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# The Mitochondrial Hypothesis: Dysfunction, Bioenergetic Defects, and the Metabolic Link to Alzheimer's Disease

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## Abstract

Alzheimer's disease (AD) features mitochondrial dysfunction and altered metabolism. Other pathologies could drive these changes, or alternatively these changes could drive other pathologies. In considering this question, it is worth noting that perturbed AD patient mitochondrial and metabolism dysfunction extend beyond the brain and to some extent define a systemic phenotype. It is difficult to attribute this systemic phenotype to brain beta-amyloid or tau proteins. Conversely, mitochondria increasingly appear to play a critical role in cell proteostasis, which suggests that mitochondrial dysfunction may promote protein aggregation. Mitochondrial and metabolism-related characteristics also define AD endophenotypes in cognitively normal middle-aged individuals, which suggests that mitochondrial and metabolism-related AD characteristics precede clinical decline. Genetic analyses increasingly implicate mitochondria and metabolism-relevant genes in AD risk. Collectively these factors suggest that mitochondria are more relevant to the causes of AD than its consequences, and support the view that a mitochondrial cascade features prominently in AD. This chapter reviews the case for mitochondrial and metabolism dysfunction in AD and the challenges of proving that a primary mitochondrial cascade is pertinent to the disease.

### Keywords

Alzheimer's disease; metabolism; mitochondria; mitochondrial DNA; proteostasis

## 1. Introduction

Dementia commonly occurs in aged individuals, as do accumulations within the brain of extracellular beta-amyloid (Aβ) protein plaques and intraneuronal, neurofibrillary tau protein tangles (Swerdlow, 2007a). The classic definition of Alzheimer's disease (AD) emphasizes the concomitant presence of all three features (dementia, plaques, and tangles), although recently proposed criteria replace this triad with qualified gradations along an "Alzheimer's continuum" (Jack et al., 2018). For example, the presence of amyloid plaques without neurofibrillary tangles defines a state called Alzheimer's pathologic change, and

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concomitant plaque and tangle histology is simply AD. Beyond this, an individual's clinical status serves mostly to qualify the AD stage. Individuals with plaques but not tangles can have preclinical Alzheimer's pathological change, Alzheimer's pathological change with mild cognitive impairment (MCI), or Alzheimer's pathological change with dementia. Depending on their cognitive state, individuals with both plaques and tangles can have preclinical AD, AD with MCI/prodromal AD, or AD with dementia.

The plaques and tangles may cause cognitive decline or represent by-products of other processes that cause cognitive decline. One popular hypothesis proposes the appearance of toxic Aβ species initiates the pathological events that ultimately result in other histology changes, neurodegeneration, and clinical decline (Hardy & Selkoe, 2002). This "amyloid cascade hypothesis" does not specifically address why toxic Aβ species first appear in the brain, although it is presumed that the initial introduction may involve a stochastic misfolding of a non-toxic Aβ peptide into a toxic Aβ peptide, or that Aβ may trigger a stochastic misfolding of tau protein. Misfolded Aβ or tau molecules might then convert other Aβ or tau molecules to the mis-folded pattern; newly misfolded Aβ or tau templates promote further Aβ or tau misfolding; and the disease spreads throughout the brain in a prion-like fashion.

While stochastic protein misfolding is a recognized phenomenon, the biological background against which the misfolding event occurs is not stochastic. This background includes factors, such as protein post-translational modifications, chaperones and chaperonins, energy levels, levels of gene expression, mRNA splicing, rates of protein translation, rates of protein removal, changes in amino acid chirality, and the specific mechanisms that mediate protein removal. The cell environment, therefore, influences protein levels, processing and folding. A deeper consideration of why protein homeostasis changes in AD could provide clues into the overall disease process. This applies whether an altered protein drives disease or simply marks its presence.

Metabolism refers to the chemical processes that play out within a cell, organ, or set of organs in order to maintain viability. Metabolism includes anabolism, which refers to the synthesis of molecules, and catabolism, which refers to their breakdown. Anabolic processes frequently consume energy, while catabolic processes release energy. In addition to playing critical roles in both anabolic and catabolic metabolism at the cellular level, mitochondria also contribute much of the energy a cell needs to build and maintain infrastructure, and in general to resist entropy. Viewed from the perspective of those who study mitochondria, a substantial proportion of cell function is geared towards monitoring energy levels and mitochondrial status, and for responding to what is monitored. It is difficult to separate metabolism and mitochondria from protein homeostasis, and on a technical level protein synthesis and removal represents a type of metabolism. This review considers AD clinical characteristics and protein hallmarks from the perspective of mitochondrial and general metabolism, and presents the case for a primary mitochondrial/metabolism etiology in AD.

## 2. Normal mitochondrial and metabolism function

### 2.1 General mitochondrial structure and organization

Mitochondria are rather large cell components whose lengths typically exceed 500 nM. Their size, though, varies dramatically because individual mitochondrial units can fuse to create larger units. Each mitochondrion is bounded by two membranes, an outer and an inner membrane, which differ in terms of phospholipid and protein content. The phospholipid components of both membranes are transferred from the endoplasmic reticulum (ER), in regions of close physical apposition termed mitochondrial-associated membranes (MAMs) (Tatsuta, Scharwey, & Langer, 2014). Extensive modification of imported phospholipids occurs, for example, phosphatidylserine transferred from the ER to the inner mitochondrial membrane is converted to phosphoethanolamine, and within the inner mitochondrial membrane phosphatidic acid transferred from the ER can undergo a multi-step conversion to cardiolipin.

The phospholipid composition within the inner membrane causes it to form invaginated envelopes called cristae. The space that defines the compartment formed by the outer and inner membranes is called the intermembrane space, and contains two definable sub-compartments, an intermembrane space lined on one side by the inner membrane and the other by the outer membrane, and an intermembrane space that is mostly bound by the inner membrane cristae invaginations. A protein complex called the mitochondrial contact site and cristae organizing system (MICOS) helps maintain the inner membrane structure and inner-outer membrane structural relationships (Kozjak-Pavlovic, 2017).

Proteins residing within the outer mitochondrial membrane and intermembrane space are exclusively expressed by nuclear genes, translated within the cytoplasm, and moved to their destination. Nuclear encoded, mitochondrial-targeted proteins frequently contain N-terminal targeting signals composed of positively charged amino acids that track to negatively charged mitochondria. Most proteins in the inner mitochondrial membrane arise from nuclear genes, although some inner mitochondrial membrane proteins are expressed by genes located within mitochondria and translated by ribosomes located within mitochondria.

The mitochondrial DNA (mtDNA) genes comprise plasmids that sit within the matrix, the interior compartment bounded by the inner membrane. Mitochondrial DNA plasmids do not associate with histones, as nuclear DNA does, although the mtDNA does associate with other proteins, such as the transcription factor A of the mitochondria (TFAM) (Scarpulla, 2008). Mitochondrial DNA plasmids are packaged into condensed structures called nucleoids, which tether to the mitochondrial inner membrane. The matrix contains over 1000 proteins which support a variety of pathways and functions, including the Kreb’s cycle, enzymes involved in the urea cycle, mtDNA replication and transcription, fatty acid oxidation, and fatty acid synthesis.

### 2.2 Mitochondrial functional aspects

Mitochondria are a major site of cell oxygen consumption. Oxygen is consumed during the process of oxidative phosphorylation, in which high energy electrons are passed down an electron transport chain (ETC) that contains four holoenzyme complexes. These

complexes are designated complex I (NADH:ubiquinone oxidoreductase), complex II (succinate dehydrogenase or succinate:ubiquinone oxidoreductase), complex III (coenzyme Q:cytochrome C oxidoreductase or cytochrome $bc_1$ complex) and complex IV (cytochrome oxidase). Energy released from electrons passing through the chain is used to pump protons from the matrix, across the inner membrane, and into the intermembrane space. This creates a proton gradient, with a negatively charged matrix separated from a positively charged intermembrane space by the inner membrane. The proton separation creates a mitochondrial membrane potential and a protonmotive force, $\Delta\psi$, which defines how avidly protons are driven to re-enter the matrix. Protons can return to the matrix through another holoenzyme, complex V (ATP synthase), which uses the energy of the proton flux it facilitates to phosphorylate ADP to ATP. The respiratory chain consists of the ETC plus the ATP synthase.

Normally, energy-depleted electrons are delivered to molecular oxygen by the cytochrome oxidase, which consumes molecular oxygen and generates water. Under various circumstances this electron transfer may terminate prior to its completion. As the membrane potential hyperpolarizes the amount of energy required to pump protons from the matrix increases, which can hinder electrons from completing their ETC journey. Electrons released from the ETC react with molecular oxygen and nitrogen to generate reactive oxygen species (ROS) and reactive nitrogen species (RNS). Conversely, depolarization across the inner membrane may induce an increase in electron passage through the ETC as the mitochondrion attempts to regenerate its membrane potential. Depolarization can arise due to proton leak through the inner membrane and back into the matrix, independent of the ATP synthase or physiologically through channels formed by uncoupling proteins (UCPs). A return of protons to the matrix through an inner membrane leak or through UCPs “uncouples” electron transport from ATP generation, redirecting energy captured from electron transport to heat production. Structural ETC perturbations can also reduce the integrity of the chain and release electrons. In this scenario, ROS and RNS production occur within the context of a relative mitochondrial membrane potential depolarization.

Mitochondria can undergo fission into smaller structures or fuse together (Chan, 2006). These are enzyme mediated processes. Critical fission enyzmes include dynamin-related protein 1 (Drp1) and mitochondrial fission 1 (Fis1). Optic atrophy 1 (OPA1), mitofusin 1 (Mfn1), and Mfn2 mediate fusion. Mitochondrial fission can help create smaller mitochondria that can travel easier within cells or segregate defective mitochondrial components through a disposal process called mitophagy (Youle & Narendra, 2011). Mitochondrial fusion produces organelles that are more respiration-efficient and allows for the functional assistance of missing or defective components through a process called complementation.

The respiratory chain holoenzymes are multimeric proteins that collectively contain over 80 subunits. The nucleus encodes all complex II subunits, while the other complexes contain a mix of nuclear DNA and mtDNA-encoded subunits. To be exact, the approximately 16.5 kB mtDNA includes seven genes that transcribe complex I subunits, one gene that transcribes a complex III subunit, three genes that transcribe complex IV subunits, and two genes that transcribe complex V subunits. In addition to these 13 structural genes, the mtDNA also

has 24 synthetic genes that generate infrastructure needed to translate the structural gene transcripts. Two of these synthetic genes encode ribosomal RNA (rRNA) subunits that create mitochondrial ribosomes, and 22 synthetic genes create the mitochondrial tRNAs. The mtDNA genes lack introns; there is very little non-coding DNA aside from a stretch called the control region, which contains the promoters for RNA synthesis, as well as sequence that initiates mtDNA replication. The mtDNA physically associates with a protein called TFAM, which contributes to mtDNA replication and transcription (Scarpulla, 2008).

On several parameters mtDNA fundamentally differs from nuclear DNA. Cells can contain thousands of copies. Mitochondrial DNA plasmids replicate as the mitochondria in which they reside undergo cycles of elimination and division, so mtDNA constantly regenerates. One consequence of ongoing replication is that mistakes occur which leads to different nucleotides at specific nucleotide positions. Such variation is called heteroplasmy. Heteroplasmy can manifest as highly variable ratios of wild type to mutant sequence, from very low to very high percentages. The percentage of mutation required to confer a biochemical consequence depends on the functional impact of the variant. If the variant has little impact, very high or even homoplasmic levels of variation are necessary to alter cell integrity. Variants with strong effects can affect cell function at lower levels of heteroplasmy. The variant's functional impact defines the "threshold" at which the heteroplasmy becomes relevant. Heteroplasmic variants can arise somatically, and when a heteroplasmic cell divides the variant code can asymmetrically segregate between the daughter cells. This produces lineages with enriched or diluted variants. Further distinguishing it from nuclear DNA, mtDNA inheritance is maternal. Ova contain many copies, and under physiological conditions, the sperm's contribution is absent.

### 2.3 Other relevant metabolism features

Mitochondria participate pervasively in carbon flux. This obviously includes catabolic fluxes, which dismantle carbon skeletons to directly or indirectly produce energy. Examples include fatty acid β-oxidation and parts of the Krebs cycle. It also includes anabolic fluxes, which enlarge carbon skeletons and frequently consume energy. These carbon fluxes connect to myriad metabolic pathways that exist outside of mitochondria.

Cells import glucose via glucose transporters. After undergoing phosphorylation, glucose carbon can enter glycolysis, and proceed to pyruvate that enters mitochondria and undergoes further catabolism. Carbon skeletons can also leave the glycolysis pathway at points at which glycolysis intermediates are in equilibrium with certain amino acids, and phosphorylated glucose additionally enters the pentose phosphate shunt where it generates ribose sugars required for nucleic acid synthesis. Glucose carbon can also terminate as lactate, which in turn is often removed by the cell that produces it. Even in the presence of adequate oxygen, therefore, not all glucose carbon is used to support oxidative phosphorylation with a consequent production of water and $CO_2$. Some refer to the processes that produce glucose-derived, non-$CO_2$ carbon products in the presence of adequate oxygen as aerobic glycolysis (Vaishnavi et al., 2010).

It is perhaps cliché to point out, but many metabolic fluxes feature carbon skeleton manipulations. These manipulations are designed to produce energy in some cases,

or to build carbon infrastructure through energy-consuming pathways. Catabolic and anabolic pathways occur within and outside of mitochondria, but even in cases in which fluxes occur outside of mitochondria, the mitochondria play a role. For example, the redirection of lactate carbon back to glucose, through gluconeogenesis, requires some transit through mitochondria. Even when glycolysis-generated pyruvate enters mitochondria and is converted to acetyl CoA, that acetyl CoA carbon can exit the mitochondria following its entry into the Krebs cycle, where it forms citrate. Citrate that has exited the mitochondria can undergo a reaction in the cytosol to generate cytosolic acetyl CoA, which is then used in lipogenesis. This represents a feature of Warburg metabolism, in which growing cells convert glucose carbon into other macromolecules (Vander Heiden, Cantley & Thompson, 2009). In general, mitochondria play a key role in cell carbon laundering.

## 3. Alzheimer's disease-relevant alterations in mitochondrial and metabolism function 3.1 General mitochondrial structure and organization

Mitochondria in the brains of AD subjects differ physically from those in the brains of non-AD subjects. On average they are smaller (Baloyannis, 2006), which coincides with a shift in the mitochondrial fission-fusion balance towards fission (Manczak et al, 2011; Wang et al., 2009). Despite this, AD brains show more frequent enlargement of individual mitochondria with cristae disruption (Baloyannis, 2006).

While there is a clear reduction in the number of normal appearing AD brain mitochondria, how mitochondrial mass changes in the disease is less straightforward. Autophagosomes reportedly contain increased amounts of mitochondrial material, which could suggest increased mitochondrial turnover (Hirai et al., 2001). On the other hand, mRNA and protein levels of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a transcriptional coactivator that drives mitochondrial biogenesis, are reduced (Qin et al., 2009; Sheng et al., 2012). The overall data seem to support a picture of enhanced mitochondrial elimination, with a concurrent reduction in replacement by new mitochondria.

A similar situation pertains to mtDNA copy number. Most studies that quantify mtDNA use polymerase chain reaction (PCR)-based methods, and there is a clear reduction in PCR-amplifiable brain mtDNA (Brown et al., 2001). However, one study that used an immunolabeling approach to assess AD brain mtDNA reported a substantial increase in mtDNA within autophagosomes (Hirai et al., 2001). In this case, mtDNA is presumably simply along for the ride as cells remove their bad mitochondria, consistent with the broader finding that AD brains contain increased amounts of mitochondrial debris.

### 3.2 Mitochondrial functional aspects

Direct assessments of mitochondrial respiration require fresh mitochondria. Freeze-thawed mitochondria are less appropriate as this disrupts membranes and uncouples mitochondrial oxygen consumption from ATP production. Despite this challenge, studies report AD brain mitochondrial respiration differs from mitochondria from control brain tissue (Sims et al., 1987).

Freeze-thawed mitochondria are suitable for determining enzyme Vmax activities, and AD brain mitochondria show a variety of Vmax activity reductions. This includes lower activities for two thiamine and lipoic acid-dependent matrix enzymes, pyruvate dehydrogenase complex and α-ketoglutarate dehydrogenase complex (Gibson et al., 1988). Within the respiratory chain, complex IV Vmax activities are consistently lower in AD than control brain tissue (Parker, et al., 1994; Swerdlow, 2012). Complex I activity reductions are also occasionally reported, and some terminal Krebs cycle enzymes activities are possibly increased (Gibson et al.,1998; Swerdlow, 2012).

Interestingly and importantly, some of these AD biochemical phenotypes are not brain limited. Fibroblast cultures prepared from AD patients, including sporadic AD patients without identifiable amyloid precursor protein (APP) or presenilin gene mutations, show similar Vmax activity reductions (Curti et al., 1997; Gibson et al., 1988). In fact, the AD complex IV Vmax activity reduction was first identified in platelet mitochondria (Parker, et al., 1990), which prompted investigators to measure its activity in brain mitochondria. In that case, the reduced systemic activity predicted a low brain activity (Swerdlow, 2012).

Mitochondria can produce free radicals, and AD mitochondria show increased free radical modifications. This includes increased markers of mtDNA oxidative damage (Lovell & Markesbery, 2007; Mecocci et al., 1994). Mitochondrial DNA shows additional damage that manifests in the form of increased mtDNA deletions (Corral-Debrinski et al., 1994). Increased mitochondrial fission and reduced mitochondrial motility are evident, and these changes too are not brain-limited (Wang et al., 2008).

The reasons that underlie these biochemical and molecular perturbations warrant consideration. These biochemical and molecular phenotypes could generally arise due to a general failure of the organelle, or alternatively any of these specific phenotypes could cause a general organelle failure. Complicating this point is the fact that Aβ protein appears to accumulate within AD brain mitochondria (Caspersen et al., 2005; Lustbader et al., 2004). It is unclear whether Aβ accumulates within AD brain mitochondria and damages them or if Aβ accumulates within AD brain mitochondria because they are damaged. Amyloid precursor protein itself targets mitochondria, and increasing mitochondrial APP or exposing them to mutant APP alters mitochondrial function (Anandatheerthavarada et al., 2003; Anandatheerthavarada & Devi, 2007; Devi et al., Anandatheerthavarada, 2006). Presenilin proteins also associate with mitochondria (Hansson et al., 2004), either through direct contact or indirectly through their presence in mitochondria-associated cell structures (Area-Gomez & Schon, 2016). Clearly links exist between mitochondria and proteins implicated in AD through genetic or histologic studies. A better understanding of these links could potentially advance our understanding of this disease.

### 3.3 Other relevant metabolism features

Glucose utilization is altered in AD brains. This is evident on fluoro-deoxyglucose positron emission tomography (FDG PET) studies (Mosconi et al., 2009). FDG PET is accomplished by injecting an individual with radiolabelled FDG. FDG accesses the brain through the circulation, with more metabolically active brain regions taking up greater amounts of FDG. The FDG undergoes phosphorylation, which traps it within cells. The

deoxyglucose modification blocks further passage through glycolysis and imaging the brain via PET reveals which brain areas took up the most glucose and by extension were most metabolically active. In AD, certain relatively posterior brain regions, including the posterior temporal, parietal, posterior cingulate and precuneal cortices, show diminished glucose uptake.

Direct molecular surveys of AD autopsy brains show reductions in insulin-initiated signalling pathway activity. This pattern suggests a likely state of brain insulin resistance, leading some to classify AD as a form of diabetes mellitus (DM) (Steen et al., 2005).

Even though AD brain insulin resistance can occur in the absence of obvious systemic insulin resistance, epidemiological studies suggest a connection between central nervous system (CNS) and peripheral insulin resistance (Morris et al., 2014). The meaning of this association is unclear. It could indicate DM or peripheral insulin resistance contributes to AD. Alternatively, this association could reflect a common underlying physiologic state. To this point, a systemic mitochondrial lesion in AD could account for the concomitant presence of CNS and systemic insulin resistance phenotypes (Morris et al., 2014).

Genome wide association (GWAS) studies implicate lipid homeostasis in the evolution of AD. The APOE gene, which encodes the cholesterol/lipid transporting protein apolipoprotein E, contains amino acid-altering genetic variants. These variants constitute the best studied and most powerful determinant of sporadic AD risk (Corder et al., 1993). One copy of the APOE4 variant increases the AD odds ratio about 3.5 times over baseline risk, and the APOE2 variant decreases AD risk. The AD research field remains uncertain over why APOE variants so profoundly influence AD odds ratios, but within the context of the GWAS studies it certainly is possible that the impact of APOE derives from differences in how the various apolipoprotein E forms influence lipid homeostasis. While the aggregate of these genetic data do not directly implicate a role for mitochondria, because mitochondria and lipid metabolism are connected, it seems reasonable to postulate genetic data implicating lipid homeostasis indirectly implicate a role for mitochondria in AD.

## 4. Metabolic endophenotypes

Investigators increasingly rely on biomarkers to reveal the secrets of AD. Biomarkers can demonstrate on-going physiologic, molecular, or subtle clinical events are underway before clearly noticeable clinical changes arise in individuals. Biomarkers can inform the earliest definable presence of the disease, mark the order in which different events occur, indicate the rate at which alterations evolve, or make mechanistic inferences. Biomarker-defined states, in the absence of a full phenotype, are endophenotypes.

Mosconi et al. (2007) reported an FDG PET-defined phenotype in which cognitively intact, middle-aged individuals with an AD-affected mother were more likely to show AD-typical brain regions with reduced glucose utilization than cognitively intact, middle-aged individuals with an AD-affected father. This FDG PET-defined endophenotype, therefore, follows a pattern of maternal inheritance that is potentially consistent with mtDNA inheritance. The same investigators used amyloid PET imaging to show the brains of

middle-aged individuals with an AD-affected mother were more likely to contain fibrillar amyloid than brains from AD-affected fathers (Mosconi et al., 2010). Spinal fluid from the children of AD mothers are more likely to show AD-consistent Aβ and oxidative stress characteristics than spinal fluid from the children of AD fathers (Mosconi et al., 2010). Brain perfusion, demonstrated through a magnetic resonance imaging (MRI)-based technique called arterial spin labelling, shows a similar pattern (Okonkwo et al., 2012), and volumetric MRI studies shows brain regions compromised in AD show greater atrophy in the children of AD mothers than in the children of AD fathers (Honea et al., 2011). Platelet mitochondria cytochrome oxidase activities are lower in blood samples from the children of AD mothers than they are in blood samples from the children of AD fathers (Mosconi et al., 2011). Maternal inheritance of AD endophenotypes, therefore, is noted across a range of studies and suggests a possible contributory role for mtDNA.

In an analysis of Framingham Longevity Study participants, memory test scores in cognitively intact middle-aged individuals were lowest in APOE4 carriers who also had an AD-affected mother (Debette et al., 2009). These scores were lower than those from APOE4 carriers who also had an AD-affected father.

## 5. Relationship to proteostasis

Proteins aggregate in the AD brain. This includes Aβ plaques, tau tangles, and cytosolic inclusions consisting of the transactivation response DNA-binding protein 43 (TDP43). One potential explanation is that one or more of these aggregating proteins are cytotoxic. Another is that proteostasis is perturbed in the dysfunctional or degenerating AD brain, which leads to protein aggregation.

On one hand, proteins implicated in AD associate with mitochondria. For example, APP and Aβ are found in or on mitochondria (Anandatheerthavarada et al., 2003; Lustbader et al., 2004), and driving these proteins to mitochondria interferes with their function. Transactivation response DNA-binding protein 43 and even tau protein as well reportedly localize to mitochondria (Choi et al., 2014; Gao et al., 2019). This suggests that altered proteostasis may drive AD brain mitochondrial dysfunction. One limitation of this hypothesis is that while it can reasonably account for brain mitochondrial dysfunction, it is challenging to see how this might lead to altered mitochondrial function in non-brain tissues.

Alternatively, mitochondrial dysfunction could alter the cell environment in ways that promote protein aggregation (Weidling & Swerdlow, 2019). Compromised mitochondrial function could cause bioenergetic or oxidative stress, which in turn could change levels of protein expression, alter post-translational protein modifications or cause protein oxidative damage. Protein chaperone or chaperonin levels could change as a result, as could levels or activities of secretase enzymes.

Another possibility, increasingly supported by experimental data, is that mitochondria may directly participate in proteostasis by acting as de facto protein disposal units. This basic principle was initially demonstrated in yeast, which direct peptides with aggregation potential into mitochondria. This process, called “mitochondria as guardians in the cytosol”

(MAGIC), raises the aggregation threshold of the implicated protein (Ruan et al., 2017). Similarly, knock-out of the protein PINK1, which helps mediate at least one mitophagy pathway, increases amyloidosis in the brains of transgenic mice (F. Du et al., 2017). Another study reported promoting mitophagy with the compound urolithin A reduced brain amyloidosis in an AD transgenic mouse model (Sorrentino et al., 2017).

The relationship between brain aging and protein aggregation is important to consider. Those who develop AD protein aggregation can live for decades before those aggregations clinically manifest. It is unclear whether a brain switches from an aggregation-free state to an aggregation-containing state because it loses its capacity to prevent protein aggregations, or because its proteins gain a unique capacity to aggregate. In the latter case, there is evidence to support the view that protein misfolding occurs as a stochastic event. As years go by, the chance of one these misfolding events occurring increases, and once it does the misfolded peptide templates the misfolding of other peptides and seeds an aggregation. Even if this is correct, though, changes in mitochondrial function would alter the background against which a stochastic protein misfolding event occurs. In this scenario, while mitochondrial dysfunction might not directly drive a specific protein misfolding event, it could still lower the threshold at which that protein misfolding event occurs.

## 6. Genetic contributions

Only very rarely, probably quite well-below frequencies of 1% of cases, does AD present within a Mendelian context. Gene mutations implicated with early onset, autosomal dominant familial AD reside in the genes for APP, presenilin 1 (PS1), and presenilin 2 (PS2). Cases of AD due to mutations in these genes typically show a relatively young age of onset, with symptoms manifesting in the fifth or sixth decade (Swerdlow, 2007a). There are infrequent exceptions to this, but in general if an AD-affected individual does not present before the end of their sixth decade, and does not have a parent who was also demented before the end of their sixth decade, genetic testing is not likely to reveal an autosomal dominant mutation in the APP, PS1, or PS2 genes.

By far most cases present sporadically or at least pseudo-sporadically. The pseudo-sporadic qualification clarifies that genes do influence the risk of sporadic disease, but not to the extent at which Mendelian inheritance is obvious. This complicates how we think about AD. Advancing age constitutes the greatest sporadic AD risk factor, and so how long an individual survives profoundly impacts whether they die with or without AD. The best way to avoid developing AD, perhaps, is to simply not survive into advanced old age.

Sporadic cases can nevertheless also present in middle age. In fact, the number of early onset sporadic cases outnumbers the autosomal dominant cases. Among the sporadic cases, an earlier age of onset suggests a greater genetic contribution. Early onset, sporadic cases frequently carry APOE4 alleles, which supports the view that possessing an APOE4 allele lowers the age of onset in those who do develop AD (Blacker & Tanzi, 1998). It turns out that given long enough survival, the proportion of those with the potential to develop AD could exceed the proportion of the population which does not have the potential to develop AD (Corrada et al., 2008).

### 6.1 Nuclear genes

Sporadic AD GWAS now implicate over thirty nuclear loci that imply a reduced or increased AD risk (Kunkle et al., 2019). GWAS most effectively reveal common variant associations. Methods better equipped to detect rare variants, including whole exon sequencing (WES) and whole genome sequencing (WGS), are increasingly utilized.

With GWAS, locus association is a first step. The next includes determining the responsible gene within the locus. While locus identification is bias-free, pinpointing the appropriate gene is not. Next, it is important to consider why the candidate gene may influence AD risk. This also introduces bias. Within the context of these challenges, genetic studies indicate a role for microglial, lipid, and endocytosis biology in AD (Karch & Goate, 2015).

At least one gene study implicates mitochondria. This study found rare variants in the PTCD1 gene influence AD risk (Fleck et al., 2019). The PTCD1 gene encodes a protein that localizes to mitochondria and likely affects the translation of mtDNA-derived mRNAs. A preliminary study also implicates a rare variant in the TAMM41 gene, which encodes a mitochondria-localized protein required for cardiolipin synthesis (Zhang et al., 2019).

It is possible that other AD-relevant genes affect mitochondria. Some of these genes produce proteins that localize to mitochondria (Pa et al., 2019). Other proteins indirectly influence, or are influenced by, mitochondrial function. In general, it is hard to dissociate lipid homeostasis from mitochondrial function.

One GWAS based study broadly considered nuclear genes whose products localize to mitochondria. These genes naturally fall within loci with previously determined AD odds ratios. By assigning the appropriate locus-associated odds ratio to each nuclear-encoded mitochondrial gene, the investigators created mitochondria-relevant polygenic risk scores (Andrews et al., 2019). Subjects with the highest mitochondrial polygenic risk scores were more likely to have AD. Essentially, the mitochondrial polygenic risk score tracked AD risk.

APOE represents a more specific case in point. APOE4-derived apolipoprotein E folds differently than APOE2 or APOE3-derived apolipoprotein E, which impacts the enzymatic processing of apolipoprotein E. APOE4-derived apolipoprotein E undergoes a cleavage event that opens a mitochondrial targeting signal. The mitochondria-targeting peptide accesses mitochondria and alters organelle function in a way that lowers complex IV activity (Chang et al., 2005; Chen et al., 2011).

The translocator of the outer mitochondrial membrane 40 (TOMM40) gene sits adjacent to the APOE gene. TOMM40 variants also associate with AD risk (Roses, 2010), but some of these variants are in linkage disequilibrium with APOE4. It remains unclear whether TOMM40 independently contributes to AD risk, although several studies report this is potentially the case. (Watts et al., 2019)

The three proteins implicated in familial AD also show mitochondrial ties. APP localizes to mitochondria (Anandatheerthavarada et al., 2003). Presenilin 1 and 2 are seen either at mitochondria or in structures that interact with mitochondria, such as mitochondrial associated membranes (MAMs) (Area-Gomez & Schon, 2016; Hansson et al., 2004).

### 6.2 Mitochondrial genes

Data to date suggest that mtDNA contributes to AD, but the nature of this contribution remains unresolved (Swerdlow, 2012). In this respect, the complexities of mtDNA render unique challenges. This includes issues related to heteroplasmy and heteroplasmy detection, its propensity for somatic mutation, and a high degree of inter-individual variability in which linked variants often occur. Interactions between mtDNA and nuclear DNA could also complicate relevant analyses (Andrews et al., 2019).

Substantial indirect data suggest an mtDNA role. One epidemiologic study found AD-diagnosed subjects were more likely to have a demented mother than father (Edland et al., 1996). This is consistent with a maternal inheritance bias. The fact that women live longer than men, paternal health records are not as comprehensive as maternal health records, and women may have a higher AD risk can confound this type of study. Multiple endophenotype studies also indirectly implicate mtDNA inheritance, as the middle-aged children of AD mothers show higher rates of AD endophenotypes than those with AD fathers (Swerdlow et al., 2014).

Other support comes from studies of cytoplasmic hybrids (cybrids), which were initially deployed to test whether mtDNA contributes to reduced AD complex IV activity (Swerdlow et al., 1997). To perform these cybrid studies, a cell line was depleted of its endogenous mtDNA to create what is called a ρ0 cell line (Swerdlow, 2007b). Platelets from AD and control subjects were isolated and mixed with ρ0 cells in the presence of a membrane-permeabilizing detergent to permit cytosol mixing to occur. This creates cybrid cells that contain the nucleus of the ρ0 cell and mtDNA from the platelet donor. Because the nuclear background remains consistent between cybrid cell lines created from different platelet donors, functional differences between cybrid cell lines most likely reflect differences in mtDNA. In these experiments, complex IV activity in cybrid cell lines containing mtDNA from AD subjects on average was lower than the activity in lines containing mtDNA from control subjects (Swerdlow et al., 1997). This outcome indicates mtDNA to at least some extent contributes to lower AD complex IV activity.

Further analyses of cybrid cell lines generated from AD and non-AD subjects find further differences. Alzheimer’s disease cybrid lines show evidence of increased oxidative stress, a reduced mitochondrial membrane potential, impaired mitochondrial calcium uptake, a reduced peak respiration rate, an overall smaller mitochondrial size, positive modification of a mitochondrial fission protein, a lower glycolysis flux, less ATP, activation of the NFκB transcription factor, increased apoptosis activity, and increased amounts of Aβ protein (Swerdlow et al., 2017). While data like these do not establish a causal role for mtDNA in AD, they do indicate mtDNA can influence several recognized AD pathologies, and may cause other functional changes.

Genetic association studies could establish a more traditional connection between mtDNA and AD, reveal specific responsible mtDNA features or variants, and address uncertainty over cause versus consequence relationships. The literature includes notable attempts, but studies are neither as extensive nor comprehensive as those involving nuclear DNA, and there are no definitive conclusions (Ridge & Kauwe, 2018). Common variants do not present

in isolation, but rather within the context of other common variants. This makes it difficult to quantify the impact of a single variant. Rare variants may confer more clear-cut associations, but studies of rare variants require the complete sequencing of large numbers of cases and controls. The datasets needed for such analysis are only now being generated (Zhang et al., 2019). Interactions between mtDNA and nuclear DNA variants represent another potential confounding factor.

Some studies focus on mtDNA haplogroups, sets of mtDNA variants that present in conjunction with each other. During prehistoric human migrations mutations arose in different populations and were fixed in those populations (Torroni et al., 1996). While haplogroups do not permit the interrogation of individual variants, they do to some extent simplify comparisons of some common variant combinations. One limitation of haplogroup analyses is that they can potentially combine mtDNA variants that increase AD risk with variants that decrease AD risk. Haplogroup studies do report effects on AD risk, but results are inconsistent between studies and preclude confident conclusions (Ridge & Kauwe, 2018).

The role of mtDNA in mediating AD pathology or influencing AD risk resides in a state of equipoise. Resolving this conundrum may ultimately require the development of mtDNA polygenic risk scores. This remains a challenging endeavour since common variants tend to travel in groups, which complicates assigning odds ratios to individual variants. Hopefully this problem will prove tractable.

## 7. A mitochondrial cascade hypothesis

Mitochondrial changes in AD could represent irrelevant artefacts of other disease pathologies, mediate their effects, or trigger them. The essential role of the mitochondria in so many aspects of cell function makes the first possibility less likely. Mitochondrial abnormalities also occur in non-degenerating tissues, and many abnormalities occur in the absence of other obvious pathologies (Swerdlow, 2012).

The AD field is increasingly open to the possibility that mitochondria are important in AD. Much of this enthusiasm derives from experiments in which other AD pathologies are used to perturb mitochondria in ways that recapitulate AD-specific mitochondrial dysfunction and drive other abnormalities. For example, delivering APP, Aβ, or APOE4-derived peptides to mitochondria can impair the respiratory chain or shift the mitochondrial fission-fusion balance (Anandatheerthavarada & Devi, 2007; Chen et al., 2011; Du et al., 2008; Wang et al., 2008). In this capacity, mitochondria could help elucidate other AD hypotheses.

The amyloid cascade hypothesis proposes that Aβ interferes with cell function and survival. Exactly how Aβ damages cells is an open question. Some postulate mitochondria in some way mediate Aβ toxicity. In one study, Aβ exposure was lethal to the Ntera2 (NT2) neuronal cell line but not its ρ0 derivative (Cardoso et al., 2001). This implies the respiratory chain mediates Aβ toxicity and is consistent with data that show Aβ interferes with respiratory chain function (Casley et al., 2002). Beta amyloid also appears to bind other mitochondrial components, including an alcohol dehydrogenase enzyme and cyclophilin D (Du et al.,

2008; Lustbader et al., 2004). Studies such as these suggest a potential important role for mitochondria in AD, within the context of the amyloid cascade hypothesis.

It is more difficult to reconcile the amyloid cascade hypothesis with the systemic AD mitochondrial phenotype (Morris et al., 2014). It remains possible, albeit unlikely, that systemically generated Aβ causes that phenotype, but if this does occur it is still important to consider what alters systemic Aβ homeostasis. Certainly, cells carefully manage APP and Aβ production and elimination, and mitochondria may contribute to that regulation.

Cybrid data are also relevant to this point (Swerdlow, 2012; Swerdlow et al., 2017). The cybrid approach specifically reveals the functional effects of specific mtDNA sequences, and even extra-mitochondrial effects presumably reflect mtDNA-derived changes in mitochondrial function. Generating cybrid cell lines relies on cytosolic mixing, which could co-transfer Aβ residing in either the platelet mitochondria or its free cytosol, but any transferred component that cannot replicate itself degrades and dilutes over the course of cell cycling and division. If transferred toxic Aβ was to account for the cybrid data, it would need to manifest prion-like properties.

While Aβ may indeed cause or amplify mitochondrial dysfunction, at least in the brains of AD subjects, it is important to consider the possibility that at least some mitochondrial changes arise independently of Aβ. Several conceptual points support this view.

Mitochondrial function changes with advancing age (Boveris & Navarro, 2008; Navarro & Boveris, 2007), which could potentially tie sporadic AD to its greatest single risk factor, advancing age (Swerdlow, 2007a). Pseudosporadic epidemiology that occurs in conjunction with maternal inheritance bias, in both the fully-fledged disease state and with endophenotypes, is consistent with mitochondrial genetics. The ability to replicate several AD-associated pathologies in cultured cells following mtDNA transfer from AD patients argues that mtDNA contributes to those pathologies and is not simply a consequence of those pathologies (Swerdlow, 2012; Swerdlow et al., 2017).

Various investigators initially envisioned a primary role for mitochondria in AD (Beal, 1995; Gibson et al., 1998; Parker, Jr. et al., 1990; Wallace, 1992). Some further proposed this role derived ultimately from mtDNA, with Parker (1990) postulating mtDNA inheritance and Wallace (1992) postulating mtDNA somatic mutation as the critical factors. Whether a consequence of inherited mtDNA variation, or somatic mtDNA mutation, or both, it is important to tie these putative mtDNA effects to nuclear genes, and at this point data support this overall concept (Andrews et al., 2019; Pa et al., 2019; Swerdlow et al., 2017). It is also important to tie mitochondrial function to protein homeostasis and aggregation in ways that allow mitochondria to drive those protein changes to some extent, even if those protein changes cycle back to alter the mitochondria (Weidling & Swerdlow, 2019). Ordering the molecular changes of AD in this way defines a mitochondrial cascade hypothesis, which uses mitochondrial dysfunction and bioenergetic defects to establish a potentially causal metabolic link to AD (Swerdlow, 2018; Swerdlow, Burns, & Khan, 2010; Swerdlow et al., 2014; Swerdlow & Khan, 2004, 2009).

## 8. Conclusions and implications

Alzheimer's disease features altered mitochondrial function, structure, maintenance, and dynamics (Swerdlow, 2012). These features are seen not only within the brain, the organ associated with clinical AD symptoms and signs, but also outside the brain. Their localization to non-degenerating and non-neuronal sites suggests they are not exclusive by-products of neurodegeneration. Outside the brain, the scope of the systemic biochemical phenotype defined by these mitochondrial pathologies exceeds currently reported systemic Aβ or tau pathology, which suggests that systemic Aβ or tau pathology should not entirely account for systemic mitochondrial pathology.

Mitochondrial dysfunction appears to drive at least some non-mitochondrial AD pathologies, including an increase in Aβ (Gabuzda et al., 1994; Khan et al., 2000; Onyango et al., 2010). Cybrid studies indicate AD mitochondrial dysfunction at least to some degree tracks with mtDNA (Swerdlow et al., 2017). Mitochondria also feature prominently in theories of aging, which could help explain potential ties between sporadic AD and its greatest risk factor, advancing age (Swerdlow, 2007a). Age-related mitochondrial changes could first initiate a period of compensated brain aging, which evolves into a state of uncompensated brain aging. Considerations such as these support the argument that mitochondria independently contribute to AD risk and progression, and support speculation of a pathological mitochondrial cascade (Swerdlow, 2018; Swerdlow et al., 2010, 2014; Swerdlow & Khan, 2004, 2009; Swerdlow et al., 2017).

Advancing a mitochondrial cascade hypothesis at this point requires advances on three fronts. First, firm associations with specific genetic variants will prove critical. This could include associations with nuclear genes that encode mitochondria-localized proteins, nuclear genes that encode proteins that do not localize to mitochondria but influence mitochondrial function, or genes encoded on the mtDNA. Substantial indirect data, including cybrid, epidemiologic, and endophenotype data are consistent with this possibility (Swerdlow et al., 2017) and recent genetic association studies implicate genes whose products localize to or influence mitochondria (Pa et al., 2019; Swerdlow et al., 2017). Additional studies should further explore these phenomena.

Second, a mitochondrial cascade hypothesis should explain altered proteostasis and protein aggregation. Decades of research provide a sophisticated picture of how cells handle AD-aggregating proteins, especially Aβ and tau, but also α-synuclein and TDP43. Despite this, it is difficult to conclude that we comprehensively understand the factors that initiate altered Aβ and tau homeostasis. It is important to determine if factors other than stochastic misfolding events are relevant, and if so whether mitochondria contribute to those factors. Data to date leave no doubt that mitochondrial function and bioenergetics influence protein homeostasis (Weidling & Swerdlow, 2019), and prior research indicates links between mitochondrial function, APP, Aβ, and tau (Anandatheerthavarada & Devi, 2007; Choi et al., 2014; Hoglinger et al., 2005; Lustbader et al., 2004). A more complete picture of how and why mitochondria could influence APP, Aβ, tau, α-synuclein, and TDP43 homeostasis in AD is worth pursuing.

Third, the AD field will need to show therapies that target mitochondria and bioenergetics can favourably influence the disease. If mitochondria are truly critical in AD, then manipulations that reverse mitochondrial dysfunction should benefit those with the disease. This will prove challenging as specific mitochondrial derangements may require very specific manipulations, it remains unclear what specific manipulations are needed most, executing the desired manipulations could prove difficult, and targeting the necessary manipulations to where they are needed may present problems. Ultimately, improving the lives of those afflicted remains the ultimate test from a conceptual perspective and the goal from a practical perspective. Currently, though, the aggregate of the evidence argues it is reasonable to target mitochondria and bioenergetics for the treatment of AD (Swerdlow, 2011; 2014).

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## List of abbreviations

**AD**
Alzheimer’s disease

**Aβ**
beta-amyloid

**MCI**
mild cognitive impairment

**ER**
endoplasmic reticulum

**MAMs**
mitochondrial-associated membranes

**MICOS**
mitochondrial contact site and cristae organizing sysem

**mtDNA**
mitochondrial DNA

**TFAM**
transcription factor A of the mitochondria

**ETC**
electron transport chain

**NADH:ubiquinone oxidoreductase**
complex I

**succinate dehydrogenase or succinate:ubiquinone oxidoreductase**
complex II

**coenzyme Q:cytochrome C oxidoreductase or cytochrome bc1 complex**
complex III

**cytochrome oxidase**
complex IV

**ATP synthase**
complex V

**ROS**
reactive oxygen species

**RNS**
reactive nitrogen species

**UCPs**
uncoupling proteins

**Drp1**
dynamin-related protein 1

**Fis1**
mitochondrial fission 1

**OPA1**
optic atrophy 1

**Mfn1**
mitofusin 1

**Mfn2**
mitofusin 2

**rRNA**
ribosomal RNA

**PCR**
polymerase chain reaction

**APP**
amyloid precursor protein

**FDG PET**
fluorodeoxyglucose positron emission tomography

**CNS**
central nervous system

**GWAS**
Genome wide association

**MRI**
magnetic resonance imaging

**TDP43**
transactivation response DNA-binding protein 43

**MAGIC**
mitochondria as guardians in the cytosol

**PS1**
presenilin 1

**PS2**
presenilin 2

**WES**
whole exon sequencing

**WGS**
whole genome sequencing

**TOMM40**
translocator of the outer mitochondrial membrane 40

**NT2**
Ntera2

**DM**
diabetes mellitus

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