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REVIEW

Broken heart: A matter of the endoplasmic reticulum stress bad management?

Souad Belmadani, Khalid Matrougui

ORCID number: Souad Belmadani (0000-0002-7355-9142); Khalid Matrougui (0000-0001-9269-2937).

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Souad Belmadani, Khalid Matrougui, Department of Physiological Science, Eastern Virginia Medical School, Norfolk, VA 23501, United States

Corresponding author: Souad Belmadani, PhD, Assistant Professor, Department of Physiological Science, Eastern Virginia Medical School, 700 W Olney Rd, Norfolk, VA23501, United States. belmads@evms.edu
Telephone: +1-757-4465880

Abstract

Cardiovascular diseases are the number one cause of morbidity and mortality in the United States and worldwide. The induction of the endoplasmic reticulum (ER) stress, a result of a disruption in the ER homeostasis, was found to be highly associated with cardiovascular diseases such as hypertension, diabetes, ischemic heart diseases and heart failure. This review will discuss the latest literature on the different aspects of the involvement of the ER stress in cardiovascular complications and the potential of targeting the ER stress pathways as a new therapeutic approach for cardiovascular complications.

Key words: Heart complications; Endoplasmic reticulum stress; Inflammation; Apoptosis; Autophagy

Core tip: The central mechanisms involved in heart failure, a public health crisis, remain unknown. Current therapies, in addition to their strong side effects, neither halt nor reverse heart complications. The endoplasmic reticulum (ER) stress has been shown to be involved in cardiovascular diseases. Here we analyzed the role and mechanism of the ER stress in heart failure.

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INTRODUCTION

The endoplasmic reticulum (ER), one of the largest organelles in the eukaryotic cells was described for the first time in 1945 by Porter *et al*[1]. The ER is responsible for protein synthesis, and folding of most secreted and membrane protein, which represent approximately 35% of all protein[2].The ER is also the site of protein translocation, calcium homeostasis, lipid, and steroid biosynthesis[3]. Effective ER function relies on various quality control factors such as molecular chaperones, protein oxidoreductases, and enzymes involved in glycosylation, sulfation and proteolysis[4]. This highly organized machinery requires an optimal ER environment. Various factors such as myocardial ischemia, diabetes, hypertension, and heart failure can disrupt this environment provoking the accumulation of misfolded proteins[4]. When the ER homeostasis is altered by the accumulation of unfolded/misfolded protein; signaling pathways are activated triggering an adaptive response known as the unfolded protein response (UPR). The primary goal of the UPR is to restore the protein balance by suppressing protein translation, increased clearance of unfolded or misfolded proteins and promoting cell survival. Unfortunately, if the ER homeostasis is not restored, the cell dysfunction and death signaling pathways is launched. The UPR re-establishes homeostasis through three distinct branches that are initiated by the ER-resident protein folding sensors, inositol-requiring protein-1 (IRE1α), activating transcription factor-6 (ATF6) or protein kinase RNA-like ER kinase (PERK). Each branch uses a unique mechanism to activate transcription factors and up-regulate UPR target genes. These three ER-transmembrane proteins serve both as sensors for the ER stress and effectors for the response to the ER stress induction. Under basal conditions, the ER-resident transmembrane proteins ATF6, IRE1, and PERK are maintained in an inactive state *via* their binding to the ER chaperone glucose-regulated protein (GRP78)[5]. Under stress conditions where misfolded proteins are increased in the ER, GRP78 binds misfolded protein and releases from the ER stress sensors, leading to their activation.

IRE1 is the most ancient ER transmembrane protein containing an ER-luminal sensor domain recognizing unfolded peptides, kinase and endoribonuclease (RNase) domain on its cytosolic portion[6]. IRE1 has two isoforms, IRE1α and IRE1β[6]. IRE1α is ubiquitously expressed whereas IRE1β is only expressed in the gut[6]. In the absence of the ER stress, GRP78 binds to the luminal domain of IRE1α. Under stress situations, IRE1 is activated by homodimerization after release from GRP78 and auto-phosphorylation leading to the activation of the kinase and the endoribonuclease activity of IRE1. Active IRE1α splices a transcription factor X-box-binding-protein-1 (XBP1) mRNA to spliced XBP1 (XBP1s). XBP1s is a potent transcription factor for a variety of genes involved in retrograde transport of proteins from the ER to cytosol and in ER-induced protein degradation[7]. Moreover, IRE1 degrades mRNAs *via* regulated IRE1-dependent mRNA decay (RIDD) mechanism to reinstate homeostasis in the ER.

ATF6, a 670 amino acids type II transmembrane protein with a bZIP transcription factor motif. At resting conditions ATF6 is localized at the ER through its interaction with GRP78. Following the stress, unfolded/misfolded proteins accumulation enhance the release of the ATF6 and its translocation to the Golgi apparatus where the luminal and transmembrane domains are cleaved by site-1 and site-2 proteases (S1P and S2P) *via* regulated intra-membrane proteolysis. This results in an active ATF6 capable of interacting with regulatory sequences called ER stress response elements and regulating the expression of chaperones, X box-binding protein 1 (XBP1) toward restoring protein folding and cellular homeostasis[8,9].

Like IRE1, PERK has a protein kinase activity, and after its dissociation from GRP78, PERK dimerizes and autophosphorylates. Active PERK phosphorylates the eukaryotic initiation factor 2α (eIF2α), which blocks unfolded protein translation promoting cell survival and also activates the transcription of the ATF4 to decrease Unfolded protein level in the ER *via* the activation of various UPR genes[10]. If the adaptive mechanisms do not sufficiently recover the ER homeostasis, the UPR can switch from a pro-adaptive to a pro-apoptotic role[11].

ER STRESS AND HEART

Numerous studies have linked the disruption of the ER homeostasis to the pathophysi-ology of many diseases including heart diseases. However, the specific role of the ER stress signaling in the heart is yet to be defined and whether ER stress signaling is detrimental or protective in the heart is still a challenging question that needs to be answered[4,12]. In cardiomyocyte, Bcl2 proteins family was shown to induce

apoptosis *via* calcium signaling during ER stress induction[13]. In line with this study, prolonged ER stress triggered cardiomyocyte apoptosis and oxidation of CaMKII, a redox-sensitive enzyme, which was rescued by antioxidant or CamKII inhibitors treatments[14]. Furthermore, it has been shown that the oxidation of CaMKII may lead to cardiac dysfunction and apoptosis[15]. In this context, Roe *et al*[14] showed that CaMKII oxidation mediates ER stress-induced cardiac dysfunction and apoptosis and could be used as a potential target in cardiac diseases triggered by the ER stress. GRP78 has been found to increase in patients with heart failure suggesting the implication of the UPR activation in heart failure[16]. Patients with heart failure display a structural and architecture alteration of the ER as well as dys-regulation of the ER proteins involved in the UPR response[17]. In fact, spliced XBP1s, GRP78, ATF4, and CHOP were all induced in failing human heart[16-20]. Using the transverse aortic constriction (TAC) mouse model to induce heart failure, Okada *et al*[20] showed that the ER stress was induced in both hypertrophic and failing heart. Remarkably, the ER stress-CHOP and apoptosis were only seen in failing heart but not in hypertrophic heart indicating the differential effect of the ER stress pathology-dependent. Moreover, the ER stress-CHOP deficient mice develop less cardiac hypertrophy, fibrosis, and cardiac dysfunction compared to wild mice. Our recent study showed that the inhibition of the ER stress protected the heart against myocardial infarction induced by ischemia-reperfusion injury[21]. Together these studies suggest that the ER stress could be involved in the development of myocardial infarction, cardiac hypertrophy, and the transition from hypertrophy to heart failure[22,23].

Recently, PERK was shown to protect the heart from pressure overload-induced heart failure[24]. Cardiomyocyte-specific disruption of PERK did not affect the cardiac structure or function under normal conditions but exacerbates the development of heart failure in response to TAC[25]. The hearts of PERK knockout mice showed a dramatic reduction in Serca2α expression and an increase in apoptosis and UPR genes expression (GRP78, GRP94, CHOP) in response to TAC. These results suggest the importance of PERK in the maintenance of intracellular calcium homeostasis, control of the ER stress level and cell survival[25].

The activation of the UPR has been shown in ischemic heart diseases[26,27]. PERK activation was also observed in ischemic hearts, and its overexpression seems to promote cell survival while its down regulation is detrimental to cells[28,29].

XBP1s and GRP78 were increased in the ischemic heart of patients and animal models[27,30]. XBP1s seem to be cardio-protective in mice after ischemia-reperfusion injury[31,32]. Moreover, the ER stress-CHOP, PUMA and Tribbles3 downstream effectors of PERK play a significant role in cell death induced by the ER stress after myocardial ischemia-reperfusion injury[33].

ATF6, the third ER stress member that is activated during myocardial I/R injury. Using genetic and pharmacological approaches, Glembotski's group and others showed that ATF6 protects the heart against myocardial I/R injury probably through the induction of the ERAD machinery leading to the degradation of misfolded proteins in the ER[34-37]. Recently, it has been found that thrombospondin-4 protects the heart by promoting the adaptive response of the ER stress through the activation of the ER stress ATF6[38,39]. The authors showed that ATF6 location and activity could be determined *via* its interaction with thrombospondin-4. These results suggest the benefit of enhancing the adaptive response mediated by ATF6 as a potential therapy to target ischemic heart diseases.

INFLAMMATION AND ER STRESS

In recent years, various studies found links between the ER stress pathways and inflammation[40]. Ischemic heart disease, a significant cause of death is recognized as an inflammatory disease involving infiltration of monocytes and macrophages. Recently, cardiac-specific expression of monocyte chemoattractant protein-1 (MCP-1) in mice causes heart failure, which was correlated with the activation of a cluster of the ER stress-related genes[41]. It has been shown that the production of the pro-inflammatory cytokine such IFNγ, TNF-α, MCP-1, and IL-8 required the activation of the IRE1 and XBP1[42,43]. IRE1 has also been linked to inflammation mediated by NFκB cascade *via* its binding to TRAF2[44,45]. Moreover, ATF 6 can also trigger NFκB mediated inflammation through AKT phosphorylation[46].

ER STRESS AND APOPTOSIS

When the UPR fails to reestablish the ER homeostasis, the detrimental apoptotic

signaling pathway is activated. Up to date, it is still a mystery how cells chose between the adaptive/survival pathway *vs* the detrimental /death once the UPR machinery is triggered. Under sustained ER stress induction, IRE1α triggers apoptosis *via* the activation of JNK and p38 through TRAF2 and ASK1 mechanism[47,48].

Cardiac myocyte lacking ASK1 were resistant to apoptosis induced by the hydrogen peroxide[49]. Cardiac overexpression of ASK1 showed an increase in cardiac apoptosis in a mice model of TAC while ASK1 deficient mice were protected from heart failure[50]. In a rat model of I/R injury, the inhibition of ASK1 was able to reduce apoptosis and myocardial infarct size[51]. The p38 activates the ER stress CHOP and both p38 and JNK can activate Bax to initiate apoptosis. IRE1 is also known to activate caspase12 leading to apoptosis[52,53]. Moreover, the RNase activity of IRE1 known as RIDD may promote cell death *via* the degradation of mRNAs involved in protein survival[54]. It is worth noting that IRE1 exerts two opposing functions: death and survival depending on the conformational of the protein and the intensity of the stress mild *vs* high. Under mild conditions of the ER stress, IRE1 helps to relieve the stress by splicing XBP-1. Under high-prolonged ER stress, IRE1 triggers apoptosis *via* the interaction with TRAF2 and ASK1[54]. Erhardt's group recently described that the ER stress requires the proapoptotic Bcl-2 family protein (Puma) to promote apoptosis in cardiac myocytes[55]. Puma is critical for cell death related to I/R[56]. Thus, the overexpression of PUMA in cardiac myocytes contributes to apoptosis induced by the ER stress while deletion protects the heart from I/R injury[57]. These results suggest inhibition of Puma activity may be used to treat cardiac infarcts or prevent heart failure by blocking ER stress-induced apoptosis[56,58]. Additionally, evidence suggests that the ER stress-CHOP plays a pivotal role in mitochondria-dependent apoptosis in the heart with pressure overload[22]. It is clear that the ER stress induction is a mechanism that leads to apoptosis and therefore tissue damage.

ER STRESS AND AUTOPHAGY

Autophagy or "self-eating" is a highly conserved cell-recycling program for the clearance of damaged proteins and organelles. Autophagy has been reported in many cells type of the cardiovascular system and been classified into microautophagy, macroautophagy, and chaperone-mediated autophagy. Autophagy is necessary for the preservation of normal cardiac function. However, deficient or excessive cardiac autophagy is considered as a maladaptive response. Moreover, autophagy is regarded as "double edge sword" for its different role in the cardiovascular system.

Recently, the ER stress emerges as an important inducer of autophagy and a link between the ER stress, autophagy and cardiac function have been proposed[59,60]. Although, abundant data showed that cross talks exist between the ER stress and autophagy, the molecular mechanism is yet to be determined[61]. Zhang *et al*[62] recently showed that mitochondrial aldehyde dehydrogenase (ALDH2) was able to alleviate ER stress-induced cardiomyopathy *via* autophagy reduction. Reticulon, a membrane-associated protein localized at the ER has been shown to be involved in the induction of autophagy leading to the ER stress induction demonstrating the relationship between autophagy, reticulum and the ER stress[63]. Furthermore, the activation of the IRE1 induces autophagy *via* its interaction with TRAF2 and the activation of JNK leading to the regulation of Beclin-1 expression. Moreover, advance glycation products (AGEs) were able to trigger autophagy in cardiac myocytes probably *via* the ER stress signaling. In fact, crosstalk between advanced AGEs and ER stress signaling could mediate the induction of autophagy by AGES[64,65]. In a mouse model of sepsis, Cardiac-specific overexpression of the antioxidant metallothionein (MT) was able to rescue cardiac contractility dysfunction probably *via* ER stress and oxidative stress modulation[66]. In a swine model of hypertension, the progression of LVH has been shown to involve an early activation of the ER stress followed by an increase in autophagy leading to apoptosis[67]. SIRT1, a member of the sirtuins family, histone/protein deacetylases known to be crucially involved in signaling related to cell death/survival and has been found to be activated in the heart to promote cell adaptation and survival under stress[68]. Recently Lemaire's group reported that in cardiac cells, Sirt1 was able to modulate the induction of autophagy in response to the ER stress induction suggesting the possibility of tuning the adaptive autophagy in cardiac pathologies related to ER stress[69].

In summary, the ER stress and autophagy play an important role in the pathogenesis of cardiac complications. Although, ample studies established the interplay and the interaction between the ER stress and autophagy, and their role in the progression of heart diseases, the molecular mechanism remained unknown. Who are the players, how can we better tune the ER stress and autophagy? It is evident now

that the ER stress and autophagy are influencing each other. Therefore, a good understanding of the interconnection between these two important physiological processes, especially under pathological conditions will be of great importance and may shed light on developing new therapeutic strategies to rescue the cardiovascular system.

ER STRESS AND MICRORNAS

MicroRNAs (miRNAs or miRs) are a class of conserved small, 20-23 nucleotide, single-stranded, non-coding RNAs that post-transcriptionally regulate gene expression[70]. They were first described in the 1993 and had been linked to various cellular stress such oxidative stress, inflammation, and the ER stress in the setting of cardiovascular complications[71]. The miRNAs are increasingly recognized as a master regulator of the ER stress and an important player in the UPR response, which manage the UPR balance between survival and cell death during the ER stress-induction. In fact, several miRNAs have been demonstrated to be regulated by the ER stress and to regulate the ER stress by optimizing the levels of key proteins involved in the UPR. For instance PERK pathway induces the expression of miR-30c-2*, which represses XBP1s synthesis at the translational level[72]. Although miR-30c-2* level increases after the ER stress induction along with the XBP1s level, miR-30c-2* was still capable of affecting the XBP1 level in the course of the UPR[72]. In cardiac myocytes and using a Tamoxifen-inducible ATF6 in the heart of transgenic mice, activated ATF6 regulates the expression of 13 miRNAs[73]. The miRNA-455, one of the miRNAs down regulated by ATF6, negatively regulates calreticulin (a calcium chaperone protein) involved in the folding of nascent polypeptides[73]. Therefore, the ER stress ATF6 down regulates miRNA-455, which up-regulates calreticulin, a cardio-protective gene. While the ER stress ATF6 regulates the expression of miRNAs, it was also a target of miR-702[74]. Together, the two studies showed the existence of interplay between miRNAs and the pro-adaptive activity of the UPR in the heart. Another class of miRNAs linked to the ER stress includes member of miRNA-30 family. The miRNA30 is one of the most abundant miRNAs expressed in the myocardium and has been shown to be down-regulated in heart failure and hypertension in both vascular smooth muscle cells and cardiac neonate cells. Under ER stress conditions, miRNA-30 was down-regulated while GRP78 was up-regulated. Moreover, GRP78 up-regulation seems to modulate miRNA-30 expression through the inhibition of the C/EBP trans-activity by CHOP in the myocardium[75]. Interestingly, Knockdown of miRNA-30 in cardiac cells triggered ER stress and identified the ER stress ATF6/CHOP and caspase-12 as indirect targets of this miRNAs. While the transfection of miR-30 was able to abolish the ER stress suggesting that miRNA30 plays a role in the regulation of cell death and miRNA30 replacement could be considered as an approach for targeting the ER stress and the related pathological diseases[76]. Recent studies indicated that miRNA214 is a negative regulator of angiogenesis in the retina and heart[19,77]. XBP1 was found to be a direct target of miR214 in endothelial cells. The blockade of the endogenous miRNA214 expression regulated cardiac function and cardiac angiogenesis. Interestingly, cardiac overexpression of miRNA-214 in mice had no morphological changes suggesting that miRNA214 regulates cardiac and vascular angiogenesis only when XBP-1 is dys-regulated[78]. This study highlighted another scenario of ''cross talk'' between miRNAs and the ER stress components in the cardiovascular system. Independently of XBP-1, a recent study proposed a new role of the ER stress sensor IRE1α in the modulation of miRNA-200 and miRNA-466 and the improvement of bone marrow derived progenitor cells (BMPC) function *via* its endonuclease activity in diabetes[79]. This study outlined the importance of the ER stress IRE1α as a crucial modulator of the fate/function of BMPCs during angio-genesis and tissue repair *via* the modulation of miRNA expression levels and may be therefore involved in another ischemic setting such ischemic heart diseases and heart failure. Further studies are needed to determine the mechanism that inhibits IRE1α activity in diabetic BMPCs and the potential of expanding these findings to other cardiovascular complications, such as the heart failure[80]. The ER stress ATF4, a downstream effector of the ER stress PERK, has been linked to miR-663 in endothelial cells[81]. The inhibition of miRNA663 during the ER stress induction leads to a decrease in the ER stress ATF4 expression as well as its target gene, the VEGF. Moreover, miRNA708 was the first ER stress-induced miRNA discovered[82].

MicroRNAs and the ER stress interaction is a very young research area. More work is required to unravel the array of microRNA targets and determine their function in the ER stress-induced death/survival. Moreover, it is essential to recognize that the results obtained so far showing the interaction/link/correlation/regulation of the ER

stress by miRNAs or vice versa represent a promising avenue for cardiovascular diseases. As mentioned above, one of the significant challenges of the ER stress response in pathological situations is the fact that it is difficult to distinguish between the protective pathways and the detrimental pathways once the UPR response is triggered. Differentiating between the detrimental pathways and the adaptive pathways of the ER stress players *via* its miRNAs target will advance the field tremendously and opens new opportunities for novel therapeutic strategies targeting ER stress *via* miRNAs in cardiovascular diseases.

ER STRESS AS A TARGET THERAPY

ER stress has been involved in numerous cardiovascular diseases such as diabetes, hypertension, myocardial infarction and heart failure. Therefore, targeting the ER stress in cardiovascular disease *via* the activation of the adaptive pathway of the UPR or the inhibition of the detrimental pro-apoptotic pathways of the UPR will be a beneficial therapy for cardiovascular diseases.

Chemical chaperones, small molecules that work similarly to the endogenous molecular chaperone machinery to stabilize misfolded proteins, facilitate their proper folding and reduce the ER stress. Among the chemical chaperones that have been extensively used in various diseases related to the ER stress, Tauroursodeoxycholic (TUDCA) and 4-phenylbutyric acid (PBA).

TUDCA is a non-toxic hydrophilic bile acid that functions as a chemical chaperone and has been extensively used in colitis, pulmonary fibrosis, biliary cirrhosis, and recently in patients with obesity and insulin resistant[83-85]. In animal models, TUDCA has been shown to protect the heart against myocardial dysfunction in obesity, and reduce apoptosis in a mouse model of myocardial infarction[86]. Under pressure overload, TUDCA was shown to attenuate cardiac remodeling through down-regulation of the GRP78 and GRP94 and the regulation of the ER stress PERK phosphorylation and eIF2α[87]. Moreover, in a mouse model of heart failure induced by calreticulin overexpression, the inhibition of the UPR using TUDCA decreased cardiac fibrosis, which was mediated through the inhibition of the ER stress IRE1 activation and XBP1 splicing[88]. Together, these results highlight the cardioprotective effect of TUDCA treatment and the therapeutic potential of using TUDCA in the management of cardiac complications[66].

PBA, a low-molecular-weight aromatic fatty acid, has a chaperone-like activity and has been shown to attenuate cardiac hypertrophy, fibrosis, and apoptosis in a pressure overload animal model[89]. In isolated rat hearts subjected to I/R injury, 4-PBA was revealed to be a potent cardioprotective agent *via*: (1) The reduction in the I/R injury-induced myocardial dysfunction and cell apoptosis; (2) The delay of the onset of the ER stress *via* the regulation of Grp78 expression, PERK phosphorylation; and (3) The inhibition of oxidative stress[90]. In a cell and a clinically relevant dog model for atrial fibrillation, the blockade of the ER stress by PBA inhibits the induction of the autophagy and suppresses cardiomyocytes remodeling suggesting the potential of using PBA to protect the heart against clinical atrial fibrillation[91]. Furthermore, PBA and TUDCA were also able to reduce the cardio-toxicity effect of doxorubicin (a chemotherapeutic agent commonly used in cancer). Moreover, PBA and TUDCA reduced cardiomyocyte apoptosis and alleviated cardiac dysfunction in a mouse model of cardiomyopathy induced by doxorubicin[92]. Considering that TUDCA and PBA are FDA-approved chemical chaperones and already used clinically for the treatment of some diseases, it will be exciting and safer to test TUDCA and PBA in patients with cardiovascular complications related to the ER disturbance. Future basic and clinical studies are critically needed to determine: (1) The right doses required to obtain the cardioprotective effect; and (2) To delineate the mechanism of how chemical chaperones promote the protein folding.

Statin therapy has been shown to be beneficial for heart failure treatment[93]. Interestingly, a recent study showed that in a mouse model of pressure overload and this effect was associated with a reduction in the ER stress[94-97]. The results suggest that the reduction in the ER stress might be a novel mechanism for the beneficial effect of statin for heart failure[98]. Moreover, in a rat model of heart failure, the modulation of the ER stress markers such as Caspase12, the ER stress-CHOP, and GRP78 was proposed as a mechanism by which Atorvastatin (another statin drug) protects the heart against heart failure[99]. Interestingly, the administration of Atorvastatin improved left ventricular ejection fraction and attenuated left ventricular remodeling in patients with heart failure[100]. These results could be clinically relevant for the treatment and the prevention of heart failure.

Apelin recently discovered as an endogenous ligand for the G protein-coupled

receptor APJ and has been shown to be a beneficial therapy for patients with heart failure[101-103]. Apelin seems to have a positive effect on peripheral and coronary vasodila-tation, cardiac output, and cardiac function[104,105]. The cardioprotective effect of apelin could be mediated through the inhibition of the ER stress dependent apoptosis[106]. Furthermore, in a mouse model of obesity-induced cardiac complications, exogenous administration of apelin attenuates myocardial contractile dysfunctions and cardiac hypertrophy through the inhibition of the ER stress and the restoration of autophagy[107]. On the other hand, apelin 13 (the main subtype of apelin in the human heart) induced cardiomyocytes hypertrophy through autophagy and the ER stress mechanisms[108]. From these studies, the benefits *vs* the detrimental role of apelin in cardiac complication seem to depend on the conditions basic *vs* stress and could be explained by the UPR status of the ER stress adaptive *vs* detrimental UPR response.

Adenosine monophosphate-activated kinase (AMPK) recognized as an intracellular energy and stress sensor that function to maintain intracellular homeostasis during stress conditions. Dysregulation of AMPK has been reported in humans and animal models of metabolic syndrome[109-111]. The 5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside (AICAR) and metformin, antidiabetic drugs activate AMPK, reduce the ER stress and slow the progression of heart failure[112]. Additionally, AICAR activates nuclear factor-E2-related factor (Nrf2) through AMPK independent pathways, which helps combat oxidative damage. Increased expression of Nrf2 reduces cardiac hypertrophy, myocardial infarct, and the progression of heart failure. However, AMPK and Nrf2 pathways show convergence as well[113]. Therapies that activate AMPK and Nrf2, as well as the UPR and apoptotic pathways, hold promise in the treatment cardiac complications. Moreover, therapeutic efforts aimed at oxidative stress also reduce the ER stress. Thus, the ER stress appears to be, a key player in cardiovascular complications and a large number of drugs seemed to protect the heart against failure involved the ER stress modulation. Targeting the ER stress pathways hold a great feature for patients with cardiac complications. As the prevalence of heart diseases raises yearly worldwide, it becomes significant to understand the relationship between heart failure and the ER stress. There is still much to understand about the contribution of the ER stress in heart complications (Figure 1).

CONCLUSION

Significant attention was given to the ER stress in the recent years from "bench to bed" due to its involvement in numerous cardiovascular diseases such as diabetes, hypertension, myocardial infarction, and heart failure. Although many studies have characterized signaling pathways of the ER stress and the UPR in general and particularly in the cardiac field, many questions remained to be addressed. How can we tame the ER stress and what is the best way to control it? How can we balance "too much or too little" of the ER stress to promote survival and inhibit apoptosis in cardiac pathology? How can we integrate conventional therapies (AMP kinase drugs, ACE inhibitors, autophagy (activators/inhibitors) with the UPR target against cardiovascular diseases? How can we use MicroRNAs and gene therapy to regulate the ER stress toward a better and safe future therapy? Can the chemical chaperone be "the ER stress therapy" by excellence against cardiac complications? Only the future will tell us.

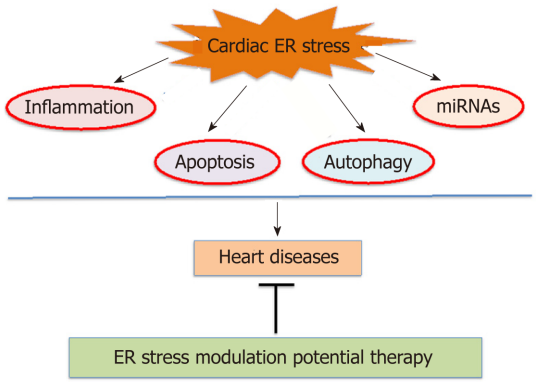

Figure 1 Schema recapitulating the involvement of the endoplasmic reticulum stress in heart diseases. ER: Endoplasmic reticulum.

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