Medicinski podmladak

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Mini review article

MOLECULAR MECHANISMS INVOLVED IN ENDOPLASMIC RETICULUM STRESS DEVELOPMENT – WHAT DO WE KNOW TODAY

MOLEKULARNI MEHANIZMI UKLJUČENI U NASTANAK STRESA ENDOPLAZMATSKOG RETIKULUMA – ŠTA ZNAMO DO SADA

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Abstract

Endoplasmic reticulum (ER) is an intracellular organelle involved in protein synthesis and folding. When the balance between cell needs for proteins and ER capacity to fold proteins is disrupted, nonfunctional, unfolded, or misfolded proteins accumulate in ER lumen, leading to endoplasmic reticulum stress (ER stress). One of the ways cell uses to overcome ER stress is unfolded protein response (UPR) activation. UPR is initiated by the activation of three ER transmembrane proteins. These proteins are IRE-1α (inositol requiring enzyme-1α), PERK (protein kinase RNA-like endoplasmic reticulum kinase) and ATF6 (activating transcription factor 6) and they are activated when ER chaperone, GRP78 (glucose-regulates protein 78) releases their intraluminal domains. Activation of these transmembrane sensors starts mechanisms that should restore ER function. If ER function is not restored and balance is not achieved, apoptosis is induced in order to maintain cell homeostasis. Activated IRE-1α leads to XBP-1 (X-box binding protein-1) mRNA splicing and activates MAP kinases and inflammatory pathways that involve nuclear factor κB (NFκB). Activated ATF 6 (ATF6f) functions as a transcriptional factor and increases gene expression for XBP-1, while PERK activation leads to phosphorylation and inactivation of eukaryotic initiation factor 2 (eIF2α) which further leads to decreased protein synthesis. Additionally, eIF2α phosphorylation leads to selective synthesis of ATF4, a transcriptional factor that in irreversibly damaged cells induces cell death activation by C/EBP homologous protein (CHOP) transcription.

It is known that ER stress and UPR have a role in different diseases pathogenesis such as diabetes, inflammation, tumors and neurodegenerative diseases. Knowing signaling pathways of UPR and mechanisms by which UPR is involved in diseases pathogenesis can be very significant in targeted therapeutic approaches development.

Keywords:
ER stress,
UPR,
IRE-1α,
PERK,
ATF6

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Sažetak

Endoplazmatski retikulum (ER) predstavlja intracelularnu organelu koja ima ulogu u sintezi i obradi proteina. Kada dođe do narušavanja ravnoteže između potreba ćelija za proteinima i kapaciteta ER za obradu proteina, nefunkcionalni, pogrešno uvijeni ili neuvijeni proteini počinju da se nakupljaju u ER dovodeći do nastanka stresa endoplazmatskog retikuluma (ER stresa). Jedan od načina kojim ćelija prevazilazi ER stres je pokretanje odgovora na neuvijene proteine (engl. *unfolded protein response* - UPR). UPR se pokreće kada dođe do aktivacije tri proteina koji se nalaze u membrani ER. Reč je o IRE-1α (engl. *inositol requiring enzyme-1α*), PERK (engl. *protein kinase RNA-like endoplasmic reticulum kinase*) i ATF6 (engl. *activating transcription factor 6*) koji se aktiviraju kada se od njihovog luminalnog domena odvoji šaperon ER GRP78 (engl. *glucose-regulated protein 78*). Aktivacijom ova tri transmembranska senzora pokreću se mehanizmi čiji je cilj obnova funkcije ER. Ukoliko funkcija ER ne bude obnovljena i ukoliko se ne dostigne stanje ravnoteže, pokreće se proces apoptoze kako bi se osigurala ćelijska homeostaza. Aktiviran IRE-1α dovodi do obrade iRNK za transkripcioni faktor XBP-1 (engl. *X-box binding protein-1*) i do aktivacije mitogenom aktiviranih kinaza (MAPK) i inflamatornih puteva koji uključuju nuklearni faktor κB (NFκB). Aktivirani ATF 6 (ATF6f) funkcioniše kao transkripcioni faktor i povećava ekspresiju gena za XBP-1, dok PERK dovodi fosforilacije, a time inaktivacije eukariotskog faktora inicijacije translacije 2 (eIF2α), što za posledicu ima smanjenu sintezu proteina. Fosforilacija eIF2α dovodi i do selektivne sinteze transkripcionog faktora ATF4 koji kod ireverzibilno oštećenih ćelija dovodi do aktivacije ćelijske smrti pokretanjem transkripcije gena za *C/EBP homologous protein* (CHOP).

Poznato je da ER stres i UPR imaju značajnu ulogu u patogenezi različitih bolesti među koje spadaju dijabetes, inflamacija, tumori i neurodegenerativne bolesti. Poznavanje signalnih puteva UPR, kao i mehanizama kojima je UPR uključen u patogenezu ovih bolesti može biti od velikog značaja u razvoju ciljanih terapeutskih pristupa za lečenje ovih bolesti.

Ključne reči:
ER stres,
UPR,
IRE-1α,
PERK,
ATF6

Introduction

Endoplasmic reticulum (ER) is the largest intracellular organelle that has numerous functions. The ER lumen represents an interconnected network of branching tubules and flattened sacs that are separated from cytosol by a single membrane which regulates component exchange between ER and cytosol (1, 2). One of the most important roles of ER is protein biosynthesis, modification, folding and transport (rough ER). ER residence proteins, plasma membrane proteins, Golgi apparatus (GA) proteins, lysosomal proteins, and proteins that will be secreted from the cell are also synthesized on rough ER. On the other hand, smooth ER has a role in lipid synthesis, carbohydrate metabolism and calcium ion storage (3). Numerous enzymes and chaperones (heat shock proteins) are involved in protein folding and modification (4). Even though there are numerous control mechanisms involved in protein folding, some proteins are not able to be folded properly. Unfolded or misfolded proteins are kept in ER and become a substrate for ER-associated degradation (ERAD), a pathway through which unfolded and misfolded proteins are removed to the cytosol where they undergo ubiquitylation and degradation by proteasome (5). Detection and removal of nonfunctional proteins are a highly controlled process which must not interfere with normal cell functions (6). When ER function is disrupted, or when there is an imbalance between protein production and ER capacity to fold proteins, nonfunctional, misfolded and unfolded proteins are accumulated inside ER, despite numerous control mechanisms that are involved in damaged proteins recognition and removal. Protein accumulation leads to the development of ER stress (7, 8). When ER stress is developed, cell has several ways to keep its function and balance using different mechanisms which include inhibition of translation, degradation of accumulated proteins, as well as increased production of chaperones and enzymes that have a role in protein folding. If these mechanisms fail to restore ER function, apoptosis is induced (9).

In order to fight ER stress, cell activates unfolded protein response, UPR (10-12). UPR controls RNA stability, regulates protein synthesis and activates genes responsible for normal protein secretion (13). Also, ER capacity for protein folding is increased (14). UPR is initiated by the activation of three ER transmembrane proteins (ER stress sensors): IRE-1α (inositol-requiring enzyme 1), ATF6 (activating transcription factor 6) and PERK (protein kinase RNA-like endoplasmic reticulum kinase) (15). So far, the physiological role of the UPR in maintaining cell homeostasis in secretory cells has mainly been investigated. ER stress has a role in embryology, development, growth, differentiation and metabolism (16). In cells such as B lymphocytes, endocrine or exocrine pancreas cells or salivary glands cells ER stress has a physiological and not pathological role (2, 17).

As mentioned before, proteins responsible for UPR onset, IRE-1α, ATF6 and PERK are transmembrane

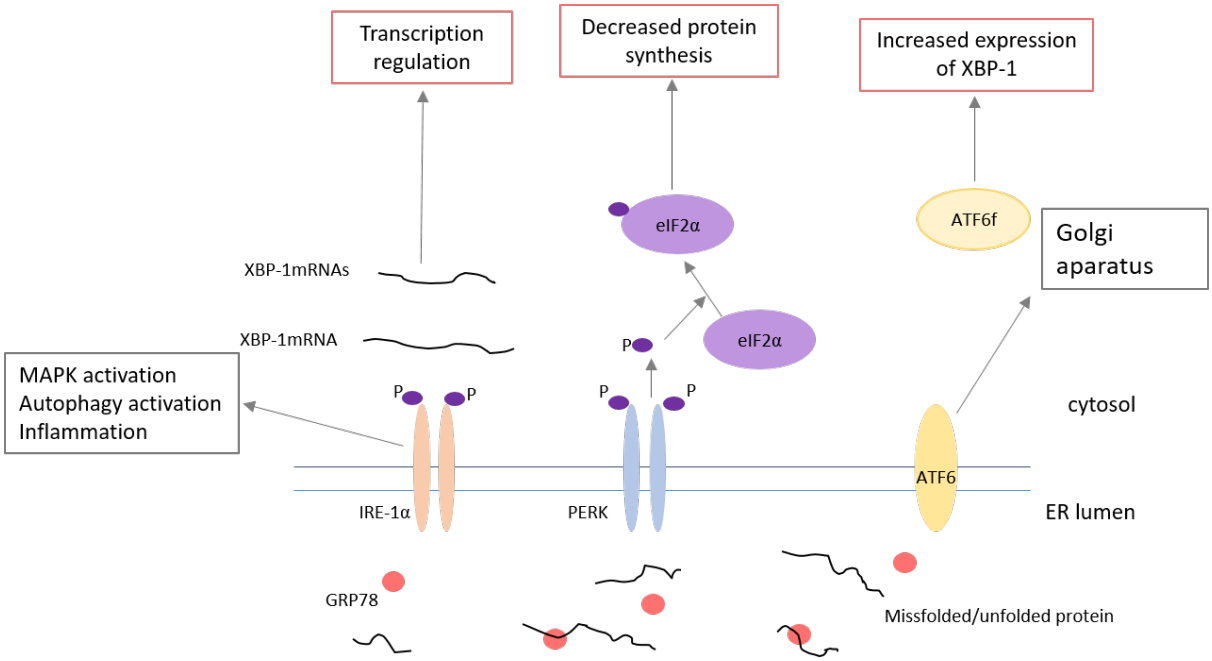

Figure 1. UPR activation and its effects. GRP78 - glucose-regulated protein 78; IRE-1α - inositol requiring enzyme-1α; PERK - protein kinase RNA-like endoplasmic reticulum kinase; ATF6 - activating transcription factor 6; XBP-1 – X box binding protein 1; eIF2α - eukaryotic initiation factor 2α; P - phosphate.

proteins anchored in the ER membrane. These proteins are inactive when GRP78 (glucose-regulated protein 78) is bound to their ER luminal domain. GRP78 is ER chaperone responsible for protein folding (18-20). Increased protein synthesis, or their misfolding, increases ER need for chaperones including GRP78. When recruited, GRP78 releases previously bound luminal domain of IRE-1α, ATF6 and PERK, which further leads to their activation (10). Downstream signaling cascade, activated by IRE-1α, PERK and ATF6 initially promotes adaptation of the cell to stress conditions, but if these adaptation mechanisms fail, and ER stress remains unresolved and becomes chronic, apoptotic mechanisms are activated to remove stressed cells (21).

Chronic ER stress and UPR have a role in the pathogenesis of numerous human diseases, such as diabetes, immune diseases, neurodegenerative diseases, and cancer. Therefore, understanding the molecular orchestra involved in the regulation of cell survival/death decision when ER stress occurs may be a key to specifically target different pathological processes and to help establishment of new therapeutic approaches (2).

The role of IRE-1α in UPR activation

Inositol-requiring enzyme 1 (IRE-1α) is the most prominent and evolutionarily conserved transmembrane protein of the ER. The signal of protein accumulation in ER lumen is transduced from IRE-1α to the nucleus as "unfolded protein response (UPR)". Activation of IRE-1α is promoted by disrupted conditions in the ER lumen (22). Its activation is promoted by the dissociation of GRP78 from the luminal domain of IRE-1α which leads to domain dimerization and autophosphorylation. Activated IRE-1α splices 26 nucleotides long intron from XBP-1 (X box binding protein 1) mRNA. This splicing increases the expression of an active and stable form of XBP-1 protein (XBP-1s) (11). It is thought that spliced XBP-1 increases cell survival through ERAD activation and increased transcription of the genes that have a role in protein folding and its control. Besides gene activation, XBP-1 increases ER and GA volume, which subsequently increases protein secretion (23).

Activated IRE-1α affects also mRNAs and microRNAs involved in regulated IRE-1α dependent decay, so-called RIDD. RIDD increases the expression of numerous proteins that have a role in apoptosis, inflammation and adaptation to stress (24). As a response to ER stress, through IRE-1α activation, UPR activates inflammatory pathways that involve NFκB (nuclear factor kappa B) and MAP kinases (mitogen-activated kinases), mainly JNK (c-Jun N-terminal kinase) and p38. Both NFκB and MAP kinases, apart from inflammation, have a role in cell death regulation (13, 23, 25).

The activation of NFκB is regulated through its contact with IκB (inhibitors of κB). IRE-1α activates IκB kinase (IKK) that has two catalytic subunits (IKKα, IKKβ) and one regulatory subunit (IKKγ). Activated IKK phosphorylates IκB and phosphorylated IκB is released from NFκB leading to NFκB activation. In the nucleus, activated NFκB increases cytokine gene expression as well as gene expression of proteins involved in cell survival (26-28). This IRE-1α effect is mediated via TRAF2 (tumor necrosis factor α receptor-associated factor 2). Aside from NFκB activation, complex IRE-1α – TRAF2 through ASK1 (apoptosis signal-regulating kinase 1) activates JNK and p38 (29, 30). IRE-1α – TRAF2 – JNK pathway leads to Bax-dependent apoptosis stimulation (31), while IRE-1α – TRAF2 – p38 pathway increases C/EBP homologous protein (CHOP) activity (32). Complex IRE-1α – TRAF2

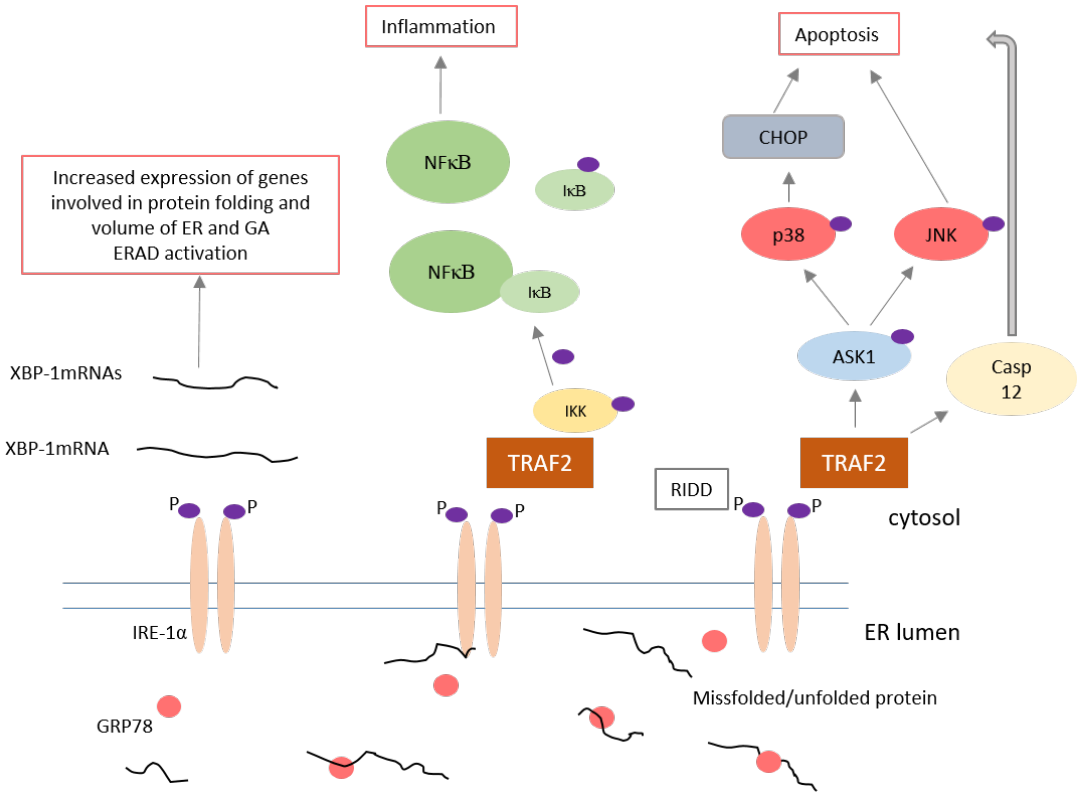

Figure 2. Downstream effects of IRE-1α activation: XBP-1splicing, NFκB and MAPK activation (JNK and p38). GRP78 - glucose-regulated protein 78; IRE-1α - inositol requiring enzyme-1α; XBP-1 - X box binding protein 1; TRAF2 - tumor-necrosis factor-α receptor-associated factor 2; IKK - IκB kinase; IκB - inhibitors of κB; NFκB - nuclear factor kappa-B; ASK1 - apoptosis signal-regulating kinase 1; Casp 12 – caspase 12; CHOP – C/EBP homologous protein; P-phosphate; RIDD - regulated IRE-1α dependent decay.

also has an effect on caspase 12, which is an important factor in apoptosis induced by ER stress (**figure 2**) (33). Based on previously described mechanisms, it can be stated that IRE-1α has two roles in response to ER stress: adjustment of the cell to stress through XBP-1 activation/splicing and apoptosis activation through MAP kinase pathway (**figure 2**).

The role of ATF6 in UPR activation

Activating transcription factor 6 (ATF6) is an ER transmembrane protein involved in UPR activation. This transcription factor belongs to the leucine zipper family and besides its role in UPR, it is involved in organogenesis and tissue homeostasis (21). The detachment of GRP78

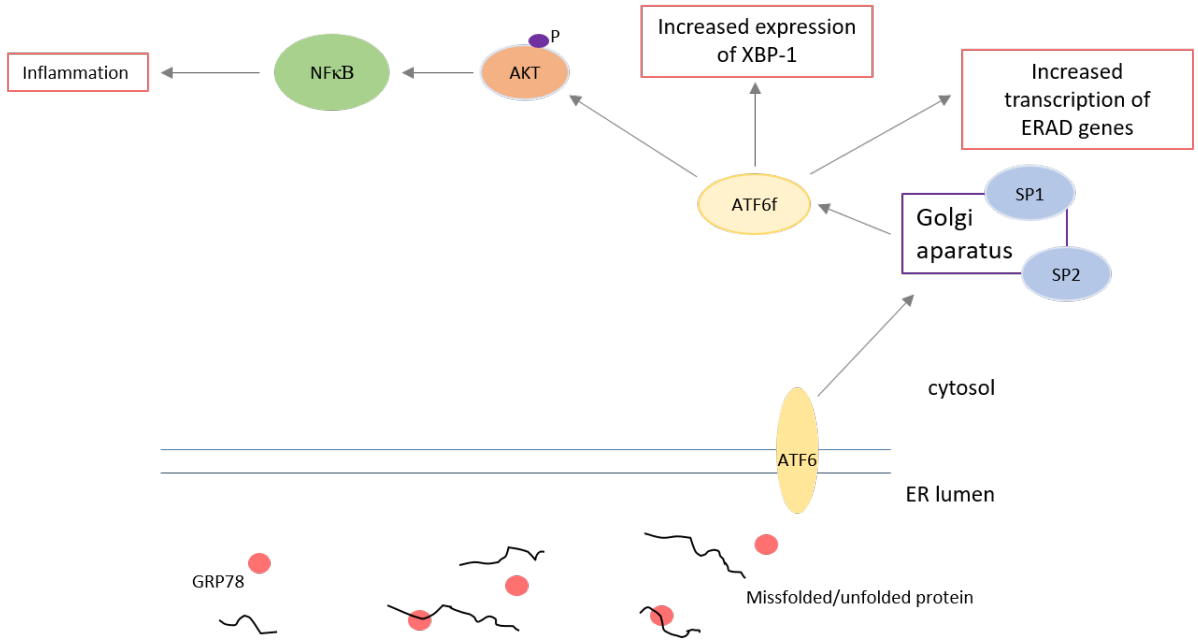

Figure 3. Downstream effects of ATF6 activation: increased expression of XBP-1, transcription of genes involved in ERAD, NFκB activation. GRP78 - glucose-regulated protein 78; ATF6 - activating transcription factor 6; SP1, SP2 – site proteases 1 and 2; AKT – protein kinase B; NFκB - nuclear factor kappa-B; P - phosphate.

from the luminal domain of ATF6 leads to its translocation to GA where it is further processed by SP1 and SP2 proteases (site 1 and site 2 proteases). Newly formed fragment functions as a transcriptional factor ATF6f, which increases XBP-1 gene transcription, as well as transcription of the genes involved in ERAD and protein folding (11). Additionally, ATF6f, independently of IRE-1α, activates NFκB by AKT (protein kinase B) phosphorylation. Even though it is known that AKT is activated during ER stress, the exact mechanisms of its activation have not been enlightened yet (**figure 3**) (34).

The role of PERK in UPR activation

Activation of RNA protein kinase similar to ER kinase (PERK) requires its dimerization/oligomerization, which leads to cytosolic domain kinase activation and autophosphorylation. PERK further phosphorylates and inactivates eIF2α (eukaryotic initiation factor 2α). The inactivation of eIF2α as a result has global inhibition of protein synthesis (11, 35). Phosphorylated eIF2α also leads to selective synthesis of ATF4, a transcriptional factor responsible for upregulation of mRNA expression for the genes that have a role in amino acids metabolism, regulation of autophagy, synthesis of the proteins and their processing in ER (ER chaperones). In irreversibly damaged cells, ATF4 induces cell death activation by increased CHOP transcription (23). This effect is mediated via CHOP activation of pro-apoptotic BH3-only Bcl-2 family members (Bad, Bim and p53), and inhibition of anti-apoptotic proteins (Bcl-2). Additionally, CHOP induces apoptosis by regulating intracellular calcium ions signaling (23, 36).

When there is constant PERK activation, CHOP accumulates and leads to the opening of the calcium channels in ER membrane. Increased calcium concentration in cytosol promotes cell death/apoptosis by activation of calcium-calmodulin-dependent protein kinase II (37). In addition to calcium-calmodulin-dependent protein kinase II activation, calcium also goes to mitochondria matrix where it leads to mitochondria membrane depolarization and increased reactive oxygen species production (38). In addition, CHOP increases gene expression for GADD34 (growth arrest and DNA damage-inducible protein 34). GADD34 in complex with serine/threonine protein phosphatase 1 (PP1) regulates eIF2 α phosphorylation. Namely, GADD34 removes phosphate from eIF2α leading to its activation and subsequent induction of translation. Consequently, protein accumulation is increased showing that adaptive mechanisms have failed and apoptosis is induced (**figure 4**) (11).

Even though the main activation pathway of NFκB is mediated through IRE-1α, PERK can also lead to its activation indirectly, by inhibition of IκB translation (IκB inhibits NFκB activation) (39).

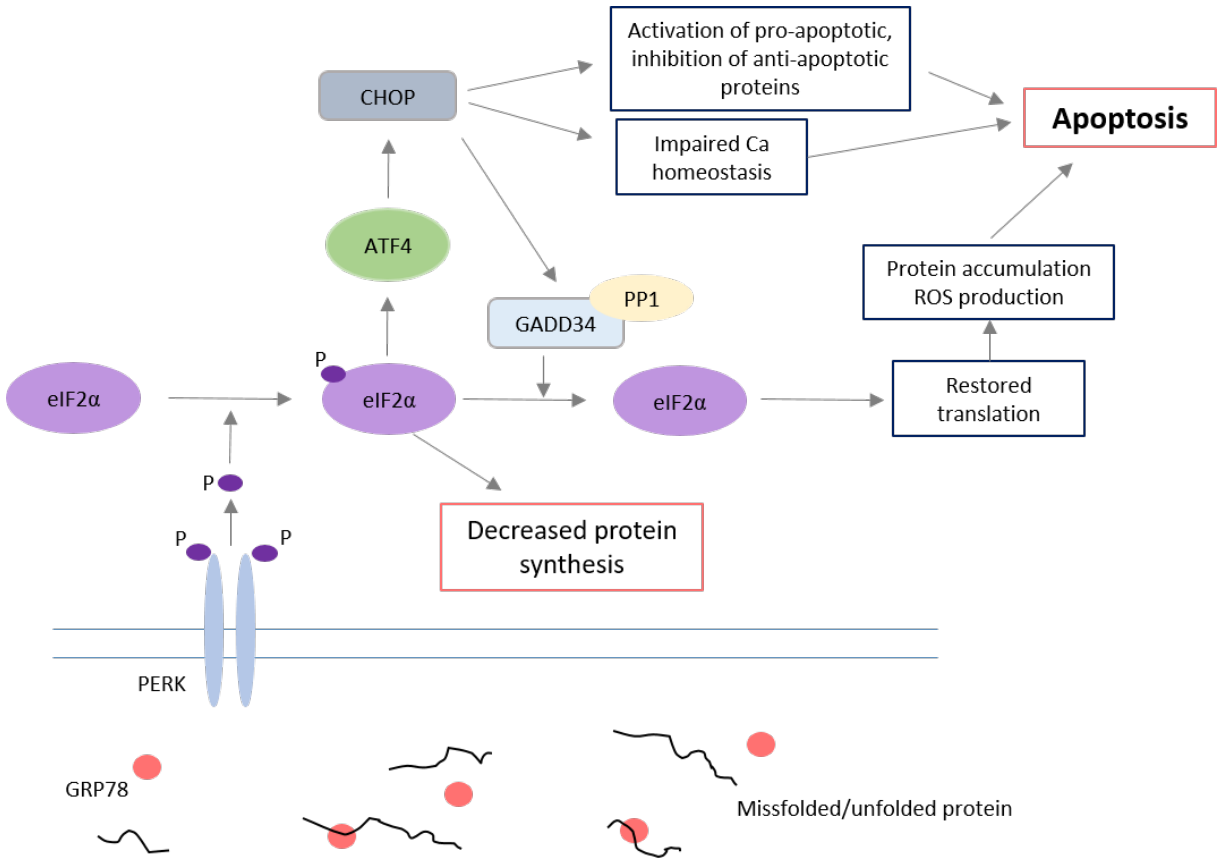

Figure 4. Downstream effects of PERK activation: eIF2α phosphorylation and apoptosis induction. GRP78 - glucose-regulated protein 78; PERK - protein kinase RNA-like endoplasmic reticulum kinase; eIF2α - eukaryotic initiation factor 2α; ATF4 - transcriptional factor ATF4; CHOP - C/EBP homologous protein; GADD34 - growth arrest and DNA damage-inducible protein 34; PP1 - serine/threonine protein phosphatase 1; P - phosphate.

The role of ER stress in disease pathogenesis

As mentioned in the introduction part, chronic ER stress and UPR signaling are considered to have a significant role in pathogenesis of different diseases, such as inflammation, cancer, neurodegeneration or diabetes. All three ER sensors (IRE-1α, PERK and ATF6), directly or indirectly, activate NFκB and subsequently induce inflammation by increasing proinflammatory cytokine production which can lead to increased reactive oxygen species (ROS) production and oxidative stress development (21). It is still unclear whether ER stress induces ROS production or other way around. For example, in fibrosarcoma cells, TNFα induces ROS production which further leads to ER stress (40). In many types of cancers such as glioblastoma, multiple myeloma, breast cancer, stomach cancer, etc., sustained activation of ER stress and UPR has been shown (2). Some studies indicate that ER protein folding enzymes and proteins, such as GRP78, are overexpressed in tumors (41). Neurodegenerative diseases, such as Alzheimer's and Parkinson's disease are also associated with ER stress and today, we know that protein accumulation has a significant role in their pathogenesis. By one of the Alzheimer's disease pathogenesis theories, β-amyloid is accumulated in ER, which leads to disruption of calcium homeostasis and subsequent apoptosis (42). In Parkinson's disease, α-syncline accumulation leads to ER stress development, most probably because of interaction with chaperons (43). Different in vivo studies have shown that genetic removal of IRE-1α, PERK or ATF6 affects diabetes development. Namely, homozygous deletion of PERK causes β-cell apoptosis in mice, while PERK mutation in humans causes rare diabetic syndrome, Wolcott-Rallison syndrome (2, 44, 45). XBP-1 gene deletion leads to impaired proinsulin processing in ER and subsequent decreased secretion. It has also been shown that ATF6 has a role in preventing the apoptosis of β cells, which is in consistence with the fact that XBP-1 depletion has a negative effect on diabetes (46, 47).

Conclusion

To sum up, UPR is a signaling pathway that is activated when a cell undergoes ER stress. Previously described perturbations enormously affect various cellular signaling events including inflammation, differentiation and apoptosis. It starts with an adaptive phase and ends with cell death if ER homeostasis is not restored. This delicate balance of ER stress and UPR, along with the fact that ER stress can have both physiological and pathological role, makes them interesting for research. Different strategies can be applied in order to modify ER stress response as a part of a therapeutic approach. Therapeutic approaches can develop in different directions. On the one hand, the adaptive phase of ER stress could be stimulated, which would make cells more resistant to ER stress, and on the other hand cell death could be induced if necessary. Also, ER function could be restored by adequate protein folding stimulation.

Accordingly, knowing the signaling pathway of UPR and the mechanism by which UPR is involved in disease pathogenesis can be very useful in aiming for new targets and therapeutic approaches in different disease treatments.

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