited DNA repair mechanisms, however, these unique features make mtDNA particularly vulnerable to oxidative damage, which could lead to harmful and influential mutations including point mutations and large-scale sporadic mtDNA rearrangements. The main products of mtDNA base damage are thymine glycol among pyrimidines [13], which has low mutagenicity, and 7,8-dihydro-8-oxo-2′-deoxyguanosine among purines [14–16], which can cause characteristic G→T transversions upon replication [13]. Large-scale sporadic mtDNA rearrangements are predominantly deletions up to 9 kb in size with one particular 5-kb deletion being the most common form (i.e., common deletion). Although the actual mechanisms remain elusive, oxidative damage-associated single- or double-strand breaks might be involved in the formation of mtDNA deletions. Indeed, numerous studies demonstrated that somatic mutations in mtDNA progressively accumulate with age in a variety of tissues in humans, and importantly, terminally differentiated tissues with active oxidative metabolism such as the brain accumulate relatively higher levels of mutant mtDNA during the aging process, starting from the mid-30s in humans [17,18].

As a result, these gradually accumulated mtDNA mutations could potentially cause decreases in the efficiency of the ETC, spurring decreased ATP production and increased ROS production. In return, the increase in ROS could cause subsequent accumulation of more mtDNA mutations and create a positive feedback loop of increasing mutations and ROS production, followed by eventual cell death. In conjunction with this hypothesis, numerous studies have shown good correlations between aging, accumulation of mtDNA mutations, mitochondrial function decline, and increased oxidative stress during aging in humans and animals [19,20]. The causal relationship between mtDNA mutations and ROS production is best demonstrated in the affected tissues of patients with mitochondrial diseases when the mutant load of mtDNA mutations reaches a threshold [21–23]. For example, the A8344G mutation in the $tRNA_{Lys}$ gene of mtDNA is the most common mutation associated with MERRF (myoclonic epilepsy with red ragged fibers) syndrome. Cytoplasmic hybrids (cybrids) harboring the A8344G mutation exhibit decreased efficiency of ATP synthesis in mitochondria and become more sensitive to extrinsic oxidative stress such as hydrogen peroxide and UV irradiation [24–26] and the skin fibroblasts from MERRF patients demonstrate higher intracellular hydrogen peroxide levels and increased oxidative damage to the mitochondrial proteins containing iron–sulfur along with imbalance in the gene expression of antioxidant enzymes [27]. Human MELAS (mitochondrial encephalomyopathy and lactic acidosis with stroke-like episodes) patients carrying the A3243G mutation of mtDNA demonstrated increased oxidative stress systemically [28]. Leber's hereditary optic neuropathy (LHON) results from one of three point mutations in mtDNA coding for complex I components and LHON cybrids have increased superoxide production compared to wild-type cells [29]. Nevertheless, this notion is challenged by the observation in mtDNA mutator mice, which harbor homozygous genetic defects in the proofreading exonuclease activity of mtDNA polymerase γ: despite the rapidly accumulated mtDNA mutations in these mice, ROS generation is not significantly increased [30].

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