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Cancer and ER stress: Mutual crosstalk between autophagy, oxidative stress and inflammatory response

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ABSTRACT

The endoplasmic reticulum (ER) acts as a moving organelle with many important cellular functions. As the ER lacks sufficient nutrients under pathological conditions leading to uncontrolled protein synthesis, aggregation of unfolded/misfolded proteins in the ER lumen causes the unfolded protein response (UPR) to be activated. Chronic ER stress produces endogenous or exogenous damage to cells and activates UPR, which leads to impaired intracellular calcium and redox homeostasis. The UPR is capable of recognizing the accumulation of unfolded proteins in the ER. The protein response enhances the ability of the ER to fold proteins and causes apoptosis when the function of the ER fails to return to normal. In different malignancies, ER stress can effectively induce the occurrence of autophagy in cells because malignant tumor cells need to re-use their organelles to maintain growth. Autophagy simultaneously counteracts ER stress-induced ER expansion and has the effect of enhancing cell viability and non-apoptotic death. Oxidative stress also affects mitochondrial function of important proteins through protein overload. Mitochondrial reactive oxygen species (ROS) are produced by calcium-enhanced ER release. The accumulation of toxic substances in ER and mitochondria in mitochondria destroys basic organelle function. It is known that sustained ER stress can also trigger an inflammatory response through the UPR pathway. Inflammatory response is thought to be associated with tumor development. This review discusses the emerging links between UPR responses and autophagy, oxidative stress, and inflammatory response signals in ER stress, as well as the potential development of targeting this multifaceted signaling pathway in various cancers.

1. Introduction

The endoplasmic reticulum (ER) is an organelle that forms a large membrane-like structure in its cytoplasm. The membranous structure of ER has a series of functions such as folding of newly synthesized proteins, maintenance of calcium homeostasis and phospholipid synthesis, and regulation of intracellular signaling pathways [1–3]. The structure of ER can be divided into a nuclear envelope domain, which is integrated in rough ER, and an ER domain for the synthesis of ribosomes. It also contains membranes, Golgi, vacuoles, mitochondria, peroxisomes, late endosomes and lysosomes, which act to promote lipid transfer to the membrane for calcium signal transmission [4]. ER is primarily used to transport and integrate proteins (secreted and membrane proteins, respectively), helping them to fold and transport (extracellular or cell membranes), lipid biosynthesis and maintenance of calcium homeostasis. In protein translation, ER is also a site that modifies N-linked glycosylation and is closely related to cellular signaling pathways [5–7]. For example, advanced ER stress hepatocytes have the function of reducing drug toxicity; the secreted proteins are synthesized in large amounts by abundant ER in other cells, and detoxification is exerted; sarcoplasmic reticulum as another special form of ER is more intramuscular cells in Exercise contraction and relaxation play a role [8]. Once the homeostasis is destroyed, the protein cannot be properly folded, including lack of molecular chaperone or cellular energy, as well as Ca^{2+} deficiency, redox environmental damage, protein variation and disulfide bond reduction [9]. Eukaryotic cells respond rapidly to ER dysfunction through a series of adaptive pathways called ER stress. And activate the unfolded protein reaction (UPR) [10,11].

The primary objective of UPR is to attenuate protein synthesis and recovery by modulating the cascade of ER-associated degradation (ERAD) systems encoding chaperone proteins, and the cascade of

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expression of the genes of the components via transcription factors. Cell homeostasis maintains cell survival and mechanical autophagy [16]. In addition, activation of UPR can trigger changes in intracellular mitochondrial function or autophagy, and can interfere with these processes by modulating UPR signals. Ubiquitin ligase controls the extent and duration of mitochondrial function during cellular stress [17]. On the other hand, the inflammatory response is the first reaction of the human immune system in the face of foreign body infection or tissue damage, which can protect the body from harm. However, when inflammation develops chronic and is incurable for a long time, it is harmful to the body. At the same time, a large number of studies have shown that inflammatory reactions also play an important role in the development of various malignant tumors such as hepatocellular carcinoma, lung cancer and breast cancer [12–14]. As the protein is out of control in more and more intracellular synthesis, the nascent polypeptide folds and unfolds in the lumen of the ER. Aggregation of misfolded proteins disrupts ER homeostasis and triggers UPR. Stress or UPR is not only essential for cell homeostasis and embryogenesis, but ER stress / UPR can trigger inflammatory responses in specialized cells and tissues, and is involved in the pathogenesis of inflammatory diseases [15]. In this review, we will summarize the effects of known ER stress and UPR unfolded proteins on cancer autophagy, oxidative stress and inflammatory response signaling pathways and related mechanisms, it also discusses how UPR combines with oxidative stress and inflammatory responses in cancer. Emphasize the importance of this process for cancer development during ER stress.

2. Unfolded protein response signaling pathway

Eukaryotic cells have evolved UPRs to ensure the authenticity and integrity of proteins when folded and to prevent unfolded or misfolded proteins from accumulating in the ER. UPR responds to cells by altering cellular transcription and translation programs. The stress state changes protein folding defects. The UPR signal consists of three major stressors located on the ER membrane: protein kinase R-like ER kinase (PERK), transcription factor 6 (ATF6), and inositol requiring enzyme 1α (IRE1α). At ER stress, these signaling pathways can attenuate protein translation processes and increase ER chaperones and protein degradation [12]. Interestingly, UPR in cancer cells requires maintenance of various stresses (including oxidative stress), and studies have shown that UPR signaling pathways are closely related to autophagy, apoptosis, inflammatory response and oxidative stress in tumor cells (Fig. 1). Therefore, UPR is currently considered to play a key role in tumor progression, metastasis, tumorigenesis and survival [13–15].

2.1. The PERK branch

PERK-(EIF2AK3) is a type I ER transmembrane protein with the N-terminus located in the ER cavity, which retains its interaction with Glucose regulatory protein 78(GRP78) and participates in the regulation of GRP78 dimerization. The C-terminus is located in the cytoplasm and contains its own phosphorylation site and a kinase domain with serine/threonine kinase activity [16]. In response to proteins accumulated in the ER lumen, PERK undergoes homodimerization after GRP78 activation and is activated by autophosphorylation. In addition, PERK is separated from kelch-like ECH-associated protein 1 (KEAP1) by nuclear translocation and activates phosphorylation of nuclear factor (erythroid-derived 2)-like 2 (NRF2) [17]. It is known to have a dual role in cancer, tumor suppression or functional and carcinogenic functions [18]. The interaction of NRF2 with can cause cytoplasmic activity to disappear when cellular stress has not yet occurred. When PERK phosphorylates NRF2, the originally interacting KEAP1 dissociates from NRF2, undergoes nuclear translocation, and activates the antioxidant gene [17,19]. The NRF2 target is closely related to redox homeostasis, and transcriptional and translational upregulation of the isoform NRF2 regulatory gene may be unrelated to classical oxidative stress, or at most transient low-level redox stress [20]. NRF2 and activating transcription factor 4 (ATF4) act synergistically as two different transcription factors because these genes are rich in AU elements in the promoter region, and NRF2 recognizes ATF4 after activation during ER stress. Also reported, PERK eukaryotic initiation factor 2 (eIF2α), phosphorylation of eIF2α is regulated to attenuate translation of its mRNA. These attenuated mRNA-encoded proteins are often associated with cell survival and proliferation [21].

The ATF4 gene is activated because the eIF2 kinase PERK and GCN2 selectively increase the translation of the ATF4 gene mRNA and induce the expression of the downstream gene C/EBP-homologous protein (CHOP)/GADD153, which enhances cell survival in an unstressed state. It plays an important role in the antioxidant response of cells and is mainly responsible for amino acid production and transfer [16]. ATF4 mRNA is an abnormal translation in the open reading frame of the 50-untranslated region, which is caused by phosphorylation of eIF2α, and only the termination of phosphorylation of eIF2α can be stopped [22,23]. ATF4 mRNA encodes a cyclic adenosine monophosphate (cAMP) response element that binds to transcription factors and activates many genes that play a role in amino acid metabolism, redox balance, protein folding, autophagy, and apoptosis [24,25]. Although ATF4 is an important gene for UPR to promote cell survival, it also plays an important role in the non-programmed death of cells through transcriptional upregulation of CHOP. The CHOP gene, in contrast to ATF4, has the effect of inhibiting cell growth and promoting DNA damage [26]. ATF4 is a key signal for ER stress-induced autophagy, and subsequent up-regulation of CHOP converts autophagy into apoptosis, the conversion of autophagy and apoptosis is between ATF4 and CHOP in the PERK pathway [27,28]. Induction of up-regulation of endoplasmic reticulum stress-related proteins ATF4 and CHOP induces autophagy in a variety of cancer cells [29,30]. In addition, CHOP knockout mice have a lower apoptotic rate for ER stress response [31]. This PERK-mediated translational blockade is also required for activation of nuclear factor-κB (NF-κB) in cancer cells [32].

2.2. The IRE1α branch

IRE1α is a type I transmembrane protein, identical to PERK. In the non-stress state, heat shock protein 90 (Hsp90) and heat shock protein 72 (Hsp72) bind to the IRE1α cytosol domain. Dynamic regulation of the folding capacity of the endoplasmic reticulum reduces the burden of ER protein folding by temporarily slowing down translation and accelerating protein efflux [33]. Homologous oligomerization of activated IRE1 activates the endo-ribonucleic acid domain by opening the Ser/Thkeinase domain at the carboxy-terminal end of the cytoplasm and reacting it with autophosphorylation [34,35]. Expression of IRE1β is restricted to epithelial cells of the intestine and lung. Most studies have focused on the functional mechanisms of IRE1α. After ER stress, unfolded and misfolded proteins bind, separate from binding immunoglobulin protein (BiP), release IRE1α, membrane fluidity affects oligomerization and autophosphorylation of PERK and IRE1α, and IRE1α endonuclease activity after oligomerization is activation [36,37]. The activated IRE1α cleaves the X-box binding protein 1 (Xbp1) mRNA into the nucleus to regulate the target gene, and removes the 26-base intron in the cytoplasm to produce a translational frameshift and a transcriptionally active Xbp1s. A gene regulated by the IRE1α-XBP1 signal, which enhances protein folding, transport and ERAD functions, and resolves protein misfolding [38,39]. When ER stress occurs, IRE1α is rapidly activated, and when ER stress is changed to chronic, the signal of IRE1α is weakened [40,41]. Attenuation of the IRE1α-XBP1 signal under sustained ER stress conditions may involve dephosphorylation, ubiquitination and degradation. Protein disulfide isomerase A6 (PDIA6) attenuates the conduction of IRE1α signaling by correlating with disulfide bonds [42]. In addition, pXBP1(U) acts as a negative regulator of the UPR-specific transcription factor ATF6, pXBP1(S) [43]. This may be a signal to block survival during chronic ER

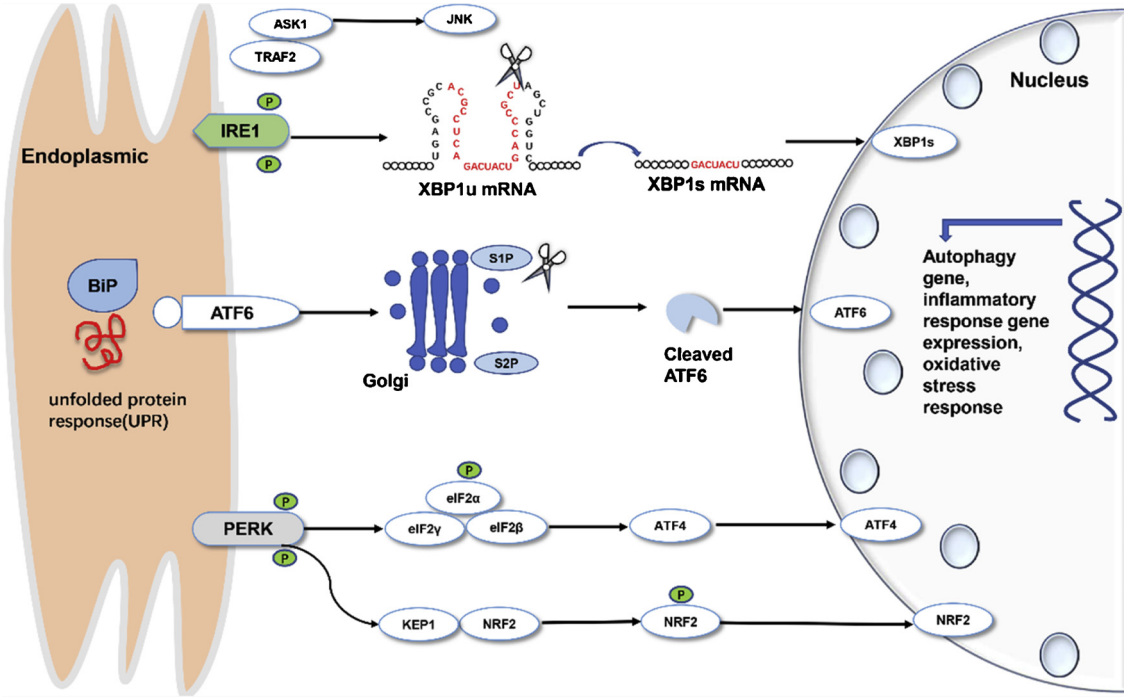

Fig. 1. Membranes and secreted proteins are synthesized by ER and translocated into ER lumen. Accumulation of unfolded proteins in the ER lumen results in activation of the UPR response in ER stress, dissociation of UPR sensors PERK, ATF6 and IRE1. PERK activates the cytosolic domain by dimerization and autophosphorylation. PERK phosphorylation of eIF2a inhibits general protein synthesis and promotes translation of ATF4 mRNA. The active PERK also phosphorylates NRF2, and the phosphorylated NRF2 dissociates from KEAP1 and translocate to the nucleus. IRE1 contains an endoribonuclease domain that is activated by dimerization and autophosphorylation. After IRE1 is activated, the unspliced XBP1 u mRNA is processed, and the spliced XBP1s mRNA is translated into an active transcription factor. IRE1 also activates the kinase domain of TRAF2 and ASK1, resulting in activation of JNK. ATF6 is activated and translocated to the Golgi apparatus, and is cleaved by site 1 and site 2 proteases (S1P and S2P) in the Golgi apparatus, and the cleaved ATF6 translocate to the nucleus.

stress. In addition to activating ribonuclease activity, cytoplasmic receptor-associated factor 2 (TRAF2) of IRE1 is known to interact with tumor necrosis factor-alpha (TNF-alpha) to activate c-Jun N-terminal kinase (JNK) [44]. This is one of the signaling pathways that activates the NF-κB pathway under ER stress [45].

2.3. The ATF6 branch

ATF6 is a member of the type II transmembrane receptor and the leucine zipper protein family, with its N-terminal DNA binding domain in the cytoplasm and its C-terminal domain in the ER lumen. [46]. The mutant ATF6, which represents the cytoplasmic region, translocates into the nucleus. After ER stress, GRP78 is isolated from ATF6 and two Golgi localization signals appear. ATF6 interacts with the protein transport vesicle coat protein COPII, resulting in translocation of ATF6 to Golgi. Processing and activating the transcription of the endogenous GRP78 / BiP gene [47]. In the Golgi, ATF6 protein is cleaved by site 1 protease (S1P) and site 2 protease (S2P), resulting in the release of ATF6 functional including basic region-leucine zipper (bZIP) fragments into the cytoplasm, followed by transfer of the fragment into the nucleus to initiate transcription [48]. Interestingly, S1P and S2P also cleave sterol regulatory element binding proteins (SREBPs), an ER-related protein involved in the processing of fatty acids and cholesterol [17].

ATF6 enhances the transcription of XBP1 mRNA and cooperates with IRE1 to produce a spliced, active transcription factor XBP1s mRNA [46]. XBP1 binds to ATF6 and produces three elements, the cis-acting response element, the ER stress response element (ERSE) and the UPR element (UPRE), which are used to enhance the expression of the ER-localized chaperone protein [49]. Contrary to the ability of XBP1 to activate UPRE, the expression of ATF6 alone is enhanced to enable complete transcription of ERSE [49]. In addition, activation of ATF6 can modulate miRNA to reduce the extent of ER stress. The cleaved ATF6 and active XBP1 isoforms induce transcription of the ER chaperone gene, promote protein folding, and increase the enzymes required for secretion and ER-related protein degradation in parallel pathways [50,51]. ATF6 has two types of ATF6α and ATF6β. Cleaved ATF6α is able to increase the transcription of the ER protein misfolding ability and the transcription of the Xbp1 expressing gene [52,53], whereas ATF6β acts as a repressor of ATF6α-mediated transcription and function. Some studies suggest that, ATF6α promote the development of hepatocellular carcinoma by adjusting hepatocellular carcinoma associated with ER stress gene targeting [54]. A missense polymorphism of ATF6 gene increases mRNA expression of ATF6 and its downstream genes, and is associated with susceptibility to hepatocellular carcinoma [55]. In addition, PERK-eIF2α signaling promotes the synthesis and trafficking of ATF6α to emphasize ATF6α signaling [56].

2.4. Unfolded protein response and cancer

The UPR response triggered by ER stress was originally thought to be a self-regulating way to protect cells from irreversible damage [57,58]. When the damage exceeds the body's own tolerance, the UPR will signal a self-destruction to remove bacteria and prevent further damage. The metabolic state of cancer is highly proliferating and metastasis in a hypoxic, low glucose, abnormally vascularized microenvironment [59]. Under hypoxic conditions, the demand for protein synthesis in cancer cells is significantly lower than that of normoxic cells, which leads to a decrease in the demand for oxygen and energy, which leads to a decrease in adenine nucleoside triphosphate (ATP), accompanied by a decrease in protein translation rate, which is unfavorable for cancer cells. Maintaining high proliferation under conditions is essential [60]. In an anoxic environment, the UPR reaction is activated [61,62]. The extent of the UPR response depends on the stress

conditions and the severity of the unfavorable factors. The UPR signaling pathway can be divided into two types to protect cells from damage or induce apoptosis [63,64]. Apoptosis is closely related to UPR response. In the development of malignant tumors, immune cells and endothelial cells serve as two cell types that support tumor growth in the tumor microenvironment when cancer cells proliferate and differentiate [65,66]. The UPR reaction stimulates tumor cells to secrete metalloproteinases that bind to specific cytokines such as angiogenic factors. In addition to the intrinsic factors, the highly proliferative properties of cancer cells can activate the UPR response by disrupting the folding of ER proteins, allowing cancer cells to continue to grow in nutrient-deficient environments [67]. Numerous studies have shown that malignant tumor growth, invasion and angiogenesis are associated with activation of the UPR signaling pathway leading to eIF2α phosphorylation. It has been reported that in different types of cancer, cells in primary tumors are able to up-regulate the UPR signaling pathway, while healthy tissue surrounding the tumor does not [54]. Moreover, the hypoxic environment of malignant tumors favors the expression of eIF2α phosphorylation [68], and the activation of ATF4 downstream of its signaling pathway weakens the ability of tumor cells to translate their own proteins, selectively inducing mRNA only [69].

3. ER stress regulates autophagy and mitochondrial and lysosomal dysfunction in cancer

3.1. ATF6 pathway and autophagy

Autophagy controls the quality of proteins and organelles by digesting cellular components and recovering nutrients [70]. Activation of autophagy-related genes (ATG) is caused by stress, nutrients, oxygen and energy deficits. The mammalian target of rapamycin (mTOR) pathways stimulate the synthesis of ATG proteins through signaling, thereby activating autophagy and producing autophagosomes [71,72]. It has also been reported that the PI3K-Akt-mTOR signaling pathway is associated with endoplasmic reticulum (ER) stress [73]. Down-regulation of ATF6α or Ras homolog enriched in brain (Rheb) restores the resistance of dormant tumor cells to rapamycin, an autophagy inducer, indicating that autophagy is regulated by targeting survival signals in tumor cells via the ATF6α-Rheb-mTOR pathway [74]. In studies of malignant osteosarcoma (OS), activation of ATF6α was found to significantly enhance chemoresistance of the mTOR inhibitor rapamycin. This occurs by inhibiting Bax activation, inhibiting RHEB-mTOR signaling. ULK / ATG13 / FIP200 complex is required for the induction of autophagy in osteosarcoma and NIH3T3 cells [75]. ULK1, Atg13 protein and FIP200 regulate autophagy by activating mTORC1 phosphorylation [76]. UNC-51-like kinase 1 (ULK1) triggers autophagy, and ULK1 is down-regulated in triple-negative breast cancer (TNBC), and ULA complex (ULK1-mATG13-FIP200-ATG101) induces autophagy [77]. In addition, down-regulation of DAPK1 expression was detected in cells knocked out of ATF6, affecting the expression of Atg9 to regulate autophagy flux [78,79]. Death-associated protein kinase (DAPK) is a metastasis-inhibiting factor that has a mechanism of inhibiting tumor metastasis, which mediates apoptosis and autophagy [80]. At the same time, ATF6-mediated up-regulation of CHOP also contributes to ATF6-induced autophagy [81]. In conclusion, autophagy induced by the ATF6 signaling pathway in endoplasmic reticulum stress in cancer is complex and diverse.

3.2. IRE1α and autophagy

ER stress can trigger autophagy in certain pathological conditions. Several studies have shown that endoplasmic reticulum stress increases lysosomes necessary for autophagy and up-regulates membrane-bound LC3-II expression in various cancers [82]. In a study of IRE1α-PERK-ATF6-deficiency in endoplasmic reticulum stress, autophagy was suppressed in the IRE1α signaling pathway, but not in the PERK and ATF6 pathways. This suggests that the IRE1α signaling pathway is closely related to ER stress-induced autophagy. Furthermore, regulation of autophagy requires the kinase domain of IRE1α, and the kinase activity of IRE1α activates the JNK pathway, Apoptosis signal-regulated kinase (ASK1) is a downstream signaling molecule of TNF receptor associated factor 2(TRAF2), which is required for sustained activation and apoptosis of JNK/p38 MAP kinase [83]. so studies have found that ER stress-induced autophagy is affected by the IRE1-TRAF2-JNK pathway [84]. Interestingly, ER stress-induced autophagy not only inhibits tumor progression, but other studies suggest that endoplasmic reticulum stress-induced autophagy protects cells in cancer [85]. In breast cancer cells, the endoplasmic reticulum stress-inducing agent tunicamycin (TM) increases the misfolded protein response, activates the endoplasmic reticulum stress-mediated protective mechanism, and regulates parallel via the IRE1 / JNK / beclin-1 pathway. Inducing autophagy and apoptosis [86]. Furthermore, we demonstrate that overexpression of Secreted protein acidic and cysteine rich (SPARC) induces IRE-JNK activation leading to induction of the transcription factor CHOP. Inhibition of ER stress (or JNK activation) leads to inhibition of autophagy-mediated apoptosis [87]

3.3. PERK pathway and autophagy

Autophagosomes have the function of capturing damaged proteins and organelles, and the autophagosome marker protein LC3-II converts LC3-I, which blocks autophagosomes and captured organelles and proteins. p62, another marker protein of autophagy, has been shown to reduce expression with induction of autophagy [88]. When autophagosomes are fused to lysosomes, LC3-II, which is located in autophagy, is degraded and the outside is cleaved by ATG4. Autophagosomes are broken down in lysosomes [71]. In studies on tumor cell BC3, ERstress-induced autophagy flux is regulated by the PERK-elF2α − CHOP pathway [89]. It was found that polyQ72 aggregates can up-regulate autophagy proteins ATG12 and CHOP to induce autophagy, and inhibition of eIF2α phosphorylation can down-regulate its expression. This suggests that ER stress-induced autophagy is mediated through the PERK pathway [90]. This view was confirmed in a large number of cancer research [91,92]. For example, in studies of neuroblastoma, ER stress causes mitochondrial dysfunction by activating eukaryotic initiation eIF2α. PLX4720 is an inhibitor of B-Raf that upregulates the PERK pathway in melanoma cells to activate ER stress-induced autophagy flux [93]. Cancer cells knocked out of the ATG5 gene have increased responses to ER stress, suggesting that inhibition of autophagy increases the extent of ER stress in cancer cells [84]. Activation of ER stress-induced autophagy by B-Raf inhibitor PLX4720 enhances apoptosis [93]. Studies have shown that autophagy induction in cancer may be helpful for cancer treatment. In a study of melanoma, small molecule HA15 was induced to induce apoptosis and autophagy in vivo and in vitro by targeting GRP78, a marker protein that activates endoplasmic reticulum stress. The occurrence of autophagy is accompanied by aggregation of vesicles and conversion of LC3-I to LC3-II and formation of autophagosomes. The therapeutic efficiency of HCA15 on melanoma cells decreased with decreasing levels of autophagy and apoptosis, suggesting that autophagy can inhibit tumors. CHOP mediates autophagy and apoptosis in HA15-induced endoplasmic reticulum stress [91]. It is demonstrated that the PERK-induced autophagy of the UPR has different roles in regulating the survival dependence of cancer cells (Fig. 2).

3.4. ER stress-mediated mitochondria and lysosomal dysfunction

It has been observed that approximately 5–20% of the mitochondrial surface is in direct contact with ER [94,95]. The close contact site between ER and mitochondria is called the mitochondria-associated ER membrane (MAM). This subdomain of ER directly promotes biogenesis through the synthesis of phospholipids and sphingolipids. Interestingly,

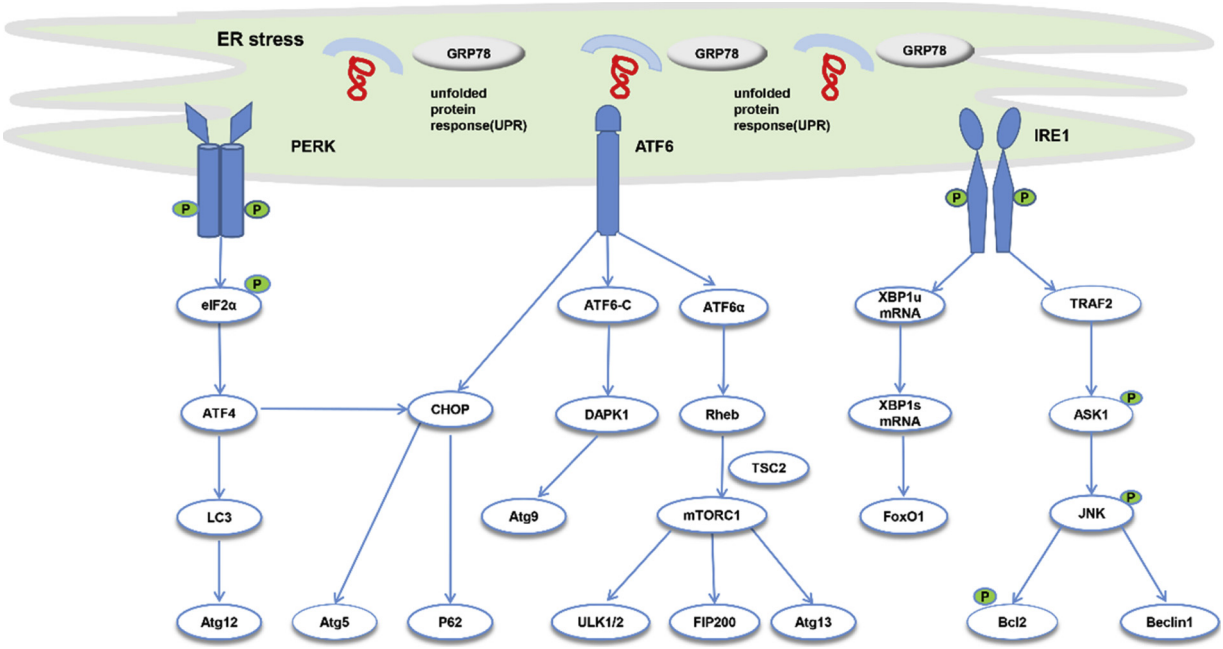

Fig. 2. The UPR response induces autophagy through multiple pathways in ER stress. In the PERK branch, PERK affects the phosphorylation of eIF2α by autophosphorylation, activating the non-canonical translation of the transcription factor ATF4. ATF4 can transcriptionally upregulate LC3 and ATG12, and ATF4 can also transcriptionally upregulate another transcription factor called CHOP. CHOP can transcriptionally upregulate ATG5 and P62. In the ATF6 branch, the cleavage of ATF6 induces DAPK1 expression, which in turn affects autophagy flux through ATG9, while ATF6α activates TSC via the Rheb-mTOR signal, thereby inhibiting mTORC1 and activating ULA complexes (ULK1-mATG13-FIP200-ATG101)) induce autophagy. IRE1 can splicing XBP1 mRNA, which affects the binding of acetylated cytoplasmic FoxO1 to ATG7, which can promoteAutophagy responds to stress and causes cell death. IRE1α phosphorylates Bcl-2 / Bcl-XL and inhibits their binding to Beclin1 by activating TRAF-ASK1-mediated JNK activation.

when mitochondrial dysfunction, most cancer cells show characteristic changes in lipid-free biosynthesis, lipogenic phenotype, and lipid metabolism [96]. Therefore, current reports have suggested that mitochondrial and lysosomal dysfunction and ER stress-related pathways involve tumorigenesis, migration, invasion and survival. Mitochondrial dysfunction has also been shown to serve as a platform for a variety of cellular signaling pathways, including oncogenic signaling [97]. In cancer background studies, Honokiol induces apoptosis in human chondrosarcoma cells through mitochondrial dysfunction and ER stress [98]. Norcantharidin-induced apoptosis in human renal cancer cells is dependent on ER stress and mitochondrial dysfunction [99]. In addition, Tubeimoside-1 exerts cytotoxicity in HeLa cells through mitochondrial dysfunction and ER stress cell death pathways [100]. It has also been found that lysosomal dysfunction enhances oxidative stress-induced apoptosis through accumulation of ubiquitinated proteins in HeLa cells [101].

4. ER stress-mediated oxidative stress and inflammatory responses in cancer

4.1. Endoplasmic reticulum stress and oxidative stress

During the accumulation of misfolded proteins in the ER lumen, the UPR response promotes the production of reactive oxygen species (ROS) in the endoplasmic reticulum, which oxidizes to form a disulfide bond that crosslinks the protein and inactivates the enzyme. Oxidative stress is caused by the imbalance of antioxidant mechanisms and ROS during stress and injury in cells [102]. Oxidative stress is insufficient in the body's antioxidant activity, ROS accumulation and oxidation reaction. Cells regulate the levels of superoxide dismutase (SOD), glutathione (GSH) and vitamins through enzymatic and non-enzymatic reactions, reducing ROS production and achieving antioxidant goals [103,104]. Under normal conditions, folding proteins in the ER is a multi-step critical process, and the formation of disulfide bonds requires an oxidative folding environment. In an abnormal state, the body recognizes a defective disulfide bond, and glutathione (GSH) reduces the formation of disulfide bonds, resulting in a decrease in the ratio of reduced glutathione/oxidized glutathione (GSSH). Increase the load of protein folding in ER, increase the ROS content of diseased cells and cause ROS accumulation [105]. When the redox is unbalanced, the antioxidant mechanism is impaired, leading to oxidative stress. Next, we will discuss how ER stress mediates oxidative stress through ROS, thereby causing apoptosis in malignant tumor cells.

Studies have reported that ROS-mediated endoplasmic reticulum stress PERK expression is down-regulated in breast cancer MDA-MB468 cells. And down-regulation of PERK expression may inhibit ROS-induced ER stress and lead to cancer cell apoptosis [106]. AP-1 / c-Jun is activated by nuclear translocation of ATF6 in ER stress and induction of ROS production in human cervical cancer HeLa cells. Moreover, c-Jun (siRNA) is capable of inhibiting the activity of the molecule caspase-3 / -7 necessary for apoptosis [107]. This indicates that ER stress and ROS-induced c-Jun are activated and regulated in HeLa cells, leading to apoptosis. It was found in breast cancer MDA-MB-231 and MCF-7 cells that ROS-induced JNK activation can induce apoptosis through mitochondrial membrane depolarization [108]. In addition, antioxidant N-acetyl cysteine (NAC) restored novel polyphenol conjugate DPP-23 depleted GSH content in pancreatic cancer MIAPaCa-2 cells, It was further verified that DPP-23-induced cell apoptosis is closely related to oxidative stress. It also shows that oxidative stress is an upstream event of endoplasmic reticulum-induced apoptosis [109]. In carnosic acid-treated cancer cells, enhanced ER stress is associated with increased ROS and GSH consumption. Replenishing GSH pools significantly scavenged ROS and rescued the cells [110]. In addition, the use of bortezomib and dipyridamole in the treatment of leukemia and lymphoma cells found that GSH and ROS levels were significantly elevated [110]. Recently, it was found that IRE1-mediated JNK activation is elevated in ovarian cancer SKOV3/DDP cells and induces apoptosis, and activation of JNK is associated with oxidative stress [111]. Peroxiredoxin 4

(PRDX4) is an enzyme that reduces intracellular reactive oxygen species ROS and has been found to promote protein folding in the endoplasmic reticulum [112]. B cell-specific transcription factor (BACH2) has been reported to be a transcriptional repressor that inhibits the expression of SOD nuclear catalase (CAT) by inhibiting nuclear accumulation of Bcl-2 in lymphoma cells and inhibits the expression of the anti-apoptotic gene Bcl-2 regulates apoptosis [113]. In addition, it has been reported that ER stress-related factors GRP78 and CHOP are associated with increased expression of NRF2 pathway-mediated oxidative stress in bladder cancer T24 cells [114]. The above studies indicate that ER stress and oxidative stress play an important role in the development of nausea. Depending on ER stress, different signaling pathways mediate ROS levels and oxidative stress, and induction of apoptosis may be one of the effective methods in cancer therapy.

4.2. Molecular mechanism of ER stress-mediated inflammatory response

Studies have shown that in the inflammatory response, a variety of pro-inflammatory molecules are closely related to the unfolded protein response (UPR), including interleukin 8 (IL8), interleukin 6 (IL-6), Monocyte chemoattractant protein 1 (MCP-1) and Tumor necrosis factor-α (TNF-α) [115]. Recent studies have shown that the three branches of UPR in ER stress, PERK, IRE1α and ATF6, cross-talk with transcription factors NF-κB and activator protein 1 (AP-1) mediated inflammatory response signaling pathways. NF-κB mediates inflammatory responses and plays an important role in cell proliferation, differentiation, and apoptosis [116,117]. NF-κB activation may be controlled by all three UPR branches, but AP-1 is also different [117]. In addition, in addition to pro-inflammatory approaches based on individual transcription factors, the UPR signaling pathway can also lead to highly complex inflammatory processes called acute phase response (APR) [117]. In the following sections, we discuss the complex mechanisms of ER stress-induced UPR signaling and NF-κB inflammatory signaling pathways, activation protein 1 (AP-1) and APR activation crosstalk (Fig. 3).

NF-κB is a dimeric protein and the NF-κB protein subunit carries the Rel-homology domain (RHD), which contains a nuclear localization sequence (NLS). RHD is an important component of NF-κB because it plays a role in sequence-specific DNA binding, dimerization, and interaction with inhibitory IκB proteins. p65 / RelA, c-Rel and RelB contain a transcriptional activation domain (TAD) beyond the RHD at the extreme carboxy terminus and are responsible for the transcription of the NF-κB target gene. Due to the lack of TAD, the NF-κB dimer consists only of p50 and p52 subunits that inhibit transcription, possessing nuclear localization and DNA binding. IκB protein is a specific inhibitor of NF-κB, which interferes with the domain function of NLS and affects its nuclear translocation. IκB is isolated in the cytoplasm and induces autophosphorylation by signaling in an inactive form, degrading subsequent protein body activation of IKK [118]. IKK is mainly used for nuclear transcription of p65-containing heterodimers. Degradation of IκB leads to the release of NF-κB, which translocates to the nucleus, binds to DNA, and transcribes its specific gene program [119]. After degradation of IκB, the transcription factor NF-κB can be activated, and NF-κB translocates to the nucleus and binds to and encodes DNA of a specific gene [120]. ER stress activates IRE1 kinase activity and activates the recruitment protein TRAF2 to indirectly activate JNK and IKK to initiate downstream signaling pathways. Determine cell survival or death [121]. Multiple negative TRAF2 with a truncated N-terminal RING effector inhibits JNK activation and induces NF-κB activation via IRE1α [122]. It has been reported that ER stress inducer thapsigargin induces IRE1 formation complex through TRAF2, promotes degradation of IκBα in NF-κB nuclear translocation, and activates NF-κB signaling pathway. IRE1α-TRAF2 induces NF-κB activation by down-regulating TRAF2 and up-regulating TNF-α. Furthermore, down-regulation of TNF-α has been shown to affect the level of activation of NF-κB and JNK and trigger TNF-α induced apoptosis [123]. On the one hand, PERK in another branch of ER stress may induce the expression of NF-κB signaling pathway mainly through eIF2α-mediated translational

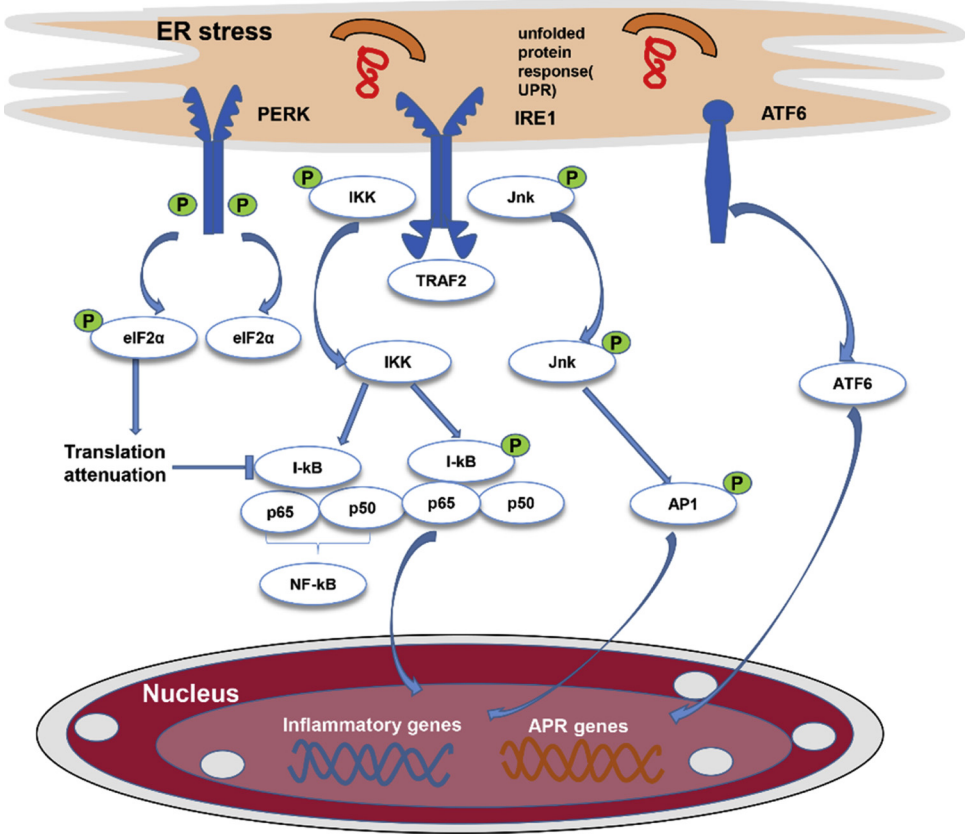

Fig. 3. NF-κB activation associated with ER stress. ER stress-induced IRE1α kinase activity activates adaptive or protein tumor necrosis factor-alpha (TNF-alpha) receptor-associated factor 2 (TRAF2), further recruits c-Jun N-terminal kinase (Jnk) to activate several transcription factors and many cells apoptosis induces the expression of inflammatory genes by phosphorylating transcription factor activator protein 1 (AP1). TRAF2 is associated with IκB kinase (IKK), which activates NF-κB by promoting degradation of IκB, resulting in nuclear translocation of NF-κB. The PERK branch of UPR is attenuated by eIF2a-mediated translation; continuous inhibition of IκBa synthesis. CREBH and ATF6 can dimerize and synergistically activate transcription of major APR genes, inducing systemic inflammatory responses in specific cells.

decay, which in turn inhibits the synthesis of IκBα. IKBα has a function of promoting nuclear translocation of NF-κB and activating its target gene [124]. It has also been reported that the initial breakdown of GRP78 causes UPR to trigger transient Akt phosphorylation and subsequent NF-κB activation, which is associated with another branch of ER stress, ATF6. Moreover, dominant negative inhibition of IRE1α, XBP1 or PERK does not attenuate the activation of NF-κB. It is clear that there may be significant overlap between these different UPR branches in terms of activation of the NF-κB inflammatory pathway.

Another inflammatory regulatory transcription factor that is activated by ER stress-induced UPR signaling is AP-1. AP-1 is a dimer composed of a homodimer or a heterodimer. The specific combination of its complexes determines the type of ER stress and inflammation. The IRE1-TRAF2 complex activates the JNK pathway, resulting in AP1-mediated transcriptional activation of pro-inflammatory genes [125]. In oral squamous cell carcinoma, shRNA-XBP1 induces IRE1α-TRAF2-ASK1 signaling activation to activate pro-apoptotic ASK1-JNK signaling and promote Tca8113 cell apoptosis [126]. Ubiquitination and translocation of TRAF2 are required for activation of JNK. Studies have reported that caspase-8/FLICE inhibitory protein viral FLICE-Inhibitory Protein (vFLIP) activates the JNK/AP1 pathway and is a TRAF-dependent fashion. Since vFLIP also activates the nuclear factor kappaB (NF-κB) signaling pathway, both NF-κB and JNK/AP1 pathways regulate the expression of the proinflammatory factor IL-6 [127]. In addition, transglutaminase 2 (TG2) up-regulates the pro-inflammatory activation of THP-1 monocytes induced by the AP1 / JNK signaling pathway [128]. This suggests that there may be some crosstalk between the IRE1 signaling pathway of ER stress and the JNK/AP1 inflammatory pathway.

It is also worth noting that there is also an activation of the acute phase response APR associated with UPR, which is activated primarily after infection, trauma, inflammation and the onset of some malignant diseases. The cAMP response element-binding protein H (CREBH) and ATF6 can dimerize and synergistically activate transcription of major APR genes, inducing systemic inflammatory responses [129]. In the presence of ER stress, intracellular protein hydrolysis (RIP) is regulated by ATF6 and CREBH, and during proteolysis, S1P protease and S2P protease are responsible for cleavage of their functional isoforms of ATF6 and CREBH. The cleaved ATF6 and CREBH fragments are capable of transferring into the nucleus to induce transcription of the APR gene [130].

4.3. UPR-mediated inflammatory response in cancer

Chronic inflammation is thought to provide assistance at all stages of tumor development. Tumor production can be promoted by increasing the mutation rate of cancer cell genes and the instability of gene expression. Mismatch repair of inactivated response genes may be associated with inflammation induction [131]. In addition, the inflammatory factor NF-κB, STAT3 or AP-1 mediates the upregulation of activation-induced cytidine deaminase (AID), thereby inducing a genomic increase in mutation probability [131,132]. The cytokine IL-6 plays a key role in the growth, survival and metastasis of tumor cells by indirectly infiltrating the immune/inflammatory cells of the tumor microenvironment or directly by cancer cells. These receptors are usually upregulated in various cancer cells. Therefore, cancer cells promote tumor growth and metastasis by promoting the expression of these cytokines [133]. UPR-driven ER stress is thought to be closely related to inflammatory responses. Prostate cancer is one of the common malignant tumors in older men. Chemotherapy is an effective treatment for metastatic castration-resistant prostate cancer, but most patients will develop drug resistance after 6–8 cycles of systemic chemotherapy, with a median survival of less than 1 year [134]. Studies have shown that induction of ER stress can enhance the cell killing efficacy of the anti-prostate cancer drugs paclitaxel and docetaxel [135]. Chronic inflammation of the prostate has potential stimulation of the development and progression of prostate cancer through inflammatory pathways and cytokines [136]. It has been reported that ER stress response in mouse and human prostate cancer cells drives the production of Lipocalin 2 (Lcn2) in NF-κB-dependent factors, and that reducing UPR significantly reduces Lcn2 transcription and translation [137]. It has also been found that prostate cancer (TRAMP) C1 transgenic mice spontaneously undergo ER stress during tumor growth and activate IL-6, interleukin 23p19 (IL-23p19) and TNF-α proinflammatory cytokine transcriptional pathway [138]. Furthermore, in renal cell carcinoma, the PERK-driven ER stress response induces the expression of the tumorigenic cytokines IL-6 and IL-8. TNF-α and TRAF2-mediated NF-κB survival programs protect tumor cells from cell death [139]. Expression and epigenetic inactivation of the tumor suppressor gene von Hippel-Lindau (VHL) is a major cause of clear cell renal cell carcinoma (ccRCC), which may be derived from chronic inflammation. It has been reported that in renal cells in which VHL function is lost, the ER stress markers of BiP and XBP1 in the IRE1α branch of UPR are significantly increased [140]. Based on various studies, it can be reasonably assumed that ER stress or ER stress or inflammation driven by UPR is activated in the tumor microenvironment. UPR-mediated inflammation may be one of the factors that promote tumorigenesis.

The above discussion suggests that ER stress-induced inflammatory responses support tumor growth. However, recent studies have shown that ER stress-induced inflammatory responses can inhibit tumor growth. Colon cancer is the third most common type of tumor in the world. Early cancer produces no symptoms and because many of the-symptoms are non-specific. In cancer classification, grade 1 colon cancer is less invasive than other cancers, and the 5-year survival rate is between 59% and 93%, while grade 2 and Grade 3 colon cancer was reduced to 33%–75% and 11%–56% respectively. The chemotherapy effect was not significant, and the risk of recurrence within 3 years of cancer was high [141]. Ulcerative colitis is considered to be one of the main factors in the development of colon cancer. The proinflammatory cytokines PYCARD, caspase-1 and NACHT, LRR and PYD domains-containing protein 3 (NLRP3), which are important components of inflammation, are resistant to colon cancer development [142]. In addition, an increase in APR neutrophils may enhance immunity against tumor development. Studies have shown that dendritic cells (DC) are affected by neutrophil enlargement from maturation, increasing the secretion of beneficial cytokines and chemokines [143,144]. Therefore, although ER stress-induced inflammation is associated with tumor growth-promoting factor, ER stress may have anti-tumor immunity. ROS-based ER stress or ER stress associated with ROS production can help resurrection anti-tumor immunity by inducing apoptosis of immunogenic cells in cancer cells.

5. Conclusion

As a dynamic organelle that maintains cell homeostasis, the endoplasmic reticulum has a key pathway that can determine cell fate. Under normal conditions, ER is involved in protein folding and degradation, and maintains homeostasis by regulating transcription factors such as ATF6, XBP1, and ATF4. If the balance is not maintained, the endoplasmic reticulum affects cell survival and death by activating the UPR unfolded protein response. Under pathological conditions, ER stress is associated with several metabolic diseases such as cardiovascular disease, diabetes, and cancer. UPR is the basis of the pro-apoptotic mechanisms of certain anti-cancer patterns. Both autophagy and UPR signaling pathways are thought to be a strategy for cell self-protection; however, if the intensity or duration of cellular stress increases, these pathways will instead activate the mechanism of cell death.

However, the molecular mechanism of ER stress activation is not simple, involving signaling pathways that have cellular autophagy and oxidative stress and inflammatory responses. Therefore, decoding how the ER stress pathway signals cellular autophagy and inflammatory

responses or preventing it is a major challenge for future research and will require the definition of the rationale for drug design and application. From this perspective, small molecule inhibitors of the kinase component of UPR, such as PERK and IRE1, are promising candidates. The challenge of cancer treatment will include the development of drugs that target the cytoprotective function of UPR while remaining intact or promoting its promoting function. In addition, in the past few years, some studies have demonstrated that ER stress is closely related to and/or affects inflammation and immune responses, and can affect the immunogenicity of cell death processes triggered by certain anticancer therapeutics or modalities. Therefore, in the future, it seems important to integrate the inflammatory/immune potential of the ER stress/UPR pathway with the current treatment (cell killing) paradigm. This will provide a new strategy for anti-tumor treatment.

Please indicate each author's contribution(s) to the manuscript, using the numbered list below:

Author's contribution

YanFei Wei: Critical revision of the article and Final approval of article.

Yuning Lin: Writing the article and Other (please specify).

Jiang Mei: Writing the article and Other (please specify).

Wanjun Chen: Final approval of article.

Tiejian Zhao: Other (please specify).

Declaration of Competing Interest

All authors declare no conflict of interest.

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