生理学报 *Acta Physiologica Sinica*, April 25, 2020, 72(2): 190–204
DOI: 10.13294/j.aps.2020.0015 http://www.actaps.com.cn

综 述

内质网应激与心血管疾病关系的研究进展

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摘 要：内质网是蛋白质折叠、转录后修饰和转运的重要细胞器，对维持细胞稳态具有重要作用。多种内外环境刺激能够引起内质网内错误折叠或未折叠蛋白的积累，即形成内质网应激。内质网应激激活未折叠蛋白反应(unfolded protein response, UPR)，进而启动一系列下游信号以维持内质网稳态。但持续或过度的内质网应激激活的UPR最终导致细胞凋亡和疾病。近年来，大量研究证据表明，内质网应激参与多种心血管疾病(cardiovascular disease, CVD)的发生和发展，包括缺血性心脏病、糖尿病性心肌病、心力衰竭、动脉粥样硬化、血管钙化、高血压和主动脉瘤等，是治疗多种CVD的重要靶点。本文就内质网应激激活UPR在多种常见CVD中的调控机制以及内质网应激与CVD关系的研究进展作一简要综述。

关键词：内质网应激；未折叠蛋白反应；心血管疾病
中图分类号：R363.1

New research advances in relationship of endoplasmic reticulum stress and cardiovascular diseases

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Abstract: Endoplasmic reticulum (ER) is an important organelle for protein folding, post-transcriptional modification and transport, which plays an important role in maintaining cell homeostasis. A variety of internal and external environmental stimuli can cause the accumulation of misfolded or unfolded proteins in the endoplasmic reticulum, and then result in ER stress. ER stress activates the unfolded protein response (UPR) and initiates a cluster of downstream signals to maintain ER homeostasis. However, severe and persistent ER stress activates UPR, which eventually leads to apoptosis and diseases. In recent years, a lot of researches suggest that ER stress plays an important role in the pathogenesis of various cardiovascular diseases (CVD), including ischemic heart disease, diabetic cardiomyopathy, heart failure, atherosclerosis and vascular calcification, high blood pressure and aortic aneurysm. ER stress might be one of the important targets for treatment of multiple CVD. Herein, the regulation mechanism of ER stress by activating UPR pathways in various common CVD and the new research advances in relationship of ER stress and CVD are briefly reviewed.

Key words: endoplasmic reticulum stress; unfolded protein response; cardiovascular disease

目前，我国心血管疾病 (cardiovascular disease, CVD) 患病率及死亡率仍处于持续上升阶段，CVD 死亡位居城乡居民总死亡原因的首位，农村为 45.50%，城市为 43.16% [1]。近年来，大量研究表明内质网应

Received 2019-08-28 Accepted 2020-02-27

Research from the corresponding author's laboratory was supported by grants from the National Natural Science Foundation of China (No. 91339203, 31872790).

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激参与了多种 CVD 的发生和发展，包括缺血性心脏病、糖尿病性心肌病、心力衰竭、动脉粥样硬化、血管钙化、高血压和主动脉瘤等，是治疗多种 CVD 的重要靶点 [2–4]。内质网是一种多功能的细胞器，它是蛋白质合成、折叠、转运、钙稳态调控和脂质生物合成的主要场所。生理或病理刺激，如氧化应激、蛋白质糖基化抑制、缺血缺氧、病原体或病原体相关成分如内毒素、钙稳态失衡和正常或异常折叠蛋白表达增多，都能引起内质网内错误折叠或未折叠蛋白的积累，即形成内质网应激 [5]。内质网应激激活未折叠蛋白反应 (unfolded protein response, UPR)，UPR 启动下游信号通路，一方面通过降低蛋白质合成和转运入内质网减轻内质网的折叠负荷，另一方面 UPR 信号促进内质网蛋白折叠基因的表达以增强内质网的折叠能力，纠正内质网应激的失衡状态 [6]，然而，如果内质网应激仍持续高水平存在，UPR 会导致细胞功能障碍和凋亡，进而导致疾病的发生和进展 [7]。本文综述内质网应激与缺血性心脏病、心力衰竭、动脉粥样硬化、血管钙化、高血压和主动脉瘤发病及其相关机制的研究进展。

1 内质网应激和UPR

目前至少发现了三种内质网应激的感受分子，分别是肌醇需求因子 1 (inositol-requiring enzyme 1, IRE1)、活化转录因子 6 (activating transcription factor 6, ATF6)、类蛋白激酶内质网激酶 (protein kinase R-like ER kinase, PERK)，它们激活了 UPR 的三条信号通路 (图 1) [8]。它们都是位于内质网膜上的跨

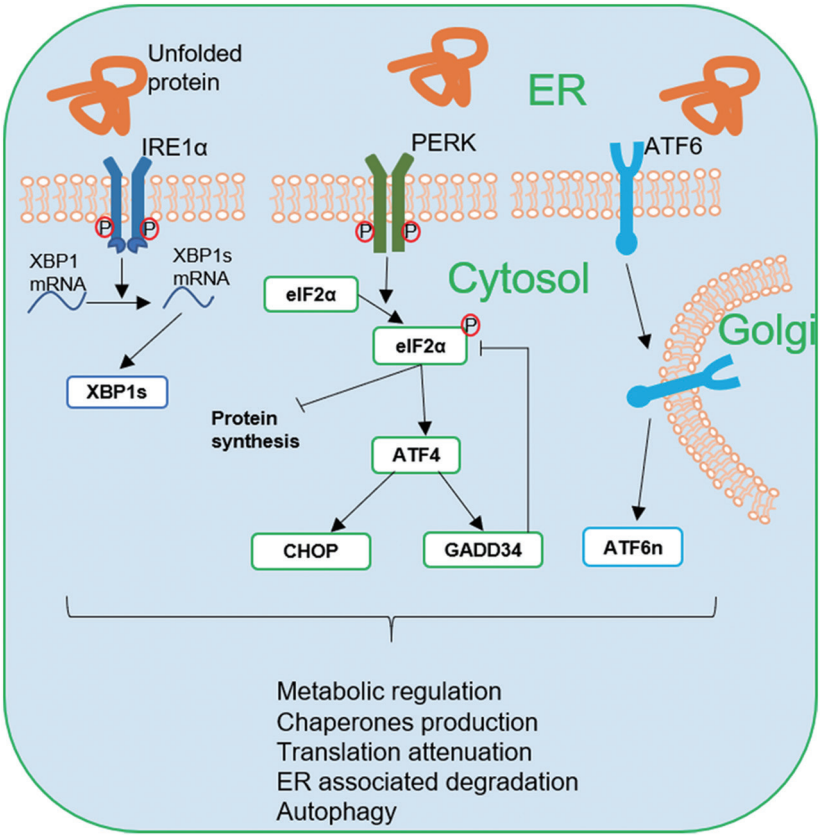

图 1. 未折叠蛋白反应的三条信号通路

Fig. 1. Three signaling pathways of the unfolded protein response (UPR). Three endoplasmic reticulum (ER) stress sensors (PERK, IRE1α, ATF6) initially activate signaling events that reduce protein load on the ER and increase its protein-folding capacity. Stimulation of the UPR leads to activation of various downstream signaling, such as metabolic regulation, chaperone production, translation attenuation, ER associated degradation and autophagy, which together aim to re-establish ER homeostasis. IRE1α: inositol-requiring enzyme 1α; ATF6: activating transcription factor 6; PERK: protein kinase R-like ER kinase; XBP1: X-box binding protein-1; eIF2α: eukaryotic translation initiation factor 2α; ATF4: activating transcription factor 4; CHOP: CCAAT/enhancer binding protein homologous protein; GADD34: growth arrest and DNA damage-inducible gene 34; ATF6n: cleaved ATF6.

膜蛋白，正常情况下三者与伴侣分子葡萄糖调节蛋白 78 (glucose-regulated protein 78/binding immunoglobulin protein, GRP78/BiP) 结合，当内质网应激发生时，GRP78 被未折叠或错误折叠蛋白招募而与 IRE1、ATF6 和 PERK 解离，解离后这三个分子分别被活化并进一步激活下游的 UPR 信号 [8, 9]。

IRE1 是内质网膜上的跨膜蛋白，同时具有激酶活性和核酸内切酶活性。当感受到内质网应激刺激时，IRE1 发生二聚化和自身磷酸化，激活 IRE1 上的核糖核酸酶域 [10]，活化的 IRE1 作用于 X 盒结合蛋白 (X-box binding protein-1, XBP1) mRNA，切除其 26 个核苷酸长度的内含子从而改变其编码读码框 [11]，由剪接过的 XBP1 mRNA 编码的 XBP1s 变得更加稳定且对 UPR 相关基因的表达具有促进作用，由此增强了内质网对蛋白质的折叠能力。

ATF6 是一种转录因子，作为内质网上的跨膜蛋白有较大的内质网腔内结构 [10]。当内质网内未折叠蛋白积累时，ATF6 被转运到高尔基体 [12]，由高尔基体上的位点 1 蛋白酶 (site-1 protease, S1P) 和位点 2 蛋白酶 (site-2 protease, S2P) 分别移除 ATF6 的腔结构域和跨膜锚，游离的 N 端 ATF6 (ATF6n) 进入细胞核，激活 UPR 相关基因，如 GRP78、蛋白二硫键异构酶、葡萄糖调节蛋白 94 (glucose-regulated protein 94, GRP94) 等促蛋白折叠分子表达增加。

PERK 也是位于内质网上的跨膜激酶，与 IRE1 类似的是感受到未折叠蛋白积累时，PERK 发生寡聚化和自身磷酸化，而与 IRE1 不同的是活化的 PERK 还能够磷酸化真核起始因子 2α (eukaryotic translation initiation factor 2α, eIF2α) —— 一种广泛存在的转录因子，间接抑制 eIF2 和 RNA 的转录，从而减少蛋白质的合成，减轻内质网应激负荷。此外，有些基因在转录因子 eIF2 受限时反而转录增多，如转录激活子 4 (activating transcription factor 4, ATF4) 基因。转录因子 ATF4 的两个靶基因分别是生长停滞和 DNA 损伤诱导基因 34 (growth arrest and DNA damage-inducible gene 34, GADD34) 和凋亡蛋白 C/EBP 同源蛋白基因 (CCAAT/enhancer binding protein homologous protein, CHOP)，GADD34 编码磷酸酶 1c (protein phosphatase 1c, PP1c) 对抗 eIF2α 的磷酸化，形成 PERK 通路的负反馈调节 [13]，而 CHOP 是调控细胞凋亡相关基因的转录因子，PERK 信号通路持续激活，诱导细胞凋亡。

2 内质网应激与CVD

近年来，慢性内质网应激引起的细胞损伤越来越多地被发现参与多种人类常见疾病的发生和发展，有大量研究表明内质网应激在糖尿病，神经退行性疾病，休克，肺纤维化，病毒感染，炎症损伤，癌症以及 CVD 中发挥了重要作用 [5, 14]。这些看似不相干的疾病却有着共同的特点，即细胞内外环境的变化影响了内质网中蛋白折叠的平衡，引起内质网应激，启动 UPR 信号通路。

2.1 内质网应激与心脏疾病

2.1.1 内质网应激与心肌缺血及缺血再灌注损伤

缺血性心脏病是世界范围内导致 CVD 相关残疾和死亡的主要原因 [15]。缺血对心脏造成严重的刺激，引起广泛病理学改变并引发心肌细胞死亡 [16]。本研究组早期研究 [17, 18] 显示，大鼠心肌缺血再灌注损伤时心肌内质网应激显著激活，心肌损伤的标志分子乳酸脱氢酶活性和丙二醛含量显著增加。2016 年，Zhao 等人 [19] 使用大鼠缺血再灌注损伤模型发现用药物抑制 PERK 和 eIF2α 磷酸化能够显著降低 ATF4 和 CHOP 的表达，明显减少心肌细胞凋亡，改善心功能并缩小大鼠心肌梗死面积，提示抑制内质网应激和 UPR 的 PERK 信号通路可减轻缺血再灌注损伤造成的心肌细胞凋亡和心肌损伤。IRE1 在心脏缺血再灌注损伤中的作用目前还存在争议。2019 年，Wu 等人 [20] 在大鼠心肌缺血再灌注损伤模型中发现内质网应激 IRE1 信号相关蛋白和 mRNA 水平升高，而当 IRE1 信号被低剂量的内毒素抑制后心肌细胞凋亡减轻，提示心肌缺血再灌注损伤时 IRE1 信号活化加重或促进心肌损伤。但也有研究显示 IRE1 信号在心肌缺血灌注损伤中发挥保护作用。2014 年，Wang 等人 [21] 在小鼠心脏缺血再灌注损伤模型中发现内质网应激 IRE1/XBP1 信号通路被激活，XBP1 通过诱导己糖胺合成通路改善心脏损伤，心肌特异性敲除 *XBP1* 小鼠在缺血再灌注后心肌梗死面积显著增大，而诱导性过表达 *XBP1* 的小鼠则表现出显著的心脏保护作用。此外，2019 年，Yan 等人 [22] 在大鼠心肌缺血再灌注损伤模型中发现，用内质网应激激动剂衣霉素预处理诱导内质网应激能够减轻病理性心肌损伤，减少心肌氧化应激损伤和心肌细胞凋亡，上调 ATF6、RACK1、PERK、GRP78 和 PGC-1α 表达，提示内质网应激预处理可以减轻糖尿病大鼠心肌缺血再灌注损伤。

与 PERK 和 IRE1 调控的 UPR 分支所不同，

ATF6 通路与促凋亡信号没有直接的联系[14]，且近年来的研究表明在心肌缺血及缺血再灌注损伤中 ATF6 起保护作用。2010 年，Toko 等人[23] 在心肌梗死小鼠模型中采用 S1P 的抑制剂间接抑制 ATF6 的活性后，心肌损伤加重、心脏功能显著降低，并且小鼠死亡率升高。近年来，有研究显示全身或心肌细胞特异性敲除 *ATF6* 的小鼠对心肌缺血再灌注损伤变得更加敏感，并且外源性过表达 *ATF6* 能减轻心脏缺血再灌注损伤[24, 25]。2019 年，Blackwood 等人[25] 在缺血再灌注损伤小鼠模型中用药物活化 ATF6 后，心肌损伤减轻且心功能得到改善，而心肌细胞特异性敲除 *ATF6* 小鼠心肌损伤加重，心功能下降。

据报道，内质网应激与磷脂酰肌醇 -3- 羟激酶 / 蛋白激酶 B (phosphatidylinositol-3-hydroxykinase/protein kinase B, PI3K/Akt) 信号通路相互作用，共同参与心脏缺血再灌注损伤的调控。2018 年，Bi 等人[26] 研究显示心脏缺血再灌注损伤能诱导 GRP78 激活 Akt 信号，共同保护心脏组织。2019 年，Zhang 等人[27] 的研究也显示，在大鼠心脏缺血再灌注损伤模型中 PI3K/Akt 通路活化能够减轻内质网应激引起的心肌细胞凋亡。用 PI3K/Akt 抑制剂抑制 PI3K/Akt 通路后心肌组织凋亡损伤加重[28]。Deng 等人的研究显示，在离体培养的 H9c2 细胞中，低氧 - 复氧处理激活的 PI3K/Akt 通路可减轻内质网应激诱导的细胞凋亡[29]。

2.1.2 内质网应激与糖尿病性心肌病

在不存在冠脉疾病、瓣膜病以及不存在高血压、血脂异常等心血管危险因素情况下，糖尿病患者发生的心肌结构和功能异常称为糖尿病性心肌病[30]。2015 年，Nam 等人[31] 在丙酮醛诱导的小鼠糖尿病性心肌病模型中发现内质网应激激活，丙酮醛处理的心肌细胞 GRP94、GRP78、ATF4、CHOP、p-PERK、p-eIF2α、p-JNK 蛋白水平显著增加，同时有心肌细胞凋亡，后者可被 CHOP siRNA 逆转。*CHOP* 敲除后小鼠心肌细胞凋亡、炎症和心脏功能障碍显著减轻，提示 CHOP 是丙酮醛诱导的小鼠糖尿病性心肌病心肌细胞凋亡和心脏功能障碍的关键信号分子。此外，2019 年，Sun 等人[32] 在糖尿病性心肌病大鼠模型中发现通过下调内质网应激相关分子 PERK 和 ATF6 的表达能够减轻心肌细胞凋亡，而过表达 CHOP 后心肌细胞凋亡加重。2019 年，Feng 等人[33] 的研究表明，1 型或 2 型糖尿病小鼠心脏内质网应激 ATF4/CHOP 通路激活。2019 年，Chengji 等人[34] 在糖尿病性心肌病大鼠中发现运动训练通过减弱内质网应激 CHOP/caspase-12 介导的心肌细胞凋亡而保护心脏组织。以上研究显示在糖尿病性心肌病发生过程中，内质网应激主要通过活化 PERK-ATF4-CHOP 信号通路，进而激活心肌细胞中的凋亡信号，导致心肌细胞凋亡增多，加重心脏损伤。近年来，研究显示内质网应激除了能通过直接激活凋亡信号介导心肌细胞损伤外，对自噬信号也具有调控作用，内质网应激通过涉及 IRE1 和 PERK 在内的 Ca^{2+} 依赖途径诱导自噬[30]，对心脏有一定的保护作用，但糖尿病对心肌细胞内的自噬起抑制作用[35]，进一步加重了心脏损伤。

2.1.3 内质网应激与心脏重塑及心力衰竭

心脏重塑是指基因组表达导致分子、细胞和间质发生改变，发生心肌细胞肥大、炎症反应和心肌纤维化等主要病理改变，是心力衰竭临床病程进展的关键因素[36]。内质网应激参与了心脏重塑的进程，2016 年，本研究组 Zhang 等人[37] 在同型半胱氨酸诱导的载脂蛋白 E (apolipoprotein E, *ApoE*) 敲除小鼠心肌纤维化模型上发现心肌组织中内质网应激显著激活，而内质网应激抑制剂 4- 苯基丁酸 (4-phenylbutyric acid, 4-PBA) 可显著抑制内质网应激，并降低 I 型胶原和 III 型胶原表达，改善心脏的纤维化。此外，2019 年，Zhang 等人[38] 在主动脉缩窄 (transverse aortic constriction, TAC) 诱导的小鼠心肌肥厚模型中发现 C1q- 肿瘤坏死因子相关蛋白 3 (C1q-tumor necrosis factor-related protein-3, CTRP3) 通过抑制 p38 诱导的内质网应激抵抗压力过载导致的心肌细胞肥大和心脏纤维化。2016 年，Duan 等人[39] 的研究显示，在异丙肾上腺素 (isoproterenol, ISO) 或压力过载诱导的心肌肥厚和心力衰竭中 XBP1 表达显著升高，而沉默 *XBP1* 基因加剧 ISO 介导的心肌损伤，并降低心肌毛细血管密度和血管内皮生长因子 -A (vascular endothelial growth factor-A, VEGF-A) 的表达，在体外细胞实验中也发现 VEGF-A 的表达受 XBP1 水平的影响，这些结果提示内质网应激通过 XBP1 调控 VEGF-A 介导的心肌血管生成，促进心肌适应性肥厚。除了 IRE1/XBP1 信号促进心脏重塑外，ATF6 也参与了心脏重塑的调控。2019 年，Blackwood 等人[40] 在 TAC 诱导的心肌肥厚小鼠模型中发现内质网应激 ATF6 信号活化，并通过激活 RHEB/mTORC1 通路诱导心肌肥厚。

心力衰竭是由于心脏结构、功能、节律或传导异常而引起的心脏泵血功能无法满足机体需求引起的综合征[41]。近年来，研究显示内质网应激在心力衰竭发生和发展中扮演着重要的角色。2019 年，Binder 等人[42]的研究显示，p21 活化激酶 2 (p21-activated kinase 2, Pak2) 心脏特异性敲除小鼠在衣霉素——内质网应激诱导剂的刺激下，出现了心力衰竭表现，并且检测到 UPR 受损，进一步通过基因序列分析发现 Pak2 是通过 IRE1/XBP1 通路发挥作用的，并且在敲除 *Pak2* 的小鼠中过表达 XBP1 能够逆转衣霉素对心脏的损害作用，表明 Pak2 通过调控 IRE1/XBP1 信号通路改善心功能。除 IRE1 通路外，PERK 对心力衰竭也有重要作用。2014 年，Liu 等人[43]的研究显示，与野生型小鼠相比，心脏特异性敲除 *PERK* 的小鼠在 TAC 手术后出现心功能下降、纤维化以及心肌细胞凋亡增多等表现。PERK 除了能影响心肌细胞凋亡外，对心肌细胞内钙离子稳态的调控因子肌浆网钙离子 ATP 酶 2a (sarco endoplasmic reticulum Ca^{2+}-ATPase 2a, SERCA2a) 也有调控作用。2011 年，Mekahli 等人[44]的研究显示，在 *PERK* 敲除的小鼠中心肌 SERCA2a 的表达量降低，同年 Liu 等人[45]的研究表明，干扰心肌细胞中 *SERCA2* 基因会引起内质网应激并促进心力衰竭。以上研究提示内质网应激中 PERK 信号通过调控心肌细胞凋亡和维持心肌 SERCA2a 表达量拮抗心力衰竭的发生，对心脏起保护作用。

内质网应激不仅参与了心脏疾病的发生和发展，它在血管损伤性疾病中也发挥了重要的作用 (图 2)。

2.2 内质网应激与血管损伤性疾病

2.2.1 内质网应激与动脉粥样硬化

大量研究表明内质网应激在动脉粥样硬化的发展过程中发挥直接作用，并且在动脉粥样硬化的各个阶段均可以检测到 UPR 信号通路活化[46, 47]。2019 年，Girona 等人[48]通过统计 405 名包括 2 型糖尿病、肥胖和代谢综合征患者的数据发现，在亚临床动脉粥样硬化患者血浆中内质网应激信号标志 GRP78 浓度升高，推测 GRP78 的血浆水平是提示动脉粥样硬化和心血管风险的重要标志。内质网应激可以通过调控炎症反应参与动脉粥样硬化形成。2017 年，Tufanli 等人[49]在巨噬细胞 RNA 测序中发现 IRE1 参与调节多种促动脉粥样硬化基因的表

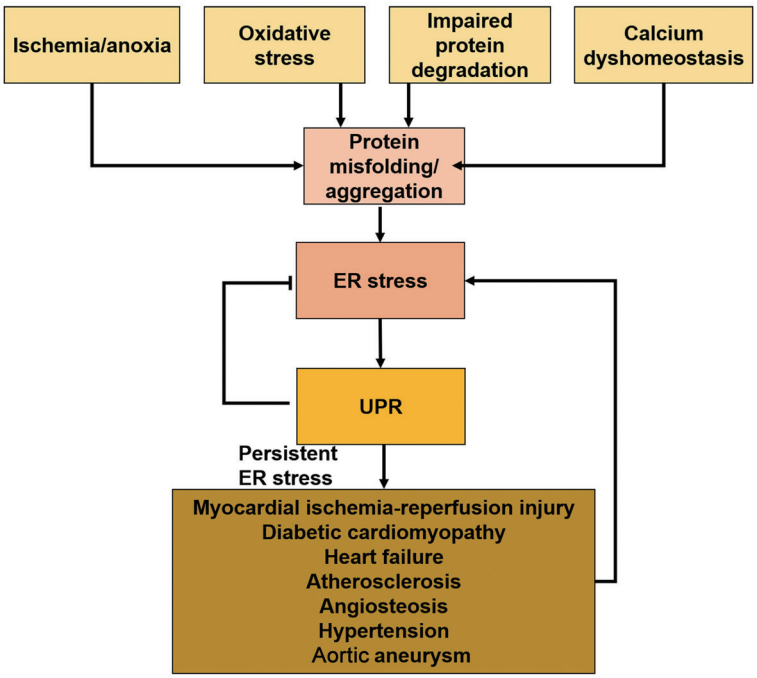

图 2. 内质网应激在心血管疾病中作用的示意图

Fig. 2. Model for the role of endoplasmic reticulum (ER) stress in cardiovascular diseases. Various harmful stimuli, such as ischemia, anoxia, oxidative stress, impaired protein degradation and calcium dyshomeostasis, can compromise protein folding and lead to ER stress. Persistent excessive ER stress can cause cardiovascular diseases. UPR: unfolded protein response.

达，包括白介素 1β (interleukin-1β, IL-1β)、趋化因子配体 2 [the chemokine (C-C motif) ligand 2, CCL2] 等重要细胞因子和趋化因子，在 *ApoE* 敲除鼠中抑制 IRE1，这些因子的表达被抑制且斑块面积减小，这些结果提示抑制 IRE1 可减轻炎症，改善动脉粥样硬化。另外，2019 年，Bailey 等人 [50] 的研究显示，水流剪切力 (hydrodynamic shear stress, SS) 通过内质网应激 IRE1/XBP1 信号诱导主动脉炎症反应并加速动脉粥样硬化的形成。除了调控炎症反应，内质网应激还参与血脂的调节。2016 年，Guan 等人 [51] 在 *ApoE* 敲除鼠中研究发现抑制肝脏内质网应激可改善高脂血症，减缓动脉粥样硬化形成。此外，内质网应激通过调控巨噬细胞的 M1 表型向 M2 表型转化参与动脉粥样硬化的形成。2012 年，Oh 等人 [52] 的研究表明，巨噬细胞由 M1 型向 M2 型表型转化能够加速摄取氧化低密度脂蛋白 (oxidized low-density lipoprotein, oxLDL) 形成泡沫细胞，而内质网应激能够通过活化 c-Jun 氨基末端激酶 (c-Jun N-terminal kinase, JNK) 以及增强过氧化物酶体增殖因子活化受体 γ (peroxisome proliferator-activated receptor γ, PPARγ) 的表达促进巨噬细胞表型转化，进而加速动脉粥样硬化的形成。内质网应激不仅参与了巨噬细胞的调控，对内皮细胞也有影响。2015 年，Chung 等人 [53] 在用扰流 (disturbed flow) 引起的动脉粥样硬化模型中发现熊去氧胆酸 (ursodeoxycholic acid, UDCA) 通过减轻内皮细胞中内质网应激，降低 XBP1 和 CHOP 的表达，抑制黏附因子的释放和内皮细胞凋亡，从而减缓动脉粥样硬化斑块形成，减小斑块面积。2018 年，Hong 等人 [54] 的研究也证实了内质网应激介导血管内皮功能障碍并促进动脉粥样硬化的形成。另外，2019 年，Tang 等人 [55] 的研究表明激活的内质网应激和 UPR 促进人冠状动脉内皮细胞凋亡，并促进动脉粥样硬化的形成。

2.2.2 内质网应激与血管钙化

血管钙化是钙、磷在血管壁的异常沉积，常在高血压、糖尿病、衰老、慢性肾脏疾病、吸烟、系统性炎症和动脉粥样硬化等情况下发生 [56]。有多种因子促进这种转分化，包括骨形态发生蛋白、氧化应激、磷酸盐、甲状旁腺激素和维生素 D [57]。2013 年，本研究组 Duan 等人 [58] 在维生素 D3 + 尼古丁 (vitamin D plus nicotine, VDN) 诱导的大鼠血管钙化模型和体外用 β- 甘油磷酸盐 + 氯化钙诱导的血管平滑肌细胞 (vscular smooth muscle cell, VSMC) 钙化模型中抑制内质网应激，从而抑制了血管钙化，并且延缓了 VSMC 收缩表型向成骨样表型转化，而在体外模型中敲低 ATF4 减轻了 VSMC 的钙化和凋亡，并抑制 VSMC 的表型转化；2019 年，本研究组 Ren 等人 [59] 在 *ApoE* 敲除鼠中发现同型半胱氨酸 (homocysteine, Hcy) 通过激活内质网应激促进动脉粥样硬化性钙化的形成，而内质网应激抑制剂 4-PBA 可逆转 Hcy 加重的动脉粥样硬化性血管钙化。2018 年，Hao 等人 [60] 在 VDN 钙化模型中阻断星状神经节 (stellate ganglion block, SGB) 可抑制内质网应激并减轻血管钙化的形成，在 SGB 情况下用衣霉素激活内质网应激，血管钙化加重。2016 年，Yang 等人 [61] 用 VDN 大鼠模型发现内质网应激是硫化氢抑制血管钙化的关键信号通路，用 4-PBA 抑制内质网应激后血管钙化减轻。2013 年，Masuda 等人 [62] 的研究显示，肿瘤坏死因子 α (tumor necrosis factor α, TNFα) 诱导 VSMC 的内质网应激，并活化 PERK-eIF2α-ATF4-CHOP 信号，从而导致 VSMC 发生矿化和成骨作用；而当用 PERK、ATF4 或 CHOP 的 shRNA 敲低相应基因时能够抑制 TNFα 引起的 VSMC 矿化和成骨作用；在 5/6 肾切除制备的慢性肾疾病 *ApoE* 敲除小鼠模型中，也检测到了主动脉 TNFα 过表达以及血管钙化，而向该模型小鼠中注入 TNFα 中和抗体后，发现小鼠中 PERK-eIF2α-ATF4-CHOP 信号被抑制，并且血管钙化减轻。此外，2018 年，Shiozaki 等人 [63] 在慢性肾病小鼠模型中发现饱和脂肪酸通过激活内质网应激 CHOP 信号通路并磷酸化 ATF4 促进血管钙化。同年，Panda 等人 [64] 的研究结果显示处于尿毒症状态下的 VSMC 中哺乳动物雷帕霉素靶点复合物 1 (mammalian target of rapamycin complex 1, mTORC1) 信号被活化，并出现内质网应激和 UPR，而 PERK-eIF2α-ATF4-CHOP 信号活化通过抑制焦磷酸盐的合成促进血管钙化；用雷帕霉素抑制 mTORC1 或用牛磺熊去氧胆酸恢复内质网稳态的情况下都能够降低主动脉中的钙离子含量，上述结果说明内质网应激及 UPR 的 PERK 信号通路促进了血管钙化的形成。除了在体外动物模型中发现内质网应激 PERK/ATF4 通路引起血管钙化外，在人组织中也发现疾病状态下内质网应激标志分子表达增加。2019 年，Fu 等人 [65] 发现主动脉狭窄患者的主动脉瓣中瓣膜间质细胞成骨样细胞分化增多，并且 ATF4 表达增加，而应用牛磺熊去氧胆酸或 siATF4 抑制内质网应激后瓣膜间质细胞

成骨样细胞分化减少。

2.2.3 内质网应激与高血压

高血压是指以体循环动脉血压增高为主要特征，可伴有心、脑、肾等器官的功能或器质性损害的临床综合征，是最常见的慢性病。大量研究表明内质网应激在高血压及其并发疾病中发挥重要作用。2019 年，Li 等人 [66] 在自发性高血压大鼠 (spontaneously hypertensive rat, SHR) 5 月龄时在心脏组织中检测到内质网应激信号 GRP78 表达升高，说明高血压刺激能够诱导内质网应激活化。此外，2019 年，Naiel 等人 [67] 在 SHR 模型中发现用 4-PBA 抑制内质网应激后能够减缓 SHR 高血压的形成，虽然不能完全将 SHR 血压恢复至正常水平，但是这项研究提示 SHR 高血压的形成至少一部分是依赖内质网应激的。在其他模型中也发现内质网应激参与高血压的形成。2019 年，Liu 等人 [68] 的研究显示，SERCA2 Cys^{674} 失活后，内质网应激信号分子 PERK、CHOP、BiP、ATF6 表达升高，动脉血压升高，而抑制内质网应激后动脉血压降低，这项研究提示内质网应激参与了 SERCA2 Cys^{674} 失活介导的高血压形成。2016 年，Carlisle 等人 [69] 向 SHR 注入 4-PBA 并监控血压，发现内质网应激被抑制后能够显著降低 SHR 的血压，减弱 SHR 小肠系膜动脉的收缩性，并增强其内皮依赖性舒张能力，而且降低了管壁 - 管腔比，即增大了小肠系膜动脉的管腔。而用衣霉素作用于正常血压的对照鼠肠系膜动脉后，该动脉的舒张能力下降，而再用 4-PBA 处理能够恢复其舒张能力，上述结果提示内质网应激通过损伤血管内皮介导的血管舒张功能参与高血压的形成。内质网应激除了通过影响内皮细胞功能外，还通过调控 VSMC 参与高血压的形成。2018 年，Camargo 等人 [70] 的研究显示，在 SHR 中内质网应激信号促进 VSMC 的增殖，加重了高血压大鼠血管功能障碍。2019 年，Han 等人 [71] 在单侧肾切除及脱氧皮质醇加速诱导的高血压大鼠模型中研究发现，高血压导致内质网应激，损伤内质网钙离子平衡，并且加重内质网应激介导的细胞凋亡，从而引起血管功能障碍。此外，内质网应激还参与了高血压对其他系统器官的损伤作用。2017 年，Wang 等人 [72] 用 Goto-Kakizaki (GK) 2 型糖尿病小鼠在两肾之间做腹主动脉缩窄建立糖尿病 - 高血压性肾病小鼠模型，8 周后在肾脏中检测到了氧化应激和内质网应激，小鼠出现肾小球滤过率降低和蛋白尿；而用牛磺熊去氧胆酸抑制内质网应激 6 周后再检测相应指标，发现该模型鼠的血压、蛋白尿以及肾小球滤过率得到改善，表明糖尿病和高血压通过内质网应激通路损伤肾功能。

2.2.4 内质网应激与主动脉瘤

主动脉瘤是指主动脉扩张超过正常大小的 1.5 倍 [73]。它们通常发病于腹主动脉，也可以位于胸主动脉。主动脉瘤引起主动脉壁软弱，增加主动脉破裂的风险。2018 年，本研究组 Ni 等人 [74] 在腹主动脉瘤患者血管组织以及用血管紧张素 II 在 *ApoE* 敲除小鼠诱导的腹主动脉瘤中发现，腹主动脉瘤组织中内质网应激标志分子 CHOP、ATF4 和 GRP94 表达明显增加，而内质网应激抑制剂 4-PBA 或牛磺酸可显著抑制腹主动脉瘤形成。2015 年，Jia 等人 [75] 在人和鼠的胸主动脉瘤样本中都检测到了过度表达的凋亡信号以及内质网应激和并发炎症，后续用 *CHOP* 敲除鼠与对照鼠研究发现，敲除 *CHOP* 后能够抑制胸主动脉瘤的形成和破裂，并且检测到 *CHOP* 敲除小鼠中凋亡信号和炎症信号都显著降低，提示内质网应激可能通过 CHOP 信号通路促进平滑肌细胞凋亡以及炎症发生来促进胸主动脉瘤的形成。除了在动物模型上证实内质网应激参与主动脉瘤的形成外，2019 年，Siegert 等人 [76] 从 4 名马凡综合征患者的升主动脉组织中亦检测到内质网应激标志分子 GRP78、CHOP 和 XBP1s 表达显著增加。近年来研究显示，内质网应激除了直接通过参与血管炎症反应和细胞凋亡促进主动脉瘤发生外，还通过与其他器官或细胞结构相互作用共同参与主动脉瘤的形成。2019 年，Navas-Madronal 等人 [77] 在患者腹主动脉瘤组织及其分离的 VSMC 中发现内质网应激通过诱导线粒体生成失调参与腹主动脉瘤的形成。另外，2019 年，Jia 等人 [78] 的研究显示，VSMC 中内质网应激 CHOP 信号通路能促进微粒在 VSMC 中形成和分泌，微粒释放到组织间隙造成血管内皮功能障碍、内皮细胞凋亡和主动脉炎症，促进主动脉瘤的形成。

内质网应激对 CVD 的作用总结见表 1。

3 调控内质网应激的药物

据报道，多种小分子药物能够参与激活或抑制内质网应激信号，更重要的是，这些小分子药物在多种疾病中表现出了一定的治疗效果 [82]。下面将分别介绍以内质网应激的三个感受分子为靶点的小分

子药物 (表 2)。

IRE1 同时具有激酶活性和核酸内切酶活性，针对 IRE1 的激酶结构域和核酸内切酶结构域，利用高通量筛选技术和传统药物学方法，近年来发现了

表1. 内质网应激参与心血管疾病的发生和发展

Table 1. Endoplasmic reticulum stress is involved in the development of cardiovascular diseases

Model	The main molecules	Inductor	Effect of ER stress	References
Myocardial ischemia-reperfusion injury				
NRVMs, SD rats	ATF6, ATF4, CHOP, PI3K/Akt	Tm/DTT/ surgery	Induction of myocardial cell apoptosis	[17]
NRVMs, Wistar rats	ErbB4 receptor, PI3K/Akt	Tm/DTT/ surgery	Induction of myocardial cell apoptosis	[18]
SD rats, H9c2 cells	PERK, eIF2α, CHOP, ATF4	Surgery/ischemic buffer	Induction of myocardial cell apoptosis	[19]
C57/B6 mice, NRVMs	XBP1	Surgery/I/R buffer	Cardioprotection through induction of the HBP	[21]
SD rats, H9c2 cells	IRE1	Surgery/hypoxia treatment	Induction of myocardial cell apoptosis through IRE1 activation	[20]
C57B/6J mice, patient sample, NRVMs	ATF6	Surgery/hypoxia treatment	Cardioprotection through ATF6 activation	[25]
C57BL/6 mice	GRP78, Akt	Surgery	Resistance to oxidative stress	[26]
SD rats	PI3K/Akt, GRP78, CHOP	Surgery	Cardioprotection through PI3K/Akt activation	[27]
Diabetic cardiomyopathy				
SD rats	IRE1, PERK, ATF6	STZ	Induction of myocardial cell apoptosis	[79]
Wistar rats, H9c2 cells	ERK1/2, XBP1s	STZ/HG	Induction of myocardial cell apoptosis	
NRVMs, MEFs	CHOP	MGO/siRNA	Induction of myocardial cell apoptosis	[31]
C57BL/6 mice	LC3B, Atg7, p62, IRE1, eIF2	STZ	Induction of myocardial cell apoptosis; Inhibition of autophagy	[35]
Heart failure				
C57BL/6 mice, CFs	GRP78, ATF6, ATF4, IRE1, XBP1, PERK	Hcy/$IMD_{1\text{-}53}$	Promote cardiac fibrosis	[37]
C57BL/6 mice, H9C2 cells, MEFs, patient sample	XBP1, VEGF-A	TAC/ISO	Regulate angiogenesis; Promote adaptive hypertrophy of the myocardium	[39]
NRVMs, C57BL/6 mice	Hrd1, ATF6, XBP1	siRNA/TAC	Cardioprotection	[80]
C57BL/6N mice, ARCMs	Pak2, PERK, ATF4, eIF2	TAC/Tm	Improve cardiac function through Pak2 signal	[42]
C57BL/6 mice	PERK, GRP78, GRP94	TAC	Improve cardiac function and relieve myocardial fibrosis	[43]
Atherosclerosis				
C57BL/6 mice, BMDM	IRE1, XBP1	*ApoE*$^{-/-}$	Aggravate atherosclerosis	[49]
C57BL/6 mice	XBP1, BiP, LPL, PPARγ	*ApoE*$^{-/-}$	Improve hyperlipidemia	[51]
Human monocytes, MPM, patient sample	CHOP, JNK, PPARγ	4-PBA/*ApoE*$^{-/-}$	Aggravate atherosclerosis	[52]
C57BL/6 mice	CHOP, eNOS, caspase-1, UCP-2	*ApoE*$^{-/-}$	Promote vascular endothelial dysfunction	[54]
Angiosteosis				
SD rats, VSMCs	ATF4	VD3+VDN/ β-glycerophosphate+ $CaCl_2$	Promote the osteogenic transformation of vascular smooth muscle cells	[58]
VSMCs	CHOP, caspase-12, GRP78, GRP94, ATF4, ATF6	Glycerophosphate+ $CaCl_2$/Tm+DTT	Increase alkaline phosphatase activity, aggravate vascular calcification	[81]

表1. 内质网应激参与心血管疾病的发生和发展(续表)

Table 1. Endoplasmic reticulum stress is involved in the development of cardiovascular diseases

Model	The main molecules	Inductor	Effect of ER stress	References
Jck mice, MOVAS cells	mTORC1, eIF2, ATF4, CHOP, ERK1/2	Tm	Inhibition of pyrophosphate synthesis promotes vascular calcification	[64]
Hypertension				
SHR, WKY rats	CHOP, GRP78, eNOS	\	Impaired arterial relaxation	[69]
GK rats, Wistar rats	CHOP	AC	Hypertension damages kidney function through ER stress	[72]
WKY rats, SHR, VSMCs	Nox1/2/4, ROS, PERK, IRE1, Bip, CHOP	\	Promote the proliferation of VSMCs and aggravate the vascular dysfunction	[70]
Aortic aneurysm				
Patient sample, C57BL/6 mice	ATF4, CHOP, ATF6	BAPN	Increased VSMCs apoptosis and vascular inflammation promote aneurysm formation	[75]
C57BL/6 mice	CHOP	BAPN	Promote endothelial cell apoptosis and vascular inflammatory infiltration promotes the formation of thoracic aortic aneurysm	[78]
Patient sample	BiP, HSP90, CHOP, XBP1	\	Promote the formation of ascending aortic aneurysm in patients with Marfan's syndrome	[76]

NRVMs: neonatal rat ventricular myocytes; Tm: tunicamycin; DTT: dithiothreitol; I/R: ischemia-reperfusion; STZ: streptozocin; BAPN: β-amino propionitrile; MEFs: mouse embryonic fibroblasts; CFs: rat fibroblasts; Hcy: homocysteine; HBP: hexosamine biosynthetic pathway; $IMD_{1\text{-}53}$: $intermedin_{1\text{-}53}$; TAC: thoracic aortic constriction; AC: aortic constriction; ISO: isoprenaline; BMDM: bone marrow-derived macrophages; PPARγ: peroxisome proliferator activated receptor-γ; LPL: low density lipoprotein; SHR: spontaneously hypertensive rat; MPM: mouse peritoneal macrophages; HG: high glucose; MGO: methylglyoxal; PBA: phenyl butyric acid; IRE1: inositol-requiring enzyme 1; ATF6: activating transcription factor 6; PERK: protein kinase R-like ER kinase; XBP1: X-box binding protein-1; GRP78: glucose-regulated protein 78; eIF2α: eukaryotic translation initiation factor 2α; CHOP: CCAAT/enhancer binding protein homologous protein.

表2. 针对内质网应激三个感受分子调控内质网应激的相关药物

Table 2. Relevant drugs regulating three sensory molecules of endoplasmic reticulum stress

Sensor	Drug	Drug target	Effect	References
IRE1	APY29	IRE1 kinase	IRE1α kinase active-site inhibitor	[83]
	Sunitinib	IRE1 kinase	IRE1α kinase active-site inhibitor	[84]
	Salicylaldimines	IRE1 RNase	IRE1α RNase active-site inhibitor	[85]
	4μ8C	IRE1 RNase	IRE1α RNase active-site inhibitor	[86]
	MKC-946	IRE1 RNase	IRE1α RNase active-site inhibitor	[87]
	STF-83010	IRE1 RNase	IRE1α RNase active-site inhibitor	[88]
	Toyocamycin	IRE1 RNase	IRE1α RNase active-site inhibitor	[89]
	3-ethoxy-5, 6-dibromosalicylaldehyde	IRE1 RNase	IRE1α RNase active-site inhibitor	[90]
	FIRE peptide	IRE1 kinase	Modulation of IRE1 oligomerization and XBP1 mRNA cleavage	[91]
PERK	GSK2606414/2656257	PERK kinase	For the treatment of multiple myeloma and pancreatic cancer	[92]
	ISRIB	eIF2B	Reduce the expression of ATF4	[93]
ATF6	Ceapins	\	Inhibit ATF6 transport	[94]
	16F16	PDIs	Inhibition of PDIs and indirect activation of ATF6	[95]
	PACMA31	PDIs	Inhibition of PDIs and indirect activation of ATF6	[96]

PDI: protein disulfide isomerases; IRE1: inositol-requiring enzyme 1; ATF6: activating transcription factor 6; PERK: protein kinase R-like ER kinase; XBP1: X-box binding protein-1; GRP78: glucose-regulated protein 78; eIF2α: eukaryotic translation initiation factor 2α; CHOP: CCAAT/enhancer binding protein homologous protein; FIRE: fraction of human IRE1.

许多 IRE1 的抑制分子 [97]。IRE1 激酶活性的抑制分子如 APY29 [83]、舒尼替尼 (sunitinib) [84]、咪唑并哌嗪类分子 [98] 为 ATP 竞争性抑制剂，靶向 IRE1 激酶结构域中的 ATP 结合位点，抑制 IRE1 的激酶活性。IRE1 核酸内切酶活性的抑制分子有水杨醛 [85]、4μ8C [86]、MKC-946 [87]、STF-83010 [88]、丰霉素 [89] 和羟基芳基醛 [90]。此外，2011 年，Ali 等人 [91] 发现人源的 IRE1 激酶结构域短肽能够促进 IRE1 的寡聚化并增强 IRE1 的核酸内切酶活性。

通过对专有文库的生化筛选和基于结构的先导优化，葛兰素史克公司发现了两种能口服使用的 PERK 的抑制剂 GSK2606414 和 GSK2656257，但这两种抑制剂具有胰腺毒性，破坏胰岛 β 细胞 [92]。另一种 PERK 通路的抑制剂 ISRIB 是一种作用于 PERK 下游 eIF2B 的抑制剂，与 GSK 抑制剂所不同的是它没有胰腺毒性 [93]。

2016 年，Walter 等人 [94] 通过高通量筛选技术发现了 ATF6 的抑制分子 Ceapins，Ceapins 属于吡唑酰胺类药物，它能在内质网内捕获 ATF6 并阻断其向高尔基体转移。在生理状况下，ATF6 的活化受到蛋白质二硫键异构酶 (protein disulfide isomerases, PDIs) 的负调控，因而 PDIs 的抑制剂如 PACMA31 [96]、P1 [99]、16F16 [95] 能够活化 ATF6 信号。

4 小结

内质网应激是机体应对刺激的适应性防御型反应，是机体自身的保护性反应，在维持细胞和机体的稳态中具有重要的调控作用。内质网应激时激活的 UPR 对内质网的折叠蛋白能力起代偿适应性作用，清除或降解错误折叠或未折叠的蛋白质，恢复内质网稳态，从而维持细胞和机体的稳态平衡。但过强或持续过久的内质网应激则导致过多的未折叠蛋白或错误折叠蛋白质堆积，内质网感应分子激活相应 UPR，启动并介导细胞凋亡，参与疾病的发生和发展，具有重要的生理和病理生理意义，可能是 CVD 发病的共同环节和作用靶点。针对内质网应激和 UPR 及其信号通路在 CVD 中作用的研究，可能为 CVD 的预防以及药物的研制提供新思路和方向。

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