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The endoplasmic reticulum stress and unfolded protein response in Alzheimer's disease: A calcium dyshomeostasis perspective

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ABSTRACT

Protein misfolding is prominent in early cellular pathology of Alzheimer's disease (AD), implicating pathophysiological significance of endoplasmic reticulum stress/unfolded protein response (ER stress/UPR) and highlighting it as a target for drug development. Experimental data from animal AD models and observations on human specimens are, however, inconsistent. ER stress and associated UPR are readily observed in in vitro AD cellular models and in some AD model animals. In the human brain, components and markers of ER stress as well as UPR transducers are observed at Braak stages III-VI associated with severe neuropathology and neuronal death. The picture, however, is further complicated by the brain region- and cell type-specificity of the AD-related pathology. Terms 'disturbed' or 'non-canonical' ER stress/UPR were used to describe the discrepancies between experimental data and the classic ER stress/UPR cascade. Here we discuss possible 'disturbing' or 'interfering' factors which may modify ER stress/UPR in the early AD pathogenesis. We focus on the dysregulation of the ER Ca^{2+} homeostasis, store-operated Ca^{2+} entry, and the interaction between the ER and mitochondria. We suggest that a detailed study of the CNS cell type-specific alterations of Ca^{2+} homeostasis in early AD may deepen our understanding of AD-related dysproteostasis.

1. Introduction

Protein folding in the endoplasmic reticulum (ER) is a central part of cellular proteostasis, which is tightly controlled to avoid the accumulation of misfolded and/or aggregated proteins. Two principal processes sustaining ER proteostasis are ER-associated protein degradation (ERAD) and ER stress/unfolded protein response (UPR). While ERAD homeostatically eliminates unfolded/misfolded proteins, ER stress/UPR represents an evolutionary conserved and ubiquitous reaction of cells to physiological or pathological pressure as a part of the integrated stress response (Pakos-Zebrucka et al., 2016). Functionally, protein folding, ER stress/UPR and ultimately apoptotic cell death are linked to ER and mitochondrial Ca^{2+} homeostasis. Both Ca^{2+} dysregulations and ER stress/UPR were suggested to contribute to pathogenesis of Alzheimer's disease (AD), gaining research interest and aspirations for the development of anti-AD therapy (Ajoolabady et al., 2022; Alzheimer's Association Calcium Hypothesis Workgroup, 2017; Berridge, 2010; Ghemrawi and Khair, 2020; Rahman et al., 2018; Singh et al., 2022). While in some diseases, such as MS, stroke, or brain trauma ER stress/UPR is evident in both neurons and glial cells, being linked to glial reactivity and neuroinflammation, in AD somewhat discordant data were reported. Activation of the ER stress/UPR pathway in AD animal models was disputed (Hashimoto and Saido, 2018), whereas non-canonical or 'disturbed,' forms of ER stress/UPR were proposed

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(Hetz et al., 2020; Kumar and Maity, 2021). In this opinion paper, we review the evidence supporting and negating the activation of ER stress/UPR in AD, and we relate these data to the progression of cellular and clinical AD pathology. We suggest that canonical ER stress/UPR is present in terminal AD stages associated with prominent AD-related neuropathology and neuronal death. Instead, in preclinical and prodromal AD stages, selected ER stress/UPR cascade components are activated in association with known and emerging phenomena of AD-related cellular physiopathology such as aberrant Ca^{2+} homeostasis, mitochondrial dysfunction, alterations of proteostasis and impairment of ER-mitochondria interaction. We discuss how ER Ca^{2+} dyshomeostasis, anomalous store-operated Ca^{2+} entry and dysregulation of ER-mitochondrial interaction may 'disturb' and tune canonical ER stress/UPR during early AD pathogenesis.

2. Alzheimer's disease progression and loss of proteostasis

Alzheimer's disease (AD) is the major cause of dementia in older people, with continuously increasing incidence worldwide. Currently, there are no disease-modifying drugs available. A minority of AD cases, (<0.5%) known as familiar AD (FAD), are linked to mutations in three genes (amyloid precursor protein (APP), and presenilin-1,2 (PS1,2), implicated in the production of amyloid-β (Aβ) peptide). In sporadic AD (SAD), also known as late-onset AD, ~70% of cases are attributable to genetic risk factors, with APOEε4 allele identified in ~40% of SAD (Lane et al., 2018; Liu et al., 2013). Pathophysiology of AD can be discerned into stages based on clinical and neuropathological criteria or on hypothesized cellular pathology, studied mostly in cellular and animal AD models. Clinical stages of AD are (i) early stage, in which neither diagnostic markers nor clinical manifestations are present; (ii) preclinical stage, with no clinical manifestations, but diagnostic markers, such as increasing levels of Aβ or Tau, are detected in cerebrospinal fluid or by in vivo neuroimaging; (iii) prodromal stage, in which patients manifest cognitive changes, known as mild cognitive impairment; and (iv) clinical (dementia) stage, in which a progressive cognitive decline leading to dementia prevails (Scharre, 2019; Vermunt et al., 2019). Neuropathological stages, proposed by Braak and Braak (stages I to VI), are based on the regional distribution of neurofibrillary tangles (NFTs) (Braak and Braak, 1991). Unlike fibrillar amyloid deposits that poorly correlate with dementia severity, NFTs and neuronal loss are the best correlates of cognitive deterioration (Braak and Braak, 1991; Giannakopoulos et al., 2009; Theofilas et al., 2018). Cellular pathology is classified into three principal phases: (i) biochemical phase, in which alterations are cell-autonomous and caused by primary AD-related insults, e.g., APP/PS mutations or APOEε4 allele; (ii) cellular phase, which involves all cell types of the nervous tissue with several feedback and feed-forward intercellular loops affecting principal homeostatic processes such as Aβ clearance, lipid metabolism, immune response and signaling, and (iii) neuronal death phase in which defensive mechanisms fail to protect neurons from demise (De Strooper and Karran, 2016). Relating clinical to cellular stages is not straightforward: roughly, biochemical and cellular stages of cell pathology correspond to preclinical and prodromal stages of the clinical classification. In the early phase, there are no indications that the person is at risk of developing AD. Preclinical signs allow providing a diagnosis based on markers that indicate changes of Aβ and/or Tau, although specific criteria for preclinical stage are under continuous evolution (Alberdi et al., 2016; Dulewicz et al., 2022; Gong et al., 2022; Porsteinsson et al., 2021). Therefore, it is impossible to correlate the cellular pathology to clinical progression of human AD directly. Moreover, until the disease is not diagnosed, any attempt to explain the cell pathology is mere speculation. Nevertheless, animal models use allows to correlate early signs of pathology with subsequent synaptic and neuronal dysfunctions, Aβ burden, and cognitive impairment (Belfiore et al., 2019; Götz and Götz, 2009; Oddo et al., 2003).

Due to the accumulation of aberrantly folded and/or aggregated proteins such as Aβ and Tau, AD has been defined as a 'proteinopathy' in which aberrant proteostasis is an integral component. Within the framework of the amyloid cascade hypothesis, changes in proteostasis start with intracellular accumulation of Aβ (Giménez-Llort et al., 2007; Soejima et al., 2013; Umeda et al., 2011), which triggers proteostatic stress, disturbing the molecular machinery of protein folding thereby impairing folding of other proteins. According to the cell pathology concept, aberrant proteostasis is linked to the biochemical phase of AD (De Strooper and Karran, 2016). However, a growing body of evidence suggests that FAD-related mutant proteins may provoke cell dysfunction through mechanisms that are not related to Aβ, disturbing ER Ca^{2+} homeostasis and ER, Golgi apparatus and mitochondrial functions (Area-Gomez et al., 2012; Area-Gomez and Schon, 2017; Galla et al., 2020; Han et al., 2021; Haukedal et al., 2023; Pchitskaya et al., 2018; Popugaeva et al., 2017). From this perspective, the dysregulation of protein synthesis and/or degradation, which rely on Ca^{2+} signals and proper function of ER and mitochondria, start as early as mutant proteins are expressed by the cell. At any rate, dysproteostasis represents one of the earliest alterations in cellular AD pathogenesis.

3. Canonical ER stress/UPR

The term 'ER stress' refers to a cellular condition in which the physiological homeostasis of the ER is compromised. Physiologically, ER exerts multiple functions, including integration of extracellular stimuli with cellular responses, control of Ca^{2+} homeostasis, storage and signaling, maturation and folding of proteins, lipid and steroid biogenesis (Chipurupalli et al., 2021; Halperin et al., 2014; Schwarz and Blower, 2016). Furthermore, ER supports interactions with plasma membrane (PM) and mitochondria, in PM-ER and mitochondria-ER contact sites (MERCS), respectively (Li et al., 2021; Moltedo et al., 2019; Verkhratsky, 2005).

Both extracellular (hormones and toxins, viral infection, energy deprivation, oxygen shortage) and intracellular (ROS production, ATP depletion, mitochondrial deficiency, and accumulation of mutated proteins) signals can alter ER homeostasis. These stressors result in an abnormal ER function, directly or indirectly compromising protein folding, which leads to the accumulation of unfolded/misfolded proteins in the lumen of ER. The abnormal ER function triggers finely tuned activation of a genetic program, the UPR (Pakos-Zebrucka et al., 2016).

UPR is triggered by the main and most abundant ER-resident chaperone Bip/GRP78, which conducts a two-faced 'Janus' life in a delicate balance. Under physiological conditions, Bip/GRP78 interacts (with high affinity) with unfolded/misfolded proteins and (with lower affinity) with the luminal domains of the three ER transmembrane proteins: PERK (PRKR-Like Endoplasmic Reticulum Kinase), IRE1α (Inositol-Requiring Protein 1) and ATF6 (Activating Transcription Factor 6) (Fig. 1A). In this scenario, Bip/GRP78 contributes to the folding of newly synthesized proteins and concomitantly inhibits activation of the ER stress sensors PERK, IRE1α, and ATF6. Stress conditions, which cause an increase in unfolded/misfolded proteins in the lumen of the ER, shift the balance towards the Bip/GRP78 folding activity, thus resulting in dissociation from and subsequent activation of these three sensors. Once released from Bip/GRP78, PERK is activated through dimerization and transphosphorylation. Active PERK phosphorylates its main downstream target eIF2α (Eukaryotic Translation Initiation Factor 2 Subunit α), leading to a transient inhibition of the general and cap-dependent translation (initiated with binding of the initiation complex to a special tag-bound 5'-end of mRNA molecule, the so-called 5'-cap (Merrick, 2004)). Protein synthesis inhibition reduces the rate of entry of newly synthesized proteins to be processed by the ER apparatus, thereby reducing ER stress. Phosphorylated eIF2α also favors the cap-independent and IRES-mediated translation of proteins such as Activating Transcription Factor 4 (ATF4), a transcription factor controling the expression of genes regulating protein folding, metabolism, and ER-Golgi trafficking (Amodio et al., 2013; Blais et al., 2004; Harding et al., 1999; Renna et al., 2006; Spatuzza et al., 2004). IRE1α is a

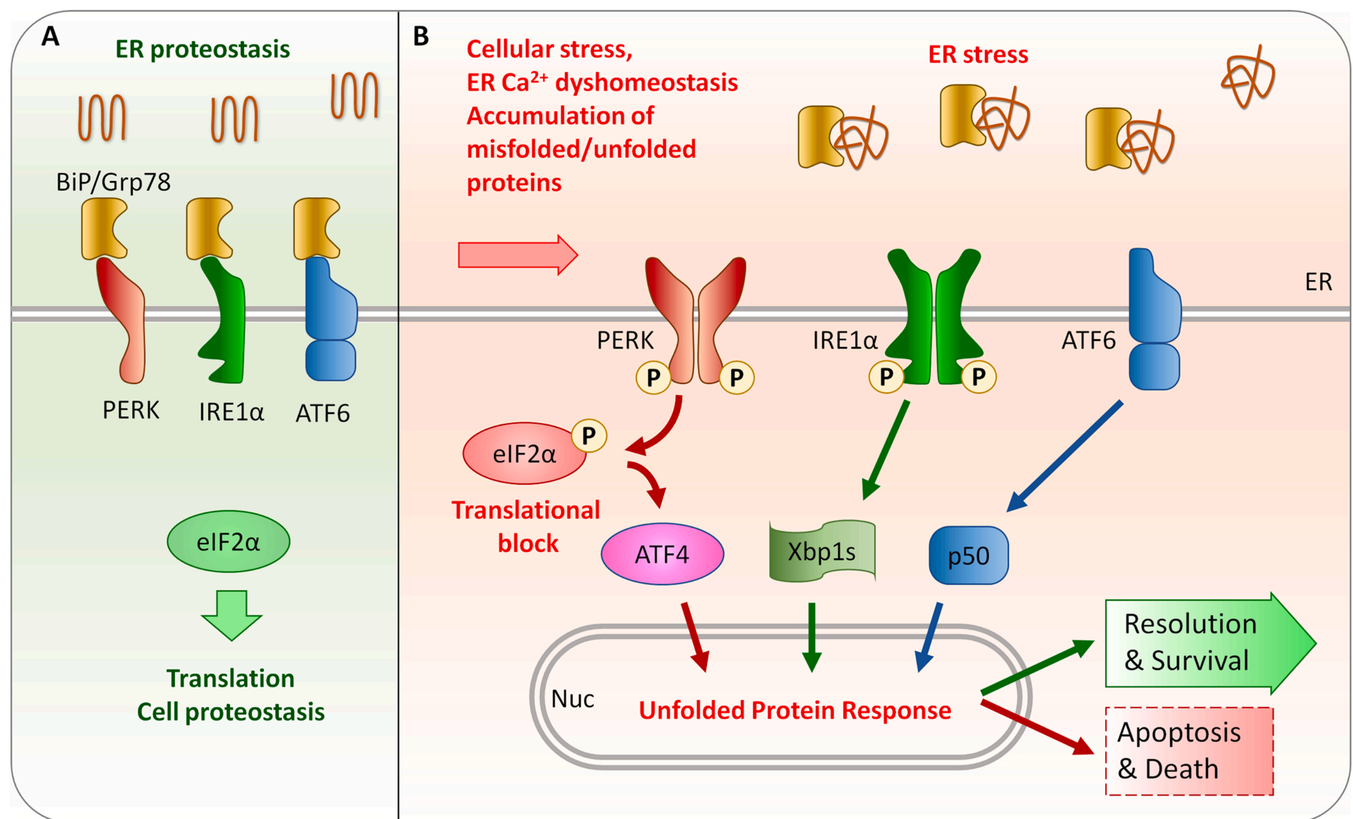

Fig. 1. Core mechanism of canonical ER stress/UPR. (A) In conditions of physiological ER proteostasis, UPR transducers PERK, IRE1α and ATF6 bind BiP/Grp78. Dephosphorylated form of eIF2α drives basal protein siynthesis maintaining cellular proteostasis. (B) In stress conditions BiP/Grp78 is recruited to accumulating unfolded/misfolded proteins and dissociates from UPR transducers resulting in phosphorylation of eIF2α and translocation of ATF4, Xbp1s and p50 into the nucleus with consequent activation of UPR. UPR activation may result in the resolution of ER stress with normalization of proteostasis and cell survival, while failure to resolve ER stress triggers apoptotic program leading to cell death.

transmembrane factor with a cytosolic serine/threonine kinase and endoribonuclease domain, which resembles PERK's activation. Once activated, IRE1α promotes the atypical splicing of *XBP1* (X-Box Binding Protein 1) mRNA, which triggers translation of the active transcription factor XBP1s (spliced XBP1) that in turn controls expression of genes responsible for protein folding, trafficking and ERAD, thus contributing to adaptation to the stress condition (Acosta-Alvear et al., 2007). The inactive transmembrane ATF6 is confined to the ER by its interaction with Bip/GRP78. The stress-mediated dissociation from Bip/GRP78 allows prompt translocation of ATF6 into the Golgi apparatus where the site-1 and site-2 proteases (S1P and S2P)- mediated cleavage releases the cytosolic active ATF6 (p50), which moves to the nucleus to regulate the expression of XBP1, chaperonins, SERCA (sarco-endoplasmic reticulum Ca^{2+} ATPase), and p58INK, a PERK inhibitor. This represents a negative feedback loop control of ER stress (Hetz et al., 2020; Renna et al., 2007; Ron and Walter, 2007; van Huizen et al., 2003). Therefore, the UPR supports cell survival through stress adaptation. However, cell death program is induced when enhanced folding capacity coupled to selective degradation of unfolded proteins is not sufficient to cope with stress conditions. The same sensors that control stress adaptation trigger up-regulation of pro-apoptotic factors such as CHOP/GADD153 (DNA Damage Inducible Transcript 3), PUMA (P53 Up-Regulated Modulator Of Apoptosis), NOXA (Phorbol-12-Myristate-13-Acetate-Induced Protein 1), and inhibition of the expression of anti-apoptotic components such as BCL-2 (B-Cell CLL/Lymphoma 2) and MCL-1 (Myeloid Cell Leukemia 1) (Corazzari et al., 2017) (Fig. 1B). Although the precise molecular mechanism(s) regulating the survival/death switch is(are) not fully understood, a key role appears to be played by the transcription factor E2F1. Indeed, the ER stress-mediated regulation of E2F1 protein levels results in the survival/death switch (see (Corazzari et al., 2017; Pagliarini et al., 2015) for details).

Mitochondria can also instigate the UPR program known as UPR^{mit}, due to the accumulation of misfolded proteins in the mitochondrial matrix or to dysregulation of mitochondrial functions such as disrupting the respiratory chain. UPR^{mit} is based on the activation of transcription factors that increase chaperone capacity and protein degradation. This mechanism was initially found in *C. elegans* and was recently described in mammals. Moreover, UPR^{mit} is involved as UPR^{ER} in cancer, aging and neurodegeneration, with ATF4 representing a common player in both signaling pathways (Shpilka and Haynes, 2018).

Finally, the Golgi apparatus can also be disturbed by extrinsic or intrinsic cellular factors, thus inducing a 'Golgi Stress Response', a genetic program in which transcription factor binding to IGHM enhancer 3 (TFE3), heat shock protein 47 (HSP47), cAMP responsive element binding protein 3 (CREB3), transcription factor E26 transformation specific sequence-1 (ETS-1), proteoglycan, and mucin pathways are the main actors. Furthermore, similarly to ER-related UPR, the Golgi stress response can also trigger cell survival or death, although the molecular mechanisms are still elusive (Gao et al., 2021; Machamer, 2015; Sasaki and Yoshida, 2019).

Thus, all major eukaryotic organelles are tightly regulated systems, which, once disturbed, activate specific signaling pathways controling cell survival or death.

4. AD-related aberrant proteostasis through the lens of canonical ER stress/UPR

4.1. ER stress/UPR in cell models of AD

Exposure of glia and neurons to ER stress inducers, such as

thapsigargin (THG, an inhibitor of SERCA pump) or tunicamycin (TUN, an inhibitor of N-linked glycosylation), evokes robust ER stress/UPR with consequent apoptotic cell death, suggesting that all neural cells possess relevant molecular toolkits (Chung et al., 2011; Dibdiakova et al., 2019; Földi et al., 2013; Sanchez et al., 2019). Numerous studies demonstrate that ER stress/UPR induction followed by apoptotic death can be induced by exogenous application of synthetic Aβ peptide to primary cultured neural cells and cell lines (Alberdi et al., 2013; Barbero-Camps et al., 2014; Chafekar et al., 2007; Costa et al., 2012; Ferreiro et al., 2006; Kim et al., 2006; J.H. Lee, J.H. Lee et al., 2010; D.Y. Lee, D.Y. Lee et al., 2010; Nakagawa et al., 2000).

Relationships between ER stress/UPR and AD-related mutant PS1 are less clear. In HEK293T or SK-N-SH cells overexpressing AD-related PS1 mutants A246E and dE9 (deletion of exon 9), TUN-induced up-regulation of BiP/GRP78 was significantly attenuated compared to WT PS1, suggesting that overexpression of mutant PS1 itself represents a stress stimulus (Katayama et al., 2001, 1999). In astrocytes from 3xTg-AD mice bearing $PS1_{M146V}$ mutation, a 2–3 fold transcriptional increase of ER stress/UPR markers ATF4, ATF6, XBP1s, and HERPUD1 (Homocysteine Inducible ER Protein With Ubiquitin Like Domain 1) was detected, although without activation of PERK (Dematteis et al., 2020; Tapella et al., 2022).

4.2. ER stress/UPR in animal AD models

In animal AD models, ER stress can be induced by the exogenous administration of Aβ in high concentrations. Thus, intraventricular infusion of 100 μL of 1 mg/ml Aβ induced upregulation of GADD153 (CHOP) in rabbits (Ghribi et al., 2001). In genetic mouse FAD models, opposite data were reported. An age-dependent overexpression of p-PERK, p-eIF2α, ATF6, CHOP, and BiP/GRP78 was found in APP/PS1dE9 mice aged between 4 and 10 months. In the APP/PSdE9 mice model (10–12 months old), no significant increase of p-PERK, p-eIF2α and ATF4 was found (Ma et al., 2013). Nevertheless, genetic deletion of PERK and GCN2 (Eukaryotic Translation Initiation Factor 2 Alpha Kinase 4, *Eif2ak4*) significantly reduced p-PERK, p-eIF2α and ATF4 (Ma et al., 2013). In 17-month-old Tg2576 mice, no changes were found in levels of PDI (Protein Disulfide-Isomerase), BiP/GRP78, CHOP and cleaved forms of caspases 3,4 and 12 (D.Y. Lee, Won et al., 2010; J. H. Lee, Won et al., 2010). A comparative study on knock-in APP(NL-G-F) (6 and 14 months old) and overexpressing APP23 (6 months old), Tg2576 (6 months old) and 3xTg-AD (23 months old) mice did not reveal up-regulation of p-eIF2α, CHOP, PDI, BiP/GRP78 or XBP1s (Hashimoto et al., 2018). Moreover, no changes were found in a P301S-Tau-Tg mouse model of tauopathy (Hashimoto et al., 2018). Contrasting data were obtained when studying 5xFAD mice, which showed no ER stress/UPR at 4, 6 and 9 months of age (Sadleir et al., 2018). Nevertheless, genetic ablation of IRE1α was beneficial in reducing Aβ depositions and restoring memory in 5xFAD mice at 6 months of age (Duran-Aniotz et al., 2017). Similarly, the constitutive knock-out of PERK in APP-PSdE9 mice was protective against AD-related physiopathology (Ma et al., 2013). Finally, in 16 months old 3xTg-AD mice, p-eIF2α was increased with no detectable changes in p-PERK or ATF4; however, a reduction of global protein synthesis with a down-regulation of GADD34 was found (Tapella et al., 2022).

Several reports demonstrated that treatment of AD mice with drugs targeting ER stress/UPR mitigated AD-related alterations such as senile plaques formation, reactive gliosis and impairment of spatial learning and memory (He et al., 2020; Krajnak and Dahl, 2018; Li et al., 2019; Panagaki et al., 2018; Ricobaraza et al., 2012, 2011; Wang, Zhao et al., 2019).

The interpretation of these contrasting data is not straightforward and the role of APP/PS mutants overexpression in model animals has been discussed (Hashimoto and Saido, 2018). Nevertheless, a positive effect of the in vivo inhibition of PERK and IRE1α signaling suggests that (i) a UPR-unrelated role of these proteins in AD pathogenesis and/or (ii) that there is an abnormal (disturbed) form of ER stress/UPR which does not fit to the canonical scheme (Hashimoto and Saido, 2018; Hetz et al., 2020; Kumar and Maity, 2021).

4.3. ER stress/UPR in postmortem human AD samples

The study of human AD pathogenesis is hampered due to the obvious impossibility of invasive manipulation. Therefore, the knowledge is procured from non-invasive assays and analyses, such as biochemical analyses of CSF or blood, or neuroimaging. However, most of the data derive from postmortem material, which, excluding the limitations of postmortem tissue processing, represents a snapshot of the brain at the moment of death.

Transcriptional induction of ER stress/UPR markers is somewhat easier to detect than protein changes. Thus, in AD subjects at Braak stage V-VI, mRNA levels of the ER stress-related genes *XBP1*, *CANX* (calnexin), *PDIA3*, *PDIA6*, *HSPA5* (Bip/GRP78) and *DNAJC3* (DnaJ Heat Shock Protein Family (Hsp40) Member C3) were significantly increased. However, no changes in protein levels were detected (Montibeller and de Belleroche, 2018). A *PDI* increase but not *HSPA5* (BiP/GRP78) was found in Braak VI stage AD brains. In the same brains a slight (~ 25%) increase of *XPB1s* mRNA was found (D.Y. Lee, Won et al., 2010; J.H. Lee, Won et al., 2010). Abnormal *PDI* was accompanied by an increased *DDIT3* (CHOP) and cleaved forms of caspases 3,4 and 12, suggesting ongoing apoptosis (D.Y. Lee, Won et al., 2010; J.H. Lee, Won et al., 2010). In human samples with postmortem confirmed AD, p-eIF2α was increased (Ma et al., 2013). PERK phosphorylation was found to increase mostly in late AD. However, no changes in levels of p-eIF2α were identified (Buchanan et al., 2020). Reactive astrocytes overexpressed BiP/GRP78 and CHOP proteins in the Braak stage VI AD brains but not at the earlier (0 – II) Braak stages (Yu et al., 2018). Protein expression of BiP/GRP78 decreased or remained unchanged in the cortices of both SAD and FAD patients (Katayama et al., 1999; Sato et al., 2000), although neuropathological stages were not indicated precluding the correlation with AD stage.

Accurate correlation with Braak stages suggests that ER stress/UPR markers become gradually activated in concomitance with, or preceding, the development of NFT, with a higher rate in Braak stages III to VI. Thus, increased BiP/GRP78 and p-PERK were found in the cortex and hippocampus of AD patients (Hoozemans et al., 2009, 2005). Activation of IRE1α gradually increased with the Braak stages of AD pathology (Duran-Aniotz et al., 2017).

Stages of the ER stress/UPR continuum must be considered in the context of the relationship between clinical cognitive decline, neuropathology (Braak stages), and synaptic and neuronal loss. Of note, caspase activation precedes neuronal loss in brain stem, which is the site of the earliest AD neuropathology (Theofilas et al., 2018). Moreover, activation of caspases and consequent apoptotic neuronal death may also be triggered by ER stress-independent excitotoxic mechanism involving mitochondrial Ca^{2+} overload and mitochondrial permeability transition pore (mPTP) opening (Quntanilla and Tapia-Monsalves, 2020; Wang and Zheng, 2019). These observations, however, are not universal and were not confirmed in studies on AD patients. Finally, ER stress/UPR was considered independent of PS1-mutations (Sato et al., 2000).

4.4. Is AD-related ER stress/UPR in need of revisiting?

As discussed in Section 2, proteostatic stress occurs quite early in AD pathogenesis, corresponding at least to the cell pathology biochemical phase (De Strooper and Karran, 2016). Accordingly, ER stress/UPR activation may evolve in three phases (Fig. 2): (i) the first phase corresponding to preclinical-prodromal AD, in which a gradual accumulation of biochemical and functional alterations occurs such as Ca^{2+} dysregulation, oxidative stress and disproteostasis with mild (if at all) transcriptional activation of ER stress/UPR markers, but with no evident up-regulation of UPR-related proteins, (ii) the second phase

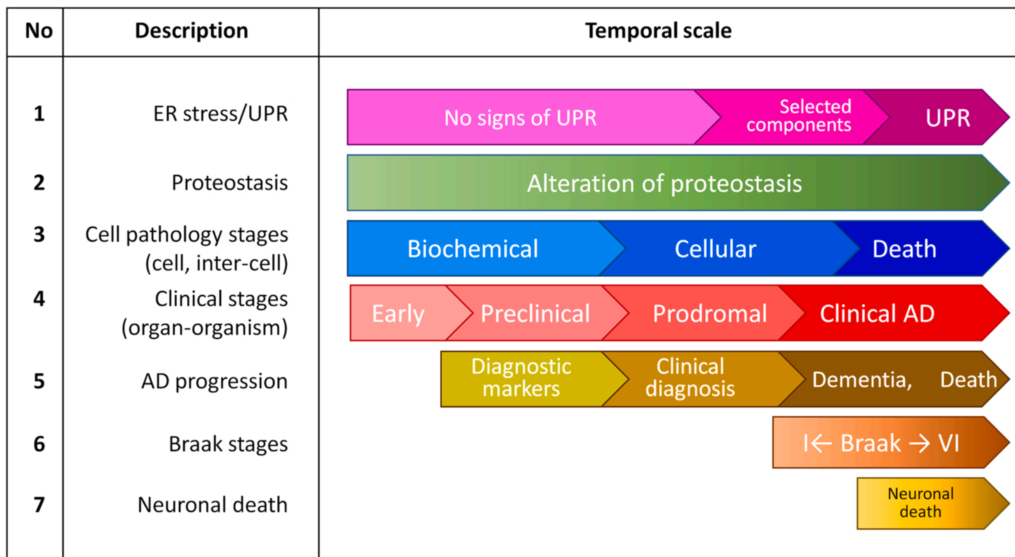

Fig. 2. Hypothetical time-course of ER stress/UPR in relation with principal phenomena of AD pathogenesis. (1) At early stages of AD pathogenesis, no signs of UPR are present. Full expression of ER stress/UPR is evident at late AD stage. (2) Alterations of cellular proteostasis are present from the earliest stages of AD pathogenesis. (3) Hypothesized phases of AD-related cell pathology according to (De Strooper and Karran, 2016). (4) Hypothesized phases of AD progression. (5) Clinical phases of AD. (6) Braak stages. (7) Neuronal death is evident at late AD stages in concomitance with full expression of ER stress/UPR (1).

corresponding to activation of some components of ER stress/UPR and progressive disproteostasis with no activation of apoptosis (clinically this phase may roughly reflect a transition from preclinical to prodromal AD), and (iii) the third phase corresponds to fully expressed ER stress/UPR with the consequent activation of apoptotic cascade leading to synaptic loss and death of neurons, which clinically corresponds to cognitive decline and dementia and Braak stages III-VI (Fig. 2).

Canonically, the ER stress/UPR activation is an immediate consequence of ER dysproteostasis. Experiments with classical inducers of ER stress, such as THG and TUN, suggest that the upregulation of the UPR-induced genes or proteins requires at most 24–72 h. Therefore, it is evident that the hypothesized long-lasting time-scale of ER stress/UPR development during AD pathogenesis does not fit the time-scale of canonical ER stress/UPR (Fig. 3). In the next paragraphs, we discuss possible factors which could interfere with the activation of ER stress/UPR.

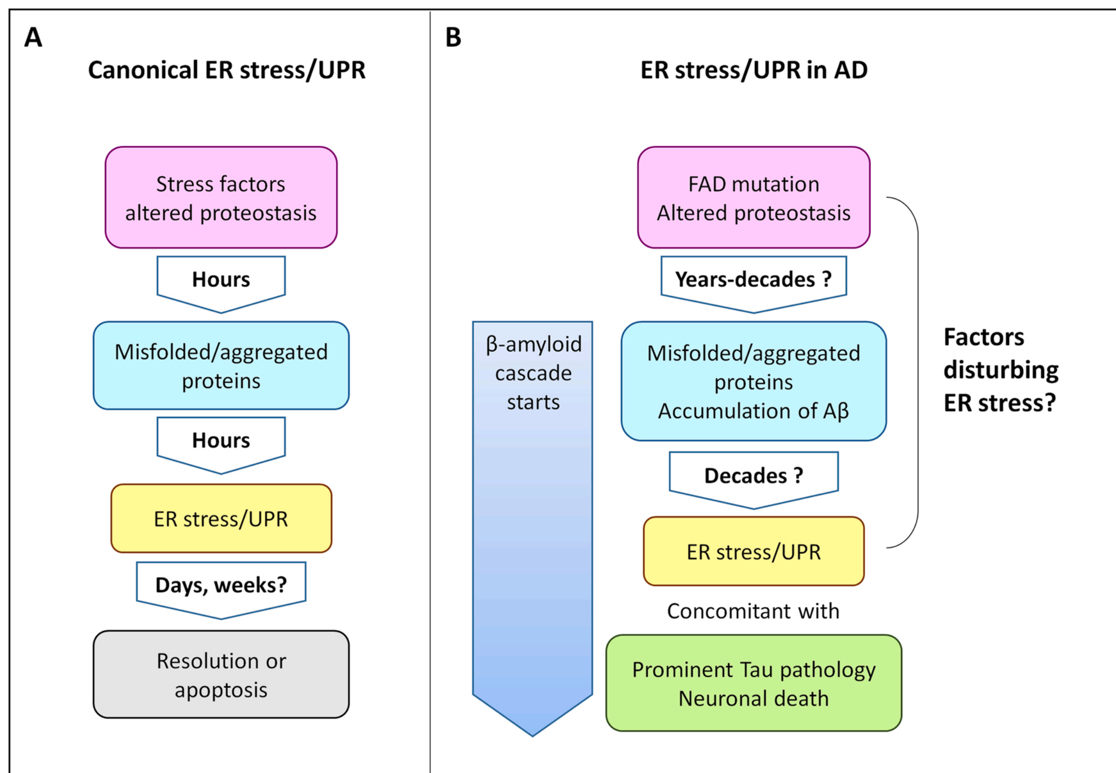

Fig. 3. Long-lasting AD pathogenesis does not fit the time-scale of canonical ER stress/UPR cascade. (A) Canonical ER stress/UPR is a conserved stereotyped program of cell response to stress which is accomplished within weeks by either resolution and survival or by apoptosis and death. (B) Hypothesized ER stress/UPR during AD pathogenesis. Decades-long period from the beginning of proteostatic alterations and accumulation of unfolded and misfolded proteins to full expression of UPR and cell death is incompatible with canonical ER stress/UPR scheme.

5. Ca^{2+} dyshomeostasis disturbs ER stress/UPR activation in AD

5.1. Dysregulation of Ca^{2+} signaling in AD

Alteration of cellular Ca^{2+} homeostasis arguably represents the earliest and most universal sign of cellular malfunction in the brain diseases, including AD (Arnst et al., 2022; Callens et al., 2022; Khachaturian, 1994; Lim et al., 2021; Nedergaard and Verkhratsky, 2010; Popugaeva et al., 2018). Increased resting cytosolic [Ca^{2+}] and spontaneous Ca^{2+} signals were described in both neurons and astrocytes in AD model mice in vivo (Kuchibhotla et al., 2009, 2008). Numerous in vitro studies demonstrated that extracellular oligomeric Aβ affects cellular Ca^{2+} signaling in several ways: binding to, and activating membrane receptors, creating Ca^{2+}-permeable pores in the plasma membrane, and remodeling molecular components of Ca^{2+} signaling toolkit (Grolla et al., 2013; Kawahara et al., 1997; Lal et al., 2007; Lim et al., 2016, 2013; Pollard et al., 1993; Supnet and Bezprozvanny, 2010). Current paradigm, focused on neurons, postulates that general Ca^{2+} overload leads to activation of mechanisms instigating neuronal death (Calvo-Rodriguez and Bacskai, 2021; Demuro et al., 2010; Tong et al., 2018). These mechanisms include (i) overactivation of Ca^{2+}-regulated kinases and phosphatases and aberrant synaptic plasticity; (ii) glutamate-mediated excitotoxicity; (iii) activation of Ca^{2+}-regulated proteases; and (iv) mitochondrial Ca^{2+} overload and activation of mPTP (Calvo-Rodriguez and Bacskai, 2021; Popugaeva et al., 2017; Schultz et al., 2021; Wang and Reddy, 2017). The three latter mechanisms directly contribute to AD-associated neuronal death in advanced Braak stages. Much less is known about AD-related Ca^{2+} dysregulation in neuroglia and other cells in the CNS. Available data suggest that astrocytes, specifically around Aβ plaques, exhibit elevated basal Ca^{2+} levels and increased abnormal spontaneous Ca^{2+} activity associated with astrogliosis and remodeling of Ca^{2+} signaling toolkit (Alberdi et al., 2013; Grolla et al., 2013; Huffels et al., 2022; Kuchibhotla et al., 2009; Lim et al., 2013; Lines et al., 2022). Spontaneous astrocytic Ca^{2+} activity was also detected in some AD mouse models (APPswe and 3xTg-AD mice) at 2–4 months of age, i.e., prior to formation of Aβ plaques, and was associated with instability of vascular tone in these AD model mice (Takano et al., 2007).

5.2. ER Ca^{2+} and ER stress/UPR

5.2.1. ER Ca^{2+} homeostasis

ER is the main Ca^{2+} store of the cell. Other Ca^{2+} stores, morphologically distinct from, but functionally connected to ER, include Golgi apparatus, endolysosomal compartment and peroxisomes (Ronco et al., 2015; Wang, Agellon et al., 2019). Total ER Ca^{2+} content in the cell is estimated in the range of 5–50 mM, whereas free luminal Ca^{2+} concentration $[Ca^{2+}]_L$ lays in the range of ~0.1–1 mM depending on the cell type and the Ca^{2+} probe/methodology used (Meldolesi and Pozzan, 1998; Solovyova and Verkhratsky, 2002). The Ca^{2+} capacity of the ER is determined by the activity of SERCA pump and the presence of ER resident Ca^{2+}-binding proteins including calreticulin (CRT), calnexin (CNX), BiP/Grp78 which bind Ca^{2+} with low affinity (0.4–0.6 mM) (Prins and Michalak, 2011). The overexpression of CRT by 2.5 fold almost doubles free $[Ca^{2+}]_L$, while CRT deletion reduces $[Ca^{2+}]_L$ by about 50% (Arnaudeau et al., 2002; Lucero et al., 1998; Nakamura et al., 2001).

In the ER, *de novo* synthesized proteins undergo two major folding processes: (i) Chaperone Grp78 –PDI cycle that consist in assisting proteins folding by binding in hydrophobic domain and catalysing oxidation and isomerization of disulfides, and (ii) CRT-CNX cycle, assisted by other chaperones (such as ERp57, CypB, and ERp29), in which proteins carrying monoglycosylated glycans undergo protein disulfide bonds formation, proline isomerization, and general protein folding.

Unfolded proteins are re-glycoyilated by UDP-glucose:glycoprotein glucosyltransferase (UGGT) and re-enter in CNX-CRT cycle. Finally, misfolded proteins are directed to ERAD pathway (Hwang and Qi, 2018). The activity of molecular chaperones, such as CRT, CNX, BiP/Grp78 and PDI depends on Ca^{2+} binding, therefore physiological ER Ca^{2+} levels are required for proper protein folding in the ER (Coe and Michalak, 2009). Ca^{2+} is transported, against its electrochemical gradient, into the ER due to the activity of SERCA. Release of Ca^{2+} from the ER is mediated through inositol-1,4,5-trisphosphate (IP_3)-sensitive ligand-gated channels known as $InsP_3$ receptors ($InsP_3R$) and ryanodine sensitive receptors (RyRs). Although $InsP_3R$-mediated Ca^{2+} release is prevalent in neurons and astrocytes, a role for RyRs has also been proposed (Abu-Omar et al., 2018; Solovyova and Verkhratsky, 2003). Even in non-stimulated conditions, the ER membrane is permeable to Ca^{2+}. Ca^{2+} gradient between the ER lumen and cytosol determines Ca^{2+} efflux through pore- or channel-like proteins, a phenomenon known as ER Ca^{2+} leak (Lemos et al., 2021). The rate of Ca^{2+} leak from the ER is relatively high: upon SERCA inhibition, ER can be emptied from releasable Ca^{2+} within several minutes.

5.2.2. ER Ca^{2+} dyshomeostasis and ER stress/UPR in AD

FAD-related mutations produce a multifaceted effect on Ca^{2+} homeostasis. For example, FAD-related PS mutations sensitize neurons to apoptotic stimuli and mitochondrial toxins to induce neuronal death through mechanism(s) involving ER Ca^{2+} (Chan et al., 2002; Guo et al., 1997; Keller et al., 1998, 1997; Mattson et al., 1998; Terro et al., 2002; Wang et al., 2013a). In FAD mutants-expressing neurons, both increased and decreased ER steady-state Ca^{2+} levels were detected (Brunello et al., 2009; Nelson et al., 2010). Canonically, initiation of ER stress/UPR is associated with a reduction of ER Ca^{2+} level (Cardozo et al., 2005; Mekahli et al., 2011).

In the CNS and model cells (neurons, fibroblasts and others) expressing FAD-related PS2, but not PS1 mutants, $[Ca^{2+}]_L$ is reduced due to the inhibition of SERCA (Brunello et al., 2009; Galla et al., 2020). This observation is in line with the activation of ER stress/UPR. Indirect support to the hypothesis of a reduced $[Ca^{2+}]_L$ in AD derives from identifying the positive effects of Xestospongin C (inhibitor of $InsP_3Rs$) (W.-A. Wang, Zhao et al., 2019; Z.-J. Wang, Zhao et al., 2019) and small SERCA activator CD1163 (Krajnak and Dahl, 2018) on behavior and neuropathology in AD models. However, the effect may be cell type-specific. Further work is necessary to clarify the issue as it has been shown that in dorsal root ganglia neurons Xestospongin C also empties the ER Ca^{2+} store by inhibiting SERCA pumps (Solovyova et al., 2002).

A scenario in which FAD-related mutations produce ER Ca^{2+} overload has also been proposed (Nelson et al., 2010). Compelling evidence suggests that PS1 and PS2 act as ER Ca^{2+} leak channels. FAD mutations disrupt Ca^{2+} leak leading to ER Ca^{2+} overload and increased agonist-induced cytosolic Ca^{2+} response (Tu et al., 2006). While the reduction of $[Ca^{2+}]_L$ can be directly linked to the dysfunction of Ca^{2+}-dependent chaperons and ER stress/UPR, activation of UPR by the ER Ca^{2+} overload is somewhat counterintuitive. Early experiments suggest that [Ca^{2+}] higher than 0.5 mM does not impair but rather facilitates the substrate-binding and protein processing capacity of ER chaperons. In addition, pharmacological or genetic manipulations with RyR or SERCA resulting at an increased steady-state $[Ca^{2+}]_L$ promoted an enhanced folding of Gaucher's disease–associated mutant glucocerebrosidase (GC) (Ong et al., 2010), suggesting that increased $[Ca^{2+}]_L$ is beneficial for protein folding and ER stress resistance. However, it was suggested that at higher $[Ca^{2+}]_{L,}$ the secretion of extracellular Ca^{2+}-dependent adhesion proteins, like cadherins, may be impaired (Collins and Meyer, 2011; Leckband and Prakasam, 2006; Pertz et al., 1999). Potentially, excessive ER Ca^{2+} overload may trigger ER stress and activation of UPR (Fig. 4). All in all, the association between ER Ca^{2+} dynamics and ER stress/UPR in neurons and neuroglia in AD cells remains an open question.

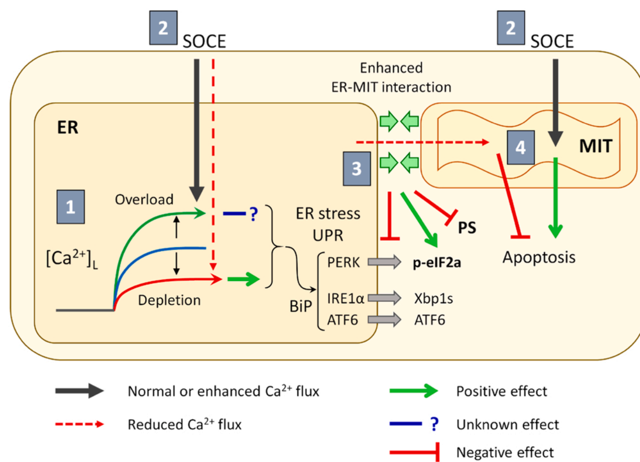

Fig. 4. Ca^{2+}-related mechanisms that may confound the development of ER stress/UPR during AD progression. (1) ER Ca^{2+} dyshomeostasis. Depletion of ER Ca^{2+} store activates canonical ER stress/UPR via PERK → p-eIF2α axis. Effect of ER Ca^{2+} overload on ER stress/UPR activation is not investigated (Unknown effect, see text for discussion). (2) Activation of SOCE can mitigate ER stress/UPR, while reduced SOCE promotes ER Ca^{2+} depletion and hence ER stress/UPR. Increased SOCE promotes mitochondrial Ca^{2+} signaling. (3) Augmented interaction between ER and mitochondria results in a reduction of general protein synthesis due to PERK-independent phosphorylation of eIF2α. (4) Reduction of mitochondrial Ca^{2+} signals inhibits apoptosis, while mitochondrial Ca^{2+} overload is pro-apoptotic.

5.3. SOCE and ER stress/UPR

5.3.1. SOCE mechanism and functions

Store-operated Ca^{2+} entry (SOCE) represents the principal route for ER refiling with Ca^{2+} in non-excitable cells (Verkhratsky and Parpura, 2014). Besides, SOCE contributes to many cellular Ca^{2+}-regulated processes, including cell differentiation and proliferation. Neuron-specific SOCE regulates excitability and synaptic plasticity (Moccia et al., 2015; Popugaeva and Bezprozvanny, 2018). Core of the canonical SOCE molecular machinery includes STIM1 (Stromal Interaction Molecule 1), a type I membrane-spanning protein of the ER membrane, containing ER-hand Ca^{2+}-binding domains on the luminal part, and ORAI1, a highly Ca^{2+}-selective hexameric plasmalemmal channel. The SOCE is triggered by ER Ca^{2+} depletion, dissociation of Ca^{2+} from STIM1 EF-hand domain, subsequent STIM1 oligomerization and its binding to ORAI1. This opens ORAI1 pore and mediates Ca^{2+} entry into the cell (Lunz et al., 2019). While STIM1 and ORAI1 remain the most studied components of SOCE machinery, a role for other isoforms, STIM2 and ORAI2/3 has also been proposed (Berna-Erro et al., 2017, 2012; Ong and Ambudkar, 2020).

5.3.2. Altered SOCE and ER stress/UPR in AD

Although the role of SOCE in the brain cells is only beginning to be elucidated, its link to AD pathogenesis has been already suggested (Briggs et al., 2017; Kraft, 2015; Moccia et al., 2015; Pchitskaya et al., 2018; Secondo et al., 2018; Wegierski and Kuznicki, 2018). A mutation-specific and cell type-specific reduction of SOCE in AD was postulated (McLarnon, 2020; Wu, 2020). Thus, contrary to other PS mutations, PS1dE9 mutation is associated with enhanced SOCE in neurons (Chernyuk et al., 2019). In Aβ-treated and KI-$PS1_{M146V}$-expressing astrocytes, SOCE is also enhanced (Lim et al., 2013; Rocchio et al., 2019; Ronco et al., 2014). Instead, in microglial cells from AD brains or in Aβ-treated primary microglia SOCE amplitude is reduced (McLarnon, 2020).

Because SOCE serves to replenish ER with Ca^{2+}, its enhancement is expected to have a mitigating effect on ER stress/UPR (Fig. 4). For example, in the majority of cancer cells SOCE is enhanced and this is proposed to promote cancerogenic transformation, increase the resistance of cancer cells to apoptosis and the angiogenic potential (Faris et al., 2022; Gui et al., 2016; Kondratska et al., 2014; Tanwar et al., 2020; Villalobos et al., 2016; Zuccolo et al., 2018). From another perspective, SOCE provides a non-ER source of Ca^{2+} for mitochondrial Ca^{2+} overload-mediated cell death in neurons (Maher et al., 2018; Wang et al., 2021) and cancer cells (Chiu et al., 2018; Spät and Szanda, 2017; Tanwar and Motiani, 2018). In neurons, SOCE has been shown to be a co-factor of ER stress/UPR-induced degeneration of mushroom spines induced by THG treatment (Chanaday et al., 2021). In addition, some TRP (transient receptor potential) channels not directly involved in SOCE can mediate Aβ toxicity in neurons and islet amyloid toxicity in pancreatic β-cells (Casas et al., 2008; Ostapchenko et al., 2015). Altogether, mutation/insult-specific SOCE alterations may differentially disturb ER stress/UPR.

5.4. ER-mitochondria interaction and ER stress/UPR

5.4.1. ER-mitochondria contacts and Ca^{2+} transfer

Points of interaction between ER and mitochondria are organized in morpho-functional units known as MERCS (mitochondria-ER contact sites), held together by protein complexes named ER-mitochondrial tethers (Lim et al., 2021). A portion of the ER membrane, often isolated together with outer mitochondrial membrane (OMM) and mitochondria, representing the ER side of MERCS is known as MAM (mitochondria-associated membrane). Prototypical ER-mitochondrial tethers were characterized in yeasts and are composed of maintenance of mitochondrial morphology 1 (Mmm1) on the ER membrane, mitochondrial distribution and morphology 10 (Mdm10) and Mdm34 on the OMM and an interacting protein Mdm12, altogether forming ERMES (ER-mitochondria Encounter Structure) complex involved in membrane lipid biosynthesis (Kornmann et al., 2009). Mammalian ER-mitochondrial tethers include (ER side/OMM side) Mfn2/Mfn1,2 (Mitofusin 1 and 2); VAPB/PTPIP51 (VAMP Associated Protein; Protein Tyrosine Phosphatase-Interacting Protein 51); BAP31/Fis1 (B Cell Receptor Associated Protein 31; Fission, Mitochondrial 1); BAP31/TOM40 (Translocase Of Outer Mitochondrial Membrane 40); VPS13D/Miro (Vacuolar Protein Sorting 13 Homolog D; Mitochondrial Rho GTPase 1) and RRBP1/SYNJ2BP (Ribosomal Receptor-Binding Protein 1; Synaptojanin 2 Binding Protein) (Anastasia et al., 2021; de Brito and Scorrano, 2008; De Vos et al., 2012; Guillén-Samander et al., 2021; Ilacqua et al., 2022; Iwasawa et al., 2011; Namba, 2019). MERCS host numerous cellular processes such as lipid and steroid biosynthesis, Ca^{2+} transfer between ER and mitochondria, formation of autophagosomes and protein synthesis. MERCS are also involved in mitochondrial remodeling, apoptosis and UPR (Barazzuol et al., 2021). The main physical parameters of the ER-mitochondrial interaction include transversal distance between ER and OMM (gap size), the number of contacts and the extension of the contact interface between ER and OMM (Giacomello and Pellegrini, 2016; Lim et al., 2021). A protein complex, responsible for direct Ca^{2+} transport from ER to mitochondria is composed of $InsP_3Rs$ (all three isoforms) on the ER membrane, VDAC1 (voltage-dependent anion channel 1) on the OMM and interacting proteins which include Grp75 (glucose-regulated protein 75), TOM70, DJ-1 (Parkinsonism Associated Deglycase), IRE1α and SigmaR1 (Sigma Non-Opioid Intracellular Receptor 1). The optimal gap size for Ca^{2+} transfer was suggested to lay between 15 and 25 nm. Such a configuration allows direct Ca^{2+} uptake by a low affinity mitochondrial Ca^{2+} uniporter complex from a high $[Ca^{2+}]_i$ hot spot generated between $InsP_3Rs$ and VDAC1. Shorter distance is sought to inhibit Ca^{2+} release form $InsP_3Rs$, while widening of the gap size results in dissipation of high $[Ca^{2+}]_i$ hot spot and reduction of $[Ca^{2+}]_i$ below the threshold of mitochondrial Ca^{2+} uptake of ~10–20 μM (Csordás et al., 2006; Giacomello and Pellegrini, 2016; Lim et al., 2021). AD-related proteins shuch as PS, APP, Tau, and APOE4, were found to be enriched in MERCS (Cieri et al., 2018; Del Prete et al., 2017; Tambini et al., 2016).

5.4.2. ER-mitochondria interaction and ER stress/UPR in AD

The interactions between ER and mitochondria gained significant interest as a possible player and pharmacological target in different diseases. In AD, data support the enhanced interaction/tethering hypothesis, leading to the shortening of the transversal distance between ER and mitochondria and the extension of the contact interface (Area-Gomez and Schon, 2017; Lim et al., 2021; Paillusson et al., 2016). An increase in the ER-mitochondria interaction and shortening of ER-mitochondria distance exerts multifaceted effects on cell physiopathology, which include impaired lipid biogenesis, ER-mitochondrial Ca^{2+} transfer, biogenesis of autophagosomes, ribosomal protein synthesis and apoptosis (Area-Gomez and Schon, 2017; Barazzuol et al., 2021; Degechisa et al., 2022). Several of these effects result from the impaired Ca^{2+} transfer between ER and mitochondria. For instance, the impairment of ER-mitochondrial Ca^{2+} transfer results in an increased ER Ca^{2+} retention and reduced mitochondrial Ca^{2+} signals, which mitigate ER stress/UPR and have an anti-apoptotic power (Fig. 4). On the other hand, reduced mitochondrial Ca^{2+} signals lead to a reduced ATP synthesis and bioenergetic deficit, which negatively impacts cell physiology.

MAMs are enriched with UPR molecular transducers, such as PERK and IRE1α (Carreras-Sureda et al., 2019; Verfaillie et al., 2012). PERK interferes with cellular Ca^{2+} signaling through complex functional and biochemical interaction with a Ca^{2+}/calmodulin-activated phosphatase

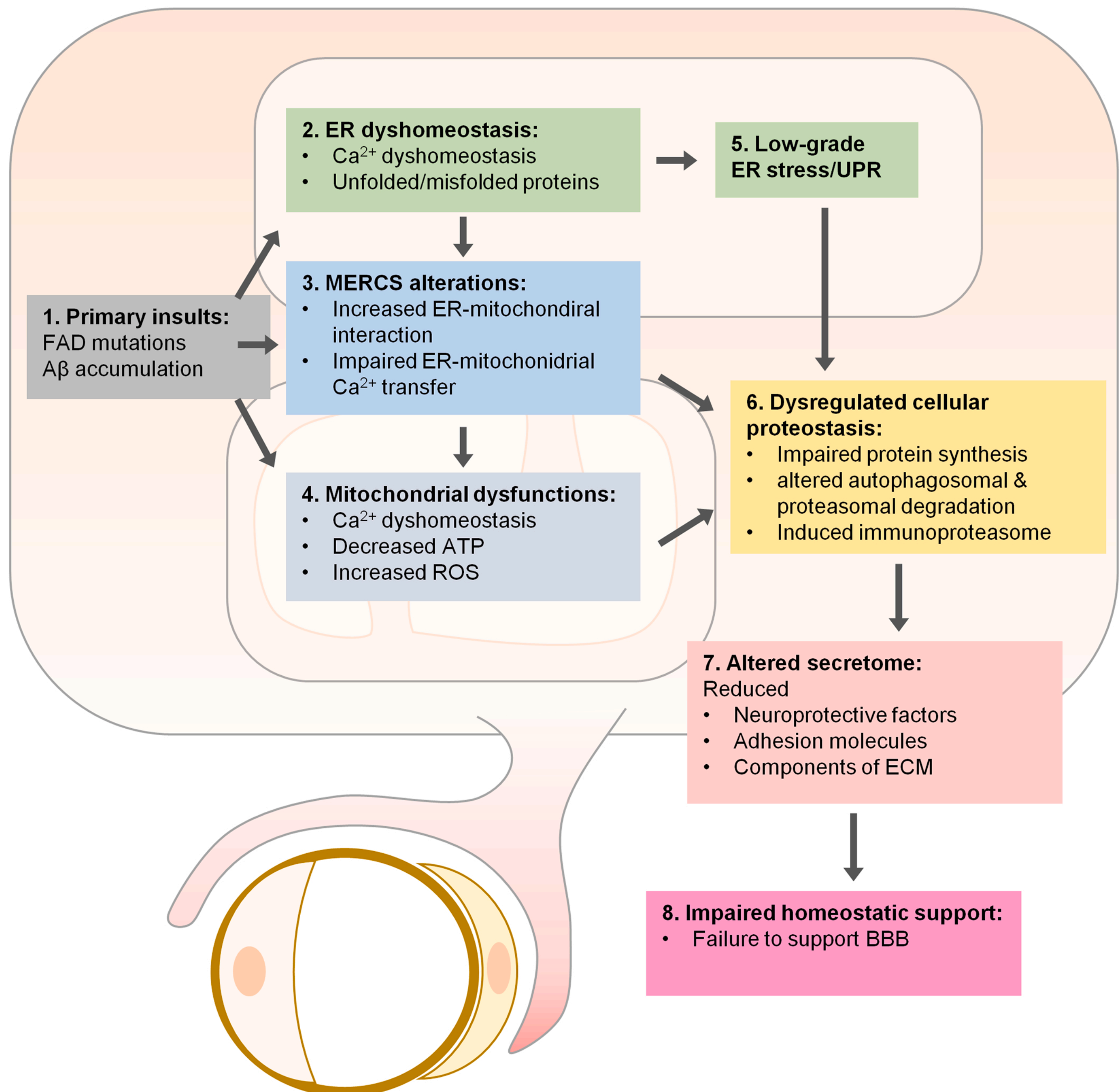

Fig. 5. Proposed mechanism of cell dysfunctions in AD astrocytes. Primary insults, represented by FAD mutations and Aβ accumulation (1), produce a spectrum of alterations including ER dyshomeostasis (2), alterations of ER-mitochondria contacts (3) and mitochondrial dysfunctions (4). ER dyshomeostasis leads to a low-grade ER stress/UPR (5) which negatively impacts cellular proteostasis (6) leading to alterations of astrocyte adhesion and secretome (7) and an insufficient homeostatic support to BBB and neurons (8). ER dyshomeostasis may lead to MERCS alteration and to mitochondrial dysfunction, which, altogether contribute to dysregulation of cellular proteostasis and impaired cell-cell communication. However, MERCS alterations alone are no sufficient to produce ER stress/UPR.

calcineurin (Bollo et al., 2010), while IRE1α interacts with and stabilizes $InsP_3Rs$ at MAMs (Carreras-Sureda et al., 2019). Bidirectional interaction may exist between UPR and ER-mitochondria interaction. Recently, relationships between proteostasis, Ca^{2+} homeostasis, mitochondrial functions and ER-mitochondria interaction has been studied on partially-immortalized astrocytic hippocampal cell lines from 3xTg-AD mice (WT-iAstro and 3Tg-iAstro) (Gong et al., 2023; Rocchio et al., 2019). In line with other AD astrocytes in vitro and in vivo, 3Tg-iAstro cells present augmented cytosolic Ca^{2+} signals and elevated steady-state $[Ca^{2+}]_L$ (Dematteis et al., 2020). However, in 3Tg-iAstro cells a reduced Ca^{2+} signaling in the mitochondrial matrix was found, associated with the inhibition of ATP production, an increased ER-mitochondria interaction and a shortening of the gap size between organelles (Dematteis et al., 2020). The MERCS abnormalities in 3Tg-iAstro cells were further associated with a suppression of protein synthesis in association with the increased phosphorylation of eIF2α without activation of PERK and were accompanied by a low-grade UPR, the phenomena found also in 3xTg-AD mouse brains (Tapella et al., 2022). Alterations of proteostasis in 3xTg-AD astrocytes include impaired autophagic and proteasomal protein degradation with induction of immunoproteasome components (Gong et al., 2023) (summarized in Fig. 5).

To assess the cause-effect relations between protein misfolding, ER stress, dysregulation of proteostasis, and alteration of ER-mitochondrial interaction, 4-phenylbutyrate (4-PBA), an FDA-approved chemical chaperon, which has been shown to rescue cognitive dysfunction in AD mouse models, was used (Ricobaraza et al., 2012, 2011). Pre-treatment of 3Tg-iAstro with 4-PBA rescued cellular pathology including protein synthesis and degradation, levels of p-eIF2α, ER-mitochondrial distance and defects of the proteolytic system (Gong et al., 2023; Tapella et al., 2022). In co-culture systems, 3Tg-iAstro failed to maintain integrity of endothelial cells (EC) in an in vitro BBB model and to support Matrigel-driven EC tubulogenesis in an astrocyte/EC co-culture (Kriaučiūnaitė et al., 2020; Tapella et al., 2022). Pre-treatment of 3Tg-iAstro with 4-PBA rescued the ability of astrocytes to support Matrigel-driven tubulogenesis (Gong et al., 2023; Tapella et al., 2022). To assess the role of the increased ER-mitochondria interaction in ER stress/UPR, a synthetic linker, which fixes the ER-mitochondrial distance at ~10 nm, was overexpressed in WT-iAstro cells. The overexpression reproduced the reduction of protein synthesis and increased p-eIF2α levels in WT-iAstro cells. Moreover, linker-overexpressing WT-iAstro failed to support Matrigel-driven EC tubulogenesis mimicking the effect of AD astrocytes (Fig. 5). However, overexpression of ER-mitochondrial linker failed to induce ER stress/UPR-related genes (Tapella et al., 2022). Based on these results it was hypothesized that both ER dysfunction and increased ER-mitochondrial interaction contribute to alteration of proteostasis in 3xTg-AD astrocytes. ER dysfunctions, including ER Ca^{2+} dyshomeostasis and accumulation of unfolded/misfolded proteins may result in a low-grade ER stress and contribute to alterations of ER-mitochondria interaction, which altogether dysregulate cellular proteostasis, and cell-cell communication. Instead, increased ER-mitochondrial interaction alone is sufficient to dysregulate cellular proteostasis, but is not able to induce ER stress/UPR (Fig. 5).

6. Other factors disturbing ER stress/UPR activation in AD

6.1. ER stress/UPR-independent functions of stress sensors and transducers

Growing evidence suggests that the physio-pathological role(s) of ER stress sensors are not limited to canonical ER stress/UPR cascade, giving rise to a concept of their involvement in cell physiology through mediating the non-canonical UPR response (Hetz et al., 2020). This, in part, may be exerted through specific localization of ER stress sensors in MERCS or ER-PM contact sites (Kumar and Maity, 2021; van Vliet et al., 2017; Verfaillie et al., 2012). In the framework of this concept, ER stress sensors have other functions not linked to proteostasis and UPR. Thus, PERK and IRE1α interact with and regulate, or are regulated by, cytoskeletal proteins (Ishiwata-Kimata et al., 2013; Urra et al., 2018; van Vliet et al., 2017). IRE1α controls mitochondrial bioenergetic and ER-mitochondria Ca^{2+} transfer in UPR-independent manner (Carreras-Sureda et al., 2019). In immune cells, IRE1α → XBP1 pathway mediates Toll-like receptor signaling and prostaglandin biosynthesis (Chopra et al., 2019; Martinon et al., 2010; Woo et al., 2012). PERK has been implicated in a calcineruin-dependent control of Ca^{2+} fluxes through ryanodine receptor 2 and store-operated Ca^{2+} channels (Liu et al., 2014; Wang et al., 2013b). ATF6 and PERK are implicated in VEGF (Vascular Endothelial Growth Factor)-mediated angiogenesis in the absence of ER stress (Karali et al., 2014).

All in all, activation/modulation of the ER stress/UPR sensors during AD pathogenesis does not necessarily translates into the ER stress and the activation of UPR program. On the other hand, ER stress/UPR sensors may play an active role in the alterations of cellular Ca^{2+} homeostasis and signaling, particularly at the interface between organelles, including ER-PM and ER-mitochondrial contact sites.

6.2. Cell type-specificity and relation to Aβ deposits

AD-related neuronal death correlates with Tau neuropathology and Braak stages (Braak and Braak, 1991; Theofilas et al., 2018). Many hypotheses of the mechanisms of neuronal death were proposed, including necrotic and apoptotic death (Behl, 2000; Mangalmurti and Lukens, 2022). Contrary to neurons, the number of astrocytes does not change during AD progression while displaying a complex behavior concerning to disease stage, brain region and proximity to Aβ deposits (Pelvig et al., 2003; Serrano-Pozo et al., 2013). In mouse AD models, reactive astrocytes are mostly found around Aβ depositions/senile plaques, while in the rest of the brain, astrocytes are found to be atrophic (Lim et al., 2013; Verkhratsky et al., 2019; Yeh et al., 2011). In human AD postmortem material, astrogliosis (as suggested by glial fibrillary acidic protein (GFAP) staining) and microgliosis (judged by CD68 or IBA1 (Ionized Calcium-Binding Adapter Molecule 1) immunoreactivity) gradually develop in the course of the disease correlating with Tau pathology but not with total Aβ burden (Ingelsson et al., 2004; Serrano-Pozo, Mielke et al., 2011). However, the density of GFAP-positive astrocytes increased in correlation with the proximity to Aβ plaques (Serrano-Pozo, Mielke et al., 2011). As stressed recently, however, GFAP is not the most reliable marker of reactive astrocytes (Escartin et al., 2021), other markers, possibly reflecting the metabolic activity of astrocytes, may also need to be considered.

It was suggested that the neurons-to-glia ratio decreases significantly towards the terminal AD stages (Serrano-Pozo, Frosch et al., 2011), possibly due to neuronal death. Currently, such an impact is difficult to estimate due to a limited number of reports addressing the cell specificity of the alterations and somewhat discrepant results. Thus, although increased levels of p-PERK, p-eIF2α, p-IRE1α and BiP/GRP78 have been detected in hippocampal neurons (Hoozemans et al., 2009, 2005), BiP/GRP78 was also up-regulated in hippocampal astrocytes (Yu et al., 2018) in Braak stage V-VI AD brains. Therefore, the contribution of astroglial cells to ER stress/UPR should be considered.

7. Conclusions

ER stress/UPR is a stereotypic reaction of cell to stress, which, canonically, results in cell survival or (when unsuccessful) cell death. ER stress/UPR has been implicated in AD pathogenesis and was proposed as a target for the development of anti-AD therapy. However, human data do not support the presence of canonical ER stress/UPR in preclinical and prodromal AD stages, while suggesting that its full activation occurs at late, dementia stage in concomitance with an increase of tau pathology and neuronal death. We hypothesize that alongside other factors, such as cell type-specificity of AD pathology and ER stress/UPR-

unrelated functions of key ER stress sensors, dysregulation of cellular Ca^{2+} homeostasis and signaling may interfere with canonical ER stress/UPR during AD progression. Specifically, Ca^{2+}-related factors include: (i) alterations of Ca^{2+} homeostasis in the ER; (ii) alterations of SOCE; and (iii) alterations of physical and functional interaction between ER and mitochondria including ER-mitochondrial Ca^{2+} transfer. The interaction between different routes of Ca^{2+} signaling adds another level of complexity. Specific questions, which will clarify the interaction between ER stress/UPR and Ca^{2+} dyshomeostasis in AD include: (i) determination of steady-state $[Ca^{2+}]_L$ and ER and mitochondrial Ca^{2+} dynamics in relation to the cell type specific alterations during progression of AD in vivo; (ii) investigation of relationships between ER stress/UPR and alterations of the ER-mitochondria interaction in vitro and in vivo; (iii) how the deficit of the ER-mitochondria Ca^{2+} transport affects UPR transduction and outcomes in vitro and in vivo; (iv) development of probes for in vivo monitoring of UPR and inter-organellar interaction. Development and in-depth investigation of cellular and multi-cellular AD models, suitable for comprehensive and reproducible investigation of different aspects of AD-related cellular pathology, will allow generation of new hypotheses and identification of novel molecular targets. Development of novel humanized AD animal models will be important for in vivo validation and preclinical research and development.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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