

Review

MAMs as a promising therapeutic strategy for age-related neurodegenerative diseases

Giacoma Galizzi^{1*}¹Institute for Biomedical Research and Innovation - National Research Council (IRIB-CNR), Palermo, Italy

[Received October 31, 2025; Revised December 2, 2025; Accepted December 3, 2025]

ABSTRACT: Aging is a natural process leading to the slow and progressive deterioration of numerous physiological functions. It is the main risk factor for several neurodegenerative diseases. Mitochondria-associated membranes (MAMs) or mitochondria-ER contacts (MERCs) are essential and dynamic sites of contact between mitochondria and the endoplasmic reticulum (ER) and are involved in numerous cellular processes, such as calcium (Ca^{2+}) homeostasis, reactive oxygen species (ROS) production, autophagy, inflammation, mitochondrial dynamics, apoptosis, lipid biosynthesis, and trafficking. As a result, they play a significant role in maintaining cellular functionality regulating metabolism and ensuring proper stress responses. Recently, MAMs have been widely investigated to understand their critical role in cell physiology as well as in different pathological conditions. Increasing evidence indicates that alterations in ER-mitochondria communication contribute to aging and the development of age-related diseases. However, the cellular mechanisms underlying this link remain unclear. Understanding how these interactions change with age could provide further insights into the aging process and the mechanisms underlying age-related diseases, suggesting potential new therapeutic strategies. This review summarizes the current knowledge on MAM biology, focusing on their role in the pathogenesis of age-related brain disorders. Their therapeutic potential in limiting the progression of some neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis, and slowing the physiological aging process are also explored.

Keywords: aging, mitochondria, Alzheimer's Disease, neurodegeneration, mitochondria-associated membranes (MAMs)

INTRODUCTION

Aging is a slow and inevitable process leading to the gradual decline of numerous physiological functions, and it is the main risk factor for several pathological conditions, such as neurodegenerative diseases, metabolic disorders, cardiovascular diseases, and cancers [1].

An increasing amount of data has indicated that mitochondrial dysfunction and endoplasmic reticulum (ER) stress play a pivotal role in both aging and age-related disorders [1]. Mitochondria, often referred to as the powerhouse of the cell, are responsible for producing adenosine triphosphate (ATP) through oxidative phosphorylation. They also play essential roles in Ca^{2+} homeostasis, phospholipid and heme synthesis, reactive

oxygen species (ROS) regulation, apoptosis, and cellular death [2]. Mitochondrial dysfunction is characterized by decreased ATP production, oxidative stress, increased release of pro-apoptotic factors, and impaired Ca^{2+} homeostasis [2].

The ER plays a critical role in protein synthesis, lipid metabolism, and Ca^{2+} storage. During aging, the ER experiences stress, activating the unfolded protein response (UPR) which can trigger apoptosis if it is not resolved [3].

The physical and functional interaction between mitochondria and the ER, known as mitochondria-associated membranes (MAMs), facilitates bi-directional communication between these two organelles [4, 5]. This complex relationship plays a significant role in several

*Correspondence should be addressed to: Dr. Giacoma Galizzi, Institute for Biomedical Research and Innovation - National Research Council (IRIB - CNR), Palermo, Italy. Email: giacoma.galizzi@irib.cnr.it.

Copyright: © 2025 Galizzi G. This is an open-access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

cellular processes, including lipid synthesis and trafficking [6-8], Ca^{2+} signaling [9, 10], mitochondrial dynamics [11, 12], ROS production [13], and the regulation of autophagy, inflammation, and apoptosis, [14-16].

Interestingly, all these mechanisms are dysregulated during aging and in age-related pathological conditions such as neurodegenerative diseases [4, 17-19], insulin resistance, and obesity [20, 21], suggesting a role for MAMs in the pathogenesis of these diseases [22-25] (Fig. 1).

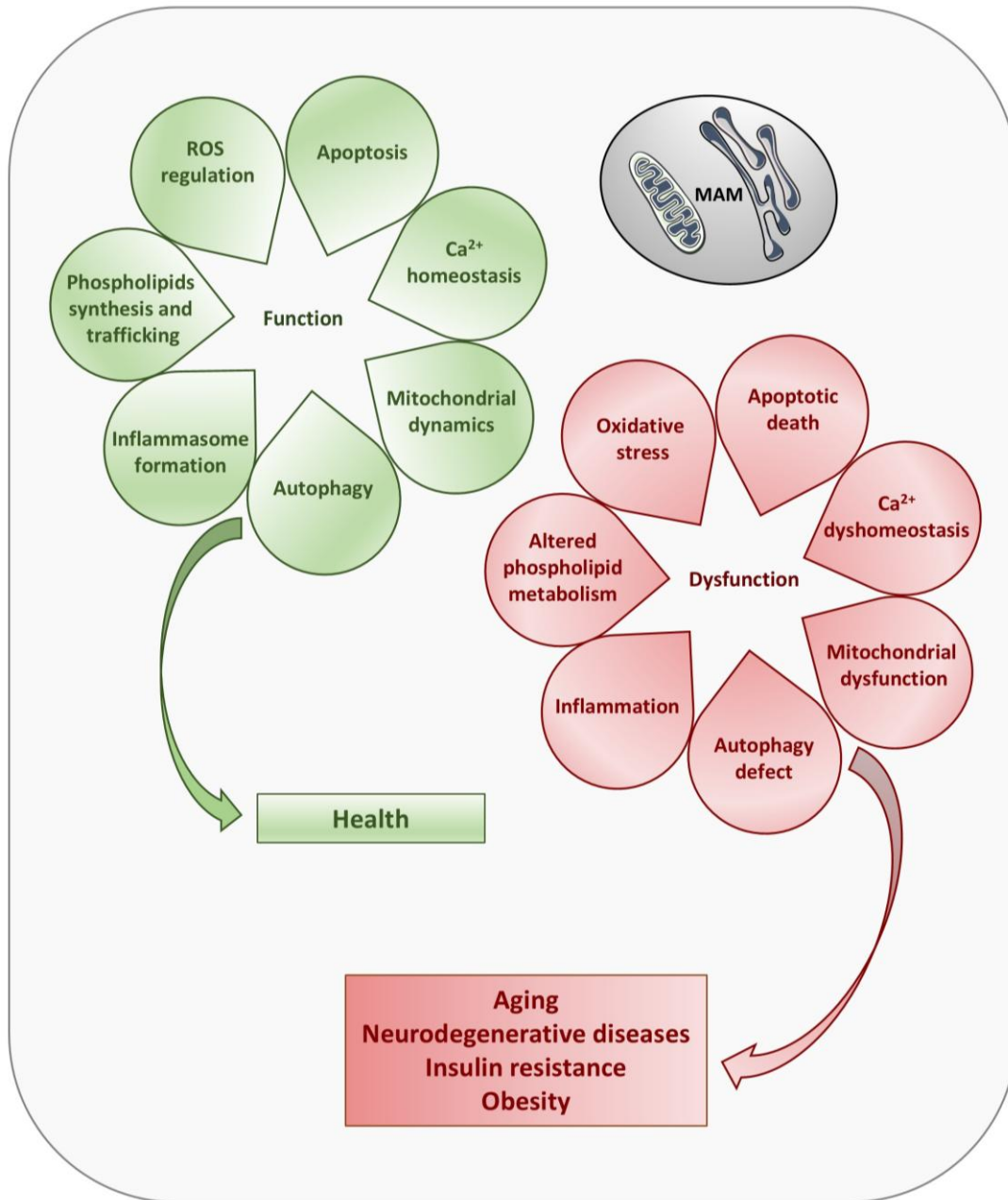


Figure 1. Impact of MAM functions and dysfunctions in cellular homeostasis. The interaction between the ER and mitochondria regulates different cellular functions, including mitochondrial dynamics, phospholipids biosynthesis and trafficking, autophagy/mitophagy, Ca^{2+} signaling, inflammasome formation, ROS production and apoptosis. The disturbance of this interaction compromises these processes inducing mitochondrial dysfunction, Ca^{2+} dyshomeostasis, altered phospholipids metabolism, autophagy defects, neuroinflammation, oxidative stress, which contribute to aging and various aging-related diseases.

Indeed, growing evidence supports the idea that a modulation of the quantity and quality of the contact sites between the ER and mitochondria could play a central role both in aging and in the onset and/or progression of neurodegenerative diseases [4, 5, 26, 27]. However, the cellular mechanisms underlying this link are still a matter of debate.

It is important to underline that there is altered ER-mitochondria communication in different age-related pathologies including cancer [28-30], type 2 diabetes (T2D) [31, 32], cardiovascular disease [33], and various neurological disorders [19, 23, 28, 34-36]. Aberrant interaction between these two organelles can lead to impaired Ca^{2+} signaling, contributing to synaptic dysfunction, neuronal apoptosis, and exacerbated pathology [37]. Understanding how this relationship changes with age could provide valuable insights into the mechanisms underlying age-related diseases and could offer new details about aging mechanisms. Moreover, improving knowledge of MAMs could open the way to new therapeutic strategies for age-associated pathological conditions. This review summarizes the structural and functional properties of MAMs, collects and provides updated information on their role in aging and age-related neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), and explores potential therapeutic approaches.

A first look at MAMs: a summary of their composition and function

MAMs are dynamic regions that originate from close contact between the outer mitochondrial membrane (OMM) and the ER membrane. They were first observed in 1959 using electron microscopy [38] but were not isolated and functionally examined until the 1990s [39]. Changes in the cell's metabolic state can influence the length and thickness of these contact sites, highlighting their plasticity. Furthermore, the length of the contacts and the distance between the two organelles significantly influence the functionality and activity of MAMs. Thus, when Ca^{2+} exchange is required, the distance between OMM and the ER membrane is approximately 20 nm [40]. Instead, autophagosome formation requires about 50 nm [41].

Furthermore, the formation and the biological functions of MAMs are influenced by specific protein composition and tethering components [42, 43]. To date, 1,212 resident proteins have been identified in MAMs, although this number is likely to increase with the discovery of new components [44]. Changes in expression levels and the composition of these proteins play a direct tethering connection role influencing communication

between mitochondria and the ER and their impact on cellular fate. Mass spectrometry analyses have shown that the proteins composing MAMs are widely expressed in different organs, especially in the brain and liver, and they are highly conserved among species [45].

Thus, the number, length, width, and composition of contact sites are important parameters for the formation and activity of MAMs and their involvement in the different cellular processes. To date, four different tethering protein complexes have been well established, identified, and studied in mammals: Mitofusins (MFN2-MFN1/MFN2-MFN2), VAPB-PTPIP51, VDAC1-GRP75-IP3R, and BAP31-FIS1 (Fig. 2). These complexes are reviewed below, with a focus on their role in aging and age-related neurodegenerative diseases.

MFN2-MFN1/2

Mitofusins (MFN2 and MFN1) are multifunctional proteins belonging to GTPase family. They are mainly located in the outer mitochondrial membrane (OMM) where they regulate the mitochondrial fusion process. In addition, MFN2 regulates apoptosis in a cell type- and age- specific manner [46, 47] and has been associated with mitophagy [48]. MFN2 can also be present on the ER and form homodimeric or heterodimeric bonds with mitofusins located on the OMM. Through these interactions, MFN2 contributes to the formation of ER-mitochondria contact sites in different tissues; however, its exact role remains controversial. Some studies report that MFN2 overexpression promotes ER-mitochondria contacts while the ablation of MFN2 reduces these contact sites [49-51]. Other authors suggest that MFN2 destabilizes MAMs by acting as a negative regulator of the contacts between the two organelles, associating the overexpression of MFN2 with the reduction of MAM integrity [52, 53].

These conflicting data may be due to differences in the types of samples analyzed, the experimental models used, or the methods employed to monitor communication between the two organelles. Further studies are needed to clarify the exact role of MFN2 on MAMs.

It is interesting to note MFN2's involvement in AD, in which it seems to play a significant role in disease pathogenesis [54, 55]. Several studies have reported a modulation of MFN2 levels in different models of pathology. In the human AD brain, a decrease in both MFN1 and MFN2 expression levels was found with an imbalance of mitochondrial dynamics [56]. Similarly, in a mouse neuroblastoma cell line (N2A) expressing the amyloid precursor protein (APP) familial Swedish mutation (APP^{swe}), a reduction in MFN1 and MFN2 levels was observed. MFN2 overexpression significantly reduced A β oligomer (A β o)-mediated cell death [57],

whereas siRNA-mediated MFN2 knockdown altered γ -secretase activity and amyloid beta ($A\beta$) generation by modulating ER-mitochondria contacts [58]. Accordingly, Presenilin 2 (PS2) seems to promote ER-mitochondria coupling only in the presence of MFN2. Furthermore, a

PS2 mutant associated with the familial form of AD (FAD) exhibited a higher binding affinity to MFN2 in MAMs, resulting in a more effective ability to modulate ER-mitochondria contact [59].

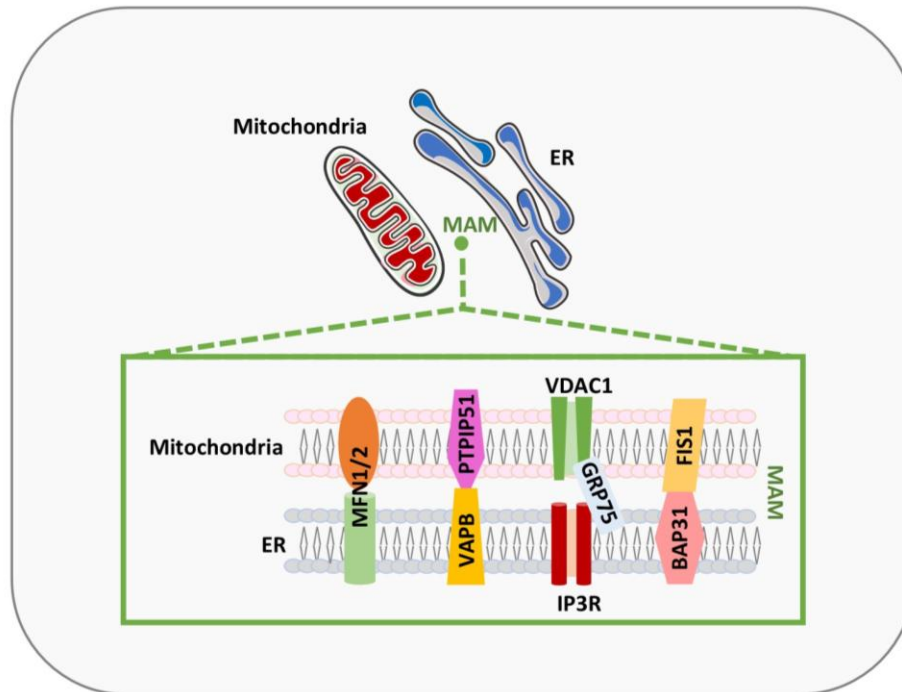


Figure 2. Proteins implicated in MAM formation. MAMs arise from the close apposition between the ER and mitochondrial membranes through the interaction of different proteins involved in several functions. Mitofusins (MFNs) located on both the ER and mitochondria surfaces form a link between the two organelles. The ER protein vesicle-associated membrane protein B (VAPB) interacts with the mitochondrial protein tyrosine phosphatase-interacting 51 (PTPIP51), regulating autophagy, phospholipids trafficking, and Ca^{2+} exchange between the ER and mitochondria. GRP75 links the IP3R and VDAC1, facilitating efficient Ca^{2+} transfer. The bridge between FIS1 and BAP31 drives the cell toward apoptosis.

VAPB-PTPIP51

The ER membrane protein vesicle-associated membrane protein associated protein B (VAPB) and the OMM protein tyrosine phosphatase-interacting protein-51 (PTPIP51), interact to form the VAPB-PTPIP51 tethering complex [60, 61]. VAPB-PTPIP51 contact sites regulate phospholipids and Ca^{2+} transfer between the ER and mitochondria, synaptic activity, and autophagy [62, 63, 15]. The overexpression of VAPB or PTPIP51 increases MAM stability and decreases autophagosome formation. While the depletion of both proteins reduces ER-mitochondria contacts, activating the autophagic process [64]. Moreover, the interruption of VAPB-PTPIP51 interaction disrupts MAMs and reduces the importation of mitochondrial Ca^{2+} and the synthesis of ATP [9, 65].

VAPB-PTPIP51 interaction seems to be regulated by GSK-3 β , which is highly expressed in the CNS and

whose activity increases with age. This age-related increase of GSK-3 β activity could potentially lead to a destabilization of MAMs through the disruption of VAPB-PTPIP51 interaction, contributing to age-related neurodegenerative diseases. Indeed, when activated, GSK-3 β reduces communication between the two proteins, inducing the autophagic process and altering Ca^{2+} homeostasis [65].

Interestingly this tethering complex seems to be involved in neurodegenerative diseases such as AD, PD, and ALS. The hallmark of PD α -synuclein (α -syn), indeed, can localize in MAMs. Moreover, α -syn mutations have been associated with a reduction of VAPB-PTPIP51 interaction, an imbalance of ER-mitochondria Ca^{2+} transfer, and ATP production [66].

Furthermore, the VAPB-PTPIP51 complex is disrupted in pyramidal neurons of the temporal cortex in the early phase of AD, and lower expression levels of

VAPB and PTPIP51 were found in the cortex of patients with advanced AD [67]. In addition, different studies have shown a reduction of VAPB-PTPIP51 interaction in both ALS cellular models and transgenic ALS mice. Stoica et al. reported that TDP-43, a protein involved in ALS and in frontotemporal dementia (FTD), disturbs VAPB-PTPIP51 communication [68]. Recently a study conducted by Hartopp et al. showed a disruption of the VAPB-PTPIP51 tether in post-mortem human motoneurons in ALS patients [69].

VAPB-PTPIP51 tethers are also disrupted in neurons derived from induced pluripotent stem (iPS) cells from patients carrying ALS/FTD pathogenic C9orf72 expansions and in affected neurons in mutant C9orf72 transgenic mice. Intriguingly, the disruption of VAPB-PTPIP51 contacts appears prior to disease onset, indicating their involvement in the pathogenesis of the disease [70].

IP3R-Grp75-VDAC1

Mitochondria and the ER are the primary locations for intracellular Ca^{2+} storage, and the formation of contact sites between them is essential to maintaining Ca^{2+} homeostasis. Mitochondrial Ca^{2+} is required for ATP production. Low Ca^{2+} levels can impair ATP production, whereas excess Ca^{2+} levels can trigger apoptosis [71, 72] and the overproduction of ROS [73].

ER Ca^{2+} channel inositol 1,4,5-triphosphate receptors (IP3Rs), OMM voltage-dependent anion channel type 1 (VDAC1), and cytoplasmic molecular chaperone glucose-regulated protein 75 (GRP75) belonging to the heat shock protein 70 (HSP70) family, form a complex that regulates Ca^{2+} transfer between the ER and mitochondria through the mitochondrial calcium uniporter (MCU) [74, 75]. It has recently been reported that deglycase (DJ-1), a protein mutated in a rare form of early-onset PD [76], also participates in this complex [77]. Indeed, it has been observed that the knockout of GRP75 or DJ-1 reduces IP3R and VDAC1 interactions and decreases mitochondria Ca^{2+} uptake [78, 79].

Conversely, DJ-1 overexpression enhances ER-mitochondria Ca^{2+} exchange [80], while the overexpression of GRP75 increases the formation of MAMs, leading to Ca^{2+} overload and compromising the mitochondrial function of neurons [81].

Interestingly, in AD, a progressive increase of VDAC1 expression according to the stages of disease was reported in the cortex of post-mortem brains, in aged APP mice, and in neuroblastoma cells treated with $\text{A}\beta$ [82]. In addition, primary hippocampal neurons treated with $\text{A}\beta$ showed augmented VDAC1 and IP3R expression, enhanced ER-mitochondria contact sites, and higher mitochondrial Ca^{2+} levels [23].

Moreover, the overexpression of PD's hallmark α -syn inhibited mitochondrial Ca^{2+} trafficking between the ER and mitochondria through MAMs by altering GRP75-IP3R interaction [83].

In this context, it is important to highlight the role of the Sigma-1 receptor (S1R). This chaperone, located in MAMs, regulates Ca^{2+} efflux into mitochondria by stabilizing the conformation of IP3R at MAMs and influencing the Grp75-VDAC1-IP3R tether [84].

FIS1-BAP31

The ER chaperone B-cell receptor-associated protein 31 (BAP31) forms a complex with the mitochondrial fission 1 protein (Fis1) located in the OMM, taking part in MAM formation. This tethering complex promotes the recruitment and activation of procaspase 8, leading cells to the apoptosis process through its cleavage into the proapoptotic p20 BAP31 fragment [85, 86].

Different investigations have indicated the involvement of FIS1 and BAP31 in AD physiopathology. Wang et al. have shown that the absence of BAP31 affects the formation of $\text{A}\beta$ plaques contributing to AD [87]. Moreover, mouse knock-down of BAP31 has revealed defects in memory and cognition and the overexpression of pro-inflammatory proteins in the hippocampus [88]. In addition, higher levels of FIS1 and DRP1 proteins and their respective mRNAs were found in the frontal cortex of patients with different stages of AD compared to controls [56].

The involvement of MAMs in the pathophysiological mechanisms of aging and age-related diseases

A look at MAMs and aging

Aging involves the physiological and progressive decline of biological functions, ultimately leading to age-related diseases such as cardiovascular diseases, musculoskeletal disorders, metabolic syndromes, neurodegenerative diseases, and cancers [1]. Currently, despite significantly increased life expectancy, there is no therapeutic strategy capable of inducing healthy aging, and most age-related neurodegenerative diseases still have no cure. Therefore, there is a need to strengthen research efforts in order to shed light on the still unclear mechanisms of these pathologies.

The main hallmark of aging is the accumulation of senescent cells for which growth and cell proliferation is permanently arrested, and which display a senescence-associated secretory phenotype (SASP) inducing the secretion of a large number of pro-inflammatory factors, chemokines, extracellular matrix proteases, and bioactive lipids. The consequences of this accumulation are a

reduction in tissue regenerative capacity and the induction of chronic inflammation, which trigger metabolic disorders, neurodegenerative diseases, and various age-related pathologies [89]. Furthermore, aging is characterized by impaired proteostasis, oxidative stress, mitochondrial dysfunction, inefficient organelle turnover, lipid dysregulation, and the accumulation of nuclear and mitochondrial DNA damage [90, 91]. Therefore, it is not surprising that MAMs, by regulating most of the above-mentioned cellular processes, can have a significant impact on these aging mechanisms.

During brain aging and in many neurodegenerative diseases, excessive amounts of misfolded proteins are observed, often resulting in the formation of aggregates such as intracellular inclusion bodies or extracellular amyloid plaques [92]. Interestingly, accumulations of α -syn and A β have been observed in MAMs, suggesting the potential involvement of ER-mitochondria contact sites in the regulation of proteostasis [92, 93]. This may be linked to reduced levels of several chaperones, including GRP78 (BiP), Calnexin, and PDI, which have been observed in different aging models, and which may lead to ER stress and activate the UPR. The alteration of mitochondrial quality control is also severely impaired in aging and many neurodegenerative diseases. With aging, mitochondrial dynamics become imbalanced and, simultaneously, autophagy dysfunction leads to an accumulation of defective mitochondria that compromise both CNS health and that of the entire organism [93]. Recently, Ca²⁺ has emerged as a key factor inducing senescence. A study conducted by Calvo-Rodríguez et al. on an *in vitro* model of aging, consisting of primary cultures of rat hippocampal neurons maintained in culture for a prolonged time, showed an increase in MCU expression and ER-mitochondria Ca²⁺ transfer that could be responsible for aging-related cognitive decline and neuronal cell death [94]. Wiel et al. have proposed that, during senescence, exaggerated Ca²⁺ transfer to mitochondria occurs, mediated by type 2 IP3Rs (IP3R2). This, in turn, causes a reduction in mitochondrial membrane potential and increased ROS production. Intriguingly, the knockdown of MCU was able to prevent senescence [95].

Analogously, the work of Ziegler et al. suggests that Ca²⁺ accumulation plays a role in promoting senescence. The authors demonstrated that IP3R2 knockout mice, which have reduced ER-mitochondrial contacts, exhibited a loss of senescence and an increased lifespan and quality of life. Conversely, an increase in MAM contacts advanced the senescence process both *in vitro* and *in vivo* models [96].

The work of Booth et al. correlates the Ca²⁺ flux between ER and mitochondria to the production of large amounts of ROS which in addition to being responsible

for oxidative damage to DNA, proteins, lipids, and cellular structures, creates a highly oxidizing environment around the MAM, modifying the function of proteins involved in ER-mitochondria coupling [97]. Therefore, altering ER-mitochondrial Ca²⁺ flux could have anti-aging effects, suggesting a novel strategy for targeting senescent cells and ameliorating the aging process.

Of particular interest is the presence in MAMs of the 66 kilodalton (kDa) isoform of the growth factor adaptor protein Shc (p66Shc). p66Shc is one of the few genes identified for aging in mammals. It controls lifespan in mammals by modulating mitochondrial function and redox signaling [98]. Furthermore, in the animal models analyzed, the level of p66Shc in MAMs increased with age [98]. This suggests a role for this protein in mechanisms related to cell fate determination and the importance of MAMs in the induction of mitochondrial oxidative stress associated with the process of growing old and senescence.

The CDGSH Iron Sulfur Domain 2 (CISD2) protein has also recently been found to be highly expressed in MAMs. CISD2 is implicated in Wolfram syndrome type 2 (WS2), an autosomal recessive neurodegenerative disease [99]. Fibroblasts from WS2 patients show a marked increase in ER-mitochondrial contacts compared to healthy controls [100]. In MAMs, CISD2 actively participates in the regulation of mitochondrial function, Ca²⁺ buffering, autophagy, and ER integrity through the formation of a macro-complex with IP3R and Bcl-2 [101, 102].

In 2009, Chen et al. demonstrated the role of CISD2 in longevity. They observed that CISD2 levels decrease in an age-dependent manner in different tissues, linking CISD2 to a premature aging phenotype characterized by the accumulation of damaged mitochondria [103]. Subsequent studies have shown that CISD2 overexpression extends lifespan by improving mitochondrial dysfunction and alleviating age-associated neuronal and muscle degeneration [104]. Moreover, studies conducted in APP/PS1 double transgenic mice have shown that CISD2 overexpression significantly attenuates the pathological aspects associated with AD by improving A β -induced mitochondrial damage, synaptic function, and reducing neuronal death [105].

Therefore, the significant role of MAMs in integrating pro-senescence signals could be a key to a better understanding of aging and related pathologies in order to plan strategies for attenuating age-related deterioration.

MAM dysfunction in Alzheimer's disease pathology

AD is a multifactorial disease whose primary risk factor is aging. AD patients show a progressive decline in

memory and cognitive abilities. The hallmarks of the disease are the accumulation of extracellular plaques of A β and intracellular neurofibrillary tangles of hyperphosphorylated tau, particularly in the cortex and hippocampus, which lead to nerve cell damage [106].

The etiopathological mechanisms of the disease are currently unknown, and no therapies have been found capable of counteracting the neuronal and synaptic loss typical of the disease. Recently, the alteration of contacts between the ER and mitochondria has experienced growing interest due to the impact of these organelles on the pathology.

Over the years, several hypotheses have been made regarding AD pathogenesis. The most widely recognized is the amyloid cascade hypothesis proposed by Hardy and Higgins in 1992. This hypothesis identifies the triggering event of AD in the accumulation in brain tissue of the A β peptide produced by the proteolysis of the amyloid precursor protein (APP) by the enzymes BACE1 (β -site APP cleavage enzyme) and the γ -secretase complex [107]. This was subsequently followed by other hypotheses, such as that of hyperphosphorylated tau and of mitochondrial cascade [108-110].

These hypotheses, however, have some limitations. In fact, there are events that are dysregulated even before the presence of amyloid plaques and neurofibrillary tangles, such as oxidative stress [111], altered phospholipid metabolism [112, 113], mitochondrial dysfunction [114, 115], high levels of circulating cholesterol [116], increased ER stress [117], and Ca²⁺ dyshomeostasis [118].

Recently, changes in the proteasome of MAMs were observed in AD mice in the early stages of the disease, before the appearance of amyloid plaques and typical symptoms of the disease [119]. So, the hypothesis that MAMs are involved in the initial phase of AD is increasingly accepted, despite some contradictory data in the literature which leave its role still unclear. In any case, the many reports linking AD and MAM suggest their full involvement in the pathogenesis of AD.

Increased ER-mitochondria contacts sites, accompanied by up-regulated MAM activity, have been observed in hippocampal neurons treated with oligomeric A β [120]. Comparable results were found in fibroblasts from patients with familial and sporadic AD and presenilin knockout cells [18]. Furthermore, an up-regulation of the MAM proteins IP3R and VDAC1 and an increase of the number of ER-mitochondria contact points were found in brain samples of AD patients and in (APP) Swe/Lon mice [23]. In this study, the increase in ER-mitochondria connections was seen within 2 months of age, significantly before the appearance of plaques and neurofibrillary tangles, highlighting the role of MAMs in early AD [23].

Recently, in the post-mortem human familial AD brain, a downregulation of MFN2 has been found [114]. Furthermore, in a report by Leal et al., MFN2 siRNA treatment improved MAM activity. MFN2 lacking cells showed impaired γ -secretase complex function and lower concentrations of intra- and extracellular A β 40 and A β 42, suggesting that the modulation of ER-mitochondria contact affects γ -secretase activity and A β generation [58].

Conversely, in the N2A cell line overexpressing the human APP with the familial Swedish mutation (APP^{Swe}), Fernandes et al. found APP accumulation in MAMs and mitochondria, altered levels of proteins implicated in ER-mitochondria tethering, changes in Ca²⁺ signaling and mitochondrial dynamics, and a reduced number of ER-mitochondria contact points [122]. In support of these data, the increase in ER-mitochondria contacts induced by artificial linkers improved the clinical aspects of AD pathology, prolonging the survival of AD models [123]. Moreover, VAPB-PTPIP51 protein expression and tether was reduced in the cortex of post-mortem patients in Braak stage III-IV AD (early/mid-dementia) [67].

Interestingly, Calvo-Rodriguez et al. demonstrated how treatment with A β o significantly increases the crosstalk between ER and mitochondria in young hippocampal neurons but reduces it in aging neurons [120]. The modulation of ER-mitochondria contacts related to age could, in some cases, explain the discrepancies observed in the different studies.

Another important aspect concerns the involvement of MAMs in the production of A β , the core component of amyloid plaques [124]. In a recent study, Zellmer et al. have shown the effects of MAM thickness on A β production. They have shown that tightening MAM gap widths (~6 nm gap width) significantly increased A β production and reduced mitochondrial axonal velocity compared to basal MAMs (~25 nm) [125].

Area-Gomez et al. have shown that APP, γ -secretase, and β -secretase localize predominantly in MAMs [126]. In addition, presenilins (PS1 and PS2), the catalytic components of γ -secretase, are found in MAMs, where they interact with IP3R [127] and MFN2 [59]. In this regard, Shilling et al. have intriguingly investigated the role of IP3R in cortical and hippocampal neurons of different mouse models of FAD. Their data show that mutated PS1 and PS2 perturbate intracellular Ca²⁺ homeostasis, opening IP3R channels and stimulating A β production. In addition, IP3R knockdown diminished aberrant Ca²⁺ signaling and reduced A β accumulation and tau hyperphosphorylation, improving memory deficits in 3xTg mice [128]. Studies conducted on fibroblasts from FAD patients with PS1 and PS2 mutations showed increased communication between ER and mitochondria

and an intensification in the lipid enzymatic function of MAMs associated with the interaction between the mutated form of PS2 and MNF2 [59].

Numerous studies have demonstrated that neuroinflammation contributes to the accumulation of A β plaques, tau hyperphosphorylation, and neuronal damage, thus playing an active role in the pathogenesis of AD [129-131].

MAMs participate in the inflammatory process and serve as platforms for the assembly and activation of the NLRP3 inflammasome, a key neuroinflammation mediator [132]. The activation of NLRP3 has been found in cerebral tissue from patients with AD as well as in transgenic mouse models of AD [133]. Levels of interleukin (IL)-1 β , a major inducer of inflammation that is processed by the NLRP3 inflammasome, are also elevated in the brains of AD patients and have been associated with the evolution of the disease [134-136]. Some data have demonstrated that inhibiting the NLRP3 inflammasome and reducing (IL)-1 β levels influence the microglial phenotype and improve behavioral tests and hallmarks of AD pathology in mouse models of the disease [137, 138], strengthening the theory that places MAMs at the center of the pathogenic events of AD.

Another very important issue concerns the appearance of early lipid alterations in the brain tissues of AD patients [119, 139-141]. Indeed, high cholesterol and phospholipid levels have been found in human AD patients [18, 142, 143] and in animal and cellular models of the disease [144-146]. Furthermore, high cholesterol levels have been associated with increased A β levels and more rapid AD-related pathology in animal models [145-147]. Furthermore, various epidemiological studies have revealed that hypercholesterolemia and obesity significantly correlate with amyloid accumulation and are a risk factor for dementia [148-150]. Since ER-mitochondria contact sites are essential for the regulation of lipid homeostasis, the key role of MAMs in the pathogenesis of AD is further confirmed. The enhanced ER-mitochondria connections and increased MAM activity detected in several AD models may, indeed, justify the elevated amounts of cholesterol and phospholipids observed in AD patients [151].

Interesting, in this regard, is the work of Harned et al. who found that the inhibition of acyl-CoA:cholesterol acyltransferase 1 (ACAT1), the cholesterol storage enzyme enriched in MAMs, increased ER-mitochondria connectivity [152]. This finding may be related to some previous work showing that blocking ACAT1/SOAT1 activity by genetic ablation or pharmacological inhibition improved cognitive deficits in AD mouse models and reduced APP and A β levels [153-156].

The discovery that the gene encoding the E4 variant of ApoE4 (APOE ϵ 4 allele) represents the major genetic

risk factor for late-onset AD added another piece of supporting evidence for the importance of MAMs in AD. Of all the plasma apolipoproteins, ApoE is the major cholesterol transporter protein in the brain [157]. In the work of Tambini et al., ApoE4 increased the production of phospholipids and cholesterol esters, and the authors associated these findings with a significant enhancement of ER-mitochondria communication [158]. Furthermore, *in vivo* and *in vitro* data have shown that the C-terminally truncated form of ApoE4 (Δ 272-299) has a neurotoxic action and impairs mitochondrial respiratory function by inducing ER stress and increasing MAM formation [159].

Taken together, these observations assign a prominent role to ER-mitochondria communication in the history of AD pathogenesis, supporting the concept of the “MAM hypothesis,” introduced by Area-Gomez et al., which places defects in MAM contacts and activity prior to the appearance of amyloid plaques and the onset of symptoms [25].

Therefore, considering the above, MAMs represent a promising therapeutic target for AD disease. It is thus worth focusing future studies on the regulation of ER-mitochondria contacts at the brain level.

The role of MAMs in Parkinson's Disease

PD is the second largest neurodegenerative age-related disease after AD. The pathological characteristics of PD include the accumulation in the brain of intraneuronal Lewy bodies, principally composed by aggregates of α -synuclein, the progressive death of dopaminergic neurons in the substantia nigra pars compacta, and a reduction of dopamine levels in the striatum [160].

Among the molecular mechanisms associated with the pathogenesis of PD are mitochondrial damage, dysfunctional autophagy, lipid dyshomeostasis, neuroinflammation, and apoptotic neuronal death [161].

Approximately 10% of PD cases involve the familial form, which can be associated with specific mutations in several genes encoding α -syn, DJ-1, PINK1, parkin, and LRRK2 [162]. α -syn, encoded by the *SNCA* gene, is a 140-amino acid lipid-binding protein that plays a critical role in the pathogenesis of PD. α -syn is highly enriched in presynaptic terminals and is thought to affect the integrity and function of synapses [160]. Its localization in different cellular compartments, including mitochondria, the ER, and MAMs, is particularly interesting because it could influence ER-mitochondria communication and MAM functioning [163]. Indeed, Guardia-Laguarta et al. have shown that α -syn mutations cause a decline in MAM contact sites, with mitochondria dysfunction and lower ATP production [164]. Paillusson et al. have found that, in MAMs, α -syn can interact with VAPB, reducing its ability to bind PTPIP51 [165]. Furthermore, α -syn could

reduce the expression of VAPB and PTPP51 and inhibit the release of synaptic vesicles [34, 62]. Although the mechanism of action is not yet well understood, the influence of α -syn on VAPB-PTPP51 levels and binding in MAMs may underlies the pathogenesis of PD. In addition, α -syn could reduce ER-mitochondria contact point through the destruction of GRP75-IP3R-VDAC1 interaction and block ER-mitochondria Ca^{2+} trafficking [82]. In both cases, the resulting Ca^{2+} signaling dyshomeostasis may affect neurotransmitter release, dendritic spine formation, and synaptic plasticity.

Instead, Cali et al. reported a significant increase in ER-mitochondria contact sites in cells overexpressing the α -syn wild type, but not in cells overexpressing mutant α -syn (1-97). The mutated protein induced a reduction in mitochondrial Ca^{2+} and a massive level of mitochondrial fragmentation [163].

This discrepancy in conclusions may be due to the analytical methods and models used. Furthermore, since it has been observed that the effects of α -syn depend on its expression levels, the dose used for the different studies could also explain their different results [162]. However, the debate remains open, and further studies need to be done to clarify the relationship between α -syn and MAM in PD.

Interestingly, other familial PD genes have also been associated with MAMs. DJ-1 is a multifunctional protein whose mutation is associated with early-onset, autosomal recessive PD. It is localized in the mitochondria, where it can regulate mitochondrial function and dynamics [166, 167], and in the MAM, where it interacts with the IP3R-GRP75-VDAC1 binding protein complex. Mutations in DJ-1 can disrupt the connection between the ER and mitochondria and compromise MAM function, resulting in impaired Ca^{2+} transfer between the two organelles [82], reduced ATP production, and mitochondrial dysfunction [77].

Similarly to α -syn and DJ-1, the mitochondrial quality control proteins parkin (an E3 ubiquitin ligase encoded by *PARK2*) and PINK (a mitochondria protein kinase encoded by *PARK6*) influence the integrity and function of MAMs, although their role is not yet fully understood [162].

The overexpression of parkin significantly enhanced the tether between ER and mitochondria, Ca^{2+} exchange, and ATP production in both HeLa and neuroblastoma cells. Moreover, in the nigral neurons, parkin overexpression increased MAM generation [168]. In agreement with a previous study, Basso et al. have shown that deficient quantities of parkin caused a decline in ER-mitochondria contact sites via MFN2. Furthermore, using a synthetic ER-mitochondria linker, they observed a recovery of locomotor deficits in a *Drosophila* model of PD [49].

Conversely, a closer proximity between ER and mitochondria and enhanced Ca^{2+} transfer were observed in primary fibroblasts from PARK2 knockout mice as well as in PD patients with PARK2 mutations compared to controls [24]. This data was supported by additional study in *Drosophila* models of PD and in hypothalamic neurons differentiated from patient-induced pluripotent stem cells (iPSCs) [169]. In Celardo et al.'s report, both PINK1 and parkin mutants showed a significant increase in mitochondria-ER contact points that could be blocked by MFN2 knockdown [170]. An interesting hypothesis was provided by McLelland et al. who argue that PINK1 and parkin damage the ER-mitochondria tether during the early step in the mitophagy pathway through the ubiquitination of MFN2 [171].

Leucine-rich repeat kinase 2 (LRRK2) is a kinase located in the OMM that plays a crucial role in remodeling of cytoskeleton and in mitochondrial dynamics and function. Mutations in LRRK2 is involved in familial PD and in several sporadic PD cases [169]. Recent studies have evidenced that the interaction of mutated LRRK2 gene with parkin inhibits the activation of the E3 ubiquitin ligase activity in MAM, leading to the ubiquitination and degradation of MAM components with a consequent decrease of Ca^{2+} exchange between the ER and mitochondria [172].

Despite recent discoveries, the exact pathological mechanism of PD is still largely unclear. It is worth focusing on studies to better understand the role played by MAMs and how interactions between the ER and mitochondria may represent a concrete target for the treatment of the disease.

The role of MAMs in amyotrophic lateral sclerosis

ALS is a fatal neurodegenerative disease characterized by progressive muscle paralysis. It affects upper motor neurons in the brain and lower motor neurons in the brainstem and spinal cord. ALS cases with unknown etiology are referred to as sporadic ALS and represent 85-90% of cases [173]. The familial form, affecting 10-15% of cases, presents mutations in several genes primarily *SOD1*, which encodes Cu/Zn superoxide dismutase-1 [174, 175], fused in sarcoma (*FUS*) [176], *C9ORF72* [177], *TARDBP* which encodes TAR DNA-binding protein 43 (TDP-43) [178, 179], *SIGMAR1* which encodes the Sigmar1 receptor (S1R) [180], and vesicle-associated membrane protein (*VAPB*) [181]. Despite numerous studies on its pathology, the causes of disease progression are unknown, and there are still no effective treatments. Several studies have suggested a close connection between MAMs and ALS. The proteins involved, to varying degrees, in the pathology influence the link between the ER and mitochondria. It has recently

been demonstrated that spinal cord motor neurons from post-mortem human ALS subjects present an interruption of VAPB-PTPIP51 tethering [72]. Furthermore, the TARDBP [68], FUS [67], and C9orf72 [70] mutants linked to familial FTD/ALS have been shown to disrupt the VAPB-PTPIP51 interaction.

Transactive response DNA-binding protein-43 (TDP-43) is an RNA and DNA binding protein involved in RNA transcription, transport, and translation [182, 183]. In the motor neurons of ALS patients, TDP-43 is found within insoluble, ubiquitinated cytoplasmic inclusions [184]. It has recently been noted that TDP-43 can reduce MAM contacts and Ca^{2+} homeostasis by disrupting the binding between VAPB and PTPIP51 through the activation of GSK-3 β [68, 71]. In a recent work, Markovinic et al. underlined the importance of MAMs in the pathogenesis of ALS through the VAPB-PTPIP51 link. They showed how the overexpression of VAPB or PTPIP51 is able to correct the damage induced by mutant TDP-43 by improving Ca^{2+} transport between the ER and mitochondria and restoring synaptic function [185].

Similarly, it has been shown that the overexpression of FUS in some forms of ALS disrupts VAPB-PTPIP51 binding and MAM functions through the activation of GSK-3 β [65]. Both wild type and mutant FUS have been shown to disrupt the VAPB-PTPIP51 connection through the activation of GSK3 β . Treatment with AR-A014418, a GSK3 β inhibitor, restores ER-mitochondrial contacts by improving mitochondrial Ca^{2+} levels and ATP production [65]. ALS patients with FUS mutations present the first symptoms much earlier than other forms of the disease, so understanding the pathological mechanisms of this form of ALS could help identify therapeutic targets capable of blocking disease onset [186].

Eleven percent of ALS cases are caused by mutations in the C9orf72 gene [187]. Studies on neurons derived from induced pluripotent stem (iPS) cells of patients carrying the C9orf72 mutation and on transgenic mice expressing the C9orf72 mutation, showed a reduction in VAPB-PTPIP51 and IP3R1-VDAC1 interactions with reduced Ca^{2+} exchange between the ER and mitochondria [70].

In support of the role of MAMs in ALS, mutations in the VAPB gene have been found in some cases of familial ALS (ALS8) [188, 189]. The mutated form of VAPB (VAPB56S) presents a higher affinity for PTPIP51, with a consequent strengthening of VAPB-PTPIP51 contacts and increased Ca^{2+} exchange between the ER and mitochondria [60]. In this perspective, the VAPB-PTPIP51 link seems to have a significant role in several forms of ALS, and the role of GSK-3 β as a regulator of ER-mitochondria contacts becomes particularly relevant in the search for effective ALS therapies.

Sigma-1 receptor (S1R) is another MAM-associated protein whose mutation has been related to familial ALS. Homozygous mutations of the S1R gene have been associated with juvenile-onset (ALS16) and adult-onset forms of ALS co-occurring with frontotemporal lobar degeneration (FTLD-ALS) [180, 190, 191]. Moreover, S1R knockout mice showed the muscle weakness and loss of motor neurons characteristic of ALS [192]. The loss of S1R causes a decrease of ER-mitochondria contact points [193, 194] and, in a SOD1(G85R) mouse model of ALS, accelerated disease onset by disrupting the integrity of MAMs [195]. The use of S1R agonists such as Pre-084 or SA4503 has improved motor neuron degeneration and symptom development in the SOD1(G93A) ALS mouse and cellular model of ALS [196, 197].

Interestingly S1R polymorphisms have also been identified as a significant risk factor for AD [198], and a reduction in S1R was observed in the post-mortem hippocampus of patients with AD [199]. So, in light of the above, S1R appears as a promising therapeutic target for several neurodegenerative diseases that is worth studying in more depth.

The accumulation of mutated SOD1 also causes MAM disruption and mitochondrial dysfunction [195]. Larrea et al. suggested that the disruption of ER-mitochondria contacts could be the cause of bioenergetic deficits observed in ALS [200]. Some authors have reported that mutant SOD1(G93A) and SOD1(G85R), but not wild type SOD1, directly bind VDAC1 [201, 202]. This interaction could disturb VDAC1's function and compromise the stability and the activity of MAMs, affecting processes like Ca^{2+} signaling and lipid transport. From the data summarized in this section, a full involvement of MAMs in ALS clearly emerges. However, further studies are needed to clarify the role of dysfunctional contacts between the ER and mitochondria in disease pathogenesis and to what extent the physiological restoration of MAM functionality can effectively block the progression of ALS and be useful in the healing process.

MAMs and current therapeutic approaches targeting age-related neurodegenerative disorders.

The discussion so far has assigned a prominent role to the link between the ER and mitochondria in the pathogenesis of AD, PD, and ALS. Numerous lines of evidence have shown alterations in the number of ER-mitochondria contacts and in the function of MAMs associated with age-dependent neurodegenerative diseases (Table 1). Therefore, it is plausible that the correction of ER-mitochondria signaling could represent a promising therapeutic strategy.

Table 1. Schematic overview of tethering complexes in MAMs and their involvement in age-related neurodegenerative diseases.

ER-Mitochondria tether	Functions	Disease	Effects	References
Mitofusin 2	GTPase involved in OMM fusion, regulates apoptosis and mitophagy.	AD	In the human AD brain and in N2a cells expressing the APP familial Swedish mutation, a decrease in expression levels of MFN2 and an imbalance of mitochondrial dynamics was found.	[56, 57]
		AD	Knockdown of mitofusin-2 (MFN2) influences γ -secretase activity and A β generation by modulating ER-mitochondria contacts.	[58, 59]
VAPB-PTPIP51	Regulates phospholipids and Ca ²⁺ transfer between the ER and mitochondria, synaptic activity, and autophagy.	AD	The VAPB-PTPIP51 complex is disrupted in pyramidal neurons of the temporal cortex in early phases of AD.	[67]
		PD	α -synuclein mutations, and α -synuclein siRNA silencing have been associated with the reduction of VAPB-PTPIP51 interactions, imbalance of Ca ²⁺ homeostasis, and lower ATP production.	[66]
		ALS	Reduction of VAPB-PTPIP51 contacts was found in a cellular model, post-mortem human ALS motoneurons, and transgenic ALS mice.	[68, 69, 70]
IP3R-Grp75-VDAC1	Regulates Ca ²⁺ transfer between the ER and mitochondria.	AD	A progressive increase of VDAC1 expression according to stages of disease was shown in the cortex of post-mortem brains, in aged APP mice, and in neuroblastoma cells treated with A β o.	[82]
		AD	Primary hippocampal neurons treated with A β showed augmented VDAC1 and IP3R expression levels and enhanced ER-mitochondria contact sites.	[23]
		PD	α -synuclein overexpression inhibited ER-mitochondrial Ca ²⁺ trafficking modifying GRP75-IP3R interaction in MAMs.	[83]
Fis1-Bap31	Promotes recruitment and activation of procaspase 8, leading the cell towards apoptosis.	AD	Knock-down of BAP31 affects the formation of A β plaques and reveals defects in memory and cognition, contributing to AD.	[87, 88]
		AD	High levels of FIS1 and DRP1 protein and mRNA were found in the frontal cortex of patients with different stages of AD.	[56]

ER=endoplasmic reticulum; OMM=outer mitochondrial membrane; AD=Alzheimer's disease; APP=amyloid precursor protein; PD=Parkinson disease; ALS= amyotrophic lateral sclerosis; MFN2=mitofusin 2; A β =amyloid beta; VAPB=vesicle-associated membrane protein-associated protein B; PTPIP51=Protein tyrosine phosphatase interacting protein 51; IP3R=inositol trisphosphate receptor; Grp75=75-kDa glucose-regulated protein; VDAC1=Voltage-dependent anion-selective channel 1; A β =amyloid- β ; A β o=amyloid beta oligomers; BAP31=B-cell receptor-associated protein 31.

To date, the use of ER-mitochondria contact sites as a pharmacological target has not yet been considered, but the number of compounds that directly or indirectly target proteins residing in MAMs is growing in parallel with the interest in this interface.

However, some considerations need to be made. The study of MAMs in the pathogenesis of neurodegenerative diseases and as a pharmacological target is not a simple endeavor, as demonstrated by the quantity of discordant data produced. It is essential to consider that MAMs are highly dynamic interfaces which are able to adapt to the

metabolic demands of cells or to shape themselves in response to various stimuli, and which can change with aging [94]. The structural characteristics to be considered are the length of the contact areas between the ER and mitochondria, the number of contact points, and the distance between the two organelles that translate into a specific functional response [40, 41]. Furthermore, the composition of MAMs is tissue-specific and varies depending on the organ from which it is extracted [42], and many of the molecules present in MAMs perform functions that also go beyond MAMs and act on other

mechanisms or in different compartments. Therefore, specific pharmacological treatments could have diverse effects on different organs, and this must be considered for possible adverse activities.

While for AD and PD conflicting data do not yet allow us to identify a common mechanism for the effects of various disease-associated insults and alteration of MAMs, for ALS/FTD, the different insults seem to converge at the disruption of ER-mitochondria interactions [36]. Much attention has been given to the VAPB-PTPIP51 tether and its modulator, GSK3 β . The correction of this anomalous binding has been studied by Markovinov et al. [185] who demonstrated that the overexpression of VAPB or PTPIP51 corrects the damage induced by the TDP-43 mutation by improving Ca²⁺ transport to mitochondria as well as synaptic function. They also showed that treatment with a ursodeoxycholic acid (UDCA) drug used for FTD/ALS therapy acts by modulating VAPB-PTPIP51 interaction through GSK3 β [185].

Recently, several studies have demonstrated the neuroprotective effects of UDCA and its taurine conjugate, tauroursodeoxycholic acid (TUDCA), in several neurodegenerative disorders, and several clinical trials have been started, confirming the therapeutic potential of MAMs in the treatment of the main neurodegenerative diseases [203-208].

The modulation of GSK3 β may offer interesting insights; in fact, it has been shown that the overexpression of GSK3 β reduces interaction between VAPB and PTPIP51. On the contrary, treatment with GSK3 β inhibitors improved VAPB-PTPIP51 binding [65]. Currently, several GSK3 β inhibitors are being employed in different studies and clinical trials, with encouraging results for neurodegenerative diseases. These include tideglusib [209, 210], lithium and lithium carbonate [211-214], with new formulations such as NanoLithium® NP03 and AL001 which improve their bioavailability. However, since GSK3 β is implicated in the regulation of several pathways also outside the nervous system, a careful evaluation of any adverse symptoms is necessary.

A molecule of potential interest is LDC-3/Dynastoptin, an aminothiazole originally developed as a dynein antagonist. Recently, it has been observed that LDC-3 interacts directly with PTPIP51 [215, 216], increasing interaction between PTPIP51 and VAPB. Although it has not yet been tested in models of neurodegenerative diseases, its ability to modify VAPB-PTPIP51 contacts makes it interesting for further future studies with possible implications for diseases characterized by a dysfunctional link between these two proteins, such as ALS [61].

Another interesting therapeutic strategy is using molecules capable of modulating the levels of the Sigma-

1 receptor which regulates MAM stability. Several studies have shown the positive effects of some Sigma-1 receptor agonists on different models of neurodegenerative diseases [217]. In Wolfram syndrome, a rare neurodegenerative disease clearly associated with MAM dysfunction [118], the treatment of different preclinical models of the disease with PRE-084 improved MAM-related dysfunctional parameters and alleviated disease symptoms [119].

Similarly, treatments with Pre-084, Pridopidine, EST79232 or SA4503 improved the symptoms associated with cellular and murine models of ALS [196, 197, 220], while Anavex2-73 is currently being evaluated in clinical trials [220].

These data provide an important perspective on the treatment of neurodegenerative pathologies related to defective communication between ER and mitochondria and encourage further studies aimed at modulating the Sigma-1 receptor and MAMs for the treatment of diseases associated with their dysfunction.

The tethering protein MFN2 is a potentially useful target for improving mitochondrial defects through the modulation of MAMs. Biochanin A preserved cognitive deterioration, diminished A β deposition, and corrected mitochondrial dynamics and mitophagy by increasing MFN2 expression in APP/PS1 mice [222, 223]. Similarly, Ligustilide [224, 225], Myricetin [226-228], Albiflorin [229], Leptin [230], Selenomethionine [231], and Trans-ferulic acid [232] were also able to normalize MFN2, reestablish mitochondrial respiration and ATP production, and ameliorate mitochondrial dysfunction.

Several studies have shown the positive effects of curcumin in different models of neurodegeneration, although its poor bioavailability has limited clinical efficacy studies. They have been summarized in the recent review by Nunes et al. [233]. In a 2015 study, Cox et al. demonstrated that supplementation with Longvida®, a solid lipid formulation of curcumin, ameliorated cognitive functions and quality of life in a healthy older population [234]. In agreement with previous work, treatment with the highly bioavailable CurQfen-curcumin has shown improvement in locomotive and cognitive functions and a significant slowing of the progression of AD [235].

Treatment with 4 μ 8c, an IRE1 α inhibitor, improved ATP content and mitochondrial health by reducing the expression of and interactions between IP3R, Grp75, and VDAC1 and restoring MAM functions [236].

Furthermore, PERK inhibition can reduce MFN contacts at the ER-mitochondria interface, and a recent work has shown that treatment with GSK2606414, a PERK inhibitor, ameliorated ER stress and mitochondrial dysfunction in a model of early-onset PD (PARK20) [237].

Another noteworthy molecule is resveratrol, a non-flavonoid polyphenol with antioxidant properties, capable of modulating the expression of proteins involved in the connection between the ER and mitochondria in various cellular systems [238]. Treatments of Parkin-mutant fibroblasts with resveratrol showed a restoration of the expression of MAM contact proteins and improved autophagic flux [239]. It should be noted that, in addition to modifying the expression of MAM-resident proteins, resveratrol could also modulate various transcription factors, such as AP-1, CREB, Egr-1, Elk-1, and Nrf2 [240], which may cause unwanted side effects.

Recently, the gut metabolite urolithin A has shown the capacity to control ER-mitochondria interactions, Ca^{2+} homeostasis, the expression of APP, BACE1, the production of A β , and Tau phosphorylation in diabetes-associated AD pathogenesis [241]. Two clinical trials will start soon to test the impact of urolithin A on cognitive function (ClinicalTrials.gov: NCT07060898) and on aging biomarkers in middle-aged and older adults (ClinicalTrials.gov: NCT06990256).

Conclusions

MAMs constitute communication platforms between the ER and mitochondria and influence Ca^{2+} signaling, redox regulation, lipid exchange, and mitochondrial quality control. These mechanisms appear to be altered during aging and in the early stages of various diseases, such as AD, PD, and ALS, suggesting a pathogenetic association between MAM dysregulation, senescence, and age-related neurodegenerative diseases.

Although there is still no consensus among the findings linking MAMs to AD and PD, the idea that dyshomeostasis of ER-mitochondria contacts may contribute to various stages of these diseases is increasingly recognized. The role of ER-mitochondrial contact dysregulation in ALS appears clearer. Current studies also show a strong impact of MAMs on the aging process. The identification of molecules capable of modulating the distance and binding between the ER and mitochondria has improved our understanding of the role of MAMs, but much remains to be done.

The data generated to date show that promoting ER-mitochondria contacts can have different outcomes depending on the cellular context, the disease, and its stage. The use of artificial ER-mitochondria linkers/uncouplers has indeed produced markedly different results. Using a synthetic linker in *Drosophila melanogaster*, Basso et al. have observed a recovery of locomotor deficits in a *Drosophila* model of PD [49]. Similarly, Garrido-Maraver et al. achieved life extension and improved cognitive function associated with the enhancement of MAMs [123]. In contrast, Hewitt et al.

reported that increased MAMs disturbed mitochondrial transport and synapse formation, accelerating age-related decline in locomotion and reducing lifespan [242].

Of great interest is the use of microRNAs (miRNAs), small non-coding RNAs that act on specific target mRNAs which post-transcriptionally regulate gene expression. miR-484 targets FIS1 which, through its binding to BAP31, influences the stability and function of MAMs [243]. It could be hypothesized that the reduction in mitochondrial fission and apoptosis observed following the reduction in FIS1 expression under hypoxic conditions are linked to the lack of tethering with BAP31 and the consequent destabilization of MAMs.

Furthermore, the presence of specific miRNAs in MAMs, such as miR-146a, miR-142-3p, miR-142-5p, and miR-223 in rat and human brain samples is an emerging area of research that may lead to the discovery of new potential biomarkers or therapeutic targets for various diseases [244].

The results of Wang et al. showed that these miRNAs produce an inflammatory response which contributes to aging and neurodegenerative diseases [244]. Moreover, miR-223, when enriched in MAMs, coordinates cholesterol homeostasis targeting methylsterol monooxygenase 1 (MSMO1), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), and a scavenger receptor, class B type 1 (SR-B1), suggesting a potential role in AD [245]. But further in-depth studies are needed to better understand the functional role of MAM-associated miRNAs in normal and pathological brain conditions.

We have seen that the development of neurodegenerative diseases is almost never traceable to a single molecular process, but rather to the disruption of the balance between multiple cellular mechanisms. MAMs regulate many of the pathogenetic aspects found in aging and related diseases. Therefore, although much work remains to be done to achieve concrete results, MAMs seem to offer new perspectives and promising opportunities for research into neurodegenerative diseases and anti-aging strategies.

Acknowledgments

Thanks to G. Spinelli, L. Caruana and G. Biddeci for their appreciated advice. This work was funded by the project Invecchiamento attivo e in salute FOE 2022_DSB. AD006.371, National Research Council (CNR).

Conflicts of interest

The author has no conflicts of interest to declare.

References

- [1] Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013). The hallmarks of aging. *Cell*, 153(6):1194-217.
- [2] Brand MD, Orr AL, Perevoshchikova IV, Quinlan CL (2013). The role of mitochondrial function and cellular bioenergetics in ageing and disease. *Br J Dermatol*, 169(2):1-8.
- [3] Schwarz DS, Blower MD (2016). The endoplasmic reticulum: structure, function and response to cellular signaling. *Cell Mol Life Sci*, 73(1):79-94.
- [4] Moltedo O, Remondelli P, Amodio G (2019). The mitochondria-endoplasmic reticulum contacts and their critical role in aging and age-associated diseases. *Frontiers in Cell and Developmental Biology*, 7:172-184.
- [5] Petkovic M, Caitlin E, O'Brien Yuh Nung Jan (2021). Interorganelle communication, aging, and neurodegeneration *Genes & Dev*, 35(7-8):449-469.
- [6] Vance JE (1990). Phospholipid synthesis in a membrane fraction associated with mitochondria *J. Biol. Chem*, 265(13):7248-56.
- [7] Rusinol AE, Cui Z, Chen MH, Vance JE (1994). A unique mitochondria-associated membrane fraction from rat liver has a high capacity for lipid synthesis and contains pre-Golgi secretory proteins including nascent lipoproteins. *J Biol Chem*, 269(44):27494-502.
- [8] Achleitner G, Gaigg B, Krasser A, Kainersdorfer E, Kohlwein SD, Perktold A, et al. (1999). Association between the endoplasmic reticulum and mitochondria of yeast facilitates interorganelle transport of phospholipids through membrane contact. *Eur J Biochem*, 264(2):545-53.
- [9] Rizzuto R, Pinton P, Carrington W, Fay FS, Fogarty KE, Lifshitz LM, et al. (1998). Close contacts with the endoplasmic reticulum as determinants of mitochondrial Ca^{2+} responses. *Science*, 280(5370):1763-1766.
- [10] Wang HJ, Guay G, Pogan L, Sauvé R, Nabi IR (2000). Calcium Regulates the Association between Mitochondria and a Smooth Subdomain of the Endoplasmic Reticulum. *The Journal of Cell Biology*, 150(6):1489-1498.
- [11] Tagaya M, Arasaki K (2017). Regulation of mitochondrial dynamics and autophagy by the mitochondria-associated membrane. *Adv Exp Med Biol*, 997:33-47.
- [12] Friedman JR, Lackner LL, West M, DiBenedetto JR, Nunnari J, Voeltz GK (2011). ER tubules mark sites of mitochondrial division. *Science*, 334(6054):358-62.
- [13] Gilady SY, Bui M, Lynes EM, Benson MD, Watts R, Vance JE, Simmen T (2010). Ero1alpha requires oxidizing and normoxic conditions to localize to the mitochondria-associated membrane (MAM). *Cell Stress Chaperones*, 15(5):619-29.
- [14] Hamasaki M, Furuta N, Matsuda A, Nezu A, Yamamoto A, Fujita N, et al. (2013). Autophagosomes form at ER-mitochondria contact sites. *Nature*, 495(7441):389-93.
- [15] Gomez-Suaga P, Paillusson S, Stoica R, Noble W, Hanger DP, Miller CCJ (2017). The ER-mitochondria tethering complex VAPB-PTPIP51 regulates autophagy. *Curr Biol*, 27(3):371-385.
- [16] Ji C, Zhang Z, Li Z, She X, Wang X, Li B, et al. (2022). Mitochondria-Associated Endoplasmic Reticulum Membranes: Inextricably Linked with Autophagy Process. *Oxid Med Cell Longev*, 2022:7086807.
- [17] Schon EA, Area-Gomez E (2010). Is Alzheimer's disease a disorder of mitochondria-associated membranes? *J Alzheimers Dis*, 20(s2):281-292.
- [18] Area-Gomez E, Del Carmen Lara Castillo M, Tambini MD, Guardia-Laguarta C, de Groof AJ, Madra M, et al. (2012). Upregulated function of mitochondria-associated ER membranes in Alzheimer disease. *EMBO J*, 31(21):4106-23.
- [19] Parakh S, Atkin JD (2021). The mitochondrial-associated ER membrane (MAM) compartment and its dysregulation in Amyotrophic Lateral Sclerosis (ALS). *Semin Cell Dev Biol*, 112:105-113.
- [20] Tubbs E, Theurey P, Vial G, Bendridi N, Bravard A, Chauvin MA, et al. (2014). Mitochondria-associated endoplasmic reticulum membrane (MAM) integrity is required for insulin signaling and is implicated in hepatic insulin resistance. *Diabetes*, 63(10):3279-94.
- [21] Zhang Z, Cui D, Zhang T, Sun Y, Ding S (2020). Swimming differentially affects T2DM-induced skeletal muscle ER stress and mitochondrial dysfunction related to MAM. *Diabetes Metab Syndr Obes*, 13:1417-1428.
- [22] Jinxuan Liu, Jinghua Yang (2022). Mitochondria-associated membranes: A hub for neurodegenerative diseases. *Biomedicine & Pharmacotherapy*, 149:112890.
- [23] Hedskog L, Pinho CM, Filadi R, Rönnbäck A, Hertwig L, Wiehager B, et al. (2013). Modulation of the endoplasmic reticulum-mitochondria interface in Alzheimer's disease and related models. *Proc Natl Acad Sci USA*, 110(19):7916-21.
- [24] Gautier CA, Erpapazoglou Z, Mouton-Liger F, Muriel MP, Cormier F, Bigou S, et al. (2016). The endoplasmic reticulum-mitochondria interface is perturbed in PARK2 knockout mice and patients with PARK2 mutations. *Hum Mol Genet*, 25(14):2972-2984.
- [25] Area-Gomez E, Schon EA (2017). On the Pathogenesis of Alzheimer's Disease: The MAM Hypothesis. *FASEB J*, 31(3):864-867.
- [26] Janikiewicz J, Szymański J, Malinska D, Patalas-Krawczyk P, Michalska B, Duszyński J, et al. (2018). Mitochondria-associated membranes in aging and senescence: structure, function, and dynamics. *Cell Death Dis*, 9(3):332.
- [27] Gil-Hernández A, Silva-Palacios A (2020). Relevance of endoplasmic reticulum and mitochondria interactions in age-associated diseases. *Ageing Research Reviews*, 64:101193.
- [28] Zhao WB, Sheng R (2025). The correlation between mitochondria-associated endoplasmic reticulum membranes (MAMs) and Ca^{2+} transport in the pathogenesis of diseases. *Acta Pharmacol Sin*, 46(2):271.

- [29] An G, Park J, Song J, Hong T, Song G, Lim W (2024). Relevance of the endoplasmic reticulum-mitochondria axis in cancer diagnosis and therapy. *Exp Mol Med*, 56(1):40-50.
- [30] Yu H, Sun C, Gong Q, Feng D (2021). Mitochondria-Associated Endoplasmic Reticulum Membranes in Breast Cancer. *Front Cell Dev Biol*, 9:629669.
- [31] Cheng H, Gang X, He G, Liu Y, Wang Y, Zhao X and Wang G (2020). The Molecular Mechanisms Underlying Mitochondria-Associated Endoplasmic Reticulum Membrane-Induced Insulin Resistance. *Front Endocrinol*, 11:592129.
- [32] Yang S, Zhou R, Zhang C, He S, Su Z (2020). Mitochondria-Associated Endoplasmic Reticulum Membranes in the Pathogenesis of Type 2 Diabetes Mellitus. *Front Cell Dev Biol*, 20(8):571554.
- [33] Lu X, Gong Y, Hu W, Mao Y, Wang T, Sun Z et al. (2022). Ultrastructural and proteomic profiling of mitochondria-associated endoplasmic reticulum membranes reveal aging signatures in striated muscle. *Cell Death Dis*, 13(4):296.
- [34] Gómez-Suaga P, Bravo-San Pedro JM, González-Polo RA, Fuentes JM, Mireia Niso-Santano M (2018). ER-mitochondria signaling in Parkinson's disease. *Cell Death Dis*, 9(3):337.
- [35] Hattori N, Arano T, Hatano T, Mori A, Imai Y (2017). Mitochondrial-Associated Membranes in Parkinson's Disease. *Adv Exp Med Biol*, 997:157-169.
- [36] Sakai S, Watanabe S, Komine O, Sobue A, Yamanaka K (2021). Novel reporters of mitochondria-associated membranes (MAM), MAMtrackers, demonstrate MAM disruption as a common pathological feature in amyotrophic lateral sclerosis. *FASEB J*, 35(7):e21688.
- [37] McDaid J, Mustaly-Kalimi S, Stutzmann GE (2020). Ca(2+) dyshomeostasis disrupts neuronal and synaptic function in Alzheimer's disease. *Cells*, 9(12):2655.
- [38] Copeland DE, Dalton AJ (1959). An association between mitochondria and the endoplasmic reticulum in cells of the pseudobranch gland of a teleost. *J Biophys Biochem Cytol*, 5(3):393-396.
- [39] Vance JE, Stone SJ, Faust JR (1997). Abnormalities in mitochondria-associated membranes and phospholipid biosynthetic enzymes in the mnd/mnd mouse model of neuronal ceroid lipofuscinosis. *Biochimica et Biophysica Acta*, 1344(3):286-299.
- [40] Dematteis G, Tapella L, Casali C, Talmon M, Tonelli E, Reano S, et al. (2024). ER-mitochondria distance is a critical parameter for efficient mitochondrial Ca²⁺ uptake and oxidative metabolism. *Commun Biol*, 10:7(1):1294.
- [41] Giacomello M, Pellegrini L (2016). The coming of age of the mitochondria-ER contact: a matter of thickness. *Cell Death Differ*, 23(9):1417-27.
- [42] Lee S, Min KT (2018). The Interface Between ER and Mitochondria: Molecular Compositions and Functions. *Mol Cells*, 41(12):1000-1007.
- [43] Csordás G, Weaver D, Hajnóczky G (2018). Endoplasmic reticulum-mitochondrial contactology: structure and signaling functions. *Trends Cell Biol*, 28(7):523-540.
- [44] Poston CN, Krishnan SC, Bazemore-Walker CR (2013). In-depth proteomic analysis of mammalian mitochondria-associated membranes (MAM). *Journal of Proteomics*, 79:219-230.
- [45] Luan Y, Luan Y, Yuan RX, Feng Q, Chen X, Yang Y (2021). Structure and Function of Mitochondria-Associated Endoplasmic Reticulum Membranes (MAMs) and Their Role in Cardiovascular Diseases. *Oxid Med Cell Longev*, 2021:4578809.
- [46] Youle RJ, Karbowski M (2005). Mitochondrial fission in apoptosis. *Nat Rev Mol Cell Biol*, 6(8):657-63.
- [47] Martorell-Riera A, Segarra-Mondejar M, Muñoz JP, Ginet V, Olloquequi J, Pérez-Clausell J, et al. (2014). Mfn2 downregulation in excitotoxicity causes mitochondrial dysfunction and delayed neuronal death. *EMBO J*, 33(20):2388-407.
- [48] Eysert F, Kinoshita PF, Mary A, Vaillant-Beuchot L, Checler F, Chami M (2020). Molecular Dysfunctions of Mitochondria-Associated Membranes (MAMs) in Alzheimer's Disease. *Int J Mol Sci*, 21(24):9521.
- [49] Basso V, Marchesan E, Peggion C, Chakraborty J, von Stockum S, Giacomello M, et al. (2018). Regulation of ER-mitochondria contacts by Parkin via Mfn2. *Pharmacol Res*, 138:43-56.
- [50] Naon D, Zaninello M, Giacomello M, Varanita T, Grespi F, Lakshminaranayan S, et al. (2016). Critical reappraisal confirms that Mitofusin 2 is an endoplasmic reticulum-mitochondria tether. *Proc Natl Acad Sci USA*, 113(40):11249-11254.
- [51] Han S, Zhao F, Hsia J, Ma X, Liu Y, Torres S, et al. (2021). The role of Mfn2 in the structure and function of endoplasmic reticulum-mitochondrial tethering in vivo. *J Cell Sci*, 134(13):jcs253443.
- [52] Filadi R, Greotti E, Turacchio G, Luini A, Pozzan T, Pizzo P (2015). Mitofusin 2 ablation increases endoplasmic reticulum-mitochondria coupling. *Proc Natl Acad Sci USA*, 112(17):2174-81.
- [53] Hernández-Alvarez MI, Sebastián D, Vives S, Ivanova S, Bartoccioni P, Kakimoto P, et al. (2019). Deficient Endoplasmic Reticulum-Mitochondrial Phosphatidylserine Transfer Causes Liver Disease. *Cell*, 177(4):881-895.e17.
- [54] Kim YJ, Park JK, Kang WS, Kim SK, Han C, Na HR, et al. (2017). Association between mitofusin 2 gene polymorphisms and late-onset Alzheimer's disease in the Korean population. *Psychiatry Investig*, 14(1):81-85.
- [55] Wang X, Su B, Lee HG, Li X, Perry G, Smith MA, Zhu X (2009). Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. *J Neurosci*, 29(28):9090-103.
- [56] Manczak M, Calkins MJ, Reddy PH (2011). Impaired mitochondrial dynamics and abnormal interaction of amyloid beta with mitochondrial protein Drp1 in neurons from patients with Alzheimer's disease: Implications for neuronal damage. *Hum Mol Genet*, 20(13):2495-509.
- [57] Park J, Choi H, Min JS, Kim B, Lee SR, Yun JW, et al. (2015). Loss of mitofusin 2 links beta-amyloid-mediated mitochondrial fragmentation and Cdk5-induced oxidative stress in neuron cells. *J Neurochem*, 132(6):687-702.

- [58] Leal NS, Schreiner B, Pinho CM, Filadi R, Wiehager B, Karlström H, et al. (2016). Mitofusin-2 knockdown increases ER-mitochondria contact and decreases amyloid β -peptide production. *J Cell Mol Med*, 20(9):1686-95.
- [59] Filadi R, Greotti E, Turacchio G, Luini A, Pozzan T, Pizzo P (2016). Presenilin 2 modulates endoplasmic reticulum-mitochondria coupling by tuning the antagonistic effect of mitofusin 2. *Cell Rep*, 15(10):2226-2238.
- [60] DeVos KJ, Mórotz GM, Stoica R, Tudor EL, Lau K, Ackerley S, et al. (2012). VAPB interacts with the mitochondrial protein PTP51 to regulate calcium homeostasis. *Hum Mol Genet*, 21:1299-1311.
- [61] Jiang T, Ruan N, Luo P, Wang Q, Wei X, Li Y, et al. (2024). Modulation of ER-mitochondria tethering complex VAPB-PTP51: Novel therapeutic targets for aging-associated diseases. *Ageing Res Rev*, 98:102320.
- [62] Gómez-Suaga P, Pérez-Nievas BG, Glennon EB, Lau DHW, Paillusson S, Mórotz GM, et al. (2019). The VAPB-PTP51 endoplasmic reticulum-mitochondria tethering proteins are present in neuronal synapses and regulate synaptic activity. *Acta Neuropathol Com*, 7(1):35.
- [63] Yeo HK, Park TH, Kim HY, Jang H, Lee J, Hwang GS, et al. (2021). Phospholipid transfer function of PTP51 at mitochondria-associated ER membranes. *EMBO Rep*, 22(6):e51323.
- [64] Li M, Zhang Y, Yu G, Gu L, Zhu H, Feng S, Xiong X, Jian Z (2024). Mitochondria-associated endoplasmic reticulum membranes tethering protein VAPB-PTP51 protects against ischemic stroke through inhibiting the activation of autophagy. *CNS Neurosci Ther*, 30(4):e14707.
- [65] Stoica R, Paillusson S, Gomez-Suaga P, Mitchell JC, Lau DH, Gray EH, et al. (2016). ALS/FTD-associated FUS activates GSK-3 β to disrupt the VAPB-PTP51 interaction and ER-mitochondria associations. *EMBO Rep*, 17(9):1326-42.
- [66] Cali T, Ottolini D, Negro A, Brini M (2012). Alpha-synuclein controls mitochondrial calcium homeostasis by enhancing endoplasmic reticulum-mitochondria interactions. *J Biol Chem*, 287:17914-17929.
- [67] Lau DHW, Paillusson S, Hartopp N, Rupawala H, Morotz GM, Gomez-Suaga P, et al. (2020). Disruption of endoplasmic reticulum-mitochondria tethering proteins in post-mortem Alzheimer's disease brain. *Neurobiology of Disease*, 143:105020.
- [68] Stoica R, De vos KJ, Paillusson S, Mueller S, Sancho RM, Lau K, et al. (2014). ER-mitochondria associations are regulated by the VAPB-PTP51 interaction and are disrupted by ALS/FTD associated TDP-43. *Nat Commun*, 5:3996.
- [69] Hartopp N, Dawn HW, Martin-Guerrero SM, Markovinov A, Morotz GM, Greig J, et al. (2022). Disruption of the VAPB-PTP51 ER-mitochondria tethering proteins in post-mortem human amyotrophic lateral sclerosis. *Front Cell Dev Biol*, 10:950767.
- [70] Gomez-Suaga P, Mórotz GM, Markovinov A, Martín-Guerrero SM, Preza E, Arias N, et al. (2022). Disruption of ER-mitochondria tethering and signalling in C9orf72-associated amyotrophic lateral sclerosis and frontotemporal dementia. *Aging Cell*, 21(2):e13549.
- [71] Tarasov AI, Griffiths EJ, Rutter GA (2012). Regulation of ATP production by mitochondrial Ca^{2+} . *Cell Calcium*, 52:28-35.
- [72] Pinton P, Giorgi C, Siviero R, Zecchini E, Rizzuto R (2008). Calcium and apoptosis: ER-mitochondria Ca^{2+} transfer in the control of apoptosis. *Oncogene*, 27:6407-6418.
- [73] Strobbe D, Robinson AA, Harvey K, Rossi L, Ferraina C, de Biase V, et al. (2018). Distinct mechanisms of pathogenic DJ-1 mutations in mitochondrial quality control. *Front Mol Neurosci*, 11:68.
- [74] Szabadkai G, Bianchi K, Várnai P, De Stefani D, Wieckowski MR, Cavagna D, et al. (2006). Chaperone-Mediated coupling of endoplasmic reticulum and mitochondrial Ca^{2+} channels. *J Cell Biol*, 175:901-911.
- [75] Jiang RQ, Li QQ, Sheng R (2023). Mitochondria associated ER membranes and cerebral ischemia: Molecular mechanisms and therapeutic strategies. *Pharmacol Res*, 191:106761.
- [76] Repici M, Giorgini F (2019). DJ-1 in Parkinson's disease: clinical insights and therapeutic perspectives. *J Clin Med*, 8(9):1377.
- [77] Basso V, Marchesan E, Ziviani E (2020). A trio has turned into a quartet: DJ-1 interacts with the IP3R-Grp75-VDAC complex to control ER-mitochondria interaction. *Cell Calcium*, 87:102186.
- [78] Liu Y, Ma X, Fujioka H, Liu J, Chen S, Zhu X (2019). DJ-1 regulates the integrity and function of ER-mitochondria association through interaction with IP3R3-Grp75-VDAC1. *Proc Natl Acad Sci USA*, 116(50):25322-25328.
- [79] Honrath B, Met, I, Bendridi N, et al (2017). Glucose-regulated protein 75 determines ER-mitochondrial coupling and sensitivity to oxidative stress in neuronal cells. *Cell Death Discov*, 3:17076.
- [80] Ottolini D, Cali T, Negro A, Brini M (2013). The Parkinson disease-related protein DJ-1 counteracts mitochondrial impairment induced by the tumour suppressor protein p53 by enhancing endoplasmic reticulum-mitochondria tethering. *Hum Mol Genet*, 22(11):2152-68.
- [81] Tiwary S, Nandwani A, Khan R, Datta M (2021). GRP75 mediates endoplasmic reticulum-mitochondria coupling during palmitate-induced pancreatic β -cell apoptosis. *Journal of Biological Chemistry*, 297(6):101368.
- [82] Cuadrado-Tejedor M, Vilariño M, Cabodevilla F, Del Río J, Frechilla D, Pérez-Mediavilla A (2011). Enhanced expression of the voltage-dependent anion channel 1 (VDAC1) in Alzheimer's disease transgenic mice: An insight into the pathogenic effects of amyloid- β . *J. Alzheimers Dis*, 23:195-206.
- [83] Erustes AG, D'Eletto M, Guarache GC, Ureshino RP, Bincoletto C, Da Silva Pereira GJ, et al. (2021). Overexpression of α -synuclein inhibits mitochondrial calcium trafficking between ER and mitochondria through MAM by altering the GRP75-IP3R interaction. *J Neurosci Res*, 99(11):2932-2947.

- [84] Hayashi T, Su TP (2007). $\sigma 1$ receptor chaperones at the ER-mitochondrion interface regulate Ca^{2+} signaling and cell survival. *Cell*, 131: 596–610.
- [85] Iwasawa R, Mahul-Mellier AL, Datler C, Pazarentzos E, Grimm S (2011). Fis1 and Bap31 bridge the mitochondria-ER interface to establish a platform for apoptosis induction. *EMBO J*, 30(3):556–68.
- [86] Wang B, Nguyen M, Chang NC, Shore GC (2011). Fis1, Bap31 and the kiss of death between mitochondria and endoplasmic reticulum. *EMBO J*, 30(3):451–2.
- [87] Wang T, Chen J, Hou Y, Yu Y, Wang B (2019). BAP31 deficiency contributes to the formation of amyloid- β plaques in Alzheimer's disease by reducing the stability of RTN3. *FASEB J*, 33(4):4936–4946.
- [88] Liu X, Jiao K, Jia C, Li G, Yuan Q, Xu J, Hou Y, Wang B (2019). BAP31 regulates IRAK1-dependent neuroinflammation in microglia. *J Neuroinflamm*, 16(1):281.
- [89] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2023). Hallmarks of aging: An expanding universe. *Cell*, 186(2):243 – 278.
- [90] Hipp MS, Kasturi P, Hartl FU (2019). The proteostasis network and its decline in ageing. *Nat Rev Mol Cell Biol*, 20:421–435.
- [91] Srivastava S (2017). The Mitochondrial Basis of Aging and Age-Related Disorders. *Genes (Basel)*, 8(12):398–420.
- [92] Carreras-Sureda A, Kroemer G, Cardenas JC, Hetz C (2022). Balancing energy and protein homeostasis at ER-mitochondria contact sites. *Sci Signal*, 15(741):eabm7524.
- [93] Lan B, He Y, Sun H, Zheng X, Gao Y, Li N (2019). The roles of mitochondria-associated membranes in mitochondrial quality control under endoplasmic reticulum stress. *Life Sciences*, 231:116587.
- [94] Calvo-Rodríguez M, García-Durillo M, Villalobos C, Núñez L (2016). In vitro aging promotes endoplasmic reticulum (ER)-mitochondria Ca^{2+} cross talk and loss of store-operated Ca^{2+} entry (SOCE) in rat hippocampal neurons. *Biochim Biophys Acta*, 1863:2637–2649.
- [95] Wiel C, Lallet-Daher H, Gitenay D et al (2014). Endoplasmic reticulum calcium release through ITPR2 channels leads to mitochondrial calcium accumulation and senescence. *Nat Commun*, 5:3792.
- [96] Ziegler DV, Vindrieux D, Goehrig D, Jaber S, Collin G, Griveau A, et al. (2021). Calcium channel ITPR2 and mitochondria-ER contacts promote cellular senescence and aging. *Nat Commun*, 12(1):720.
- [97] Booth DM, Enyedi B, Geiszt M, Várnai P, Hajnóczky G (2016). Redox Nanodomains Are Induced by and Control Calcium Signaling at the ER-Mitochondrial Interface. *Mol Cell*, 63(2):240–248.
- [98] Lebedzińska M, Duszynski J, Rizzuto R, Pinton P, Wieckowski MR (2009). Age-related changes in levels of p66Shc and serine 36-phosphorylated p66Shc in organs and mouse tissues. *Arch Biochem Biophys*, 486(1):73–80.
- [99] Amr S, Heisey C, Zhang M, Xia XJ, Shows KH, Ajlouni K, et al. (2007). A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for Wolfram syndrome 2. *Am J Hum Genet* 81:673–683.
- [100] Rouzier C, Moore D, Delorme C, Lacas-Gervais S, Ait-El-Mkadem S, Fragaki K, et al. (2017). A novel CISD2 mutation associated with a classical Wolfram syndrome phenotype alters Ca^{2+} homeostasis and ER-mitochondria interactions. *Hum Mol Genet*, 26(9):1599–1611.
- [101] Shen ZQ, Huang YL, Teng YC, Wang TW, Kao CH, Yeh CH, Tsai TF (2021). CISD2 maintains cellular homeostasis. *Biochim Biophys Acta Mol Cell Res*, 1868(4):118954.
- [102] Delprat B, Maurice T, Delettre C (2018). Wolfram syndrome: MAMs' connection? *Cell Death Dis*, 9(3):364.
- [103] Chen YF, Kao CH, Chen YT, Wang CH, Wu CY, Tsai CY, et al. (2009). Cisd2 deficiency drives premature aging and causes mitochondria-mediated defects in mice. *Genes Dev*, 23(10):1183–94.
- [104] Wu CY, Chen YF, Wang CH, Kao CH, Zhuang HW, Chen CC, et al. (2012). A persistent level of Cisd2 extends healthy lifespan and delays aging in mice. *Hum Mol Genet*, 21(18):3956–68.
- [105] Chen YF, Chou TY, Lin IH, et al. (2019). Upregulation of Cisd2 attenuates Alzheimer's-related neuronal loss in mice. *J Pathol*, 250(3):299–311.
- [106] Checler F (1995). Processing of the beta-amyloid precursor protein and its regulation in Alzheimer's disease. *J Neurochem* 65:1431–1444.
- [107] Hardy JA, Higgins GA (1992). Alzheimer's disease: the amyloid cascade hypothesis. *Science*, 256:184–185.
- [108] Kametani F, Hasegawa M (2018). Reconsideration of Amyloid Hypothesis and Tau Hypothesis in Alzheimer's Disease. *Front Neurosci*, 12:25.
- [109] Arnsten AFT, Datta D, Del Tredici K, Braak H (2021). Hypothesis: Tau pathology is an initiating factor in sporadic Alzheimer's disease. *Alzheimers Dement*, 17(1):115–124.
- [110] Swerdlow RH, Burns JM, Khan SM (2010). The Alzheimer's disease mitochondrial cascade hypothesis. *J Alzheimers Dis*, 20(2):S265–79.
- [111] Arimon M, Takeda S, Post K, Svirskey S, Hyman BT, Berezovska O (2015). Oxidative stress and lipid peroxidation are upstream of amyloid pathology. *Neurobiol Dis*, 84:109–119.
- [112] Wells K, Farooqui AA, Liss L, Horrocks LA (1995). Neural membrane phospholipids in Alzheimer disease. *Neurochem Res*, 20:1329–1333.
- [113] Pettegrew JW, Panchalingam K, Hamilton RL, McClure RJ (2001). Brain membrane phospholipid alterations in Alzheimer's disease. *Neurochem Res*, 26:771–782.
- [114] Terada T, Obi T, Bunai T, Matsudaira T, Yoshikawa E, Ando I, et al. (2020). In vivo mitochondrial and glycolytic impairments in patients with Alzheimer disease. *Neurology*, 94(15):e1592–e1604.
- [115] Wang X, Su B, Zheng L, Perry G, Smith MA, Zhu X (2009). The role of abnormal mitochondrial dynamics in the pathogenesis of Alzheimer's disease. *J Neurochem*, 109:153–159.

- [116] Ahmed H, Wang Y, Griffiths WJ, Levey AI, Pikuleva I, Liang SH, Haider A (2024). Brain cholesterol and Alzheimer's disease: challenges and opportunities in probe and drug development. *Brain*, 147(5):1622–1635.
- [117] Ajoalabady A, Lindholm D, Ren J, et al (2022). ER stress and UPR in Alzheimer's disease: mechanisms, pathogenesis, treatments. *Cell Death Dis*, 13(8):706.
- [118] Bezprozvanny I, Mattson MP (2008). Neuronal calcium mishandling and the pathogenesis of Alzheimer's disease. *Trends Neurosci*, 31:454–463.
- [119] Völgyi K, Badics K, Sialana F.J, et al (2018). Early Presymptomatic Changes in the Proteome of Mitochondria-Associated Membrane in the APP/PS1 Mouse Model of Alzheimer's Disease. *Mol Neurobiol*, 55:7839–7857.
- [120] Calvo-Rodriguez M, Hernando-Perez E, Nuñez L, Villalobos C (2019). Amyloid β Oligomers Increase ER-Mitochondria Ca^{2+} Cross Talk in Young Hippocampal Neurons and Exacerbate Aging-Induced Intracellular Ca^{2+} Remodeling. *Front Cell Neurosci*, 13:22.
- [121] Leal NS, Dentoni G, Schreiner B, Naia L, Piras A, Graff C, et al. (2020). Amyloid beta-peptide increases mitochondria-endoplasmic reticulum contact altering mitochondrial function and autophagosome formation in alzheimer's disease-related models. *Cells*, 9(12):2552.
- [122] Fernandes T, Resende R, Silva DF, Marques AP, Santos AE, Cardoso SM, et al. (2021). Structural and Functional Alterations in Mitochondria-Associated Membranes (MAMs) and in Mitochondria Activate Stress Response Mechanisms in an In Vitro Model of Alzheimer's Disease. *Biomedicines*, 9(8):881.
- [123] Garrido-Maraver J, Loh SHY, Martins LM (2020). Forcing contacts between mitochondria and the endoplasmic reticulum extends lifespan in a *Drosophila* model of Alzheimer's disease. *Biol Open*, 9(1):bio047530.
- [124] Schreiner B, Hedskog L, Wiehager B, Ankarcrona M (2015). Amyloid-beta peptides are generated in mitochondria-associated endoplasmic reticulum membranes. *J. Alzheimers Dis*, 43:369–374.
- [125] Zellmer JC, Tarantino MB, Kim M, Lomoio S, Maesako M, Hajnóczky G, Bhattacharyya R (2025). Stabilization of mitochondria-associated endoplasmic reticulum membranes regulates $\text{A}\beta$ generation in a three-dimensional neural model of Alzheimer's disease. *Alzheimers Dement*, 21(2):e14417.
- [126] Area-Gomez E, de Groof A.J, Boldogh I, Bird TD, Gibson GE, Koehler CM, et al. (2009). Presenilins are enriched in endoplasmic reticulum membranes associated with mitochondria. *Am J Pathol*, 175:1810–1816.
- [127] Cheung KH, Shineman D, Muller M, Cardenas C, Mei L, Yang J, et al. (2008). Mechanism of Ca^{2+} disruption in Alzheimer's disease by presenilin regulation of InsP_3 receptor channel gating. *Neuron*, 58:871–883.
- [128] Shilling D, Muller M, Takano H, Mak DO, Abel T, Coulter DA, Foscett JK (2014). Suppression of InsP_3 receptor-mediated Ca^{2+} signaling alleviates mutant presenilin-linked familial Alzheimer's disease pathogenesis. *J Neurosci*, 34:6910–6923.
- [129] Lee CY, Landreth GE (2010). The role of microglia in amyloid clearance from the AD brain. *J Neural Transm*, 117(8):949–60.
- [130] Zhao J, Bi W, Xiao S, Lan X, Cheng X, Zhang J, et al. (2019). Neuroinflammation induced by lipopolysaccharide causes cognitive impairment in mice. *Sci Rep*, 9(1):5790.
- [131] Shah S, Jain H (2024). Microglia-Associated Neuroinflammation in Alzheimer's Disease and Its Therapeutic Potential. *Neuroglia*, 5:452–466.
- [132] Zhang Y, Rao X, Wang J, Liu H, Wang Q, Wang X, et al. (2025). Mitochondria-Associated Membranes: A Key Point of Neurodegenerative Diseases. *CNS Neurosci Ther*, 31(5):e70378.
- [133] Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, et al. (2013). NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature*, 493(7434):674–8.
- [134] Griffin WS, Stanley LC, Ling C, White L, MacLeod V, Perrot LJ, et al. (1989). Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. *Proc Natl Acad Sci USA*, 86(19):7611–5.
- [135] Cacabelos R, Alvarez XA, Fernández-Novoa L, Franco A, Manges R, Pellicer A, et al. (1994). Brain interleukin-1 beta in Alzheimer's disease and vascular dementia. *Methods Find Exp Clin Pharmacol*, 16(2):141–51.
- [136] Patel NS, Paris D, Mathura V, Quadros AN, Crawford FC, Mullan MJ (2005). Inflammatory cytokine levels correlate with amyloid load in transgenic mouse models of Alzheimer's disease. *J Neuroinflammation*, 2(1):9.
- [137] Lonnemann N, Hosseini S, Marchetti C, Skouras DB, Stefanoni D, D'Alessandro A, et al. (2020). The NLRP3 inflammasome inhibitor OLT1177 rescues cognitive impairment in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci USA*, 117(50):32145–32154.
- [138] Kitazawa M, Cheng D, Tsukamoto MR, Koike MA, Wes PD, Vasilevko V, et al. (2011). Blocking IL-1 signaling rescues cognition, attenuates tau pathology, and restores neuronal β -catenin pathway function in an Alzheimer's disease model. *J Immunol*, 187(12):6539–49.
- [139] Kao YC, Ho PC, Tu YK, Jou IM, Tsai KJ (2020). Lipids and Alzheimer's Disease. *Int J Mol Sci*, 21(4):1505.
- [140] Fraser T, Tayler H, Love S (2010). Fatty acid composition of frontal, temporal and parietal neocortex in the normal human brain and in Alzheimer's disease. *Neurochem Res* 35(3):503–513.
- [141] Pani A, Dessì S, Diaz G, La Colla P, Abete C, Mulas C, Paoletti F (2009). Altered cholesterol ester cycle in skin fibroblasts from patients with Alzheimer's disease. *J Alzheimers Dis*, 18(4):829–841.
- [142] Cerasuolo M, Di Meo I, Auriemma MC, Paolisso G, Papa M, Rizzo MR (2024). Exploring the Dynamic Changes of Brain Lipids, Lipid Rafts, and Lipid Droplets in Aging and Alzheimer's Disease. *Biomolecules*, 14:1362.
- [143] Cutler RG, Kelly J, Storie K, Pedersen WA, Tammara A, Hatanpaa K, Mattson MP (2004). Involvement of oxidative stress-induced abnormalities in ceramide and

- cholesterol metabolism in brain aging and Alzheimer's disease. *Proc Natl Acad Sci USA*, 101(7):2070-2075.
- [144] Panchal M, Loeper J, Cossec JC, Perruchini C, Lazar A, Pompon D, Duyckaerts C (2010). Enrichment of cholesterol in microdissected Alzheimer's disease senile plaques as assessed by mass spectrometry. *J Lipid Res*, 51(3):598-605.
- [145] Sparks DL, Scheff SW, Hunsaker JC 3rd, Liu H, Lander T, Gross DR (1994). Induction of Alzheimer-like beta-amyloid immunoreactivity in the brains of rabbits with dietary cholesterol. *Exp Neurol*, 126(1):88-94.
- [146] Refolo LM, Pappolla MA, Malester B, LaFrancois J, Bryant-Thomas T, Wang R, Duff K (2000). Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. *Neurobiol Dis*, 7(4):321-331.
- [147] Reiss AB, Voloshyna I (2012). Regulation of cerebral cholesterol metabolism in Alzheimer disease. *J Invest Med*, 60(3):576-82.
- [148] Ghribi O, Larsen B, Schrag M, Herman MM (2006). High cholesterol content in neurons increases BACE, β -amyloid, and phosphorylated tau levels in rabbit hippocampus. *Exp Neurol*, 200:460-467.
- [149] Pappolla MA, Bryant-Thomas TK, Herbert D, Pacheco J, Fabra Garcia M, Manjon M, Refolo LM (2003). Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. *Neurology*, 61(2):199-205.
- [150] Beydoun MA, Beydoun HA, Wang Y (2008). Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obes Rev*, 9(3):204-218.
- [151] Agrawal RR, Montesinos J, Larrea D, Area-Gomez E, Pera M (2020). The silence of the fats: A MAM's story about Alzheimer. *Neurobiology of Disease*, 145:105062.
- [152] Harned TC, Stan RV, Cao Z, Chakrabarti R, Higgs HN, Chang CCY, Chang TY (2023). Acute ACAT1/SOAT1 Blockade Increases MAM Cholesterol and Strengthens ER-Mitochondria Connectivity. *Int J Mol Sci*, 24(6):5525.
- [153] Pera M, Montesinos J, Larrea D, Agrawal RR, Velasco KR, Stavrovskaya IG, et al. (2020). MAM and C99, key players in the pathogenesis of Alzheimer's disease. *International Review of Neurobiology*, Academic Press, 154:235-278.
- [154] Zampese E, Fasolato C, Kipanyula MJ, Bortolozzi M, Pozzan T, Pizzo P (2011). Presenilin 2 modulates endoplasmic reticulum (ER)-mitochondria interactions and Ca^{2+} cross-talk. *Proc Natl Acad Sci USA*, 108:2777-2782.
- [155] Hutter-Paier B, Huttunen HJ, Puglielli L, Eckman CB, Kim DY, Hofmeister A, et al. (2004). The ACAT Inhibitor CP-113,818 Markedly Reduces Amyloid Pathology in a Mouse Model of Alzheimer's Disease. *Neuron*, 44:227-238.
- [156] Huttunen HJ, Havas D, Peach C, Barren C, Duller S, Xia W, et al. (2010). The Acyl-Coenzyme A:Cholesterol Acyltransferase Inhibitor CI-1011 Reverses Diffuse Brain Amyloid Pathology in Aged Amyloid Precursor Protein Transgenic Mice. *J Neuropathol Exp Neurol*, 69:777-788.
- [157] Murphy SR, Chang CCY, Dogbevia G, Bryleva EY, Bowen ZD, Hasan MT, Chang TY (2013). Acat1 Knockdown Gene Therapy Decreases Amyloid- β in a Mouse Model of Alzheimer's Disease. *Am Soc Gene Cell Ther*, 21:1497-1506.
- [158] Tambini MD, Pera M, Kanter E, Yang H, Guardia-Laguarta C, Holtzman D, et al. (2016). ApoE4 upregulates the activity of mitochondria-associated ER membranes. *EMBO Rep*, 17(1):27-36.
- [159] Liang T, Hang W, Chen J, Wu Y, Wen B, Xu K, et al. (2021). ApoE4 (Δ 272-299) induces mitochondrial-associated membrane formation and mitochondrial impairment by enhancing GRP75-modulated mitochondrial calcium overload in neuron. *Cell Biosci*, 11(1):50.
- [160] Elbaz A, Carcaillon L, Kab S, Moisan F (2016). Epidemiology of Parkinson's disease. *Revue Neurologique*, 172(1):14-26.
- [161] Mehra S, Sahay S, Maji SK (2019). α -Synuclein misfolding and aggregation: Implications in Parkinson's disease pathogenesis. *Biochim Biophys Acta Proteins Proteom*, 1867:890-908.
- [162] Barbuti PA (2024). A-Syn(ful) MAM: A Fresh Perspective on a Converging Domain in Parkinson's Disease. *Int J Mol Sci*, 25(12):6525.
- [163] Cali T, Ottolini D, Negro A, Brini M (2012). α -synuclein controls mitochondrial calcium homeostasis by enhancing endoplasmic reticulum-mitochondria interactions. *J Biol Chem*, 287(22):17914-17929.
- [164] Guardia-Laguarta C, Area-Gomez E, Rüb C, Liu Y, Magrané J, Becker D, et al. (2014). α -Synuclein is localized to mitochondria-associated ER membranes. *J Neurosci*, 34:249-259.
- [165] Paillusson S, Gomez-Suaga P, Stoica R, Little D, Gissen P, Devine MJ, et al. (2017). α -Synuclein binds to the ER-mitochondria tethering protein VAPB to disrupt Ca^{2+} homeostasis and mitochondrial ATP production. *Acta Neuropathol*, 134:129-149.
- [166] Wang X, Petrie TG, Liu Y, Liu J, Fujioka H, Zhu X (2012). Parkinson's disease-associated DJ-1 mutations impair mitochondrial dynamics and cause mitochondrial dysfunction. *J Neurochem*, 121:830-839.
- [167] Irrcher I, Aleyasin H, Seifert EL, Hewitt SJ, Chhabra S, Phillips M et al. (2010). Loss of the Parkinson's disease-linked gene DJ-1 perturbs mitochondrial dynamics. *Hum Mol Genet*, 19(19):3734-46.
- [168] Cali T, Ottolini D, Negro A, Brini M (2013). Enhanced parkin levels favor ER-mitochondria crosstalk and guarantee Ca^{2+} transfer to sustain cell bioenergetics. *Biochimica Et Biophysica Acta (Bba) - Molecular Basis of Disease*, 1832:495-508.
- [169] Sunanda T, Ray B, Mahalakshmi AM, Bhat A, Rashan L, Rungratanawanich W, et al. (2021). Mitochondria-Endoplasmic Reticulum Crosstalk in Parkinson's Disease: The Role of Brain Renin Angiotensin System Components. *Biomolecules*, 11(11):1669.
- [170] Celardo I, Costa AC, Lehmann S, Jones C, Wood N, Mencacci NE, et al. (2016). Mitofusin-mediated ER

- stress triggers neurodegeneration in pink1/parkin models of Parkinson's disease. *Cell Death Dis*, 7(6):e2271.
- [171] McLelland GL, Goiran T, Yi W, Dorval G, Chen CX, Lauinger ND, et al. (2018). Mfn2 ubiquitination by PINK1/parkin gates the p97-dependent release of ER from mitochondria to drive mitophagy. *Elife*, 7:e32866.
- [172] Toyofuku T, Okamoto Y, Ishikawa T, Sasawatari S, Kumanogoh A (2020). LRRK2 regulates endoplasmic reticulum-mitochondrial tethering through the PERK-mediated ubiquitination pathway. *EMBO J*, 39(2):e100875.
- [173] Liu J, Yang J (2022). Mitochondria-associated membranes: A hub for neurodegenerative diseases. *Biomed Pharmacother*, 149:112890.
- [174] Yamanaka K, Boillee S, Roberts EA, Garcia ML, McAlonis-Downes M, Mikse OR, et al. (2008). Mutant SOD1 in cell types other than motor neurons and oligodendrocytes accelerate onset of disease in ALS mice. *Proc Natl Acad Sci USA*, 105:7594-7599.
- [175] Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, et al. (1993). Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature*, 362(6415):59-62.
- [176] Kwiatkowski TJ Jr, Bosco DA, Leclerc AL, Tamrazian E, Vanderburg CR, Russ C, et al. (2009). Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. *Science*, 323(5918):1205-8.
- [177] Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, et al. (2011). A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron*, 72(2):257-68.
- [178] Sreedharan J, Blair IP, Tripathi VB, Hu X, Vance C, Rogelj B, et al. (2008). TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. *Science*, 319(5870):1668-72.
- [179] Van Deerlin VM, Leverenz JB, Bekris LM, Bird TD, Yuan W, Elman LB, et al. (2008). TARDBP mutations in amyotrophic lateral sclerosis with TDP-43 neuropathology: a genetic and histopathological analysis. *Lancet Neurol*, 7(5):409-16.
- [180] Al-Saif A, Al-Mohanna F, Bohlega S (2011). A mutation in sigma-1 receptor causes juvenile amyotrophic lateral sclerosis. *Ann Neurol*, 70(6):913-9.
- [181] Nishimura AL, Mitne-Neto M, Silva HC, Richieri-Costa A, Middleton S, Cascio D, et al. (2004). A mutation in the vesicle-trafficking protein VAPB causes late-onset spinal muscular atrophy and amyotrophic lateral sclerosis. *Am J Hum Genet*, 75(5):822-31.
- [182] Ignatius SH, Wu F, Harrich D, Garciamartinez LF, Gaynor RB (1995). Cloning and characterization of a novel cellular protein, Tdp-43, that binds to human-immunodeficiency-virus type-1 Tar DNA-sequence motifs. *J Virol*, 69:3584-3596.
- [183] Ishiguro T, Sato N, Ueyama M, Fujikake N, Sellier C, Kanegami A, et al (2017). Regulatory role of RNA chaperone TDP-43 for RNA misfolding and repeat-associated translation in SCA31. *Neuron*, 94(1):108-124.e7.
- [184] Arai T, Hasegawa M, Akiyama H, Ikeda K, Nonaka T, Mori H, et al. (2006). TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Biochem Biophys Res Commun*, 351(3):602-11.
- [185] Markovinovic A, Martín-Guerrero SM, Mórotz GM, Salam S, Gomez-Suaga P, Paillusson S, et al. (2024). Stimulating VAPB-PTPIP51 ER-mitochondria tethering corrects FTD/ALS mutant TDP43 linked Ca²⁺ and synaptic defects. *Acta Neuropathol Commun*, 12(1):32.
- [186] Assoni AF, Foiijer F, Zatz M (2023). Amyotrophic Lateral Sclerosis, FUS and Protein Synthesis Defects. *Stem Cell Rev Rep*, 19(3):625-638.
- [187] DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, et al. (2011). Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron*, 72:245-256.
- [188] Nishimura AL, Mitne-Neto M, Silva HC, Richieri-Costa A, Middleton S, Cascio D, et al. (2004). A mutation in the vesicle-trafficking protein VAPB causes late-onset spinal muscular atrophy and amyotrophic lateral sclerosis. *Am J Hum Genet*, 75(5):822-31.
- [189] Fasana E, Fossati M, Ruggiano A, Brambillasca S, Hoogenraad CC, Navone F, et al. (2010). A VAPB mutant linked to amyotrophic lateral sclerosis generates a novel form of organized smooth endoplasmic reticulum. *FASEB J*, 24(5):1419-30.
- [190] Ullah MI, Ahmad A, Raza SI, Amar A, Ali A, Bhatti A, et al. (2015). In silico analysis of σR1 variant (rs4879809) segregating in a consanguineous Pakistani family showing amyotrophic lateral sclerosis without frontotemporal lobar dementia. *Neurogenetics*, 16:299-306.
- [191] Luty AA, Kwok JB, Dobson-Stone C, Loy CT, Coupland KG, Karlström H, et al. (2010). Sigma nonopioid intracellular receptor 1 mutations cause frontotemporal lobar degeneration-motor neuron disease. *Ann Neurol*, 68(5):639-49.
- [192] Mavlyutov TA, Epstein ML, Andersen KA, Ziskind-Conhaim L, Ruoho AE (2010). The sigma-1 receptor is enriched in postsynaptic sites of C-terminals in mouse motoneurons. An anatomical and behavioral study. *Neuroscience*, 167(2):247-255.
- [193] Su TP, Hayashi T, Maurice T, Buch S, Ruoho AE (2010). The sigma-1 receptor chaperone as an inter-organelle signaling modulator. *Trends Pharmacol Sci*, 31(12):557-566.
- [194] Bernard-Marissal N, Médard JJ, Azzedine H, Chrast R (2015). Dysfunction in endoplasmic reticulum-mitochondria crosstalk underlies SIGMAR1 loss of function mediated motor neuron degeneration. *Brain*, 138(4):875-890.
- [195] Watanabe S, Ilieva H, Tamada H, Nomura H, Komine O, Endo F, et al. (2016). Mitochondria-associated membrane collapse is a common pathomechanism in σR1- and SOD1-linked ALS. *EMBO Mol Med*, 8:1421-1437.

- [196] Mancuso R, Oliván S, Rando A, Casas C, Osta R, Navarro X (2012). $\sigma 1$ R agonist improves motor function and motoneuron survival in ALS mice. *Neurotherapeutics*, 9:814–826.
- [197] Ono Y, Tanaka H, Takata M, Nagahara Y, Noda Y, Tsuruma K, et al. (2014). SA4503, a sigma-1 receptor agonist, suppresses motor neuron damage in in vitro and in vivo amyotrophic lateral sclerosis models. *Neurosci Lett*, 559:174–8.
- [198] Fehér Á, Juhász A, László A, Kálmán J, Pákási M, Kálmán J, Janka Z (2012). Association between a variant of the $\sigma 1$ receptor gene and Alzheimer's disease. *Neurosci Lett*, 517:136–139.
- [199] Jansen KL, Faull RL, Storey P, Leslie RA (1993). Loss of sigma binding sites in the CA1 area of the anterior hippocampus in Alzheimer's disease correlates with CA1 pyramidal cell loss. *Brain Res*, 623(2):299–302.
- [200] Larrea D, Tamucci KA, Kabra K et al (2025). Altered mitochondria-associated ER membrane (MAM) function shifts mitochondrial metabolism in amyotrophic lateral sclerosis (ALS). *Nat Commun*, 16(1):379.
- [201] Israelson A, Arbel N, Da Cruz S, Ilieva H, Yamanaka K, Shoshan-Barmatz V, Cleveland DW (2010). Misfolded mutant SOD1 directly inhibits VDAC1 conductance in a mouse model of inherited ALS. *Neuron*, 67(4):575–87.
- [202] Shteinfer-Kuzmine A, Argueti S, Gupta R, Shvil N, Abu-Hamad S, Gropper Y, et al. (2019) A VDAC1-Derived N-Terminal Peptide Inhibits Mutant SOD1-VDAC1 Interactions and Toxicity in the SOD1 Model of ALS. *Front Cell Neurosci*, 13:346.
- [203] Parry GJ, Rodrigues CMP, Low WC, Hilbert SJ, Steer CJ (2016). Ursodeoxycholic Acid May Slow the Progression of Amyotrophic Lateral Sclerosis. *Ann Neurodegener Dis*, 1(3):1013.
- [204] Dionísio PA, Amaral JD, Ribeiro MF, Lo AC, D'Hooge R, Rodrigues CM (2015). Amyloid- β pathology is attenuated by tauroursodeoxycholic acid treatment in APP/PS1 mice after disease onset. *Neurobiol Aging*, 36(1):228–40.
- [205] Song H, Liu J, Wang L, Hu X, Li J, Zhu L, et al. (2024). Tauroursodeoxycholic acid: a bile acid that may be used for the prevention and treatment of Alzheimer's disease. *Front Neurosci*, 18:1348844.
- [206] Lo Giudice M, Cocco A, Reggiardo G, Lalli S, Albanese A (2023). Tauro-Urso-Deoxycholic Acid Trials in Amyotrophic Lateral Sclerosis: What is Achieved and What to Expect. *Clin Drug Investig*, 43(12):893–903.
- [207] Payne T, Appleby M, Buckley E, van Gelder LMA, Mullish BH, Sassani M, et al. (2023). A Double-Blind, Randomized, Placebo-Controlled Trial of Ursodeoxycholic Acid (UDCA) in Parkinson's Disease. *Mov Disord*, 38(8):1493–1502.
- [208] Payne T, Sassani M, Buckley E, Moll S, Anton A, Appleby M, et al. (2020). Ursodeoxycholic acid as a novel disease-modifying treatment for Parkinson's disease: protocol for a two-centre, randomised, double-blind, placebo-controlled trial, The 'UP' study. *BMJ Open*, 10(8):e038911.
- [209] Martínez-González L, Gonzalo-Consuegra C, Gómez-Almería M, Porras G, de Lago E, Martín-Requero Á, Martínez A (2021). Tideglusib, a Non-ATP Competitive Inhibitor of GSK-3 β as a Drug Candidate for the Treatment of Amyotrophic Lateral Sclerosis. *Int J Mol Sci*, 22(16):8975.
- [210] del Ser T, Steinwachs KC, Gertz HJ, Andrés MV, Gómez-Carrillo B, Medina M, et al. (2013). Treatment of Alzheimer's disease with the GSK-3 inhibitor tideglusib: a pilot study. *J Alzheimers Dis*, 33(1):205–15.
- [211] Shen Y, Zhao M, Zhao P, Meng L, Zhang Y, Zhang G, et al. (2024). Molecular mechanisms and therapeutic potential of lithium in Alzheimer's disease: repurposing an old class of drugs. *Front Pharmacol*, 15:1408462.
- [212] Noble W, Planel E, Zehr C, Olm V, Meyerson J, Suleman F et al. (2005). Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration in vivo. *Proc Natl Acad Sci USA*. 102:6990–6995.
- [213] Wiseman AL, Briggs CA, Peritt A, Kapecki N, Peterson DA, Shim SS, Stutzmann GE (2023). Lithium Provides Broad Therapeutic Benefits in an Alzheimer's Disease Mouse Model. *J Alzheimers Dis*, 91(1):273–290.
- [214] Miller RG, Moore DH, Forsheve DA, Katz JS, Barohn RJ, Valan M, et al. (2011). WALIS Study Group. Phase II screening trial of lithium carbonate in amyotrophic lateral sclerosis: examining a more efficient trial design. *Neurology*, 77(10):973–9.
- [215] Höing S, Yeh TY, Baumann M, Martinez NE, Habenberger P, Kremer L, et al. (2018). Dynarrestin, a Novel Inhibitor of Cytoplasmic Dynein. *Cell Chem Biol*, 25(4):357–369.e6.
- [216] Dietel E, Brobeil A, Delventhal L, Tag C, Gattenlöhner S, Wimmer M (2019). Crosstalks of the PTP1B51 interactome revealed in Her2 amplified breast cancer cells by the novel small molecule LDC3/Dynarrestin. *PLoS One*, 14(5):e0216642.
- [217] Ryskamp DA, Korban S, Zhemkov V, Kraskovskaya N, Bezprozvanny I (2019). Neuronal Sigma-1 Receptors: Signaling Functions and Protective Roles in Neurodegenerative Diseases. *Front Neurosci*, 13:862.
- [218] Filadi R, Pizzo P (2024). Endoplasmic reticulum-mitochondria lockdown in Wolfram syndrome. *Cell Calcium*, 124:102955.
- [219] Crouzier L, Danese A, Yasui Y, Richard EM, Liévens JC, Patergnani S, et al. (2022). Activation of the sigma-1 receptor chaperone alleviates symptoms of Wolfram syndrome in preclinical models. *Sci Transl Med*, 14(631):eab3763.
- [220] Ionescu A, Gradus T, Altman T, Maimon R, Saraf Avraham N, Geva M, et al. (2019). Targeting the Sigma-1 Receptor via Pridopidine Ameliorates Central Features of ALS Pathology in a SOD1^{G93A} Model. *Cell Death Dis*, 10(3):210.
- [221] Macfarlane S, Grimmer T, Teo K, O'Brien TJ, Woodward M, Grunfeld J, et al. (2025). Blarcamesine for the treatment of Early Alzheimer's Disease: Results from the ANAVEX2-73-AD-004 Phase IIB/III trial. *J Prev Alzheimers Dis*, 12(1):100016.
- [222] Hou Y, Zhao W, Yu H, Zhang F, Zhang HT, Zhou Y (2022). Biochanin A alleviates cognitive impairment and

- hippocampal mitochondrial damage in ovariectomized APP/PS1 mice. *Phytomedicine*, 100:154056.
- [223] Singh L, Kaur N, Bhatti R (2023). Neuroprotective potential of biochanin-A and review of the molecular mechanisms involved. *Mol Biol Rep*, 50(6):5369-5378.
- [224] Zhu WL, Zheng JY, Cai WW, Dai Z, Li BY, Xu TT, Liu HF, et al. (2020). Ligustilide improves aging-induced memory deficit by regulating mitochondrial related inflammation in SAMP8 mice. *Aging*, 12(4):3175-3189. Erratum in: *Aging* 12(6):5587.
- [225] Zhang Q, Zhang X, Yang B, Li Y, Sun XH, Li X, Sui P, et al. (2024). Ligustilide-loaded liposome ameliorates mitochondrial impairments and improves cognitive function via the PKA/AKAP1 signaling pathway in a mouse model of Alzheimer's disease. *CNS Neurosci Ther*, 30(3):e14460.
- [226] Yao X, Zhang J, Lu Y, Deng Y, Zhao R, Xiao S (2022). Myricetin Restores A β -Induced Mitochondrial Impairments in N2a-SW Cells. *ACS Chem Neurosci*, 13(4):454-463.
- [227] Wang L, Tang Z, Li B, Peng Y, Yang X, Xiao Y, et al. (2024). Myricetin ameliorates cognitive impairment in 3 $\times$ Tg Alzheimer's disease mice by regulating oxidative stress and tau hyperphosphorylation. *Biomed Pharmacother*, 177:116963.
- [228] Liu P, Zhou Y, Shi J, Wang F, Yang X, Zheng X, et al. (2023). Myricetin improves pathological changes in 3 $\times$ Tg-AD mice by regulating the mitochondria-NLRP3 inflammasome-microglia channel by targeting P38 MAPK signaling pathway. *Phytomedicine*, 115:154801.
- [229] Xu YJ, Mei Y, Shi XQ, Zhang YF, Wang XY, Guan L, et al. (2019). Albiflorin ameliorates memory deficits in APP/PS1 transgenic mice via ameliorating mitochondrial dysfunction. *Brain Res*, 1719:113-123.
- [230] Cheng Y, Buchan M, Vitanova K, Aitken L, Gunn-Moore FJ, Ramsay RR, Doherty G (2020). Neuroprotective actions of leptin facilitated through balancing mitochondrial morphology and improving mitochondrial function. *J Neurochem*, 155(2):191-206.
- [231] Chen C, Chen Y, Zhang ZH, Jia SZ, Chen YB, Huang SL, Xu XW, Song GL (2021). Selenomethionine Improves Mitochondrial Function by Upregulating Mitochondrial Selenoprotein in a Model of Alzheimer's Disease. *Front Aging Neurosci*, 13:750921.
- [232] Qian W, Wei-wei Q, Jie-wen Z (2019). Effect of Ferulic Acid on Learning and Memory Impairment by the Repairing of Mitochondrial Fission-Fusion Imbalance in AD Mice. *Chin Pharm J*, 54:703-710.
- [233] Nunes YC, Mendes NM, Pereira de Lima E, Chehadi AC, Lamas CB, Haber JFS, et al. (2024). Curcumin: A Golden Approach to Healthy Aging: A Systematic Review of the Evidence. *Nutrients*, 16(16):2721.
- [234] Cox KH, Pipingas A, Scholey AB (2015). Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population. *J Psychopharmacol*, 29(5):642-51.
- [235] Das SS, Gopal PM, Thomas JV, Mohan MC, Thomas SC, Maliakel BP, et al. (2023). Influence of CurQfen®-curcumin on cognitive impairment: a randomized, double-blinded, placebo-controlled, 3-arm, 3-sequence comparative study. *Front Dement*, 2:1222708.
- [236] Chu B, Li M, Cao X, Li R, Jin S, Yang H, Xu L, Wang P, Bi J (2021). IRE1 α -XBP1 Affects the Mitochondrial Function of A β 25-35-Treated SH-SY5Y Cells by Regulating Mitochondria-Associated Endoplasmic Reticulum Membranes. *Front Cell Neurosci*, 15:614556.
- [237] Celardo I, Costa AC, Lehmann S, Jones C, Wood N, Mencacci NE, Mallucci GR, Loh SH, Martins LM (2016). Mitofusin-mediated ER stress triggers neurodegeneration in pink1/parkin models of Parkinson's disease. *Cell Death Dis*, 7(6):e2271.
- [238] Robb EL, Moradi F, Maddalena LA, Valente AJF, Fonseca J, Stuart JA (2017). Resveratrol stimulates mitochondrial fusion by a mechanism requiring mitofusin-2. *Biochem Biophys Res Commun*, 485(2):249-254.
- [239] Signorile A, Ferretta A, Pacelli C, Capitanio N, Tanzarella P, Matrella ML, et al. (2021). Resveratrol Treatment in Human Parkin-Mutant Fibroblasts Modulates cAMP and Calcium Homeostasis Regulating the Expression of Mitochondria-Associated Membranes Resident Proteins. *Biomolecules*, 11(10):1511.
- [240] Thiel G, Rössler OG (2017). Resveratrol regulates gene transcription via activation of stimulus-responsive transcription factors. *Pharmacol Res*, 117:166-176.
- [241] Lee HJ, Jung YH, Choi GE, Kim JS, Chae CW, Lim JR, Kim SY, Yoon JH, Cho JH, Lee SJ, Han HJ (2021). Urolithin A suppresses high glucose-induced neuronal amyloidogenesis by modulating TGM2-dependent ER-mitochondria contacts and calcium homeostasis. *Cell Death Differ*, 28(1):184-202.
- [242] Hewitt VL, Miller-Fleming L, Twynning MJ, Andreazza S, Mattedi F, Prudent J, Polleux F, Vagnoni A, Whitworth AJ (2022). Decreasing pdzd8-mediated mito-ER contacts improves organismal fitness and mitigates A β 42 toxicity. *Life Sci Alliance*, 5(11):e202201531.
- [243] Wang K, Long B, Jiao JQ, Wang JX, Liu JP, Li Q, Li PF (2012). miR-484 regulates mitochondrial network through targeting Fis1. *Nat Commun*, 3:781.
- [244] Wang WX, Prajapati P, Nelson PT, Springer JE (2020). The Mitochondria-Associated ER Membranes Are Novel Subcellular Locations Enriched for Inflammatory-Responsive MicroRNAs. *Mol Neurobiol*, 57(7):2996-3013.
- [245] Vickers KC, Landstreet SR, Levin MG, Shoucri BM, Toth CL, Taylor RC, Palmisano BT, Tabet F, Cui HL, Rye KA, Sethupathy P, Remaley AT (2014). MicroRNA-223 coordinates cholesterol homeostasis. *Proc Natl Acad Sci U S A*, 111(40):14518-23.