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Endoplasmic Reticulum Stress and Pancreatic Cancer

Endoplazmik Retikulum Stresi ve Pankreas Kanseri

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Abstract

Endoplasmic reticulum (ER) stress, which results from different stimuli, is an important cellular event. There are different types of response to ER stress. One of them is evolutionarily conserved unfolded protein response (UPR). UPR has three sensors for further activation of molecules. These sensors are inositol-requiring enzyme 1 (IRE1), activated transcription factor 6 (ATF6), and ER-resident protein kinase RNA (PKR)-like ER kinase (PERK). In the absence of ER stress, these sensors are maintained in an inactive state. However, under ER stress conditions, they became activated and induce the downstream targets. As a consequence of ER stress, the cell may stay alive or became dead. Several studies have shown that ER stress is associated with different types of diseases such as diabetes mellitus, Alzheimer's disease, prion disease, and cancer. As a cancer type, it has been shown that pancreatic cancer is also associated with ER stress. Pancreatic cancer has a low cure potential with its late diagnosis. Its association with ER stress is seen as a new therapeutic approach. The aim of this is review is to provide an overview of the mechanisms of ER stress and its relationship with pancreatic cancer, one of the diseases in which ER stress affects pathogenesis.

KEYWORDS: Endoplasmic reticulum, pancreatic cancer, stress

Özet

Endoplazmik retikulum (ER) stres, farklı uyaranlar sonucu gelişen önemli hücresel bir olaydır. ER strese farklı yanıt türleri vardır. Bunlardan biri evrimsel olarak korunmuş katlanmamış protein cevabıdır (UPR). UPR'nin moleküllerin sonraki aktivasyonu için üç sensörü vardır. Bu sensörler inozitol gerektiren enzim 1 (IRE1), aktive edici transkripsiyon faktörü 6 (ATF6) ve protein kinaz RNA (PKR)-benzeri ER kinaz (PERK). ER stresin olmadığı durumlarda bu sensörler inaktif durumda tutulurlar. Ancak ER stres durumunda aktif hale gelirler ve yolaktaki alt basamak hedeflerini indüklerler. ER stresin sonucunda hücre ya canlı kalabilir ya da ölebilir. Pek çok çalışmada ER stresin farklı tipte hastalıklarla; örneğin diyabet, Alzheimer hastalığı, prion hastalığı, kanser vb; bağlantılı olduğu gösterilmiştir. Bir kanser türü olarak pankreas kanserinin de ER stres ile ilişkili olduğu gösterilmiştir. Pankreas kanseri geç tanısı ile birlikte düşük tedavi edilebilme potansiyeline sahiptir. Pankreas kanserinin ER stres ile olan ilişkisi yeni bir tedavi yaklaşımı olarak görülmektedir. Bu derlemenin amacı ER stresin tetiklediği mekanizmalar üzerine ve patogenezinde etkili olduğu hastalıklardan biri olan pankreas kanseri ile olan ilişkisine genel bir bakış yapmaktır.

ANAHTAR KELİMELER: Endoplazmik retikulum, pankreas kanseri, stres

1. Endoplasmic Reticulum (ER) Stress

The ER is an important organelle composed of cisternae in eukaryotic cells. It is the basic component of the secretory pathway and has a role in protein, lipid, and steroid synthesis; proper protein folding and trafficking; post-translational modifications (PTMs); and calcium homoeostasis (1). Because of its important role in different processes, its functions are under tight control (2).

Stress in ER, which may result from conditions such as hypoxia, changes in Ca^{2+} concentrations, ischemia, viral infections, inflammation, and errors in PTM, causes accumulation of misfolded or unfolded proteins in the ER. These situations generate a stress condition for this organelle, named as ER stress (3).

Cells use some mechanisms to deal with ER stress. One of them is unfolded protein response (UPR) and the other one is ER-associated degradation (ERAD) to provide ER homeostasis back (4). As a result of UPR activation, protein synthesis is arrested and expression of chaperons and ERAD processes are activated (1). However, if these events are not enough to cope with ER stress and there is prolonged ER stress, then the cell chooses programmed cell death mechanisms (5, 6).

2. UPR Pathways

Unfolded protein response is an evolutionarily conserved adaptive signaling mechanism that contains three ER stress sensors: inositol-requiring enzyme 1 (IRE1), activated transcription factor 6 (ATF6), and ER-resident protein kinase RNA (PKR)-like ER kinase (PERK) (7). In the absence of stress, UPR is maintained in an inactive state. This is achieved by binding of BiP/GRP78 (glucose-regulated protein) to

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these three ER stress sensors (8). However, in an ER stress condition, GRP 78 dissociates from IRE1, PERK, and ATF-6, and results in the activation of stress response (1).

IRE1 is a type 1 ER transmembrane kinase and has two isoforms, IRE1α and IRE1β (9). After induction of UPR, IRE1 dimerizes and autophosphorylates to become active (10). Activated IRE1 ensures the splicing of X-box-binding protein 1 (XBP1) mRNA, which results in the expression of transcription factors and upregulates UPR target genes responsible for protein folding, such as chaperons and protein disulfide isomerase (PDI) (11). PERK is another type 1 ER transmembrane kinase similar to IRE1. In an ER stress condition, PERK dimerizes and autophosphorylates itself and becomes activated. This process is followed by phosphorylation of eukaryotic initiation factor 2 (eIF2α) on its Ser51 resides in α subunit (12). This phosphorylation attenuates the global mRNA translation through inhibition of ribosomal initiation complex formation. Expressions of some specific genes carry on such as activating transcription factor 4 (ATF4) (13). ATF4 is an important transcription factor for the regulation of several UPR target genes such as C/EBP homologous protein (CHOP), which has a role in ER stress-mediated apoptosis (14). A third regulator of UPR is ATF6, which is a type II ER transmembrane protein, a basic leucine zipper transcription factor, and has two isoforms: ATF6α and ATF6β (15). Upon ER stress, ATF6α transits to the Golgi and becomes activated after being subjected to proteolytic cleavage (1). Thereafter, the activated ATF6 translocates to the nucleus and activates downstream UPR response genes (16, 17).

These processes ensure the adaptation and provide homeostasis back. However, in case of high levels of chronic and prolonged ER stress that the UPR response cannot cope with, programmed cell death, i.e., apoptosis and autophagy, occurs (5).

3. ER Stress and Cell Death Mechanisms

a. ER stress and apoptosis

Apoptosis is induced through downstream effectors of ER stress sensors. ER stress can induce both intrinsic and extrinsic apoptotic pathways (18). Similar to the mitochondria, the ER contains components of both proapoptotic (caspase-12, p28Bap31, and GADD153) and antiapoptotic molecules [GRP78, calreticulin, PDI, oxygen-regulated protein (ORP-150), and defender against apoptotic death-1 (DAD1)] (19-24).

CHOP, also known as growth arrest and DNA damage-inducible protein 153 (GADD 153), is the main component of the apoptosis in response to ER stress (25). PERK and ATF6 pathways activates CHOP, which in turn activates the expression of pro-apoptotic factors such as Tribbles 3, GADD34, and death receptor 5 (DR5). The other components of the ER stress-mediated apoptotic pathway are Bcl-2 family members (Bak/Bax), caspase-12, and c-jun NH2 terminal kinase (JNK) (26).

There are some pathways that play a role in the induction of ER stress-mediated apoptosis. One of them starts with homodimerization and autophosphorylation of PERK. After PERK activation, it phosphorylates eIF2α, which blocks the global gene expression and induces selective ATF4 gene expression. Then, this transcription factor induces the expression of CHOP (27), which induces the expression of many proapoptotic factors including DR5, Tribbles homolog 3 (TRB3), carbonic anhydrase VI (CAVI), and proapoptotic Bcl-2 family proteins (28). It has been shown that cells lacking CHOP are protected from ER stress-induced apoptosis (29). Under non-stressed conditions, CHOP expression is maintained at a very low level (17). Growth arrest and DNA damage-inducible protein 34 (GADD34) and an ER oxidase, ERO1α, are activated by CHOP, which leads to apoptosis through increasing the protein synthesis and oxidation in the ER of stressed cells (28). It has been shown that CHOP can also be activated by ATF6 (17).

Another pathway starts with the activation of IRE1α by homodimerization and autophosphorylation. After activation, IRE1 α interacts with TNF receptor-associated factor-2 (TRAF 2). TRAF2 activates apoptosis signaling kinase 1 (ASK1) and they form a complex. This complex subsequently activates the JNK-mediated apoptotic pathway. JNK activation results in the phosphorylation of proapoptotic Bcl-2 family proteins. In addition, it inactivates antiapoptotic Bcl-2 family proteins (30).

Besides these pathways, ER stress can be induced by the Bcl-2 family members Bax and Bak. Their localization and oligomerization at the ER promotes calcium release from the ER to the cytosol (31). With the increase in Ca^{2+} concentration in the cytoplasm, the calcium-dependent cysteine protease m-Calpain becomes activated, resulting in the cleavage and activation of the ER-resident procaspase-12 (32, 33). Active caspase-12 leads to the activation of the caspase cascade (28). In addition, increase in cytosolic calcium concentration increases the calcium influx into the mitochondrial matrix, which can change the polarization profile of the inner membrane and result in the transition of the outer membrane permeability pore. This event causes the release of cytochrome c and activation of apoptosomes, leading to apoptosis (28, 34).

Thus, in general, it can be considered that UPR is double-faced mechanism as it can induce cell survival by induction of GRP78 and cell death through induction of CHOP (35).

b. ER stress and autophagy

There are three different types of autophagy: macroautophagy, microautophagy, and chaperon-mediated autophagy (36). Macroautophagy is a lysosomal pathway involved in the turnover of cellular macromolecules and organelles. It consists of some basic steps, such as induction, formation of isolation membrane by nucleation, elongation, docking, fusion with lysosomes, and breakdown (37). It has been shown that macroautophagy also has a role in dealing with ER stress (38). However, the molecular association between UPR and macroautophagy is not fully understood.

It has been reported that phosphorylation of eIF2α is very important for the induction of autophagy after ER stress. After the phosphorylation of eIF2α, ATF4 is activated and this induces the expression of ATG12, which is important for the elongation step of macroautophagy (39). In addition, ATF4 increases the regulation of Tribbles homologue 3 (TRB3), which inhibits the Akt/mTORC1 pathway and ensures the induction of autophagy. Another ER stress sensor, IRE1, activates TRAF2 and ASK1. The activated ASK1 then induce JNK. Depending on JNK activation, Bcl2 phosphorylation increases (40). As a result, Bcl2 disassociates from Beclin1, resulting in the induction of autophagy (41). The other mechanism to induce autophagy through ER stress is carried out by inositol 1, 4, 5-triphosphate receptor (IP3R)

that resides in the ER membrane. IP3R can interact with Beclin1. Thus, inhibition of IP3R pharmacologically causes its disassociation from Beclin1, which induces autophagy (42). Another reason of autophagy induction by ER stress is the release of calcium ions from the ER lumen. Three pathways have been identified. The first one includes the phosphorylation and activation of AMP-activated protein kinase (AMPK) by Ca^{2+}/calmodulin-dependent kinase kinase β (CaCMKKβ). Because activated AMPK inhibits the mammalian target of rapamycin complex 1 (mTORC1), autophagy is induced. The second pathway depends on the activation of death-associated protein kinase 1 (DAPK) as a result of calcium release. After activation, DAPK phosphorylates Beclin1 and cause its disassociation from Bcl2. In the third pathway, it is believed that autophagy can be induced through the activation of protein kinase C theta (PKCθ) (40).

4. ER Stress and Diseases

The activated ER stress response has been found several human diseases. It is known that prolonged ER stress and thereby cell death is associated with some neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (43, 44). In addition, it has been shown that there is an association between ER stress and some other diseases such as type 2 diabetes (45-47), atherosclerosis (48), alcoholic liver disease (49), HBV and HCV infection (50), Huntington disease (51), prion disease (52), and cancer (53-55).

Cancer cells need an increased rate of protein folding and assembly in the ER because of their fast growth and proliferation pattern. Cancer cells produce hostile microenvironmental conditions, such as hypoxia, hypoglycemia, and acidosis, which are known to be triggers of ER stress (17). Evidence indicates that the UPR pathway is important for cancer cell survival. Several findings suggest that there is an association between ER stress and cancer. One of them is the tumor-specific microenvironment that causes activation of ER stress. Because of hypoxia (which is a general consequence of solid tumors), ATF4 becomes activated, resulting in the activation of UPR (56). Thus, in general, it can be considered that UPR activation has a positive effect on tumor survival under hypoxic conditions. The other is shown by the knockdown of GRP78 or CHOP, which results in chemosensitivity. In addition, it is known that cancer cells display chronic ER stress markers (17). For example, increased Grp78 expression has been observed in malignant breast cancer and colon adenocarcinoma cell lines and in hepatocellular carcinomas (57). This high expression of Grp78 is thought to aid the survival of cancer cells and is important for drug resistance (58). However, proapoptotic CHOP as an opposite of the GRP78 is generally not expressed in tumor tissues because GRP78 acts to keep CHOP transcription at low levels (59, 60). Furthermore, it has been shown that in PERK-deficient cancer cells, the amount of angiogenesis is decreased, resulting in a smaller size of the tumor (61). Besides, XBP1 overexpression has been shown in different cancer types, including breast cancer and hepatocellular carcinomas (62). Therefore, these pathways are targeted for chemotherapy of different types of cancers (62). In contrast to these studies, a recent study has shown that UPR is downregulated in mouse prostate cancer models (63). This observation suggests that the role of ER stress in cancer is more complex than thought.

5. ER Stress and Pancreatic Cancer

The pancreas has both endocrine and exocrine parts. There are two types of tumors in pancreas depending on the affected part of the organ. Tumor formation in the exocrine pancreas is more frequent than that in the endocrine pancreas. In addition, the symptoms and cures are different. Pancreatic cancer is characterized by rapid invasiveness, progression, and profound resistance to treatment. Pancreatic cancer is slightly more common in women than in men and the risk increases with age. In addition, family history is an important risk factor (64). Pancreatic cancer has a very high rate of mortality because there are no effective therapies for this type of tumor at present. Pancreatic cancer often has poor prognosis, even when diagnosed early. Detection of pancreatic cancer in the early stages is very rare, which is a major reason why it is a leading cause of cancer-associated death. The reason for late detection is that the signs and symptoms may not appear until the cancer has reached an advanced stage. At this stage, surgical removal of the complete tumorigenic part is not possible (65).

Pancreatic epithelial cells have high hormone and enzyme secretion function. Therefore, it has highly developed ER (66). A previous study has shown that ER stress is involved in the induction of apoptosis in pancreatic cancer cells by capsaicin, which is a homovanillic acid derivative and used as an analgesic. It has been shown that capsaicin increases the expression of GRP78, PERK, eIF2α, ATF4, and GADD153 in tumor tissues. In addition, its effects on the induction of apoptosis and association with ER stress have been shown (65). Another treatment agent, bortezomib (a proteosome inhibitor), induces apoptosis in pancreatic cancer cells through ER stress process (67). A previous study that used bortezomib showed that there is an increase in the expression of CHOP and BIP but inhibition of PERK and phosphorylated eIF2α (67) and that bortezomib induces ER stress-mediated apoptosis in pancreatic cancer cell lines (68). Another study investigating the effects of different agents (such as quercetin, anticancer agents, and antiapoptotic agent) on pancreatic cancer cell line revealed that there is activation of PERK and an increase in the expression of Grp78/BiP and GADD153/CHOP (69). Therefore, there is a definite association between ER stress and pancreatic cancer; however, studies on this topic are not enough, necessitating further research in this field.

ER is a very important organelle because of its multifunctional properties. It is particularly important for tissues that have high protein synthesis and secretion potential. Abnormalities in ER function lead to ER stress, whose connection with a variety of diseases is already known. As a result of ER stress, UPR response is activated, which is an evolutionarily conserved homeostasis mechanism. This mechanism is well known, but there are some missing parts that need to be elucidated. It should be kept in mind that UPR has dual function in cell survival and cell death. There are several studies that target the relevant UPR pathway component for treatment of the associated disease. Besides some of these studies are hopeful. However, more studies are needed, particularly on pancreatic cancer treatment, that not only target the UPR pathway but also elucidate the general mechanisms. Worldwide, cancer treatment is improving, but pancreatic cancer still has a low cure potential with its insidious progress. Deeper understanding of the mechanisms and missing points of UPR and ER stress and the association with certain types of diseases will be important because it may provide novel therapeutic approaches.

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