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Review Article

ER-stress in Alzheimer's disease: turning the scale?

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Abstract: Pathogenic mechanisms of Alzheimer's disease (AD) are intensely investigated as it is the most common form of dementia and burdens society by its costs and social demands. While key molecules such as A-beta peptides and tau have been identified decades ago, it is still enigmatic what drives the disease in its sporadic manifestation. Synthesis of A-beta peptides as well as phosphorylation of tau proteins comprise normal cellular functions and occur in principle in the healthy as well as in dementia-affected persons. Dyshomeostasis of Amyloid Precursor Protein (APP) cleavage, energy metabolism or kinase/phosphatase activity due to stressors has been suggested as a trigger of the disease. One way for cells to escape stress based on dysfunction of ER is the unfolded protein response - the UPR. This pathway is composed out of three different routes that differ in proteins involved, targets and consequences for cell fate: activation of transmembrane ER resident kinases IRE1-alpha and PERK or monomerization of membrane-anchored activating transcription factor 6 (ATF6) induce activation of versatile transcription factors (XBP-1, eIF2-alpha/ATF4 and ATF6 P50). These bind to specific DNA sequences on target gene promoters and on one hand attenuate general ER-prone protein synthesis and on the other equip the cell with tools to de-stress. If cells fail in stress compensation, this signaling also is able to evoke apoptosis. In this review we summarized knowledge on how APP processing and phosphorylation of tau might be influenced by ER-stress signaling. In addition, we depicted the effects UPR itself seems to have on molecules closely related to AD and describe what is known about UPR in AD animal models as well as in human patients.

Keywords: Alzheimer's disease, secretases, APP, tau, unfolded protein response, calcium homeostasis, autophagy, apoptosis

Introduction

The term amyloidosis describes a family of diseases that are characterized by abnormal protein deposition within the extracellular space. Examples are the cardiac amyloidosis or Alzheimer's disease (AD). Pathological features of this type of disease are mediated on one hand by direct malfunction of the affected tissue or organ. Amyloid deposits in the ventricles and atria of the heart e.g. result in biventricular wall thickening with an ensuing elevation of pressure in the thin-walled part of the respective atrium [1, 2]. On the other hand, interference of already deposited material or intermediate protein oligomers with cellular function has been described to lead to dysbalance and subsequent pathogenesis. For example, amyloidogenic light chains are able to evoke oxidative stress, cellular dysfunction, and apoptosis in primary cardiomyocyte cultures via MAPK signaling [3]. In case of Alzheimer's disease the scientific landscape was dominated for a long time by the assumption that large aggregates of A-beta peptides (designated as senile plaques) are triggering neuronal degeneration. More recent investigations led to the insight that small oligomers (reviewed e.g. in [4]) or even intraneuronal A-beta peptides are culprit to pathogenic derailment [5, 6]. Tau protein with its microtubule binding properties is another characteristic of the disease and has been suggested to act downstream of neurotoxic A-beta species (reviewed e.g. in [7]).

A-beta peptides derive from proteolytic processing of a large type I transmembrane protein - the amyloid precursor protein (APP). This protein matures within trafficking through ER and the Golgi-apparatus by being cleaved by signal peptidases and being modified in regard of carbohydrate-attachment. Despite having the

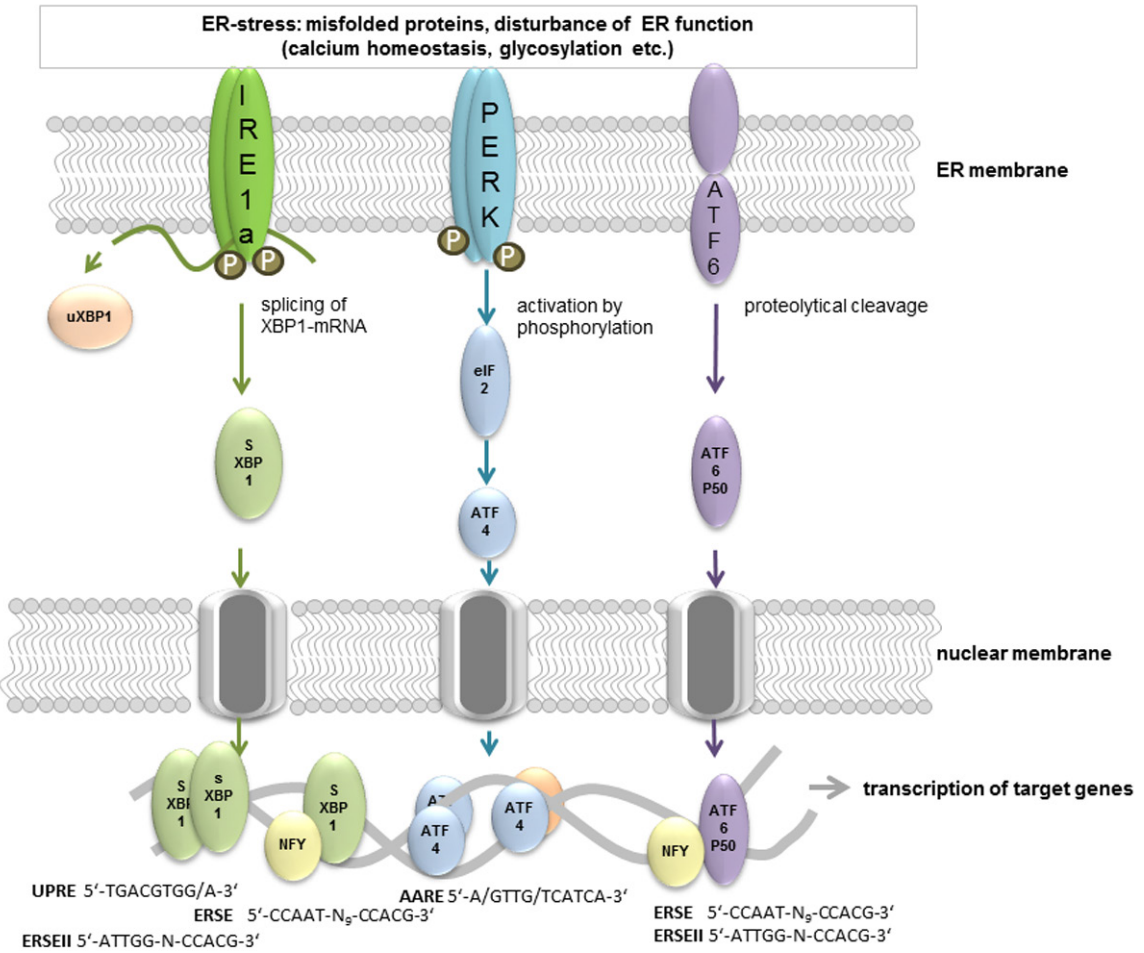

Figure 1. Three different signaling pathways conduct UPR upon ER-stress induction. ER-stress is sensed by the luminal proportion of three distinct transmembrane ER resident proteins: IRE1-alpha, PERK and ATF6. There are several mechanisms that have been proposed for this activation step such as direct binding of unfolded proteins or displacement of GRP78 binding (reviewed in [151]). Activation subsequently leads to changes in oligomerization status and the signal is transmitted via the C-terminus of all three proteins. PERK and IRE1-alpha homodimerize and perform autophosphorylation. PERK also phosphorylates the translation initiation factor eIF2-alpha resulting in a reversible attenuation of translation. Only single translational events such as ATF4 protein biosynthesis are enhanced under these conditions. Delayed reinitiation by reduced amount of eIF2-GTP allows ribosomes to scan through an inhibitory upstream open reading frame of ATF4 mRNA and instead reinitiate at the coding region [152]. ATF4 binds to a consensus motif of target gene promoters (e.g. AARE) as a homodimer or heterodimer with e.g. Fos, Jun [153] or other cofactors such as PCAF [154]. IRE1-alpha conducts its endonuclease function and splices XBP-1 mRNA as well as other mRNAs. This process is termed regulated IRE1-alpha-dependent decay (RIDD; [62]) and may further contribute to limitation of translation. Target genes of the active sXBP-1 (binding to UPRE, ERSE or ERSEII) produced by splicing are proteins involved in protein folding, maturation, secretion, and degradation. ATF6 translocates to the Golgi upon activation where it is cleaved by site-1-and 2 proteases. This generates the b-Zip transcription factor ATF6 P50 which initiates transcription of target genes in combination with NF-Y via ERSE motifs in its target genes.

knowledge about distinct function of each proteolysis product, the proteolytic degradation of this protein has been described in detail: subsequent cleavage by the beta-secretase BACE-1 (beta-site APP cleaving enzyme 1) and the gamma-secretase complex gives rise to the already mentioned A-beta peptides (e.g. [8, 9]). Alternatively, alpha-secretase leads to prevention of A-beta peptide formation and to secretion of the so-called APPs-alpha fragment (for example [10-13]). The latter has been described to conduct neurotrophic and neuroprotective properties (reviewed in e.g. [14]). APP is a ubiquitously expressed protein and A-beta peptides are generated not only under pathological conditions but also in healthy human subjects.

Nevertheless, under certain circumstances, synthesis and/or degradation of A-beta peptides are disturbed and oligomers and fibrils rise that are deposited in brain parenchyma or blood vessel walls. Some human beings seem to cope with these deposits very well and show no signs of cognitive decline despite having high plaque loads while others do not [15]. Understanding the underlying resilience factors might lead to development of new therapeutic approaches since directly inhibiting A-beta production or immunization strategies in the first line failed regarding curing this disease.

An adaptable access to gain resilience might be given by the cellular response to endogenous stressors. One cellular organelle that is related to stress mediation by its multifunctionality is the endoplasmic reticulum (ER, for example [16, 17]): 1) the ER assists and closely monitors quality of nascent proteins. Protein disulfide isomerase (PDI) and ERp57 (thio-oxidoreductases) e.g. catalyze disulfide bond formation using the oxidative capacity provided by ER oxidoreduction 1 (ERO1). Glucose-regulated protein 78 (BiP or GRP78) or 94 (GRP94, calreticulin), stabilize as chaperones of the heat-shock protein family unfolded proteins. 2) Calcium-storage in the ER and regulated release protects the cell from cell death caused by calcium concentration dysbalance. This is driven by calcium import via SERCA (sarcoplasmic/endoplasmic reticulum calcium-ATPase) and ion release via Rhyanodine and IP3 receptors. Calcium binding proteins such as calreticulin and calnexin further buffer the calcium content of the cell.

Disturbance of ER homeostasis is not separated from general cellular function. The peripheral ER is in contact to other cellular organelles and for example forms physical interaction zones with mitochondria. These structures - designated as MAM in mammals (Mitochondrial-associated endoplasmic reticulum Membranes, [18], reviewed in [19]) - are enriched by certain proteins such as Mitofusin-2 or the autocrine motility factor receptor which allow attachment [20, 21]. In case of perturbations regarding ER function these are not only sensed by the ER but also transduced to the cytoplasm and nucleus to evoke an appropriate response. This response includes enhanced expression of chaperones, transiently inhibited translation, increase in ER volume and enhanced degradation of misfolded proteins as well as enhanced autophagy [22, 23]. If this attenuation of stressors and capacity compensation along the unfolded protein response (UPR) is not sufficient within a certain time frame, cells undergo apoptosis (reviewed in [24]).

APP as a central player in Alzheimer's disease matures via bypassing the ER and beta- as well as gamma-secretase cleavage takes place in the Golgi apparatus [25, 26]. In addition, mitochondrial dysfunction, disturbed autophagy and aberrant calcium signaling have been repeatedly connected to Alzheimer's disease (reviewed e.g. in [27-29]). A general role of the UPR in neurodegenerative processes has been summarized previously [30]. Hence, a contribution of activated UPR signaling in the pathology of Parkinson's or in particular Alzheimer's disease has been discussed as an early event of disease progression [31]. Therefore, we focused on known correlations of APP, its processing products and related proteins with ER-stress events in this review.

ER-stress: three routes of UPR signal transduction

Three signal pathways operate in parallel to sense ER-stress and to react as the UPR (**Figure 1**). They have in common that signaling is transduced by a protein with an ER luminal domain, a transmembrane part and a cytoplasmic effector domain: IRE1-alpha (inositol requiring enzyme 1, [32-34]), PERK (double-stranded RNA-activated protein kinase (PKR)-like ER kinase, [35]), and ATF6 (activating transcription factor 6, [36-38]). All three proteins use a specific signal transduction mechanism but end in activation of b-Zip transcription factors that subsequently lead to altered transcription of target genes.

ATF6 and PERK represent evolutionary newer pathways that evolved in metazoans [39]. ATF6 exists partially oligomerized in the absence of stress through intermolecular disulfide bonds [40]. These are reduced upon accumulation of unfolded proteins, subsequently the monomeric form leaves the ER via transport vesicles and is cleaved within the Golgi apparatus by site-1 and site-2 proteases [41]. The cytoplasmic domain then is liberated from its transmembrane anchor and acts as a transcription factor on target genes such as GRP78 or GRP94 [42].

Both are part of the functional ER machinery and therefore might contribute to enhanced ER capacity.

PERK is a transmembrane kinase that oligomerizes during ER-stress and performs trans-autophosphorylation of its C-terminal cytoplasmic kinase domain at multiple residues [43, 44] as well as phosphorylation of the general translation factor eIF2-alpha [45]. This inhibits eIF2-alpha which lowers translation rates regarding a wide variety of mRNAs [46, 47] and consequently reduces protein burden within the ER. Only few mRNAs show increased translation upon eIF2-alpha phosphorylation such as ATF4 which by itself acts as a transcription factor on targets such as CHOP (transcription factor C/EBP homologous protein, [48]) or GADD34 (growth arrest and DNA damage-inducible 34, [49]). CHOP regulates expression of components of the apoptotic pathway (reviewed in [50]) while GADD34 encodes a regulatory subunit of PP1C - the protein phosphatase that dephosphorylates eIF2-alpha [51]. This on one hand indicates that the PERK branch contains both, alleviating strategies and death triggering ones, and that it is strictly regulated.

IRE1-alpha represents the third branch which also exists in lower eukaryotes [39]. By sensing ER-stress this bifunctional enzyme dimerizes and becomes activated [52]. During the dimer assembly trans-autophosphorylation takes place [53] which is discussed to be mandatory for the human enzyme activity or regulation [54, 55]. Formation of the active dimer then evokes endonuclease function and the ER-associated mRNA of the transcription factor XBP-1 (X-box binding protein 1) is spliced to yield the active protein sXBP-1 (for the splicing mechanism see: [56]). In non-yeast organisms unspliced XBP-1-mRNA is translated to uXBP-1 which might act as an inhibitory counterbalance of sXBP1 action [57]. Downstream targets of activated XBP1 include ER chaperones as well as so-called ERAD (ER associated degradation) components such as HRD1 [58], PDI [59] or ER-localized DnaJ (Erdj4) [60]. Besides specifically activating XBP-1, IRE1-alpha is involved in activation of JNK [61] and degradation of other ER-associated mRNAs (e.g. its own mRNA: [53]; regulated IRE1-alpha-dependent decay (RIDD): [62]) further contributing to relief of ER machinery by decreasing translation into the ER lumen. In secretory cells such as B-cells IRE1-alpha also mediates UPR-independent enhancement of secretion [63, 64].

The three signaling pathways are not fully isolated but also comprise cross-linkage. For example PERK facilitates synthesis and trafficking of ATF6 from ER to the Golgi [65] and IRE1-alpha activity also steers ATF6 activation [66].

Target genes of the UPR contain conserved binding sequences (**Figure 1**) designated as UPRE (UPR element, [67]) or ERSE (ER-stress element, [68]) or ERSEII [69]). ERSE sites consist of the conserved sequence CCAAT-N_9-CCACG; the 9 nucleotide spacing between both half site motifs has been suggested to be quiet important for their functionality [70]. A recent report nevertheless described a functional XBP-1-responsive element with a 26 nt spacer [71]. ATF6 binds e.g. to the CCACG sequence of the ERSE motif, if the general transcription factor NF-Y has bound to the CCAAT part of the sequence. Active XBP-1 also binds to this sequence instead of ATF6 [70, 72]. The ERSEII (ATTGG-N-CCACG) might be occupied by ATF6 NF-Y-dependent [69] or by XBP-1 without further binding of NF-Y [67]. To the UPRE (TGACGTGG/A) sXBP-1 binds as a homodimer [70].

A genome wide approach to identify targets of XBP-1 in myotubular, plasma and pancreatic cells by Acosta-Alvear and colleagues [73] revealed that XBP-1 is able to bind the promoters of a wide variety of target genes whereof 40% are not directly linked to ER-stress compensation. One of the unexpected GO categories contained disease-associated genes, including genes connected to Alzheimer's disease. In cell culture studies UPR as indicated by eIF2-alpha phosphorylation is evoked by compounds such as Tunicamycin, Thapsigargin or DTT (e.g. [74]) which impair N-glycosylation of proteins, calcium homeostasis or formation of disulfide bonds. In addition, brefeldin A, 2-deoxy-glucose or eeyarestatin function as UPR inducers. These compounds seem to belong to two different clusters of drugs as shown by analysis of expression patterns of nine typical UPR target genes by [75]. Endogenous provokers of ER-stress are under intensive investigation and several molecules

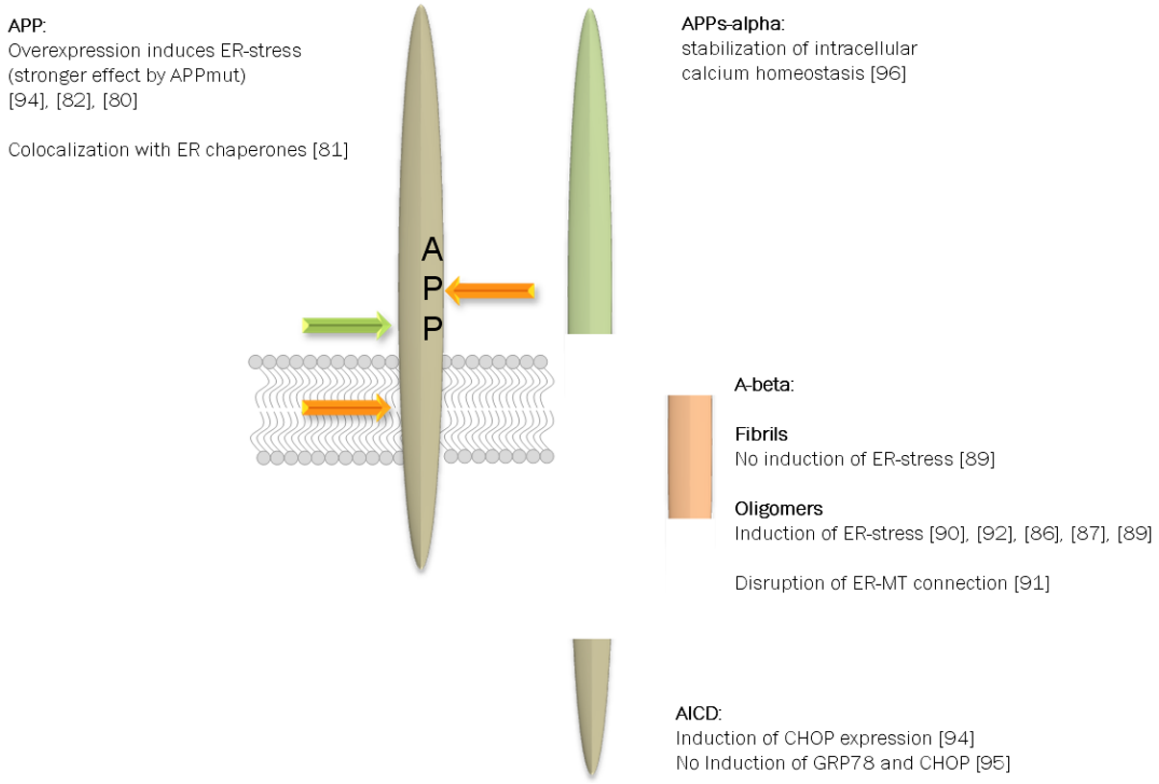

Figure 2. APP processing products and their potential role in UPR. APP is subject to a wide variety of posttranslational modifications such as phosphorylation and glycosylation (e.g. [62, 155]). In addition, the type I transmembrane protein is cleaved by several proteases yielding protein fragments of different size and function [14]. In regard of ER-stress not all protein fragments have been analyzed but for the full length protein, A-beta peptides and the alpha-secretase derived soluble ectodomain correlation to subsequent signaling events have been reported. In this scheme only the most prominent facts are included but one has to consider that contradictory results have been published.

associated with Alzheimer's disease are under suspicion.

Influence of APP-cleavage products on ER-stress

Shortly after cloning of the mammalian PERK and IRE1-alpha [43, 32], first investigations indicated a potential link to Alzheimer dementia: Katayama et al. [76] described that mutations in Presenilin 1 (PS1), the catalytic component of the gamma-secretase complex, decreased GRP78 expression by interfering with IRE1-alpha function in cell culture experiments. Moreover, they already assessed reduced amount of GRP78 and GRP94 within temporal cortex tissue from sporadic and familiar Alzheimer patients. A potential role of PS1 in UPR was further confirmed by Niwa et al. [77], where a reduced nuclear translocation and attenuated UPR was reported for PS1 knockout fibroblasts. A direct cleavage of IRE1-alpha has been suggested but could not be confirmed for human fibroblasts due to technical problems [77]. In addition, cleavage of ATF6 has been analyzed but no influence of gamma-secretase inhibitor or dominant negative PS1 could be demonstrated [78]. Gamma-secretase is a very promiscuous endoproteolytic complex that cleaves a wide variety of substrates (e.g. reviewed in [79]) such as APP. Therefore, regulation of UPR by several proteolysis products could be assumed.

For APP as a substrate of gamma-secretase, there have been reports about correlation with ER-stress and subsequent UPR signaling: APP overexpression led for example to an enhanced upregulation of CHOP in PC12 cells upon Thapsigargin administration [80]. For other typical ER-stress associated chaperones such as GRP94 this was not confirmed in this cell line. However, colocalization of APP with ER chaperones calnexin, calreticulin, GRP94, GRP78, and

ERp72 has been demonstrated in sporadic inclusion body myositis (s-IBM) muscle biopsies with APP containing aggregation products [81]. This was also confirmed for APP overexpressing human muscle fibers. While basal expression of UPR-related proteins in another report did not differ in APP overexpressing cells from wild type cells, UPR induction by ER-stress was augmented [82]. This was even higher in cells with overexpression of mutant APP. In contrast, elevated but comparable GRP78 mRNA levels were measured in B103 cells expressing either mutated or wild type APP after UPR induction with Tunicamycin [83]. In PC12 cells, APP has been reported to be protective against ER-stress evoked by brefeldin A application while GRP78 or CHOP expression remained unaffected. In sum, there is a rather inhomogeneous picture of how APP might interfere with ER-stress and subsequent signaling. This might be explained by different types of cells used in either investigation which might be characterized by differential APP processing activities since for proteolytic fragments of APP there is growing evidence for interfering with UPR and ER-stress (**Figure 2**). Mostly, reduction of A-beta is correlated with attenuated ER-stress and vice versa. For example, aged PS2 mutant mice revealed inhibited BACE-1 activity and C99 amount in brain tissue upon treadmill exercise [84]. This was accompanied by a down-regulation of GRP78 and PDI enzymes as well as an inhibited activation status of PERK, eIF2-alpha, ATF6 and sXBP-1. In GNE myopathy that is characterized by A-beta deposition, muscle biopsies showed enhanced expression of molecular chaperones such as GRP78 [85]. This might be interpreted as mere coincidence but direct application of A-beta also has been demonstrated to lead to ER-stress signaling: GRP78 and XBP-1 protein levels increased for example in neurons treated with A-beta [86] which could be further augmented by mitochondrial dysfunction. SK-S-SH cells displayed activation of the PERK pathway as well as increase in CHOP upon A-beta administration [87]. Another publication on the contrary found triggering of eIF2-alpha phosphorylation and calcium depletion from the ER, but no activation of UPR (as shown e.g. by splicing of XBP-1 mRNA, amount of XBP-1 mRNA and PERK phosphorylation) in primary cortical neurons [88]. The A-beta1-42 peptide used in this study comprised both, oligomeric and fibril forms and this might be the cause of observing no induction of UPR. Chafekar and colleagues demonstrated mild induction of the signaling pathway only by oligomers and not by fibrils [89]. A very recent report on human iPSC derived neurons from familial and sporadic Alzheimer cases confirmed that A-beta oligomer accumulation leads to ER as well as oxidative stress [90]. The mechanism behind this is still not fully understood: low molecular A-beta peptides have been described to interrupt mitochondria-ER anchoring and thereby to evoke ER collapse [91]. Yoon *et al* reported an AMPK-mediated translational block upon application of A-beta 42 oligomers [92]. This subsequently inhibited mTOR signaling and resulted in activated ER-stress as shown by eIF2-alpha phosphorylation in rat hippocampal neurons [92]. Interestingly, monomeric A-beta peptides as well as fibrils here failed to activate AMPK.

Not only A-beta peptides are thought to interfere with ER-stress but single reports also exist on other cleavage products - the APP intracellular domain (AICD) and the fragment produced by alpha-secretase-cleavage (APPs-alpha). The AICD is discussed to act as a transcription factor in analogy to the Notch C-terminal domain [93]. Regarding this, infliction in signal transduction to the nucleus by the UPR-prone transcription factors ATF6, 4 and sXBP-1 seems plausible. Takahashi and coworkers found increased CHOP mRNA and protein level in APP overexpressing cells. This could be attenuated by treatment with DAPT (a potent gamma-secretase inhibitor) and occurred also upon transfection with a tagged AICD variant [94]. CHIP assays in AICD transfected HEK293 cells additionally indicated a physical interaction of the AICD with the CHOP promoter region. Nevertheless, another group reported that AICD overexpression in SHEP neuroblastoma cells did not enhance GRP78 and CHOP expression but led to potentiation of ER-stress driven apoptosis [95]. This would rather indicate that AICD might act downstream or independently from UPR. APPs-alpha, which is released via alpha-secretase activity on APP, seems to provide protection against ER-stress: Guo et al. [96] described an NF-kappa B-dependent stabilization of intracellular calcium homeostasis in differentiated PC12 cells by APPs-alpha. In addition, enhancement of APPs-alpha secretion via DHA-treatment was observed to be protective against apoptosis induced by ER Ca(2+)

store depletion via Thapsigargin in HEK293-APP cells [97]. This protective potential could be transferred to untransfected HEK293 or PC12 cells using the supernatant of DHA-treated cells.

For other cleavage products of APP such as APPs-beta, C99 and C83 as wells as p3 to our knowledge no literature exist so far that describes entangling in ER-stress and downstream signaling.

Influence of tau and APP-modifying molecules on ER-stress

A-beta peptides are just one component that triggers or induces AD pathology: a growing number of molecules has been correlated to this type of dementia, which makes it difficult to reflect a complete picture of interference with ER-stress. Therefore, we here focus on tau as the second central player and proteins, directly acting on APP.

An investigation by Unterberger [98] indicated the importance for tau proteins in ER-stress response by demonstrating that in human prion diseases activated PERK and eIF2-alpha only occurred concomitantly to neurofibrillary pathology. In contrast, phosphorylated PERK correlated with hyperphosphorylated forms of tau protein in AD. This connection of UPR activation and the microtubule-associated protein tau has been confirmed in a wide range of publications within the last years. Hoozemans and colleagues described that phospho-PERK was absent from neurofibrillary tangles but abundantly detectable in neurons with hyperphosphorylated tau [99]. The percentage of affected neurons thereby increased with the Braak stage for neurofibrillary changes. In frontotemporal lobar degeneration with Tau pathology (FTLD-tau) phospho-PERK and phospho-IRE1-alpha were increased in a similar way while FTLD without tau pathology or non-neurological control cases showed no signs of UPR activation in neurons and glia [100]. The implication of tau in UPR has also been shown in animal models of tau-pathology such as in [101] where high levels of activated PERK and eIF2-alpha were identified in the hippocampus of aged tau-transgenic mice (P301L). This is contradicted by a paper from Spatara and colleague [102]: they were not able to demonstrate activation of UPR in a mouse line where the P301S variant of tau was expressed (aged 6 and 11 months). They investigated XBP-1 splicing by splice variant specific PCR which might be difficult in tissue with low abundance of sXBP-1. No significant changes as compared to tissue of wild-type mice in calreticulin and GRP78 mRNA levels were found; unfortunately it is not clear whether those samples were from 6 month or 11 month old mice, which impairs a direct comparison with the data from Ho et al. [101]. In 9 month old rTg4510 mice (advanced stage of disease) phospho-PERK was significantly increased in comparison to non-transgenic control mice [103]. This was accompanied by an increase in GRP78 and occurred in the hippocampus and cortex of the mice, regions severely affected by tau pathology in this disease model. Suppression of the transgene by the TET-off-system for one month revised the phospho-PERK elevation as did the acute suppression for 4 days: decrease of phospho-PERK and GRP78 strongly suggests reversibility of ER-stress induction by tau protein [103].

Besides the colocalization of phospho-PERK and phospho-tau, Ho et al. [101] described a direct influence of ER-stress on tau metabolism: Thapsigargin stimulated phosphorylation of tau (Thr231, Ser262 and Ser396) as well as its cleavage [101]. This "vicious cycle" was also shown for neuronal and non-neuronal cell lines SH-SY5Y and HEK293 and rat brain preparations [104]. Recently, in addition an increase of total endogenous tau protein in cultured neurons and primary cultured neurons has been described due to a reduction in the degradation rate of tau under ER-stress [105].

Interestingly, UPR here directly links A-beta and tau pathology via ER-stress signaling: oligomeric A-beta peptides have repeatedly been linked to ER-stress (see **Figure 2**) and release of calcium from the ER leads to activation of GSK3-beta, a major tau-kinase, in primary rat embryonic cortical neurons [106]. Moreover, ventricular infusion of ER-stressors in rats resulted in GSK3-beta activation and tau hyperphosphorylation [107]. In addition, GRP78 was elevated and an enhanced binding of GSK3-beta and tau to this chaperone was demonstrated in brain tissue from Tunicamycin-treated animals. In HEK293 cells with overexpression of GRP78 and tau this increase in binding levels occurred in a similar manner. siRNA-mediated knock down of GRP78 in HEK/

Table 1. Changes in ER-stress signaling in AD and AD animal models

AD (human patients)	Severity of disease/tissue	Components of ER-stress pathway	Reference
	Stage 5 to 6	Accumulation of CD3-delta (ERAD substrate)	[103]
		Correlation of toxic turn A-beta with GRP78	[133]
		Reduced HRD1 protein levels, increased mRNA (function in ERAD)	[140]
		Increase in p-eIF2-alpha, ATF4, CHOP, and PERK	[92]
		Pro-apoptotic ER-stress pathway molecules increase with AD severity Pro-homeostatic ER-stress molecules mainly upregulated in the intermediate stage of AD	[137]
	Hippocampus and frontal lobe	PDI immuno-positive inclusions (NFTs)	[139]
	Stage 1 to 6 Temporal cortex	Increased XBP-1 splicing and PDI expression CHOP activation	[87]
	Temporal cortex	Reduction in GRP78 and 94	[76]
	Frontal cortex	Phosphorylation of eIF2-alpha upregulated	[110]
	Temporal cortex	Phosphorylation of eIF2-alpha upregulated	[113]
	Hippocampus CA1 region	Phospho-PERK immunopositive neurons	[99]
	Hippocampus and temporal cortex	Phosphorylation of eIF2-alpha upregulated	[131]
	Stage 3 to 6 Temporal and frontal cortex	sXBP-1 mRNA level downregulated	[120]
AD models	Model		
	rTg4510 mice (tauopathy) 9 months	Activation of PERK Accumulation of CD3-delta (ERAD substrate)	[103]
	3x Tg-AD mice 2 months	Increased GRP78	[133]
	APP(E693Δ) mice 18 months	up-regulation of GRP78 and HRD1	[135]
	A-beta transgenic flies	suppression of neurotoxicity by sXBP-1	[138]
	Tg2576 mice 17 months	No activation of UPR or apoptosis	[87]
	5xFAD 6 months	Phosphorylation of eIF2-alpha upregulated	[110]
	APP/PS1 9 months	Phosphorylation of eIF2-alpha upregulated	[113]
	5xFAD 1 and 9 month APP/PS1 6 and 9 month	sXBP-1 mRNA level increased (1 and 6 month) sXBP-1 mRNA level decreased (9 month)	[120]

tau cells revised tau hyperphosphorylation upon Thapsigargin-application while GSK3-beta was still activated [107]. This in sum reflects the ambivalence of ER-stress driven signaling: once induced, it might even worsen degenerative processes, but activation of ER-stress induced UPR - e.g. via tau hyperphosphorylation - might also contribute to protection against apoptosis. HEK cells that overexpress tau for example revealed attenuated apoptosis in response to treatment with ER-stress inducers such as staurosporine or camptothecin [107].

For involvement of APP-modifying proteinases in ER-stress signaling, only scattered reports exist: for instance increased production of BACE-1 mRNA and non-coding antisense transcript has been reported in sporadic inclusion-body myositis muscle fibers [108] which have been correlated with increased ER-stress signaling [81]. Both transcripts were also elevated by experimentally evoked ER-stress via Tunicamycin or Thapsigargin in cultured human muscle cells [108]. In the APP/PS1 AD mouse model at 3, 6 and 12 months of age hippocampal neurons showed increased staining for PERK phosphorylation [109]. At 3 month also phospho-eI2Fa levels were elevated in brain tissue homogenates in comparison to wild type mice. Salubrinal, an inhibitor of eIF2-alpha

phosphatase PP1c, increased BACE1 and subsequently A-beta production in primary neurons [110]. HSV1 transfection of SH-SY5Y cells which leads to activation of PRK - an alternative kinase that phosphorylates eI2F-alpha - strongly increased BACE-1 protein amounts [111]. Moreover, inhibition of eIF2-alpha phosphatase de-repressed the signal from a BACE1-5'UTR-luciferase reporter in HeLa cells, indicating that this is an important pathway regulating BACE1 translational repression [112]. If PKR or PERK both contribute in a similar manner to the regulation has to be investigated. However, CSF levels of PKR and phospho-PKR were found to be elevated in AD and amnestic mild cognitive impairment subjects [113] and the latter was also linked to cognitive decline measured by longitudinal MMSE changes [114].

Regarding gamma-secretase, very early on correlation to ER-stress has been suggested (see above) by the observation that PS1 knock-out fibroblasts revealed a reduction in nuclear translocation and lowered UPR signaling [77]. But again, the influence seems to be a mutual one: Tunicamycin application *in vivo* enhanced PS1 expression in mouse kidney [115]. Furthermore, it has been demonstrated that ATF4 binds to the amino acid response element (AARE) regulatory region of human PS1 gene. Quercetin, which induces XBP-1 splicing but suppresses ATF4 activation, prevented the Tunicamycin-evoked increase in PS1 and subsequently production of A-beta peptides in HEK293 cells [116].

Takahashi et al. described in 2009 that Tunicamycin not only induces AICD production in HEK293 but also C83, the C-terminal fragment derived by cleavage of APP by alpha-secretase [94]. Treatment of retinal pigment epithelia cells (ARPE19) with Tunicamycin or Thapsigargin for 24hrs revealed enhanced amounts of TACE-mRNA [117]. TACE (tumour necrosis factor alpha converting enzyme, ADAM17) is widely accepted as the regulated alpha-secretase (for a comparison of ADAM10 and 17 physiological roles see [118]). The TACE-induction by ER-stress was also observed for several tumor cell lines such as HeLa or MCF7 [119]. By applying siRNA targeted against central players of the three arms of UPR - ATF4, XBP-1 and ATF6 - it was demonstrated that only ATF4 and 6 are able to act as regulators of TACE expression. ATF4 had the most prominent effect and was shown to bind at least to one of the three predicted binding sites of the TACE promoter by CHIP analysis [119]. This has been confirmed by overexpression of active XBP-1 in SH-SY5Y human neuroblastoma cells where TACE mRNA as well as protein was not elevated [120]. Interestingly, despite the failure of XBP-1 in enhancing TACE expression, secretion of APPs-alpha was induced. This has been shown to be based on upregulation of ADAM10 expression, the major alpha-secretase in neuronal tissue [11, 121, 122]. Mice with B-cells deleted in Adam10 contained normal numbers of plasma cells but were impaired in antibody responses [123]. This was accompanied by reduced amounts of transcription factors implicated in plasma cell function such as XBP-1.

In sum, different parts of ER-stress and UPR signaling are involved in a multimodal manner in APP processing as well as tau metabolism and players of AD pathogenesis by themselves affect ER-stress and adequate response of the cell due to stress.

ER-stress signaling in animal models of AD and human patients

Most transgenic models of AD are based on the amyloid hypothesis and therefore are predicated on genetic mutations of human AD-relevant genes such as APP or PS1, which have been identified in familial AD cases. These models mimic in part AD-like pathological features indicated e.g. by increased A-beta peptide generation, tau fibrillization or even cognitive impairment (reviewed in [124]). In this section we summarize the regulation of crucial ER-stress components belonging to one of the three branches (PERK, ATF6 or IRE1-alpha) in AD animal models and compare them to knowledge obtained by brain samples derived from human AD-patients (for an overview see **Table 1**).

Regarding the PERK pathway, in the rTg4510 tau-based Alzheimer mouse model a significant increase in activated phosphorylated PERK was observed at 9 month of age [103]. This is a rather aggressive model, where pathological features such as tangle formation, deficits in neuronal function or cognitive decline occur as early as 3 or 5.5 months of age [125, 126]. Tissues severely affected by tau fibrillization such as hippocampus and cortex displayed a 2.4-fold increase in phospho-PERK [103].

These findings are consistent with analyses regarding AD brain samples: immunopositive phospho-PERK neurons were found in hippocampal CA1 region and the amount was significantly increased as compared to non-demented [99]. Furthermore, activation of PERK was positively correlated with advanced Braak scores and consequently with severity of disease. Longitudinal study of tau pathology and accumulation of phospho-PERK revealed also a correlation in the rTg4510 mouse model as early as 6 month of age (first time point investigated: 3 month) [103]. The influence of tau on ER-stress might be rather indirect because pathological tau did not colocalize with an ER-marker. Human cortical sections of advanced Braak stages (5-6) which also display robust accumulation of hyperphosphorylated tau confirmed that aberrant tau and the-ER marker calnexin are not colocalized. As tau was shown to co-immunoprecipitated with the ERAD protein complex members VCP and HRD1 this might explain triggering of ER-stress by tau.

In whole brain lysates of Tg2576 mice, which overexpress the Swedish mutant of human APP [127] activation/phosphorylation of the PERK downstream target eIF2-alpha was demonstrated and positively correlated with an increased expression of BACE-1 [110]. For this analysis 9 month old mice which already exhibit maximum plaque formation were further challenged by energy deprivation, therefore activation of PERK signaling might be due to the specific experimental paradigms. However, the induction of ER-stress in an APP-based mouse model was further substantiated by analysis using an aggressive amyloid deposition mouse model - 5xFAD, which display detectable A-beta peptide generation already at 1 month of age [128]. In 6 month old 5xFAD mice with a severe amyloid pathology the BACE-1 expression level was increased 1.7-fold as compared to non-transgenic littermates [110]. This was accompanied by an increased ratio of phospho-eIF2-alpha to total eIF2-alpha. The regulation of the BACE-1 expression by active eIF2-alpha could be mechanistically elucidated by Mouton-Liger and colleagues: in 9 month old APP/PS1 mice, which already show neuronal loss (detectable at 6 month of age [129]) the expression of BACE-1 was regulated by active eIF2-alpha under the control of PKR [113]. On the contrary, analysis of cortical samples of aged Tg2576 mice (17 month of age) with massive plaque formation revealed no significant change in CHOP expression, which is the most prominent downstream target of the PERK pathway [49]. These contradictory results might be explained by the different ages of animals used in the studies. ER-stress is known to be a transient process with the IRE1-alpha-branch being down-regulated with prolonged exposure to respective signals [130]. As CHOP induction was reported to maintain due to sustained stress at least in human cells, counter-regulation in old mice is to be debatable. Nevertheless, immunoblot analysis of human post-mortem frontal cortex tissue of AD-patients revealed a positive correlation of active eIF2-alpha with BACE-1 protein level and also with amyloid load of AD brain samples [110]. Increased levels of active eIF2-alpha have also been described in temporal cortex [113, 131] and hippocampal tissue [131] of AD-patients. Moreover, CHOP has been reported to be increased in temporal [87] and frontal [92] cortex tissue as compared to age-matched controls.

In sum, literature is almost consistent with an overall upregulation of single PERK-pathway components e.g. PERK, eIF2-alpha and CHOP in AD or aggressive disease models. CHOP is responsible for the regulation of apoptosis under ER-stress conditions e.g. by ATF5 induction [132]. Therefore neuronal cell death in AD might be partially understood as a consequence of long lasting ER-stress in the brain.

For the most prominent ATF6-mediated ER-stress marker GRP78 the field of literature is more heterogeneous: for example it has been demonstrated that GRP78 is significantly upregulated in two different AD mouse models. In neurons of 3xTg AD mice aged 2 month an increase in GRP78 expression was detected [133]. Mice at this age are cognitively unimpaired und consequently are representative for a pre-pathological stage [134]. Umeda and colleagues described an increase of GRP78 expression in hippocampal neurons and cerebral cortex of APP (E693Δ) mice aged 18 month [135]. These mice display impaired hippocampal synaptic plasticity at an age of 8 month and even neuronal loss detectable at 24 month of age [136]. In addition, no expression changes of GRP78 were found in in the brain of 17 month old Tg2576 mice [87]. Comparably, analysis of human post mortem samples of AD-patients are characterized by contradictory

results: a positive correlation of intraneuronal A-beta peptides with the expression of GRP78 has been reported by double-label immunostaining of AD brain sections as compared to those of healthy controls [133]. Consistent with this, the GRP78 protein level was significantly increased in cortical tissue derived from AD brains as compared to samples from non-demented [131]. On the contrary, Katayama and colleagues have shown that expression level of this protein was slightly reduced in temporal cortex samples derived from sporadic AD cases and even more reduced in the brain of patients with familial AD linked to PS1 mutations [76].

Existing literature does not allow a final appraisal of GRP78 expression in brain tissue of AD-patients due to missing characterization of samples regarding e.g. Braak stages. However, one possible attempt to explain these heterogeneous results might be the two-sited direction of ER-stress signaling dependent on the intensity and the duration of stress signals. Expression of molecules ensuring recovery of ER function and homeostasis were rather induced at intermediate disease stages while for progressed disease severity pro-apoptotic mediators were predominant in an investigation from de la Monte and colleagues [137].

Concerning the IRE1-alpha pathway, a *Drosophila* model with human A-beta expression underlined a potential neuroprotective function of XBP-1, the main downstream target of IRE1-alpha [138]. Those flies show a strong A-beta-dependent phenotype in the eye regarding structure and size of the organ. These pathological changes were alleviated by introducing XBP-1. Such a protective effect of XBP-1 regarding neurodegenerative processes has been further substantiated by a sXBP-1-mediated induction of ADAM10 gene expression [120]. Within two different AD mouse models (APP/PS1 and 5xFAD) sXBP-1 mRNA level were significantly increased in whole brain samples as compared to non-transgenic littermates at early time points of pathological changes (APP/PS1: 6 month; 5xFAD: 1 month). This was accompanied by an increase of ADAM10 expression [120]. Analyzing more advanced stages (9 month of age for both models), XBP-1 returned to wild type levels or was even decreased [120]. However, mRNA level of spliced/active XBP-1 has been reported to be increased in temporal cortex tissue of AD-patients as compared to healthy controls (Braak scores ranged from 1 to 6 for AD samples, [87]). Our own study with a more defined stage of disease (Braak scores 3-6) demonstrated a significant decrease of sXBP-1 in temporal as well as frontal cortex tissue of AD-patients in a larger cohort of individuals [120]. Analyzing the same samples, a significant reduction of ADAM10 as a novel downstream target of XBP-1 in both tissue types was observed. Another downstream target of the transcription factor XBP-1 is the protein disulfide isomerase (PDI) for which Lee and colleagues revealed an unaltered expression level as demonstrated by immunoblot analysis in 17 month old Tg2576 mice (advanced stage of AD-like pathology [87]). However, in the same report this enzyme was found to be upregulated in cortical AD brain tissue and PDI immune-positive neurofibrillary tangles (NFTs) were described in slices from hippocampus and frontal lobe of AD-patients [139]. On the contrary, PDI protein level was unaffected in cerebral cortex samples derived from AD-patients as compared to healthy controls [140]. HRD-1, which is an ERAD-associated E3 ubiquitin ligase acting downstream of XBP-1 [58], was investigated immunohistochemically in 18 month old APP (E693Δ) mice with severe amyloid pathology [135]. Analysis revealed an intense immunoreactivity in hippocampal neurons and cerebral cortex tissue of the animals. However, Kaneko and colleagues showed that HRD1 is downregulated in the cerebral cortex of AD-patients [140]. This is in accordance with an increase of a subunit of the T-cell antigen receptor - CD3-delta, which is a well characterized substrate for ERAD driven proteolysis, in hippocampus of 9 month old rTg4510 mice [103]. Increased accumulation of CD3-delta was also described in temporal brain tissue from AD-patients (Braak scores: 5-6) as compared to non-demented controls (Braak scores: 1-2) and would rather support a defect in XBP-1 evoked ERAD in AD.

Conclusions

Literature predominantly hints at an early but transient induction of XBP-1 signaling in the AD context and an activation of the PERK-dominated pathway throughout to late stages of disease. This suggests ER-stress functioning as a scale in AD pathogenesis, balancing cells between coping with protein misfolding associ-

ated stress and undergoing cell death. Double-edged properties of ER-stress signaling comes clear e.g. in a recent investigation of a *C. elegans* model of Alzheimer's disease: basal activity of the UPR was beneficial under normal conditions, but repression of the signaling delayed toxicity evoked by inducible A-beta peptide expression [141]. Age-onset loss of ER proteostasis could be reversed by neuronal expression of sXBP-1 in *C. elegans* and enhanced longevity [142], pointing at a potential role of UPR in age-related changes which will be interesting to investigate in humans.

All these observations lead to the rather alluring prospect that interfering with ER-stress might bear novel therapeutic approaches regarding neurodegenerative diseases such as AD and has been presented in previous reviews (e.g. [143-145]). For example, administration of CNB-001, a pyrazole-inhibitor of 5-lipoxygenase, was able to induce PERK signaling and improve memory in AD model mice [146]. Nevertheless, several uncertainties and open questions regarding the role of ER-stress in AD remain: 1) Animal models used for investigation of ER-stress signaling under pathological conditions are differing in time of onset of pathological features and no real scaling exists for comparison of "severity of disease" at the investigated age of animals. Only a minority of reports give a longitudinal picture on evolvement of stress which would allow estimating the role of single components in pathology. Investigations using human tissue partly miss characterization of disease stages and data concerning MCI patients and normal aging are missing - at least to our knowledge. 2) The actors of the three signaling branches are phosphorylated proteins and transcription factors and per se are rather unstable or regulated by further posttranslational processing, translocation events or protein interactions (e.g. interplay of ATF4 with p300 acetyltransferase, [147] or SUMO-conjugase UBC9 with sXBP-1, [148]). This might explain why a wide variety of investigations are based on mRNA quantitation which might distort the underlying scenario. 3) Crosstalk of the ER-stress signaling pathways among themselves and with other signal transduction pathways such as insulin signaling [149, 150] further complicate entangling ER-stress involvement in AD. Nevertheless, elucidating ER-stress function or failure in AD might help turning the scale in therapeutic considerations or for evolvement of new highly diagnostic biomarkers.

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Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

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