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Review

A Synergistic Dysfunction of Mitochondrial Fission/Fusion Dynamics and Mitophagy in Alzheimer's Disease

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Abstract. Alzheimer's disease (AD), the most common form of dementia in the elderly, can have a late-onset sporadic or an early-onset familial origin. In both cases, the neuropathological hallmarks are the same: senile plaques and neurofibrillary tangles. Despite AD having a proteinopathic nature, there is strong evidence for an organelle dysfunction-related neuropathology, namely dysfunctional mitochondria. In this regard, dysfunctional mitochondria and associated exacerbated generation of reactive oxygen species are among the earliest events in the progression of the disease. Since the maintenance of a healthy mitochondrial pool is essential given the central role of this organelle in several determinant cellular processes, mitochondrial dysfunction in AD would be predicted to have profound pluripotent deleterious consequences. Mechanistically, recent reports suggest that mitochondrial fission/fusion and mitophagy are altered in AD and in *in vitro* models of disease, and since both processes are reported to be protective, this review will discuss the role of mitochondrial fission/fusion and mitophagy in the pathogenesis of AD.

Keywords: Alzheimer's disease, fission, fusion, mitochondrial dysfunction, mitophagy

INTRODUCTION

Alzheimer's disease (AD), the most common form of dementia, impacts more than 35 million people worldwide and represents over 50% of autopsy cases and patients with clinical records. The incidence of the disease doubles every 5 years after 65 years of age, with the diagnosis of 1,275 new cases per year per 100,000 persons older than 65 years of age [1]. Clinically, AD is characterized by progressive memory loss, impair-

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ments in behavior, language, and visuospatial skills, and culminates in the premature death of the individual typically within 3–9 years after diagnosis. The etiology of AD is not fully understood; it has either a sporadic origin with a late onset, in which the main risk factor is aging, or an early-onset familial form with a genetic origin involving mutations in the amyloid-β protein precursor (AβPP) and presenilin 1 and 2 (PS1 and PS2) genes [2]. Neuropathologically, AD is characterized by a selective neuronal and synaptic loss and the accumulation of extracellular aberrant protein aggregates of amyloid-β (Aβ), usually referred to as senile plaques, and intracellular aggregates of hyperphosphorylated tau protein, usually referred to as neurofibrillary tangles [3]. Aβ peptides are 36 to 43 amino acids in length. Aβ_{40} is the more abundant monomeric form, but Aβ_{42} has a greater tendency to aggregate, being the most toxic form of the peptide. Aβ aggregates to form soluble oligomeric species (composed of 2 to 6 peptides) and insoluble fibrils (β-pleated sheets) [1]. It is noteworthy that currently it is believed that the soluble/oligomeric Aβ is the most toxic entity [4,5]. The number of neurofibrillary tangles reflects the severity of AD. In this form, hyperphosphorylated tau is insoluble and aggregates to form paired helical filamentous structures that are thought to impair axonal transport. Intermediate abnormal tau aggregates are cytotoxic [1]. The molecular mechanisms underlying the pathogenesis of AD remain largely unclear, however, several hypotheses are currently being investigated to uncover early events in the development of the disease. The hope is that the discovery of such early events of disease will provide a clinical opportunity for an efficient therapeutic intervention. The different hypotheses include, but are certainly not limited to: the mitochondrial cascade hypothesis [6–8], oxidative stress [9], cerebrovascular damage [10,11], tau hyperphosphorylation [12–14], and the dominating amyloid cascade hypothesis [15–17]. This article will position mitochondria center stage and suggest a mitocentric view of AD pathogenesis with other aspects as secondary byproducts of abnormal mitochondrial function. Indeed, the mitochondrial cascade hypothesis implicates these organelles in the formation of Aβ aggregates and hyperphosphorylated tau. According to Swerdlow and Khan [6,7], the authors of this hypothesis, Aβ is unlikely to be the cause of mitochondrial dysfunction in sporadic AD, but rather a downstream product of mitochondrial functional decline with aging. This is further supported by observations that found AβPP and the γ-secretase enzymatic complex present in mitochondria. Similarly, tau phosphorylation is increased by cellular energetic deficits via mechanisms involving the failure of glycogen synthase kinase 3β inhibition (for further reading, see [7]).

Several key physiological functions are attributed to mitochondria, including cellular energetic maintenance, intracellular Ca^{2+} homeostasis, and cell life and death decisions [18,19]. Since neurons have a reduced glycolytic capacity, they are highly dependent on mitochondrial energy production [20]. Unfortunately, the generation of energy by mitochondria generates toxic byproducts such as reactive oxygen species (ROS) – highly reactive, reduced species of oxygen that are responsible for the oxidative damage of lipids, proteins, and nucleic acids including the mitochondrial components themselves, predisposing to apoptotic cell death [21,22]. Such oxidative injury to mitochondria and other cellular structures accumulates with time, leading to several deleterious effects related with aging and age-related neurodegenerative disorders, as postulated by the free radical theory of aging [21–23]. Given the sensitivity of neurons to changes in mitochondrial function [24], it is not surprising that dysfunctional mitochondria are implicated in neuronal function and survival and in neuronal diseases associated with mutations in mitochondrial genes [25]. Indeed, mitochondrial dysfunction and oxidative injury have a recognized role in the pathophysiology of AD [7,26, 27], suggesting they might have an early role in the development of the disease [27–32]. However, the mechanisms underlying mitochondrial dysfunction in AD and how mitochondrial dysfunction contributes to disease pathogenesis remains unclear. Nonetheless, significant recent findings demonstrate the involvement of mitochondrial fusion/fission and mitophagy in the disease process. Mitochondrial fission and fusion processes, besides maintaining a normal mitochondrial distribution and morphology, provide a mechanism for the segregation of mitochondrial-damaged constituents waiting to undergo mitophagic elimination [33–35]. This review will discuss the role of mitochondrial fission/fusion events and their relation with the elimination of damaged mitochondria by mitophagy, emphasizing the importance of these processes in AD.

MITOCHONDRIAL DYSFUNCTION IN ALZHEIMER'S DISEASE

The mitochondrial electron respiratory chain is responsible, ultimately, for reducing molecular oxygen to

water creating a proton gradient across the membrane and electron transport through the respiratory complexes; however, during this efficient process there is a leak of some electrons, which prematurely reduce oxygen to generate ROS [36]. ROS have a dual role in the cell depending on their rate of production. Low or moderate levels of ROS can act as signaling molecules in several physiological processes, however, an overproduction of these reactive species, as occurs in many pathological situations such as AD, leads to the damage of cellular macromolecules and organelles including mitochondria [37–41]. It was recently demonstrated that an imbalance in the oxidative status of the triple transgenic mouse model of AD occurs during the Aβ oligomerization period, i.e., before the appearance of Aβ plaques and neurofibrillary tangles, corroborating the notion that oxidative stress is an early event in AD pathology [28,42]. Also, others have shown that mitochondrial dysfunction, translated as bioenergetic deficits, precedes the appearance of pathology in mouse models of AD [43]. Likewise, it has been previously shown that in the brains of AD patients a decrease in cytochrome oxidase (COX) activity, an increase in free radical generation, and a reduction in energy metabolism occur prior to senile plaque formation suggesting that mitochondrial function impairment and oxidative damage are early events in the progression of AD [27–32,44]. Oxidative damage occurs when ROS oxidize biomolecules, such as proteins, lipids, or nucleic acids, inducing alterations in their native features which result in the loss of function or gain of deleterious function. Somewhat surprisingly, fewer amyloid plaques are observed in the brains of COX-deficient AD mice when compared with the COX-competent transgenic mice. The reduction in amyloid plaques in the COX-deficient AD mice is accompanied by a reduction in Aβ_{42} level, β-secretase activity, and oxidative damage [45], with the conclusion that partial defects in COX do not increase oxidative damage nor predispose to the formation of Aβ deposits [45]. Despite these seemingly contradictory findings, several studies point out a number of probable mechanisms to explain how Aβ induces decreased COX activity. Indeed, it has been shown that Aβ is imported into mitochondria by the translocase of the outer membrane (TOM) complex [46], complexes heme groups (critical redox centers found in subunit I of COX) [47,48], and interacts with Aβ-binding alcohol dehydrogenase (ABAD) [49, 50]. Additionally, AβPP has a sequence signal that targets it to mitochondria, blocking the mitochondrial import channels (TOM40 and TIM23) and thus preventing the import of nuclear-encoded complex IV subunits [51]. In line with these data that interconnect mitochondrial respiratory deficits and Aβ neuropathology, it has been recently reported that there is a decreased density (number of mitochondria/μm^3 of cytoplasm) of succinic dehydrogenase-positive mitochondria (mitochondrial respiratory complex II) in the CA1 hippocampal region of 3xTg-AD mice [52]. However, it has come to light that Aβ is not the only player which exacerbates mitochondrial dysfunction; indeed it was discovered that Aβ and tau exert synergistic effects in the impairment of oxidative phosphorylation system in 3xTg-AD mice [53].

Mitochondria are also intracellular buffers of cytoplasmic Ca^{2+} thus having a key role in normal neurotransmission, short- and long-term plasticity, excitotoxicity and regulation of gene transcription, processes highly dependent on Ca^{2+} levels [18,54–60]. Notably, Ca^{2+} homeostasis is compromised in the presence of Aβ such that Aβ decreases the capacity of mitochondria to accumulate and retain Ca^{2+} promoting the induction of the permeability transition pore (PTP) [61–63]. Moreover, intra-mitochondrial Aβ directly interacts with cyclophilin D (CypD), providing a molecular basis for the Aβ-induced PTP opening [64].

The instability and irreparability of the brain mitochondrial genome allows for the gradual accumulation of mtDNA mutations, especially those induced by oxidative modification, notably oxidative-induced alteration of purines and pyrimidines [1]. Such mtDNA alterations have been linked to an increased incidence of AD [65,66]. In fact, there are many more sporadic mutations in the mtDNA control region in AD patients compared with control cases and several mutations in the mtDNA control region (e.g., T414G, T414C, and T477C) that are unique to AD [66]. The mtDNA control region, the only major noncoding area of the mtDNA, is typically 1122bp in length and regulates and initiates mtDNA replication and transcription [67].

All the mitochondrial function impairments outlined above exacerbate ROS production, creating a positive feedback cycle, pushing cells to an apoptotic "death spiral". Indeed, high levels of ROS promote the induction of the PTP, a nonselective, high conductance channel, that, when open, allows the release of apoptotic factors such as cytochrome c and the apoptosis-inducing factor (AIF) [68]. A recent study provided evidence of a molecular interaction between AβPP, heat shock proteins and Bcl-2, diminishing their capacity to protect against insults, which is likely to lead to a diverse array of mitochondrial disturbances including apoptosis [69].

Mitochondrial disturbances are undoubtedly associated with the pathogenesis of AD. Since these organelles occupy a strategic position in several cellular processes, it is imperative to maintain a healthy mitochondrial pool within cells, which would be accomplished by the elimination of damaged mitochondria by mitophagy, preserving intact mitochondria. The next sections of this review will be devoted to discussing whether mitochondrial fission/fusion is a process that tags damaged mitochondria to mitophagic elimination and if these processes are efficient in this disease context.

MITOCHONDRIAL FISSION/FUSION

Mitochondria are dynamic organelles that have the ability to divide and fuse with each other. The processes of fission and fusion allow the intermixing of metabolites and mtDNA, the proliferation and distribution of mitochondria, and cellular adaptation to energy demands. This dynamic feature of mitochondria is especially important in polarized cells like neurons, which have a high dependence on energy to maintain their basic physiological functions, such as neurotransmission through the generation of action potentials across the membrane [70]. Mitochondrial fission allows mitochondrial renewal, redistribution, and proliferation into synapses, whereas mitochondrial fusion facilitates mitochondrial movement and distribution across axons into the synapses [33,71,72]. Mitochondrial fusion is suggested as a protective mechanism since it helps maintain sufficient bioenergetic levels in case of injury to individual mitochondria [33,73]; additionally, the fission process is also implicated in the maintenance of a healthy mitochondrial cellular pool, since it allows for the segregation of damaged and inactive mitochondria, a feature observed by a decrease in the levels of optic atrophy 1 (OPA1) protein, thus tagging them for autophagic elimination by a mechanism not fully understood (Fig. 1) [35,74].

A group of GTPases mediates both processes of mitochondrial fission and fusion, however, the mechanisms by which they govern those processes remain to be completely elucidated. Fission-related proteins are dynamin-like protein 1 (DLP1, also referred as Drp1) and Fis1 [2,75]. DLP1 is a member of the conserved dynamin large GTPase superfamily that controls membrane fission, existing constitutively in a cytosolic pool and being recruited to the mitochondrial membrane where it is often detected as a pattern of punctated spots. The putative mechanistic action of DLP1 on mitochondrial membrane relies on the formation of a ring-like complex structure within the mitochondrial surface that constricts the organelle upon the hydrolysis of GTP, initiating fission [76]. Fis1 is a mitochondrial outer membrane protein suggested to act as a receptor for DLP1 [77]. As result of mitochondrial fission, two spherical mitochondria arise [25,70]. Regarding the proteins involved in the process of mitochondrial fusion, three large GTPase proteins assume different functions and ultrastructural locations. For the fusion of the outer membrane to occur, two mitofusins – Mfn1 and Mfn2 – interact by their coiled-coil domains, forming homo- and hetero-oligomeric complexes, thus connecting the mitochondrial outer membranes of close mitochondria [78–80]. However, the inner mitochondrial membrane also needs to be fused, and OPA1, being an inner membrane protein that faces the intermembrane space, is implicated in this event, requiring Mfn1, but not Mfn2, to mediate this process [78,81].

Mitochondria divide and fuse in response to several stimuli [25,70], however, the precise mechanisms controlling these events are largely unclear. Some studies have examined post-translational modifications of mitochondrial dynamics-related proteins such as DLP1 and OPA1. DLP1 is known to undergo post-translational modifications such as phosphorylation [82–84], ubiquitinylation [85], s-nitrosylation ([86], and sumoylation [87]. Whereas phosphorylation at Ser616 [82–84], sumoylation [87], and s-nitrosylation are known to potentiate mitochondrial fission, ubiquitinylation [85] decreases the rate of mitochondrial fission. For mitochondrial fusion to occur, the proteolytic cleavage of OPA1 into long and short isoforms is critical [88]. The machinery that cleaves OPA1 is not completely clear, nevertheless, several proteases of the inner mitochondrial membrane have been associated with its processing [80,81,88–90]. However, low mitochondrial ATP levels, the dissipation of the membrane potential across the inner membrane ($\Delta\psi_m$), or apoptotic stimuli [89] induce OPA1 cleavage, resulting in the loss of long isoforms, impairing mitochondrial fusion [80,91–93].

MITOPHAGY

Macroautophagy is a lysosomal-dependent, self-digestive, evolutionarily-conserved cellular process involved in the degradation of misfolded proteins and damaged organelles, which is also activated in situ-

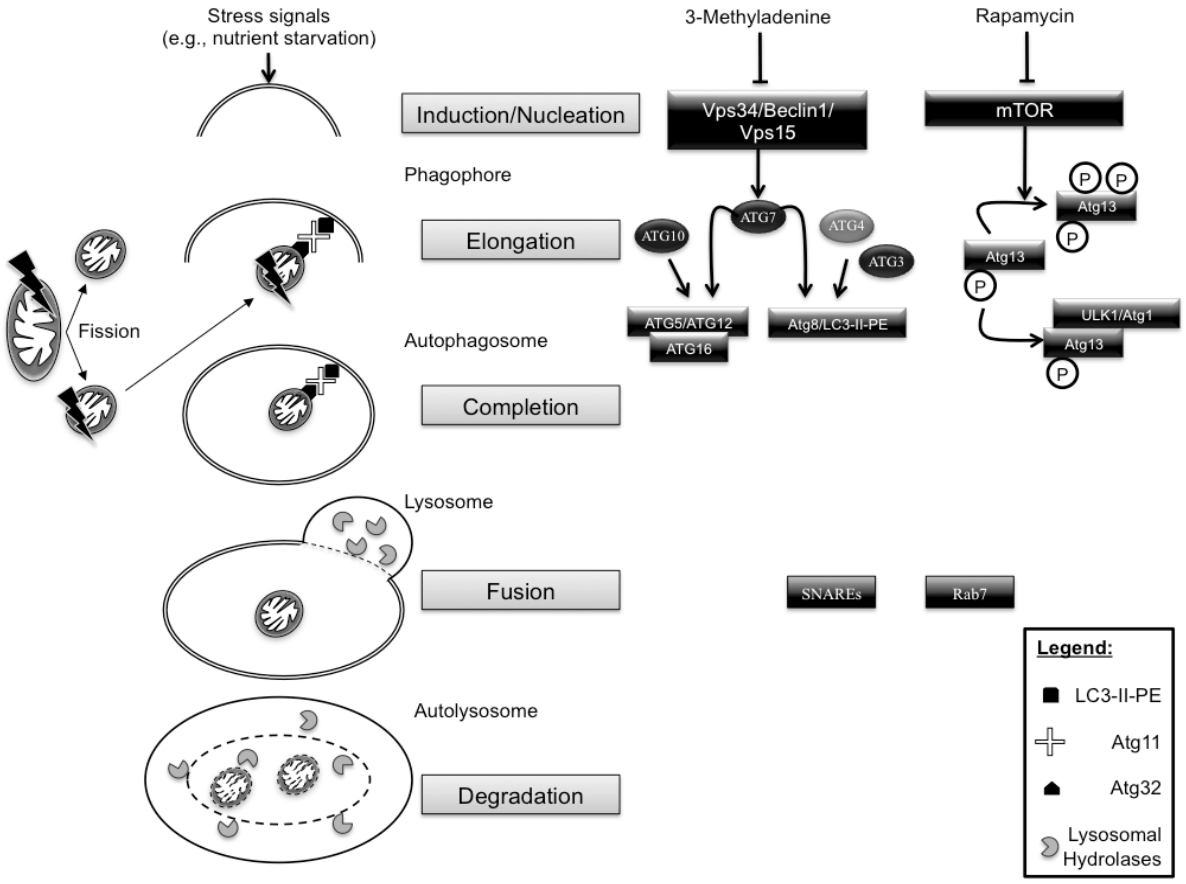

Fig. 1. Core molecular machinery involved in the formation of the autophagosome during the autophagic process. Autophagy occurs at basal levels but can also be upregulated by a number of stress signals such as starvation. Moreover, autophagy is negatively modulated by 3-methyladenine, through the inhibition of phosphatidylinositol 3-kinase (PI3K–Vps34/Beclin1/Vps15), and positively modulated by rapamycin, through its inhibitory action on mammalian target of rapamycin (mTOR). Both PI3K and mTOR are involved in the induction/nucleation phase of the formation of the autophagic vacuole (AV). At this stage an isolation membrane called phagophore is formed. PI3K activity renders the activation of two different protein conjugation systems: Atg5/Atg12/Atg16 and Atg8, the yeast homologue of the mammalian LC3. The conjugation of Atg12 to Atg5 and Atg16 is possible upon the activation of the E1-like enzyme Atg7 and the E2-like enzyme Atg10. The conjugation of LC3 to phosphatidylethanolamine (PE) is made possible by the sequential action of the protease Atg4, the E1-like enzyme Atg7 and the E2-like enzyme Atg3. mTOR activity leads to the phosphorylation of Atg13, disabling its conjugation to ULK1, the mammalian homologue of the yeast Atg1, inhibiting autophagy. When mTOR is inactive, Atg13 conjugates to ULK1. The conjugation of these proteins to the lipidic membranes enables their elongation, leading ultimately to the fusion of the edges of the forming vesicle. The fusion of the AV with the lysosome is enabled by the action of the soluble NSF attachment protein receptor (SNARE) and Rab protein, particularly, Rab7, forming the autolysosome, a degradation-competent structure. A more specific mechanism was suggested to explain the selective degradation of mitochondria, which involves the conjugation of Atg11, an adaptor protein involved in selective types of autophagy, with LC3, followed by the anchoring of Atg32, proved as a protein specifically involved in mitophagy, to Atg11. Which signals trigger the mitophagic process is still controversial, but mitochondrial fission has been suggested to play role in this process (for more detail see text).

ations of starvation to provide energy to cells. Although this review is not intended to give a detailed analysis on the autophagic pathway, it will provide a brief overview of its core machinery. During autophagy, several cytosolic components are engulfed in double-membrane structures termed autophagic vacuoles (AVs) or autophagosomes [94,95]. Although, in mammals, the origin of these membranes is not completely understood, in yeast, the proposed site for AVs formation is the phagophore assembly site (PAS). Most of the proteins involved in the assembly of the phagophore and its elongation to form an AV are located at the PAS [96,97]. It has been suggested that a possible source of autophagosomal membranes is the trans-Golgi network [98]. The formation of AVs involves a very specific molecular machinery in which only some proteins are shared with the endocytic pathway, such as the Class III phosphatidylinositol 3-kinase. How-

ever, during the maturation of AVs they can fuse with endosomes before fusing with the lysosomes [96,98]. The formation of AVs undergoes a multistep process of maturation, such as regulation/nucleation, in which a signal triggers the formation of an isolation membrane called a phagophore. The autophagosome is completely formed when the membrane edges of the phagophore fuse, followed by the last events of the maturation process, which are the dissolution of the inner membrane, fusion with lysosomes, cargo degradation, and release of macromolecules (Fig. 1) [94,95]. During the vesicle nucleation process, two kinases are involved: 1) the Ser/Thr protein kinase mammalian target of rapamycin (mTOR), with an inhibitory action on autophagy, its activity being negatively modulated by rapamycin; and 2) the Class III phosphatidylinositol 3-kinase (Class III PI3K) complex, composed of three highly conserved proteins, the protein kinase vacuolar protein sorting 15 (Vps15), the phosphatidylinositol 3-kinase Vps34, and a modulatory component named Beclin 1/Atg6, with a positive modulatory action on autophagy, where activity is negatively modulated by 3-methyladenine (Fig. 1) [99,100]. Both these molecules act upstream of autophagy-related (Atg) proteins [96,99,101]. The activity of mTOR is positively modulated by the Class I PI3K/Akt pathway [99]. The inhibitory action of mTOR on autophagy is due to the phosphorylation of the regulatory subunit Atg13, disabling its conjugation with Atg1, the yeast homologue of the mammalian unc-51-like kinase 1 (ULK1) (Fig. 1) [102]. Despite this knowledge, very little is known about this branch of the autophagic signaling pathway. Indeed, recently, more proteins were found to belong to this enzymatic complex (for further reading, see [103–106]). The role of Class III PI3K in the assembly of AVs is also poorly understood, one suggestion being that the formation of phosphatidylinositol 3-phosphate by Class III PI3K activity enables Atg proteins to bind to the membrane, since these proteins bind to this phospholipid [96,100]. There are two evolutionarily conserved ubiquitin-like conjugation systems of Atg proteins, essential for the vesicle elongation and vesicle completion processes in both yeast and mammals (Fig. 1) [107]. Atg5/Atg12 and Atg16 are one of the conjugation systems and the other is composed by lipidated LC3, the mammalian homologue of yeast Atg8 (Fig. 1) (for further readings, see [108]). Despite the relevance of these proteins in the autophagic process, recent work performed by Nishida and co-workers [109] demonstrated the existence of an alternative process, independent of Atg5, in which the lipidation of LC3 to form LC3-II does not occur. Additionally, the same authors found that this alternative process of autophagy is regulated by several autophagic proteins including ULK1 and Beclin1 [109]. This aside, ultimately, the AV fuses with the lysosome to form the autolysosome, exposing the content of the AV to the action of hydrolases. The fusion process of the AVs to the lysosomes can be inhibited with bafilomycin A1 [110] and requires two families of proteins, the soluble NSF attachment protein receptors (SNAREs) and Rab proteins, specifically, Rab7 (Fig. 1) [111,112].

The term mitophagy was coined by Lemasters to describe the selective degradation of mitochondria by autophagy [113]. Since then, the search for molecular specificities in the process of mitophagic elimination has gained attention [114]. The most exciting reports recently brought together data that suggest a molecular mechanism that tags mitochondria for mitophagy. A screening of several mitophagy-deficient yeast mutants revealed Atg32 as a new protein that is specifically implicated in the selective degradation of mitochondria by mitophagy [115]. Atg32 is an integral membrane protein localized in the mitochondrial outer membrane, docking Atg11, an adaptor protein involved in selective types of autophagy, which subsequently binds Atg8/LC3, recruiting mitochondria to AVs (Fig. 1) [115–117]. However several questions remain to be answered such as: What is the mammalian homologue of Atg32? What kind of signals trigger this molecular machinery? In the latter, it has been suggested that Atg32 intramitochondrial motif may be a sensor of mitochondrial dysfunction [117]. In yeast, a number of mitochondrial perturbations were shown to trigger mitophagy such as impairment of the oxidative phosphorylation system [118], loss of cation homeostasis by the alteration of K^+/H^+ exchanger activity [119], and increased ROS levels, as suggested by the impairment of the reduced glutathione pool [120]. Lemasters group demonstrated in mammalian cells that the induction of autophagy was preceded by the depolarization of mitochondria and PTP opening [113,121,122]. Coenzyme Q_{10} (CoQ_{10}) deficiency in human fibroblasts was shown to be associated with decreased efficiency in the electron transport chain, decreased $\Delta\psi_m$, increased ROS production, and susceptibility to PTP opening, and these features strongly correlate with increased expression of autophagy-related genes, lysosomal markers, and mitophagy [123]. This observation is not surprising since CoQ_{10}, the most predominant form of CoQ in humans, is part of the electron transport chain, accepting electrons from respiratory complexes I and II and has a described antioxidant action [30].

As already discussed, in mammalian cells, depolarized mitochondria fail to undergo fusion and fission events, which target them for mitophagic clearance [35]. Indeed, inhibition of autophagy results in decreased $\Delta\psi_m$ and fusion arrestment in rat myoblasts and human fibroblasts [124].

Altogether, these observations suggest that fission/fusion events exert a protective effect against mitochondrial dysfunction through the segregation of damaged components into a mitochondrion that undergoes mitophagy.

MITOCHONDRIAL FISSION/FUSION AND MITOPHAGY IN ALZHEIMER'S DISEASE: IS THERE A CONNECTION?

AD brains show ultrastructural alterations in mitochondrial morphology such as reduced size and broken internal membrane cristae [125,126]. Moreover, it is recognized that mitophagy exerts protective effects in a number of deleterious situations, such as CoQ_{10} deficiency [123], hypoxia [127], and rotenone exposure [128]. Little is known about mitophagy in AD brains; however, it is known that autophagy loses efficiency with the progression of the disease, mainly through a decrease in the efficiency of the lysosomal system [129–133]. As discussed previously, mTOR activity can be positively modulated by the Class I PI3K/Akt pathway. This pathway, which affects the autophagic pathway, has also been shown to be affected in AD. While some studies show that Aβ reduces Akt activity and that elevating its activity rescues cell death [134], others show that Aβ upregulates Akt phosphorylation [135]. More recently, in a *Drosophila* genetic model of AD that overexpresses Aβ, it was demonstrated that Aβ stimulates Class I PI3K activity [136]. Importantly, an increase in Akt activity is found in the temporal cortex of postmortem AD brains suggesting an upregulation of the Class I PI3K/Akt pathway in patients [137–140] and increased phosphorylation of the Akt substrate mTOR [137,141,142]. Evidence showing mitophagy in AD is very scarce; however, Moreira and coworkers [143,144] showed that there is increased mitochondrial autophagy in AD. Nevertheless several questions are still unanswered: 1) Are sequestered mitochondria in AVs being efficiently delivered to lysosomal degradation?; 2) Is increased mitophagy being protective?; 3) Does the process begin at the early stages of disease, or does it start too late to render protection to the cells?; 4) What tags damaged mitochondria for degradation, or is mitophagy not selective to damaged mitochondria?

The first and the latter questions are already being examined and answered. Based on previously discussed subjects, it is expected that despite increased mitochondria sequestration in AVs, they are probably not being efficiently degraded. Also since there are indications that mitochondrial fission and selective fusion direct the elimination of damaged mitochondria (Fig. 1) [35], it is expected that the same happens in AD. Indeed, Wang and coworkers determined the state of mitochondrial fission/fusion events in fibroblasts from sporadic AD patients [145,146] and M17 neuroblastoma cells overexpressing the Swedish variant of AβPP (AβPPswe) [147]. The imbalance induced by Aβ in mitochondrial fission/fusion proteins occurs either by post-translational modification, such as S-nitrosylation [86], or by alteration of their expression [145–147]. Whereas it is reported in fibroblasts from sporadic AD patients that DLP1 protein levels are decreased, thus impairing fission, which is translated into the development of elongated mitochondria [145, 146], at the same time it is described in M17 neuroblastoma cells overexpressing AβPPswe that besides decreased levels of DLP1, OPA1 proteins levels are decreased and Fis1 levels increased [147]. AβPP overexpression further induces a severe mitochondrial fragmentation phenotype in both M17 and primary hippocampal neurons, concomitantly with a reduction in the number of mitochondria [147]. Altogether these data suggest that mitochondrial fission is upregulated, probably in an attempt to segregate damaged mitochondria to degradation by mitophagy, which is in agreement with the observation of reduced mitochondrial number [125]. However, the destination of these fissioned mitochondria to mitophagy needs to be further clarified and more importantly, the hypothesis that mitophagy is not efficient due to an impairment of the lysosomal system remains to be addressed.

CONCLUSION

Mitochondrial dysfunction is now consensually accepted as being a feature in AD brain, however, whether it is an early causal event or a consequence of other neuropathological events remains under intense debate. Maintaining a large number of healthy mitochondria in cells is critical to cellular survival since these organelles occupy a strategic position in several key cellular processes. This is particularly important

in cells with high energetic demands such as neurons. It has been observed that mitochondria are highly dynamic organelles, dividing and fusing with each other. Both fission and fusion processes have been established as beneficial, responding to reestablish energetic levels in case of an injury to individual mitochondria or by segregating damaged mitochondrial components to a single mitochondrion that is tagged to undergo mitophagy. The role of mitophagy in AD is not currently understood, and it is unclear whether mitochondria are eventually degraded or if the process fails to efficiently eliminate mitochondria. Further knowledge about these mitochondrial events in AD will hopefully provide a window for therapeutic intervention targeting improvements in mitochondrial function.

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