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Organelle abnormalities in Alzheimer's disease

Ju Gao,[1] Lauren Vicuna,[1] and Xinglong Wang[1,*]
[1]Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson, AZ 85721, USA
*Correspondence to: Xinglong Wang, Department of Pharmacology & Toxicology, University of Arizona, 1703 E Mabel Street, Skaggs Bldg Rm 112, Tucson AZ 85721, UNITED STATES, 520-626-5963, xlwang@arizona.edu

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia, pathologically characterized by extracellular amyloid plaques and intracellular neurofibrillary tangles. While these pathological hallmarks remain central to our understanding of AD, they do not fully explain the complex cellular failures observed throughout the disease course. Neurons are highly specialized and polarized cells that depend on an integrated and dynamic network of specialized subcellular compartments named organelles to maintain structure, metabolism, and communication. Given these critical roles, organelle dysfunction is increasingly recognized as a key contributor to AD pathogenesis. Structural and functional impairments in conventional organelles, including mitochondria, endoplasmic reticulum (ER), lysosomes, Golgi apparatus, and peroxisomes, are consistently observed in AD brains and experimental models. These impairments are believed to cause energy failure, disrupted proteostasis, intracellular trafficking defects, and elevated oxidative and ER stress. In parallel, abnormalities in membraneless organelles (MLOs) further compromise RNA regulation, protein synthesis, and cellular stress responses. Additionally, perturbed communication between organelles, such as at mitochondria-associated ER membranes (MAMs), lipid droplets, and primary cilia, further exacerbates signaling imbalances and neuronal vulnerability. In this review, we not only provide a comprehensive overview of abnormalities in both membrane-bound and membraneless organelles in AD, emphasizing how their dysfunction contributes to cellular stress, impaired homeostasis, and neurodegeneration, but also discuss how disruptions in organelles intersect with amyloid, tau, and other AD-associated pathologies to intensify disease progression. A deeper understanding of organelle dysfunction in AD may provide new mechanism insights and advance the development of effective disease modifying interventions.

Key words: Alzheimer's disease; organelle dysfunction; amyloid plaques; tau pathology; mitochondria; endoplasmic reticulum stress; membraneless organelles; liquid-liquid phase separation

INTRODUCTION

Alzheimer's disease (AD), first described in 1906 by Dr. Alois Alzheimer, is now recognized as the most common cause of dementia globally [1]. AD primarily targets brain regions critical for cognition and memory, including the cerebral cortex, basal forebrain, and hippocampus [2]. Clinically, it presents as a gradual and relentless decline in cognitive, behavioral, and motor functions, beginning with memory impairment and disorientation, and eventually progressing to severe neuropsychiatric symptoms and loss of motor control [2]. Neuropathologically, AD is characterized by extracellular senile plaques (SPs) composed of amyloid-β (Aβ) fibrils and intracellular neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau [3]. These hallmark lesions are accompanied by widespread neuronal loss, synaptic degeneration, dystrophic neurites, neuropil threads, and cerebral amyloid angiopathy (CAA) [3]. In recent years, TAR DNA-binding protein 43 (TDP-43) pathology has emerged as a common co-pathology in AD and related conditions such as limbic-predominant age-related TDP-43 encephalopathy (LATE) and cerebral age-related TDP-43 with sclerosis (CARTS), further compounding disease complexity and progression [4–7] (**Figure 1**).

Beyond these classical proteinopathies, organelle dysfunction has been long implicated as a critical contributor to the pathogenesis of AD. Organelles are specialized subcellular compartments responsible for essential cellular functions such as energy production, protein processing, intracellular trafficking, and stress responses. These structures can be classified as membrane-bound (e.g., mitochondria, lysosomes, endoplasmic reticulum [ER], and Golgi apparatus) or non–membrane-bound (e.g., nucleoli, ribosomes, stress granules, and proteasomes). In AD–affected neurons, both categories show pronounced structural abnormalities and functional decline. Mitochondria in AD brains are frequently fragmented, swollen, and exhibit inner structure loss [8]. These alterations are associated with impaired oxidative phosphorylation, reduced ATP production, and elevated reactive oxygen species (ROS), leading to oxidative stress and neuronal damage [9,10]. Lysosomal defects have also been widely reported in AD and are believed to impair autophagic degradation, resulting in the accumulation of undegraded substrates and misfolded proteins [11]. Similarly, persistent endoplasmic reticulum (ER) stress has been observed in AD and is associated with maladaptive activation of the unfolded protein response (UPR), which disrupts protein folding and activates pro-apoptotic pathways [12]. Fragmentation of the Golgi apparatus further interferes with vesicular trafficking and protein maturation,

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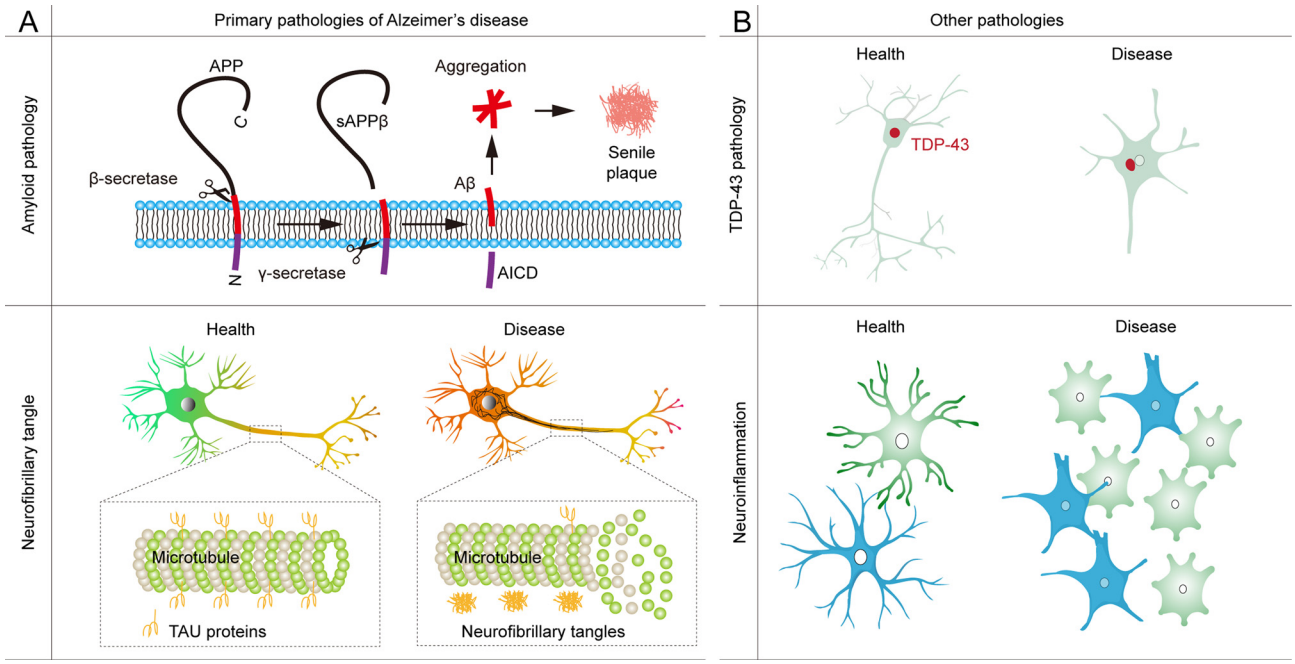

Figure 1. Pathologies in Alzheimer's disease.

(**A**) Amyloid plaques and neurofibrillary tangles are the two primary pathological hallmarks of AD. Full-length amyloid precursor protein (APP) undergoes sequential processing to generate amyloid peptides that ultimately aggregate into amyloid plaques. Microtubule-associated protein tau (MAPT) normally stabilizes microtubules, but under disease conditions, it becomes hyperphosphorylated, dissociates from microtubules, and forms fibrillar aggregates known as neurofibrillary tangles. (**B**) Other pathological features in AD include TDP-43 inclusions, recently identified as a secondary pathology present in over 50% of AD cases. Under physiological conditions, TDP-43 is in the nucleus, but in AD, shows nuclear clearance and cytoplasmic aggregation. Alongside these protein aggregates, widespread neuroinflammation is obvious in AD brains, with increased numbers of activated glial cells, such as microglia and astrocytes, showing altered morphology and immunological states.

aggravating intracellular dysfunction [13]. Non–membrane-bound or membraneless organelles (MLOs) organelles are also affected: proteasomal activity is often overwhelmed, allowing toxic protein aggregates such as amyloid-β and hyperphosphorylated tau to accumulate, while ribosomal dysfunction impairs protein synthesis [14–16]. In addition, nucleolar abnormalities and chromatin instability have been implicated in transcriptional dysregulation [17]. Cytoskeletal defects, including disorganization of actin filaments and microtubules, further disrupt intracellular transport and synaptic integrity, contributing to widespread neuronal degeneration in AD [18].

Given the widespread impact of organelle dysfunction in AD, emerging therapeutic strategies targeting these cellular components are gaining attention. Approaches to restore mitochondrial bioenergetics using targeted antioxidants, enhance lysosomal clearance through pharmacologic TFEB activation, or alleviate ER stress via chemical chaperones and UPR modulators have shown promise in preclinical studies [19–21]. Additionally, stabilizing the cytoskeleton with compounds such as epothilones may improve axonal transport and neuronal connectivity [22]. These interventions collectively aim to reestablish cellular homeostasis and reduce vulnerability to Aβ, tau, and other pathogenic factors. In this review, we provide a comprehensive overview of organelle abnormalities in AD, highlighting their contribution to disease progression and evaluating the therapeutic potential of strategies designed to restore organelle function.

Membrane-bound Organelles

Mitochondria: Mitochondria are essential organelles involved in ATP production, metabolite synthesis, calcium (Ca^{2+}) buffering, apoptosis regulation, and ROS generation. Once considered static, they are recognized as highly dynamic and are constantly undergoing fission and fusion to adapt their morphology and distribution based on cellular needs [23]. Neurons are particularly reliant on mitochondrial function due to their high energy demands, limited glycolytic capacity, and vulnerability to calcium imbalance and oxidative stress [24]. As such, mitochondrial dysfunction has severe consequences for neuronal health and is a prominent early feature of AD [25]. Although the precise mechanisms remain unclear, growing evidence implicates disrupted mitochondrial dynamics, particularly excessive fission and impaired fusion, in promoting bioenergetic failure, oxidative damage, and neurodegeneration in AD (**Figure 2**).

One of the core mitochondrial functions is the production of ATP through oxidative phosphorylation (OXPHOS), which takes place in the inner mitochondrial membrane. This process involves the electron transport chain (ETC), consisting of four protein complexes (I through IV) that transfer electrons from NADH and $FADH_2$ to oxygen. As electrons move through the ETC, protons are pumped across the inner membrane, generating an electrochemical gradient. The return flow of protons into the mitochondrial matrix through ATP synthase (complex V) drives the synthesis of ATP [26]. In AD, OXPHOS is impaired, and several studies have reported deficits in the activity of ETC complexes. Notably, complex IV activity is consistently reduced in post-mortem AD brains [27–34], as well as in APP/PS1 (Amyloid precursor protein/Presenilin 1) and tau transgenic mouse models for AD [35–38], making it a hallmark of AD-related mitochondrial dysfunction. While the involvement of complexes I and II appears more variable in human studies, animal models frequently demonstrate their reduced activity [39–41], indicating broader ETC impairment. The mechanisms underlying complex IV dysfunction remain unclear, but evidence suggests that mitochondrial

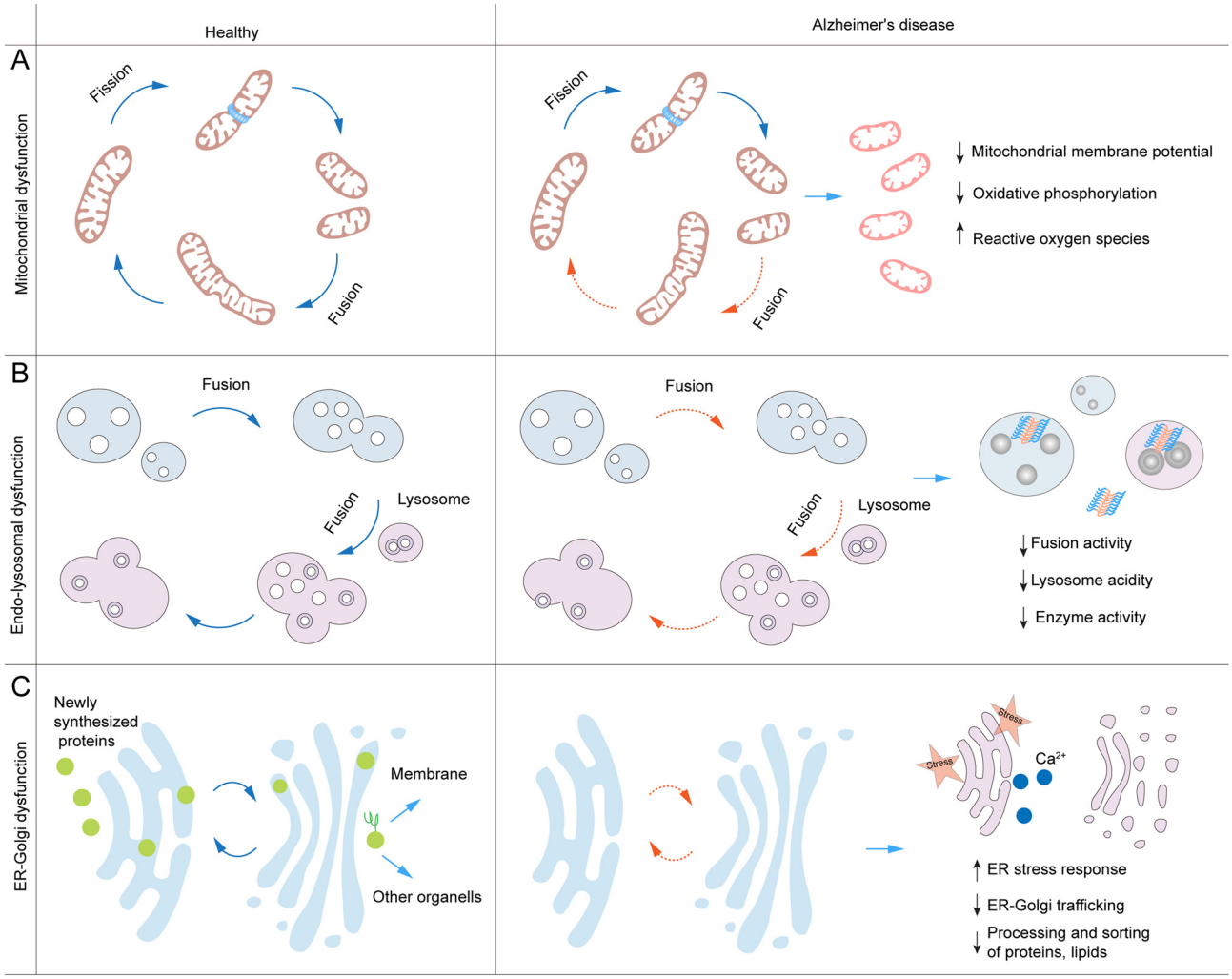

Figure 2. Abnormalities of membrane-bound organelles in Alzheimer's disease.
(**A**) In healthy individuals, mitochondria undergo balanced fission and fusion dynamics. However, in AD, there is excessive mitochondrial fission, leading to fragmented mitochondria in neurons and glia. These damaged mitochondria lose their membrane potential, show reduced oxidative phosphorylation activity, and produce increased levels of reactive oxygen species. (**B**) Endosomes, autophagosomes, and lysosomes normally undergo dynamic fusion and maturation. Early endosomes fuse to form late endosomes, which then fuse with lysosomes to degrade protein aggregates and damaged organelles, such as mitochondria. In AD, this fusion process is disrupted, leading to enlarged, high-pH lysosomes and the accumulation of protein aggregates. (**C**) The ER-Golgi network is critical for protein processing and sorting. Newly synthesized proteins enter the ER for folding and are then transported to the Golgi for further modification. Some proteins return to the ER, while fully processed proteins are sent to the plasma membrane or other organelles. In AD, increased ER stress and fragmented Golgi structures have been observed, causing abnormalities in protein, lipid processing and sorting, as well as calcium handling.

accumulation of Aβ may inhibit complex IV by binding to essential subunits such as COX1 and cofactors like Cu^{2+} and heme [42–45]. In contrast, tau pathology appears to predominantly impact complex I, potentially through oxidative stress and downregulation of complex I subunit expression [46,47].

Mitochondrial morphology is tightly regulated by the delicate balance between fusion and fission processes, which are essential for maintaining mitochondrial function, distribution, and quality control, particularly in neurons with high energetic and metabolic demands [48]. This balance is orchestrated by a set of evolutionarily conserved large GTPase proteins, primarily belonging to the dynamin-related protein family [49–52]. Mitochondrial fission, the division of a single mitochondrion into two, is predominantly regulated by dynamin-related protein 1 (DRP1, also known as DLP1), which translocates to the outer mitochondrial membrane (OMM) upon activation. This recruitment is mediated by membrane-anchored receptors such as mitochondrial fission factor (MFF), mitochondrial fission protein-1 (Fis1), and mitochondrial dynamic factors of 49 kDa (MiD49) and 51 kDa (MiD51) [53]. Once at the membrane, DRP1 assembles into oligomeric rings around the mitochondrial surface. Through GTP hydrolysis, the rings then constrict and sever the membrane, producing two separate mitochondria [49,51,54,55]. Fusion, by contrast, allows for the mixing of mitochondrial contents and is crucial for maintaining mitochondrial function and genome integrity. It is regulated by Mitofusins (MFN1 and MFN2) which mediate outer membrane fusion, and optic atrophy-1 (OPA1), which controls inner mitochondrial membrane (IMM) fusion [56,57]. These GTPases undergo conformational changes and self-assemble into oligomeric complexes to physically tether and merge mitochondrial membranes [58]. Fusion helps buffer mitochondrial defects by

allowing damaged mitochondria to mix with healthy ones, supporting cellular resilience. In AD, the fission-fusion balance is frequently disturbed, leading to an overrepresentation of fragmented, dysfunctional mitochondria. Studies in AD patient brain tissues and mouse models (e.g., APP/PS1, tau transgenics) have consistently shown increased mitochondrial fragmentation, which is associated with altered expression or activity of mitochondrial dynamics regulators [59–63]. Notably, DRP1 activity is often enhanced by disease-related post-translational modifications such as phosphorylation (e.g., at Ser616) and S-nitrosylation, promoting excessive fission [64,65]. In contrast, suppression of DRP1 expression or activity has been demonstrated to mitigate Aβ and Tau-associated mitochondrial and synaptic dysfunction, achieved either through genetic downregulation or pharmacological inhibition [66–68]. At the same time, levels of fusion proteins like MFN1, MFN2, and OPA1 are often reduced. This imbalance contributes to impaired mitochondrial bioenergetics, increased oxidative stress, and synaptic dysfunction, all of which are prominent features of AD pathogenesis. In addition to altered morphology, mitochondrial transport is impaired in AD neurons. Proper positioning of mitochondria along axons and dendrites is critical to support synaptic function and local energy demands. Neurons treated with extracellular Aβ or expressing mutant APP show reduced mitochondrial motility and density, particularly in axons [69–72]. Tau pathology also interferes with mitochondrial transport, possibly by disrupting microtubules or motor protein function [73,74]. Importantly, studies show that inhibition of mitochondrial fragmentation can restore transport, indicating that trafficking defects may occur downstream of abnormal fission [8,62].

In neurons, precise regulation of intracellular calcium is critical for maintaining axonal transport, synaptic transmission, and overall cellular homeostasis. Mitochondria act as key calcium buffers, taking up and releasing Ca^{2+} to shape cytosolic calcium transients during neuronal activity [75]. The OMM is freely permeable to ions and small molecules under 10 kDa, largely due to the presence of high-conductance channels such as the mitochondrial permeability transition pore (mPTP) [76,77]. In contrast, the inner mitochondrial membrane (IMM) is impermeable to most ions, including Ca^{2+}, and thus requires tightly regulated transport mechanisms to mediate calcium flux [78]. The IMM contains ion channels and transporters, including the mitochondrial Ca^{2+} uniporter (MCU) complex or the $Na^{+}/Ca^{2+}/Li^{+}$ exchanger (NCLX), which facilitates mitochondrial membrane potential-dependent Ca^{2+} influx into the mitochondrial matrix and Ca^{2+} extrusion respectively [79–81]. Regulation of calcium entry through the MCU is further refined by associated proteins. MICU1 and MICU2 serve as essential gatekeepers, sensing cytosolic calcium levels and preventing MCU opening under resting conditions to avoid calcium overload [82,83], while MICU3, highly expressed in the brain, enhances mitochondrial Ca^{2+} uptake, and its silencing in cortical neurons reduces stimulation-induced mitochondrial Ca^{2+} levels [84]. Disruption of mitochondrial calcium homeostasis is an early and prominent feature of AD, occurring before the appearance of hallmark pathologies. AD patient fibroblasts and mouse models (e.g., APP/PS1, 5xFAD, 3xTg) show elevated mitochondrial Ca^{2+} and persistent activation of the mPTP channel [75,85–87]. Soluble Aβ oligomers drive mitochondrial Ca^{2+} overload by activating mPTP [75,88], while tau and Aβ together impair Ca^{2+} efflux by inhibiting NCLX, the main mitochondrial Ca^{2+} exporter [37,87,89,90]. Notably, deletion of the mPTP subunit CypD or partial inhibition of calcium uptake restores Ca^{2+} balance, improves synaptic plasticity, and protects against cognitive decline in AD models [91,92]. These findings implicate mitochondrial calcium regulation as a promising target for AD therapy.

Pathological protein accumulation within mitochondria represents another critical mechanism contributing to mitochondrial dysfunction and neurodegeneration in AD. Proteins such as Aβ, tau, and TDP-43 have been shown to translocate into mitochondria, where they interfere with mitochondrial function and induce cellular stress [93–95]. To defend against this proteotoxic burden, mitochondria are equipped with a diverse set of 25 proteases, categorized into three catalytic classes: 2 Cys proteases, 15 metalloproteases, and 8 Ser proteases [96]. These enzymes not only safeguard mitochondrial protein quality but also influence longevity and stress adaptation, with their dysregulation linked to reduced healthspan and increased vulnerability to neurodegenerative stressors [97,98]. In AD, this mitochondrial proteostasis network is often impaired. For example, loss of the mitochondrial metalloprotease PITRM1, which degrades Aβ within the organelle, leads to mitochondrial Aβ accumulation and amyloid plaque formation in mouse models [99]. Similarly, PITRM1 deficiency in human cerebral organoids results in proteotoxic stress and AD-like pathology [100]. The m-AAA protease subunit AFG3L2, essential for mitochondrial protein turnover and transport, has also been implicated; its loss causes defective mitochondrial distribution and enhances tau hyperphosphorylation [101]. TDP-43, found in nearly half of AD patients, becomes particularly toxic when accumulated in mitochondria, a process exacerbated by downregulation of the mitochondrial matrix protease LONP1 [40,95,102]. Notably, recent findings suggest that under conditions of impaired cytosolic proteostasis, mitochondria may serve as a secondary site for degrading misfolded cytosolic proteins [103], highlighting their broader role in cellular protein quality control during neurodegeneration.

Endoplasmic reticulum (ER): The ER is a multifunctional and highly dynamic organelle that plays critical roles in protein synthesis and folding, lipid metabolism, calcium storage, and cellular stress response [104,105]. These diverse functions are made possible by its complex architecture, a continuous membrane system composed of morphologically distinct domains, including highly curved tubules and flattened cisternal sheets [106]. Extending from the nuclear envelope to the cell periphery, the ER dynamically adapts its structure to meet varying cellular demands [107,108]. In AD, significant alterations in both ER morphology and function have been reported, underscoring the vulnerability of this organelle to neurodegenerative stress. Disruptions in ER structure, such as imbalances between tubular and sheet domains, may impair the organelle's ability to maintain protein and calcium homeostasis, contributing to neuronal dysfunction and disease progression (**Figure 2**).

The structural organization of the ER is tightly regulated by a group of ER-shaping proteins that control the formation, maintenance, and remodeling of its tubular and sheet domains. Key players include reticulons (RTNs), DP1/Yop1, REEPs, and atlastins (ATLs), which coordinate to induce membrane curvature, promote membrane fusion or fission, and maintain the dynamic balance between tubules and cisternal sheets [109]. RTNs are particularly important for generating the high curvature characteristic of ER tubules, while ATLs mediate the homotypic fusion of adjacent tubules to maintain network connectivity [110]. In contrast, fission of ER tubules is driven by DP1/Yop1p and DRP1, which assemble at constriction sites to sever the membrane [111]. REEPs further support tubular network organization by forming complexes with ATLs and Spastin to facilitate membrane remodeling [112]. Disruption of these regulatory mechanisms

has pathological implications. In AD, studies have demonstrated progressive accumulation of tubular ER within dystrophic neurites (DNs) in both patient brains and 5xFAD mouse models [113]. Moreover, RTNs and REEPs are enriched near DNs, and genetic manipulation of these proteins exacerbates neuritic pathology and impairs cognition [114,115]. These findings suggest that dysregulation of ER structural dynamics contributes to neuronal dysfunction and is an important factor in AD pathogenesis.

The core function of the ER is to support protein synthesis and folding, processes essential for maintaining cellular homeostasis. ER-bound ribosomes are responsible for producing approximately one-third of all cellular proteins, which are co-translationally translocated into the ER lumen. Once in the ER lumen, they undergo proper folding and structural maturation before being delivered to their final destinations, such as the plasma membrane or various organelles [116]. While early studies reported that tau co-localizes with ribosomes and ER membranes in the brains of AD patients, the functional implications of this interaction remain poorly understood [117,118]. ER-specific tau interactome analyses have shown that tau's interaction with ribosomal proteins is significantly elevated in AD[119]. This aberrant association correlates with reduced protein synthesis, suggesting that tau may impair translational efficiency at the ER, potentially disrupting the production of critical proteins required for neuronal function [119]. Similarly, oligomeric Aβ has been shown to suppress global RNA translation and reduce protein synthesis in cultured neurons [120]. Notably, such translational impairments are already evident during the mild cognitive impairment (MCI) stage of AD, even before neuronal loss occurs [121], indicating that ER-associated protein synthesis dysfunction may represent an early and contributing factor in AD pathogenesis.

The ER also plays a pivotal role in maintaining intracellular calcium homeostasis, functioning as the primary reservoir within cells. Calcium is actively transported into the ER lumen by the sarco/endoplasmic reticulum calcium ATPase (SERCA), which maintains high luminal calcium concentrations critical for various cellular processes [122]. In contrast, calcium release from the ER into the cytosol is precisely controlled through channels such as inositol trisphosphate receptors (IP3Rs) and ryanodine receptors (RyRs), in response to signaling cues [123]. Stromal interaction molecules (STIM1 and STIM2) act as ER calcium sensors and initiate calcium influx from the extracellular space via plasma membrane channels when ER stores are depleted [124]. In AD, multiple lines of evidence link disrupted ER calcium handling to disease pathology, particularly through mutations in presenilin 1 and 2 (PS1/PS2), key components of the γ-secretase complex [125–130]. Wild-type presenilins facilitate a calcium leak from the ER via low-conductance ion channels, a function lost in AD-linked mutants such as PS1 M146V and PS2 N141I[130]. Presenilins interact with SERCA, and mutations impair this interaction, further disturbing ER calcium uptake [131]. Additionally, mutant presenilin mediated Ca^{2+} dysregulation is also linked to alterations in the activity of IP3Rs and RyRs. For example, the expression of PS1 mutants amplifies IP3-mediated Ca^{2+} release in cortical neurons isolated from PS1 M146V knockin mice and in cells expressing PS1 ΔE9 mutant [132,133]. And, increased RyR-mediated Ca^{2+} release has been reported in primary cultured neurons derived from 3xTg mice [132,134]. Studies have further shown that PS1 mutations contribute to aberrant cleavage and inactivation of STIM1, thereby disrupting extracellular calcium replenishment [135]. These alterations likely impair calcium balance at multiple levels, including uptake, release, and influx, highlighting ER calcium dysregulation as a critical factor contributing to neuronal dysfunction in AD.

The ER is also involved in the cellular stress response through activation of the unfolded protein response (UPR), a protective mechanism triggered by the accumulation of misfolded protein. In AD, the UPR has been implicated in neuronal dysfunction and death. Postmortem studies of AD brains consistently show elevated levels of UPR markers, including phosphorylated eIF2α (p-eIF2α), PERK, CHOP, and PDI, indicating sustained ER stress [136–138]. Similarly, increased expression of p-PERK, p-eIF2α, and ATF4 has been reported in several AD-related mouse models, including APP/PS1 and tau transgenics [139–142]. Mechanistic studies have demonstrated that both Aβ oligomers and tau aggregates can directly induce ER stress *in vitro*, supporting a potential causal link [143,144]. However, this association is not uniformly observed across models. For instance, the App^{NL-G-F} knock-in and tau transgenic PS19 mice do not show activation of the ER stress response despite exhibiting substantial Aβ and tau pathology [145,146]. These discrepancies suggest that the relationship between protein aggregation and ER stress may be context-dependent, influenced by genetic background, disease stage, or other cellular factors. As a result, the precise contribution of ER stress and its connection to tau pathology in AD remains to be fully clarified.

Endo-lysosome: Expanding further, the integrity and efficiency of the endo-lysosomal system are crucial for maintaining cellular homeostasis, especially in long-lived cells like neurons, which rely heavily on precise protein and organelle turnover. This system includes specialized compartments such as early endosomes, recycling endosomes, and late endosomes, each contributing to the sequential maturation and sorting of cargo [147]. Lysosomes, on the other hand, serve as organelles for the storage of hydrolases and are primarily considered as the final destination for proteolytic degradation. The luminal pH of endosomes and lysosomes, maintained between 6.5 and 4.5 by ATP-dependent proton pumps, is essential for optimal enzyme activity, in contrast to the neutral cytoplasmic pH [148]. Internalized proteins entering this network are either trafficked to late endosomes and lysosomes for degradation via the endosomal sorting complexes required for transport (ESCRT), or rerouted to the trans-Golgi network (TGN) or plasma membrane for recycling via the retromer pathway [149]. Dysfunction in this system manifests as upregulation of endocytic genes, accelerated endocytosis, impaired transport of enlarged endosomes, and aberrant signaling, all of which may contribute to the pathogenesis of AD (**Figure 2**).

The initial indication of the involvement of the endo-lysosome system in AD arises from the participation of multiple organelles within the endo-lysosomal and autophagic networks in the metabolism of APP [150,151]. These networks serve not only as degradative pathways but also as dynamic platforms for sorting, trafficking, and proteolytic processing of APP. The cleavage of APP to generate Aβ peptides occurs in several intracellular compartments, and this compartmentalization aligns closely with the distinct localization patterns of γ-secretase complexes. For example, studies have shown that γ-secretase complexes containing PS2 are primarily localized in late endosomes and lysosomes, which are acidic compartments ideally suited for amyloidogenic processing. In contrast, γ-secretase complexes containing PS1 are more widely distributed, including in early endosomes, TGN, and the plasma membrane [152]. The preferential localization of PS2 in late endosomes and lysosomes is particularly significant, as has been associated with a higher level of intracellular

Aβ production, a key contributor to amyloid pathology in AD [152]. This compartment-specific activity suggests that alterations in endo-lysosomal function, such as impaired acidification, disrupted trafficking, or accumulation of undigested material, could disproportionately enhance Aβ generation within these compartments.

Given the established role of the endo-lysosomal network in APP metabolism and Aβ generation, it is not surprising that disruptions in this system are consistently observed in AD. One of the most frequently reported abnormalities is the enlargement of endosomes in the brains of individuals with AD, a feature that is notably absent in age-matched controls without the disease [153–157]. Importantly, such endocytic and lysosomal alterations are detectable in the earliest stages of AD. Even cognitively normal individuals who exhibit neuropathological evidence of early-stage AD show clear signs of endo-lysosomal network dysfunction, particularly in brain regions that have not yet developed local Aβ plaques or tau tangles [154]. The appearance of enlarged endosomes also coincides temporally with the initial rise in Aβ peptide levels [156], suggesting a potential causal relationship. *In vivo* studies further support this link, demonstrating that endosomal pathology may promote increased β-secretase–mediated processing of APP, leading to elevated Aβ production [158,159]. Additionally, the acidic environment within the endo-lysosomal system favors the formation of Aβ42 oligomers [160], which are known to be particularly neurotoxic and trigger tau mis-sorting. Complementing these structural and biochemical alterations, multiple studies have reported dysregulation of lysosomal protein expression and activity in both human AD tissue and animal models [161], supporting the notion that lysosomal dysfunction is an early event in AD pathogenesis. For example, the Niemann-Pick type C1 (NPC1) protein, which mediates cholesterol trafficking from lysosomes to other organelles, is elevated in the hippocampus and cortex of AD patients and in APP/PS19 mice [162]. Similarly, lysosomal glycohydrolases including β-galactosidase, β-hexosaminidase, and α-mannosidase show increased activity in skin fibroblasts from both symptomatic and presymptomatic individuals with familial AD mutations [163,164]. These enzyme elevations are also observed in the cortex of TgCRND8 mice [165]. Additionally, cathepsin D and β-hexosaminidase A levels are elevated in neurons from AD patients [166].

In addition to endo-lysosomal abnormalities, AD is marked by a significant increase in both the number and size of vesicles associated with degradative pathways, indicating widespread dysfunction in cellular clearance mechanisms [166,167]. Among these, lysosomal-like organelles such as autophagosomes, amphisomes, and autolysosomes are frequently observed within dystrophic neurites that surround extracellular amyloid plaques [166,168,169]. This accumulation begins early in disease progression, as these vesicles are found in axons that contact amyloid deposits during the initial stages of Aβ pathology [170]. Consistently, axonal dystrophy is evident around plaques even in the earliest detectable phases of AD [171]. Importantly, the buildup of autophagic vesicles in axons have been attributed to a failure in retrograde axonal transport, which is functionally linked to deficits in lysosomal degradation capacity [172]. These observations provide further evidence that lysosomal impairment may not be merely a consequence of degeneration, but an early and active contributor to AD pathogenesis.

Golgi: The Golgi apparatus is a central organelle in the secretory pathway, composed of flattened membrane-bound cisternae and associated vesicles. These structures originate from vesicular clusters that bud off ER. A defining feature of the Golgi is its structural and functional polarity: proteins enter the cis face, which is convex and oriented toward the nucleus, then transit through the medial cisternae to exit at the concave trans face, which is also convex and oriented toward the nucleus. The proteins then transit through the medial cisternae to exit at the concave trans face [173]. At the trans-Golgi network, proteins are sorted and packaged into vesicles destined for lysosomes, secretory vesicles, or the plasma membrane [174,175]. The architecture and integrity of the Golgi apparatus are maintained by a group of Golgi matrix proteins, including coiled-coil domain-containing golgins and the stacking proteins GRASP55 and GRASP65 [176–179]. These proteins are localized on the cytoplasmic surface of Golgi membranes and are essential for stacking cisternae and maintaining Golgi structure. Disruption or depletion of these structural components leads to Golgi fragmentation, which has been associated with accelerated protein trafficking, impaired glycosylation, and misrouting of proteins [178].

Alterations in Golgi morphology have been reported in AD [180,181] (**Figure 2**). Expression of the mutant APP and PS1, as well as exposure to synthetic Aβ peptides, has been shown to cause Golgi fragmentation in neuronal cultures and mouse brains [182]. This fragmentation appears to be directly driven by Aβ accumulation, as the removal of Aβ from the culture medium can reverse the effect, suggesting that Golgi fragmentation is a downstream consequence of amyloid pathology [182]. However, the relationship between Golgi and APP metabolism is bidirectional. A substantial portion of APP localizes to the Golgi, where it undergoes post-translational modifications, while smaller amounts are found in the ER and plasma membrane [183]. Thus, proper Golgi structure is critical for accurate APP trafficking and processing. Fragmentation of the Golgi has been linked to enhanced APP trafficking and increased Aβ production, suggesting that Golgi disruption may further exacerbate amyloidogenic pathways. In addition to Aβ, tau pathology also contributes to Golgi dysfunction. Tau has been shown to interact with Golgi membranes and mediate their association with microtubules [184]. Overexpression of wild-type or mutant tau proteins induces Golgi fragmentation in primary hippocampal neurons [185], suggesting that tau accumulation and neurofibrillary tangle formation may precede or amplify Golgi disruption during AD progression.

Further mechanistic insights implicate the CDK5-p35 complex in the regulation of Golgi integrity. CDK5, which is known to phosphorylate tau in AD, also phosphorylates GRASP65, leading to disruption of its stacking function and subsequent Golgi fragmentation [186]. This process enhances APP trafficking and Aβ production, reinforcing the feed-forward loop between structural disintegration and pathogenic processing. Notably, the use of CDK5-specific inhibitors or expression of non-phosphorylatable GRASP mutants can reverse Golgi fragmentation and significantly reduce Aβ production without detectable degradation of Golgi structural proteins [182]. These findings suggest that Golgi fragmentation in the early stages of AD is driven by reversible phosphorylation events, occurring in parallel with tau hyperphosphorylation. Altogether, these observations position the Golgi apparatus as both a target and modulator of AD-related pathology. Golgi fragmentation disrupts essential neuronal functions such as protein processing and trafficking, while also accelerating APP processing and Aβ production, thereby reinforcing the pathological cycle in AD.

Peroxisome: Peroxisomes are small, single-membrane-bound organelles found throughout eukaryotic cells, essential for lipid metabolism and redox balance. They perform β-oxidation of very-long-chain fatty

acids (VLCFAs) such as C22:0, C24:0, C26:0, and are involved in the synthesis of bile acids, cholesterol, ether phospholipids, and docosahexaenoic acid (DHA), a neuroprotective lipid that also promotes peroxisomal proliferation via PEX11β oligomerization [187]. Peroxisomes also generate and detoxify ROS, accounting for up to 35% of cellular hydrogen peroxide production [188]. To maintain redox homeostasis, they contain key antioxidant enzymes including catalase, SOD1, GPX, PRX5, and others [187,189,190]. Additional proteins such as LONP2, insulin-degrading enzyme, and PEX11β also participate in ROS detoxification [191,192]. Peroxisome abundance is regulated by fission-driven biogenesis, involving PEX11β, DRP1, MFF, and selective degradation through pexophagy, under transcriptional control of regulators such as PPARα and the PEX11 gene family [193,194].

In AD, peroxisomal dysfunction emerges as an early and dynamic pathological event. A progressive decline in peroxisome density has been observed in early affected brain regions such as the entorhinal cortex [195], likely reflecting chronic oxidative stress and impaired lipid metabolism. Supporting this, elevated VLCFA levels and reduced plasmalogens have been detected in areas with neurofibrillary tangles, while hippocampal DHA levels are significantly decreased [196]. Inhibition of peroxisomal β-oxidation experimentally enhances Aβ production, suggesting a direct mechanistic link between metabolic failure and amyloidogenesis [197]. Long-term oxidative stress, combined with nutrient deprivation caused by extracellular Aβ deposits, can further promote peroxisomal degradation via autolysis and NBR1-dependent pexophagy [198]. Interestingly, some studies report a transient increase in peroxisome abundance during early disease stages, likely reflecting an initial compensatory response to rising ROS. For example, in transgenic AD mice, levels of peroxisomal proteins such as PEX14, ABCD3/PMP70, catalase, and SOD2 increase at three months of age but return to baseline by six months [199]. In Aβ-treated cortical neurons, peroxisome numbers rise initially but decline within two weeks. This coincides with increased oxidative stress and reduced expression of key antioxidants like catalase, SOD2, and thiolase A [200], indicating that early peroxisomal adaptation is eventually overwhelmed by sustained oxidative burden. The accumulation of VLCFAs and the depletion of DHA and hydroxy-DHA further support the transition from peroxisomal adaptation to functional collapse [201]. Moreover, inhibition of peroxisomal β-oxidation has been shown to increase Aβ synthesis, while extracellular Aβ deposition may promote peroxisome degradation through autolysis and NBR1-dependent pexophagy [197,202], suggesting a bidirectional relationship between peroxisomal failure and amyloid pathology.

Of note, this dysfunction is not limited to neurons. Oligodendrocyte peroxisomes are essential for maintaining axonal integrity by producing lipids and plasmalogens necessary for myelination [203]. Their loss leads to axonal degeneration, demyelination, and neuroinflammation [204]. In microglia, restoring peroxisomal proteins such as PMP70, PEX11β, PEX5, and catalase during inflammatory stress improves both cellular and behavioral outcomes in AD mouse models [205]. Importantly, peroxisomes help degrade pro-inflammatory lipid mediators such as prostaglandins and leukotrienes [206–208]. When peroxisomal function is compromised, these derivatives accumulate and exacerbate inflammation [209]. Downregulation of ABCD3/PMP70 may also hinder the clearance of oxidized lipid species via β-oxidation [210]. As part of a self-amplifying cycle, elevated TNFα levels can suppress catalase expression, thereby reducing peroxisomal β-oxidation capacity and further amplifying oxidative and inflammatory stress [211]. Taken together, peroxisomal failure in AD contributes to a complex cascade of lipid imbalance, oxidative stress, and inflammatory dysregulation. These often overlooked organelles are emerging as key players in the early stages of neurodegeneration and represent potential therapeutic targets for modifying disease progression.

Nucleus: The nucleus is a defining organelle of eukaryotic cells, acting as the control center for gene expression, ribosome synthesis, and chromatin organization. Structurally, it consists of two major components: the nuclear envelope- composed of the inner and outer membranes, nuclear pores, and the nuclear lamina- and the nuclear interior, which contains chromatin, the nucleoskeleton, and subnuclear bodies such as the nucleolus and promyelocytic leukemia (PML) bodies. These compartments collectively coordinate critical cellular processes such as gene transcription, DNA repair, RNA processing, and nucleocytoplasmic transport [212]. Under physiological conditions, the nucleus maintains homeostasis by integrating environmental and intracellular cues, relaying them through signaling pathways to regulate transcriptional programs. In AD, sustained oxidative stress, protein misfolding, neuroinflammation, and the accumulation of neurotoxic molecules such as Aβ oligomers and phosphorylated tau, converge on the nucleus, disrupting its integrity and function. As a central stress response hub, the nucleus undergoes profound structural and molecular alterations that contribute to the pathogenesis of neurodegeneration.

One of the early nuclear pathologies in AD involves the disruption of nucleocytoplasmic transport. This system, which regulates the exchange of proteins and RNA between the nucleus and cytoplasm, relies on nuclear pore complexes (NPCs) and associated transport factors. In AD brains, several studies have reported aberrant localization and accumulation of nucleoporins and NPC-associated proteins, such as nuclear transport factor 2 (NTF2) and importin α, particularly in hippocampal CA1 neurons [213,214]. Mislocalization of key transcription factors like TDP-43 and ATF2 to the cytoplasm further reflects transport dysfunction [215]. Emerging evidence links pathological tau to these deficits. Specifically, tau has been shown to directly interact with NPC components, including Nup98, promoting tau mislocalization and aggregation while impairing nucleocytoplasmic trafficking. In rTg4510 mice, reduction of soluble p-tau and Nup98 restores nucleocytoplasmic transport, confirming this mechanistic link [216]. Similarly, tau hyperphosphorylation and its mislocalization from axons to somatodendritic compartments induce nuclear membrane deformation and NPC dysfunction in human stem cell-derived neurons [215]. These findings highlight that tau pathology not only disrupts cytoskeletal integrity but also directly interferes with nuclear transport, contributing to neuronal stress and degeneration.

Nucleolus, the nuclear substructure responsible for ribosome biogenesis, is also increasingly recognized as a critical stress-sensing organelle in AD. It comprises the fibrillar center, dense fibrillar component, and granular component, which coordinate rDNA transcription, pre-rRNA processing, and ribosomal ribonucleoprotein (RNP) assembly [217,218]. Given that ribosome biogenesis consumes approximately 80% of the cell's energy, nucleolar function is tightly linked to the cell's cellular metabolic state [219]. Interestingly, asymptomatic AD has demonstrated significant neuronal hypertrophy, especially profound nucleoli hypertrophy in CA1 neurons of the hippocampus. Compared with MCI cases with a similar load of AD pathology (Braak III-V), this indicates a compensatory mechanism that prevents the disease progression into dementia [220,221]. In contrast, advanced AD cases (Braak IV–VI) show marked nucleolar atrophy, paralleling neuronal shrinkage and cell loss. Similarly, nucleolar volume is significantly reduced in the basal nucleus of Meynert, with volume loss correlating with neuronal depletion [222].

Molecular evidence supports that the nucleolus is compromised early in AD. *In vitro* exposure to Aβ42 oligomers rapidly reduces upstream binding factor (UBF), a key nucleolar transcription regulator, while promoting oxidative stress [223]. Moreover, oxidative damage to ribosomal RNA (rRNA) increases its iron-binding capacity, exacerbating redox imbalance [224]. Consistently, ribosomes isolated from AD hippocampus exhibit increased RNase-sensitive iron and redox activity [225]. Human AD and MCI cortical samples also show elevated rRNA oxidation and decreased rRNA abundance [226,227]. Perturbations in nucleolar function—whether through oxidative damage or impaired rRNA transcription—can activate p53 signaling and trigger slow neuronal degeneration [228]. Therefore, these data suggest that the nucleolus acts as a gatekeeper of neuronal stress tolerance. Its dysfunction may not only reflect but also promote neurodegenerative cascades by impairing ribosome production, increasing oxidative burden, and activating apoptotic signaling pathways.

Lipid droplet: Lipid droplets (LDs) are dynamic, spherical organelles that store and regulate intracellular lipids. Structurally, they consist of a neutral lipid core, primarily triglycerides (TAGs) and cholesterol esters (CEs), surrounded by a phospholipid monolayer that hosts proteins essential for droplet formation, stability, and organelle interactions. LDs function as cellular energy reservoirs, sequestering excess lipids to prevent lipotoxicity and releasing them when energy demands rise. In addition to their metabolic role, LDs participate in lipid trafficking, modulate intracellular lipid concentrations, and engage in signaling pathways related to cellular stress and inflammation [229].

Although Alois Alzheimer first noted lipid inclusions in glial cells over a century ago, the pathological relevance of LDs in AD has only gained attention recently [1]. Accumulation of LDs have been observed in postmortem AD brains and in 3xTg mouse models, where LD formation precedes the appearance of amyloid plaques and tau tangles [230]. This early accumulation suggests LDs may contribute to upstream pathological events in AD. The strongest genetic risk factor for AD, Apolipoprotein E4 (ApoE4), has been directly linked to enhanced LD formation. Compared to ApoE3 or ApoE2, ApoE4-expressing glial cells and hiPSC-derived microglia accumulate significantly more LDs [231,232]. Transcriptional profiling of ApoE4 microglia reveals marked downregulation of genes involved in oxidative phosphorylation and lipid catabolism [232,233], potentially impairing fatty acid oxidation and promoting lipid accumulation. Similarly, LD accumulation has been reported in astrocytes of 5xFAD mice [234], further supporting a general disruption in lipid metabolism across glial populations. LDs may also modulate AD pathology by influencing tau phosphorylation. Cholesterol accumulation within LDs increases phosphorylated tau (p-tau) levels, an effect reversible by inhibiting cholesterol synthesis [235]. Neuronal hyperactivity alone is sufficient to trigger LD formation in astrocytes and exacerbate AD-related phenotypes [235]. Notably, elevated CE levels within lipid droplets have been shown to impair proteasome activity, leading to the accumulation of phosphorylated tau [236]. Pharmacological reduction of CE using statins or by activating cholesterol 24-hydroxylase (CYP46A1) lowers p-tau levels in human neurons [237], suggesting that modifying lipid droplet composition can influence tau pathology.

In microglia, LD accumulation has been associated with a dysfunctional, pro-inflammatory phenotype characteristic of aging and neurodegeneration [238]. ApoE4-driven LD accumulation in microglia renders them less responsive to neuronal signals, potentially impairing homeostatic interactions between neurons and glia [232]. However, LD formation may also reflect a protective adaptation to neurotoxicity: glial LDs sequester harmful lipids, and their formation can mitigate cell damage. Blocking LD biogenesis in glial cells indeed worsens neurodegeneration, indicating a complex and context-dependent role [239]. An additional layer of complexity is highlighted by recent findings implicating LDs in immune regulation at choroid plexus. Neutral lipid staining in postmortem AD brains revealed abundant LDs in this region, particularly in ApoE4 carriers [240]. ApoE binds to complement component C1q on LDs, potentially modulating classical complement activation at the CNS–vasculature interface [240]. This suggests LDs serve as regulatory hubs that integrate lipid metabolism with innate immune signaling. The extent of lipid accumulation in the choroid plexus correlates with AD neuropathological staging, raising the possibility that ApoE-LD-C1q interactions influence disease progression. Collectively, these findings establish LDs as multifunctional organelles involved in lipid metabolism, tau phosphorylation, immune modulation, and cellular stress adaptation. Whether LD accumulation in AD is protective, pathogenic, or both likely depends on context, cell type, and disease stage. Further research is needed to determine how manipulating LD biogenesis or composition could be harnessed for therapeutic purposes.

Mitochondrial-associated ER membranes: Mitochondria-associated ER membranes (MAMs) are specialized contact sites where the endoplasmic reticulum (ER) and mitochondria are closely apposed and connected by proteinaceous tethers. These domains not only act as structural linkages but serve as functional hubs regulating a wide array of cellular processes, including calcium signaling, lipid metabolism, mitochondrial dynamics, autophagy, apoptosis, and inflammation [241]. Disruption of MAM integrity and function has been increasingly recognized as a contributing factor in AD, particularly in relation to mitochondrial dysfunction, calcium dysregulation, aberrant lipid processing, and amyloidogenic APP metabolism.

In AD-related models, both morphological and molecular changes in MAMs have been observed. Enhanced ER-mitochondrial interactions have been reported in AD cell lines and APP transgenic mouse models, accompanied by altered expression of key MAM-associated proteins, including phosphatidylserine synthase 1 (PSS1), PACS-2, and sigma-1 receptor (Sig-1R) [242,243]. Notably, PS1 and PS2 are enriched in MAM fractions, implicating these domains as potential hotspots for amyloidogenesis [244]. Additional components of MAMs contribute to this pathogenic process. Acyl-CoA:cholesterol acyltransferase 1 (ACAT1), a cholesterol-esterifying enzyme, is localized to MAMs and has been shown to influence APP processing [245–247]. Palmitoylated APP, also enriched in MAMs, is preferentially processed via the amyloidogenic pathway. Disruption of MAM integrity or inhibition of APP palmitoylation reduces this processing, further highlighting the functional significance of MAMs in Aβ production [248,249].

MAMs also serve as calcium signaling hubs. Both PS1 and PS2 interact with inositol 1,4,5-trisphosphate receptors (IP3Rs) to regulate ER-to-mitochondria calcium transfer. Familial AD-linked mutations in these proteins exaggerate this calcium flux, contributing to the elevated intracellular calcium stores observed in AD [250]. The pathological consequences of increased MAM tethering include enhanced mitochondrial calcium uptake, impaired energy metabolism, and activation of apoptotic pathways. In tauopathies, MAM alterations also emerge. In models expressing mutant tau (P301L), an increased number of ER-mitochondria contact sites are observed, along with tau colocalization at ER membranes. Similar findings are reported in AD brain tissues, suggesting that pathological tau may promote excessive

ER-mitochondrial tethering, compounding calcium dyshomeostasis and mitochondrial stress [250]. Overall, although not yet extensively studied, current findings suggest MAMs as important hubs in AD pathogenesis, serving as convergence points for multiple pathological processes including aberrant amyloid processing, calcium dysregulation, and mitochondrial dysfunction.

Exosome: Exosomes are small extracellular vesicles, typically 30–150 nanometers in diameter, formed during the maturation of multivesicular bodies (MVBs) or via direct budding from the plasma membrane [251]. Their biogenesis begins with endocytic invagination of the plasma membrane to form early endosomes, which subsequently mature into late endosomes or MVBs. Within these structures, intraluminal vesicles are formed that encapsulate proteins, lipids, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and messenger RNAs (mRNAs) [252]. Fusion of MVBs with the plasma membrane results in the release of these intraluminal vesicles into the extracellular space as exosomes. The membranes of exosomes are enriched with tetraspanins such as CD9, CD63, CD81, and CD82, as well as proteins like TSG101, Alix, flotillin-1, integrins, and cell adhesion molecules, although no marker is uniquely specific to exosomes [253]. Once thought to function solely in waste disposal, exosomes are now recognized as active participants in intercellular communication, transporting bioactive molecules between cells and playing critical roles in regulating metabolism, stress responses, and disease progression [254].

In the context of AD, exosomes have gained attention for their dual roles in both clearance and propagation of pathological proteins. Previous studies have detected full-length APP and its cleavage products in exosomes derived from postmortem AD brains, transgenic mouse models, and cultured neurons [255–257]. Initially, exosomal secretion of APP and Aβ was thought to facilitate clearance via uptake by microglia [258]. However, with disease progression, increased levels of exosomal Aβ oligomers may instead promote neuron-to-neuron transmission of toxic species, exacerbating pathology [259]. Inhibiting exosome biogenesis or uptake has been shown to reduce both Aβ spread and associated neurotoxicity [259,260].

Similarly, exosomes carry tau and phosphorylated tau, as shown in samples from AD patients' cerebrospinal fluid and plasma, as well as from tau transgenic mice [261–263]. Elevated exosomal tau levels in blood have been reported even in preclinical AD stages [264], suggesting their potential as early biomarkers. Although the origin of tau-containing exosomes is not fully understood, evidence suggests that microglia internalize exosomes from neurons containing aggregated tau and then release tau-loaded exosomes, facilitating its transmission [265]. Notably, depletion of microglia or inhibition of exosome synthesis markedly reduces tau propagation in tau-overexpressing models [266]. Additionally, Aβ may influence the seeding capacity of exosomal tau, indicating possible interplay between the two hallmark pathologies [267]. These findings suggest exosomes as central mediators of intercellular propagation of Aβ and tau pathology in AD. Beyond their role in pathogenesis, exosomes hold promise as biomarkers for early diagnosis and as novel therapeutic targets aimed at halting the spread of neurotoxic proteins.

Membraneless Organelles (MLOs)

Proteasome: The proteasome, also known as the 26S proteasome, is a critical MLO for intracellular protein quality control. It degrades polyubiquitinated proteins through a highly regulated, ATP-dependent process. Structurally, it comprises a 20S core particle flanked by one or two 19S regulatory particles. The 19S unit recognizes and binds ubiquitin-tagged substrates, unfolds them, and translocates them into the 20S catalytic chamber, where proteolysis occurs. The resulting peptide fragments are then released and further processed into amino acids. By continuously eliminating damaged, misfolded, or excess proteins, the proteasome maintains protein homeostasis and governs essential cellular functions such as cell cycle regulation, stress responses, and signal transduction [268]. Given its central role, dysfunction of the proteasome system has been increasingly implicated in neurodegenerative diseases, including AD (**Figure 3**). The involvement of the proteasome in AD was first recognized when ubiquitinated proteins were identified within hallmark lesions, including amyloid plaques and neurofibrillary tangles [269–271]. Both human AD brain tissue and transgenic mouse models expressing mutant APP or tau exhibit reduced proteasome activity [272–274]. Mechanistic studies have demonstrated that oligomeric forms of Aβ40 and Aβ42 directly impair proteasomal function in a dose-dependent manner by binding to and altering the conformation of the 20S core, effectively inhibiting substrate degradation [275]. Aβ oligomers also impair the proteasome by inducing conformational changes in the 20S core particle, which blocks protein degradation [15]. Similarly, the degradation of tau is linked to the ubiquitin-proteasome pathway. The E3 ubiquitin ligase CHIP (carboxy terminus of Hsp70-interacting protein) promotes the ubiquitination and proteasomal degradation of tau [276–278]. Recently, TRIM11, another E3 ligase, was found to enhance the proteasomal clearance of mutant tau species, a function markedly diminished in AD brains [279]. These findings suggest a reciprocal relationship between proteasome dysfunction and AD pathology: impaired proteasomal degradation exacerbates Aβ and tau accumulation, while these toxic species in turn inhibit proteasomal activity. As such, therapeutic strategies aimed at enhancing proteasome function or preventing its inhibition may offer potential for slowing AD progression.

Ribosome: Ribosomes are small, granular, MLOs composed of ribosomal RNA (rRNA) and ribosomal proteins, serving as the cellular machinery for translating mRNA into polypeptides. Each eukaryotic ribosome consists of two subunits: the small 40S subunit, which binds to messenger RNA (mRNA), and the large 60S subunit, which facilitates tRNA binding and peptide bond formation. Structurally, the 40S subunit is composed of 18S rRNA and 33 proteins, while the 60S subunit contains 5S, 5.8S, and 28S rRNAs, along with 46 ribosomal proteins. Ribosomes are approximately 65% RNA and 35% protein by mass, with rRNA forming the core catalytic elements of the complex [280]. Ribosomal dysfunction has emerged as an early and significant event in AD pathogenesis [16]. It is marked by reduced protein synthesis capacity, diminished rRNA and tRNA levels, and elevated RNA oxidation. Several ribosomal protein genes are aberrantly expressed in AD, and altered levels of key translation factors such as eIF2α, eIF3η, and eIF5 for initiation, and eEF2 for elongation have been reported in AD patient brains [281]. Both Aβ and tau contribute to ribosomal impairment through distinct but overlapping mechanisms. Studies have shown that Aβ and tau interact directly with ribosomes, leading to their co-aggregation and impairing normal function [119,282]. Aβ exposure induces time- and dose-dependent downregulation of ribosomal proteins and rRNA, highlighting its detrimental impact on ribosomal biogenesis and stability [120,283]. Interestingly, nanomolar levels of Aβ have also been shown to transiently enhance protein synthesis regulated by the fragile X mental retardation protein (FMRP), suggesting a complex, possibly concentration-dependent biphasic effect on translation [284]. Similar to Aβ, tau disrupts the synthesis of ribosomal proteins and other essential

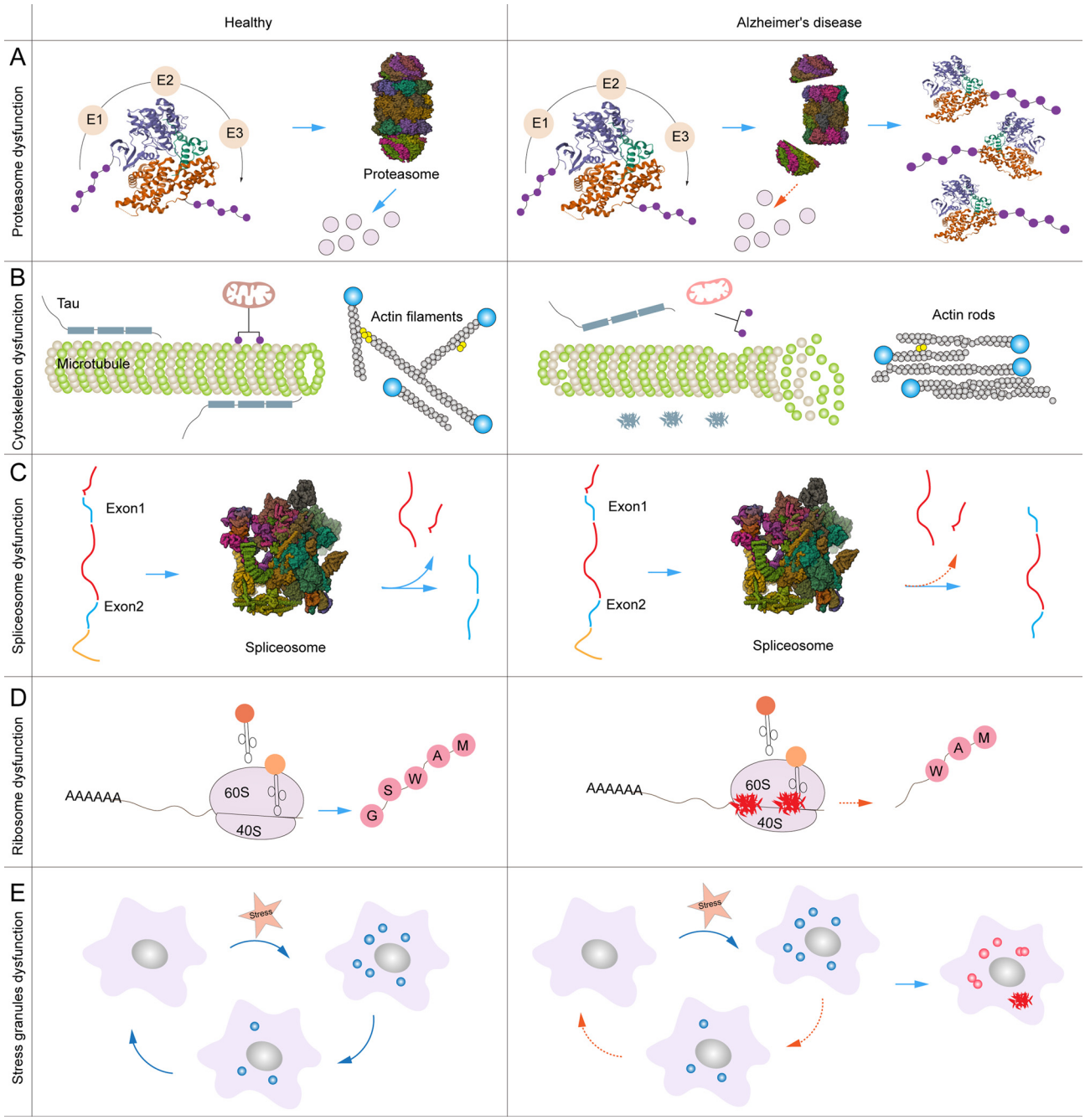

Figure 3. Abnormalities of membraneless organelles (MLOs) in Alzheimer's disease.
(**A**) In healthy cells, target proteins are ubiquitinated via the E1, E2, and E3 enzyme system and degraded by the proteasome, which consists of a 20S catalytic core and 19S regulatory subunits. In AD, pathological protein aggregates impair proteasome assembly, reducing enzymatic activity and causing the accumulation of ubiquitinated proteins. (**B**) Tau normally stabilizes microtubules, while actin filaments form dynamic networks; however, in AD, hyperphosphorylated Tau dissociates from microtubules, leading to their disassembly and disrupted organelle trafficking, while actin filaments abnormally form rods in axons and dendrites. (**C**) Spliceosomes, large nuclear complexes that assemble on pre-mRNA to mediate accurate splicing, are disrupted by pathological aggregates, resulting in aberrant splicing events such as intron retention. (**D**) Ribosomes, which normally translate mRNA into proteins essential for cellular function, also become compromised as aggregates disrupt their structure and impair translation, leading to reduced protein synthesis. (**E**) Stress granules, normally dynamic cytoplasmic structures that transiently regulate protein translation during stress, fail to properly assemble and disassemble in AD, a process thought to promote protein aggregation and exacerbate cellular dysfunction.

neuronal proteins such as PSD95, further contributing to synaptic dysfunction [285–287]. Additionally, *in vivo* studies have demonstrated that Aβ injection increases the formation of heavy polyribosomes in the cytoplasm of CA1 pyramidal neurons, a change that may reflect altered translational control during disease progression [288]. These changes suggest that ribosome-related pathology contributes to impaired protein synthesis and synaptic dysfunction in the early stages of neurodegeneration.

Cytoskeleton: The cytoskeleton is a dynamic and intricate network of protein filaments that not only provides structural support to eukaryotic cells, but also orchestrates diverse cellular processes, including intracellular transport, signal transduction, and organelle positioning. In neurons, this system is critical for maintaining cell shape, sustaining long axonal projections, supporting synaptic function, and mediating responses to physiological stimuli. The neuronal cytoskeleton comprises three main filament systems: intermediate filaments, actin filaments, and microtubules. Intermediate filaments include type IV neurofilament triplet proteins (NF-L, NF-M, NF-H), α-internexin, and type III peripherin [289]. Actin filaments are composed of polymerized globular actin (G-actin) that assemble into flexible strands essential for spine morphology and synaptic plasticity. Microtubules, formed by α- and β-tubulin dimers, are rigid tubular polymers that serve as tracks for axonal transport and preserve neuronal architecture. Beyond their structural roles, cytoskeletal assemblies exhibit properties akin to MLOs. These filamentous networks undergo dynamic remodeling, phase separation, and transient protein-protein interactions, forming localized domains that organize cellular activities without a delimiting membrane [290]. Such behavior allows the cytoskeleton to act as a platform for signaling and trafficking hubs, making it susceptible to dysregulation in neurodegenerative conditions.

Cytoskeletal abnormalities are widely implicated in neurodegenerative diseases such as AD (**Figure 3**). Microtubule-associated protein tau plays a central role in regulating microtubule stability. Tau loss in animal and cellular models results in reduced microtubule numbers and smaller axon calibers, although partial compensation by other MAPs such as MAP2 has been observed [291]. In cultured neurons, acute tau inactivation reduces neurite length and branching and impairs growth cone dynamics [292]. Under pathological conditions, tau becomes hyperphosphorylated, truncated, or oxidized, which reduces its microtubule-binding ability and promotes its mislocalization to axonal and somatodendritic compartments [293]. This contributes to synaptic loss and neuronal death. Multiple kinases, including MAPK, GSK-3β, MARK/PAR-1, CDK2, and CDK5, regulate tau phosphorylation, and their inhibitors have been investigated in AD clinical trials [294–298]. Furthermore, phosphorylated or aggregated tau is normally cleared through autophagy, but impairment in the endo-lysosomal system in AD interferes with this degradation process, exacerbating tau accumulation [299].

Pathological changes in the actin cytoskeleton are also prominent in AD. Hirano bodies, which are intracytoplasmic inclusions observed in affected neurons, consist primarily of actin along with associated proteins such as tropomyosin, vinculin, α-actinin, actin-depolymerizing factor (ADF), and cofilin [300,301]. Actin rods, another hallmark feature, are rod-shaped bundles composed of ADF/cofilin-actin complexes that are frequently observed in hippocampal and cortical neurites in AD brains [302]. These structures co-accumulate with vesicles containing APP and γ-secretase components, indicating impaired axonal transport and protein trafficking [291]. Cofilin, which is more abundantly expressed than ADF in neurons, plays a central role in regulating actin filament turnover and is critically involved in actin-based pathologies [303,304]. Elevated cofilin activity has been reported in both AD brains and APP transgenic models [305,306]. Its activation, particularly under oxidative stress, leads to the formation of actin rods through intermolecular cysteine oxidation [307]. Moreover, activated cofilin can translocate to mitochondria, where it contributes to mitochondrial fragmentation and dysfunction [308,309]. These findings collectively suggest that cytoskeletal dysfunction in AD, driven by pathological changes in tau and cofilin, disrupts neuronal transport, synaptic integrity, and mitochondrial function, making it a likely central driver of neurodegeneration.

Spliceosome: The spliceosome is a large and dynamic ribonucleoprotein complex located in the nucleus, where it catalyzes the removal of introns and the ligation of exons from pre-messenger RNA transcripts. This process is essential for generating mature mRNAs and enabling accurate gene expression in eukaryotic cells. The core components of the major spliceosome include five small nuclear ribonucleoproteins: U1, U2, U4, U5, and U6. Each snRNP contains a specific small nuclear RNA, seven core Sm or Lsm proteins, and a set of snRNP-specific splicing factors such as U1-70K, U1A, and U1C. The spliceosome assembles stepwise on nascent RNA polymerase II transcripts, undergoing several dynamic conformational changes to ensure precise intron removal and exon joining [310]. Importantly, the spliceosome exhibits key characteristics of an MLO. It is not enclosed by a lipid membrane but rather forms through a biophysical process known as liquid–liquid phase separation (LLPS). LLPS describes the demixing of specific proteins and RNAs from the surrounding nucleoplasm to form distinct, dynamic compartments that concentrate biochemical activity without a physical barrier [311]. This self-organizing property allows the spliceosome to assemble transiently at transcription sites and rapidly respond to changes in cellular signaling or RNA processing demands. The multivalent interactions between RNA and protein components further facilitate its dynamic behavior, similar to other nuclear MLOs such as the nucleolus and Cajal bodies [311].

Recent studies have implicated spliceosome dysfunction in the pathogenesis of AD. Disruption of splicing activity, particularly involving the U1 snRNP complex, has emerged as a consistent molecular feature [312]. Transcriptomic profiling of postmortem brain tissues from multiple AD cohorts has revealed widespread splicing abnormalities, including intron retention, exon skipping, and the use of cryptic splice sites [313,314]. These transcriptome-wide defects are accompanied by the abnormal deposition of spliceosomal proteins in insoluble aggregates isolated from AD brains. Specifically, U1 snRNP subunits have been found in association with pathological inclusions, suggesting their sequestration and loss of function [313,315,316]. Proteome and phosphoproteome analyses further support these findings, revealing altered expression and phosphorylation of splicing regulators and RNA-binding proteins in AD brain tissues [317] (**Figure 3**). One proposed mechanism for this disruption involves tau pathology. Neurofibrillary tangles composed of hyperphosphorylated tau have been shown to interfere with spliceosome activity [318]. In Drosophila models expressing pathogenic tau, extensive RNA splicing errors have been observed, including retention of introns and activation of non-annotated splice junctions [318]. Together, these findings suggest that the spliceosome functions not only as a fundamental RNA-processing machine, but also as a dynamic, membraneless compartment whose integrity is vulnerable to tau-mediated stress. Its disruption in AD likely contributes to transcriptomic instability and aberrant neuronal gene expression, reinforcing its emerging role in disease pathogenesis.

Stress granule: Stress granules (SGs) are cytoplasmic, MLOs composed of protein and RNA, ranging in size from 0.1 to 2 micrometers. They form in response to environmental stressors such as oxidative stress, heat shock, hypoxia, viral infection, and ultraviolet radiation [319]. SGs act as a rapid and reversible mechanism by which cells alter their translational landscape. Their assembly

sequesters mRNA transcripts of non-essential proteins, thereby halting their translation and prioritizing the synthesis of stress-responsive, cytoprotective proteins [320]. Key RNA-binding proteins that nucleate SG formation include TIA-1, TIAR, Caprin1, and G3BP1, which aggregate with untranslated mRNAs during stress exposure [321–323]. SGs are also formed through LLPS, as previously described, allowing SGs to remain dynamic and reversible under physiological conditions. However, under chronic stress or disease-associated perturbations, SGs may lose their dynamic, liquid-like properties and transition into more stable, less reversible aggregates. Such pathological transformation has been implicated in the formation of protein inclusions in various major neurodegenerative diseases, including AD [319,324].

In AD, stress granule-associated proteins have been detected within both amyloid plaques and neurofibrillary tangles, implicating SG components in the pathological aggregation of disease-related proteins (**Figure 3**). Notably, TIA-1 and USP10 colocalize with hyperphosphorylated tau in the brains of AD patients and tau transgenic mouse models [325–327]. The interaction between TIA-1 and tau is particularly enriched in regions with severe tau pathology [325]. Functionally, TIA-1 promotes tau aggregation and accelerates neurotoxicity by driving the formation of tau-positive stress granules [326]. Similarly, USP10 overexpression induces the assembly of tau-containing SGs even in the absence of exogenous stress, indicating its potent role in modulating SG dynamics and tau pathology [327]. Beyond tau aggregation, SGs also contribute to AD-related neuroinflammation. In microglia, exposure to stressors such as sodium arsenate or Aβ1–42 fibrils induce SG formation and leads to the sequestration of SYK, a kinase essential for microglial activation and phagocytic function. This sequestration impairs the clearance of Aβ fibrils, thereby exacerbating amyloid pathology [328]. Additionally, SGs aberrantly entrap various RNA species, including transcripts of AD-related genes and long non-coding RNAs. This persistent RNA sequestration disrupts normal RNA metabolism and protein synthesis, further contributing to neuronal dysfunction, synaptic loss, and cognitive decline [329]. Together, these findings highlight the maladaptive role of SGs in AD, linking chronic stress responses to impaired protein and RNA homeostasis and the propagation of neurodegenerative pathology.

Others

Primary cilium: Primary cilia are solitary, non-motile, microtubule-based projections that extend from the surface of nearly all mammalian cells. Unlike typical intracellular organelles, primary cilia are not surrounded by a distinct membrane but are continuous with the plasma membrane, functioning as specialized signaling hubs on the cell surface [330]. Structurally, they consist of an axoneme organized in a 9 + 0 microtubule arrangement, which includes nine peripheral doublets without a central pair. This configuration distinguishes them from motile cilia, which have a 9 + 2 arrangement with a central microtubule pair. The assembly and disassembly of primary cilia are tightly regulated and vary according to cell type and developmental stage [330]. Functionally, primary cilia are essential for transducing extracellular signals and regulating multiple developmental and homeostatic pathways. These include Wnt, Sonic Hedgehog (Shh), Notch, platelet-derived growth factor (PDGF), and mTOR signaling [331]. A range of receptors, such as G protein-coupled receptors (GPCRs), localize to the ciliary membrane where they detect chemical and mechanical cues [332].

Several *in vivo* studies have examined ciliary morphology in AD models, yielding inconsistent results. One study found a significant reduction in primary cilia length in hippocampal dentate granule cells of 3xTg mice [333]. In contrast, another study reported a significant increase in cilia length in hippocampal neurons of APP/PS1 mice, although neither study detected changes in cilia frequency [334]. In the 5xFAD mouse model, elongated cilia were observed in enteric neurons, accompanied by reduced expression of β-catenin, a key effector of Wnt signaling that is modulated by ciliary function [335]. These discrepancies may be attributed to differences in animal models, experimental conditions, or technical limitations, such as reliance on single-plane imaging for measuring cilia length. More advanced approaches, including three-dimensional imaging and cell-type-specific analyses, are necessary to clarify these inconsistencies. Supporting *in vitro* studies further show that Aβ reduces cilia length and frequency in cultured neurons, providing additional evidence that AD-related pathology interferes with ciliogenesis [335,336]. Overall, these findings suggest that primary cilia play a critical role in maintaining neuronal signaling and plasticity, and that their dysfunction may contribute to the impaired neurogenesis and signaling disturbances characteristic of AD.

CONCLUSION

Age remains the most significant risk factor for neurodegenerative diseases, including AD, yet it also represents one of the greatest challenges in experimental modeling. Conventional cell lines and animal models often fail to replicate the multifaceted progression of human neurodegeneration. As a result, they may not fully capture the temporal dynamics, cellular heterogeneity, or mechanistic complexity inherent in the aging human brain. This limitation has hindered efforts to pinpoint the earliest molecular events and to determine how cellular disturbances accumulate and interact over time to form neuropathologies. As outlined throughout this manuscript, nearly all major organelles exhibit functional and structural abnormalities in AD, both in postmortem human tissue and in experimental models. Mitochondria, lysosomes, and ER have long been implicated in AD, each showing disruptions in processes such as energy metabolism, proteostasis, calcium signaling, and redox regulation.

More recently, attention has expanded to include other critical compartments such as peroxisomes, lipid droplets, MAMs, exosomes, proteasomes, ribosomes, the cytoskeleton, stress granules, spliceosomes, and primary cilia. Many of these compartments are not isolated systems but are dynamically interconnected, participating in essential processes including intracellular trafficking, RNA metabolism, protein degradation, organelle-organelle communication, and stress responses. A particularly important insight is the involvement of MLOs, such as stress granules and spliceosomes, which form through LLPS. These assemblies lack lipid boundaries but are governed by multivalent interactions and phase behavior that confer high spatial and temporal responsiveness. Although MLOs are adaptive under normal conditions, their dysregulation in AD, often exacerbated by pathological protein aggregation, suggests that they may act as critical nodes where cellular resilience is compromised. The propensity of such organelles to transition from liquid-like to solid-like states under chronic stress could drive the formation of irreversible aggregates and impede essential cellular functions.

The widespread organellar changes in AD collectively reflect a structured breakdown in cellular homeostasis, rather than a random or uniform disruption. Instead, they suggest a complex hierarchical model of dysfunction where certain organelles may act as early sensors or effectors of pathological processes, while others respond in a

compensatory or downstream fashion. For example, mitochondrial dysfunction may initiate a series of metabolic and oxidative stress responses that subsequently affect lysosomal clearance, cytoskeletal transport, and ER stress responses. Similarly, impairments in RNA splicing or stress granule dynamics may precede overt protein aggregation by subtly altering transcriptomic fidelity or proteome balance. Understanding the causative links of these responses remain one of the challenges in AD. It is essential to determine which organellar changes are primary drivers of disease and which represent adaptive or maladaptive responses to upstream insults, and they remain critical for identifying therapeutic targets that are both mechanistically relevant and temporally actionable.

To achieve this goal, future research must leverage integrative and high-resolution technologies capable of resolving organellar behavior over time and across diverse cellular contexts. Techniques such as live-cell imaging with super-resolution microscopy, spatial transcriptomics, single-cell and single-nucleus omics, and proteomic profiling of subcellular compartments can reveal how organelle-specific functions are altered in early versus late stages of disease. Additionally, new models that better replicate human aging such as human brain organoids, induced pluripotent stem cell-derived neurons from aged donors, or long-lived non-human primates will be critical for studying chronic neurodegeneration in physiologically relevant contexts.

In sum, the study of organelle biology in AD offers more than an inventory of dysfunctions. It provides a framework for understanding how complex intracellular networks fail in disease and how reestablishing coordination among these systems might restore neuronal health. Organelle dysfunction should be viewed not as discrete damage, but as part of a coordinated failure in cellular organization, where impairments in one compartment can propagate and exacerbate vulnerabilities in others [337]. This approach holds promise for identifying novel biomarkers that reflect early dysfunction across multiple compartments and for developing therapeutics that act on converging points of vulnerability within the cell. A better understanding of how organellar systems interact to maintain homeostasis and how their failure leads to irreversible decline will be essential for transforming our ability to diagnose, prevent, and treat this devastating disease.

AUTHOR CONTRIBUTIONS

JL and XW provided expert guidance. XW finalized the manuscript. JG, LV, and XW contributed to the literature review and drafting. All authors reviewed and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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