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REVIEW

Endoplasmic reticulum stress-mediated cell death in cardiovascular disease

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Abstract
The endoplasmic reticulum (ER) plays a vital function in maintaining cellular homeostasis. Endoplasmic reticulum stress (ERS) can trigger various modes of cell death by activating the unfolded protein response (UPR) signaling pathway. Cell death plays a crucial role in the occurrence and development of diseases such as cancer, liver diseases, neurological diseases, and cardiovascular diseases. Several cardiovascular diseases including hypertension, atherosclerosis, and heart failure are associated with ER stress. ER stress-mediated cell death is of interest in cardiovascular disease. Moreover, an increasing body of evidence supports the potential of modulating ERS for treating cardiovascular disease. This paper provides a comprehensive review of the UPR signaling pathway, the mechanisms that induce cell death, and the modes of cell death in cardiovascular diseases. Additionally, we discuss the mechanisms of ERS and UPR in common cardiovascular diseases, along with potential therapeutic strategies.

Keywords Endoplasmic reticulum stress · Unfolded protein responses · Cell death · Cardiovascular disease · Therapeutic strategies

Introduction

The endoplasmic reticulum (ER) is a vital membrane organelle, which exhibits a characteristic tubular structure. The ER functions include protein synthesis, folding, translocation, calcium homeostasis, and lipid biosynthesis.[1] The ER plays a crucial role in protein quality control and supporting cellular activities.[2,3] Disruption of ER homeostasis due to physiological or pathological stimuli leads to the accumulation of misfolded and unfolded proteins, initiating *endoplasmic* reticulum stress (ERS) and triggering the unfolded protein response (UPR).[4] In the short term, the UPR serves as an adaptive response, enhancing the cell's capacity to handle ERS and restore ER homeostasis through protein processing, thereby promoting cell survival.[5] However, prolonged ERS surpasses the adaptive capacity of the UPR, causing terminal UPR activation that triggers cell death through various pathways.[6] Dysfunction or loss of function of the ER affects cell survival and death, thereby influencing the development of cardiovascular disease.[7] Extensive research indicates a strong association between ERS and cardiovascular ailments such as hypertension, atherosclerosis, and heart failure (HF).[8] Stress, ischemia, and injuries to the heart commonly trigger ERS-induced UPR, resulting in varying degrees of cardiac damage and pose significant risks to human health.[9] Given that cardiomyocytes possess limited replicative potential as terminally differentiated cells, maintaining protein homeostasis is critical for their function and survival.[10,11] Inhibiting ERS and preserving cardiac protein homeostasis represent new therapeutic strategies for promoting heart health and combating heart disease.[12] In this paper, the main signaling pathways and molecular mechanisms of ERS-induced UPR are reviewed comprehensively. We outline pathways and regulatory roles linking ERS to distinct forms of cell death and explore the significance of ERS in cardiovascular

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diseases, providing novel insights into the prevention and treatment of these conditions.

Regulation of ERS and UPR

In maintaining normal cellular homeostasis, molecular chaperones within the ER lumen assist newly synthesized proteins in achieving their correct three-dimensional conformation for proper functionality.[13] External stimuli can trigger ERS, activating the UPR. UPR activation transmits stress signals from the ER to the nucleus, leading to the regulation of relevant genes. Ultimately, this process restores ER homeostasis; and promotes cell survival by reducing protein synthesis, facilitating proper protein folding, and accelerating the degradation of misfolded and unfolded proteins. Continuous generation of stressful stimuli during ERS can result in cell death.[14] The ER contains three transmembrane protein receptors: firstly, inositol requiring enzyme 1α (IRE1α), secondly, protein kinase-like endoplasmic reticulum kinase (PERK), and finally activating transcription factor 6 (ATF6). Under physiological conditions, these proteins are inhibited through their binding to the molecular chaperone immunoglobulin heavy chain-binding protein (BiP) or glucose-regulated protein 78 (GRP78). Upon UPR activation, dissociation of molecular chaperones from these receptors occurs, initiating three protein-mediated signaling pathways that ultimately regulate the expression of related genes[15] (Figure 1).

IRE1α signaling pathway

IRE1 is an evolutionarily highly conserved ERS receptor protein, a type I transmembrane protein in the ER membrane, and IRE1α is an isoform of IRE1 expressed in all cell types and tissues.[16] IRE1 consists of a stress-sensing luminal domain that senses unfolded and misfolded proteins in the ER and a cytoplasmic tail that contains both a serine/threonine protein kinase structural domain and a ribonuclease structural domain.[17] Under physiological conditions, IRE1α is maintained in an inactive monomeric state

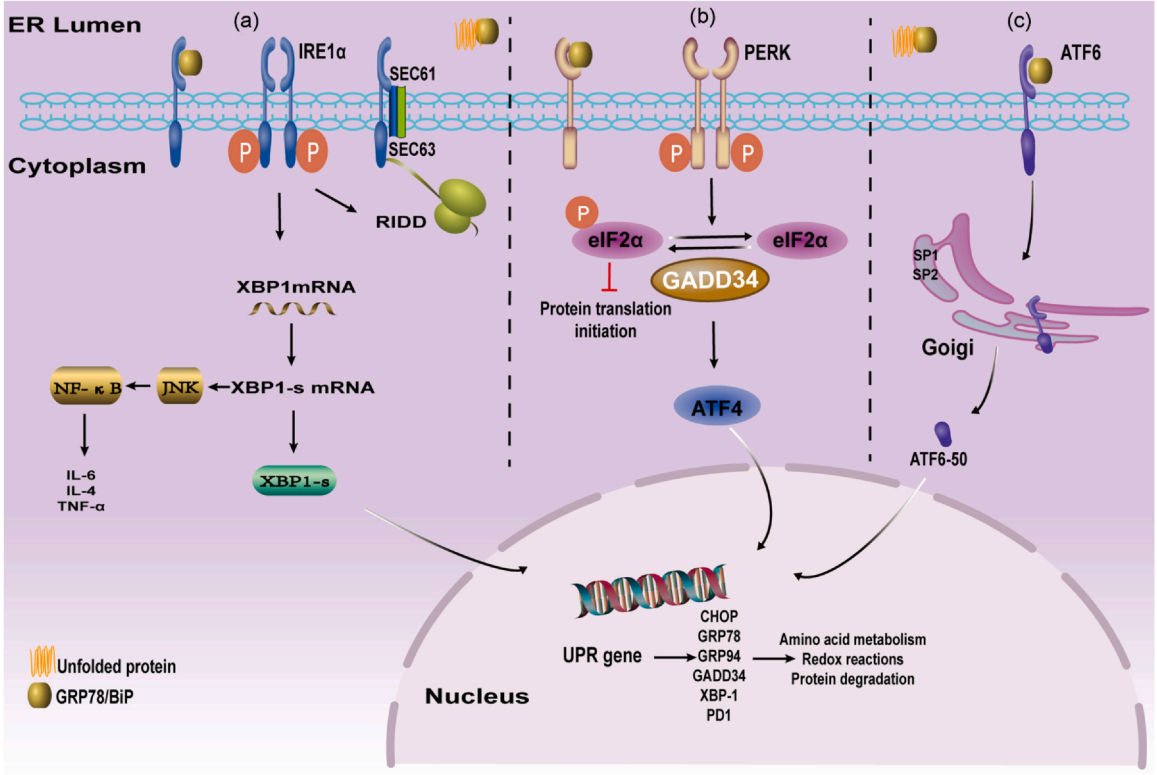

Fig. 1 Major signaling pathways of the UPR. Three transmembrane receptors, (a)IRE1α, (b)PERK, (c)and ATF6, mediate ERS and UPR. UPR can regulate the corresponding genes upon activation through three pathways, and participate in corresponding physiological and pathological processes to play a role. Abbreviations used: ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; BiP, binding protein; eIF2α, eukaryotic translation initiation factor 2α ER, endoplasmic reticulum; ERS, endoplasmic reticulum stress; GADD34, growth arrest and DNA damage-inducible protein 34; GRP78, glucose-regulated protein 78; GRP94, glucose-regulated protein 94; IRE1α, inositol requiring enzyme 1α PDI, protein disulfide isomerase; RIDD, regulated IRE1α-dependent decay; PERK, protein kinase-like endoplasmic reticulum kinase; UPR, unfolded protein response; XBP1, X-box binding protein 1.

through interaction with BiP/GRP78.[18] During ERS, BiP/GRP78 interacts with UPR proteins, resulting in the dissociation and autophosphorylation of IRE1α with BiP. Phosphorylated IRE1 exhibits kinase and endonuclease activity.[19,20] The ribonucleas(RNase) structural domain can cleave X-box binding protein 1 (XBP1) to convert it into a spliced form, the active transcription factor spliced XBP1.[21,22] XBP1 messenger RNA(mRNA) is the only characterized target of mammalian IRE1α ribonucleas activity.[23] Presentation of cleaved XBP1 to the nucleus elicits UPR-related target genes such as GRP78, glucose-regulated protein 94, and XBP1. IRE1α activation also recruits and causes activation of the c-Jun-N-terminal kinase (JNK) cascade.[24] Inflammatory factors such as interleukin-6 (IL-6) are induced to be upregulated through activation of the JNK/nuclear factor ***kappa-B***(NF-κB) signaling pathway.[25] In addition, regulated IRE1α-dependent decay is a process, and the specific mechanism is not yet fully understood. Research has shown that IRE1α forms a complex with the translocation protein 61(Sec61)/translocation protein 63(Sec63) translocation in cells. This leads to the attenuation of IRE1α ribonucleas[26] (Figure 1(a)).

PERK signaling pathway

The PERK pathway involves the activation of PERK, a type I transmembrane protein. Structurally, PERK shares similarities with IRE1α and is regulated by its binding to BiP, leading to its inactivation as a serine/threonine transmembrane ER kinase. During ERS, PERK dissociates from BiP and undergoes oligomeric and trans-self-phosphorylation, thereby phosphorylating eukaryotic translation initiation factor 2α (eIF2α), resulting in the termination of translation for most mRNAs. Phosphorylation of eIF2α (p-eIF2α) is a crucial adaptive signaling event essential for cell and organism survival, observed across various species from yeast to humans. eIF2α is a subunit of eIF2 that loses its activity after phosphorylation. This phosphorylation has broad physiological, pathological, and therapeutic implications.[27] Notably, specific kinases phosphorylate eIF2α, selectively upregulating the translation of ATF4 in response to different microenvironmental stresses. ATF4 functions as a transcriptional activator that translocates to the nucleus and upregulates genes involved in amino acid synthesis, redox homeostasis, protein maturation, and degradation. Consequently, ATF4 activation leads to autophagy and apoptosis.[28] The p-eIF2α selectively enhances ATF4 translation, promoting the expression of its related functional genes and sustaining cell survival.[29] Furthermore, ATF4 upregulates the expression of growth arrest and DeoxyriboNucleic Acid(DNA) damage-inducible protein 34 (GADD34), leading to p-eIF2α dephosphorylation and decreased ERS[30,31] (Figure 1(b)).

ATF6 signaling pathway

Unlike IRE1 and PERK, ATF6 is a type II transmembrane protein localized and resident in the ER. It belongs to the leucine zipper family of transcription factors.[32] In mammals, two homologous ATF6 proteins are expressed: ATF6α and ATF6β. Among them, ATF6α functions as a potent transcriptional activator.[33] The C-terminus of the ATF6 isoform contains large structural domains that act as transcription factors within the ER lumen. This is followed by the attachment of a transmembrane structural domain consisting of 20 amino acids.[34] During conditions of high protein synthesis in the ER, leading to ERS, the ATF6 signaling pathway is activated. This activation involves the dissociation of ATF6 from its bound immunoglobulin BiP. Unlike PERK and IRE1α, the detachment of BiP allows ATF6 to expose two Golgi-localized sequences within its ER luminal structural domain. Consequently, ATF6α is translocated to the Golgi *via* vesicles, which are then cleaved by serine site 1 protease(SP1) and metalloproteinase site 2 protease(SP2) in the Golgi. This cleavage generates the soluble active transcription factor, p50ATF6, which then enters the nucleus. In the nucleus, p50ATF6 binds to ERS-responsive element-associated genes to exert its role[35] (Figure 1(c)).

UPR-mediated cell death

Autophagy

Firstly, autophagy is a molecular phenomenon crucial for eliminating damaged organelles and protein aggregates, playing a significant role in maintaining cellular homeostasis.[36] Secondly, it is characterized by the formation of autophagosomes and their subsequent interaction with lysosomes. The underlying mechanism of autophagy involves three stages: the formation of phagosomal membranes derived from the Golgi, mitochondria, plasma membrane, and ER; the generation of autophagosomes; and the fusion between autophagosomes and lysosomes to form autolysosomes.[37] Studies have demonstrated a strong association between ERS and autophagy, with a particular emphasis on nonselective macroautophagy.[38] Cellular autophagy is initiated through the UPR when ERS is detected, aiming to eliminate the excessive protein accumulation within the ER.[39] Therefore, autophagy acts as an alternative pathway to remove excess proteins from the ER in conjunction with ER-associated degradation.

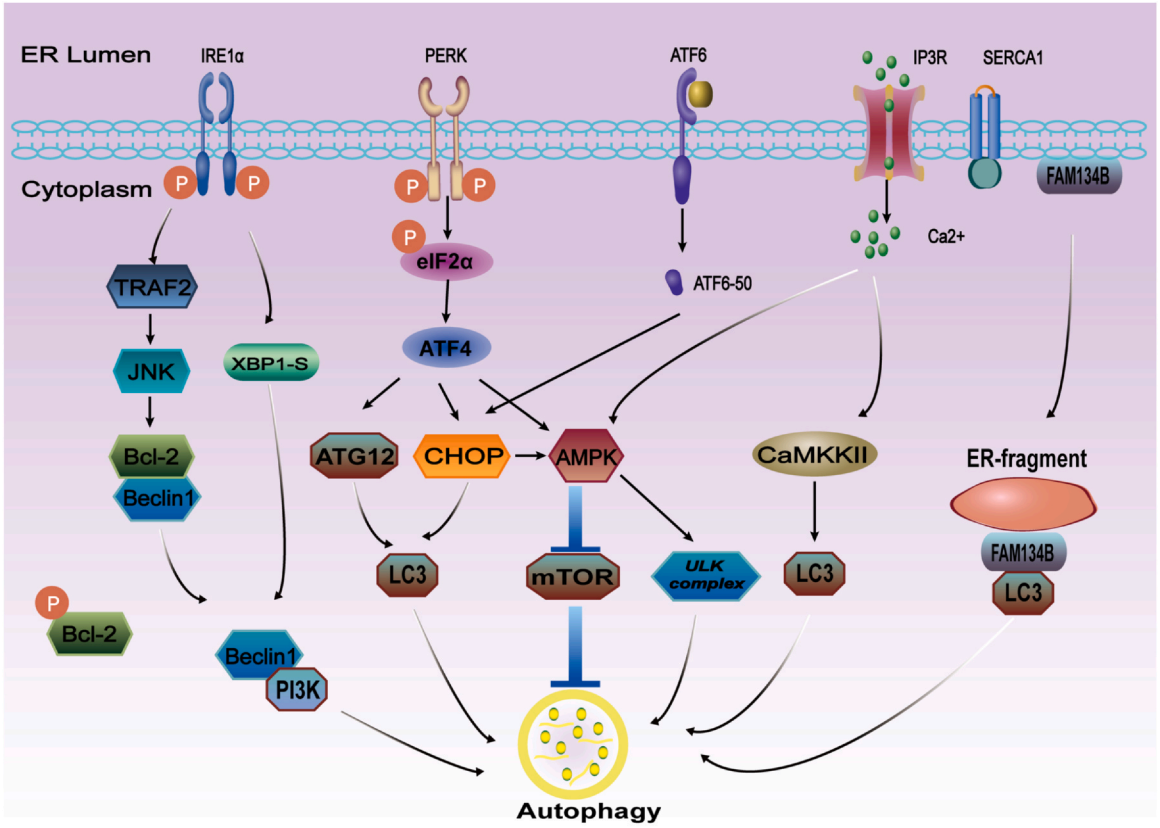

Fig. 2 UPR-mediated autophagy and partial mechanisms. ERS can mediate autophagy through IRE1α, PERK, ATF6, and Ca^{2+}. When ERS is activated, IRE1α promotes autophagy through the signaling pathway of TRAF2/JNK/Beclin1; PERK induces autophagy by activating downstream ATG12/CHOP through the ATF4 signaling pathway; ATF6 activates its downstream CHOP-activated autophagy; Ca^{2+} can participate in autophagy through CaMKII, In addition, FAM134B can bind to lipidated LC3 and cause autophagy. Abbreviations used: ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; ATG12, autophagy related 12; CAMKKII, calcium/calmodulin-dependent protein kinase II; eIF2α, eukaryotic translation initiation factor 2α ER, endoplasmic reticulum; ERS, endoplasmic reticulum stress; IP3R, inositol 1,4,5-trisphosphate receptors; IRE1α, inositol requiring enzyme 1α PERK, protein kinase-like endoplasmic reticulum kinase; TRAF2, tumor necrosis factor receptor-associated factor 2; UPR, unfolded protein response; XBP1, X-box binding protein 1.

Notably, some inducers of ERS concurrently stimulate autophagy.[40]

Although the specific molecular mechanisms remain largely unexplored, the three UPR sensors, IRE1α, PERK, and ATF6, have been found to regulate autophagy through respective pathways (Figure 2). IRE1 can promote the activation of JNK through the formation of the apoptosis signal-regulating kinase 1–tumor necrosis factor receptor-associated factor 2 complex, and JNK induces autophagy by the transcription of Beclin-1 through c-Jun.[41] Interestingly, IRE1 acts as a negative regulator and may not require activation to carry out its function.[42] Additionally, within the context of ERS, IRE1/XBP1 signaling directly binds to and enhances the transcription of the Beclin-1 promoter. This upregulates Beclin1 levels and activates autophagy.[43] PERK signaling plays a vital role in ER-induced autophagy, and both PERK and ATF4 are essential for ERS-induced autophagy.[42,44] ATF4 can directly bind and upregulate multiple autophagy gene promoters and plays an important role in ERS regulation of autophagy gene expression.[45] The PERK/eIF2α/ATF4/CHOP signaling pathway can activate autophagy.[46] Furthermore, ER stress can impact the expression of autophagy-related proteins (e.g., C/EBP Homologous protein, CHOP; and autophagy related 12), leading to an upregulation of light chain 3(LC3) expression and downstream activation of autophagy through the PERK/eIF2α/ATF4 signaling pathway.[47] Upon activation of the UPR pathway, the signaling pathway CHOP/adenosine 5'-monophosphate-activated protein kinase(AMPK)/mammalian target of rapamycin(mTOR)C1 is activated and facilitates the formation of the unc-51-like kinase 1(ULK1) complex, activating autophagy.[48,49] The ULK1 protein kinase complex plays a crucial role in autophagosome formation. ATF can be involved in cell proliferation, apoptosis, differentiation, and inflammation-related pathologies.[50] The ATF6 signaling pathway is implicated in ER stress-induced cellular autophagy, which is activated through the ATF6/CHOP

signaling pathway.[51] Additionally, ERS increases the expression of the inositol 1,4,5-trisphosphate receptor (IP3R) Ca^{2+} release channel and decreases the expression of the sarcoplasmic reticulum calcium ATPase 1(SERCA1) Ca^{2+} uptake pump. These changes ultimately lead to autophagy through the upregulation of autophagy-related genes (e.g., calcium/calmodulin-dependent protein kinase CAMKKII, AMPK, and Beclin1), while downregulating mTOR expression.[52] In addition, the ER also has a selective autophagy pathway. In the case of ER membrane fragmentation and formation of ER fragments, family with sequence similarity 134, member B(FAM134B) is an ER-phagy receptor, which can aggregate through ubiquitination and then bind to lipidated LC3, recognized by autophagosomes and leads to autophagy[53] (Figure 2). Notably, ERS can have a dual role in initiating or inhibiting autophagy, and impaired autophagic flow has also been associated with ERS.[54] Both ERS and autophagy are crucial determinants of cell fate and require tight regulation.[55]

Apoptosis

Apoptosis, a process of programmed cell death, is characterized by cell shrinkage, organelle and chromatin condensation, and the formation of apoptotic vesicles. Notably, apoptosis occurs with intact cell membranes and without a secondary inflammatory response.[56,57] It serves as a crucial process for sustaining life activity and can be triggered through two main pathways: the extracellular death ligand-receptor pathway and the intracellular pathway. ERS has been shown to be an additional regulatory pathway for apoptosis.[58] Upon ERS in cells, the ER transmembrane protein receptors become activated, ultimately leading to apoptosis[59] (Figure 3).

IRE1α plays a pivotal role in connecting ERS and apoptosis. Upregulation of the IRE1α pathway promotes Apoptosis signal-regulating kinase phosphorylation, which mediates apoptosis; and induces oxidative stress through

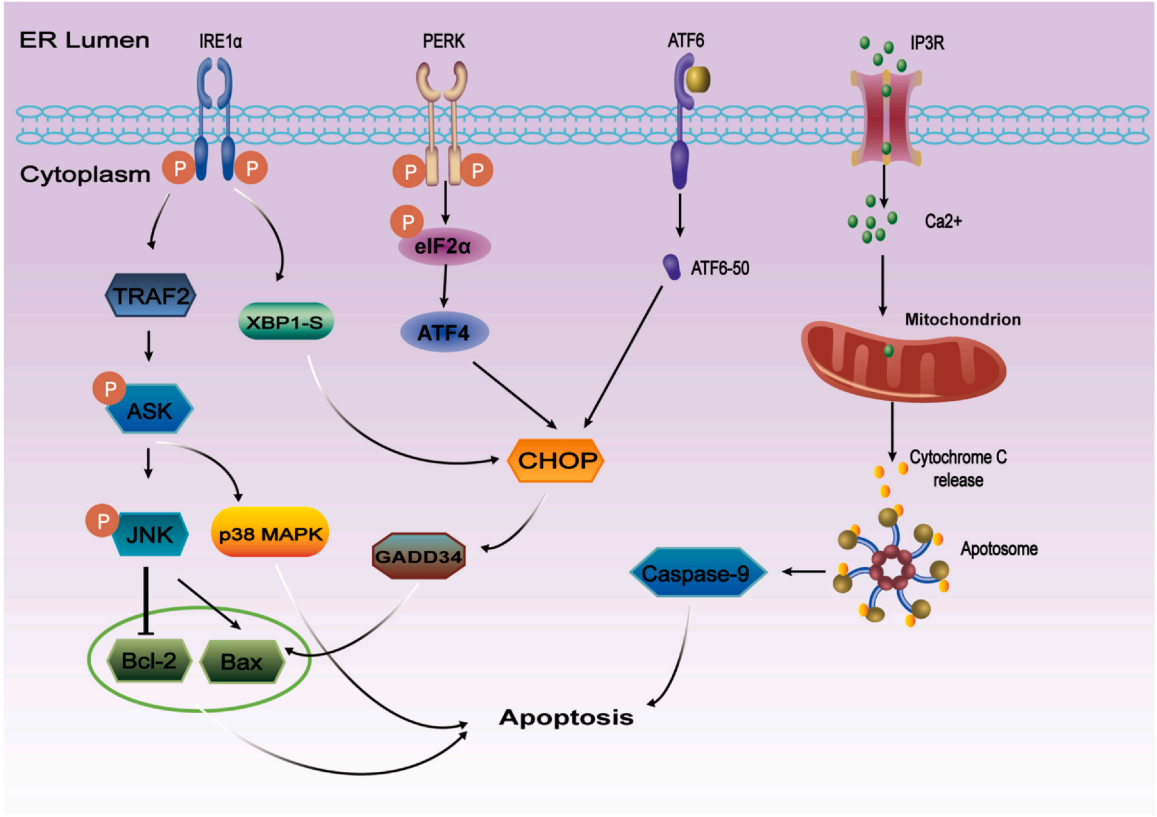

Fig. 3 UPR-mediated apoptosis and partial mechanisms. ERS mediates apoptosis through IRE1α, PERK, ATF6, and Ca^{2+}. When ERS was activated, the IRE1α/tumor necrosis factor receptor-associated factor 2 (TRAF2) and IRE1α/XBP1/CHOP signaling pathways mediated apoptosis; PERK induces apoptosis by activating downstream CHOP through the ATF4 signaling pathway; ATF6 activates its downstream CHOP to activate apoptosis. In addition, caspase9-dependent induction of apoptosis through modulation of the Ca^{2+} transfer pathway from the endoplasmic reticulum to mitochondria. Abbreviations used: ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; eIF2α, eukaryotic translation initiation factor 2α ER, endoplasmic reticulum; ERS, endoplasmic reticulum stress; GADD34, growth arrest and DNA damage-inducible protein 34; IP3R, inositol 1,4,5-trisphosphate receptors; IRE1α, inositol requiring enzyme 1α PERK, protein kinase-like endoplasmic reticulum kinase; UPR, unfolded protein response; XBP1, X-box binding protein 1.

the activation of JNK or p38 mitogen-activated protein kinase.[60,61] Activation of JNK inhibits the antiapoptotic protein Bcl-2 and facilitates the translocation of the proapoptotic protein Bax to the mitochondrial membrane *via* direct phosphorylation. The IRE1α/XBP1 signaling pathway also contributes to apoptosis through CHOP.[62] Pretreatment with the ERS inhibitor or knockdown of CHOP partially enhances cell viability and attenuates apoptosis.[63] PERK promotes the p-eIF2α, subsequently inducing ATF4 translocation. Once ATF4 enters the nucleus, it upregulates CHOP and GADD34 levels, alters the expression of apoptotic proteins such as Bax and Bcl-2, and participates in proapoptotic processes.[64,65] Similarly, ATF6 can also contribute to apoptosis through the CHOP pathway.[66] Nucleotide-binding oligomerization domain protein 2 interacts with the ERS sensor molecule ATF6 and acts as a negative regulator of ATF6 activation and its downstream target molecule CHOP, thereby regulating ERS-induced apoptosis.[67] Furthermore, ATF6 induces the transcription factor XBP1.[68] Transcription factor XBP1 directly activates the transcription of UPR target genes, such as CHOP, GRP78, and XBP1, exerting a prosurvival effect.[69,70] However, the specific mechanism of ATF6 involvement in apoptosis requires further investigation. Additionally, the ER plays a crucial role in maintaining Ca^{2+} concentration homeostasis and protein biosynthesis. The release of Ca^{2+} from the ER is primarily regulated by IP3Rs,[71] and ERS promotes intracellular Ca^{2+} release, ultimately leading to apoptosis.[72] IP3R-mediated regulation of ER Ca^{2+} release and mitochondrial Ca^{2+} uptake facilitates the transfer of Ca^{2+}, subsequently triggering cytochrome C release from the mitochondria. The released cytochrome C generates apoptotic bodies, thus initiating caspase-9-mediated apoptosis[73–76] (Figure 3).

Chronic ERS leads to the disruption of ER integrity, ultimately resulting in apoptosis and cardiovascular dysfunction.[77] The apoptotic and inflammatory signaling pathways mediated by ERS play pivotal roles in cardiovascular disease.[78] Doxorubicin is a tumor drug currently in clinical use that can cause cardiotoxicity. The activation of the PERK/eIF2α/ATF4/CHOP axis may contribute to apoptosis induced by Doxorubicin in cardiac cells.[79]

Ferroptosis

Ferroptosis is a distinct, regulated form of iron-dependent nonapoptotic cell death.[80] Ferroptosis can spread through cell populations in a wave-like fashion.[81,82] Its main characteristics include increased mitochondrial membrane density, mitochondrial swelling, and reduced levels of glutathione peroxidase 4 (GPX4) (a core enzyme involved in the regulation of lipid peroxidation and antioxidant systems) leading to cell death.[83] The accumulation of lipid peroxidation and depletion of plasma membrane polyunsaturated fatty acids accelerate the progression of ferroptosis and subsequent cell death.[84] To some extent, ferroptosis arises as a result of disrupted cellular redox homeostasis.[85] Negative regulators of desferrioxidation, which limit reactive oxygen species (ROS) production and decrease cellular iron uptake, include GPX4, heat shock protein beta-1, and heat shock protein 27. On the other hand, P53 is a positive regulatory factor for ferroptosis, which can promote the production of ROS and regulate the levels of solute carrier family 7 member 11 (SLC7A11).[86] Iron metabolism and lipid peroxidation signaling involve core regulators of this process.[87] The export of iron is facilitated by solute carrier family 7 member 3, an iron efflux pump that oxidizes Fe^{2+} to Fe^{3+}. In addition, the Fenton reaction can also promote the production of ROS. Activation of mitogen-activated protein kinase, upregulation of ERS, and inhibition of cystine/glutamate counter transporter proteins are involved in the induction of ferroptosis.[86]

There is a strong interaction between ferroptosis and ERS. Additionally, the ER constitutes over half of the lipid bilayer in cells and may be crucial in triggering ferroptosis as the primary lipid source for most membranes.[88] Crosstalk between the IRE1/JNK signaling pathway and ferroptosis has been observed, with inhibition of the IRE1/JNK signaling pathway leading to the inhibition of ferroptosis.[89] Activation of the PERK/eIF2α/ATF4 signaling pathway is associated with ferroptosis, and reducing ERS through inhibition can lessen ferroptosis.[90] ATF4 serves as a key regulator that promotes cardiomyocyte survival by upregulating SLC7A11 and inhibiting ferroptosis[91] (Figure 4(a)). Iron also plays a vital role in maintaining heart function, although iron overload can result in tissue damage.[92]

Pyroptosis

Pyroptosis is pro-inflammatory necrotic cell death, which is mediated by the Gasdermin protein family. It is characterized by nuclear cohesion, random DNA breaks, and chromatin degradation, as well as penetrating the cell membrane to form numerous pores. These events induce an inflammatory response that ultimately leads to cell rupture.[93] The activation of pyroptosis primarily occurs through classical and nonclassical inflammasome pathways, which independently promote the activation of Caspase-1 or Caspase-11/4/5 and the subsequent cleavage of gasdermin D (GSDMD).[94] Upon sensing an external stimulus, inactive caspases are cleaved by multiprotein complexes within the inflammasomes, leading to the

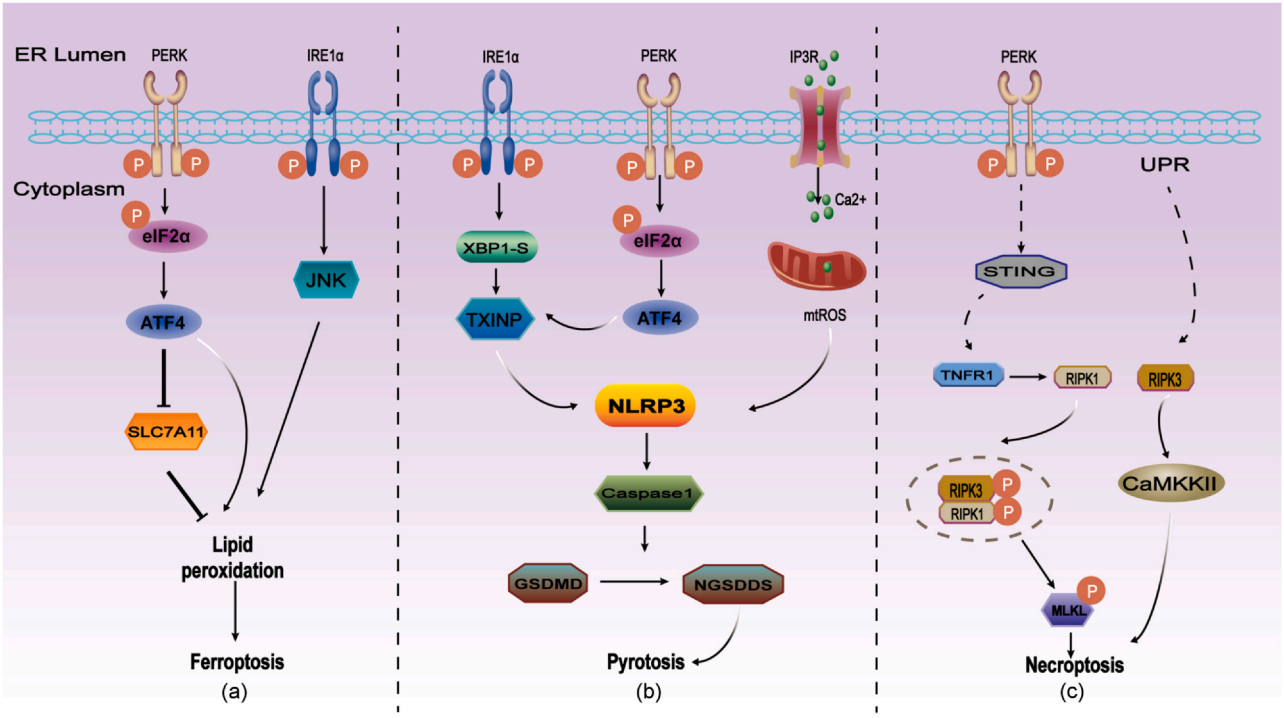

Fig. 4 Ferroptosis, pyroptosis, and necroptosis are involved in the UPR pathway. (a) ERS-induced ferroptosis is mainly induced by the PERK/SLC7A11 as well as the IRE1α/JNK pathway, resulting in the accumulation of lipid peroxides, which ultimately leads to the development of ferroptosis. (b) ERS-induced pyroptosis is induced by IRE1α, PERK, and Ca^{2+}. Upon activation of PERK and IRE1α, downstream NLRP3 is activated to induce focal death. Ca^{2+} can act on NLRP3 to induce pyroptosis by upregulating the level of mitochondrial mtROS release. (c) ERS-induced necroptosis is mainly mediated by UPR-mediated activation of necroptosis by the RIPK1/RIPK3/MLKL signaling pathway, as well as direct induction of necroptosis by RIPK3/CaMKKII. Abbreviations used: ATF4, activating transcription factor 4; CAMKKII, calcium/calmodulin-dependent protein kinase II; eIF2α, eukaryotic translation initiation factor 2α ER, endoplasmic reticulum; ERS, endoplasmic reticulum stress; GSDMD, gasdermin D; IRE1α, inositol requiring enzyme 1α IP3R, inositol 1,4,5-trisphosphate receptors; MLKL, mixed lineage kinase-like domains; NGSDDS, N-terminal GSDMD fragments; PERK, protein kinase-like endoplasmic reticulum kinase; RIPK1, receptor-interacting protein kinase 1; RIPK3, receptor-interacting protein kinase 3; SLC7A11, solute carrier family 7 member 11; UPR, unfolded protein response; XBP1, X-box binding protein 1.

activation of caspase-1. Caspase-1 then cleaves and activates GSDMD proteins, resulting in the release of N-terminal GSDMD fragments. These fragments bind to the cell membrane and form pores sized at approximately 1–2 nm. This disrupts the integrity of the cell membrane, leading to changes in osmotic pressure and ultimately resulting in cell swelling and rupture.[95]

The occurrence of ERS-induced pyroptosis[96] (Figure 4(b)). ERS induces activation of the IRE1 and PERK signaling pathways. Within this cascade, the IRE1/TXNIP/NLRP3 signaling pathway mediates the release of GSDMD proteins and exacerbates pyroptosis. On the other hand, the PERK pathway can result in NLRP3 inflammatory vesicle activation, which depends on caspase-1 to initiate cellular pyroptosis.[97,98] Inhibiting the PERK/eIF2α pathway downregulates TXNIP expression and reduces the activation of NLRP3 inflammatory vesicles, consequently decreasing cellular pyroptosis.[98] Furthermore, inhibiting ERS alleviates NLRP3-induced cellular pyroptosis.[99] Notably, disruption of Ca^{2+} transfer leads to increased release of mitochondrial reactive oxygen species(mtROS) from mitochondrial damage, further facilitating the activation of NLRP3 inflammatory vesicles and inducing pyroptosis.[100]

Necroptosis

Necroptosis is a type of cell death, primarily carried out through death receptors (e.g., Tumor necrosis factor-receptor I (TNFR1); Indian Federation of Neurorehabilitation; and toll-like receptor 3). [101–104] Necroptosis can proceed *via* typical and atypical signaling pathways. Typical pathway signaling molecules for necroptosis include receptor-interacting protein kinase 1 (RIPK1), receptor-interacting protein kinase 3 (RIPK3), and mixed lineage kinase-like domains (MLKL).[105] RIPK3, a serine/threonine protein kinase, regulates both apoptosis and necroptosis. This pathway depends on the death receptor TNFR1, where binding of TNF-α leads to the recruitment of adaptor proteins to the cytoplasmic tail of TNFR1, including TNFR1-associated death

structural domains, TNFR-associated factor 2, RIPK1, and apoptosis inhibitor class ubiquitin ligases (cIAP1 and cIAP2), which together form protein complexes.[106] These protein complexes serve as signaling nodes, with RIPK1 playing a key role in triggering different death or survival pathways. Interaction between RIPK1 and RIPK3 forms a protein complex called the necrosome, leading to the phosphorylation of MLKL protein. Phosphorylated MLKL disrupts the plasma membrane by inducing phospholipid perturbation, translocating to the plasma membrane, oligomerizing, and forming pores, ultimately initiating necroptosis.[107,108] Each regulatory pathway of cell death is governed by specific molecular components.[109] Cellular responses to death receptor activation are influenced by the cellular environment. The cysteine protease caspase-8 in complex with cellular Fas-associated death domain-like IL 1-beta-converting enzyme-inhibitory protein cleaves RIPK1 and RIPK3. High activity of caspase-8 inhibits necroptosis and triggers apoptosis, while low levels of caspase-8 promote necroptosis.[110,111] Potential targets for regulating mitochondria-triggered necroptosis include RIPK3 expression, MLKL phosphorylation, and the opening rate of mitochondrial permeability transition pores.[112]

Activation of ER-mediated IRE1, ATF6, and GADD34 has been observed in necroptotic cells.[113] ER stress-related proteins can induce necroptosis (Figure 4(c)). ERS can induce necroptosis through the TNFR1-mediated RIPK1/RIPK3/MLKL signaling pathway.[114] Additionally, the ER stress-related protein PERK induces necroptosis through the stimulator of interferon genes-mediated RIPK3 signaling pathway.[115] Moreover, the RIPK3/CaMKII signaling pathway axis may also mediate ERS-induced necroptosis, although the specific mechanisms remain unexplored.[116] However, cell necroptosis in the heart is not directly associated with RIPK1/RIPK3/MLKL signaling.[117] Instead, RIPK3-induced activation of the novel substrate CaMKII triggers myocardial necroptosis through phosphorylation or oxidation.[118]

Cardiovascular disease

Hypertension

Hypertension and ERS

Hypertension is one of the significant risk factors for cardiovascular diseases and has emerged as a major global public health concern, posing a primary threat to human well-being. It is a multifactorial, complex disease involving numerous interacting mechanisms across various organ systems, including the heart, kidneys, brain, blood vessels, and immune system.[119,120] Oxidative stress is a common feature in the pathophysiology of hypertension, and an important and major trigger is the large production of ROS. In pathological states, their overproduction triggers inflammation and fibrosis, leading to oxidative damage to the vascular system and subsequent pathological changes such as vascular remodeling and reduced vascular compliance.[121]

There is mounting evidence linking hypertension to ERS. Throughout the development of hypertension, several members of the ER stress pathway, such as GRP78, PERK, and CHOP, show increased expression.[122] The presence of ER stress contributes to the induction of neurogenic hypertension associated with oxidative stress.[123] Stromal interaction molecule 1, an essential ER protein for maintaining Ca^{2+} homeostasis, has been identified as upregulated in hypertensive disorders due to ERS, leading to negative cardiovascular effects.[124] Deleting the ER stress chaperone protein Ddit3 (CHOP) entirely prevents renin-dependent hypertension induced by vitamin D deficiency in mice.[125]

ERS also holds significance in hypertensive target organ injury, particularly in hypertension-induced myocardial fibrosis. Elevated expression of ERS signaling has been observed in hypertensive heart tissue.[126,127] Single-cell transcriptomics of angiotensin II-infused mouse hearts highlights the extensive involvement of ERS in hypertensive cardiac remodeling.[128] Furthermore, ERS plays a crucial pathogenic role in cardiac fibrosis.[129] Suppression of ERS has shown promising results in reducing heart damage and improving vascular function among hypertensive patients.[130] The study further reveals sex differences in Ang II-induced brain ERS, suggesting that estrogen protects women from Ang II-mediated hypertension by mitigating brain ERS.[131] In conclusion, ERS plays a critical role in both hypertension and its associated target organ damage.

Hypertension and cell death

Autophagy can be induced by mechanical stress on blood vessels in hypertension, and ERS can induce autophagy *via* ATF4, but further evaluation of the relationship between ERS and autophagy in hypertension is necessary.[132] The mechanism of vascular remodeling is associated with a reversal between apoptosis of vascular smooth muscle cells (VSMCs) and vascular hypertrophy. Iron metabolism is an independent risk factor for hypertensive disorders, but detailed mechanisms of action are lacking.[133] Pyroptosis can mediate endothelial cell dysfunction, which is one of the pathogenic mechanisms of hypertension, but the specific relationship between

pyroptosis and hypertension has not been fully determined.[134] Inhibition of hypertension-associated neuronal programmed necroptosis improves cognitive function, but the specific relationship between programmed necroptosis and hypertensive disorders, as well as the molecular mechanisms, are not fully understood.

Atherosclerosis

Atherosclerosis and ERS

Atherosclerosis is a common chronic disease of the cardiovascular system, a progressive inflammatory disease, which mainly affects the middle and large arteries. Inflammatory cytokines contribute to the exacerbation of atherosclerosis by attracting more immune cells to infiltrate, while atherosclerotic plaques become less stable and prone to rupture when macrophages and macrophage-derived foam cells dominate.[135] Macrophage apoptosis plays a crucial role, as the formation of necrotic cores can convert benign lesions into an unstable phenotype.[136] Notably, atherosclerotic lesion cells, particularly macrophages, exhibit markers of ER stress during lesion progression.[137]

Atherogenesis occurs primarily at specific vulnerable sites characterized by ER stress-related protein biosynthesis and activation of two out of the three UPR signaling pathways. Chronic ER stress defines the prepathological state of the atherosclerosis-susceptible endothelial phenotype in vivo.[138] Additionally, within the context of chronic ERS, apoptosis may accelerate the pathophysiological process of atherosclerotic disease.[139] ERS induces endothelial cell apoptosis through the CHOP signaling pathway, leading to atherosclerotic plaque formation as well as destabilization of plaques.[140,141] Numerous studies have emphasized the dominant role of ERS as an immune response in atherosclerosis and its significant contribution to apoptosis in advanced lesion macrophages, ultimately leading to necrosis of atherosclerotic plaques.[142–144] Furthermore, reducing ER stress through macrophage lipid chaperones can help alleviate the central role of lipid chaperones in regulating macrophage ER homeostasis in atherosclerosis.[143] Clec4e, also known as the macrophage-inducible C-type lectin, is predominantly distributed on the surface of monocytes/macrophages and has an important role in sterile inflammation. CHOP and IRE1 deficiency attenuated Clec4e-induced atherosclerotic lesions and inflammatory responses.[145] XBP1 serves as a crucial signal transducer in the ERS response and has been identified to play an important role in maintaining endothelial integrity and participating in the occurrence and development of atherosclerosis.

Atherosclerosis and cell death

Various cell deaths present in endothelial cells in atherosclerosis, such as apoptosis, autophagy, ferroptosis, pyroptosis, and necroptosis.[146] Moderate autophagy plays a positive role in atherosclerosis, and both excessive autophagy and absence of autophagy lead to endothelial cell death and plaque instability. In atherosclerosis, iron overload and oxidized low-density lipoprotein induce lipid peroxidation, which triggers ferroptosis, ultimately leading to endothelial dysfunction and plaque instability.[147] Pyroptosis of endothelial cells, VSMCs, and macrophages is involved in intimal damage and repair in atherosclerosis.[148] Proteins involved in classical (NLRP3, ASC, cystatinase-1, IL-1β, and IL-18) and nonclassical (cystatinase-11) pyroptosis have been identified as contributors to atherosclerosis models.[149,150] GSDME-mediated cellular pyroptosis can promote the progression of atherosclerosis.[151] GSDMD emerges as a promising pharmacological target for pyroptosis in atherosclerosis.[133] Numerous studies have demonstrated the role of RIPK-1 and MLKL-mediated programmed macrophage death in atherosclerosis.[152]

Heart failure

Heart failure and ERS

HF is a clinical syndrome characterized by impaired circulation, insufficient tissue perfusion, and pulmonary congestion. It represents the advanced stage of various cardiovascular diseases. The occurrence and progression of HF involve multiple factors, and its underlying mechanisms remain incompletely understood. However, the degree of oxidative stress damage can serve as an indicator of HF severity. In failing hearts, elevated oxidative stress contributes to the exacerbation of ERS. Notably, HF often exhibits histological features indicative of ER hyperplasia, signifying ER overload. Moreover, ERS has been observed in chronic myocardial ischemia-induced HF and models of stress-induced myocardial loading, with ERS-associated apoptosis playing a role in the pathophysiology of chronic myocardial ischemia-induced HF.[153,154] Additionally, ERS plays a crucial role in the development of several cardiovascular diseases, including HF.[155]

PERK, a sensor of ERS, prevents pressure overload-induced HF.[156] ERS induces apoptotic through the activation of the CHOP signaling pathway, which induces

apoptosis in cardiac cells, leading to HF.[157–159] Response to ER stress in CHOP knockout mice showed attenuated pressure overload-induced myocardial hypertrophy and dysfunction and reduced apoptosis.[159] ERS can induce cardiomyocyte apoptosis through CHOP involvement leading to HF. Isoproterenol causes abnormal ER stress, and cardiomyocyte apoptosis through AMPK inactivation, which leads to HF.[160] The activin A-follicular repressor system can influence apoptosis in HF cardiomyocytes *via* the ERS pathway.[161] Ubiquitin-fold modifier 1 (Ufm1) is part of a novel ubiquitin-like modification system involved in maintaining ER homeostasis. The Ufm1 system maintains cardiac homeostasis by regulating ER function. The Ufm1 ligase 1 is an enzyme essential for Ufm1 modification, and upregulation of Ufm1 ligase 1 can prevent HF.[162] DDRGK1 is an ER membrane protein that is a key component of the Ufm1 system, and depletion of DDRGK1 inhibits the IRE1α-XBP1 signaling pathway and induces apoptosis.[163] Caspase12 belongs to the Cysteine protease and is expressed only in the ER, where it is often used to detect ERS-induced apoptosis.[164] Inhibition of the ERS-related Caspase-12 signaling pathway attenuated HF.[165] NF-κB is an inflammatory signaling pathway, of which NF-κB p65 is its classical active form. ERS can activate inflammatory responses by activating the NF-κB pathway. Targeted blockade of p65 in cardiac injury may be a useful therapeutic strategy to alleviate cardiac injury, maintain homeostatic response to ERS, and ameliorate myocyte loss in remodeled hearts.[166]

HF and cell death

Cell death is critical in the pathogenesis of HF. Autophagy, apoptosis, pyroptosis, ferroptosis, and necroptosis mediate Heart cell death. Cardiomyocyte autophagy is associated with various cardiovascular diseases and sustained autophagy has been implicated in the pathogenesis of HF. Excessive autophagy leads to the loss of ER and cellular function, leading to apoptosis and necroptosis.[167] Pyroptosis occurs primarily in cardiac fibroblasts, and the reduced number of cardiomyocytes induced by pyroptosis is a key mediator leading to HF.[168] Ferroptosis plays an important role in HF due to myocardial infarction. Ferroptosis has regulatory mechanisms for the formation of many ferroptosis regulators. GPX4 and SLC7A11 can be involved in regulation through Glutathione. Acyl-CoA synthetase long-chain family member 4 is involved in the regulation of polyunsaturated fatty acid. NRF2 and P53 function as regulators affecting transcription.[169] Necroptosis is an important part of the pathophysiology of cardiovascular disease. The mediators of necroptosis, RIPK1, RIPK3, and MLKL, are upregulated in HF, and the pathogenesis of necroptosis in HF has been demonstrated by drugs targeting necroptosis.[170] Bisphenol A can induce necroptosis *via* the RIP3/CaMKII-dependent signaling pathway, leading to the weakening of coronary vessel walls, delayed repair process, rupture hemorrhage, and ultimately cardiac dysfunction.[171]

The treatment of ERS in cardiovascular diseases

Activation of ERS in cardiovascular disease can lead to various types of cell death through the UPR, contributing to disease progression. Inhibiting ER stress has the therapeutic potential to reduce cardiovascular damage, making pharmacological interventions targeting ERS promising strategies for treating systemic cardiovascular diseases.[8] ERS inhibitors play a protective role in the vasculature by restoring ER calcium homeostasis, reducing apoptosis, correcting vascular dysfunction, and ameliorating ERS-related inflammation and fibrosis, thus improving hypertension-induced cardiac dysfunction.[172–174] Additionally, ERS inhibitors can ameliorate vascular dysfunction by enhancing Beclin-1-dependent autophagy.[175] Chemical chaperones offer a means to modulate ER stress effectively, thereby alleviating atherosclerosis. Targeting specific pharmacological modulation of IRE1 demonstrates counteractive effects against hyperinflammation, presenting a potential therapeutic approach for managing atherosclerotic disease.[176] Angiogenin is essential for cellular adaptation to ERS. Intracellular Angiogenin in endothelial cells represents a novel therapeutic approach with anti-atherosclerotic effects, exerting atheroprotective effects by inhibiting ERS through ST3 beta-galactoside alpha-2,3-sialyltransferase 5-mediated mechanisms.[177] Phosphodiesterase type 5 inhibitors have shown potential in attenuating cardiomyocyte apoptosis and HF by alleviating ERS.[178] Dapagliflozin is a new type of sodium-glucose cotransporter 2 inhibitor. Dapagliflozin demonstrates the ability to inhibit ERS, attenuate pressure overload-induced myocardial remodeling, and activate SIRT1 and PERK/eIF2α/CHOP signaling pathways in mice.[179]

ERS plays a significant role in the development of cardiovascular disease. Therefore, it is feasible to intervene in ERS as an entry point for cardiovascular disease prevention and treatment. However, more basic and clinical studies are needed to confirm this. Research drugs that inhibit ERS response, regulate UPR-mediated signaling pathways, reduce cell death, and enrich treatment plans for cardiovascular diseases. Analyzing the proteins accumulated during ERS induced by various

cardiovascular diseases can uncover the molecular mechanisms underlying disease occurrence, providing new insights for precision therapy and potential strategies.

Other molecular chaperones and cardiovascular disease

The previous part of this paper focuses on the role of GRP78 and the UPR signaling pathway in cardiovascular disease. In addition, other molecular chaperones such as heat shock protein 70 (Hsp70), heat shock protein 90 (Hsp90), B-cell lymphoma-2-associated athanogene 3 (BAG-3), C-terminus of Hsc70 interacting protein, protein disulfide isomerase, and small heat shock proteins (sHSPs) are also associated with cardiovascular disease. HSPs are a group of highly conserved proteins with increased expression levels after stress, which can restore the structure of misfolded proteins and realize the normal physiological functions of proteins. HSPs can be categorized as Hsp70, Hsp90, etc. Hsp70 is a chaperone protein induced by cells subjected to various stresses. The development of hypertension is associated with an immune response against Hsp70 overexpression.[180] Hsp70 is present in human and rabbit arteries and concentrates in the lipid accumulation site of atherosclerosis, contributing to the amelioration of atherosclerosis.[181,182] Hsp70 has a critical role in the protection of cardiomyocytes, but elevated HSP70 accelerates HF in the presence of pressure overload.[183,184] Elevated levels of HSP90 have been observed in hypertensive model rats. The expression of Hsp90 is increased in atherosclerotic plaque and atherosclerotic serum from patients, which plays an important role in cardiovascular disease.[185,186] BAG-3, a highly conserved anti-apoptotic protein, can be involved in the pathogenesis of atherosclerosis by facilitating the phenotypic transformation of VSMCs, with elevated levels of expression in the serum of patients with hypertension and patients with advanced HF.[187,188] However, the regulatory activity of BAG-3 in cardiomyocytes is an area that has not yet been fully explored. The C-terminus of Hsc70 interacting protein can bind to Hsp70 to regulate its chaperone activity and protect against cardiac injury.[189,190] Protein disulfide isomerase plays a vital role in the development and progression of cardiovascular diseases.[191] sHSPs are ATP-independent chaperones that maintain protein homeostasis.[192] Dysfunction of sHSPs is associated with cardiovascular disease.[193]

Conclusions and perspective

ERS, a highly conserved signaling pathway, plays a crucial role in both physiological processes and pathological conditions. First, it contributes to the restoration of ER homeostasis through the UPR, promoting cell survival. Second, continuous stimulation leads to insufficient ER regulation and the UPR is activated, resulting in different types of cell death. ERS has become an increasingly prominent research area, with progress being made in elucidating the specific mechanisms by which ERS regulates cell death types and its involvement in various cardiovascular diseases. However, certain questions still remain unanswered. Can reliable biomarkers be identified to predict ERS in cardiovascular disease? Is there consistent involvement of ERS across all cardiovascular diseases? How are cell death types determined in different cardiovascular diseases under ERS induction? Do cell death types occur simultaneously, and if so, how? As well, as through which signaling pathway ERS induces cell death, whether there is a major signaling pathway, and whether there is a crosstalk of the signaling pathway. If there is crosstalk in the signaling pathway that induces cell death, can inhibiting ERS affect multiple pathways simultaneously? Can targeted strategies be effectively designed to prevent and treat ERS-related cardiovascular diseases? The acquisition of more clinical data is necessary to determine whether inhibiting ERS improves cardiovascular diseases. These questions should serve as key research directions for future studies. Moreover, utilizing the ERS pathway for therapeutic interventions holds potential as a novel approach to disease treatment.

Ethics statement and consent to participate

The manuscript has neither been previously published nor is under consideration by any other journal. All authors have approved the content of the paper and agree to submit it to Cell Stress and Chaperones.

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Declarations of interest

The authors declare no conflict of interest.

Data availability statement

No data were used for the research described in the article.

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