

## Endoplasmic reticulum stress in abdominal aortic aneurysm

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### ABSTRACT

Abdominal aortic aneurysms (AAAs) are characterized by permanent dilatation of the abdominal aorta, which is accompanied by inflammation, degradation of the extracellular matrix (ECM) and disruption of vascular smooth muscle cell (VSMC) homeostasis. Endoplasmic reticulum (ER) stress is involved in the regulation of inflammation, oxidative stress and VSMC apoptosis, all of which are critical factors in AAA development. Although several studies have revealed the occurrence of ER stress in AAA development, the specific biological functions of ER stress in AAA development remain largely unknown. Given that targeting ER stress is a promising strategy for treating AAAs, further investigation of the physiological and pathological roles of ER stress in AAA development is warranted.

### 1. Introduction

Abdominal aortic aneurysms (AAAs) are characterized by progressive dilatation of the abdominal aorta and partial attenuation of the vessel structure [1]. Aortic rupture, which accounts for approximately 150,000–200,000 deaths worldwide each year, is the major risk factor associated with AAA [2]. AAA development is influenced by multiple mechanisms, including extracellular matrix (ECM) regression, inflammation, and vascular smooth muscle cell (VSMC) apoptosis [1,3]. Emerging evidence has indicated that the development of AAA is often accompanied by endoplasmic reticulum (ER) stress. Hence, increase our understanding of the role of ER stress in AAA development is vital.

The ER is a multifunctional organelle that plays crucial roles in cellular protein trafficking, protein synthesis and folding [4,5]. Various *in vitro* and *in vivo* factors may disrupt ER homeostasis, resulting in ER stress, which is characterized by the accumulation of unfolded and misfolded proteins [6,7]. ER stress has been demonstrated to participate in pathophysiological processes of the cardiovascular system, including myocardial ischemia, atherosclerosis, and cardiomyopathy [8–10]. Emerging evidence suggests a link between ER stress and AAA development [11,12]. Hence, further investigations into the functions of ER

stress in AAA development is warranted.

In our review, we aim to provide an overview of recent knowledge about the involvement of ER stress in the pathological process of AAA development. We will specifically highlight the potential applications of targeting ER stress.

AAAs are characterized by permanent ectasia or bulging of the abdominal aorta [13]. The major cause of death among AAA patients is aortic rupture, with a reported prevalence of 4.4 per 100,000 patients [14]. It is estimated that the risk of AAA development increases as the diameter of the aorta increases. An AAA with a diameter less than 50 mm has an annual risk of rupture of less than 5 %, whereas an AAA with a diameter exceeding 80 mm has a 30–50 % annual risk of rupture [14,15]. A history of long-term cigarette smoking is the strongest risk factor for AAA development, with smokers having a 5.9-fold higher risk of AAA development than nonsmokers [16,17]. This association may be explained by the fact that toxic reactive compounds, such as acrolein, easily form protein adducts, which induces the unfolded protein response (UPR) and triggers ER stress. In addition, patients with cardiovascular disease associated with lipoperoxidation have a greater carbonyl burden, which can trigger ER stress [18–21]. Other risk factors include advanced age, male sex, coronary artery disease (CAD),

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hypertension, and atherosclerosis in the coronary artery [22–24]. The pathogenic mechanisms underlying aortic aneurysm development include inflammatory responses, SMC apoptosis, oxidative stress, and ECM impairment, which contribute to aortic dilation and rupture [25,26]. Several studies have investigated the role of ER stress and mitochondrial oxidative stress in the formation of AAAs [12].

2. ER stress and the UPR

The ER is a vital intracellular organelle that is involved in various

cellular processes, including protein biosynthesis, folding, modification, calcium ion (Ca<sup>2+</sup>) storage, and lipid synthesis [27,28]. Under certain physiological or pathological conditions, such as hypoxia, increased intracellular calcium levels, oxidative stress, inflammation, metabolic starvation, and glucose deficiency, the accumulation of unfolded and misfolded proteins leads to ER stress [29]. To resolve ER stress, the UPR is activated, which facilitates the transfer and removal of accumulated unfolded proteins during the early stages of ER stress [30]. The UPR triggers multiple signaling processes that promote protein folding, posttranslational modifications, and the restoration of ER homeostasis

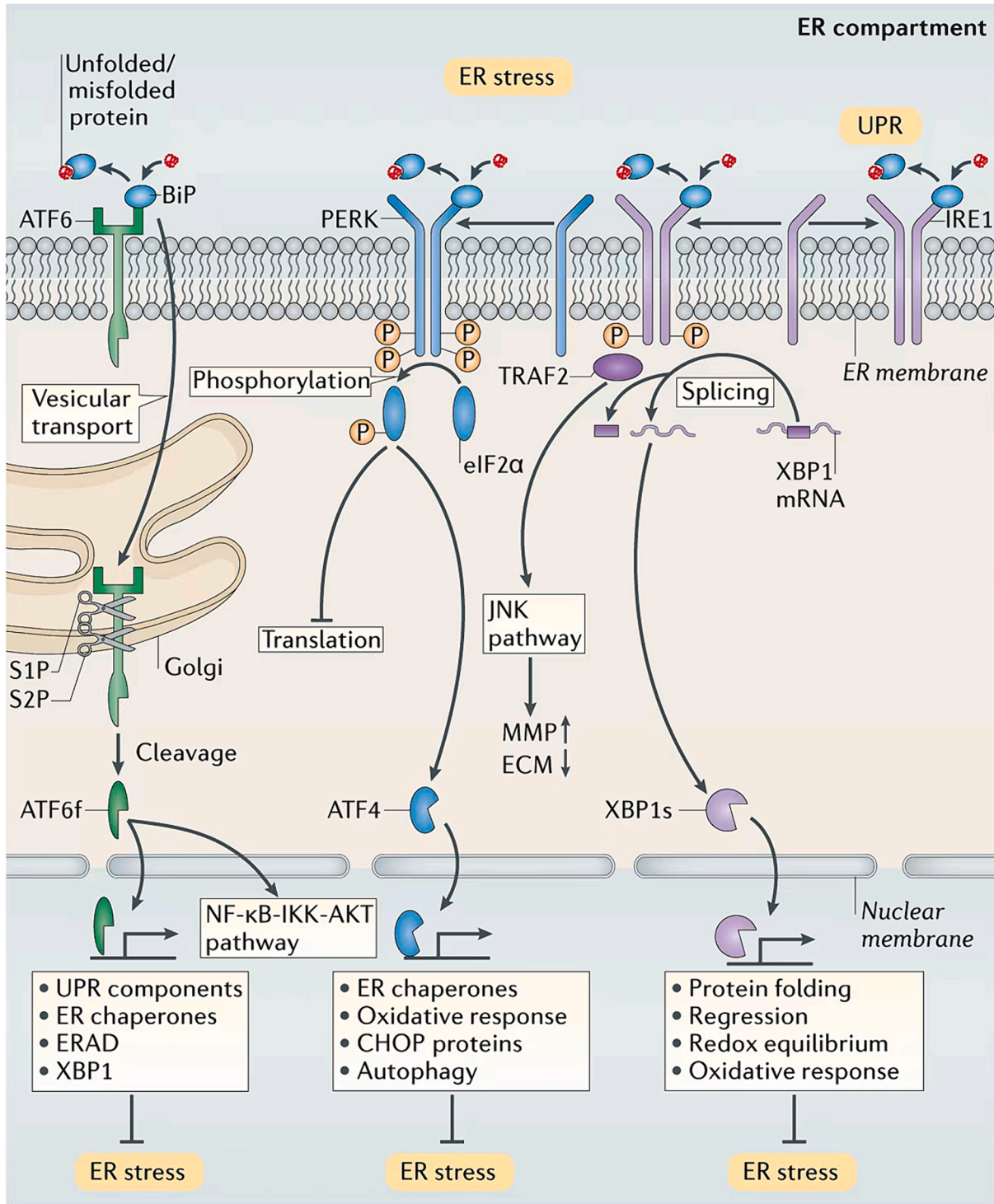


Fig. 1. UPR and Inflammation mechanisms of ER stress in AAA.

to alleviate ER stress [31,32]. However, if the UPR fails to relieve prolonged or overwhelming ER stress, apoptosis is ultimately induced [33,34].

The UPR involves three transmembrane proteins that are localized to the ER: inositol requiring enzyme-1 (IRE-1), protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6) [35]. Under normal physiological conditions, the immunoglobulin protein (BiP), which is also known as GRP78, prevents the activation of ATF6, PERK, and IRE1 by binding to them; this was first discovered in a mouse model of polycystic ovary syndrome (PCOS) following metformin treatment and the dihydrotestosterone (DHT)-mediated induction of ER stress [36]. However, when misfolded proteins accumulate, BiP binds to these proteins, releasing ATF6, PERK, and IRE1. These three transmembrane proteins coordinate the UPR and activate a broader gene expression program [37]. The activation of PERK during ER stress leads to the phosphorylation of eukaryotic initiation factor 2 $\alpha$  (eIF2 $\alpha$ ), which results in a temporary reduction in overall protein translation, including that of ATF4, to alleviate the ER load [38]. On the other hand, persistent PERK activation by prolonged ER stress induces cell apoptosis through the C/EBP homologous protein (CHOP)/GADD153 pathway [39]. Additionally, once released from BiP, the endoribonuclease activity of IRE1 is increased via its dimerization and autophosphorylation, leading to the translation of X-box-binding protein 1 (XBP1) [40,41]. XBP1 translocates to the nucleus and regulates protein folding, regression, and factors that are involved in redox equilibrium and the oxidative stress response, thereby mitigating the ER burden [42]. However, excessive and severe ER stress can lead to hyperactivation of IRE1 autophosphorylation, triggering maladaptive responses and cell death. Moreover, under ER stress conditions, ATF6 translocates to the Golgi apparatus, where it undergoes intramembrane cleavage mediated by site-1 protease (S1P) and site-2 protease (S2P), releasing the cytoplasmic portion of ATF6. The released and activated ATF6 then enters the nucleus and transactivates genes that encode UPR components, chaperones, ERAD components, and XBP1 [43,44]. Under stress conditions, ATF6 activates genes that promote proper ER folding, eliminate misfolded proteins, restore redox homeostasis of the ER, and induce autophagy. These processes play important roles in maintaining cell viability. However, when the adaptive UPR fails to maintain ER homeostasis, ATF6 promotes inflammation and apoptosis (Fig. 1) [45].

Recent studies have demonstrated an increase in the expression of key ER stress markers, including XBP-1, cleaved ATF6, and CHOP, in AAAs [12]. 7-Ketocholesterol (7-KC) is an ER stress inducer, and its expression is related to the expression of ER stress markers. The regulation of 7-KC expression can regulate the ER stress level and mediate AAA progression [12,25,46]. On the other hand, ER stress inhibitors attenuate ER stress and significantly inhibit AAA development [25,47]. These findings indicate that ER stress plays a significant role in AAA development. Therefore, suppression of ER stress has emerged as a potentially effective therapeutic strategy for preventing AAA formation and rupture [25,48]. However, the precise mechanisms underlying the involvement of ER stress in AAA formation have yet to be fully elucidated. Further research is needed to elucidate the potential role of ER stress in AAA pathogenesis.

### 3. The contribution of ER stress to inflammation during AAA formation

Inflammatory cells are well known to produce inflammatory cytokines in response to tissue injury, and these cytokines can increase protein misfolding and trigger ER stress [49,50]. The UPR is activated in affected tissues during various inflammatory diseases, including inflammatory bowel disease, neuromuscular inflammatory diseases and rheumatoid arthritis [50,51].

The three UPR signaling pathways can also promote the expression of proinflammatory factors, such as MCP-1, TNF- $\alpha$ , and IL-8, which play crucial roles in the development of aortic aneurysms [47]. UPR

activation is tightly interrelated with inflammatory signaling pathways, including the JNK and/or NF- $\kappa$ B signaling pathways, as well as potentially other pathways [52,53]. JNK signaling regulates ECM metabolism by increasing MMP secretion and attenuating ECM biosynthesis during AAA formation [54,55]. Several studies have shown that NF- $\kappa$ B promotes the expression of cytokines, such as MMP-1, MMP-3 and MMP-9, inducing AAA formation [56,57]. ER stress-induced NF- $\kappa$ B accumulation contributes to the formation of aortic aneurysms via the regulation of SMC phenotypes [58].

During ER stress, activated IRE1 $\alpha$  triggers the adaptor protein TNF-receptor activating factor 2, resulting in the retrogradation of the NF- $\kappa$ B protein I $\kappa$ B kinase; this finding indicates an association between ER stress and NF- $\kappa$ B activation [59]. This signaling pathway plays a crucial role in the regulation of numerous inflammatory pathways and has been reported to be a key player in AAA pathogenesis. Activated IRE1 also promotes important inflammatory pathways via activated JNK, thus integrating ER stress with other key signaling pathways that can regulate the transcription of various inflammatory cytokines [60]. Following ER stress and protein misfolding, the proteases S1P and S2P (site 1 and site 2) cleave ATF6 as it translocates from the ER to the Golgi, leading to the release of activated transcription factors and their translocation to the nucleus. The ATF6 pathway of the UPR has been reported to activate the NF- $\kappa$ B-IKK pathway, resulting in downstream AKT phosphorylation [61]. Furthermore, activated PERK, which inhibits protein translation by phosphorylating eIF2 $\alpha$  in cells undergoing ER stress, leads to the upregulation of I $\kappa$ B $\alpha$ , which ultimately activates the NF- $\kappa$ B signaling pathway (Fig. 1) [62].

### 4. VSMC development and ER stress in AAA-related diseases

VSMCs are the predominant cell type in the medial layer of the aorta, and they play crucial roles in maintaining vascular tone, strength, and elasticity by synthesizing various factors, such as elastin, collagen, laminin, and proteoglycans [62]. In the early stages of AAA development, the number of VSMCs in the medial layer of the arterial wall decreases. This depletion alters vascular tone and increases the susceptibility of the arterial wall to ectasia, ultimately resulting in aneurysm formation [26,63]. Moreover, ER stress has been reported to promote severe VSMC apoptosis in human AAA tissues (Fig. 2) [64].

### 5. The role of sarcoplasmic/endoplasmic reticulum Ca<sup>2+</sup>-ATPase 2 (SERCA2) in AAA formation via the regulation of ER stress

SERCA is located on the SR membrane, and it plays a critical role in maintaining Ca<sup>2+</sup> homeostasis [65]. The main function of SERCA is to transport cytosolic Ca<sup>2+</sup> back into the SR lumen from the cytoplasm in response to muscle contraction [65,66]. SERCA is a P-type ATPase, and it is an integral membrane protein of the SR/ER. It is encoded by three genes: ATP2A1, ATP2A2, and ATP2A3 [67]. SERCA1a is expressed predominantly in striated muscle cells, whereas SERCA2a is expressed mainly in cardiac muscle, smooth muscle, and nonmuscle tissues. SERCA2b is a ubiquitous isoform and serves as the housekeeping SERCA protein in muscle tissues, whereas SERCA3 is almost inactive in muscle tissues and is expressed at very low levels in nonmuscle cell types [68]. It has been reported that an irreversible oxidizing reaction of SERCA2 C674 contributes to the formation of aortic aneurysms by inducing ER stress and promoting SMC apoptosis [48]. Several studies have revealed that inactivation of SERCA2 C674 modulates SMC phenotypes due to intracellular Ca<sup>2+</sup> accumulation, which triggers calcineurin-regulated NFAT/NF- $\kappa$ B signaling, thereby accelerating the development of aortic aneurysms (Fig. 3) [58,69].

### 6. ER stress-related targets of AAA formation

On the basis of evidence that indicates that ER stress is involved in



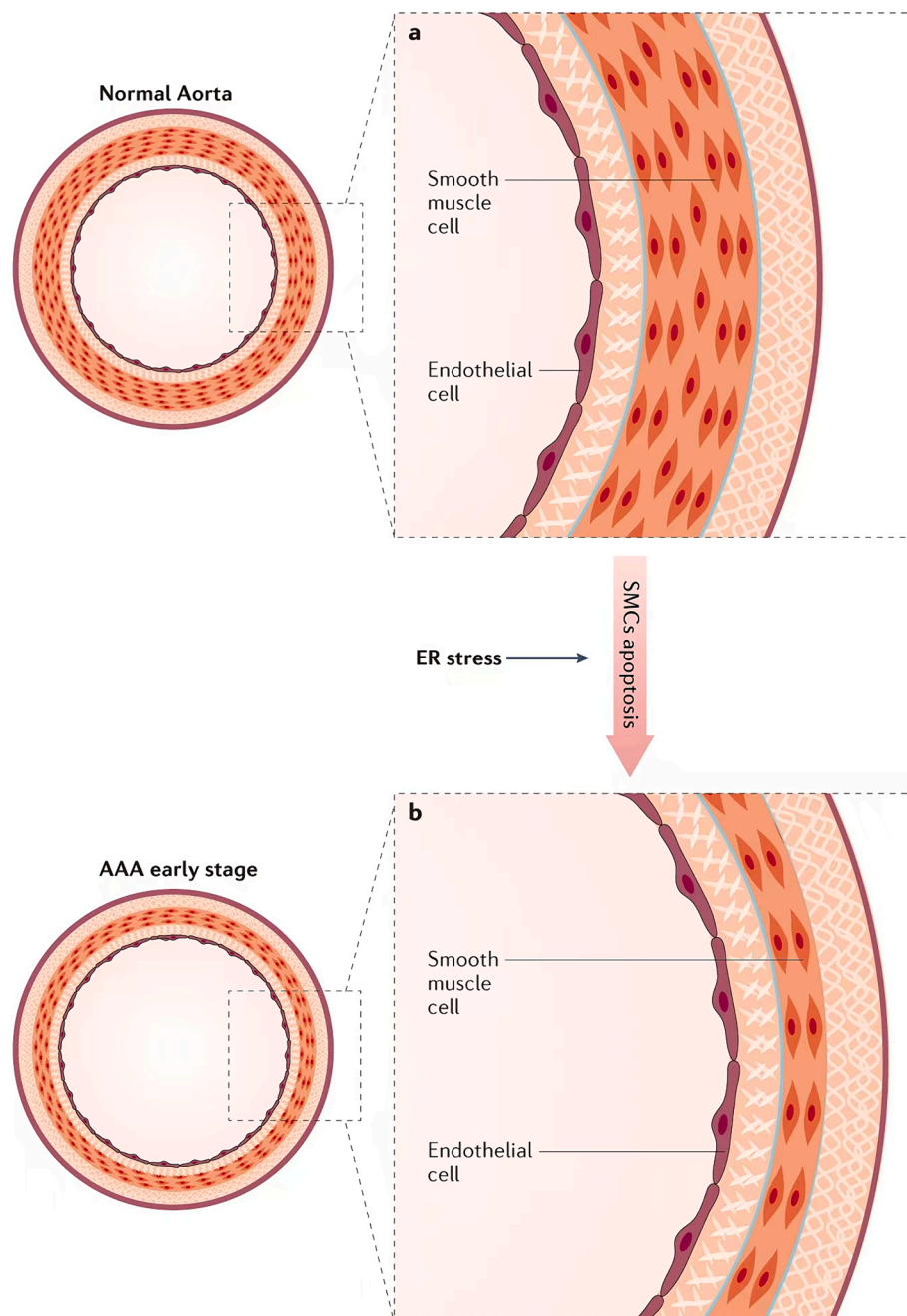
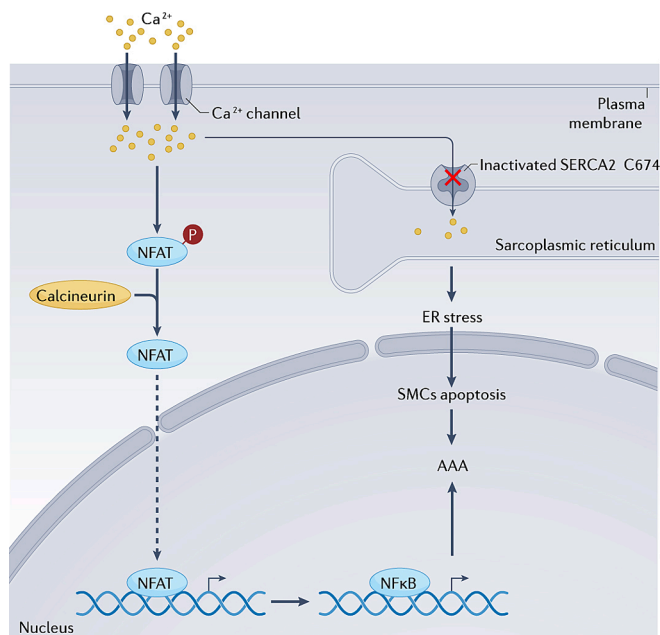


Fig. 2. VSMC apoptosis mechanisms of ER stress in AAA.

the pathological process of AAA development, approaches that regulate factors related to ER homeostasis/UPR signaling are emerging as potential therapeutic approaches for treating AAAs. Alternative strategies that aim to enhance the adaptive UPR, which promotes cell survival and recovery, or suppress ER stress-associated apoptosis have shown promise in preventing AAA formation. The ER stress inhibitor tauroursodeoxycholic acid (TUDCA) has been reported to significantly inhibit Ang II-induced AAA development by attenuating ER stress-induced apoptosis [25]. Similarly, the ER stress inhibitor 4-PBA regulates BAPN-induced aortic aneurysm formation by inhibiting SMC apoptosis, ER stress, and inflammation. Thus, ER stress inhibitors show potential as treatments for aortic aneurysms [47]. TUDCA and 4-PBA have been found to exert many effects, including ER stress-modulatory, anti-apoptotic and anti-inflammatory effects, and they have potential therapeutic benefits in many diseases, such as AAAs,

diabetes, obesity, neurodegenerative diseases, and cancer. However, the exact molecular pathways that are activated after treatment with these agents remain to be determined. Therefore, further extensive examination is still needed to reveal the novel roles of these inhibitors [70–72]. In addition, the EGFR inhibitor erlotinib has been shown to prevent Ang II-induced AAA formation by inhibiting EGFR protein aortic aneurysm formation, ER stress and oxidative stress responses [73]. The Cys674 residue (C674) in SERCA2 plays a vital role in maintaining the physiological functions of the ER. Oxidative inactivation of SERCA2 C674 exacerbates aortic aneurysm formation by promoting ER stress and subsequent SMC apoptosis and inflammation, suggesting that SERCA2 and ER stress are potential targets for treating aortic aneurysms [48]. Intermedin (IMD)1–53, which is a bioactive peptide, has been shown to prevent AAA development by inhibiting ER stress via the induction of AMPK phosphorylation. These findings provide novel insights for the



**Fig. 3.** Sarcoplasmic/Endoplasmic Reticulum Ca<sup>2+</sup> ATPase2 mechanisms of ER stress in AAA.

development of potential therapeutic strategies for treating AAAs by targeting ER stress (Fig. 3) [65]. Additionally, a previous study demonstrated that silencing cav1 (caveolin 1) protects mice from AAA formation by preventing Ang II-induced ADAM17 activation/induction, ER stress, oxidative stress responses and inflammation [74]. These findings further support the notion that targeting ER stress could be a novel therapeutic approach for AAA development.

## 7. Conclusion

Emerging evidence indicates that ER stress and the UPR play key functions in the pathological processes of AAA formation. This evidence has been found primarily in AAA animal models; however, there are some differences between various AAA models and AAAs in humans. The most common approach for examining the mechanisms underlying AAA pathogenesis is the use of mouse and rat animal models. Three methods are commonly used to induce AAA development in animal models: angiotensin II infusion, elastase perfusion, and calcium chloride or phosphate administration. The angiotensin II-induced model typically involves suprarenal abdominal aortic aneurysms, which are different from the infrarenal abdominal aortic aneurysms that are common in humans. The typical features of this model are aortic dissection and intramural hematoma, which often rupture, leading to substantial differences between this model and human AAAs. However, the angiotensin II-induced model remains the most commonly studied AAA model. The elastase perfusion model typically involves infrarenal abdominal aortic aneurysms, which are similar to human AAAs. In contrast to human AAAs, elastase perfusion-induced AAAs do not rupture, and unlike the angiotensin II model, elastase perfusion-induced AAAs lead to expansion of the whole aortic wall. Compared with the other two models, the calcium chloride or phosphate model usually involves infrarenal abdominal aortic aneurysms, which have a relatively mild degree of aortic dilation. Moreover, this model has pathological features that are consistent with human AAAs, such as inflammation, angiogenesis, elastin rupture, and calcification, but this model also lacks some features of human AAAs, such as luminal thrombosis and aortic rupture [75,76].

In this review, we aim to summarize the various ways in which ER stress contributes to AAA formation, including the UPR, inflammation,

and SMC apoptosis. Although increasing evidence suggests the involvement of ER stress and the UPR in AAA formation, further research is needed to gain a deeper understanding of the mechanisms that drive these pathological processes. This knowledge will be invaluable for the development of more effective strategies for treating AAAs.

ER stress markers are early warning signs of impending AAA development and can be used to help prevent the occurrence of AAAs; however, there is currently insufficient evidence to prove this. GRP78 prevents the activation of ATF6, PERK, and IRE1 by binding to them [36]. However, GRP78 is a chaperone protein that is expressed mainly in the ER lumen, and it plays an important role in ER stress by assisting in the assembly of misfolded proteins and can translocate to the cell surface to initiate various intracellular pathways under certain conditions [77]. Masashi Miyao et al. reported that compared with those in healthy patients, 7-KC levels were significantly higher in the plasma of AAA patients. 7-KC levels are positively correlated with the vascular expression of ER stress markers in AAA patients, which contributes to AAA development. At present, ER stress markers have not been detected in circulating blood. 7-KC can reflect ER stress in AAA patients and is expected to be used as a biomarker of ER stress and as an early warning sign of imminent AAA formation [12,78,79].

## Authors' contributions

Z.X. and P.Z. designed the study and composed the manuscript. ZH.S. contributed to write the first version of manuscript. P.Z. corrected the manuscript for revision and finalized the manuscript. All authors read and approved the final manuscript.

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## Registration number of clinical studies

NA.

## CRediT authorship contribution statement

**Zhaohai Su:** Writing – original draft, Investigation. **Weiling Lu:** Writing – original draft, Methodology. **Jun Cao:** Writing – original draft, Investigation. **Zheng Xie:** Writing – review & editing, Supervision. **Pei Zhao:** Writing – review & editing, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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