A “mitochondrial cascade hypothesis” for sporadic Alzheimer’s disease

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Summary Alzheimer’s disease (AD) includes etiologically heterogenous disorders characterized by senile or presenile dementia, extracellular amyloid protein aggregations containing an insoluble amyloid precursor protein derivative, and intracytoplasmic tau protein aggregations. Recent studies also show excess neuronal aneuploidy, programmed cell death (PCD), and mitochondrial dysfunction. The leading AD molecular paradigm, the “amyloid cascade hypothesis”, is based on studies of rare autosomal dominant variants and does not specify what initiates the common late-onset, sporadic form. We propose for late-onset, sporadic AD a “mitochondrial cascade hypothesis” that comprehensively reconciles seemingly disparate histopathologic and pathophysiologic features. In our model, the inherited, gene-determined make-up of an individual’s electron transport chain sets basal rates of reactive oxygen species (ROS) production, which determines the pace at which acquired mitochondrial damage accumulates. Oxidative mitochondrial DNA, RNA, lipid, and protein damage amplifies ROS production and triggers three events: (1) a reset response in which cells respond to elevated ROS by generating the \(\beta\)-sheet protein, beta amyloid, which further perturbs mitochondrial function, (2) a removal response in which compromised cells are purged via PCD mechanisms, and (3) a replace response in which neuronal progenitors unsuccessfully attempt to re-enter the cell cycle, with resultant aneuploidy, tau phosphorylation, and neurofibrillary tangle formation. In addition to defining a role for aging in AD pathogenesis, the mitochondrial cascade hypothesis also allows and accounts for histopathologic overlap between the sporadic, late-onset and autosomal dominant, early onset forms of the disease.

Introduction

As described by Alois Alzheimer in 1906 and named by Emil Kraepelin in 1910, Alzheimer’s disease (AD) applied to a state of presenile dementia, extraneuronal protein aggregations (plaques), and intraneuronal protein aggregations (tangles) \cite{1,2}. Although it was recognized at the time that brains of persons with senile dementia could also manifest plaques and tangles, in the elderly this was not felt to represent an actual disease state \cite{3–6}.
Alzheimer's disease

In the latter half of the 20th century, the AD spectrum expanded to include all plaque and tangle dementias regardless of age [7–10]. It was further proposed that this now common neurodegenerative condition was not a consequence of either normal or accelerated aging, but rather distinctly abnormal pathophysiologic events. To clarify the nature of this abnormal pathophysiology, investigators elucidated genetic defects underlying multiple (albeit rare) families with autosomal dominant, early onset forms. It was found mutation of the amyloid precursor protein (APP) gene and two other genes likely involved with APP processing, presenilin 1 and presenilin 2, cause presenile dementia with plaque formation [11–13]. In particular, the ability of APP mutation to cause an AD-consistent clinical and histopathologic phenotype justified the "amyloid cascade hypothesis" [14,15]. According to this hypothesis, the primary event in AD neurodegeneration is production of the beta amyloid (Aβ) derivative of APP [16–18].

Accumulating evidence suggests that although the amyloid cascade hypothesis is potentially (if not likely) viable in cases of APP, presenilin 1, or presenilin 2 derived AD, it may not apply in its current form to the late-onset, sporadic type of the disease (the vast majority) [19]. First, persons with the common form of AD generally lack mutations of these genes, and so it is unclear what initiates plaque formation in such cases. Second, plaques are a relatively common finding in the non-demented elderly [20–22]. Third, pathways through which plaques generate tangles and other recently described AD pathophysiology are unknown. This includes neuronal apoptosis, neuronal aneuploidy, and cerebral/extracerebral mitochondrial dysfunction [19,23–25].

AD is now identified as a “disease of aging”, which implies aging itself is not a disease (otherwise the term is an oxymoron). This semantic trap requires one to overlook the fact that boundaries between late-onset AD and "normal” aging are not absolute. Neuropsychologic test performance decline, brain atrophy, neuronal loss, and plaque/tangle deposition all occur with aging in the absence of frank dementia [26]. For late-onset AD, therefore, it is reasonable to place the causal molecular events within an aging spectrum, rather than consider them distinct disease phenomena. By this logic, some individuals are "set” to develop sporadic AD at a relatively young age, others at an intermediate age, and yet others only at a very advanced age.

We now propose a hypothesis that places AD within the context of developmental and aging theory. The hypothesis takes into account current molecular knowledge of cell division, differentiation, de-differentiation, and demise. We first review relevant scientific principles.

**The cell cycle, redox status, and reactive oxygen species**

All nucleus-endowed cells contain genetic programs that allow for their division and execution. Recent data suggest a single mediator, the cell redox state (which is reflected by ratios of particular oxidized and reduced substrate variants, such as NAD+ and NADH), and by extension reactive oxygen species (ROS), regulates the balance between these diametric processes [27–30]. The main determiner of intracellular ROS and overall cell redox states is the mitochondrial electron transport chain (ETC) [31–33]. In experimental systems, limited ROS (H2O2 and O2•−) exposures induce multiple cell types to enter the proliferation cycle, while increasing ROS amounts above such limited thresholds activates apoptotic cell death pathways [34]. Redox status and ROS levels outside ranges specifically associated with either cell proliferation or cell demise are found in cells that are neither dividing nor dying, but rather existing in a stable state of physiologic growth arrest ("G0"). Stem or progenitor cells comprise a unique category of cells that can undergo growth arrest, yet do not lose their ability to pass through the cell cycle [35].

The avascular status of a developing organism during embryogenesis limits aerobic metabolism. Thus, the expanding, unperfused cell mass must flourish under relatively anaerobic conditions [36]. It is by necessity over-reliant on glycolytic (anaerobic) metabolism, which generates NADH. Mitochondrial ROS production is limited [37]. Accordingly, when embryo cells are delivered from mitosis ("M") into the initial "gap” period (G1) of interphase, ROS and NAD+/NADH regulation signals are not set to prompt the cell’s exit from reproductive cycling [38,39]. G0 status is not achieved, G1 proceeds, and proteins ultimately necessary for cell division are produced. Subsequent DNA replication (in the "S" phase) results in tetraploidy.

Cells reaching the post-S phase “second gap” (G2) are not obligated to proceed from interphase to mitosis ("G2-M arrest"). The bioenergetic status of the cell, in particular, regulates whether passage from G2 to M occurs. Low ATP levels are associated with G2-M arrest [40,41].

When mitosis does occur, microtubules form spindles that appropriately segregate chromosomes
into daughter nuclei. Tau protein is likely relevant to cell cycling physiology at this point, because as a microtubule-associated protein it is designed to bind microtubules [42]. This transpires whether microtubules act as cytoskeletal elements in differentiated cells or mitotic spindles in undifferentiated cells [43]. In the rapidly dividing cells of developing organisms, tau is present in a phosphorylated state (fetal tau). Tau phosphorylation is therefore seen not only in the neurofibrillary tangles of AD and normal aging, but also during early development and, in general, mitotic cells [26,42,44–46].

**Mitochondria: relation to aging, cell death, and APP**

A "mitochondrial" or "free radical" theory of aging derives from data suggesting (1) ETC activity declines with age [47–50], and (2) mitochondrial-based oxidative stress increases with age [51–61]. The underlying basis for this age-dependent mitochondrial decline is controversial. Some emphasize mitochondrial DNA (mtDNA) deletions and point mutations accumulate with age, perhaps due to oxidative stress [57,58,62–69]. Detractors counter demonstrable mutational burdens are low, and question their phenotypic significance [70]. Some argue within post-mitotic cells malfunctioning mitochondria have a replicative advantage, and thereby assume an ever-increasing proportion of the total cell mitochondria [71,72]. Others hypothesize damaged mitochondria are favored because of reduced degradation rates [73–75].

Mechanistic issues notwithstanding, oxidative stress does appear to influence longevity. Life extension occurs in fruit flies engineered to better detoxify the free radical byproducts of oxidative metabolism [76]. Experimental caloric restriction in animals also extends life span, perhaps by indirectly reducing oxidative metabolism-related oxidative stress [77,78].

Recent data now implicate mitochondrial dysfunction as an initiating event in apoptotic programmed cell death (PCD) pathways [79,80]. In the "intrinsic" apoptosis pathway, when mitochondrial depolarization, oxidative stress, or bioenergetic failure surpasses a threshold, permeability transition is triggered. This allows efflux of molecules typically sequestered within the mitochondrial compartment, and subsequent activation of cell death cascades [81–86].

Proteins that affect ETC function may influence mitochondrial ROS production [87–89]. In this respect APP is relevant, since it is partly targeted to mitochondria and under pathologic conditions may induce ETC dysfunction and alter oxidative stress levels [90]. Oxidative stress, in turn, can induce soluble proteins to adopt insoluble β-sheet conformations, or else yield β-sheet derivatives. Interestingly, precedent exists for the insertion of β-sheet proteins in mitochondrial membranes, where they are predicted to form pores [91]. It is tempting to consider existence of a feedback loop, in which mitochondria overproducing ROS initiate conformational changes in local proteins that then "shut down" the mitochondria that drive their formation.

The ability of the APP derivative Aβ to complex elemental and organic cations may also serve to alter mitochondrial function. Aβ is a β-sheet "bioflocculant" that chelates organic and elemental iron and copper, redox-active metal ions abundant in mitochondria [92]. Attomolar concentrations of copper and iron induce monomeric Aβ to oligomerize, forming insoluble precipitates that in turn sequester the ions that enable their aggregation [93]. As copper and iron are required for electron transport, chelation of these ions may indirectly inhibit oxidative phosphorylation. In indirect support of this are two findings: (1) micromolar concentrations of Aβ(25–35) peptide have no effect on cells that do not possess a functional ETC [94], and (2) glycolytic upregulation ameliorates Aβ toxicity by decreasing cell reliance on oxidatively derived ATP production [95]. Subsequent extracellular secretion of metal-chelated Aβ from the cytoplasm via the Golgi apparatus would predictably give rise to insoluble amyloid plaques, which presumably would activate local gliosis and microglial invasion.

Pre-translational mRNA oxidation may also contribute to a protein aggregation diathesis in both aging and AD [96,97]. Peptides produced from oxidized mRNA species are more likely to aggregate than peptides produced from non-oxidized mRNA species [98]. Excessive mRNA oxidation is observed in AD brain, but appears to represent a highly selective process that affects only particular transcripts [98]. This selectivity may arise from the fact that translation is a cytoanatomically specific event. Indeed, as is the case with yeast, in human cells certain mRNA species are translated by ribosomes that reside tethered to the mitochondrial outer membrane [99–101]. In the case of increased mitochondrial ROS production, peri-mitochondrial translation would promote cytoanatomically selective mRNA free radical exposure, with subsequent aggregation of the translational products. To date, however, it remains to be shown that APP and tau mRNA from AD brain exhibit excessive oxidation [98].
One final point about ROS production is in order. ROS are an unavoidable byproduct of cell metabolism. Cell metabolism, in turn, is defined by the interplay between multiple interdependent enzyme systems that are designed to facilitate substrate cycling. Compromise of one biochemical system tends to induce compensatory (although not necessarily advantageous) changes in other systems. In addition to the mitochondrial ETC, other sites and enzyme systems participate in the redox cycling reactions that maintain appropriate cell NAD$^+$/NADH ratios. These include cytoplasmic glycolysis and lactate production, fatty acid ß-oxidation and conversion of pyruvate to acetyl CoA in the mitochondrial matrix, peroxisomal oxidation of fatty acids, and activity of the plasma membrane oxidoreductase system. Further, it appears that diminished redox cycling by the mitochondrial ETC is associated with increased redox cycling at other cell sites, specifically the plasma membrane oxidoreductase complex [102–104]. "Shifting" of certain redox chemical reactions from one cell locale to another facilitates conservation.

Cytoanatomic redox shifts are seen in various cell types and under various conditions. Cells that lack a functional ETC because of mtDNA depletion (ρ0 cells) show elevated plasma membrane ROS production [102,103]. Tumor cells are also characterized by low levels of cytoplasmic ROS and elevated levels of plasma membrane ROS [105,106]. Specific ETC enzyme activities and overall oxidative phosphorylation are reduced in tumor cells [107]. Similar mechanisms may also apply to non-tumor hepatocytes, in which reduced oxidation phosphorylation capacity is part of a physiologic "de-differentiation" process that occurs when local tissue repair responses are activated [108]. Taken together, these findings are consistent with the view that relatively anaerobic/glycolytic cells are capable of cell division, and shift redox maintenance from the mitochondrial ETC to the plasma membrane oxidoreductase system.

Mitochondrial function in development and aging

The most distinctive feature of mitochondria is their ability to perform electron transport. Evolution has facilitated the development of several ETC enzyme complexes for this purpose. Four particular ETC complexes (I, II, III, and IV) harness energy from mobilized free electrons, and use this energy to drive proton translocation. An additional complex (V) allows protons to re-access the matrix, and couples energy from this proton flux to ADP phosphorylation.

Multimeric ETC complexes contain protein subunits that derive from two cell genomes, the nuclear and mitochondrial. For example, 7 of the over 40 proteins that comprise complex I are mitochondrial DNA (mtDNA) encoded. One of 11 complex III, three of 13 complex IV, and two of 14 complex V subunits also arise from mtDNA.

There is substantial polymorphic variability in both the mtDNA and nuclear DNA (nDNA) ETC subunit genes [109,110]. These polymorphisms frequently alter amino acids. With so many polymorphic genes giving rise to participant peptides, considerable ETC structural variation exists between individuals. Emerging data indicate this variability may influence a spectrum of ontologic events, including development, aging, and neurodegeneration [111–114]. Current paradigms emphasizing mitochondrial contributions to embryogenesis, aging, and PCD implicate mitochondrial ROS as a crucial intermediate in each case. Indeed, a small percentage (1–4%) of electron transfer normally goes towards production of the superoxide radical [53,60]. Although classically considered detrimental in any form, there is an emerging consensus that ROS in physiologic amounts are required to regulate intracellular signaling mechanisms [115,116].

ETC efficiency therefore determines an individual’s basal ROS production rate. ETC efficiency, in turn, is likely influenced by the large number of polymorphism combinations generated by the over 80 ETC peptide-encoding genes of mtDNA and nDNA. Basal ROS production is potentially relevant to the rate at which mitochondrial oxidative damage accumulates in an individual over time. Specifically, over the course of physiologic aging mtDNA progressively acquires deletion and point mutations [57,58,62,64,65,67]. Precedents exist that show somatic mtDNA mutation influences ETC function [117–119].

Unifying hypothesis for AD histopathology and pathophysiology

We believe low rates of mitochondrial oxidative phosphorylation, increased reliance on anaerobic glycolysis, and high rates of mitochondrial ROS production ultimately account for, either directly or indirectly, the histopathologic and pathophysiologic
features of sporadic, late-onset AD. We therefore propose a unifying "mitochondrial cascade hypothesis" for this form of the disorder. In formulating the hypothesis, we considered recent data on cell cycle regulation, programmed cell death dynamics, ROS-mediated protein modification, and ROS-mediated DNA modification. Much of this data post-dates introduction of the mitochondrial theory of aging and amyloid cascade hypothesis. Accordingly, we attempted to update these two constructs within the context of an advancing body of knowledge. Whenever possible, we modify rather than discard aspects of both constructs, and synthesize the most relevant parts into a comprehensive whole. The mitochondrial cascade hypothesis for sporadic, late-onset AD maintains:

1. Inherited polymorphic variations in the mtDNA and nDNA genes that encode ETC subunits determines ETC efficiency and basal mitochondrial ROS production;
2. A correlation exists between basal mitochondrial ROS production rates and accumulating mtDNA damage, with higher basal ROS production rates causing more rapid accumulation of mtDNA damage;
3. Somatic mtDNA mutation decreases mitochondrial ETC efficiency from its inherited set point, which manifests as reduced oxidative phosphorylation and/or increased mitochondrial ROS production. This triggers a three part compensatory response:
   a. Reset the system: mitochondrial ROS overproduction in terminally differentiated neurons triggers Aβ production from APP, which further reduces ETC activity. Cell redox activities may eventually shift to the plasma membrane oxidoreductase system, where excess plasma membrane ROS would increase extracellular Aβ production and contribute to amyloid plaque formation.
   b. Remove the most dysfunctional cells: apoptosis is activated in terminally differentiated neurons that continue to manifest or go on to manifest suprathreshold ROS and/or subthreshold oxidative phosphorylation.
   c. Replace lost cells: impaired mitochondrial oxidative phosphorylation increases cell reliance on anaerobic glycolysis, initiating hypoxic signaling and also altering ROS homeostasis. In neurons with residual proliferative ability, this provides a signal for re-entry into mitotic cycling. Cell cycle re-entry ultimately fails (perhaps due to bioenergetic considerations), but before or during G2-M arrest there is cyclin protein upregulation, DNA synthesis/aneploidy, tau phosphorylation, and tangle formation. These cells eventually lose viability not from their failure to complete the cell cycle per se, but rather from the underlying mitochondrial dysfunction that prompted cell cycle re-entry in the first place.

We intend the mitochondrial cascade hypothesis to apply only in cases of sporadic, late-onset AD. For the early onset, autosomal dominant cases that arise from mutation of APP, presenilin 1, or presenilin 2, we see no reason to challenge the ascendancy of the amyloid cascade hypothesis. At the same time, our hypothesis predicts mitochondria should occupy a relatively upstream position in the amyloid cascade hierarchy, rather than the peripheral, downstream location most reviews typically ascribe them [17,18]. This view is consistent with tissue culture data indicating ETC function is requisite for Aβ toxicity. The fact that Aβ does not harm cells artificially depleted of mtDNA (and as a consequence lack a functional ETC) potently argues direct Aβ-mitochondria interactions are highly relevant in autosomal dominant AD [94].

We propose bioenergetic dysfunction and mitochondrial ROS overproduction represents a nexus between the mitochondrial cascade hypothesis of sporadic AD and the amyloid cascade hypothesis (which we feel is most likely to apply in early onset, autosomal dominant cases). Further, the mitochondrial cascade hypothesis helps address some of the more poorly defined aspects of the amyloid cascade hypothesis, such as the mechanisms through which Aβ production might drive neurofibrillary tangle formation. Mitochondrial dysfunction also results in synaptic degradation [120], and our hypothesis provides a mechanism through which both sporadic, late-onset and autosomal dominant, early onset AD cases acquire synaptic pathology.

Two essential features distinguish the mitochondrial and amyloid cascade hypotheses. First, unlike what is the case with the early onset, autosomal dominant forms of AD, in sporadic, late-onset AD the defining histopathology and pathophysiology are initiated by mitochondrial dysfunction. Second, in sporadic, late-onset AD, increased Aβ production may represent a compensatory event occurring in response to the primary mitochondrial pathology, while in early onset, autosomal dominant AD Aβ production is strictly a toxic phenomenon.
Key points of the mitochondrial cascade hypothesis are emphasized in Figs. 1 and 2. Fig. 1 summarizes components that derive from cell cycling and differentiation theory and relates them to the aging process. Fig. 2 addresses how mitochondrial dysfunction gives rise to AD histopathology. Fig. 3 synthesizes both aspects into one construct, and indicates the proposed point of
overlap between the mitochondrial and amyloid cascade hypotheses.

**Support for the hypothesis**

Data supporting a role for mitochondria and, in particular, mtDNA in aging and age-related diseases are generally consistent with the first part of the AD mitochondrial cascade hypothesis (Fig. 1). Some of these data derive from basic epidemiologic studies of aging. Longevity analysis of the Framingham cohort, for instance, reveals that although the best predictor of an individual’s longevity is biparental longevity, maternal longevity carries a greater impact [121]. Epidemiologic studies of both AD and PD further suggest for subjects that have a parent with the disease, among the affected parents there is maternal overrepresentation [122–124]. Taken together, these studies argue that a maternally inherited genetic factor (mtDNA) helps determine how long one lives, as well as contributes to AD risk.

Some studies suggest mtDNA haplogroups (which are defined by mtDNA polymorphism patterns) influence longevity. In northern Italy, haplogroup J is present to statistical excess in centenarians [112]. Certain mtDNA polymorphisms are more common in the extremely old than they are in the general population [113]. Mitochondrial DNA haplogroup variations may also affect an individual’s odds of developing a neurodegenerative disease. One recent study of mtDNA polymorphisms in Parkinson’s disease (PD) found that mtDNA haplogroups J and K (which share a common SNP 10398G polymorphism) are associated with a robust PD risk reduction [114].

Cyttoplasmic hybrid (“cybrid”) studies of persons with various sporadic neurodegenerative diseases also argue mtDNA inheritance at least partly determines mitochondrial ETC efficiency, oxidative-phosphorylation capacity, and ROS production. Cybrid cell lines are generated when mtDNA from a designated subject is expressed within cultured cells depleted of endogenous mtDNA [125,126]. This technique allows explorations of mitochondrial genotype–phenotype relationships while controlling for nDNA variability. If cybrid cell lines with a common nuclear background but mtDNA from different donors have distinct mitochondrial phenotypes, the root cause is likely differences between the donor mtDNAs [127].

Relative to cybrids expressing mtDNA from age-matched control individuals, cybrids expressing mtDNA from AD, PD, amyotrophic lateral sclerosis (ALS), and progressive supranuclear palsy subjects show bioenergetic impairment and increased oxidative stress [128–139]. These cybrid lines also exhibit altered calcium homeostasis, mitochondrial membrane potential depolarization, abnormal mitochondrial morphology, molecular stress response pathway activation, increased activation and expression of apoptotic proteins, and excessive protein aggregation (including Aβ in AD cybrids and α-synuclein in PD cybrids) [128,132,134, 136, 40–149]. Interestingly, mtDNA used to generate cybrid cell lines in these experiments is derived not from brain but rather from platelets, a non-degenerating tissue. This suggests the relative functional impairment observed in cell lines with disease subject mtDNA represents a systemic defect. Systemic mitochondrial dysfunction is more consistent with inherited rather than somatic mtDNA aberration.

To date, only limited published data indicate inherited mtDNA variation influences somatic mtDNA mutation acquisition [61]. There is, however, considerable evidence showing mtDNA does acquire mutations during the course of an individual’s lifespan, including the brain, the tissue with the greatest rate of oxidative metabolism and therefore ROS production [65,67,150,151]. Over a decade ago it was shown that mtDNA deletions (specifically, a particular 5 kb deletion called the “common deletion”) accumulate with age [152–156]. Tissues with lower rates of oxidative mutation than brain acquire less deletion burden. More recently, investigators have uncovered an entire layer of age-dependent mtDNA mutation in the brains of deceased individuals [67,157]. These presumed somatic mutations are not detected using routine sequencing strategies, but rather require laborious clonal mtDNA analysis. It is currently unclear whether these mutations represent low abundance “microheteroplasmy” that is widely distributed between many or most cells of a brain parenchyma region, or if it arises from limited numbers of individual cells that carry unique homoplasmonic mutations. These scenarios, however, may not be mutually exclusive, since somatic mutations (that by definition are in low abundance when they arise) tend to clonally expand towards high abundance intracellular heteroplasmy or even homoplasmy [158–160]. Ultimately, through either clonal expansion or “compound microheteroplasmy”, mtDNA mutational burdens within individual cells may reach thresholds at which the resultant mitochondrial dysfunction becomes critical.

There is some debate as to how aging effects mitochondrial ETC function. Data supporting an age-related decline are strongest for liver, and also indicate a similar phenomenon in muscle,
fibroblasts, and brain [161–170]. The status of brain mitochondria ETC function has also been extensively evaluated in subjects with neurodegenerative disorders. Relevant to this discussion is the well-replicated finding that complex IV (cytochrome oxidase) activity is reduced in AD brain [19]. Some argue this is an epiphenomenal consequence of neuronal de-afferentation. Indeed, it has been shown that surgically de-afferented neurons downregulate cytochrome oxidase [171,172]. The mechanistic explanation for this is that de-afferented neurons have reduced synaptic connections, less synaptic activity, and require less ATP to maintain ion gradients across their membranes. This cannot entirely explain the AD cytochrome oxidase deficit, which is also present in sporadic AD subject platelets and fibroblasts [173–178].

One AD chicken-and-egg controversy revolves around whether mitochondrial dysfunction causes Aβ over-production, or whether Aβ over-production causes mitochondrial dysfunction. When viewed outside the charged confines of the AD debate, it certainly seems clear that cytochrome oxidase inhibition promotes amyloidigenic fragmentation of APP, and that Aβ inhibits cytochrome oxidase [179–183]. For the sporadic late-onset forms, available data argue amyloidogenesis follows mitochondrial dysfunction. Specifically, in sporadic AD mitochondrial dysfunction is more anatomically widespread than is Aβ deposition, and therefore mitochondrial dysfunction cannot entirely be accounted for by Aβ [19]. Further, cybrid cell lines that express mtDNA from AD subjects, in addition to showing reduced cytochrome oxidase activity and increased ROS production relative to control cybrid lines, also produce substantially increased amounts of both intracellular and extracellular Aβ [19,146].

AD brain shows evidence of increased apoptotic cell death, cyclin protein expression, and nuclear DNA replication with excess aneuploidy [23–25]. The concept that tau phosphorylation promotes tangle formation in neurons attempting to re-enter the cell replication cycle is not novel [24], nor is the idea that mitochondrial function can determine tau phosphorylation. Indeed, tau phosphorylation is promoted in AD fibroblasts exposed to an ETC uncoupler [184].

Conclusion

The mitochondrial cascade hypothesis provides a unifying framework for AD pathology. In developing this hypothesis, we approached sporadic AD from an aging theory perspective, since sporadic AD incidence and prevalence progressively rise at least into the ninth decade [185]. Indeed, if half those over age 85 meet criteria for AD [186], can it truly be considered a disease?

Our hypothesis posits mitochondrial dysfunction represents primary pathology in sporadic, late-onset AD, and drives both Aβ plaque and neurofibrillary tangle formation. We further provide a rationale for how mitochondrial dysfunction surpassing certain thresholds triggers compensatory events that cause the various histopathologic and pathophysiologic features of AD. Other sporadic neurodegenerative diseases also manifest mitochondrial dysfunction, oxidative stress, and protein aggregation [127,187,188]. It is tempting to consider whether similar principles may underlie these disorders at the molecular level.

References


