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Mitochondria as a Therapeutic Target for Aging and Neurodegenerative Diseases

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Abstract

Mitochondria are cytoplasmic organelles responsible for life and death. Extensive evidence from animal models, postmortem brain studies of and clinical studies of aging and neurodegenerative diseases suggests that mitochondrial function is defective in aging and neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Several lines of research suggest that mitochondrial abnormalities, including defects in oxidative phosphorylation, increased accumulation of mitochondrial DNA defects, impaired calcium influx, accumulation of mutant proteins in mitochondria, and mitochondrial membrane potential dissipation are important cellular changes in both early and late-onset neurodegenerative diseases. Further, emerging evidence suggests that structural changes in mitochondria, including increased mitochondrial fragmentation and decreased mitochondrial fusion, are critical factors associated with mitochondrial dysfunction and cell death in aging and neurodegenerative diseases. This paper discusses research that elucidates features of mitochondria that are associated with cellular dysfunction in aging and neurodegenerative diseases and discusses mitochondrial structural and functional changes, and abnormal mitochondrial dynamics in neurodegenerative diseases. It also outlines mitochondria-targeted therapeutics in neurodegenerative diseases.

Keywords

Abnormal mitochondrial dynamics; Aging; Alzheimer's disease; Huntington's disease; Mitochondria; Mitochondria-targeted antioxidants; Neurodegenerative Disease; Parkinson's disease

Introduction

Mitochondrial abnormalities and aging are the primary risk factors in the development of age-related neurodegenerative diseases, such as Alzheimer's (AD), Parkinson's (PD), Huntington's (HD), and amyotrophic lateral sclerosis (ALS). Tremendous progress has been made in better understanding the role of genetic mutations in the onset of age-related neurodegenerative diseases, and progress has also been made in developing cell and animal models that have been developed to research the progression of neurodegenerative diseases

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Conflict of interest

Authors declare that they do not have any conflict of interest.

[1]. Most neurodegenerative diseases share similarities: 1) the diseases manifestation in the brain, 2) they have early and late onset states, 3) aging plays a key role in neurodegenerative disease progression, in both early- and late-onset disease states, 4) mitochondrial dysfunction and oxidative stress are involved in the etiology of these diseases, and 5) mitochondria have been found to be associated with mutant protein(s) in persons with these diseases, and differences among neurodegenerative diseases, including AD, PD, HD and ALS are: 1) affected populations of neurons, 2) disease causing genetic mutations, and 3) clinical symptoms. Despite the tremendous progress that has been made in elucidating similar and different features of neurodegenerative diseases, we still do not have a clear understanding of their etiology and of the cellular mechanisms that are involved in their progression. For example, A β has been associated with AD; mutant fSOD1 with ALS; mutant parkin, mutant α -synuclein, mutant DJ1 with PD and mutant Htt with Huntington's [reviewed in 1–5]. This article discusses the latest developments of role of aging and mitochondria, in the progression of neurodegenerative diseases, particularly AD, PD, HD, and ALS. This article also discusses the recent progress of mitochondrial therapeutics for neurodegenerative diseases.

Aging

In recent years, aging has been defined in several ways. A basic definition is that aging is the process of gradual and spontaneous change, leading to maturation through childhood, puberty, and young adulthood and then a decline through middle and late ages [6]. Aging in mammals has also been defined as a complex process of the accumulation of molecular, cellular, and organ damage leading to a loss of function and an increased vulnerability to disease and death [7]. The human phenotype of aging is the failure of one tissue or organ [8,9].

Healthy aging in humans, a universal and natural phenomenon, has been of particular interest to many researchers who study features of healthy lifespans and mechanisms of aging and age-related diseases. Recently, researchers have demonstrated that calorie-restricted diets can extend the healthy lifespan of lower organisms (e.g., yeast, worms), as can manipulations of the genes of lower organisms [7]. Recent epidemiological studies of humans who lived over 110 years of age suggest that humans age uniformly, with multiple similar pathologies (e.g., diabetes, heart disease, cancer, arthritis, and kidney disease) and with neurodegenerative diseases (e.g., AD, PD, HD, ALS), and that the number of these pathologies increases with age. However, some pathologies, such as sinusitis, remain relatively constant with age, while others, such as asthma, decline with age.

Several hypotheses have been proposed to explain biochemical causes of aging, including mitochondrial abnormalities, reactive oxygen species (ROS) production (or the free radical theory of aging), the shortening of telomerase, DNA methylation, and epigenetics [10–14]. Among these, the free radical theory of aging has been given much attention recently because of its connection with mitochondrial defects and oxidative damage. This theory hypothesizes that ROS – generated by an increase in mitochondria, over time – causes defects in mitochondrial DNA and in mitochondrial structural components, resulting in accelerated cell death and senescence [15–17].

Recent research in lower and higher organisms revealed several important cellular pathways in healthy aging: 1) insulin/IGF – 1 Signaling, in which decreased signaling promotes increased stress resistance and lifespan; 2) sirtuins – an increase in the expression of sirtuins can extend the healthy lifespan; 3) target of rapamycin (TOR) - decreased TOR signaling results in increased lifespan; 4) calorie-restricted diets or optimal diets result in increased lifespan; and 5) modestly decreased mitochondrial function causes increased lifespan [18] (Fig 1). Further, increased telomere length may also contribute to increased lifespan in all

organisms [7,19] (Fig. 1). These cellular pathways still need to be examined in higher organisms such as nonhuman primates and humans. Extensive experimental evidence points to a connection between aging and mitochondria in rodents, nonhuman primates, and humans. Mitochondrial abnormalities have been found to be associated with age. Such abnormalities include accumulations of mtDNA changes, increased production of free radicals, decreased respiratory function, and low ATP production in the brains of aged people [2,3,20–26]. These age-dependent mitochondrial abnormalities may contribute to the development of age-related neurodegenerative diseases such as AD and PD.

Mitochondrial structure and function

Mitochondria are cytoplasmic organelles that are essential for the life and death of the cells. They are usually transmitted maternally, but in rare situations, they can be transmitted paternally [27]. They perform or contribute to the performance of several cellular functions, including: 1) the regulation of intracellular calcium, 2) ATP production, 3) the release of proteins that activate the caspase family of proteases, 4) alteration of the reduction-oxidation potential of cells, and 5) free-radical scavenging [1, 21].

Mitochondria are compartmentalized into 2 lipid membranes: the outer mitochondrial membrane and the inner mitochondrial membrane. The outer membrane is porous and allows the passage of low molecular-weight substances between the cytosol and the inter-membrane space of mitochondria. The inner membrane provides a highly efficient barrier to ionic flow, houses the mitochondrial respiratory chain or electron transport chain (ETC), and covers the mitochondrial matrix. The mitochondrial matrix contains tricarboxylic acid (TCA) and beta-oxidation (see Fig. 2) [27].

Mitochondria are controlled by both nuclear and mitochondrial genomes. MtDNA consists of a 16,571 base pair, double-stranded, circular DNA molecule [28]. A mitochondrion contains 2–10 copies of mtDNA [1]. mtDNA contains 13 polypeptide genes that encode essential components of the ETC. mtDNA also encodes the 12S and 16S rRNA genes and the 22 tRNA genes required for mitochondrial protein synthesis [27]. Nuclear genes encode the remaining mitochondrial proteins, metabolic enzymes, DNA and RNA polymerases, ribosomal proteins, and mtDNA regulatory factors, such as mitochondrial transcription factor A. Nuclear mitochondrial proteins are synthesized in the cytoplasm and are subsequently transported into mitochondria.

Mitochondrial ATP is generated via oxidative phosphorylation (OXPHOS) within the inner mitochondrial membrane (Fig. 2) [21]. Free radicals are generated as a byproduct of OXPHOS. In the respiratory chain, complexes I and III leak electrons to oxygen, producing primarily superoxide radicals. The superoxide radicals are dismutated by manganese superoxide dismutase (Mn-SOD), generating H_2O_2 and oxygen. Complex I generates only toward the mitochondrial matrix, but complex III generates toward both the inter-membrane space and the matrix. In addition, the components of tricarboxylic acid, including α -ketoglutarate dehydrogenase, generate superoxide radicals in the matrix [21]. These mitochondrially generated free radicals and superoxide radicals are carried to the cytoplasm via voltage-dependent anion channels and participate in lipid peroxidation, and protein and DNA oxidation.

Mitochondria and aging

Studies of mitochondria using a mitochondria-targeted antioxidant transgenic model of aging suggest that healthy mitochondria and mitochondrial DNA play a large role in perpetuating healthy aging and extending lifespan. In contrast, abnormalities in mitochondria and mtDNA accelerate premature aging.

Mitochondrial dysfunction has been well documented in aging and neurodegenerative diseases [1,3]. To understand the mechanisms of aging, particularly the role of mtDNA in the brain, several researchers studied mtDNA, free radical production, and mitochondrial function in young and aged tissues from rodents, nonhuman primates, and humans [reviewed in 5, 7, 18, 19, 23 and 29, 30]. In aged tissues relative to young tissues from rodents, nonhuman primates, and humans, researchers found an accumulation of mtDNA defects, an increased production of ROS, and decreased mitochondrial function in the brain tissues from old rodents, nonhuman primates and humans [7, 18, 19, 29, 30], indicating that age-related accumulation of mtDNA defects is involved in aging. It has been reported that mitochondrial ETC is responsible for the transfer of electrons from NADH or FADH, to electron acceptors, and to oxygen, the final transfer of which leads to the production of H₂O. These biochemical events lead to a small amount (0.5–5%) of electron leakage and, subsequently, to ROS production [reviewed in 1].

MtDNA is localized close to the source of ROS production and may be vulnerable to DNA damage. Oxidized guanosine levels are higher in mtDNA relative to nuclear DNA. It has been reported that several DNA repair mechanisms may operate within mitochondria, but one such repair mechanism – nucleotide excision repair – may be absent in mtDNA, leaving mtDNA vulnerable to a number of DNA changes [1]. MtDNA defects that reduce the accuracy of electron transfer may increase the production of ROS and decrease the production of ATP. An increase in the production of ROS may further damage mtDNA.

mtDNA changes and aging—Changes in mtDNA have been found to be responsible for aging phenotypes [29, 31, 32]. For example, many tissues from aged rodents have lower respiratory function compared to those from younger rodents [29] (Cooper et al. 1992). Both mtDNA single-nucleotide mutations and deletions are highly prevalent in aged cells. There is evidence that damaged mtDNA is more prevalent in aged tissues [33, 34, 35].

To understand the role of mtDNA mutations in aging, two investigators independently created mouse lines containing a point mutation in the proofreading region of DNA polymerase gene, the catalytic subunit of mtDNA polymerase [31, 32]. The mutant mice in both studies exhibited normal DNA polymerase activity but lacked the exonuclease activity necessary for proofreading the mutated mice did not live as long as control mice and experienced an early onset of age-associated features, including weight loss, reduction in subcutaneous fat, hair loss, curvature of the spine, and osteoporosis. Such similar findings from two independent studies suggest that mtDNA changes are involved in the aging process.

Contrary to these studies, a recent study supports the involvement of mitochondria-targeted antioxidants in the healthy aging [36]. To determine the protective effects of catalase, Schriener and colleagues [36] created transgenic mouse lines that over-expressed human catalase localized to peroxisomes (PCAT mice), nuclei (NCAT mice), and mitochondria (MCAT mice). The transgenic mice that were targeted to mitochondria showed about a 20% increase in median and maximal life span compared to the life span of non-transgenic, age-matched wild-type littermates. That catalase increases longevity was most apparent when catalase was targeted to mitochondria (MCAT mice) but not in nuclear (NCAT mice) or in peroxisomal targeted mice (PCAT mice) [36].

Overall, findings from these studies suggest that mutations in mitochondrial DNA play a large role in premature aging. On the contrary, over-expression of mitochondria-targeted antioxidants extend healthy lifespan.

Mitochondrial dysfunction in Neurodegenerative diseases

Several lines of evidence suggests that mitochondria play a large role in neurodegenerative diseases, including AD, PD, HD and ALS: 1) defective mitochondrial enzyme activities, 2) mitochondrial DNA defects, 3) mitochondrial dysfunction and oxidative stress, and 4) mitochondrial structural changes [1–4]. Further, in 1990s, Swerdlow and colleagues studied the role of mtDNA in mitochondrial function using cytoplasmic hybrids (cybrids) of peripheral cells from patients with AD, PD and ALS and control subjects. They found that peripheral cells from AD, PD and ALS lacking mtDNA did not exhibit mitochondrial dysfunction, suggesting that mitochondria are important for mitochondrial function in disease progression in AD, PD and ALS [37–39].

Mitochondrial dysfunction in Alzheimer's disease

AD is a late-onset, progressive neurodegenerative disease, characterized by the progressive decline of memory, cognitive functions, and changes in behavior and personality [21, 24]. The prevalence of AD is high among aged persons with AD: 13% of individuals 65 years old have AD and 50% of individuals 85 years of age and older have AD [40]. By the year 2050, 50% of people worldwide will have AD. Currently, 5.3 million Americans suffer from AD [41]. In addition to the personal and family hardships that AD creates, these numbers translate into extremely high health care costs. With increasing lifespan in humans, AD is a growing health concern in the society.

Two major pathological features have been observed in postmortem brains from AD patients: 1) intracellular neurofibrillary tangles and 2) extracellular A β deposits in the regions of the brain that are responsible for learning and memory. AD is also associated with the loss of synapses, synaptic function, mitochondrial structural and functional abnormalities, inflammatory responses, and neuronal loss [24, 37, 38, 42]. Genetic mutations in APP, PS1, and PS2 genes cause a small proportion (about 1%) of all AD cases; however, causal factors are still unknown for the vast majority of AD patients. Several factors – including lifestyle, diet, environmental exposure, apolipoprotein allele E4, and a genetic variant in sortilin-related receptor 1 gene, clusterin, and complement component receptor 1 – may contribute to late-onset AD [24, 43, 44]. Above all, aging has been considered 'number one' risk factor in the progression and development of AD.

AD affects brain regions involved in learning, memory, and cognitive functions: the hippocampus, entorhinal cortex, temporal cortex, frontoparietal cortex, and, subcortical nuclei [45]. A β secretion also occurs mainly in these regions; however, the reasons for A β secretion and the formation of A β deposits in these areas are not fully understood, nor are the relationship between A β deposits and AD understood.

Although AD pathogenesis involves a large number of molecular and cellular events, two events that are known to occur early in AD development are: 1) synaptic damage and 2) mitochondrial dysfunction [4, 24, 45–47]. It is generally accepted that an age-dependent accumulation of A β at synapses and in synaptic mitochondria probably interferes with synaptic activities, including the release of vesicles and neurotransmitters, and interferes with the production of ATP at the synapses. For normal communication across neurons, and normal cognitive and memory functions, it is critical that synaptic activities and the supply of ATP are normal [24]. However, it is these events that are interrupted more and more frequently in elderly individuals and in AD patients.

In normal, healthy neurons, mitochondria move from cell body to axons, dendrites, and synapses by an anterograde mechanism, supplying ATP at nerve terminals. Mitochondria then travel back to the cell body from synapses through a retrograde mechanism. However,

in AD neurons, these mechanisms are abnormal primarily due to defective or functionally inactive mitochondria [4, 22].

Recently, mitochondrial abnormalities have been linked to AD: 1) changes in mtDNA, 2) decreased mitochondrial enzyme activities, 3) abnormal mitochondrial gene expressions, 4) the association of mutant APP and A β with mitochondrial membranes in neurons affected by AD, 5) increased mitochondrial structural alterations – increased fragmentation and decreased mitochondrial fusion [4], 6) abnormal mitochondrial trafficking in neurons affected by AD, 7) decreased mitochondrial function and 8) defective synaptic mitochondria.

1. Mitochondrial DNA changes and AD—Mitochondrial DNA defects were found increased in postmortem brain tissue from AD patients and in aged-matched healthy subjects, compared to DNA changes in postmortem brain tissue from young, healthy subjects, suggesting that the accumulation of mitochondrial DNA in AD pathogenesis is age-related [48, 49].

Recently, Coskun and colleagues [50] investigated whether the mtDNA copy number was related to disease progression in AD. Using molecular methods, they investigated the mtDNA copy number in DNA from patients with AD and Down syndrome. They found increased mtDNA changes and decreased mtDNA copy number in postmortem brains from AD and Down syndrome patients. Further, in the brain tissues from aged control patients who did not have AD, the researchers found that mutations in the control region of mtDNA increased; and in patients with Down syndrome, mutations in the control region of mtDNA were associated with a reduced mtDNA copy number and L-strand transcripts. The increase in mtDNA mutations was also seen in peripheral blood DNA and in lymphoblastoid cell DNAs of AD and Down syndrome patients [50]. In aging, Down syndrome, and Down syndrome AD, mtDNA mutations positively correlated with β -secretase activity, and the copy number of mtDNA was inversely correlated with the levels of A β 40 and A β 42. Therefore, mtDNA mutations may be responsible for neuropathological changes observed in AD and Down syndrome AD [50].

Lakatos et al [51] investigated mitochondrial DNA variations (haplotypes) in 138 mitochondrial polymorphisms in 358 subjects in the Caucasian Alzheimer's Disease Neuroimaging Initiative subjects. They found that the mitochondrial 'haplogroup UK' may confer genetic susceptibility to AD independently of the apolipoprotein E4 allele [51].

2. Defective mitochondrial enzyme activities and AD—Studies of mitochondrial enzyme activities found decreased levels of cytochrome oxidase activity, pyruvate dehydrogenase, and α -ketodehydrogenase in fibroblasts, lymphoblasts, and postmortem brains from AD patients, compared to neurons, fibroblasts, and lymphoblasts from age-matched healthy subjects [reviewed in 24]. Further, decreased levels of cytochrome oxidase activity were found in transgenic mouse models of AD [52–54].

3. Abnormal mtDNA expressions and AD—Recently, our laboratory investigated mitochondrial gene expressions in postmortem brains from AD patients [55] and in brain specimens from AD transgenic mice [56] and mouse neuroblastoma cells incubated with A β peptide (25–35) [57]. We found mitochondrially encoded genes abnormally expressed in the diseased brain specimens. A recent, time-course global gene expression study of Tg2576 mice and age-matched non-transgenic littermates revealed an up-regulation of mitochondrial genes in the Tg2576 mice, suggesting that mitochondrial metabolism is impaired by mutant APP/A β and that the up-regulation of mitochondrial genes may be a compensatory response to mutant APP/A β [56]. Further, We also found an abnormal expression of mitochondrial-

encoded genes in postmortem AD brains compared to the brains from healthy subjects [55], suggesting impaired mitochondrial metabolism in AD.

Very recently, the Reddy laboratory investigated mitochondrial-encoded electron transport chain genes in mouse neuroblastoma (N2a) cells treated and untreated with the A β peptide 25–35 [57]. In N2a cells treated with the A β peptide, they found significantly increased mRNA expression of mitochondrial-encoded electron transport chain genes in complex I (subunit 1, subunit 5), complex III (CytB), complex IV (COX1, COX III) and complex V (ATPase 6) relative to N2a cells untreated with A β peptide, indicating that mitochondrial function is impaired by A β peptide.

4. Mutant APP and A β association with mitochondria—We [52] and others [53, 54, 58–61] reported that A β PP, and monomeric and oligomeric forms of A β have been found in mitochondrial membranes (Fig. 3) Lustbader et al [58]. found A β normally interacting with the mitochondrial matrix protein ABAD, with this interaction leading to mitochondrial dysfunction. Caspersen et al. [54] found an accumulation of A β in the mitochondria from postmortem brain specimens of AD patients and A β PP transgenic mice. Recently, the Reddy laboratory found A β monomers and oligomers in mitochondria isolated from the cerebral cortex of A β PP transgenic mice and from N2a cells expressing A β P [52]. A digitonin fractionation analysis of isolated mitochondria from A β PP transgenic mice revealed A β in the outer and inner membranes and matrix of mitochondria. We found that mitochondrial A β decreases cytochrome oxidase activity and increases free radicals and carbonyl proteins. Du et al [61] found A β interaction with mitochondrial matrix protein, cyclophilin D, and this abnormal interaction causes mitochondrial dysfunction in the brains of AD transgenic mice. More recently, Yao et al. [53] found A β in mitochondrial membranes of cortical tissues from triple transgenic mice. Figure 3 summarizes the localization of A β in mitochondrial membranes.

5. Abnormal mitochondrial dynamics in AD—Increasing evidence suggests that mitochondrial dynamics are impaired in neurons affected by AD.

Using confocal and electron microscopy, and human neuroblastoma (M17) cells transfected with wild-type or mutant A β PP, Wang and co-workers [62] investigated the effects of A β PP and A β on mitochondrial structural changes. Confocal and electron microscopic analysis revealed that about 40% of M17 cells overexpressing wild-type A β PP and more than 80% of M17 cells overexpressing mutant A β PP displayed alterations in mitochondrial morphology, particularly fragmented mitochondria. They also found that increased levels of Fis1 are critical for mitochondrial fission in A β PPwt and A β PPswe M17 cells [62].

Using electron and confocal microscopy, gene expression analysis, and biochemical methods, the Reddy laboratory studied mitochondrial structure and function, and neurite outgrowth in neurons treated with A β [57]. In neurons treated with only A β , we found increased expressions of mitochondrial fission genes (Drp1 and Fis1) and decreased expressions of fusion genes (Mfn1, Mfn2, and Opa1), indicating abnormal mitochondrial dynamics in AD neurons. mRNA expression of antioxidant enzyme-encoded genes (peroxiredoxins 1–6) was significantly decreased in neurons treated with A β relative to untreated neurons. Our electron microscopy of neurons treated with A β revealed a significant increase in mitochondrial fragmentation, further supporting abnormal mitochondrial dynamics. We also found significantly decreased neurite outgrowth and decreased mitochondrial function in cells treated with A β [57]. These findings suggest that A β fragments mitochondria and causes abnormal mitochondrial dynamics, leading to mitochondrial dysfunction.

Using neurons from adult fruit flies, Zhao and colleagues [63] studied the effects of wild-type and an arctic form of A β ₄₂. They performed extensive time-course analyses to determine the function and structure of both axon and presynaptic terminals of individual neurons. They found A β accumulated intracellularly, and they found a wide range of changes typically associated with aging, including the depletion of presynaptic mitochondria, a slow-down of bi-directional transports of axonal mitochondria, decreased synaptic vesicles, increased large vacuoles, and elevated synaptic fatigue [63].

Taken together, these findings suggest A β enters mitochondria and causes abnormal mitochondrial dynamics in neurons that are affected by AD, and that such abnormal mitochondrial dynamics cause mitochondrial dysfunction and abnormal mitochondrial trafficking in AD neurons.

In addition, it has been proposed that defective synaptic mitochondria may cause synaptic abnormalities and cognitive decline in AD [24]. Recently, the Reddy laboratory investigated the effects of the mitochondria-targeted antioxidants, MitoQ and SS31, and the anti-aging agent resveratrol on neurons from a mouse model (Tg2576 line) of AD and on mouse neuroblastoma (N2a) cells incubated with the A β peptide [57]. Using electron and confocal microscopy, gene expression analysis, and biochemical methods, we studied mitochondrial structure and function and neurite outgrowth in N2a cells treated with MitoQ, SS31, and resveratrol, and then incubated with A β . In N2a cells treated with MitoQ, SS31, and resveratrol, and then incubated with A β , abnormal expression of peroxiredoxins and mitochondrial structural genes did not develop, and mitochondrial function was normal; intact mitochondria were present and neurite outgrowth was significantly increased. In primary neurons from amyloid- β precursor protein transgenic mice that were treated with MitoQ and SS31, neurite outgrowth was significantly increased and cyclophilin D expression was significantly decreased. These findings suggest that MitoQ and SS31 prevent A β toxicity, which would warrant the study of MitoQ and SS31 as potential drugs to treat patients with AD [57].

6. Impaired mitochondrial trafficking and AD—Mitochondrial shape and morphology are regulated and maintained by mitochondrial fission and mitochondrial fusion [4, 22, 62, 64]. In a healthy neuron, fission and fusion mechanisms balance equally. Through mitochondrial trafficking, mitochondria alter their shape and size to move from the cell body to the axons, dendrites, and synapses, and back to the cell body. Fission and fusion are controlled by evolutionary conserved, large GTPases belonging to the dynamin family. Fission is controlled and regulated by the dynamin-related protein Drp1 and the mitochondrial fission 1, the latter of which is localized to the outer membrane of mitochondria [22]. The increase in mitochondrial free radicals activates Fis1, which is also critical for mitochondrial fission.

Three GTPase proteins control mitochondrial fusion: two outer-membrane localized proteins Mfn1 and Mfn2, and one inner-membrane-localized protein Opa1 [4, 22]. The C-terminal part of Mfn1 mediates oligomerization between Mfn1 molecules of adjacent mitochondria and facilitates mitochondrial fusion. In AD neurons, mitochondrially generated free radicals activate Fis1 and promote an increase in mitochondrial fragmentation, which in turn produces defective mitochondria that ultimately damage neurons.

In AD neurons, mitochondrial dynamics are impaired mainly because of fragmentation of mitochondria caused by A β . Further, A β interacts with mitochondrial proteins and causes structural damage to mitochondria, ultimately leading to the increased production of defective mitochondria. These defective mitochondria might not move from cell body to the nerve terminals and might not produce sufficient levels of ATP at synapses. Such abnormal

mitochondrial trafficking and decreased production of ATP at synapses may lead to synaptic degeneration, axonal damage in AD neurons, and may be responsible for cognitive decline in AD patients.

7. Mitochondrial dysfunction, oxidative stress and AD—Mitochondrial dysfunction has been observed in postmortem brain tissue from patients with AD, in platelets from AD patients, in brain tissues from AD transgenic mice, in cell lines that express mutant APP, and in cells treated with A β [4]. Several biochemical and cellular studies found increased free radical production, lipid peroxidation, oxidative DNA damage, oxidative protein damage, decreased ATP production, and decreased cell viability in postmortem brain specimens from AD patients, compared to brain specimens from age-matched healthy subjects [60, 65–68].

8. Defective synaptic mitochondria, A β and synaptic damage—Very recently, Dragicevic et al [69] studied synaptic mitochondrial abnormalities in the A β PPsw and A β PP+PS1 mouse lines, focusing on the hippocampus, cortex, striatum, and amygdala of 12-month-old A β PPsw and A β PP+PS1 mice as well as nontransgenic mice. They measured mitochondrial respiratory rates, ROS production, membrane potential, and cytochrome c oxidase activity. Hippocampal and cortical mitochondria showed the highest levels of mitochondrial dysfunction, while striatal mitochondria were moderately affected, and amygdala mitochondria were minimally affected. Mitochondria in affected brain tissues from A β PP+PS1 mice were more impaired than those from A β PP mice. Synaptic mitochondria were more impaired than nonsynaptic mitochondria in both the A β PPsw and A β PP+PS1 mouse models. The A β PP/PS1 mice showed more impairment in the cognitive interference task of working memory than did the A β PP mice. The correspondence between levels of mitochondrial A β and levels of mitochondrial dysfunction in AD mouse models supports a primary role for mitochondrial A β in AD pathology. Dragicevic et al [69] studied the relationship between mitochondrial A β levels and mitochondrial dysfunction in AD mouse models. Moreover, the degree of cognitive impairment in AD transgenic mice was linked to the extent of mitochondrial dysfunction and mitochondrial A β , suggesting that a mitochondrial A β -induced signaling cascade may contribute to cognitive impairment [69].

Du et al [46] also investigated APP transgenic mice for synaptic mitochondria and A β in AD progression. They detected synaptic mitochondrial pool of A β in APP mice as early as 4 months of age, and well before the extracellular A β accumulation. A β -insulted synaptic mitochondria revealed early deficits in mitochondrial function, as shown by increased mitochondrial permeability transition, decline in both respiratory function and activity of cytochrome c oxidase, and increased mitochondrial oxidative stress [46].

Overall, as described above, mitochondria are damaged both structurally and functionally, in AD mice and AD patients, and critically involved in the progression and development of AD. Further, damaged mitochondria at synapses, may be responsible for synaptic damage and cognitive decline in patients with AD.

Mitochondrial dysfunction in Huntington's disease

HD is a midlife, neurodegenerative disease with an autosomal-dominant inheritance. HD is characterized by involuntary movements, chorea, dystonia, changes in personality, and cognitive decline [70–72]. Four to 10 people per 100,000 suffer from HD, and they are mostly of Caucasian origin. Key features found in postmortem brain tissues from patients with HD are the loss of medium spiny neurons in the caudate and putamen of the striatum of basal ganglia [70, 73, 74]. In patients in advanced stages of HD, neuronal loss has also been reported in the cortex and hippocampus.

HD is a genetic disease, caused by a genetic mutation in the exon 1 of the HD gene, resulting in an expanded polyglutamine encoding repeat. In persons affected by HD, the number of polyglutamine repeats ranges from 36–120, whereas in unaffected persons, polyglutamine repeats range from 6–35 [75]. Htt, a product of the HD gene, is a 350 kDa protein, ubiquitously expressed in the brain and peripheral tissues [76–82]. In the HD brain, Htt is localized mainly in the cytoplasm of neurons [77, 80–82].

Causes of neuronal loss that characterizes HD are not known, and also not well understood is how the mutant Htt causes HD progression. Several mechanisms and pathways have been proposed to explain HD progression, including: 1) transcriptional dysregulation, 2) the interaction of expanded polyglutamine repeat Htt proteins with other proteins in the central nervous system [83, 84], 3) caspase activation [85–88], 4) NMDAR activation [89–90], 5) calcium dyshomeostasis [90–98], and 6) abnormal mitochondrial bioenergetics and 7) abnormal axonal trafficking [80, 99–103].

Several lines of evidence suggest that mitochondrial abnormalities are involved in the brains of HD patients and HD mouse models: 1) decreased mitochondrial enzyme activities have been found in HD brain, 2) mitochondrial DNA defects, 3) abnormal mitochondrial dynamics 4) mitochondrial trafficking abnormalities, 5) calcium dyshomeostasis, and 6) mitochondrial dysfunction and oxidative stress.

1. Decreased mitochondrial enzyme activities and HD—Biochemical studies of mitochondria in brain tissues from HD patients revealed reduced mitochondrial enzyme activities [99, 104–107]. Further, in studies of HD transgenic and knock-in mice, and in experimental HD rodent models, decreases in enzyme activities of complexes I, II, III, and IV were found in postmortem brain tissues from HD patients [108], suggesting that mitochondria are involved in HD pathogenesis. Recent studies of HD knock-in striatal cells and lymphoblasts from HD patients found expanded polyglutamine repeats associated with decreased mitochondrial ATP and decreased mitochondrial ADP-uptake, suggesting that in HD, mutations in the HD gene may be associated with functional defects in mitochondria [109].

2 Mitochondrial DNA defects and HD—Several recent studies found age-dependent mitochondrial DNA (mtDNA) defects in postmortem brain tissues from HD patients and HD mouse models, and in peripheral cells from HD patients [110–112].

Acevedo-Torres et al [110] investigated mitochondrial DNA defects in two HD mouse models: the chemically induced 3-nitropropionic acid model and the HD transgenic mouse model of the R6/2 strain containing 115–150 polyglutamine repeats in the HD gene [110]. Using quantitative PCR, they measured nuclear and mtDNA damage in the striatum of 5- and 24-month-old untreated and 3-NPA-treated C57BL/6 mice. They found an increase in damage in both nuclear and mitochondrial DNA in the untreated 24-month-old mice, and in the 5-month-old mice, 3-NPA induced 4 to 6 times more damage in the mtDNA than in the nuclear DNA. These data suggest that mtDNA damage may be an early biomarker for HD-associated neurodegeneration, and they support the hypothesis that mtDNA lesions may contribute to the pathogenesis observed in patients with HD [110].

Chen et al. [111] investigated whether pathological changes in HD brains may also be present in peripheral tissues. Deleted and total mtDNA copy numbers were increased, whereas the mRNA expression levels of mtDNA-encoded mitochondrial enzymes were not increased in the HD leukocytes compared to the leukocytes from normal humans [111].

Banoei et al [112] investigated 4 mtDNA deletions based on the size of deletion: 9 kb, 7.5 kb, 7 kb, and 5 kb in the mitochondrial DNA of HD patients and found mitochondrial DNA deletions are present in brains and peripheral tissues of HD patients. Findings from these studies suggest that mutant Htt cause mitochondrial DNA defects in HD brains and peripheral tissues from HD patients.

Overall, these mtDNA studies suggest that mtDNA defects are present in the brains and peripheral cells from HD patients.

3. Abnormal mitochondrial dynamics and HD—In HD neurons, mitochondrially generated free radicals activate Fis1 and promote an increase in mitochondrial fragmentation, which in turn produces defective mitochondria that ultimately damage neurons. Mitochondrial fusion protects cells from the toxic effects of mitochondrial DNA and from mitochondrial mutant Htt by allowing functional complementation of mitochondrial DNA, proteins, and metabolites. Cell hybrids resulting from the fusion of parental cells carrying pathogenic mutations have been found to restore mitochondrial ETC activity [113]. Increased mitochondrial fission may be due to mutant Htt in HD neurons, which may in turn decrease mitochondrial fusion and ultimately damage HD neurons.

4. Abnormal mitochondrial trafficking and HD—Recently, several studies have reported that mutant Htt, interacting with mitochondria and microtubules, impairs the axonal transport of mitochondria to nerve terminals [101–103]. Figure 4 summarizes the localization of mutant Htt in mitochondria in neurons affected by HD. This defective mitochondrial transport ultimately impairs neural transmission and results in synaptic damage and selective neuronal damage or loss.

Trushina et al [101] investigated the involvement of mutant Htt in the impairment of fast axonal trafficking in HD neurons. The expression of full-length mutant Htt in these neurons was found to impair vesicular and mitochondrial trafficking and in whole animals. In neurons from HD mice, mitochondria, became progressively immobilized and stopped more frequently than in neurons from control mice. These defects occurred early in the development of HD, before the onset of measurable mitochondrial abnormalities. Findings indicated that the loss of Htt function may cause toxicity; mutant Htt-mediated aggregation sequestered Htt and components of trafficking machinery, leading to a loss of mitochondrial mobility and eventually to mitochondrial dysfunction [101].

Chang et al [102] investigated whether mutant Htt alters mitochondrial trafficking and morphology in primary cortical neurons taken from HD mice. They demonstrated that the full-length mutant Htt was more effective than the N-terminal mutant Htt in blocking mitochondrial movement. Cytosolic Htt aggregates impaired the passage of mitochondria along neuronal processes, causing mitochondria to accumulate adjacent to the aggregates and to become immobilized. Further, mitochondrial trafficking was reduced specifically at sites of aggregates but remained unaltered in regions lacking aggregates. They concluded that in primary cortical neurons, an early event in HD pathophysiology may be the aberrant mobility and trafficking of mitochondria caused by cytosolic Htt aggregates [102].

Orr and colleagues [103] investigated the association of N-terminal mutant Htt fragments with mitochondria in HD knockin mice expressing N-terminal 150 polyglutamine repeats. They found the N-terminal expands the polyglutamine repeat protein that is associated with mitochondria and that this association increases with age in knock-in mice [103]. They also found that the interaction between soluble N-terminal mutant Htt and mitochondria interferes with the *in vitro* association of microtubule-based transport of proteins and mitochondria. Mutant Htt reduced the distribution and transport rate of mitochondria in the

processes of cultured neuronal cells. These findings suggest that before aggregates form, N-terminal mutant Htt fragments directly impair mitochondrial function.

These studies indicated that abnormal axonal transport and mitochondrial trafficking early events in HD progression.

5. Calcium dyshomeostasis and HD—Biochemical studies of cell lines in HD mice revealed that calcium-induced mitochondrial permeability is a major factor in HD pathogenesis [91, 92]. Calcium dyshomeostasis was found in patients with HD [88, 90–97] (Fig. 4).

6. Mitochondrial dysfunction and oxidative stress and HD—Increasing evidence suggests that mitochondrial dysfunction is involved in HD progression.

Recently, Solans et al. [114] investigated mitochondrial respiration in yeast cells using an expanded polyglutamine repeat protein. They found cell respiration was reduced after 4–6 h of induction with galactose, and after 10 h of induction, cell respiration further reduced to 50% compared to that of the control yeast cells. They also found defects in cell respiration when the function and the amount of mitochondrial respiratory chain complex II+III were altered during HD progression. The production of ROS was also found significantly enhanced in yeast cells expressing expanded polyglutamines. Mitochondrial morphology and distribution were also altered in HD neurons, possibly from the interaction of aggregates and portions of the mitochondrial network and from a progressive disruption of the actin cytoskeleton. Interactions of misfolded aggregated polyglutamine domains with the mitochondrial and actin networks led to disturbances in mitochondrial distribution and function and to an increase in ROS production. Oxidative damage preferentially affected the function of enzymes containing iron-sulfur clusters, such as complexes II and III. Findings from this mitochondrial study further supported the involvement of mitochondrial dysfunction in HD [114].

With strong evidence indicating the involvement of mitochondrial dysfunction in HD, treating mitochondria with mitochondria-targeted antioxidants is important option to treat patients with HD.

Mitochondrial dysfunction in Parkinson's disease

PD is characterized by muscle rigidity, tremors, and a slowing of physical movement. Pathological changes in PD are the loss of dopaminergic neurons in the pars compacta region of the substantia nigra and the presence of cytoplasmic inclusions, or Lowy bodies, containing α -synuclein [115–118]. PD is both chronic and progressive. One percent of people 65–69 years of age suffer from PD. Both genetic and environmental toxins are involved in the development of PD [1].

Recent studies revealed that environmental toxins induce PD in humans. The exposure of humans to the environmental toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) results in permanent PD syndrome [119]. Thus, the MPTP mouse model is now used as an experimental model for PD since it rapidly develops PD-like symptoms. The chronic administration of the ETC complex I inhibitor, rotenone, resulted in an model that replicates the loss of dopaminergic nigral neurons, the PD phenotype, and α -synuclein inclusions found in humans with PD.

Several recent genetic studies in PD have revealed DNA mutations in α -synuclein [120], Parkin [121], DJ1 [122], PTEN- induced kinase 1 [123], OMI/HTRA2 [124], leucine rich repeat kinase LRRK2 [125], and ubiquitin carboxy-terminal esterase L1 [126] linked to PD.

Multiple lines of evidence suggest that mitochondrial abnormalities are involved in PD progression: 1) abnormalities in mitochondrial ETC complex I, 2) mitochondrial DNA mutations and DNA defects and PD, 3) abnormal mitochondrial dynamics, and 4) mutant proteins association with mitochondria.

1. Mitochondrial electron transport chain complex 1 defects and PD—Complex I defects were found in PD patients, and complex I activity was found to be reduced by 30% in brain and muscle tissues and in platelets from idiopathic PD patients [127, 128]. Complex I defects were found to induce the generation of free radicals that cause oxidative stress and the depletion of ATP [115, 129]. Elevated levels of lipid peroxidation and protein nitration have been found in substantia nigral cells and Lewy bodies [130]. Reduced levels of glutathione and oxidized glutathione, which act as antioxidants, are the earliest marker of nigral cell loss in the brains of PD patients [131].

2. MtDNA mutations and DNA alterations in patients with PD—Mutations in mtDNA are known to cause PD. A point mutation in the mitochondrial 12SrRNA has been found in patients with PD [see review in 1], and the G11778A mutation in the complex I gene (ND4) has been found in a PD family associated with Leber's optic neuropathy [132]. In persons with PD, mutations in the nuclear-encoded mtDNA polymerase- γ gene impair mtDNA replication and result in multiple mtDNA deletions, typically causing chronic, progressive external ophthalmoplegia and myopathy. In this PD family, polymerase- γ gene mutations co-segregate with PD.

Further, age-dependent accumulation of somatic mtDNA changes have been reported in substantia nigral neurons in patients and mouse models of PD [133]. These findings indicate that both germ-line and somatic mtDNA defects are involved in PD pathogenesis.

3. Abnormal mitochondrial dynamics in PD—Several recent studies have found abnormal mitochondrial fission and fusion, suggesting that mitochondria play a large role in PD [134–136]. Although mitochondrial dysfunction is well established in PD, the involvement of Drp1 (a fission protein responsible for mitochondrial fragmentation) and mitochondrial fission and fusion imbalance is unclear. Dagda et al [134] studied the connection between PTEN-induced kinase 1 (PINK1) knocking down and mitochondrial dysfunction in PD. They found mutations in PINK1 associated with familial PD. Although overexpressed PINK1 is neuroprotective, less is known about neuronal responses to loss of PINK1 function. Stable knockdown of PINK1 induced mitochondrial fragmentation and autophagy in SH-SY5Y cells both of which were reversed by the reintroduction of an RNA interference (RNAi)-resistant plasmid for PINK1. Moreover, stable or transient overexpression of wild-type PINK1 increased oxidant production played an essential role in triggering mitochondrial fragmentation and autophagy in PINK1 shRNA lines. Autophagy/mitophagy served a protective role in limiting cell death, and overexpressing parkin further enhanced this protective mitophagic response. Furthermore, PINK1 and parkin may cooperate through different mechanisms to maintain mitochondrial homeostasis.

Poole et al [135] studied genetic alterations affecting abnormal mitochondrial dynamics on the PINK1 and parkin mutant phenotypes in fruit flies. They found that heterozygous loss-of-function mutations of Drp1 are lethal in PINK1 or parkin. Conversely, increased Drp1 expression suppresses the flight muscle degeneration and mitochondrial morphological alterations that result from mutations in PINK1 and by heterozygous loss-of-function mutations affecting the mitochondrial fusion-promoting factors Opa1 and Mfn2. This study suggests that the PINK1/Parkin pathway promotes mitochondrial fission and that the loss of mitochondrial and tissue integrity in PINK1 and parkin mutants derives from reduced mitochondrial fission.

Deng et al [136] explored interactions between pink1/parkin and the mitochondrial fusion/fission. Muscle-specific knockdown of the fly homologue of Mfn (Marf) or Opa1, or overexpression of Drp1, results in significant mitochondrial fragmentation. Mfn-knockdown flies also displayed altered cristae morphology. Interestingly, knockdown of Mfn rescued the phenotypes from muscle degeneration, cell death, and mitochondrial abnormalities in pink1 or parkin mutants. These results suggest that pink1 and parkin are likely not core components of the Drp1-mediated mitochondrial fission machinery. Modification of fusion and fission may provide a novel therapeutic strategy for PD

Overall, evidence suggests that mitochondrial dysfunction is involved in the pathogenesis of PD.

4. Mutant proteins association with PD—Recently, several groups found mutant α -synuclein in mitochondrial membranes, in mice with PD [137–139]. Figure 5 summarizes the localization of mutant proteins from PD in mitochondrial membranes.

Devi and colleagues [137] investigated the connection between α -synuclein and mitochondria. They found that 32 amino acids of N-terminal human α -synuclein contain cryptic mitochondrial targeting signals, and it is important for targeting α -synuclein into mitochondria. Mitochondria in PD-affected regions, including the substantia nigra and striatum, but not in the cerebellum from PD subjects showed a significant accumulation of α -synuclein and decreased complex I activity [137].

Recent cellular and biochemical studies of animal models of LRRK2 suggest that LRRK2 plays a role in synaptic vesicle functions, including neurite outgrowth. LRRK2 resides diffusely throughout the cytoplasm and is associated with the outer membrane of mitochondria [140]. Kinase activity may be the link between LRRK2 and its role in PD pathogenesis, and disease-causing mutations in LRRK2 gene affects cell viability due to mitochondria-dependent cell death [118].

Recent evidence suggests that DJ-1 is localized to the mitochondrial matrix and the mitochondrial intermembrane space, in addition to its cytoplasmic pool [141]. Interestingly, a quantitative proteomic study of the substantia nigra of mice treated with MPTP revealed a significant increase in the protein DJ-1 in mitochondrial fraction of the substantia nigra. Together, this evidence suggests that DJ-1 may play an important role in neuroprotection against oxidative damage caused by mitochondrial toxins.

Overall, as discussed above, mitochondrial abnormalities are overwhelmingly involved in the progression of PD and treating mitochondria with mitochondria-targeted molecules is an ideal option to treat PD.

Mitochondrial dysfunction in amyotrophic lateral sclerosis

ALS is a progressive, invariably fatal neurological disease that attacks the neurons responsible for controlling voluntary muscles. In ALS, both the upper and lower motor neurons degenerate or die, ceasing to send messages to muscles [1]. Unable to function, the muscles gradually weaken, twitch, and waste away. Eventually, the brain loses its ability to control voluntary movement [117, 142, 143]. Unlike AD, ALS affects far fewer numbers of humans, 1 to 2 persons per 100,000. ALS affects persons from all ethnic groups, but mainly aged individuals are affected. Mutations superoxide dismutase gene 1 cause ALS [117, 142, 143].

Similar to AD and PD, ALS is characterized by mitochondrial dysfunction and oxidative stress. Evidences in support of the involvement of mitochondrial dysfunction in ALS are: 1)

Mitochondrial dysfunction in postmortem brain and mutant SOD1 transgenic mice, 2) mutant SOD1 is associated with mitochondria dysfunction and 3) abnormal mitochondrial dynamics and ALS.

1. Mitochondrial dysfunction and ALS—Histo-pathological studies revealed that mitochondria may be targets of toxicity in ALS since vacuolated and dilated mitochondria with disorganized cristae and membranes in motor neurons have been observed in patients with ALS [144–150]. Mitochondrial defects have been reported in the spinal cords and muscle biopsies of patients with ALS; such defects range from impaired mitochondrial respiration to increased levels of uncoupling proteins [151, 152].

2. Mutant SOD1 and mitochondrial association—Recently, several lines of transgenic mice have been generated for SOD1 to mimic ALS features, and all of these transgenic mice exhibited mitochondrial abnormalities [146]. A small proportion of the cytosolic SOD1 mitochondria, in postmortem brain samples from ALS rodent models and in patients with ALS. In these samples, mutant SOD1 was present in fractions enriched for mitochondria that were derived from affected tissues, but not from unaffected tissues [153–156]. Mitochondrial localization of SOD1 has been confirmed by electron microscopy in both isolated mitochondria [155] and motor neurons in situ [157]. SOD1 mutants that cause disease at the lowest accumulated levels (hSOD1G85R and hSOD1G127X) have the highest relative proportions that are mitochondrially associated [155]. Mutant SOD1 has been reported in the intermembrane space and the matrix, as well as both in the inner and outer membranes of the spinal cord and brain mitochondria [153–157]. Figure 6 summarizes the SOD1 localization of mitochondrial membranes, matrix and intermembrane space.

3. Abnormal mitochondrial dynamics and ALS—Recently, Magrané et al. [158] have generated motor neuronal cell lines expressing wild-type or mutant SOD1 containing a cleavable intermembrane space (IMS) targeting signal to directly investigate the pathogenic role of mutant SOD1 in mitochondria. They demonstrated that mitochondrial-targeted SOD1 localizes to the IMS, where it is enzymatically active. The mutant IMS-targeted SOD1 causes neuronal toxicity under metabolic and oxidative stress conditions. They found that neurite mitochondrial fragmentation and impaired mitochondrial dynamics in motor neurons expressing IMS mutant SOD1

Overall, mitochondrial dysfunction is largely involved in patients with ALS and therapeutic approach targeting mitochondrial may be an important option to treat patients with ALS [159].

Therapeutic approaches to treating the mitochondria of aging and neurodegenerative diseases

Overwhelming evidence suggests that mitochondrial dysfunction and oxidative stress are involved in aging and neurodegenerative diseases. It is possible to treat these mitochondrial pathogenic events using molecules that target ROS and boost mitochondrial ATP, decrease free radical production and oxidative damage, and boost overall mitochondrial function, and ultimately increases synaptic branching of neurons.

Recently, several groups treated mouse models of neurodegenerative diseases with antioxidants-enriched diet, including blue berry juice, grape juice, vitamin C, E, beta carotene, coenzyme Q10 [160–164], polyphenols and other herbal products [reviews of 165, 166, 167, 168, 5] and IGF insulin signaling drugs [169]. Transgenic mice fed with antioxidants-enriched diet have shown beneficial effects, including extended lifespan, decreased toxic proteins and improved phenotypic behavior [164–169]. Some of these

antioxidants are in clinical trials of patients with AD, PD, HD and ALS, and the outcome of these ongoing trials is much awaited.

Further, given the huge involvement of mitochondrial dysfunction in aging and neurodegenerative diseases, it is reasonable to treat patients with neurodegenerative diseases or to supplement their diet with antioxidants. Recent antioxidant intake studies in patients with AD, HD and PD did not show strong beneficial effects and gave mixed results. Some epidemiologic studies suggest that the increased intake of the antioxidant vitamins vitamin E, vitamin C, and beta carotene might reduce the risk of developing AD or PD [22, 170]. Other studies did not show beneficial effects [170]. Available antioxidant approaches are not effective in treating neurodegenerative diseases because naturally occurring antioxidants, such as vitamins E and C, do not cross the blood-brain barrier and so cannot reach the relevant sites of free radical generation. To overcome these problems and to better assess whether antioxidant approaches may be valuable therapeutic treatments, improved delivery of antioxidants to the brains of patients with neurodegenerative diseases is needed.

In the last decade, considerable progress has been made in developing mitochondria-targeted antioxidants. To increase the delivery of antioxidants into mitochondria, several antioxidants have been developed: Olesoxime, the triphenylphosphonium-based antioxidants (MitoQ, MitoVitE, and MitoPBN), the cell-permeable, small peptide-based antioxidant SS31, and mitochondrial permeability transition pore inhibitors such as Dimebon [1, 171–174]. The application of these mitochondria-targeted agents to neurodegenerative diseases is at its early stages and is focused on animal models of AD, PD and ALS. Recent work in our lab using MitoQ, SS31 and resveratrol in N2a cells and primary neurons from A β PP transgenic mice have shown beneficial effects. In N2a cells treated with MitoQ, SS31, and resveratrol, and then incubated with A β compared to N2a cells incubated with A β abnormal expression of peroxiredoxins and mitochondrial structural genes were prevented and mitochondrial function was normal; intact mitochondria were present and neurite outgrowth was significantly increased. In primary neurons from amyloid- β precursor protein transgenic mice that were treated with MitoQ and SS31, neurite outgrowth was significantly increased. These findings suggest that MitoQ and SS31 prevent A β toxicity in AD neurons, which warrants the study of MitoQ and SS31 as potential drugs to treat patients with AD. However, further research is still needed to test the efficacies of mitochondria-targeted molecules using animal models of aging and neurodegenerative diseases.

Concluding remarks and future directions

Tremendous progress has been made in understanding relationships between aging and age-related neurodegenerative diseases. It is now clear that mitochondrial abnormalities play a large role in age-related neurodegenerative diseases, such as AD, PD, HD and ALS. Age-dependent accumulation of mitochondrial abnormalities and mutant proteins lead to both structural and functional changes in neuronal function and to cell death. Through studies that are elucidating the role of mitochondria in disease onset and development, investigators have begun focusing research efforts on developing therapies, such as molecules that target and protect mitochondria and neurons from the toxicity of aging and mutant proteins. Recent evidence from studies investigating antioxidants (e.g., SS31 and MitoQ) that targets mitochondria indicate that they protect neurons against mutant proteins, mitochondrial structural, and functional abnormalities and that they enhance neurite outgrowth and neuronal connectivity. However, these antioxidants need to be studied in mouse models of neurodegenerative diseases and patients with neurodegenerative diseases.

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Abbreviations

Aβ	amyloid beta
AβPP	amyloid beta precursor protein
AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
ATP	adenosine triphosphate
CR	caloric restricted
COX1	cytochrome oxidase 1
Drp1	dynamain related protein 1
ETC	electron transport chain
H₂O₂	hydrogen peroxide
Mfn1	mitochondrial fusin 1
mtDNA	mitochondrial DNA
O₂^{•-}	superoxide radical
Opa1	optic atrophy 1
PD	Parkinson's disease
ROS	reactive oxygen species
SOD1	superoxide dismutase 1
SS31 peptide	Szeto-Schiller 31 peptide
TCA	tricarboxylic acid

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Figure 1.
Factors those are critical for healthy and extended lifespan in humans.

Figure 2. Structure of mitochondria

Mitochondria are bag like structures, comprised of 2 lipid membranes (outer and inner), and matrix that harbor components of tricarboxylic acid cycle, beta-oxidation. The electron transport chain is localized in the inner mitochondrial membrane. Outer mitochondrial membrane is porous, whereas mitochondrial inner membrane restricts ionic flow and protects the contents of matrix. Mitochondrial ATP is generated via oxidative phosphorylation within the inner mitochondrial membrane. Free radicals are generated as a byproduct of oxidative phosphorylation, primarily due to electron leaks in complex I and III of respiratory chain. The components of tricarboxylic acid, including α -ketoglutarate dehydrogenase, generate superoxide radicals in the matrix. These mitochondrially generated free radicals and superoxide radicals are carried to the cytoplasm via voltage-dependent anion channels and participate in lipid peroxidation, and protein and DNA oxidation.

Figure 3. Localization of mutant proteins of AD in the mitochondria in neurons affected by AD
 In early-onset AD, genetic mutations of APP, PS1 and PS2 genes activate beta and gamma secretases, cleave from c-terminal region of amyloid beta precursor protein, and produce A β peptides. The toxic A β peptides enter mitochondria, interact with mitochondrial proteins, including cyclophilin D and ABAD --induce free radicals, decrease cytochrome oxidase activity, inhibit ATP generation and damage mitochondria both structurally and functionally. Further, in late-onset AD, APP is transported to outer mitochondrial membrane, blocks the import of nuclear cytochrome oxidase proteins to mitochondria and may be responsible for decreased cytochrome oxidase activity. In addition, N-terminal portion of ApoE4 is associated with mitochondria, induce free radicals and cause oxidative damage. In AD, complex IV of mitochondrial respiratory chain is affected.

Figure 4. The association of mutant huntingtin with mitochondria of HD neurons

In HD neurons, mutant Htt binds to outer mitochondrial membrane and induces free radical production, and may interrupt with calcium uptake. In HD, complex II of mitochondrial respiratory chain is affected.

Figure 5. Localization of mutant proteins of PD in the mitochondria in neurons affected by PD
In PD neurons, mutant proteins of α -synuclein, parkin, PINK1, and DJ1 are associated with mitochondria and cause mitochondrial dysfunction. Complex I activity is inhibited in PD neurons.

Figure 6. Localization of mutant proteins of SOD1 in the mitochondria in neurons affected by ALS

In ALS, mutant SOD1 is localized to inner, outer mitochondrial membranes, intermembrane space and matrix, and induce free radical production and oxidative damage. Impairment of Complex II and IV are associated with ALS.