INVITED REVIEW

Modulation of mitochondrial bioenergetics as a therapeutic strategy in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is an increasingly pressing worldwide public-health, social, political and economic concern. Despite significant investment in multiple traditional therapeutic strategies that have achieved success in preclinical models addressing the pathological hallmarks of the disease, these efforts have not translated into any effective disease-modifying therapies. This could be because interventions are being tested too late in the disease process. While existing therapies provide symptomatic and clinical benefit, they do not fully address the molecular abnormalities that occur in AD neurons. The pathophysiology of AD is complex; mitochondrial bioenergetic deficits and brain hypometabolism coupled with increased mitochondrial oxidative stress are antecedent and potentially play a causal role in the disease pathogenesis. Dysfunctional mitochondria accumulate from the combination of impaired mitophagy, which can also induce injurious inflammatory responses, and inadequate neuronal mitochondrial biogenesis. Altering the metabolic capacity of the brain by modulating/potentiating its mitochondrial bioenergetics may be a strategy for disease prevention and treatment. We present insights into the mechanisms of mitochondrial dysfunction in AD brain as well as an overview of emerging treatments with the potential to prevent, delay or reverse the neurodegenerative process by targeting mitochondria.

Key Words: *Alzheimer's disease; mitochondria; bioenergetics; mitochondrial DNA; neuroinflammation; mitohormesis; caloric restriction; hypometabolism; mitophagy; mitochondrial biogenesis; recombinant-human mitochondrial transcription factor A; antioxidants; proteasome; mitochondrial transcription activator-like effector nucleases; clustered regularly interspaced short palindromic repeats/associated protein 9 (CRISPR/Cas9); caloric restriction; stem cells*

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Introduction

Alzheimer's disease (AD) is a major health issue affecting over 46 million people worldwide. Without therapeutic breakthroughs, the number could reach 75 million in 2030 and exceed 131.5 million by 2050 (www.alz.co.uk/worldreport2016). The current annual global economic cost associated with managing dementia exceeds US$818 billion, and AD will become a trillion-dollar disease by 2018 (https://www.alz.co.uk/research/WorldAlzheimerReport2016.pdf).

AD is categorized into two major forms: sporadic AD (sAD) and familial AD (fAD) with < 10% of AD cases being familial (Thinakaran, 1999) and showing autosomal-dominant transmission within affected families. Although sAD has a heterogeneous etiology and heritability of 70% to 80% (Gatz et al., 2006; Wingo et al., 2012), age is its most prominent biological risk factor (Carr et al., 1997) with APOE4 gene being an additional risk factor (Dorszewska et al., 2016). Female gender is also an important contributor that is partially explainable by the fact that postmenopausal women lose the protection that estrogens confer to neuronal mitochondria against beta-amyloid (Aβ) toxicity. Older women are also more likely than age-matched men to suffer from metabolic diseases, such as diabetes and obesity, that increase their chances of developing AD (Vina and Lloret 2010).

Most fAD patients have at least one affected first-degree relative (van Duijn et al., 1994; Campion et al., 1999; Jarmolowicz et al., 2014), and in 10% to 15% the mode of inheritance is autosomal dominant transmission (Campion et al., 1999; Jarmolowicz et al., 2014). fAD is triggered by gene mutations of amyloid precursor protein (APP) (chromosome 21), presenilin 1 (PSEN1) (chromosome 14), or presenilin 2 (PSEN2) (chromosome 1). This elicits Aβ aggregation in earlier years and the onset of the disease is as early as 20–30 years of age (Su et al., 2008; Muirhead et al., 2010) with the majority being diagnosed between 45 and 60 years.

Additional risk genes that have been identified by genome-wide association studies (GWAS) include: the gene for clusterin (CLU) also known as apolipoprotein J (localized on chromosome 8), the gene encoding the complement component (3b/4b) receptor 1 (CR1) (chromosome 1), the gene encoding PI-binding clathrin assembly protein (PICALM) (chromosome 11), the gene encoding the bridging integrator 1 (BIN1) (chromosome 2), and the disabled homolog 1 (DAB1) (chromosome 1). Additional novel risk loci associated with sAD are: sortilin-like receptor 1 (SORL1), triggering receptor expressed on myeloid cells 2 (TREM2), the membrane-spanning 4-domains, subfamily A (MS4A), ATP-binding cassette transporter A1 and A7 (ABCA1 and 7), methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) and CD33 (Allen et al., 2012). These newly identified genes are involved in transport, lipid metabolism (Zhu et al., 2015; El gaamouch et al., 2016), immune response and APP metabolism (De Strooper and Karran, 2016).

The drugs currently approved by the US Food and Drug Administration (FDA) for AD treatment include cholinesterase inhibitors (CIs) such as galantamine which is indicated for mild to moderate AD and rivastigmine, donepezil for all stages of AD (Kim et al., 2017). Tacrine, a centrally acting anticholinesterase and indirect cholinergic agonist is less prescribed due to its hepatotoxicity. Memantine, a

glutamate agonist is a therapeutic option for moderate to severe AD (McShane et al., 2006; Jan et al., 2017). While these drugs ameliorate symptoms in the early stages of AD, they show no evidence of stopping or reversing the neurodegenerative process (De la Monte, 2012). This could be because they do not directly target the underlying pathology in the degenerating neurons and they may be more effective if administered in the prodromal stages of the disease.

Of the 244 drugs for AD tested in clinical trials registered with clinicaltrials.gov, a National Institutes of Health (NIH) registry of publicly and privately funded clinical studies between 2002–2012, only one has successfully completed clinical trials and received approval from the FDA (https://www.alz.org/documents_custom/2017-facts-and-figures.pdf). So far, all clinical trials designed to lower levels of Aβ by either blocking activity of β or γ secretases, preventing Aβ aggregation, or promoting Aβ clearance by immunotherapy have failed (Cummings et al., 2014; Feldman et al., 2014) emphasizing an urgent need to find new therapies for AD.

It is widely accepted that alterations in mitochondrial function and glucose metabolism are consistent antecedents leading to AD pathology including Aβ plaque and neurofibrillary tangles (Gibson and Shi, 2010). This mitochondrial dysfunction is characterized by impaired biogenesis and inefficient bioenergetics i.e. defects the activity of key respiratory enzymes and is accompanied by the generation and accumulation of reactive oxygen species (ROS) (Chen and Yan, 2010). As Aβ accumulates, it impairs cerebral blood flow (CBF). This leads to less glucose being available for energy expenditure continuing a vicious cycle that exacerbates the compromised CBF and resulting in the degeneration of neurons (Popa-Wagner et al., 2015).

Additionally, Aβ impaired electron transport chain (ETC) function promotes the phosphorylation and polymerization of tau, a mitochondrial protein involved in microtubule assembly. This causes generation of more ROS that further stimulates tau phosphorylation leading to neurofibrillary tangle formation and neurodegeneration (Simoncini et al., 2015). Post-mortem brains of AD patients have fewer mitochondria and increased presence of mitochondrial DNA (mtDNA) and mitochondrial proteins in the cytosol (Arun et al., 2016).

Numerous positron emission tomography (PET) studies demonstrate a decline in glucose utilization in the hippocampal and entorhinal cortical regions that precedes the clinical diagnosis of AD by decades and predict the cognitive decline in normal aging (Calsolaro and Edison, 2016) or the progression of patients from mild cognitive impairment (MCI) to AD (Chetelat et al., 2003) with high accuracy. Mitochondrial biogenesis is a highly regulated process that requires coordination and crosstalk between the nuclear and mitochondrial genomes and plays an essential role in maintaining an adequate functional neuronal mitochondrial mass by compensating for damaged mitochondria that have been eliminated (Onyango et al., 2016).

To achieve better outcomes in patients with AD, a paradigm that addresses the bioenergetic deficit in the vulnerable neurons of affected brain regions is needed. This can be achieved by targeting mitochondria and alleviating mitochondrial dysfunction in AD.

The Mitochondrion

A mitochondrion contains 2–10 copies of mtDNA (Reddy, 2008). The human mtDNA consists of a 16.5 kb, double-stranded, circular DNA molecule (Anderson et al., 1981). mtDNA contains 13 polypeptide genes that encode essential components of the ETC. mtDNA also encodes the 12S and 16S ribosomal RNA (rRNA) genes and the 22 transfer RNA (tRNA) genes required for mitochondrial protein synthesis (Reddy and Beal, 2005). 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. mtDNA is inherited exclusively from the mother and is present in thousands of copies per cell. Mitochondrial number and morphology are controlled by an equilibrium of mitochondrial fusion and fission (Chan, 2006) that is vital for metabolism, energy production, Ca^{2+} signaling, ROS production, apoptosis, and senescence (Chen et al., 2005; McBride et al., 2006; Yu et al., 2006). Fusion allows the exchange of mitochondrial components including mtDNA between different mitochondria. mtDNA due to their proximity to the respiratory chain and a lack of protective histones have a very high mutation rate that is about ten times faster compared to the nuclear DNA (nDNA).

New mtDNA mutations arise frequently in the maternal lineage and initially present as a mixture of the wild-type and mutant mtDNAs, defining the so-called heteroplasmic state. mtDNA mutations are most often heteroplasmic (mixed population of normal and mutant mtDNAs). During cellular divisions, the mutant mtDNAs will be randomly segregated into the daughter's cells and the percentage of mutant mtDNAs in different cell lineages will drift toward either pure mutant or normal (or homoplasmy) (Stewart and Chinnery, 2015). As the percentage of mutant mtDNAs increases in the cell, energy output falls, resulting in an overall mitochondrial dysfunction in the cell. Hence, the ratio of mutant to normal mtDNA contributes to the severity of the disease. Severe mitochondrial damage impairs fusion resulting in fragmentation of mitochondria that are then selectively removed by an autophagic process called mitophagy (Kim et al., 2007).

Mitochondria are structurally and functionally altered in AD (Burte et al., 2015; Cai and Tammineni, 2016; Onyango et al., 2016), and compounds that are able to induce and/or restore their bioenergetic capacity present an attractive strategy AD therapy. Here we review nascent developments of mitochondrially targeted approaches that show promise for AD treatment.

Cellular Therapy

Cell-based therapies are a promising alternative currently being developed to enable the reversal of neurodegeneration in AD either directly by replacing injured neuron or indi-

rectly by stimulating neuronal repair *via* paracrine signaling at the injury site (Baraniak and McDevitt, 2010). Neurons and glial cells have successfully been generated from embryonic stem cells (ESCs), neural stem cells (NSCs), neural progenitor cells (NPCs), mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), induced neuronal cells (iN), induced neuronal progenitor cells (iNPCs). Transplantation of NSCs into animal models of neurodegenerative diseases, including AD, increases the total amount of mtDNA, messenger RNA and protein levels of mitochondrial biogenesis-related factors as well as protein levels of mitochondrial fission genes. This results in a significant increase in the number of morphologically well-structured mitochondria in neurons and is associated with a reversal of cognitive defects, clinical improvement and life extension of these animals (Kim et al., 2013; Zhang et al., 2015; Mendivil-Perez et al., 2017). While still in its formative phase, this new field shows great therapeutic promise for AD and other neurodegenerative diseases.

Drug Therapy

Targeting ROS

Targeting detrimental neuronal ROS at the production stage without affecting ROS signaling would be ideal in preventing and treating AD. In this regard, it has been shown that mitochondria-targeted antioxidants potently sequester reactive oxygen intermediates and confer greater protection against oxidative damage in the mitochondria than untargeted cellular antioxidants. The ability of mitochondria-targeted antioxidants to confer greater protection against oxidative damage in the mitochondria than untargeted cellular antioxidants provide has been attributed to their ability to cross the mitochondrial phospholipid bilayer and eliminate ROS where it is being generated (Oyewole and Birch-Machin, 2015).

These mitochondria-targeted antioxidants such as (10-(6′-plastoquinonyl) decyltriphenyl-phosphonium) (SkQ1), MitoQ, MitoTEMPOL and MitoVitE prevent apoptosis by mitigating the oxidative damage more effectively than untargeted antioxidants such as 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox) (Oyewole and Birch-Machin, 2015). Other such antioxidants include: 4,5-dihydroxybenzene-1,3-disulfonate (Tiron), which has been engineered to accumulate within the mitochondria by permeabilizing the mitochondrial membrane (Fang et al., 2012) and astaxanthin, a mitochondrion-permeable antioxidant, that can penetrate the blood-brain barrier and is effective in preventing and treating macular degeneration (Piermarocchi et al., 2012; Wu et al., 2014).

Various compounds, such as coenzyme Q_{10} (CoQ_{10}), vitamin E, curcumin, *Gingko biloba*, melatonin and lipoic acid, have been demonstrated to reduce Aβ accumulation, protect mitochondria from Aβ toxicity, restore mitochondrial function and attenuate cognitive impairment in animal models of AD possess mitochondrial restoring and anti-oxidant properties (Du and Yan, 2010; Zhang et al., 2015).

Antioxidants can also be targeted to mitochondria through the use of small, aromatic-cationic sequence motif called Szeto-Schiller (SS) tetrapeptides which enables them to be delivered and localized to the inner mitochondrial membrane with an approximate 1,000–5,000-fold accumulation (Smith and Murphy, 2011; Jin et al., 2014). Novel XJB peptides which consist of an electron and ROS scavenger (4-NH_2-TEMPO) conjugated to the Leo-D-Phe-Pro-Val-Orn fragment of gramicidin S have been invented. This pentapeptide fragment can specifically target the XJB peptides to mitochondria. One of these peptides, XJB-5-131, improved mitochondrial function and enhanced the survival of neurons in a mouse model of Huntington's disease (Xun et al., 2012) and might offer a viable therapeutic opportunity in AD. Another approach of targeting mitochondria with small bioactive molecules involves polymer based nano-carriers. These include biodegradable poly-lactide-co-gylcolide (PLGA) like PLGA-CoQ_{10} nanoparticles (Nehilla et al., 2008) although their biological effects are yet to be fully elucidated.

Targeting the inflammasome

Mitochondria are capable of regulating the pro-inflammatory response of the cell through activation of the inflammasome. The inflammasome is a multi-protein complex on which proIL-1β and proIL-18 processing occurs. The NLRP3 inflammasome, detects the inflammatory aggregates of Aβ and inactive IL-1β, and responds by secreting caspase-1 (Casp-1) to activate IL-1β (Saco et al., 2014).

NLRP3 activation is crucial in the pathogenesis of AD (Walsh et al., 2014) and has been proposed to be associated with mitochondrial dysfunction including: mitochondrial ROS (Zhou et al., 2011), mitochondrion-derived damage associated molecular patterns (mtDAMPs), such as oxidized mitochondrial DNA (Shimada et al., 2012; Wilkins et al., 2015), and translocation of cardiolipin from the inner to the outer mitochondrial membrane (Iyer et al., 2013). Additionally, extracellular ATP at various concentrations can activate microglia and induce neuroprotective or neurotoxic effects by expressing pro- or anti-inflammatory cytokines (Inoue, 2002; Davalos et al., 2005).

Several studies in cell lines, genetic rodent models, and humans indicate that redox control might serve as a bidirectional link between energy metabolism, redox control and neuroinflammatory responses in the brain that might serve as an integrated mechanism for AD etiology (Yin et al., 2016). It has been reported that small molecule inhibitors of the NLRP3 inflammasome ameliorate AD pathology in animal models of AD (Dempsey et al., 2017; Yin et al., 2017). Further, CAD-31, a safe, orally active and brain-penetrant neurotrophic drug that targets inflammation has been shown to reduce synaptic loss, normalize cognitive skills and enhance brain bioenergetics in genetic mouse models of AD (Daugherty et al., 2017).

Targeting the proteasome

The ubiquitin proteasome system (UPS) and mitochondria systems are tightly interdependent. Once a vicious cycle of dysfunction starts in diseases such as AD, it is difficult to identify which system was the trigger. Mitochondrial dysfunction and impairment of the UPS are two hallmarks of

aging and both are implicated in AD (Riederer et al., 2011; Ross et al., 2015). Proteasome activation by small molecules is a promising strategy to treat or prevent neurodegenerative diseases characterized by the accumulation of toxic protein aggregates (Lee et al., 2010; Dantuma and Bott, 2014; Myeku et al., 2016). As a proof of concept, it has been shown that proteasome activation by genetic manipulation ameliorates the aging process and increases lifespan in different models including *C. elegans*, human fibroblasts and yeast cells (Chondrogianni et al., 2015). Proteasome function is activated by a pathway involving protein kinase A and cyclic AMP (cAMP). Selective phosphodiesterase-4 inhibitors such as rolipram which increase cAMP levels have been shown to increase proteasome function, reduce aggregated tau levels, and improve cognitive performance and ameliorate the early stages of neurodegeneration in a genetically engineered mouse model of tauopathy (Myeku et al., 2016).

Proteosomal activity can also be enhanced by using Pyrazolone containing small molecules which block USP14, a proteasome-associated deubiquitinating enzyme that inhibits the processing of ubiquitin–protein complexes destined for degradation by the proteasome (Lee et al., 2010). PD169316 is a novel small molecule p38 MAPK inhibitor and a very potent activator of proteasome activity enhanced Proteolysis Targeting Chimeric (PROTAC)-mediated and ubiquitin-dependent protein degradation and decreases the levels of both overexpressed and endogenous α-synuclein in a bimolecular fluorescence complementation (BiFC) assay (Outeiro et al., 2008), without affecting the overall protein turnover. It also increased the viability of cells overexpressing toxic α-synuclein assemblies (Leestemaker et al., 2017).

Gene Therapy

Targeting mtDNA

mtDNA are relatively unstable and susceptible to damage because they lack histones and have limited enzymatic repair system, as well as their crucial role in oxidative phosphorylation (OXPHOS). As a result, mtDNA mutations accumulate with age (Smigrodzki and Khan, 2005; Casoli et al., 2015) and are a significant risk factor for AD (Swerdlow et al., 2014).

(i) The clustered regularly interspaced short palindromic repeats (CRISPR)/associated protein 9 (CRISPR/Cas9) technology has now been developed to produce mitochondrial sequence-specific cleavage with the potential of targeting specific mitochondrial genes (Jo et al., 2015). It utilizes a custom single guide RNA (sgRNA) fragment that acts as a guide to find the piece of DNA to be modified and binds to it and recruits mitoCas9, whose localization is restricted to mitochondria matrix. This mitoCas9 could be applied to edit mtDNA together with gRNA expression vectors without affecting genomic DNA.

(ii) Transcription activator-like effector nucleases (TALENs) comprise a non-specific DNA-cleaving nuclease fused to a DNA-binding domain that can be easily engineered so that TALENs can target essentially any sequence. When directed specifically at the mtDNA, mitoTALENs (Bacman et al., 2013) can be used to cleave the mutated mtDNA, efficiently reducing the levels of the targeted pathogenic mtDNAs in the respective cell lines. This enables cells with heteroplasmic mutant mtDNA to recover respiratory capacity and oxidative phosphorylation enzymes activity (Hashimoto et al., 2015).

Targeting mitochondrial cholesterol

The accumulation of cholesterol in mitochondria can lead to mitochondrial dysfunction and may be a key step in AD progression. This dysfunction includes reduced fluidity of mitochondrial membranes (Colell et al., 2003), reduced ATP generation (Echegoyen et al., 1993; Yu et al., 2005) and decreased mitochondrial glutathione (GSH) import (Marí et al., 2006; Garcia-Ruiz et al., 2009) and may be a key step in AD progression (Aufschnaiter, et al., 2016). Furthermore, there is a direct link between altered membrane lipids and mitochondrial function, which is detrimental for brain bioenergetics (Rosales-Corral et al., 2012). Cholesterol turnover in the brain is modulated by cytochrome P450 46A1 (CYP46A1) which initiates the major pathway of its elimination. In the APP23 AD mouse model, Aβ peptides accumulate following inhibition of CYP46A1 expression resulting in widespread neuronal death compared to normal mice. On the other hand, decreasing CYP46A1 gene expression in hippocampal neurons of normal mice increases the cholesterol concentration in neurons with subsequent cognitive deficits and hippocampal atrophy due to apoptotic neuronal death (Djelti et al., 2015). Preclinical pharmacological tests are ongoing for gene therapy targeting CYP46A1 as a means to restore cholesterol metabolism in AD brain (Djelti et al., 2015) with clinical trials anticipated to begin in 2021 (www.brainvectis.com).

Biologics

The human mitochondrial genome can be manipulated from outside the cell to change expression and increase mitochondrial energy production. Mitochondrial transcription factor A (TFAM), has been engineered to rapidly pass through cell membranes and target mitochondria. Expression of human TFAM (hTFAM) significantly improved cognitive function, reducing accumulation of both 8-oxoguanine, an oxidized form of guanine, in mtDNA and intracellular Aβ in 3xTg-AD mice and increasing expression of transthyretin, known to inhibit Aβ aggregation (Oka et al., 2016). We previously showed that recombinant-human TFAM (rhTFAM) acts on cultured cells carrying a mtDNA disease (Iyer et al., 2012) as well as lab mice, energizing the DNA of the mice's mitochondria, improving the memory of aged mice (Iyer et al., 2009; Thomas et al., 2012) and enabling them to run two times longer on their rotating rods than a control group cohort (Thomas et al., 2012).

Caloric Restriction (CR)

CR, *i.e.* the limitation of ingested calories without malnutrition, is known to enhance animal life span and prevent age-related diseases, including neurological deficits, brain atrophy, and cognitive decline (Colman et al., 2009). CR induces mitochondrial biogenesis (Cerqueira et al., 2012) in a

NO•-mediated manner that culminates in increased mitophagy and the production of new, more efficient mitochondria that have reduced membrane potential, produce less ROS, consume increased levels of oxygen and exhibit an improved ATP/ROS ratio - leading to decreased energy expenditure (Onyango et al., 2010). In particular, the tissue-specific effects of CR include the prevention of the age-related loss of mtDNA in rat liver (Cassano et al., 2006) and the partial preservation of TFAM binding to mtDNA in rat brain with enhanced reserve respiratory capacity and improved survival in neurons (Picca et al., 2013).

Exercise

Endurance exercise (EE) is neuroprotective against AD. Exercise activates continuous oxidative stress that induces a series of counteractive mechanisms that enhance mitochondrial function and mitigate ROS-induced neurotoxicity *i.e.*, mitohormesis (Onyango et al., 2010; Radak et al., 2016), and this is especially important in the hippocampus which is particularly sensitive to oxidative stress (Intlekofer and Cotman, 2013). In animal models of AD, physical exercise reduces the noxious effects of oxidative stress, the production of total cholesterol, and insulin resistance, while increasing vascularization and angiogenesis, improving glucose metabolism as well as neurotrophic functions, thereby facilitating neurogenesis and synaptogenesis, and as a consequence improving memory and cognitive functions (Paillard et al., 2015; Chen et al., 2016; Koo et al., 2016).

A combination of CR and EE is reported to deliver more beneficial effects than either regimen alone in ameliorating neurological and cognitive deficits (Cherif et al., 2016).

Conclusion

Mitochondrial impairment and loss play a critical role in neuronal degeneration and disease progression in AD. Damaged mitochondria are less bioenergetically efficient and produce increased amounts of ROS with detrimental structural and functional consequences for the AD neurons. Dysfunctional mitochondrial accumulate from the combination of impaired mitophagy, which can also induce injurious inflammatory responses, and inadequate neuronal mitochondrial biogenesis.

Identifying mechanisms that are critical in enhancing mitochondrial quality control, reducing bioenergetic defects while limiting generation of detrimental quantities of ROS may provide therapeutic opportunities that preserve neuronal viability and function and delay or reverse features of AD (**Figure 1**).

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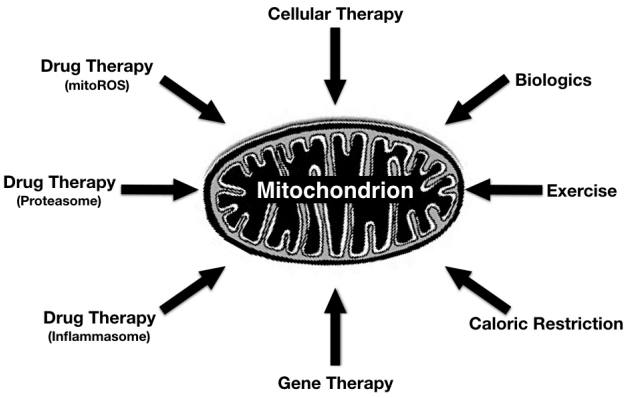

Figure 1 Approaches to enhance bioenergetic capacity in Alzheimer's disease (AD).
Cellular therapy and biologics can enhance mitochondrial biogenesis. Drug therapy can be used to reduce detrimental reactive oxygen species (ROS) without altering ROS signaling, rejuvenate proteasome function, inhibit the inflammasome. Gene therapy can manipulate mitochondrial DNA (mtDNA) without altering genomic DNA and also be targeted at regulating mitochondrial cholesterol. Exercise and caloric restriction can enhance mitochondrial function by mitohormesis. mitoROS: Mitochondrial ROS.

Open peer review report:
Reviewer: *Aurel Popa-Wagner, University Medicine Rostock, Germany.*
Comments to author: *To date, all clinical trials designed to lower levels of Aβ by either blocking activity of β or γ secretases, preventing Aβ aggregation, or promoting Aβ clearance by immunotherapy have failed. The idea that alterations of mitochondrial function and glucose metabolism may lead to AD pathology is gaining acceptance in the scientific community. The authors make a survey of current therapies that might make mitochondria of AD patients bioenergetically more efficient. The article is well organized.*

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