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New Targets for Diagnosis and Treatment Against Alzheimer's Disease: The Mitochondrial Approach

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder and the most common form of dementia. AD is characterized by brain presence of senile plaques, which are formed by aggregates of A β peptide and neurofibrillary tangles (NFTs), formed by pathological forms of tau protein. Evidence suggests that these elements affect neurons compromising energy supply, antioxidant response and synaptic activity. AD principally affects the memory and cognitive functions of the patients, and currently, successful strategies for diagnosis and early treatment are lacking. In this scenario, accumulative evidence suggests that mitochondrial dysfunction precedes the establishment of tau and A β pathology and contributes to synaptic degeneration observed in AD. Therefore, reducing mitochondrial injury may have beneficial effects for neuronal dysfunction and cognitive decline observed in AD patients. Interestingly, the examination of peripheral cells from AD patients also presents mitochondrial dysfunction, suggesting that tracking these mitochondrial defects in peripheral cells could be a potential mechanism of early diagnosis of AD. In this chapter, we analyse current evidence that suggests that mitochondrial injury is an important factor in the pathogenesis of AD and how studying this process could reveal new strategies to mitigate neurodegeneration and to develop new diagnostic methods for an early detection of AD.

Keywords: Alzheimer's disease, mitochondria, oxidative stress, tau, A β , synaptic dysfunction

1. Introduction

Alzheimer's disease (AD) is a complex and irreversible neurodegenerative disorder characterized by a progressive memory and cognitive impairment. AD patients present a deficiency in short-term memory and problem-solving skills, affecting his daily activities and quality of life [1]. According to the World Alzheimer's report, this pathology comprises over the 60% of all causes of dementia, and they estimate that there are around 46.8 million people living with the disease at 2015. Because of their importance in public health, it is necessary to study the causes, diagnosis methods and possible treatments of this pathology [1]. AD is pathologically characterized by the presence of extracellular deposition of $A\beta$ in the brain called senile plaques and intracellular neurofibrillary tangles (NFTs) containing pathological forms of tau protein [2]. Several studies had shown that these aggregates and its precursors induce neuronal dysfunction, leading to the memory and cognitive impairment [3]. Interestingly, in cellular and animal models of AD in which $A\beta$, tau or both pathological aggregates have been induced, impairment of mitochondrial function even prior to the characteristic establishment of NFTs and $A\beta$ plaques [4] is shown.

Mitochondria are cellular organelles required for energy and bioenergetics processes and it is also involved in amino acid and lipid metabolism, calcium homeostasis, free radical production and apoptosis [5]. In the brain, mitochondria are involved in energy supply, antioxidant defences, vesicle transport and synaptic communication [4]. These defects could lead to the memory and cognitive impairment seen in AD patients [4].

In this chapter, we discuss the pathways involved in mitochondrial dysfunction observed in different animal and cellular models of AD. These alterations in mitochondrial function include: mitochondrial dynamics, bioenergetics and mitochondrial axonal transport [4]. All these mitochondrial defects lead to an impaired neuronal communication and that could explain the cognitive and memory failure seen in AD [2]. Also in this chapter, we discuss new strategies to diminish mitochondrial injury in AD, in order to ameliorate the pathology progression of this disease.

The references and articles utilized in the development of this chapter were obtained using online compressive search engines like PUBMED and MEDLINE. Scientific articles were obtained from the online subscription services provided by Universidad Autónoma de Chile.

1.1. Defects of mitochondrial dynamics in AD

Mitochondria is a versatile organelle that forms an intracellular network that undergoes continuous fission and fusion processes named mitochondrial dynamics [6]. This process plays a crucial role in the control of mitochondrial shape, size and number, which influences important mitochondrial properties including bioenergetics and quality control [7]. Mitochondrial fusion serves to unify the mitochondrial compartment, and mitochondrial fission contributes to the removal of damaged organelle via mitophagy and may facilitate apoptosis in conditions of cellular stress [8]. Generally, mitophagy is initiated when mitochondrial membrane potential is compromised [9]. Under this condition, the phosphatase and tensin

homolog induced protein kinase 1 (PINK1) and Parkin complex ubiquitinates the mitochondrial outer membrane proteins called, mitofusins, leading to mitochondrial fragmentation and recruitment of optineurin [9]. This process induces recruitment of the autophagy-related binding protein LC3 (microtubule-associated protein light chain 3) that promotes nucleation of the autophagosome leading to mitochondrial degradation [9]. Defects in mitochondrial dynamics have been linked to several diseases, and particularly important is the process in neurons [10]. Neurons' requirements are extremely unique, because of their dependence on energy production from mitochondria, which are needed in the synaptic process [8].

Mitochondrial biogenesis occurs to supply cellular energy through the fission of preexisting mitochondria followed by growth [11]. Little is known about the regulatory mechanisms of mitochondrial biogenesis in mammalian neurons under physiological or pathological conditions. However, these processes quickly respond to changes due to mitochondrial damage or increased stimulation of PGC-1 α , Nrf1/2 and TFAM pathways [5]. Interestingly, expression levels of those proteins were significantly decreased in both AD hippocampal tissue and a neuronal cell line with overexpression of Swedish mutant forms of APP protein (APP^{swe}), suggesting that mitochondrial biogenesis was affected during neurodegeneration and contributes to mitochondrial dysfunction in AD [12].

On the other hand, mitochondrial dynamics depends on the interaction of different proteins within the mitochondrial membranes [13, 14]. Mitochondrial fission depends on dynamin-related protein 1 (Drp1) and mitochondrial fission protein 1 (Fis1) [6]. Drp1 is mainly located in cytoplasm and is recruited by Fis1 that is in the mitochondrial outer membrane [14]. Then Drp1 by its guanosine triphosphatase (GTPase) activity assembles itself constricting mitochondrial membrane until the formation of two daughter mitochondrias [15]. Moreover, fusion of the mitochondria is control by optic atrophy protein (Opa1) and both, mitofusins 1 and 2 (Mfn1 and Mfn2) [16]. This fusion of outer mitochondrial membrane is mediated by the concerted GTPases actions of Mfn 1 and Mfn 2, and fusion of the inner membranes are mediated by Opa1 through its proteolytic processing [4, 7].

Several studies showed that mitochondrial morphological changes are present in AD [17, 18]. Brain-derived mitochondria from AD patients are smaller and more fragmented compared to age-matched individuals [19], and reduced mitochondrial density in synaptic structures and shorter mitochondria in brain axons were found in mouse overexpressing APP/A β (mAPP transgenic mouse) [20]. In different neuronal cell models treated with A β or with overexpression of Swedish mutant forms of APP protein, mitochondria present changes in their structure: a fragmented and punctiform form and a reduction of mitochondrial density in neurites [19–21]. On the other hand, tau also has a role on the A β -induced mitochondrial impairment. In mature neurons, it has been shown that truncated and pseudo-phosphorylated forms of tau mediates mitochondrial shortening, reducing mitochondrial movement and mitochondrial potential and increasing superoxide levels induced by A β [22–24]. All this morphological changes are related to changes in mitochondrial dynamics.

An increase in Fis1 protein expression and a reduced expression of Drp1, Mfn1, Mfn2 and Opa1 in the cytosolic fraction was found in post-mortem brain tissue and neuroblastoma cell line M17 treated with amyloid- β -derived diffusible ligands (ADDLs) [19]. However, Drp1

expression was increased in brain frontal cortex from AD patients [25], suggesting a deregulation of Drp1 activity associated with mitochondria [25]. Furthermore, it has been shown that oxidative stress-mediated S-nitrosylation of Drp1 induced by A β triggers mitochondrial fragmentation [26]. Interestingly, in another model of AD, N2a cells that expressed APP Swedish mutation, A β accumulation induced a decrease in both Mfn1 and Mfn2 levels, with a subsequent fragmentation of mitochondria [27]. On the other hand, in transgenic mouse models of AD a direct interaction between Drp1 and hyperphosphorylated tau has been found, suggesting a direct effect of tau on the mitochondrial dynamics dysfunction [28].

All these data suggest that tau pathology and A β impairs mitochondrial morphology even before the NFTs and senile plaques establishment. These are important features because a regulated fusion-fission cycle is needed to maintain a healthy mitochondrial pool. In AD, mitochondrial biogenesis is impaired, mitophagy process is reduced and alterations in cycle of mitochondria dynamics generate mitochondrial fragmentation [9, 29]. Overall, these defects could be the cause of an increase in the number of damaged organelles in AD neurons and the source of mitochondrial bioenergetics dysfunction that this disease presents.

1.2. Reduction of mitochondrial bioenergetics performance in AD

The main function of the mitochondria is generating ATP [30]. In the organelles, the electron transport chain (ETC) is responsible for oxidative phosphorylation, which is the biochemical pathway that produces ATP by consuming oxygen [30]. The electrons pass through the respiratory complexes I–IV of the ETC and as a consequence, a membrane potential is generated for the electrochemical force of a proton gradient [30]. This process generates ATP by complex V, and this energetic molecule would help, among other things, to regulate the intracellular calcium homeostasis [4]. This process normally generates reactive oxygen species (ROS); however, oxidative stress occurs when the balance between the production of oxidants molecules and the endogenous antioxidant defences in cells is deregulated [31].

Bioenergetics damage includes low ATP production, failure in ETC, mitochondria depolarization, defects in calcium buffering capacity and increase of ROS [10, 18]. Mitochondria are the primary source of oxidative species, and mitochondria-linked oxidative stress has been found to be a major factor associated with the development and progression of AD [31–33]. In fact, excessive generation of ROS contributes to neuronal dysfunction and bioenergetics failure in AD even before the appearance of A β plaques and NFTs [32, 34], thus supporting the hypothesis that mitochondrial failure is an early event in the AD progression.

In animal models of AD, several data suggest that the A β pathology is an important participant in mitochondrial bioenergetics dysfunction [35, 36]. Brain slices from APP/A β transgenic mice shows A β localization in mitochondria and increased levels of oxidative markers, carbonylated proteins and reduced cytochrome c oxidase (CoxIV or Complex IV) activity, suggesting increased oxidative stress and impaired mitochondrial metabolism in this AD model [32]. Besides, several experiments with neuronal cell lines treated with different forms of the A β peptide indicated that the treatment generate impairment of ETC, mitochondrial depolarization and also, opening of mitochondrial permeability transition pore (mPTP) with the resulting calcium leaking and ROS production [36, 37].

Interestingly, studies have shown that the increased oxidative stress seen in AD could generate a vicious circle in which ROS promotes A β generation in *in vitro* and *in vivo* models [38]. For example, in brain mitochondria from a variant of APP^{swe} mouse, mitochondrial depolarization, low ATP levels and decreased cytochrome c oxidase activity have been found prior to A β plaque deposition [39]. Similar results were found in triple Tg (PS1^{M146V}/APP^{swe}/TauP301L) mice [40], suggesting that both A β and tau pathology present mitochondrial dysfunction prior to the formation of toxic protein aggregates [41, 42].

As we already discussed, neurons are particularly sensitive to mitochondrial dysfunction since they are extremely energy dependent with many cellular activities, such as synaptic transmission and axonal and dendritic transport [43, 44]. Therefore, it is proposed that mitochondrial bioenergetics defects could be considered as a hallmark in AD, since there is evidence that is an early event in the progression of the disease.

1.3. Mitochondria are not properly transported in AD

Defects in axonal transport of mitochondria in AD have been reviewed by our group and others [4, 45]. The axonal transport comprises the action of motor proteins that carry organelles, vesicles and other proteins through microtubules [46]. Kinesins family protein commands anterograde transport (from cell body to terminals) and dynein-dynactin complexes are responsible for the retrograde transport (from terminals to cell body) [46]. Also, each cargo proteins need adaptor proteins to bring specificity to the transport process such the Miro GTPase and trafficking kinesin (TRAK) family of proteins [46]. By the other hand, the docking protein syntaphilin helps mitochondria to stay at zones of higher energy demand, such as synaptic terminals, in a way to modulate the energy requirements of the neurons [47].

Studies on APP^{swe} mice show reduced axonal transport *in vivo* [48]. Neurons from human APP Tg mice showed reduced moving mitochondria when they were treated with A β , and interestingly, knocking down of tau protein prevented this effect [49]. Inversely, neurons of tau knock out mouse transfected with wild-type tau protein make these cells sensitive to A β , showing deficits in axonal transport [49, 50]. Also this group has suggested that GSK-3 β is involved in this mechanism due to its interaction with presenilin 1 (PS1) a transmembrane protein related with A β production [50]. Furthermore, in neurons from PS1^{-/-} [51] and PS1^{M146V} mutation related to familiar AD [52], mice show impaired anterograde axonal transport [53]. Also, in SH-SY5Y neuroblastoma cells, it has been found that tau directly interacts with dynactin complexes suggesting a potential effect on retrograde axonal transport in tau pathology [54]. Complementary to these studies, the TPR50 transgenic mice that contain a human P301S tau, a tau gene mutant form found in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) [55], exhibited early cognitive impairment, reduced retrograde transport and increased kinesin protein expression [56].

Interestingly, Guo and coworkers found that reduction of cyclophilin D (CycD) prevented axonal transport impairment induced by A β [57]. CycD is a component of the mPTP located through the outer and inner mitochondrial membranes [58]. mPTP plays a key role in cell death inducing the release of cytochrome c, collapsing mitochondrial membrane potential and releasing calcium at the cytosol [58]. Furthermore, defects of mitochondrial dynamics and

axonal transport induced by A β were prevented in CycD-depleted neurons obtained from CycD knockout mice (Ppif^{-/-}). In addition, restoration of mitochondrial dynamics was replicated using the CycD inhibitor cyclosporin A in the same neuronal model [57].

Overall, defects of mitochondrial transport through axons include the reduced anterograde or/and retrograde movement, increased stationary mitochondria and reduced mitochondrial density in synaptic terminals [45]. These alterations affect neuronal function including autophagy, vesicle transport and energy supply leading to synaptic failure [45].

Mitochondrial defects in dynamics, bioenergetics and transport are tightly related (**Figure 1**). Morphology alterations impair mitochondrial bioenergetics, and this deficiency generates fragmented and dysfunctional mitochondria. Also, defects in both transport and dysfunctional mitochondria could affect the energy and bioavailability of fresh mitochondria in demand zones such as nervous terminals. Together with an increased oxidative stress and reduced mitophagy may affect synaptic communication. Altogether, these alterations in mitochondrial health suggest the possibility that modulating mitochondrial function could be a key strategy to prevent or retard the progression of AD (**Figure 1**).

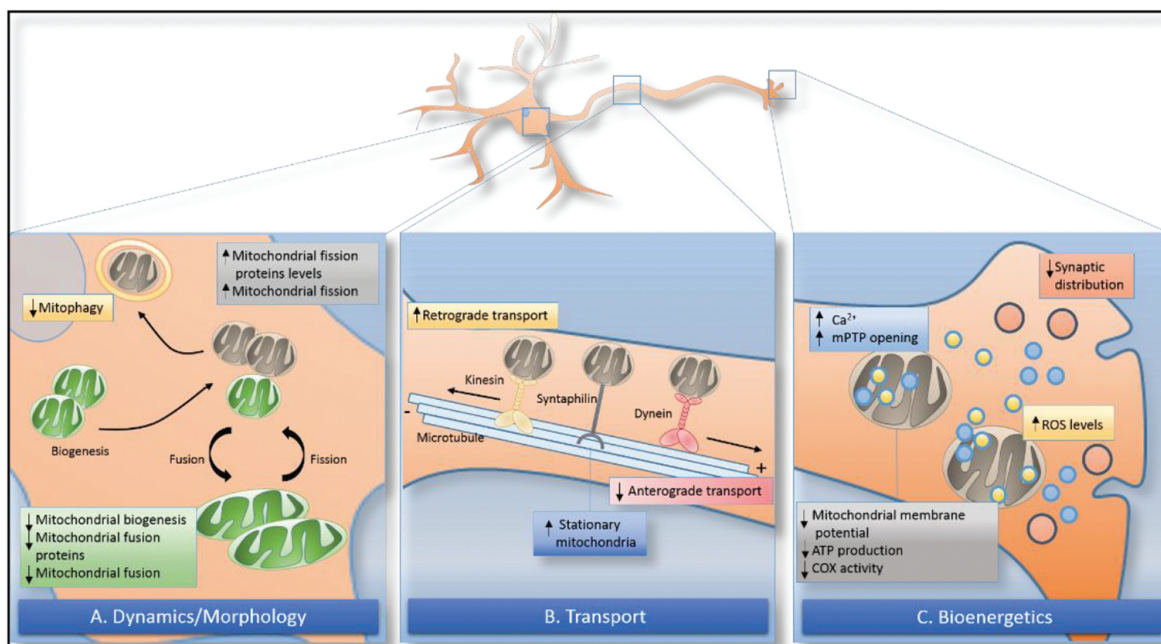


Figure 1. Mitochondrial function defects in AD. (A) **Dynamics/morphology.** The regulation of mitochondrial dynamics, such as fusion, fission, biogenesis and mitophagy, represents an important mechanism that control neuronal fate. Mitochondrial morphological alterations are present in all levels in AD, and the consequence is the accumulation of fragmented and dysfunctional mitochondria in all the cell body (B). **Transport.** Kinesin and dynein proteins mediate axonal transport of mitochondria. Generally, this movement is bidirectional in an anterograde (kinesin) and retrograde direction (dynein). In several models of AD, a deregulated mitochondrial movement together with an increase of immobile mitochondria population associated with syntaphilin has been reported. This alteration generates a decrease in the total mitochondria movement and their distribution to the synaptic space (C) **Bioenergetics.** Neuronal models of AD present a severe mitochondrial dysfunction with an increase in oxidative stress. This alteration leads to a bioenergetic imbalance that affects ATP levels in the presynaptic neuron, with an increase in calcium overload and a consequent synaptic dysfunction.

2. Improving mitochondrial health as a valid therapy for AD

AD is one of the most common forms of dementia in elderly and one of the biggest health problems worldwide [59, 60]. This disease represents a high monetary, personal and family cost, and despite the large number of investigations and tremendous progress that has been made in understanding the molecular mechanism underlying the disease progression, currently there are no available therapies to cure AD. Nowadays, existing treatments for AD are only symptomatic [60]. The current therapies are palliatives that focus on reducing symptoms, but they do not delay the progression of the disease [60].

Currently, the most used drugs to treat AD are the inhibitors of the enzyme acetylcholinesterase [61, 62], as donepezil [62–66], which acts by increasing the availability of acetylcholine in the synaptic space of cholinergic neurons [62, 67, 68]. Another drug used is memantine, which is a pharmacological antagonist of glutamatergic receptor N-methyl-D-aspartate (NMDA) [62, 69, 70]. Both drugs protect neurons against glutamate excitotoxicity, which is considered a major player in the neuronal damage observed in AD progression [70]. However, the approval of these drugs has not been based on their ability to slow down the disease progression but to improve the clinical symptomatology [62]. Therefore, only symptomatic drugs with transient benefits have been approved for clinical use in AD patients by the US Food and Drug Administration (FDA) [62].

Today, multiple therapies for AD are being studied [62, 70, 71]. The progress in the knowledge of the molecular characteristics of the disease and the availability of several animal models for study, it has open the boundaries to test and develop new therapies [61, 62, 72], for example, strategies for modifying AD progression include reducing neuroinflammation, metabolic approaches such as lipid-lowering agents, estrogen, antioxidants, anti-A β immunotherapy and recent neurotrophin-based approaches [62, 69, 72, 73]. In this scenario, and given the importance and the temporality of mitochondrial damage in AD, we believe that mitochondrial-targeted therapeutic strategies are one of the most promising areas of interest.

Mitochondria-targeted protective compounds that prevent or minimize mitochondrial dysfunction represent a potential target in the prevention and treatment of the pathogenesis of ageing-related diseases [4, 10, 74–79]. Recently, it have been reported several progresses in the use of mitochondrial therapies against several neurodegenerative diseases [44]. These strategies include preventing mitochondrial fragmentation, reducing ROS levels and increasing ATP production in the brain [4, 10, 36, 79].

2.1. Reducing defects of mitochondrial dynamics as a therapeutic target against AD

As mentioned earlier, mitochondrial dynamics is an essential mitochondrial process for the maintenance of cell viability [20, 59, 79], and apparently, it is involved in the development of many neurodegenerative diseases [44, 80]. Mitochondrial dynamics defects may result in an impaired bioenergetics and reduced mitochondrial localization in the synaptic area [20, 78, 80]. In AD, extensive researches based on the analysis of post-mortem brains, cell and animal models have reported several defects in mitochondrial dynamics [44, 81]. Therefore, increasing

mitophagy and mitochondrial biogenesis may represent a promising therapeutic strategy in the treatment and prevention of common neurodegenerative diseases [82].

Preventing defects in mitochondrial dynamics reduce neuronal injury in neurodegenerative diseases [83]. For example, in Parkinson's disease (PD) the use of different compounds that regulate mitochondrial dynamics as Mdivi-1 (mitochondrial division inhibitor-1), an inhibitor of Drp1 activity, restored dopamine release, reduced mitochondrial fragmentation and prevented cell death in dopaminergic neurons [78]. In C57BL/6 mice hippocampal neurons incubated with $A\beta_{25-35}$, the use of the antioxidant peptide SS31 decreased the levels of both mitochondrial fission proteins, Drp1 and Fis1, and managed to increase the number of healthy and intact mitochondria [44, 78]. Mitochondria plays several key roles in synaptic communication [81, 84], and to exert their synaptic roles, mitochondria must be actively transported from the soma to distal synapses zones through cytoskeleton [80, 85–87]. Interestingly, the treatment with SS31 peptide was able to reverse both the trafficking deficit and the occurrence of excess mitochondrial fission [88], restoring mitochondrial transport defects and increasing mitophagy of defective mitochondria in dopaminergic neurons [78].

Stimulation of mitophagy can also equilibrate the dysfunctional mitochondria in AD; in fact, the use of candidate drugs that increase mitophagy appears to be a promising target against many neurodegenerative diseases [89]. PINK1 is a key molecule in the signal transduction of mitophagy [90], and drugs enhancing the activity of this pathway increase the elimination of depolarizing mitochondria, which seems to be an interesting alternative for mitochondrial therapy [89, 91]. Also, the use of autophagy inducers such as rapamycin presents another tool to increase the mitophagy [90, 91]. For example, treatment with rapamycin prevented mitochondrial fragmentation and bioenergetics defects in a rat model of PD [92].

Mitochondrial biogenesis seems to be an interesting alternative to reduce or prevent mitochondrial dynamics defects in AD. Peroxisome proliferators-activated receptors gamma (PPAR γ) are nuclear receptors that, together with PGC1-alpha, participate in lipid metabolism, and they are key players in the control of energy metabolism and mitochondrial biogenesis [93, 94]. PPAR γ are significantly reduced in AD as the severity of the disease increases. [93, 95] and, interestingly, improvement of neuronal mitochondrial biogenesis through PPAR γ activation has been suggested to be a potential therapeutic target to reduce mitochondrial dysfunction in AD [94]. In fact, activation of those receptors using antidiabetic drugs called thiazolidinediones (TZDs) reduced mitochondrial dysfunction, decreased oxidative stress and improved memory impairment in AD mice models and patients with mild to moderate AD [22, 96, 97].

2.2. Improving mitochondrial bioenergetics in AD

Neurodegeneration and synaptic damage in AD are primarily mediated by defective mitochondrial function [31, 57, 59, 98]. This mitochondrial alteration, together with the progressive accumulation of $A\beta$ and pathological tau, affects mitochondrial membrane potential, respiration and energy metabolism and calcium homeostasis; promotes mPTP opening; and increase oxidative stress [57, 99]. Because the bioenergetics functions are closely related to each other,

overall treatments of mitochondrial-targeted compounds will generate a general improvement in several aspects of this organelle performance [79].

Several groups have reported that enhanced antioxidant capacity lowers the risk of development and progression of neurodegenerative diseases [60, 100–102]. At the same time, other studies have explored the use of mitochondrial antioxidants in order to reduce neurodegeneration in AD [4, 10, 103, 104]. Mitochondrial-targeted antioxidants have been developed in this regard and they are currently undergoing preclinical testing [106]. For example, treatment with CoQ10 decreased oxidative stress, A β 42 levels and β -amyloid burden, and improved cognitive impairment in AD transgenic mice [4, 10, 105]. CoQ10 is an essential biologic factor of the ETC, where it accepts electrons from complexes I and II, and also serves as an important antioxidant molecule in mitochondrial lipid membranes [10, 103].

Another example of mitochondrial targeted antioxidant is the MitoQ drug, a lipophilic cation compound with strong antioxidant actions that has been successfully targeted to mitochondria, where it reduce ROS levels, leading to the protection of neurons in AD [78, 106]. MitoQ and MitoE, both are mito-targeted compounds and they accumulate in the mitochondria, enhancing ETC function and preventing oxidation of an important lipidic component of the mitochondrial membrane called cardiolipin [78, 107].

Also, in experiments with AD mice models and neuronal cultures treated with MitoQ, it was shown that mitochondria maintain their integrity and function, decrease CycD expression and prevent mitochondrial depolarization, with an additional prevention of the caspases activation [105]. In addition, in N2a cells treated with A β , MitoQ decreased abnormal expression of mitochondrial structural genes and reduced mitochondrial population [106]. Other studies showed that in primary cortical neurons treated with A β and in the 3xTg-AD mice, MitoQ showed prevention of A β -induced oxidative stress, reduced A β accumulation, improved synaptic loss and caspase activation in the brain [105]. Additionally, in a PD pharmacological model, treatment with MitoQ inhibited the activation of mitochondrial apoptotic pathway, decreasing the levels of Bax and Drp1 protein, which suggests a possible role in the control of mitochondrial dynamics [78, 108].

Another bioenergetics feature that is significantly affected in AD mitochondria is the calcium homeostasis and the opening of mPTP [99, 109, 110]. Research has demonstrated that mitochondria isolated from the hippocampus of AD patients showed elevated levels of CypD [109, 110]. CypD is a necessary component of mPTP formation, triggering the opening of mPTP by translocation of CypD to the inner membrane [57]. Studies of the genetic deletion of CypD showed a decrease in the probability of mPTP opening and a great increase in mitochondrial capacity to buffer calcium [57, 87, 110–112].

Evidence indicates that the use of CypD inhibitors may improve mitochondrial function, and even if these inhibitors can cross the blood-brain barrier, it can have considerable potential as prevention and treatment drugs against AD [57]. Additionally, it has been shown that the treatment with CsA could have mitochondrial protective effects in neurons [99, 113]. That is, because treatment with this drug enhances mitochondrial transmembrane potential, the releasing of cytochrome c outside the mitochondria is prevented and superoxide dismutase

activity is increased [113], suggesting an important role of the mPTP in mitochondrial injury in AD [113, 114].

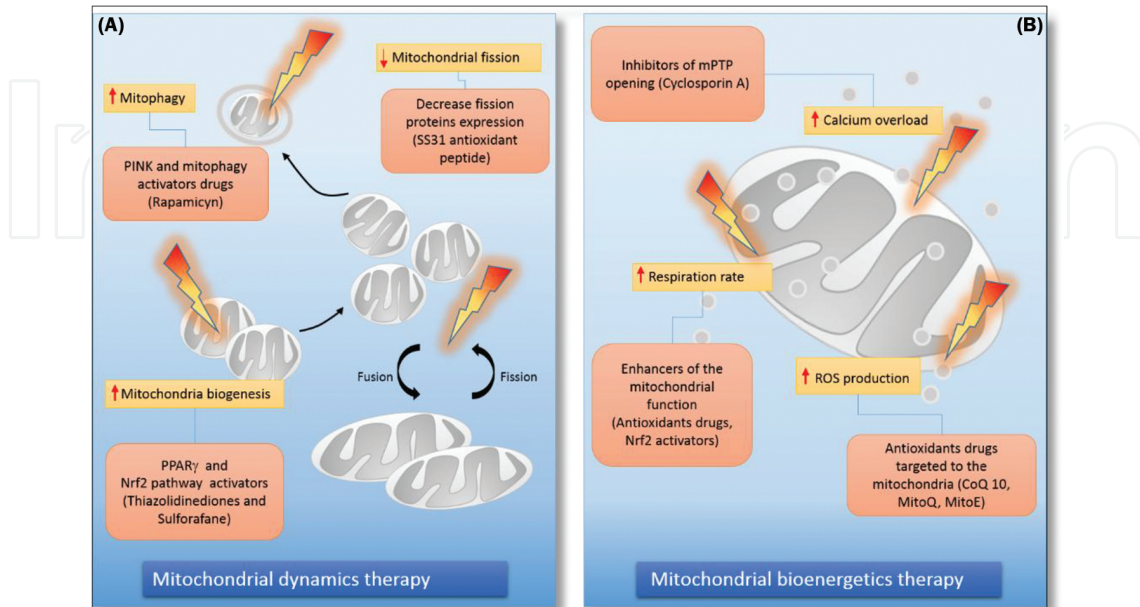


Figure 2. Improving mitochondrial health as a valid therapy for AD. (A) Mitochondrial morphology therapy. Manipulating the processes of mitochondrial dynamics has a considerable potential for treating neurodegenerative diseases. Therapies that increase mitochondrial biogenesis and fission/fusion cycle may improve mitochondrial function and decreased oxidative stress. Mitophagy is a selective autophagy process that removes dysfunctional mitochondria and maintains adequate mitochondria quality control. Increasing PINK1-mediated mitophagy improves mitochondrial integrity and function. **(B) Mitochondrial bioenergetics therapy.** Several agents that boost bioenergetics could have efficacy in improving mitochondrial function. These compounds show neuroprotective effects, which may be a useful target for treating neurodegenerative diseases. Treatment with CoQ10, MitoQ and MitoE prevented oxidative stress; cyclosporine A, a substance that blocks the opening of mPTP, prevented mitochondrial depolarization, blocks cytochrome c release and increased superoxide dismutase activity. Drugs that mediate the activation of Nrf2 induce the expression of antioxidant enzymes and improve mitochondrial function and biogenesis.

In that context, several groups have found that some compounds not only improve one aspect of mitochondrial damage but also improve several alterations at once by the activation of several pathways like nuclear factor E2-related factor 2 (Nrf2) [10, 101, 102]. The Nrf2 and the Nrf2-Are pathways have been studied in mitochondrial dysfunction and neurodegeneration [10, 115]. In response to oxidative stress, the Nrf2 translocate from the cytoplasm into the nucleus and activates the expression of several antioxidant genes [116]. Nrf2 is the principal regulator of the antioxidant cellular response and seems to be a promising target in the treatment of age-related neurodegenerative diseases [10, 101, 102, 117]. Nrf2 activation induces changes in mitochondrial structure and function, which is of particular importance under conditions of oxidative stress [10, 102, 118]. In primary murine cortical cultures, neurons lacking Nrf2 are more susceptible to oxidative stress induced by H₂O₂ and glutamate [116, 119] and overexpression of Nrf2, totally prevented these changes [116]. Furthermore, overexpression of Nrf2 can rescue neurons from mitochondrial complex II inhibition and ischemic insult in animal models of Huntington disease and stroke [116, 120, 121].

Interestingly, it has been suggested that Nrf2 may play a role in the pathogenesis of AD [102, 116]. Positive outcomes of Nrf2 activation include decreasing oxidative stress, reducing inflammation and increasing autophagy [115, 122]. Studies from human AD brains showed a decrease in Nrf2 levels in the cytoplasm of hippocampal neurons [115, 116]. In addition, studies in neuronal cultures derived from Nrf2 knockout mice show increased susceptibility to oxidative damage, as well as damage produced by mitochondrial electron transport gene complex inhibitors such as MPP⁺ and rotenone [10, 102]. Interestingly, small food-derived molecule such as sulforaphane (SFN) is a nutritional and natural activator of Nrf2 and presented neuroprotective effects and attenuated oxidative damage induced by A β ₂₅₋₃₅ [102].

Overall, improving mitochondrial defects using the strategies mentioned above could have a potential impact reducing neurodegeneration in AD (**Figure 2**).

3. Mitochondrial dysfunction can help us to predict AD?

In 2011, the National Institute of Aging (NIA) and the Alzheimer's Association proposed a revised criteria and new guidelines for diagnosing Alzheimer's disease [123]. They proposed three stages of progression of AD, preclinical AD, mild cognitive impairment (MCI) due to AD and dementia due to AD. Also, they incorporated the use of biomarker tests to corroborate the presence or absence of AD or the risk to develop it [124]. Biomarker tests will be essential to identify which individuals are in the early stages of the disease and if they should receive some disease-modifying treatment. They are also critical for monitoring the effects of treatment against AD [123, 124].

AD mainly affects memory and cognitive functions and to this date, there is no early biomarker that shows the reliability and accuracy needed to diagnose the disease [125]. Currently, AD can be diagnosed with over 90% of confidence but with invasive and expensive tools based on cerebrospinal fluid (CSF) analysis and neuroimaging with positron emission tomography, with Pittsburgh compound-B radiotracer (PET/PiB) [126]. For this reason, the diagnosis is based on neuropsychological surveys and in the exclusion of other age-related dementias only when there is an advanced cognitive impairment [127]. The conclusive diagnosis of AD is only possible in autopsy with the presence of characteristic pathological brain lesions [125, 127].

Despite that AD early treatment can slow down the progression of the disease, the ability to diagnose AD at early stages is currently limited. In the search for potential biomarkers for early diagnosis of AD, several studies have shown that a significant number of peripheral tissues, both in animal models and patients, showed from early stages of the disease an abnormal presence of markers normally associated with nerve tissue [128].

For example, deposits of A β have been reported in skin, blood vessels, glandular structures and fibroblasts in human tissue [129–131], and the presence of total and phosphorylated tau protein were detected in plasma of AD and healthy patients [132, 133]. These facts suggest that the use of peripheral tissues as a source of inexpensive and minimally invasive samples is taking force in the diagnosis of AD. Interestingly, several studies have shown that there is an

important relationship between the peripheral tissue in patients and animal models that develop AD and mitochondrial damage. Here, we show that AD peripheral tissues present different mitochondrial alterations that include mitochondrial defects in morphology, dynamics and bioenergetics.

3.1. Evidence for mitochondrial dynamics defects in AD peripheral tissues.

Mitochondrial dynamics is a complex cellular process that controls the shape, localization, turnover and function of mitochondria. As we previously discussed, several findings in patients and animal models of AD suggest that the deregulation of mitochondrial dynamics is a common feature in the disease, but may vary from case to case [134]. In the case of peripheral tissue of patients with AD, different studies indicated an altered mitochondrial morphology that could be related with changes in mitochondrial dynamics [21, 140, 141].

Several studies had proposed that the platelets could be a promising peripheral surrogate to detect AD [135], which is because these cell fragments express high levels of APP [136], tau protein [137, 138] and they have an increased GSK3 β activity, a kinase responsible for tau hyperphosphorylation [139]. More important, in studies with cytoplasmic hybrid (cybrid) cells created from human neuroblastoma cells repopulated with mitochondria from platelets obtained from sporadic AD and control donors, it was shown that cybrid cells from AD patients contained a significantly increased percentage of enlarged or swollen mitochondria, and they also present a reduced mitochondrial membrane potential [140].

Using another blood cell component, the analysis of peripheral blood lymphocytes from AD patients showed an increase in SNO-Drp1 and Fis1 and reduced Drp1 levels compared with healthy controls, PD patients and vascular dementia patients [141]. The protein expression pattern observed here suggests the presence of morphological alterations of mitochondria [141].

On the other hand, in a study with fibroblasts of sporadic AD patients, an abnormal mitochondrial distribution characterized by elongated mitochondria that are accumulated in perinuclear areas with a significant decreased in Drp1 levels was found [21]. These findings are very relevant because several publications suggest that the basic pathogenic mechanism of amyloidogenesis is similar in brain and skin fibroblasts, with an increase in the production and depositions of A β [128, 142]. Therefore, a mitochondrial deregulation in the fibroblasts of AD patients could be indicative of the neurological progression of the disease [143, 144].

3.2. Mitochondrial bioenergetics is altered in AD peripheral tissues.

Evidence of a primary role for mitochondrial damage in AD development has also been provided through post-mortem examination of AD brains, revealing oxidative stress, mitochondrial DNA damage and bioenergetic deficiencies in MCI and AD patients [145–147]. In contrast, studies on peripheral tissues of AD patients have generated inconsistent findings [135, 140, 148–174].

Different studies reviewed by Cervellati's group have reported changes in the hydroperoxide levels, a biomarker of oxidative stress, in plasma and serum of AD patients [148]. In addition,

these studies revealed that the levels of the oxidant damage markers, MDA and 4-HNE, were increased in plasma and serum of AD and MCI patients compared to controls [148]. Complementary, in blood samples of individuals with mild cognitive impairment and AD, there are evidence of mitochondrial dysfunction with decreased expression of respiratory complex genes, TOMM40, and subunits of the core mitochondrial ribosome complex [149, 150]. In addition, in human peripheral blood mononuclear cells was found an increase in oxidative stress and phosphorylated levels of Nrf2 [151].

On the other hand, several studies had shown that blood platelets from AD patients also present an increase in markers related to mitochondrial bioenergetics damage [135]. Platelets presented intracellular calcium deregulation [152, 153], an increase in oxidative damage [152, 153], a decrease in CoxIV and ATP synthase activities [154–158], and as we previously mentioned, a reduced mitochondrial potential in the cybrid condition [140]. Interestingly, in a study with cognitively normal individuals with maternal history of late onset of AD was found a reduced activity of platelet CoxIV compared to those with paternal or negative family history [159]. These findings suggest not only a possible mitochondrial peripheral biomarker but also an exclusively maternally inherited marker in humans [159].

Mitochondria isolated from AD lymphocytes showed an increase in several markers of oxidative stress [160, 161], increased susceptibility to oxidative death [162, 163], and the extent of this oxidative damage inversely correlated with dementia severity [161, 162, 164]. Also, this cell type presented alterations in proteins levels of mitochondrial-related factors categorized as energetic, structural and antioxidants such as glyceraldehyde 3-phosphate dehydrogenase (GAPDH), lactate dehydrogenase B chain and ATP synthase [164]. Furthermore, analysis of mitochondrial function in lymphocytes of AD patients showed a reduction in basal respiration and a lower ATP turnover that could finally lead to accumulate mutations in mitochondrial DNA [161].

Furthermore, a recent study determined that mitochondrial population, ATP production and respiratory function are altered in fibroblasts of patients with genetic type of AD [165]. While genetic forms of the disease do not account for the majority of cases, these observations marks an important precedent that directly links mitochondrial dysfunction in peripheral tissue of AD patients [165]. Also, in this cell type, mitochondrial dysfunction is associated with high levels of ROS and oxidative damage [166–168]. This alterations could be explained because of the lower levels of antioxidant defences observed in AD patients [169], and more interesting is the fact that these fibroblasts exhibit an alteration of the calcium buffering capacity compared to control cells [170, 171].

Based on that, recent studies have shown that fibroblasts of sporadic and familial AD present an enhanced link between the endoplasmic reticulum (ER) and mitochondria, through the mitochondria-associated ER membranes structures (MAMs) [172]. This alteration in the communication between these organelles could affect the mitochondrial dynamics and function, calcium homeostasis and production of ROS [172]. This is an interesting observation, since a recent study showed that nanomolar concentrations of oligomeric A β regulated MAM and mitochondrial calcium in neuronal cells of human AD cortical tissue, as well as in

AD mouse models [173]. These findings suggest that these subcellular structures are affected in AD and this would not be considered an isolated effect of fibroblasts culture.

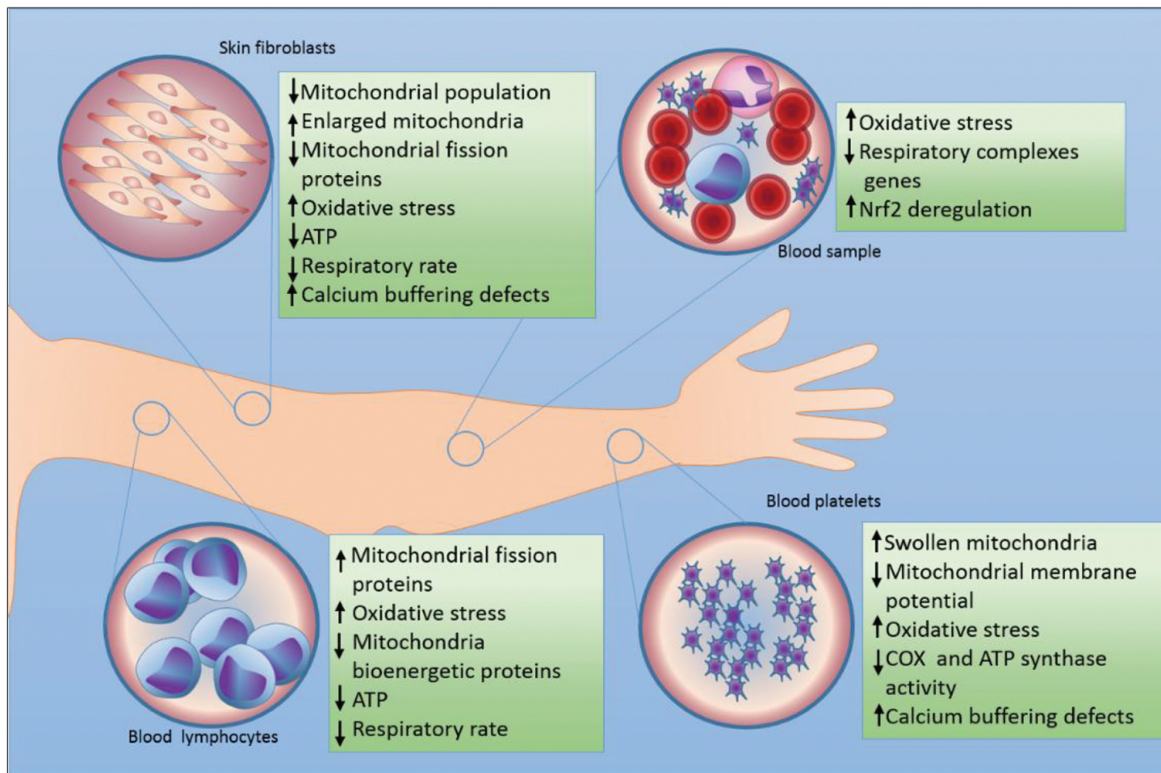


Figure 3. Mitochondrial impairment as a potential biomarker for early diagnosis of AD. Diagram shows that possible markers of mitochondrial damage could be present in blood plasma, blood cells and skin fibroblasts from AD patients. The comprehensive evaluation of mitochondrial health in these tissues could early detect neurodegenerative changes reported in AD.

Interestingly, a recent study with fibroblasts from an AD patient demonstrated that it is possible to induce the differentiation of dermal fibroblasts into neuronal cells [174]. This study demonstrated that those neurons derived from fibroblasts expressed significant levels of phosphorylated tau and presented significant changes in the expression of genes associated with AD [174]. These studies indicate that the fibroblasts of patients could be a reliable tool for obtaining physiological information that reflects the neurological state of the patients.

Peripheral biomarkers with effective action in the early detection of Alzheimer's pathology are currently unknown, but the evidence of possible markers of mitochondrial damage in blood plasma, blood cells and skin fibroblasts represents an important step in the search for an AD biomarker (**Figure 3**). Although the fact that these tissues may provide less invasive and inexpensive sources to investigate AD progression, the finding of a new biomarker would not only be important for early diagnosis but also be an opportunity to prove direct and personalized therapies in patients with AD. Future research should focus not only in search for therapies of the disease but also in the search for a good and safe model to test the effectiveness of these pathways proposed.

4. Conclusions

The focus of this chapter is to discuss the principal pathways involved in mitochondrial dysfunction seen in different models of AD. We present clear evidence that showed defects in mitochondrial morphology, bioenergetics and mitochondrial axonal transport, and how these alterations lead to an impaired neuronal communication in AD. Also, we discussed different therapeutic that reduce mitochondrial damage in AD. It is important to say that several of these therapies had probe to improve not only mitochondrial health but also the neuropathological damage in AD. Finally, we showed that those mitochondrial alterations are also present in several peripheral tissues. This is a relevant aspect to consider because it could represent a promising diagnostic method, and also an easy and accessible tool for measuring the progression and development of AD.

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