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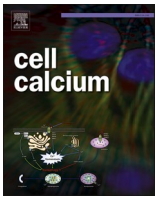

Mitochondrial Ca^{2+} signaling and Alzheimer's disease: Too much or too little?

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease, caused by poorly known pathogenic mechanisms and aggravated by delayed therapeutic intervention, that still lacks an effective cure. However, it is clear that some important neurophysiological processes are altered years before the onset of clinical symptoms, offering the possibility of identifying biological targets useful for implementation of new therapies. Of note, evidence has been provided suggesting that mitochondria, pivotal organelles in sustaining neuronal energy demand and modulating synaptic activity, are dysfunctional in AD samples. In particular, alterations in mitochondrial Ca^{2+} signaling have been proposed as causal events for neurodegeneration, although the exact outcomes and molecular mechanisms of these defects, as well as their longitudinal progression, are not always clear.

Here, we discuss the importance of a correct mitochondrial Ca^{2+} handling for neuronal physiology and summarize the latest findings on dysfunctional mitochondrial Ca^{2+} pathways in AD, analysing possible consequences contributing to the neurodegeneration that characterizes the disease.

1. Introduction

Alzheimer's disease (AD) represents worldwide the most common neurodegenerative disease and the leading cause of dementia [1]. Despite intense efforts in neurobiology and pharmacology research, to date there is no effective cure for AD and early cellular mechanisms responsible for neuronal degeneration are still largely undefined. Although the most frequent forms of the pathology have an unknown etiology (with old age as the main risk factor), autosomal dominant mutations in the amyloid precursor protein (APP), presenilin-1 (PS1) or presenilin-2 (PS2) encoding genes cause familial AD (FAD, representing < 2–3% of all AD cases) [1]. Functionally, these three proteins are involved in the pathway producing toxic amyloid β (Aβ) peptides, which accumulate in extracellular plaques (one of the histological hallmarks of the disease) in the brain of AD patients, exerting toxicity, triggering neuroinflammation and, ultimately, neurodegeneration. In particular, APP is a type-I transmembrane protein, substrate of two proteases acting in sequence, β-secretase and γ-secretase, generating Aβ peptides. PS1 and PS2 form, alternatively, the catalytic subunit of the γ-secretase complex. Importantly, most of FAD-linked mutations in the three genes shift the production of Aβ toward the 42 amino acid-long peptide, which results in a more abundant Aβ plaque deposition in diseased brains [1]. Because of that, the "amyloid cascade" represents the main widely accepted hypothesis for AD pathogenesis [2], although most clinical trials targeting Aβ have so far failed to significantly slow down disease progression [3] (but see recent promising results for Lecanemab; [4]), hinting to additional and as yet unidentified crucial pathogenic mechanisms.

More recently, other signaling pathways have been also proposed as early deregulated events in AD, leading to the formulation of different hypotheses for the pathogenesis of the disease, such as those based on tau aggregation, inflammation, infectious events, cholinergic and glutamatergic signaling pathways [5].

Importantly, from many studies performed in FAD animal models, in which one or more of the FAD-linked genes are mutated, multiple data emerged (also confirmed in human AD samples) indicating a deregulation in several intracellular signaling pathways involving the calcium ion (Ca^{2+}) [6–8]. Therefore, this second messenger might be a pivotal

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factor in triggering the neurodegenerative process that characterizes the disease (see below). In fact, in neurons, Ca^{2+} is involved in the regulation of numerous processes including neuronal excitation, synaptic plasticity, learning and memory. Thus, the regulation and maintenance of Ca^{2+}homeostasis is essential for proper neuronal function.

2. Cellular Ca^{2+} signaling in AD: molecules and (dys)function

The concentration of Ca^{2+} within the cell is finely controlled by the concerted activity of several molecules. The Ca^{2+} signaling toolkit is composed of ion channels, exchangers and pumps, most of which are located at the plasma membrane (PM), endoplasmic reticulum (ER) and mitochondria [9]. Briefly, PM Ca^{2+} channels allow the entrance of the cation into the cell from the extracellular medium upon stimulation and can be divided in three different groups, depending on their activation mechanism. In particular, voltage-operated channels (VOCs, of key importance in excitable cells such as neurons) are activated by changes in membrane potential, receptor-operated channels by the binding of specific ligands and store-operated channels by depletion of intracellular stores (mainly ER) Ca^{2+} content. Moreover, in the PM, two different Ca^{2+} extrusion systems (*i.e.*, the PM Ca^{2+} ATPase and the Na^{+}/Ca^{2+} exchanger) allow the efflux of Ca^{2+}, facilitating the restoration of resting Ca^{2+} concentrations inside the cell.

In the ER, the main intracellular Ca^{2+} store, two different Ca^{2+}-releasing channels allow, upon specific activation, the emptying of the stores and the increase of Ca^{2+} concentration in the cytosol: the ryanodine receptors (RyRs), mainly activated by increases of cytosolic Ca^{2+} concentration (a phenomenon known as Ca^{2+}-induced Ca^{2+} release; CICR), and the inositol-1,4,5-tris-phosphate receptors (IP3Rs), activated by the binding of IP3 (in turn formed upon stimulation of different G-protein-coupled receptors). Conversely, the recovery of ER Ca^{2+} levels is achieved by the activity of the Sarco/endoplasmic Reticulum Ca^{2+} ATPase (SERCA). Mitochondria also contribute substantially to the regulation of intracellular Ca^{2+} homeostasis, by taking up Ca^{2+} from the cytosol, whenever a sufficient increase in cytosolic cation concentration occurs, and then releasing it (see below for details).

As stated above, deregulation of several intracellular Ca^{2+} signaling pathways have been described in AD [6–8]. Indeed, the Ca^{2+} hypothesis for AD pathogenesis was firstly proposed by Khachaturian in 1994, and it was mainly based on the observation that different AD cellular samples presented increased resting cytosolic Ca^{2+} concentrations [10]. Then, in 2002, La Ferla further elaborated the hypothesis, suggesting that an augmented Ca^{2+} content within the ER in both AD and FAD cells, was upstream, and causal, to a dysregulated APP processing [11] and kinase activity [12,13] in diseased neurons, leading to an exaggerated toxic Aβ peptide production, tau hyper-phosphorylation and Ca^{2+}-dependent cell death [14]. The ER Ca^{2+} overload hypothesis was based on findings obtained in FAD experimental models, mainly in neurons from FAD-PS1-based transgenic mice, in which an increased agonist-evoked Ca^{2+} release from intracellular stores has been consistently measured [15–19]. In subsequent years, two possible molecular mechanisms were proposed through which, in AD cells, an ER Ca^{2+} overload is reached: a) PSs act as ER Ca^{2+} leak channels, and this function is abolished by FAD mutations [20]; b) SERCA activity, responsible for pumping back Ca^{2+} to the ER lumen once released into the cytosol, is potentiated in the presence of PSs [21].

However, these findings have been challenged [22,23] and the matter is still debated. By directly measuring ER Ca^{2+} content in different FAD models [22–26], an unchanged or a decreased ER Ca^{2+} content has been found (see [8] for a recent review), due to both an inhibitory action of FAD-PS2 on SERCA activity [22] and/or a direct sensitization of IP3R activity in the presence of FAD-PSs [23,24,27]. These data changed the original view of an ER Ca^{2+} overload in FAD neurons in a more comprehensive hypothesis of a Ca^{2+} hyper-excitability in AD [28]. In the latter, an exaggerated Ca^{2+} release, as a consequence of IP3R-gating modulation (see below for an additional mechanism) by PS mutants, is independent from the ER Ca^{2+} content. Interestingly, this feature makes FAD neurons more sensitive to excitotoxicity and network dysfunction [29–31].

The neuronal Ca^{2+} hyper-excitability is in line with a higher expression of RyRs and the enhanced RyR-mediated Ca^{2+} release (that could also depend on the potentiated activity of IP3Rs [32]) found in FAD neurons, impacting on CICR, APP processing and synaptic transmission [7,16,22,33–36].

Of note, FAD cells expressing different PS mutations, including patient-derived samples, also display a decreased Store-Operated Ca^{2+} Entry (SOCE) [17,25,37–45], *i.e.*, the pathway which refills ER with Ca^{2+} when the organelle is depleted [46]. This defect has been linked to an increased APP processing [40] and alterations of long-term potentiation [47].

Altogether, these findings strongly suggest a pivotal role for Ca^{2+} signaling in the pathogenesis of AD. Of note, AD is an aging-linked disorder and similar dysregulated Ca^{2+} phenotypes, including alterations of mitochondrial Ca^{2+} efflux (see below) [48], have been also described in aged neurons [49], further suggesting the pivotal role of a correct Ca^{2+} signaling in neuronal physiology and the possible connection between Ca^{2+} dysregulation, aging and AD.

Indeed, alterations in cellular Ca^{2+} handling influence not only APP processing and Aβ peptide accumulation, but also a plethora of key cell processes important for the correct functioning of neurons. For example, several defects in the autophagy flux have been reported in different FAD-PS models and often linked to altered Ca^{2+} signaling (reviewed in [50]). In particular, mutation-specific effects have been described, but the majority of studies converge on an impairment of the late steps of autophagy. For instance, in FAD-PS1 fibroblasts and different PS1-KO cell models, autophagosome accumulation has been reported to possibly depend on a defective lysosomal acidification [51] and/or on a reduced lysosomal Ca^{2+} handling [52,53], which might be critical to regulate autophagosome-lysosome fusion [53]. Similarly, in different cell types expressing FAD-PS2 mutations, we recently reported a defective fusion of autophagosomes with lysosomes, leading to autophagosome accumulation [54]. Mechanistically, the effect was associated with the FAD-PS2-induced depletion of ER and cis-medial Golgi Ca^{2+} content, in turn triggering lower cytosolic Ca^{2+} rises upon IP3-dependent cell stimulations, affecting the recruitment of the small GTPase Rab7 to autophagosomes and their fusion with lysosomes [54]. Of note, the reduction of RyR2 activity in FAD-APP and FAD-APP/PS1 mice (whereby RyR2 is overactivated and cytosolic Ca^{2+} levels are higher) has been shown to rescue the defective autophagy, triggered by the calcineurin-dependent inhibition of AMP-activated protein kinase [55]. These data suggest that multiple Ca^{2+} signaling pathways might converge on the modulation of autophagy in AD. Finally, defective mitophagy (*i.e.*, the selective removal of damaged mitochondria by autophagy) has been reported to be critical in AD onset (reviewed in [56]) and mitochondrial Ca^{2+} signaling has been suggested to be potentially involved in this pathway [57,57].

Moreover, a mitochondrial bioenergetic impairment has been described in neurons from different FAD-PS2 mouse models [58], due to a lower ER-to-mitochondria Ca^{2+} transfer, as a consequence of a reduced ER Ca^{2+} content in cells expressing PS2 mutants [25,38,39,58–60]. In general, mitochondria have been reported to be strongly affected in multiple AD samples and, in addition to a defective mitochondrial Ca^{2+} handling, various other organelle functions are consistently dysregulated, such as reactive oxygen species (ROS) production, organelle polarization, dynamics and axonal transport. These observations led to the formulation of the mitochondrial cascade hypothesis for AD, in which defective organelles trigger extensive neuronal oxidative stress, bioenergetic crises, synaptic dysfunction and neuronal death [61,62].

In the following paragraphs, we briefly describe the Ca^{2+}-mediated modulation of mitochondrial activities and the major players shaping mitochondrial Ca^{2+} handling, focusing on AD-associated alterations.

3. Mitochondrial Ca^{2+} signaling

Mitochondria are intracellular organelles endowed with multiple functions, the main of which are to produce energy necessary for cell homeostasis, modulate Ca^{2+} and ROS signaling, participate in key steps of lipid metabolism and regulate apoptosis. Of note, Ca^{2+} signaling finely tunes several mitochondrial functions, such as ATP production, a key process for sustaining neuronal cell energy demands (mainly relaying on oxidative phosphorylation) and activities [63,64]. In particular, mitochondrial Ca^{2+} uptake regulates energy production in an activity-dependent manner [65]. Specifically, synaptic activity requires and induces ATP synthesis [65,66] by triggering mitochondrial Ca^{2+} rises, creating a precise requirement-synthesis matching [66]. Mitochondrial energy production relies on the synergistic work of the Krebs cycle (also known as TCA cycle) enzymes, present in the organelle matrix, and the Electron Transport Chain (ETC) complexes located in the inner mitochondrial membrane (IMM), which fuel ATP synthase. This machinery works under the control of a series of cellular messengers and regulators, including Ca^{2+}. In particular, Ca^{2+} in the intermembrane space (IMS) regulates the activity of IMM-located Ca^{2+}-binding mitochondrial carriers transporting crucial metabolites, while Ca^{2+} signals in the matrix regulate pyruvate dehydrogenase, some of the TCA cycle enzymes and ATP synthase activity [63,67,68]. Importantly, while physiological elevations of mitochondrial [Ca^{2+}] are necessary to push bioenergetics, answering to dynamic cellular needs, an exaggerated and prolonged mitochondrial Ca^{2+} rise may lead to organelle depolarization and cell death, being a positive signal for mitochondrial permeability transition pore (mPTP) opening and apoptosis [69]. Moreover, neuronal mitochondria are strategically located at active zones and, thanks to their ability to rapidly and transiently take up Ca^{2+}, finely tune cytosolic Ca^{2+} rises, modulating synaptic vesicle release [70–72].

Thus, the correct Ca^{2+} handling by mitochondria guarantees neuronal functionality, sustaining bioenergetics, modulating synaptic transmission and avoiding organelle depolarization and cell death. It is therefore not surprising that any perturbation of the delicate equilibrium between mitochondrial Ca^{2+} uptake and efflux can induce cell dysregulations associated with neurodegenerative diseases [64,73]. As mentioned, a mitochondrial cascade hypothesis for AD has been also proposed [61,62] in which an extensive mitochondrial Ca^{2+} overload triggers oxidative stress, bioenergetic crises, mPTP opening, release of apoptotic factors and neuronal death. However, recent data have showed a lower mitochondrial Ca^{2+} concentration in different FAD samples ([59] and see below), still impacting cell bioenergetics and neuronal function [74]. In this context, an important issue still to address is whether mitochondrial Ca^{2+} defects have a primary and causative role in AD (thus representing a new potential therapeutic target) or they are consequences of a pathological cascade culminating in cell death. On this point, the development of tools to measure mitochondrial Ca^{2+} dynamics *in vivo* (see [75] for a review) is critical for an in-depth, longitudinal characterization of the alterations of mitochondrial Ca^{2+} signaling occurring in AD models.

As to the role of Ca^{2+} in the modulation of mitochondrial metabolism, as well as the mechanisms/molecules governing mitochondrial Ca^{2+} homeostasis, they have been extensively reviewed elsewhere [76,77]. Here, we limit ourselves to briefly mention the key players directly controlling mitochondrial Ca^{2+} uptake and release, for which it has been recently suggested a possible association with AD.

Mitochondria are equipped with a specific Ca^{2+} molecular toolkit. While the outer mitochondrial membrane (OMM) is relatively permeable to Ca^{2+}, likely thanks to the presence of the voltage-dependent anion channels (VDAC), the crossing of the IMM is tightly regulated. Specifically, the IMM-located mitochondrial Ca^{2+} uniporter (MCU) complex (MCUC) allows Ca^{2+} uptake, whereas the Na^{+}/Ca^{2+} (NCLX) and H^{+}/Ca^{2+} (mHCX, mostly expressed in non-excitable cells) exchangers [78,79] guarantee Ca^{2+} efflux. The thermodynamic force of the IMM potential created by the ETC ($\Delta\Psi$, ~ -180 mV) drives Ca^{2+} entry through the MCUC. Moreover, to efficiently take up Ca^{2+}, mitochondria have to be located in close proximity to the sources of Ca^{2+} rises, *i.e.*, intracellular Ca^{2+}-releasing channels or PM-located Ca^{2+} channels (see below). Indeed, MCU is a high capacity, low affinity ($K_d \approx 15$ μM) Ca^{2+} channel and to efficiently trigger its opening, allowing Ca^{2+} entry into the mitochondrial matrix, mitochondria have to experience high Ca^{2+} concentrations, much higher than those induced by cell stimulations in the bulk cytosol (1–3 μM) [80]. The formation of the so-called Ca^{2+} hotspots (*i.e.*, small cell areas of high Ca^{2+}concentration) is crucial for allowing mitochondrial Ca^{2+} uptake because MCUC itself is regulated by Ca^{2+} thanks to its regulatory subunits [81]. Specifically, the MCUC is formed by different components: the pore-forming subunits (MCU and MCUb), EMRE, and the two regulatory proteins MICU1 and MICU2. These latter bind Ca^{2+} and exert an opposite regulation on MCU, finely tuning its opening [81]. Remarkably, MCUC composition differs among tissues. In particular, in the central nervous system, a third regulatory subunit, called MICU3, is abundantly expressed and acts as an enhancer of MCU activity (see *De Mario A.* et al. in this SI for further details).

Of note, the positioning of mitochondria within specific subcellular regions is an additional, potent modulator of mitochondrial Ca^{2+} signaling. In particular, the OMM physically interacts with other intracellular membranes hosting Ca^{2+} channels, *e.g.*, ER membranes or PM, generating micro-domains in which Ca^{2+} can reach very high concentrations, upon cell stimulations. Specifically, the domains of juxtaposition between ER and mitochondria (mitochondria-ER contact sites, MERCS; also called mitochondria-associated membranes, MAMs), have been deeply studied in the recent years and shown to be crucial not only for Ca^{2+} transfer between the two organelles, but also for lipid synthesis, inflammatory response, autophagy and apoptosis induction [82–84]. The presence of IP3Rs on ER membrane is critical to generate, near the mouth of these channels, high-concentration Ca^{2+} microdomains sensed by nearby mitochondria, allowing an efficient IP3-dependent ER-mitochondria Ca^{2+} transfer in most cell types [80,85–89]. Similarly, mitochondria can detect high-concentration Ca^{2+} microdomains formed upon opening of RyRs, though the contribution of this pathway to mitochondrial Ca^{2+} uptake has been mostly studied in cardiomyocytes/muscle cells [90–93] and scarcely investigated in neurons. Different molecules contribute to MERCS modulation, with some of them being ubiquitous, whereas others (such as the neuronal protein PDZ domain containing 8 (PDZD8), [94]) are cell-specific [83,84]. Of note, PS2, one of the three proteins mutated in FAD, is also a crucial modulator of MERCS (see below), suggesting these latter, as well as mitochondrial Ca^{2+} signaling, are altered in AD.

As to the mitochondria-PM juxtaposition, it has been much less investigated. In most transmission electron microscopy studies in mammalian cells, mitochondria hardly locate at a distance $<$ 50–300 nm from the PM, likely because of the presence of cortical actin cytoskeleton and/or of interleaving ER stacks ([88], reviewed in [95]). Nevertheless, in specific cell types, such as cardiac myocytes [96] or mouse photoreceptors [97], regions of very close mitochondria-PM apposition ($<$ 10 nm) were described, though the molecules mediating this tethering are still unknown. Recently, it has been suggested that mitochondria can be recruited close to PM in response to stressors linked to specific metabolic conditions, and this pathway might be functional to transfer mitochondria between neighbouring cells by tunneling nanotubes. Interested readers are referred to a recent review [95]. Here, we limit ourselves to briefly mention the functional significance of the cross-talk between mitochondria and PM as far as mitochondrial Ca^{2+} uptake is concerned. In particular, evidence has been provided suggesting that, in excitable cells, Ca^{2+} hot-spots are generated near the OMM upon PM depolarization and VOC-mediated Ca^{2+} entry [86], as well as upon N-methyl--D-aspartate receptor-mediated Ca^{2+} influx [98]. More debated is the capacity of mitochondria to take advantage of their physical location to take up Ca^{2+} during SOCE activation. In certain cell types, such as in T cells, the contribution of mitochondria in buffering SOCE-linked

cytosolic Ca^{2+} rises is well known [99]. Moreover, mitochondria are known to be critical in the regulation of SOCE [100–102]. However, in another report, SOCE activation in HeLa cells was not associated with the generation of Ca^{2+} hot-spots on the OMM [86], possibly because of the limited accessibility of mitochondria to ER-PM contacts. Nevertheless, consensus has been reached on the mutual relationship between mitochondrial Ca^{2+} uptake and Ca^{2+} influx through the PM. To the best of our knowledge, the relevance of this mitochondria-PM axis has not been explored in the context of AD models. However, it is tempting to speculate that the reported, AD-linked alterations of SOCE (see above), as well as of mitochondria positioning at synapses whereby VOCs are abundant [103], might substantially impact on mitochondrial Ca^{2+} signaling.

Below, we provide a brief overview of the most frequent perturbations of these pathways observed in AD, as well as discuss their possible role in disease progression.

4. Alterations of mitochondrial Ca^{2+} handling in AD

Although the link between Ca^{2+} signaling dysregulation and AD has been known for several decades, the experimental evidence indicating a remodeling of the mitochondrial Ca^{2+} molecular toolkit during AD is much more recent. Several studies reported that mitochondrial [Ca^{2+}] is overall higher in AD samples, although increasing evidence has highlighted that this process is not caused by just one mechanism. Rather, it is a consequence of numerous altered regulatory events, including reduction in the expression of different cytosolic Ca^{2+}-binding proteins [104–107] and alterations of mitochondrial Ca^{2+} influx and efflux capacity [108,109].

Recent studies, although contradictory, have described changes in the expression of the main mitochondrial Ca^{2+} transporters involved in the influx and efflux Ca^{2+} pathways. On one hand, genes related with mitochondrial Ca^{2+} influx, including those for the MCUC, are downregulated in samples from AD patients. Moreover, those samples that showed a decrease in the expression of MCUC also exhibited an increased NCLX (the main Ca^{2+} exchanger in mitochondria) expression [108]. These findings could appear contradictory, since a reduction in the ability of mitochondria to take up Ca^{2+} and an increase in the mitochondrial Ca^{2+} efflux should result in a lower mitochondrial Ca^{2+} concentration, whereas a mitochondrial Ca^{2+} overload was observed in neurons of APPswe/PSEN1ΔE9 transgenic mice. This suggests that the remodeling of the molecular apparatus for mitochondrial Ca^{2+} handling might represent a counteracting process to avoid mitochondrial Ca^{2+} overload, in turn triggered by exaggerated cytosolic Ca^{2+} levels, which might associate with Aβ deposition [108].

Other studies, on the other hand, performed in samples from sporadic AD patients, have described a reduction in the expression of different subunits of the MCUC, including the negative regulatory components MICU1 and MCUB [109], leading to an increased MCUC activity. The same AD samples also showed a downregulation of NCLX, therefore resulting in a reduced mitochondrial Ca^{2+} efflux [109]. In this case, the changes in the expression of these mitochondrial Ca^{2+} handling molecules would trigger directly a mitochondrial Ca^{2+} overload, instead of being an adaptation to high levels of cytosolic Ca^{2+} (Fig. 1).

Recently, it has been demonstrated that several microRNAs (miRNAs) are deregulated in AD. Particularly, mitochondria-linked miRNAs seem to be highly affected in AD, including miR-7 and miR-29a, both molecules acting as regulators of VDAC expression (reviewed in detail in [110]), favoring the passage of Ca^{2+} through the OMM to reach the MCUC (Fig. 1).

In addition to change the expression level of mitochondrial Ca^{2+} handling proteins, AD related proteins can also modulate mitochondrial Ca^{2+} signaling by different pathways. For example, Aβ peptides in neurons cause an increase in mitochondrial Ca^{2+} influx that can be reverted by blocking MCUC, suggesting the need of a fully functional MCUC for Aβ to induce changes in this pathway [108]. Moreover, direct exposure of neurons to the protein tau (which is prone to aggregation), or the presence of a neurodegeneration-linked mutation in the Microtubule-Associated Protein tau gene *(MAPT)* in human neurons derived from induced pluripotent stem cells, inhibits NCLX activity,

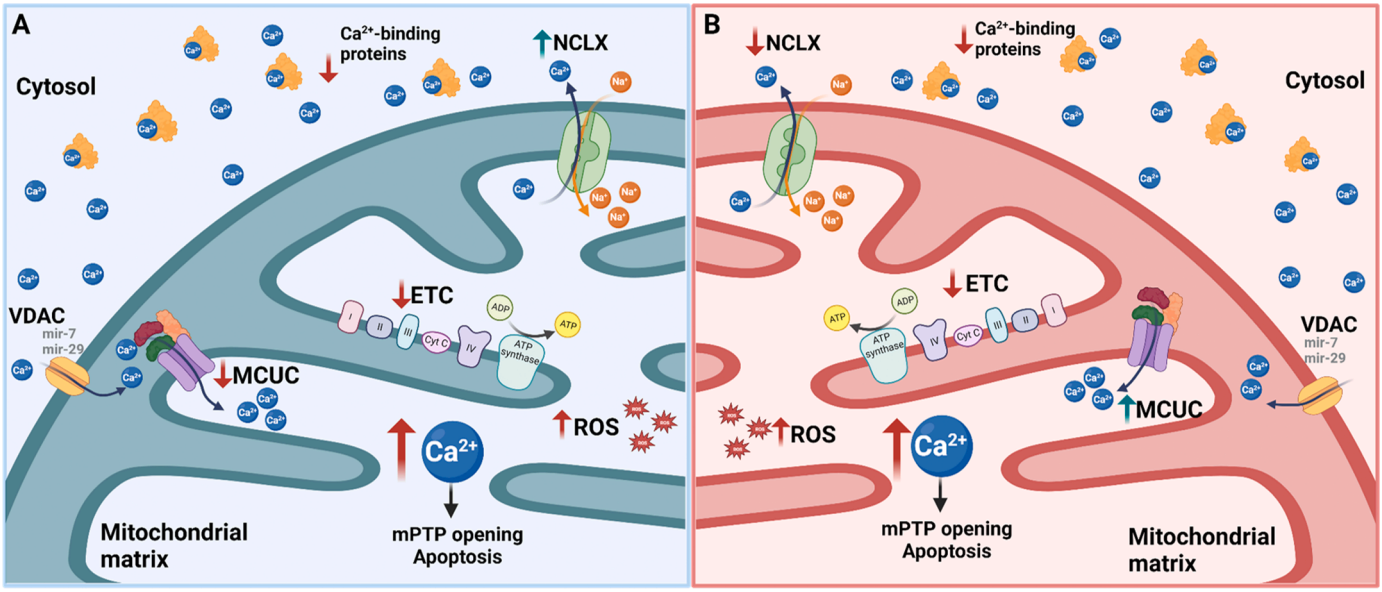

Fig. 1. Mitochondrial Ca^{2+} molecular toolkit remodeling in AD. Mitochondrial Ca^{2+} dysregulation is an early event in AD, with mitochondrial Ca^{2+} overload as a final outcome. Importantly, a remodeling of Ca^{2+} handling molecules in the organelle has been described. Panel A represents a possible scenario in AD in which an increase in free cytosolic Ca^{2+}, due to a decrease in the expression of Ca^{2+}-binding proteins, causes the downregulation of MCUC and the upregulation of the NCLX. Although counterintuitive, the consequent reduction in mitochondrial Ca^{2+} influx and the increase in the organelle Ca^{2+} efflux do not correlate with a lower mitochondrial Ca^{2+} concentration, but with a higher value. This phenomenon could be explained as a compensatory mechanism of the cells to try and reduce the amount of Ca^{2+} entering mitochondria driven by the increased cytosolic Ca^{2+} concentration. In panel B, another model is represented in which the AD phenotype correlates with an increase in the expression and activity of the MCUC and a reduction of the NCLX. In this case, the increased cytosolic Ca^{2+} concentration, together with the potentiated mitochondrial Ca^{2+} influx and the blunted Ca^{2+} efflux would be the direct cause of mitochondrial Ca^{2+} overload.

causing a reduction in mitochondrial membrane potential and increasing cell vulnerability to death [111].

The relevance of mitochondrial Ca^{2+} dysregulation (specifically, the changes in the mitochondrial influx and efflux Ca^{2+} pathways) in the symptomatology of AD has been highlighted by different studies, that have tried to genetically or pharmacologically rescue the defective activity of MCUC and NCLX. For example, the downregulation of MCU in hippocampal neurons improves memory performance in 3xTg-AD mice (triple transgenic for APP, PS1 and MAPT; [112]), by ameliorating synaptic structure and function, reducing neuroinflammation and improving mitophagy [57]. Also, the inhibition of mitochondrial Ca^{2+} uptake through pharmacological interventions reduces amyloidosis and protects against dementia [113]. Finally, the dysregulation of mitochondrial Ca^{2+} efflux has been reported to affect learning and memory pathways, increasing also amyloidosis. Indeed, all these defects could be rescued by the manipulation of NCLX expression level in 3xTg-AD mice [109].

5. ER-mitochondria contacts as modulators of mitochondrial Ca^{2+} signaling in AD

The close juxtaposition of mitochondria with ER is a key regulator of mitochondrial Ca^{2+} uptake, as detailed above. Therefore, alterations of the ER-mitochondria axis, frequently reported in different AD models, are endowed with the potential to substantially impact mitochondrial Ca^{2+} signaling in this neurodegenerative disorder.

In most AD models, a strengthened ER-mitochondria connectivity has been reported [59,60,114–116], though more rarely no difference, or even a reduction, in this parameter has been observed in other models and/or different stages of disease-progression [117–119]. Importantly, however, consensus has been reached suggesting that key cellular pathways, leading to AD-associated neurodegeneration, converge at MERCS (Fig. 2). For instance, PSs (both PS1 and PS2), APP, the APP-processing machinery (including active β- and γ-secretase), as well as Aβ itself, are enriched/present at MERCS [120–122], hinting a mutual relationship between Aβ processing (*i.e.*, a key pathway involved in AD onset/progression) and MERCS modulation. The precise molecular mechanism linking MERCS to Aβ has not been completely understood. However, the activity of Mitofusin 2 (Mfn2, either favoring [114] or inhibiting [60,123] MERCS formation in AD models) is likely involved, because its downregulation decreases γ-secretase activity [114,123]. Moreover, it has been recently demonstrated that, in neurons differentiated from FAD-APP-expressing human neuronal progenitor cells, MERCS assembly (modulated by Sigma-1 Receptor) promotes the trafficking of palmitoylated APP to the cell surface. This favors its β-secretase-mediated cleavage and Aβ generation at neuronal processes [124], further suggesting that ER-mitochondria interface might be critical for Aβ turnover (Fig. 2).

In addition, MERCS are lipid-raft-like platforms whereby essential steps of lipid synthesis/metabolism take place [125], and APP processing is known to be modulated by the composition of cholesterol-rich raft domains where it is enriched [126–128]. Notably, early alterations of lipid metabolism, including hypercholesterolemia and accumulation of lipid droplets, have been consistently reported in AD models and patients [114,122,129–133]. Remarkably, the ε4 variant of apolipoprotein E (ApoE, a cholesterol/lipid transporter) represents the most frequent risk factor for sporadic AD onset and progression [134]. These observations suggest the intriguing possibility that perturbations of ER-mitochondria coupling might be linked to alterations in lipid homeostasis and contribute to AD pathogenesis (Fig. 2). However, whether changes in MERCS dynamics underlie dysregulated lipid homeostasis in AD, or *vice versa* lipid imbalance alters ER-mitochondria communication

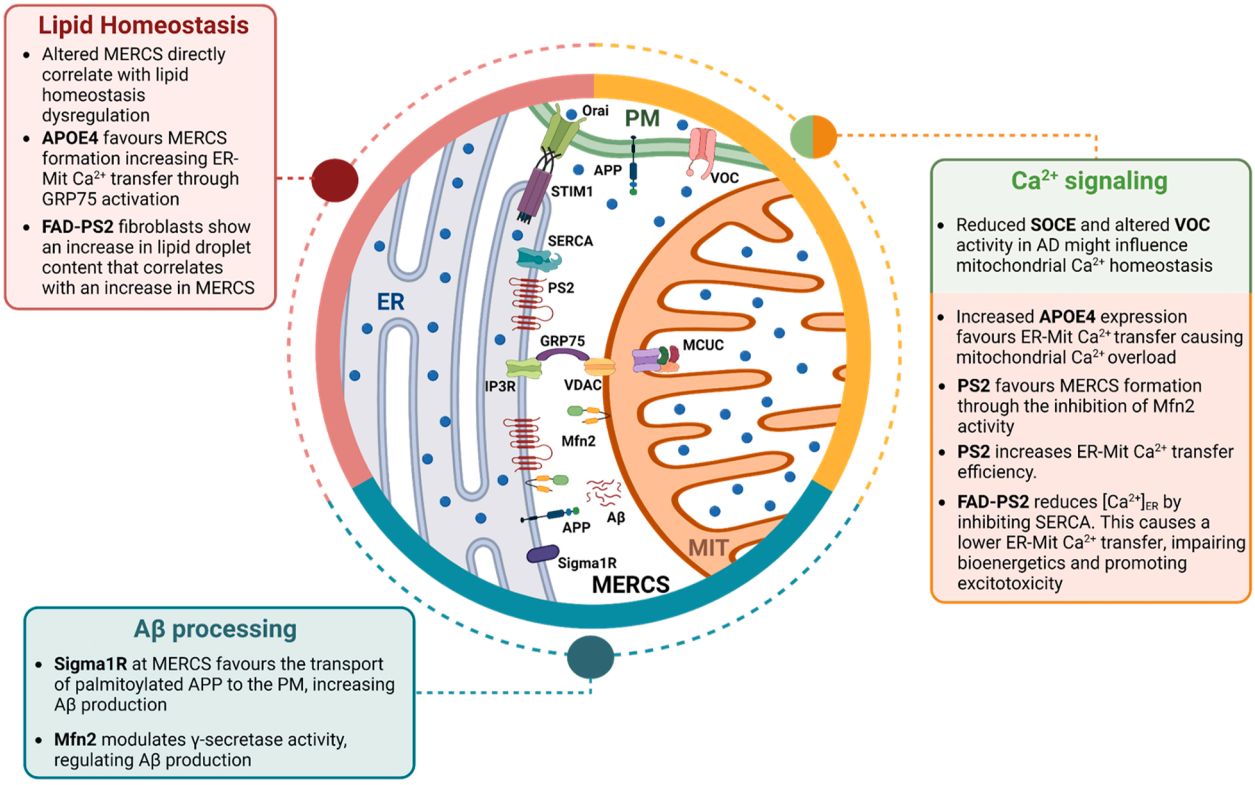

Fig. 2. Organelle contacts and mitochondrial signaling in AD. Mitochondria-ER contact sites (MERCS) play an essential role in regulating different processes including lipid homeostasis, ER-mitochondria Ca^{2+} transfer and Aβ processing. Changes in the coupling between ER and mitochondria associated with AD cause alterations in all of these processes, supporting the idea that these two events correlate. Therefore, MERCS act as central regulatory domains where lipid homeostasis and Ca^{2+} signaling modulate each other, contributing to the physiopathology of AD. Mitochondria-PM contacts also regulate mitochondrial Ca^{2+} signaling, though direct experimental evidence suggesting possible AD-linked alterations in this pathway is still lacking.

(as well as whether/how this MERCS-lipid crosstalk impacts on Ca^{2+} signaling), is not clear. For instance, recent evidence suggests that ApoE4 expression increases MERCS formation and enhances glucose regulated protein 75 (GRP75)-mediated Ca^{2+} transfer from ER to mitochondria through the IP3R-GRP75-VDAC axis [135], potentially triggering mitochondrial Ca^{2+} overload [136]. Moreover, in human fibroblasts from a FAD-PS2-N141I patient, whereby MERCS are upregulated, lipid droplets are more abundant and the efficiency of ER-to-mitochondria Ca^{2+} transfer is higher compared to control fibroblasts, the expression of a cytosolic, dominant-negative fragment of PS2 (corresponding to its large cytosolic loop) rescues all these parameters [132], further suggesting they might be interdependent.

Nevertheless, despite the large number of studies investigating ER-mitochondria interface in AD, just a few of them directly tested whether and how alterations of this inter-organelle crosstalk affect Ca^{2+} shuttling between the two organelles. Among them, our group extensively investigated the direct role of PSs and of their FAD-linked mutants, in the modulation of the physical and functional ER-mitochondria coupling. We found that endogenous PS2, but not PS1, favors the association between these two organelles [59,60,115,137]. The effect depends on the capacity of PS2 to bind and negatively modulate the activity of Mfn2 [60,138]. Importantly, expression of two different FAD-PS2 mutants (specifically, PS2-N141 and PS2-T122R) and the catalytically inactive PS2-D366A mutant (not linked to FAD), but not of FAD-PS1-A246E, increases ER-mitochondria tethering [59,60,115]. This suggests that PS2 interactome/structure (which is likely modulated by the presence of FAD-linked or artificial/catalytically-inactivating mutants) might be important for this activity.

As far as mitochondrial Ca^{2+} signaling is concerned, the effects of FAD-PS2 mutants is peculiar. On the one hand, consistently with their effect on ER-mitochondria tethering, they increase the efficiency of ER to mitochondria Ca^{2+} transfer, by favoring the formation of Ca^{2+} hotspots on the OMM [59]. However, they dampen ER Ca^{2+} content (mostly by inhibiting SERCA pump activity, [22]), thus reducing the overall amount of Ca^{2+} transferred from ER to mitochondria upon IP3R activation [58–60]. The net effect is a lower mitochondrial Ca^{2+} uptake, which has important bioenergetic consequences in FAD-PS2 expressing models [58] and might associate with AD-linked neuronal excitotoxicity [58,74] (Fig. 2).

In other AD models, either a reduced or increased ER-mitochondria Ca^{2+} coupling has been observed. For instance, in Purkinje cells from FAD patients, the PS1-E280A mutant has been reported to reduce MERCS, as well as the expression of proteins mediating Ca^{2+} shuttling [117], but ER-mitochondria Ca^{2+} transfer has not been directly tested. Similarly, in hippocampal neurons from FAD-APP-expressing transgenic mice, reduced very close MERCS (ER-OMM distance < 10 nm, referred to as lipid MERCS), but similar intermediate distance MERCS (10–20 nm, possibly involved in Ca^{2+} transfer) were retrieved [118], yet Ca^{2+} shuttling was not evaluated. Although definitive experimental evidence has not been provided, very close MERCS are thought to be involved in lipid metabolism/exchange between ER and mitochondria, because lipids cannot freely diffuse in the cytosol and require the activity of specialized proteins, transferring these molecules between juxtaposed membranes [139]. Instead, intermediate distance MERCS are more likely involved in Ca^{2+} shuttling, because the head of tetrameric IP3Rs span in the cytosol for at least 10 nm [140] (*i.e.*, it hardly accommodates whereby the distance between ER and mitochondria is < 10 nm) and Ca^{2+} can diffuse in the aqueous cytosolic environment, easily crossing this range of distances.

In the mouse neuroblastoma cell line N2A overexpressing FAD-APPswe, reduced close MERCS and mitochondrial Ca^{2+} uptake upon ER Ca^{2+} release have been observed, though this latter could also depend on the lower mitochondrial respiration and membrane potential observed by the same group [119]. Conversely, in most cases, direct exposure to Aβ oligomers has been reported to increase ER-mitochondria juxtaposition and favor the efficiency of inter-organelle Ca^{2+} transfer [116,141]. More MERCS were also observed in the hippocampus of two different FAD-APP knock-in mouse models [142]. In addition, Aβ42 toxicity has been shown to be mitigated by decreasing PDZD8-mediated MERCS in an AD fly model [143].

As to the possible role of tau protein, few studies are available. Mice overexpressing P301L tau mutant display increased ER-mitochondria tethering in motor neurons [144]. The expression of a caspase 3-cleaved tau (2N4RΔC20; able to induce fibrillation and seeding of endogenous tau) increases close MERCS and the efficiency of ER-to-mitochondria Ca^{2+} transfer [145], though this latter parameter is masked by reduced ER Ca^{2+} content (similarly to what has been found in FAD-PS2-expressing samples, see above).

6. Conclusion

Overall, recent evidence has been provided suggesting that the maintenance of mitochondrial Ca^{2+} homeostasis might be critical to prevent AD onset, or attenuate its progression. Nevertheless, the information about the mechanisms underlying the remodeling of mitochondrial Ca^{2+} handling is still insufficient and sometimes contradictory. In our opinion, most of the discrepancies described in literature could be due to the different methods used to measure Ca^{2+} [75], the specific AD models and, importantly, the different stages of the disease under investigation. Supporting this concept, exposure to Aβ oligomers has been reported to increase ER-mitochondria juxtaposition both in young and aged rat hippocampal neurons, but to enhance Ca^{2+} shuttling only in young neurons, because in the aged ones the transfer is almost completely suppressed by mitochondrial depolarization and higher ROS generation [141].

Some contradictory results might be puzzling because they complicate the development and testing of possible AD-modifying therapies, yet they warn about the need to further deepen our knowledge about the complex bi-directional crosstalk between mitochondrial Ca^{2+} signaling and the cell pathways closely linked to AD onset/progression (such as MERCS dynamics, Aβ processing, lipid metabolism and mitochondrial bioenergetics). Encouragingly, different MERCS-focused drugs have been recently tested *in vitro* [146,147] (for a recent review, see [148]). We foresee that the search of new molecules aiming at restoring mitochondrial Ca^{2+} homeostasis will open a new interesting line of action in the attempt to treat AD.

CRediT author statement

All the authors wrote and edited the manuscript.

Declaration of competing interest

Authors report no conflicts of interest.

Data availability

No data was used for the research described in the article.

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