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HSPs在心肌细胞保护中的作用及其研究进展

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摘 要:热休克蛋白(heat shock proteins,HSPs)作为一类关键的分子伴侣蛋白,在维持心肌细胞稳态及应对应激损伤中发挥核心作用。本文系统综述了HSPs通过多重分子机制实现心肌保护的最新研究进展,重点聚焦其激活蛋白质稳态通路、抑制凋亡信号转导、激活抗氧化通路以及调节免疫炎症网络等核心路径。在心肌缺血/再灌注损伤和氧化应激等病理条件下,HSPs通过上述机制增强对心肌细胞的保护效应,为开发相关疾病的创新治疗策略提供理论支持。此外,本文系统梳理了不同运动模式通过调控HSPs的表达发挥心肌保护效应的潜在影响,期望为心血管疾病的非药物干预提供理论依据与转化视角。

关键词:HSPs;心肌保护;心肌细胞;心肌缺血/再灌注损伤;蛋白质稳态
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Research progress on HSPs in myocardial cell protection

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Abstract: This paper aims to systematically review the latest research advances on how heat shock proteins (HSPs) exert cardioprotective effects through multiple molecular mechanisms. It also systematically examines the potential of different exercise modalities to achieve myocardial preservation by regulating HSPs expression. This review provides theoretical support for developing innovative therapeutic strategies for related diseases and offers a theoretical basis and novel translational perspective for non-pharmacological interventions in cardiovascular diseases. As evolutionarily conserved molecular chaperones, HSPs play a central role in physiological and pathological processes, including myocardial ischemia/reperfusion injury (MI/RI) and oxidative stress (OS). They have become a hotspot in cardiovascular disease mechanism research and therapeutic strategy development. In maintaining protein homeostasis, HSPs (such as HSP27, HSP60, HSP70, HSP90) protect cardiomyocytes by facilitating proper folding of nascent polypeptide chains, preventing aggregation of misfolded proteins, activating the ubiquitin-proteasome system, and modulating autophagy-lysosomal pathways. In regulating myocardial survival and apoptosis, HSPs (such as HSP22, HSP27, HSP70, HSP90) exert crucial protective effects on cardiomyocytes through multiple pathways, including inhibiting apoptosome formation and blocking apoptotic signaling cascades. In promoting injury repair, HSP90 prevents adverse myocardial remodeling by enhancing angiogenesis and regulating cardiac fibroblast activation and collagen metabolism. In response to OS and inflammation, HSPs mitigate damage through multiple mechanisms. They counteract OS by scavenging free radicals, upregulating antioxidant enzyme activity, and activating pathways such as Keap1-Nrf2. Concurrently, HSPs attenuate excessive inflammatory responses during MI/RI by regulating key signaling pathways, including nuclear factor kappa-B (NF-κB) and Toll-like receptor 4 (TLR4). To maintain calcium homeostasis and counteract endoplasmic reticulum (ER) stress under conditions like MI/RI, HSPs (such as HSP27, HSP60, HSP70) act by modulating proteins including sarcoplasmic/endoplasmic reticulum calcium ATPase 2a (SERCA2a) and inhibiting the p38-MAPK signaling pathway, thus preventing pathogenic calcium overload. ER-localized HSPs also alleviate excessive ER stress by regulating sensors like R-like ER kinase (PERK) and inositol-requiring enzyme 1α (IRE1α). As key regulators of myocardial protection, HSPs enhance cardioprotective effects through these mechanisms. However, several critical scientific questions remain to be explored in this field. Notably, exercise, as the most potent physiological stressor, holds

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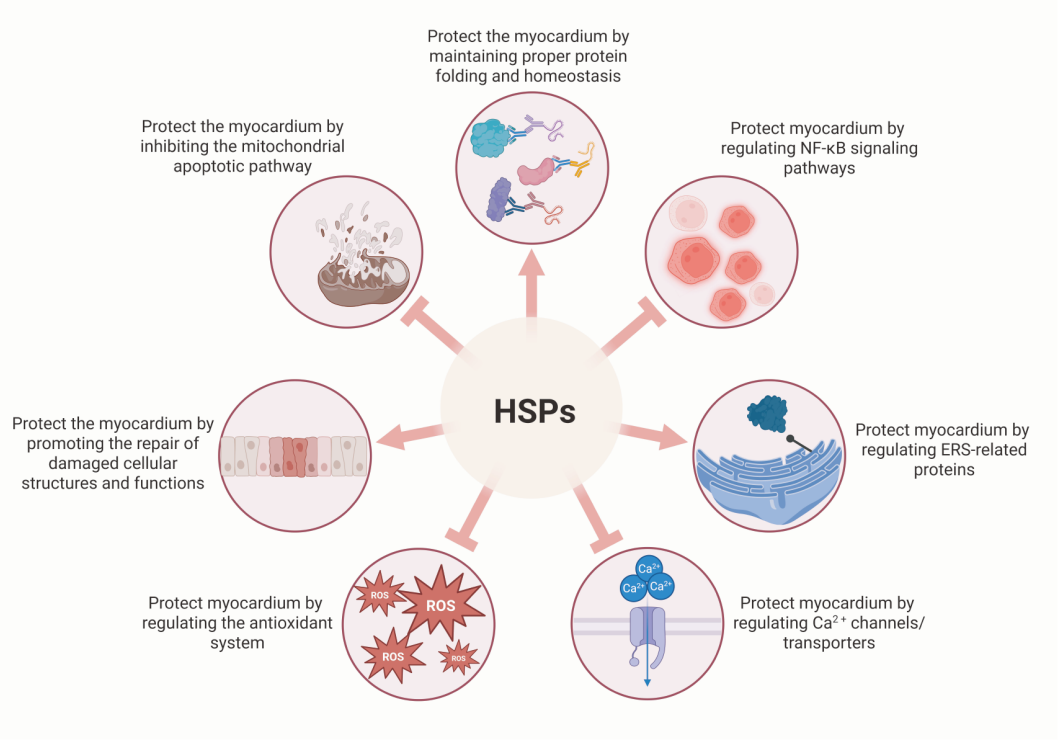
unique value in regulating HSPs expression and inducing cardio-protection, offering a distinct perspective for non-pharmacological interventions in cardiovascular diseases. Exercise intensity correlates closely with HSPs induction levels. Moderate-intensity aerobic exercise may strike an optimal balance between inducing HSPs expression and achieving myocardial protective benefits. It effectively upregulates HSP70, HSP27 and others, thereby enhancing antioxidant capacity, maintaining protein homeostasis, and promoting autophagy. Different exercise modalities (such as endurance training, interval training) may selectively induce distinct HSP family members, generating myocardial protection through differentiated mechanisms. Although the cardioprotective role of HSPs is well-established, functional redundancy and environmental dependence among family members may render them double-edged swords under specific pathologies. Future research should therefore focus on three areas: first, elucidating the specific functional networks and interactive dialogues of different HSPs within cardiomyocytes; second, elucidating the relationship and mechanisms between exercise-mediated HSPs and myocardial protection; third, exploring novel therapeutic strategies targeting HSPs pathway through exercise or pharmacology. This not only holds promise for identifying new targets in cardiovascular disease prevention and treatment but may also provide a new scientific foundation and intervention strategies for cardiac rehabilitation medicine.



Key words: HSPs; myocardial protection; cardiomyocytes; myocardial ischemia/reperfusion injury; protein homeostasis

心血管疾病是全球范围内导致死亡的主要原因之一,其核心病理环节常涉及心肌细胞的损伤与死亡[1,2]。由于成年心肌细胞再生能力极其有限,其内在的自我保护与修复机制对于维持心脏功能至关重要[3]。在此背景下,热休克蛋白(heat shock proteins,HSPs)作为细胞应激防御系统的核心组成部分,其研究已成为心血管领域的热点。

HSPs是一类在进化上高度保守的分子伴侣蛋白,通过调控蛋白质折叠、组装、转运及降解等过程,在生理和病理条件下维持细胞内蛋白质稳态。在心肌缺血/再灌注损伤(myocardial ischemia/reperfusion injury,MI/RI)和氧化应激(oxidative stress,OS)及热休克等应激条件下,HSPs(如HSP27、HSP70和HSP90)表达显著上调,尤其在代谢活跃且易受损的心肌细胞中发挥关键保护作用。HSPs通过多维度机制参与心肌保护:(1)蛋白质质量控制:直接抑制错误折叠蛋白聚集,稳定线粒体功能,并通过调控B淋巴细胞瘤-2(B-cell lymphoma-2,Bcl-2)家族蛋白及含半胱氨酸的天冬氨酸蛋白水解酶(cysteine aspartate-specific protease,Caspase)活性减轻内质网应激(endoplasmic reticulum stress,ERS)和细胞凋亡[4];(2)促生存信号通路:激活磷脂酰肌醇3-激酶/

蛋白激酶B(phosphatidylinositol 3-kinase/protein kinase B,PI3K/AKT)和细胞外信号调节激酶1/2(extracellular signal-regulated kinase 1/2,ERK1/2)等通路,增强心肌细胞对氧化损伤的抵抗能力[5];(3)代谢稳态调控:动态调节自噬-溶酶体途径,清除受损细胞器并维持能量代谢平衡[6]。值得注意的是,HSPs的功能多样性还受到翻译后修饰(如磷酸化、乙酰化)和亚型特异性时空表达模式的精细调控,但其在心脏病理生理学中的精确调控网络仍需进一步阐明。本文系统综述HSPs在心肌细胞保护中的分子机制进展,并探讨靶向HSPs通路治疗心血管疾病的潜在转化价值。

1 HSPs的发现及分类

HSPs的发现源于1962年Ritossa[7]在果蝇中观察到的热诱导染色体“膨化”现象。1974年,Tissieres等[8]证实该现象与一组特定蛋白的快速合成有关。1986年,Lindquist[9]进一步揭示HSPs也可由多种应激源诱导合成并普遍存在于多种物种中。此后,Ellis[10]关于HSPs“分子伴侣”功能的阐述是该领域的重大突破,揭示了其维持细胞内蛋白质稳态的核心作用。

根据分子量、结构和功能,HSPs可分为多个进化上保守的家族[11]。尽管各家族在寡聚状态、ATP依赖性、结构域组成及细胞定位上存在差异,但它们均具备识别未折叠肽段、防止蛋白质聚集、协助其再折叠的核心分子伴侣功能[12]。大多数HSP家族利用ATP水解驱动构象变化以完成功能循环,这些差异使得不同家族在细胞内精密分工、协同作战,共同完成从蛋白质折叠、修复到降解的全过程。人与小鼠的HSPs在核心家族成员上呈现一一对应的同源关系,核心差异在于二者的亚型和基因数。其中,HSP70家族差异最大,小鼠相较于人缺失HSPA6基因与HSPA7假基因[13],但HSPA7作为非编码RNA具有调控功能[14]。HSP90家族则缺失一个HSPC2基因[11]。其余如Dnajc30基因等HSP家族成员,多为同源基因,但功能不完全相似。大鼠与小鼠的HSPs种类则基本相同,仅命名规则存在差异。表1对研究广泛的HSPs的分子量、分布位置、亚型以及结构进行了对比。

2 HSPs在心肌细胞中的保护作用

HSPs研究的重大转折,源于对其在心脏这一低再生能力器官中核心保护作用的深刻认识。成年心肌细胞作为终末分化细胞,其有限的增殖能力使得细胞存活与功能维持尤为关键,而这一过程高度依赖于HSPs介导的蛋白质质量控制系统。在生理状态下,HSPs通过协助新生肽链的正确折叠、组装及转运,维持心肌细胞蛋白质组的稳定,保障其正常的收缩与代谢功能。在病理条件下(如缺血、缺氧、OS等),HSPs的表达上调成为细胞自主防御的关键环节,通过维持心肌细胞蛋白质稳态、促进细胞存活、推动组织修复及缓解氧化应激损伤,有效减轻心肌损伤并促进修复。因此,对HSPs功能的深入研究,

表1 根据不同分子量对研究广泛的HSPs进行分类

Table 1 Classification of widely studied HSPs based on molecular weight

HSP类型	分子量(kDa)	主要位置	亚型	结构特点	文献
小HSP	12~43	细胞质	10种(HSPB1~10),各亚型对应1个基因	寡聚化、动态性、底物结合	[15,16]
HSP40	40	细胞质/细胞核,Ⅲ型在线粒体、内质网、高尔基体等分布	分3种,Ⅰ型成员数6个;Ⅱ型≥10个;Ⅲ型>25个	4个结构域,其中N端与HSP70的ATP结构域结合,决定HSP70底物选择性并增强ATP酶活性	[11,17]
HSP60	60	细胞质(1/5)、线粒体和内质网(4/5)	HSPD1对应1个基因;TRiC型对应8个基因	空心双低聚合物,由赤道(ATP结合)、中间、顶端(与底物和HSP10结合)结构域组成	[18,19]
HSP70	70	细胞质、细胞核(应激时转移至细胞核,应激后回到细胞质)	可诱导型3个、组成型1个、细胞器型4种(共10个,含假基因)	包含ATPase结构域(45 kDa)、多肽结合域(18 kDa)和氨基酸序列域(10 kDa)	[20-22]
HSP90	90	细胞质、细胞核	胞质诱导型对应1个成员;胞质管家型、内质网型、线粒体型各对应1个成员	非对称性,分为N端(ATP结合)、中间(客户蛋白识别)、C端(二聚化)结构域	[23-29]
HSP110	110	细胞质、细胞核	(HSPH1~4)4种亚型,亚型成员数目均为1条	N端(ATP结合)、中间(结合肽类底物)、C端(与Hsp70同源,结合底物)	[11,30]

不仅揭示了心肌细胞自我保护的分子基础,也为心脏疾病的新型治疗策略开发开辟了全新视角。

2.1 维持蛋白质稳态

1992年,Horwitz实验室首次提出小HSP具有分子伴侣功能,它通过调控蛋白质的折叠、组装、转运及稳定性来维持细胞蛋白质稳态[31]。这一发现为理解HSPs在细胞保护中的作用奠定了基础。作为终末分化细胞,心肌细胞的存活与功能高度依赖于其蛋白质组的精密调控,而HSPs正是这一蛋白质质量控制系统(protein quality control,PQC)的核心执行者。它们通过参与"蛋白质生命周期"的各个环节——包括正确折叠、构象维持、靶向定位以及异常蛋白的识别与清除——共同抵御各类病理应激对心肌细胞的损害。

蛋白质的正确折叠与构象稳定是维持其生物学活性的关键。错误折叠的蛋白质若未被及时识别并清除,将逃逸细胞的质量控制机制,进而发生聚集,成为多种退行性病变的共同病理基础,并显著增加心血管疾病的发病风险[32]。在生理条件下,HSPs通过其分子伴侣功能,持续维护心肌细胞的蛋白质稳态。例如,HSP60与HSP10协同作用,协助新生肽链的正确折叠并促进变性蛋白的功能恢复[33];HSP27则以多聚体形式存在,通过结合并稳定部分变性的蛋白质,防止其进一步聚集,并促进其复性[34,35]。此外,HSP90通过其高度动态的构象变化,稳定并调控AKT等关键信号蛋白的活性,进而参与调控如AKT/Bcl-2等重要的细胞存活通路[36]。

在病理应激(如MI/RI)条件下,心肌细胞内蛋白质更易发生错误折叠,导致蛋白质稳态失衡。HSPs能维持蛋白质正确折叠和质量组装,保护心肌细胞。具体而言,MI/RI应激条件下HSPs发生的泛素化在蛋白质质量控制中尤为重要,它通过标记受损或错误折叠的蛋白质底物,确保其降解,从而维护心肌细胞正常活性[37]。当心肌遭受如MI/RI等应激时,心肌细胞膜的通透性和完整性发生改变,血液中肌钙蛋白减少,影响心脏的收缩和舒张功能[38]。HSP27通过维持肌动蛋白稳定性,促进心肌健康。肌动蛋白通过维持心肌细胞的形态结构、机械强度和收缩功能在心肌细胞中起到关键作用[39]。HSP27不仅促进肌动蛋白聚合形成稳定的肌动蛋白纤维,还在应激条件下,发挥封端蛋白(end blocking protein)的功能,通过结合肌动蛋白纤维末端来防止其过度解聚,维持肌动蛋白的稳定性[40]。HSP27对肌动蛋白的这种调控和稳定性保护作用,对心肌细胞骨架、心肌正常生理功能至关重要。

2.2 参与调控心肌细胞存活和凋亡

HSPs的抗凋亡功能最早由Saleh和Jaattela团队发现[41,42],随后在心肌缺血模型中得到了充分验证,现已成为心脏保护机制研究的核心内容之一[43]。在病理方面,HSPs通过抑制凋亡来保护心肌细胞,促进心肌细胞存活。在MI/RI或OS等应激条件下,HSP70通过抑制凋亡诱导因子,发挥抗凋亡作用,维持线粒体功能,从而促进心肌细胞存活[44];同时,在心肌缺血条件下,HSP70也能够通过抑制肿瘤坏死因子-α(tumor necrosis factor-alpha,TNF-α)[45]与Caspase-3过表达[46],进一步保护心肌细胞免受应激伤害,从而发挥重要的抗凋亡作用。HSP27通过多种机制对抗应激诱导的心肌细胞凋亡和坏死[47,48]。在热应激条件下,HSP27通过抑制促凋亡因子Caspase依赖的BH3相互作用域死亡激动剂(BH3-interacting domain death agonist,Bid)的激活,增强心肌细胞对热诱导凋亡的抵抗力[49]。此外,HSP70的异构体HSP72位于溶酶体腔面,可有效抑制水解酶和细胞死亡介质的释放[50]。

2.3 促进心肌细胞修复

1995年,Dillmann团队首次发现HSPs在心肌MI/RI中发挥关键修复功能[51]。在正常生理情况下,HSPs不仅能稳定心肌细胞和线粒体,防止其失衡,还刺激心肌成纤维细胞和血管内皮细胞,加快心肌细胞胶原瘢痕形成、微血管修复和代谢适应,为心肌细胞修复或再生提供结构和能量基础。

病理研究显示,心梗后HSP90表达显著升高,能稳定血管内皮细胞生长因子受体2(vascular endothelial growth factor receptor-2,VEGFR2)和内皮型一氧化氮合酶(endothelial nitric oxide synthase,eNOS),促进内皮祖细胞(endothelial progenitor cells,EPC)向缺血或损伤组织微血管迁移,进而促进心肌微血管修复[52,53]。而HSP72则在动物模型与细胞实验中被证实是MI/RI后减少心肌损伤和改善心脏功能障碍的核心环节[54]。血液指标与心脏超声检测表明,经HSP72治疗后细胞死亡率下降一半,且MI/RI后的左心室功能障碍得到改善。因此,HSP72在MI/RI中直接发挥了缓解心功能障碍的关键作用。HSP47作为分子伴侣协助细胞外基质(extracellular matrix,

ECM)正确折叠,促进心肌修复[55]。HSP27通过调节细胞骨架重组促进心脏成纤维细胞活化与转化,应急修补伤口,防止心脏血管破裂;同时通过稳定和调节ECM蛋白分泌,促进Ⅰ/Ⅲ型胶原沉积,参与瘢痕形成与组织重塑;参与纤维化调控,抑制ECM过度沉积,防止纤维化和心衰[56]。

2.4 抗氧化应激

2003年,Yamamoto团队首次系统证实了HSPs在MI/RI中的抗氧化功能[57]。抗氧化即抑制机体的氧化反应,抵消自由基对人体细胞的氧化攻击。在正常生理状况下,HSPs在维持机体氧化还原平衡、应对OS过程中发挥关键作用。具体而言,HSP70通过增强心肌细胞的抗氧化能力,协同抗氧化系统中和活性氧(reactive oxygen species,ROS),同时通过增加游离20S蛋白酶体的水平来促进氧化蛋白降解,防止其在心肌细胞内积累[58,59]。HSP70通过调节AKT信号通路,促进AKT形成复合物并维持其稳定,从而保护心肌细胞免受OS引起的凋亡[60]。当ROS水平升高且谷胱甘肽(glutathione,GSH)抗氧化储备能力下降时,HSPs表达上调,为心肌细胞提供早期保护[61]。HSP70水平增加可通过抑制Janus激酶2/信号转导与转录激活因子3(Janus kinases 2/signal transducers and activators of transcription 3,JAK2/STAT3)通路来调节心肌细胞氧化还原状态,而其水平下调则会加剧OS并导致心肌细胞凋亡[62]。HSP60通过与核因子κB(nuclear factor kappa-B,NF-κB)相互作用调控IκB激酶(IκB kinase,IKK)的活化和磷酸化,保护心肌细胞免受线粒体源性OS的损伤[63]。HSP90作为一种抗氧化因子,在心肌细胞存活中起着重要作用,其铁结合特性可参与调控芬顿反应,从而减缓OS的发展[64]。此外,HSP90和HSP70均可与氧化脂质结合,防止其进一步氧化[65-67]。HSP27能上调GSH水平,增强心肌细胞抗氧化能力[68,69]。

HSPs还在多种病理过程中发挥抗氧化作用,如动脉粥样硬化、MI/RI等[58,70]。小分子HSPs在MI/RI中作为抗氧化剂发挥心血管保护作用[71]。MI/RI和缺氧会导致ROS过量产生,HSP27和HSP22不仅直接结合抗氧化酶并促进其表达,还稳定线粒体蛋白辅酶Q9,从而维持线粒体功能,减少ROS,减轻OS对心肌细胞的损伤[72]。HSP27通过减少线粒体通透性转换孔的开放,维持线粒体膜电位,抑制细胞色素C(cytochrome C,Cyt C)的释放,从而阻断线粒体介导的凋亡途径[73]。

3 HSPs在心肌保护中的分子机制

HSPs在生理与病理状态下展现了核心保护功能,然而其具体分子机制有待深入探索。因此,为完整描绘HSPs的心脏保护图谱,本文将系统阐述HSPs的不同亚型通过独特的分子协作,在压力应激中的具体作用机制。

3.1 维持蛋白质稳态

在分子机制方面,HSPs通过稳定关键信号蛋白的构象,间接调控细胞的命运决策。AKT是重要的凋亡信号调节因子,但在应激情况下,其构象容易发生改变,致使其功能发生异常;HSP70在缺氧条件下通过其ATP驱动的构象循环来动态调控底物的结合,有效促进蛋白质正确折叠,稳定AKT构象,抑制心肌细胞凋亡,促进心肌细胞存活和调节能量代谢[74]。除此以外,在MI/RI、OS条件下,HSP70还稳定c-Jun氨基末端激酶(c-Jun N-terminal kinase,JNK)的结构,协助JNK正确折叠以维持蛋白稳态,使JNK信号通路有效表达,促进心肌细胞存活[75]。HSP70通过稳定一氧化氮合酶(nitricoxide synthase,NOS)的构象以激活该通路,NOS激活后生成的一氧化氮(nitric oxide,NO)对调节心肌细胞的血管舒张功能和血管张力至关重要[76]。在MI/RI模型中,HSP60与HSP10通过协助Cyt C和Caspase的正确折叠,阻止Cyt C和Caspase从线粒体释放,抑制Cyt C与凋亡蛋白酶激活因子1(apoptotic protease activating factor-1,APaf-1)结合形成凋亡体,从而减少心肌细胞凋亡[77]。在遭受应激时,B细胞淋巴瘤2相关X蛋白(Bcl2 associated X protein,BAX)插入线粒体外膜形成孔道[78],HSP60协助Bax正确折叠并维持其蛋白稳定性[79],从而抑制Bax异常激活导致的线粒体膜通透性改变和线粒体蛋白稳态失调,阻止凋亡因子的激活与释放。HSP27对Bax和Cyt C有类似的抑制作用[80]。

除了协助蛋白质正确折叠与质量组装,HSPs在识别、清除与降解错误折叠蛋白质的过程中也发挥了关键作用。HSP70可识别并结合错误折叠的蛋白质,激活P62/LC3/自噬溶酶体信号通路,将错误折叠的蛋白质转运至自噬体中,最终被溶酶体降解,减少这些蛋白质堆积,促进心肌细胞健康[6]。

在内质网中,HSP70还通过与HSP40协同作用,识别内质网中错误折叠的蛋白质,激活内质网信号通路,将错误折叠的蛋白质递送至蛋白酶体降解,以缓解心肌细胞内的ERS[81]。HSP60则作为分子伴侣识别错误折叠蛋白,并通过伴侣介导的自噬途径将其靶向运送至溶酶体降解[82]。对于已形成的蛋白聚集物,HSP110与HSP70、HSP40共同协作,识别并解聚这些聚集物,使其恢复至溶解状态,因此HSP110的解聚性有助于心肌细胞维持稳定状态[83]。在病理状态下,如心力衰竭中,HSP90通过激活蛋白激酶B/雷帕霉素靶蛋白(AKT/mammalian target of rapamycin,AKT/mTOR)信号通路来调节自噬水平,减少自噬过度导致的心肌细胞受损[84]。

综上,HSPs作为核心分子伴侣通过“纠错”与“维稳”双重机制,确保蛋白质从合成到降解的全生命周期功能正常,是心肌细胞应对环境压力、维持稳态的核心调控者。更重要的是,它们构成了一个从快速隔离(小HSPs)到精细修复与命运抉择(HSP70/HSP90),再到细胞器特异性维护(HSP60)的多层次、网络化的防御体系。深入理解这一网络中各个成员的独特分子路径与协同互作,不仅具有重要的理论意义,也将为通过靶向调控特定HSPs或模拟其相互作用来治疗心血管疾病提供新的思路。

3.2 调控心肌细胞存活和凋亡

在MI/RI或OS等病理条件下,HSPs通过多层次、多靶点的调控机制,有效抑制心肌细胞凋亡,促进细胞存活。Cyt C从线粒体释放后,可触发Apaf-1与Caspase-9结合形成凋亡复合体,进而激活procaspase-3,启动凋亡蛋白酶级联反应。反之,HSP90则通过直接结合Apaf-1,抑制其寡聚化,从而阻断procaspase-9的激活,有效抑制心肌细胞凋亡[85]。此外,当HSP70构象发生变化且ATP酶活性提高后,其与Apaf-1结合的能力也有效增强。在MI/RI中,HSP70保护线粒体功能并维持线粒体膜通透性,是保持心肌结构完整性的关键环节。免疫荧光和共聚焦显微镜结合蛋白质印记检测结果直接表明,HSP70维持线粒体结构及膜电位稳定,阻止了Cyt C和细胞凋亡诱导因子(apoptosis-inducing factor,AIF)发生易位。因此,HSP70通过稳定线粒体,在MI/RI中直接发挥保护心肌结构完整性和缓解心功能障碍的关键作用[86]。同时,HSP70还能减少Cyt C向细胞质的释放,直接抑制Cyt C与Apaf-1的相互作用,或间接抑制由Apaf-1、Cyt C和Caspase-9组成的凋亡小体,从而抑制心肌细胞凋亡[86]。值得注意的是,HSP27于心肌细胞内能通过多种生物学途径发挥抑制细胞凋亡的作用,尤其在应对MI/RI及缺氧等不利环境条件时,其抗凋亡效应尤为显著。当心肌细胞感知到如热应激等应激信号源时,可激活p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase,p38-MAPK),p38-MAPK磷酸化HSP27的Ser15位点。磷酸化后的HSP27由多聚体重组为较小的寡聚体,这种构象变化使得HSP27能够更有效地与其他蛋白质相互作用。HSP27上Ser78和Ser82两个位点的磷酸化进一步增强了HSP27的抗凋亡功能[87]。HSP27能够直接与Cyt C结合,防止其从线粒体释放到细胞质中,从而抑制凋亡小体的形成[73]。HSP27可与Caspase-3等凋亡执行蛋白结合,抑制其活性,阻止凋亡信号的传递,从而减少心肌细胞凋亡[88]。在应激条件下,HSP22能够上调抗凋亡蛋白Bcl-2的表达,同时下调促凋亡蛋白Bax的表达,从而减少Cyt C的释放。除此以外,HSP22在应激条件下还可与HSP27结合,共同加强对Bax等促凋亡蛋白的抑制作用[72,89]。进一步的研究表明,短期递送HSP22基因不仅可有效减少MI/RI导致的心肌梗死面积,并减轻心肌结构破坏程度。双重染色法测定心肌危险区与梗死面积结果显示,HSP22预处理组的心肌梗死面积较对照组降低约40%。心脏超声和血流动力学检测提示,HSP22预处理组的心肌收缩力恢复显著优于对照组。因此,HSP22在MI/RI中显著减轻了心肌结构损伤程度,从而发挥心脏保护作用[16]。

综上,HSPs通过干预死亡受体通路、线粒体通路及溶酶体途径等多个关键凋亡节点,精确调控信号通路的启动和放大,构成了一个立体的、多层次的抗凋亡防御网络。HSP27和HSP70等主要成员通过信号阻断与结构维稳的协同作用,有效抑制Caspase级联反应的激活,并稳定线粒体及溶酶体等细胞器的功能完整性,从而显著增强心肌细胞在缺血、OS等多种病理条件下的存活能力。

3.3 促进心肌细胞修复

虽然大量伤口愈合研究揭示了HSPs促进组织修复的详细机制,但这些发现在心脏修复中的直接适用性仍需进一步验证。值得注意的是,HSP90在皮肤伤口愈合中的促进作用[90]与其在心肌保护中的作用可能存在机制相似性。Hippo-YAP通路对心

脏发育、再生及修复至关重要[91]。在热应激条件下，HSP90结合大肿瘤抑制因子(large tumor suppressor，LATS)并阻止其磷酸化Yes相关蛋白(Yes-associated protein，YAP)，未磷酸化的YAP/TAZ留在细胞核中并与TEA结构域转录因子(TEA-domain transcription factor，TEAD)结合，形成YAP/TAZ-TEAD复合物。这一复合物能够结合到特定基因的启动子区域，激活这些基因的转录，包括多个与心肌细胞增殖相关的基因，如半胱氨酸富集蛋白61(circulating cysteine rich protein 61，Cyr61)、结缔组织生长因子(connective tissue growth factor，CTGF)等。这些基因的表达通过促进心肌细胞周期的进展和增加细胞增殖来加速心肌损伤后的修复与再生[92]。其机制涉及DNA修复酶与HSP90AB1相互作用，后者发生寡聚化并与辅伴侣CDC37及细胞周期激酶结合，进而推动心肌细胞周期进程，促进心脏再生和心肌细胞增殖[84,93]。

综上，HSPs通过促进微血管新生、协调胶原代谢、维持细胞稳态及潜在影响细胞重编程，共同推动心肌损伤后的修复进程。它们既是瘢痕成熟与结构重塑的“建筑师”，也是维持修复微环境稳态的“监督员”(图1)。

3.4 抗氧化应激

在机制方面，HSPs能够直接清除自由基，减轻OS。如HSP32通过催化血红素降解，生成具有抗氧化作用的一氧化碳和胆红素(total bilirubin，TBil)等代谢产物[94]。HSP70能够提高抗氧化酶，如超氧化物歧化酶(superoxide dismutase，SOD)、过氧化氢酶(catalase，CAT)的活性，从而增强细胞的抗氧化能力，减少ROS的积累；此外，它还可以通过调节核因子红细胞2相关因子2(nuclear factor erythroid 2-related factor 2，Nrf2)信号通路，激活下游抗氧化基因的表达，进而减轻OS。Nrf2被激活后抑制NF-κB信号通路，减轻炎症反应。同时，Nrf2上调抗凋亡蛋白Bcl-2的表达，并抑制ROS介导的细胞凋亡[95,96]。

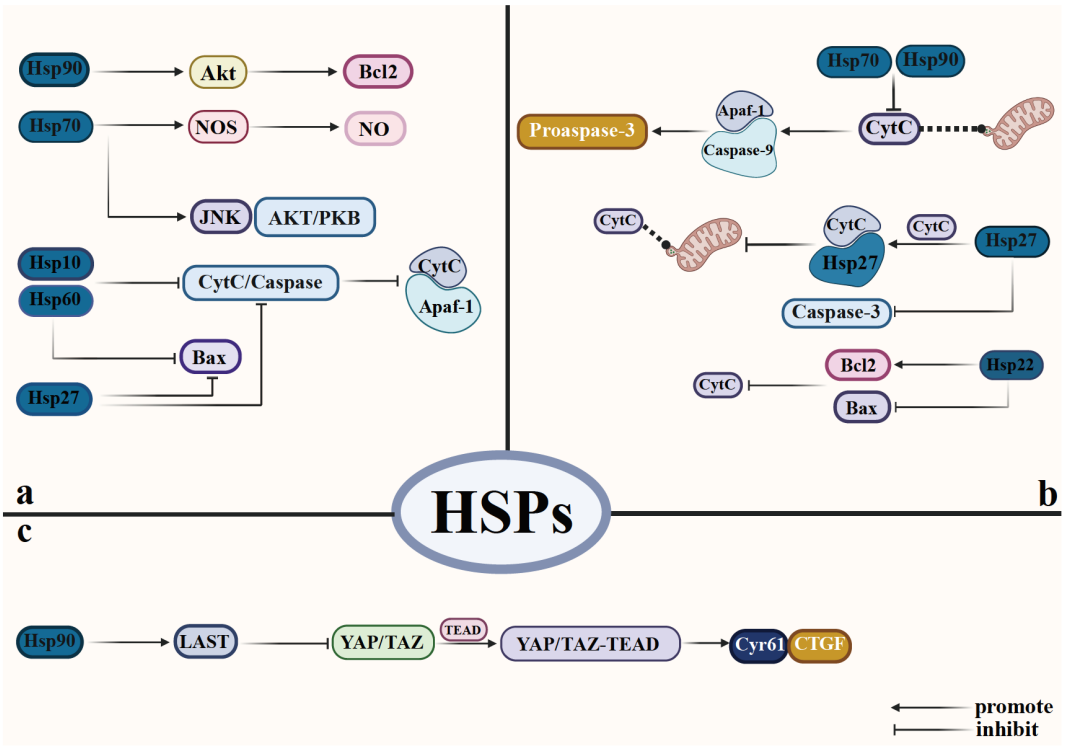


图1 HSPs通过维持蛋白质稳定、抑制凋亡与促进细胞修复保护心肌

(a)HSPs通过维持蛋白质正确折叠与稳态保护心肌；(b)HSPs通过抑制线粒体凋亡通路保护心肌；(c)HSPs通过促进受损细胞结构与功能修复保护心肌。本图使用Biorender(https://app.biorender.com)自行绘制。

Figure 1 HSPs protect the heart muscle by maintaining protein stability, inhibiting apoptosis, and promoting cell repair

(a)HSPs protect the heart muscle by maintaining the correct folding and stability of proteins; (b)HSPs protect the heart muscle by inhibiting the mitochondrial apoptosis pathway; (c)HSPs protect the heart muscle by promoting the repair of damaged cellular structures and functions. This figure was created using Biorender (https://app.biorender.com).

细胞内调节蛋白Kelch样ECH相关蛋白1(Kelch-like ECH-associated protein 1,Keap1)参与OS和蛋白质稳态调控过程,HSP90可以与Keap1相互作用,激活Keap1-Nrf2信号通路,解离Keap1-Nrf2复合物,释放Nrf2进入细胞核,激活抗氧化反应元件(antioxidant response element,ARE),从而提高下游抗氧化酶血红素氧合酶1(heme oxygenase-1,HO-1)和GSH的表达[97]。26S蛋白酶体主要通过泛素-蛋白酶体系统(ubiquitin-proteasome system,UPS)降解泛素化标记的错误折叠蛋白或功能受损的蛋白[98],而在OS条件下,HSP70能促进26S蛋白酶体解离为20S形式,20S蛋白酶体能直接降解氧化损伤的蛋白质,无需泛素化标记,从而快速清除损伤蛋白,维持心肌细胞内环境的稳定。在动物研究中,HSPB1通过Keap1-Nrf2信号通路保护大鼠心肌细胞免受OS带来的损害,并维持还原性GSH的水平和线粒体膜稳态,显示出较强的抗氧化活性。此外,它还能通过调节Hippo-YAP信号通路稳定氧化还原状态,抑制OS,从而减少DNA损伤和脂质过氧化[99]。

综上,HSPs通过增强抗氧化酶活性、调节关键信号通路(Keap1-Nrf2、Bcl-2)、清除氧化损伤蛋白等多种机制,在维持心肌细胞氧化还原平衡中发挥核心作用,从而保护心肌细胞并降低心血管疾病风险。

3.5 调控钙稳态

1988年,Currie等[100]的标志性研究首次提示HSPs可能通过改善钙稳态来保护MI/RI的心脏。钙超载是MI/RI中的关键病理机制之一,可导致心肌细胞凋亡和功能障碍。p38-MAPK的激活会导致细胞内钙离子超载,进而引发心肌细胞凋亡,HSP70通过抑制p38-MAPK信号通路减轻钙超载[101]。在MI/RI中,HSP70还能够调节肌浆/内质网钙离子ATP酶2a(sarcoplasmic/endoplasmic reticulum calcium ATPase 2a,SERCA2a)的表达来减轻钙超载[101]。在心肌缺氧/复氧损伤中,HSP70通过抑制肌醇1,4,5-三磷酸受体/基质相互作用分子1(inositol 1,4,5-trisphosphate receptor-stromal interaction molecule 1,IP3R/STIM1)的表达,减少心肌细胞内钙离子聚集,减轻钙超载[102]。Cyt C的释放会引起线粒体功能障碍,削弱线粒体对钙离子的再摄取能力,进一步加剧钙超载,而HSP27能抑制Cyt C释放,减少钙超载对心肌细胞带来的损伤。HSP27也能调节心肌细胞中的OS反应,从而减轻钙超载[103]。HSP60在MI/RI中通过调节线粒体功能来减轻钙离子超载,保护心肌细胞[104]。

综上,在MI/RI中HSPs通过调节p38-MAPK信号通路、抑制Cyt C释放、调节线粒体功能等多种方式,从源头调控钙稳态,减少心肌细胞内钙离子聚集。这些机制通过稳定心肌细胞内的钙离子稳态,从而减轻了钙超载引发的凋亡与功能障碍,共同保护心肌细胞。

3.6 调控内质网应激

1992年,Kaufman团队首次明确了HSPs在内质网腔中特异性表达[105]。ERS是心肌细胞损伤和炎症反应的重要机制之一。在生理状态下,HSPs能调节ERS反应,减轻心肌细胞的损伤和炎症反应。GRP78是属于HSP70家族且位于内质网的分子伴侣,当创伤型心肌损伤引发ERS时,GRP78的表达水平显著增高。在ERS早期阶段,GRP78对心肌细胞具有保护作用,但若ERS持续存在,它反而会促进心肌细胞凋亡[106]。在病理方面,HSP70和HSP90在MI/RI中与ERS的传感器蛋白——激酶R样内质网激酶(protein kinase R-like ER kinase,PERK)、肌醇所需酶1α(inositol-requiring enzyme 1 α,IRE1α)和激活转录因子6(activating transcription factor 6,ATF6)相互作用,稳定这些蛋白的构象,抑制它们的激活,从而保护心肌细胞[107]。

综上,HSPs在调控ERS相关通路以维护心肌细胞稳态中扮演双重角色。在生理状态下,HSPs在ERS早期发挥保护作用;而在病理过程中,HSPs则通过与关键传感器相互作用,抑制ERS的过度激活,阻断其下游信号的转导,从而减轻心肌细胞的损伤与凋亡。

3.7 抑制炎症

2002年,Brit Dybdahl博士团队首次揭示了HSPs的炎症调节功能,初步确立了其作为炎症调节枢纽的概念[108,109]。进一步的研究发现在心肌损伤(如心肌炎、心肌梗死)过程中,HSP27通过抑制NF-κB的活化来调节炎症,减少白介素-6(interleukin-6,IL-6)的表达,进而减轻心肌损伤[73,103]。此外,HSP60在MI/RI中通过线粒体/NF-κB调节免疫与炎症反应,抑制心肌细胞凋亡[104]。需要特别指出的是,HSPs的免疫调节功能具有显著的背景依赖性和器官特异性。在肠道上皮细胞模型中,HSP27被证实可通

过调控炎症小体或紧密连接蛋白发挥抗炎作用[110]，提示其在心肌炎中可能具有类似的保护潜力；在小鼠小肠中HSP60也被证实可调节局部免疫稳态[63]。然而，心脏作为一个免疫豁免且以心肌细胞为主要功能单元的器官，其炎症微环境与肠道等组织存在本质差异。因此，直接将其他组织的机制推论至心脏须格外谨慎，必须通过心脏特异性模型加以验证。HSP70通过与TLR4直接结合并抑制其表达，阻止TLR4介导的信号转导，进而阻碍NF-κB的激活与核转位，从而减少TNF-α、IL-1β、IL-6等炎症因子的释放，减轻MI/RI中的心肌炎症反应[111]。HSP70与TLR4直接结合并抑制其表达，阻止TLR4介导的信号转导，进而阻碍NF-κB的激活与核转位，减少炎症。HSP70通过与p38-MAPK和PI3K/AKT直接相互作用，抑制p38-MAPK与PI3K/AKT磷酸化，进而阻止p38-MAPK和PI3K/AKT下游信号的转导，减少促炎症因子的产生，从而在缺氧/复氧和MI/RI模型中保护心肌细胞[101]。

总之，HSPs不同亚型在MI/RI中既各司其职又相互协同，通过维持蛋白质稳态、抑制凋亡信号转导、增强抗氧化能力、调节炎症反应等核心路径共同构成多层次心肌保护网络(表2)。综上，HSPs通过调控NF-κB等关键信号通路，在心肌免疫炎症反应中发挥复杂而核心的调节作用。它们既可通过细胞内机制抑制过度炎症、保护心肌，也可能在特定条件下作为损伤相关分子加剧免疫应答(图2)。

4 不同运动强度和类型对心肌细胞中HSPs的作用

运动作为一种生理性应激源，可通过调控HSPs的表达诱导心肌适应性反应，这一机制在运动相关的心脏保护中起着关键作用。运动强度是调控HSPs表达的关键因素[112]。低强度运动(60%VO_2max)时，大鼠心肌HSP72 mRNA的表达水平无明显变化，但随着时间的延长，其表达水平逐渐增加[113]。相比之下，中等强度运动的心肌保护作用更为明确，其机制涉及增强HSPs的抗氧化功能和诱导心肌细胞自噬。具体而言，急性中等强度运动可迅速上调大鼠心肌中HSP72 mRNA的表达，并伴随SOD活性增强；而长期中等强度耐力运动进一步降低心肌脂质过氧化物水平，提高心肌在应激状态下的适应性和耐力，维持心肌细胞的稳定状态，提示长期中等强度耐力运动能通过HSP72诱导抗氧化因子SOD表达，从而减轻心肌应激性损伤[114]。此外，中等强度游泳训练可经LC3介导的自噬通路促进小鼠心肌HSP70表达以减轻损伤[115]。而中等强度间歇运动(28~30 m/min)则使大鼠心肌中HSP70与蛋白激酶C的表达水平显著上升，提示二者之间存在相互调控关系，共同保护心肌细胞[116]。高强度运动(85%VO_2max)对HSPs的诱导作用更为显著，运动后心肌

表2 HSPs不同亚型对MI/RI的主要作用和相应机制

Table2 Primary effects of different HSP subtypes on MI/RI and corresponding mechanisms

HSPs亚型	主要作用	关键机制	参考文献
HSP90	维持蛋白质稳态	促进AKT构象稳定, 调控自噬-溶酶体通路	[84]
HSP70		稳定AKT、JNK、NOS构象, 调节凋亡通路, 改善心功能	[74-76]
HSP60、HSP10、HSP27		协助CytC、Caspase、Bax正确折叠, 抑制凋亡信号通路	[77-80]
HSP90、HSP70	抗凋亡	抑制Apaf-1形成凋亡复合体, 阻断凋亡信号通路	[85,86]
HSP27		结合CytC, 抑制凋亡小体形成	[73,87,88]
HSP22		增加抗凋亡蛋白Bcl-2水平, 减少凋亡蛋白Bax水平, 调控抗凋亡信号通路	[72,89]
HSP90	促进修复	促进YAP/TAZ激活心肌细胞增殖基因, 促进心肌修复	[92]
HSP90	抗氧化应激	激活Keap1-Nrf2信号通路	[97,98]
HSP70		提高抗氧化酶活性, 调控Nrf2信号通路, 激活抗氧化基因；调控泛素-蛋白酶体降解通路	[95,96]
HSPB1		调控Keap1-Nrf2、Hippo-Yes信号通路	[99]
HSP32		催化血红素降解, 激活抗氧化信号通路	[94]
HSP70	抑制钙超载	抑制p38-MAPK信号通路, 调节SERCA2a、IP3R-STIM1表达	[101,102]
HSP60		调节线粒体, 减少钙超载	[104]
HSP27		抑制CytC释放, 调节氧化反应	[103]
HSP90、HSP70	抗内质网应激	调节内质网应激, 与PERK、IRE1α、ATF6协同作用	[110]
HSP70、HSP27	调节炎症反应	调控NF-κB信号通路	[73,103,104]

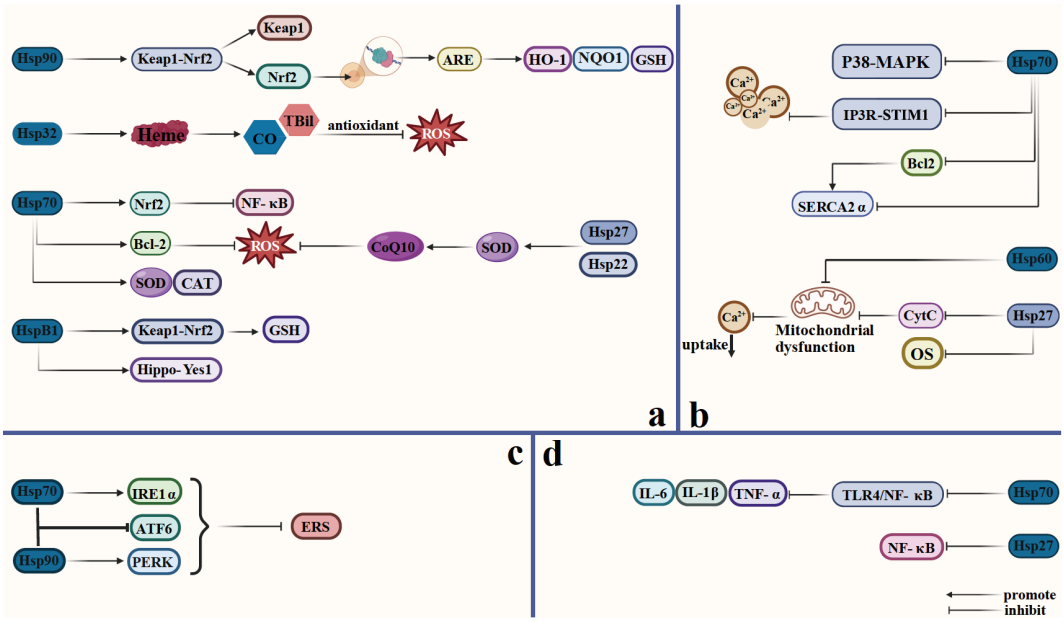


图2　HSPs通过缓解OS、钙超载、内质网应激及炎症反应保护心肌

(a)HSPs通过调控抗氧化系统保护心肌;(b)HSPs通过调节钙离子通道/转运蛋白保护心肌;(c)HSPs通过调控ERS相关蛋白保护心肌;(d)HSPs通过调控NF-κB等信号通路保护心肌。本图使用Biorender(https://app.biorender.com)自行绘制。

Figure 2　HSPs protect myocardium by alleviating OS, calcium overload, ER stress, and inflammation

(a)HSPs protect myocardium by regulating the antioxidant system; (b)HSPs protect myocardium by regulating Ca^{2+} channels/transporters;(c)HSPs protect myocardium by regulating ERS-related proteins; (d)HSPs protect myocardium by regulating NF-κB signaling pathways. This figure was created using Biorender (https://app.biorender.com).

细胞HSP72的表达量与运动持续时间成正比[113]。此外,在大鼠模型中,不同运动类型对HSPs家族成员的诱导具有选择性。耐力运动(如长跑、游泳)主要促进HSP70家族(如HSP72)的表达,其在运动后5小时达到峰值,并可维持高达12小时[117]。长期中等强度耐力训练还能延长HSP70的表达持续时间,并促进HSP20等小分子热休克蛋白的表达,有助于心肌损伤后的功能恢复[118]。而抗阻训练和高强度间歇训练(HIIT)则可能更显著地影响HSP27、HSP60等的表达,这些蛋白在维持细胞骨架稳定性、线粒体功能等方面具有重要作用,但其具体调控机制仍需进一步研究(表3)。

综上,HSPs的表达水平与运动强度及持续时间密切相关,中等强度有氧运动在诱导HSPs表达与实现心肌保护之间取得最佳平衡,通过诱导HSPs抗OS、维持蛋白质稳态、促进心肌细胞自噬等途径促进心肌细胞存活。不同的运动强度和类型所诱导的HSPs,其生物学功能和作用机制存在差异,这为运动训练在心血管疾病预防和康复中的应用提供了科学依据。

5　总结与展望

HSPs作为心肌保护的关键调控因子,通过维持蛋白质稳态、抑制细胞凋亡、缓解OS及调节炎症反应等多重机制,在心脏适应性反应与损伤修复中发挥核心作用。然而,该领域仍存在若干重要科学问题有待深入探讨。

目前研究的局限性主要体现在两个方面。其一,HSPs家族成员之间复杂的功能关系尚不明确。尽管HSP27、HSP60、HSP70和HSP90等均被报道参

表3　不同运动强度和类型下HSPs在心肌细胞中的表达

Table 3　Expression of HSPs in cardiac myocytes under different exercise intensities and types

运动强度	运动类型	研究对象	HSPs	表达	参考文献
低强度	持续性运动	大鼠	HSP72 mRNA	短期内无明显变化, 随时间延长而增加	[109]
中等强度	耐力运动	大鼠	HSP72、HSP20	表达水平提高	[110,114]
	游泳/间歇/耐力运动	小鼠	HSP70	表达持续时间更长	[111-114]
高强度	急性运动	大鼠	HSP72	表达水平随运动时间递增	[109]

与心肌保护，但它们之间的功能冗余、协同或拮抗等潜在关系仍需系统解析。例如，在MI/RI中，HSP70表现出明确的保护效应，而HSP60在某些条件下可能促进凋亡进程。其二，HSPs的作用具有显著的环境依赖性。在生理状态下，HSPs主要维持基础水平的细胞稳态；而在病理应激下，其表达上调可能呈现“双刃剑”效应——既可抑制炎症反应、增强细胞耐受，也可能异常激活免疫应答而加剧损伤，这为相关靶向治疗策略的开发带来挑战。

值得注意的是，运动作为最有效的生理性应激源，能够诱导多种HSPs在心脏中特异性表达，这为心血管疾病的非药物干预提供了独特视角。尽管面临挑战，靶向HSPs的心肌保护策略仍具有重要临床意义。基于运动干预的HSPs调控尤其具有独特优势：首先，其诱导过程模拟生理状态，安全性良好；其次，该干预方式具有代谢改善与心脏保护的多重效益，适宜长期应用。未来转化研究应着重通过整合运动生理学、分子生物学和临床医学的多学科交叉研究，深入解析HSPs在运动相关心肌保护中的机制，这不仅有望为心血管疾病防治提供新靶点，也可能为心脏康复医学提供新的科学基础和干预策略。

参考文献

[1] Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2023 update: a report from the american heart association. Circulation, 2023, 147: e93–621.

[2] Del Re DP, Amgalan D, Linkermann A, et al. Fundamental mechanisms of regulated cell death and implications for heart disease. Physiol Rev, 2019, 99: 1765–817.

[3] Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. J Clin Invest, 2013, 123: 92–100.

[4] Sklifasovskaya AP, Blagonravov M, Ryabinina A, et al. The role of heat shock proteins in the pathogenesis of heart failure. Int J Mol Med, 2023, 52: 106.

[5] Ghafouri-Fard S, Khanbabapour Sasi A, Hussen BM, et al. Interplay between PI3K/AKT pathway and heart disorders. Mol Biol Rep, 2022, 49: 9767–81.

[6] Mauthe M, van de Beek N, Mari M, et al. A chaperone-proteasome-based fragmentation machinery is essential for aggrephagy. Nat Cell Biol, 2025, 27: 1448–64.

[7] Ritossa F. A new puffing pattern induced by temperature shock and DNP in *Drosophila*. Experientia, 1962, 18: 571–3.

[8] Tissières A, Mitchell HK, Tracy UM. Protein synthesis in salivary glands of *Drosophila melanogaster*: relation to chromosome puffs. J Mol Biol, 1974, 84: 389–98.

[9] Lindquist S. The heat-shock response. Annu Rev Biochem, 1986, 55: 1151–91.

[10] Ellis J. Proteins as molecular chaperones. Nature, 1987, 328: 378–9.

[11] Kampinga HH, Hageman J, Vos MJ, et al. Guidelines for the nomenclature of the human heat shock proteins. Cell Stress Chaperones, 2009, 14: 105–11.

[12] Hartl FU, Bracher A, Hayer-Hartl M. Molecular chaperones in protein folding and proteostasis. Nature, 2011, 475: 324–32.

[13] Parsian AJ, Sheren JE, Tao TY, et al. The human HSP70B gene at the HSPA7 locus of chromosome 1 is transcribed but non-functional. Biochim Biophys Acta, 2000, 1494: 201–5.

[14] Ann SJ, Bang H, Lee CJ, et al. LncRNA HSPA7 in human atherosclerotic plaques sponges miR-223 and promotes the proinflammatory vascular smooth muscle cell transition. Exp Mol Med, 2021, 53: 1842–9.

[15] Albinhassan TH, Alharbi BM, AlSuhaibani ES, et al. Small heat shock proteins: protein aggregation amelioration and neuro- and age-protective roles. Int J Mol Sci, 2025, 26: 1525.

[16] Wu W, Lai L, Xie M, et al. Insights of heat shock protein 22 in the cardiac protection against ischemic oxidative stress. Redox Biol, 2020, 34: 101555.

[17] He Y, Wang Z. The roles of HSP40/DNAJ protein family in neurodegenerative diseases. Zhejiang Da Xue Xue Bao Yi Xue Ban, 2022, 51: 640–6.

[18] Singh MK, Shin Y, Han S, et al. Molecular chaperonin HSP60: current understanding and future prospects. Int J Mol Sci, 2024, 25: 5483.

[19] Tang Y, Zhou Y, Fan S, et al. The multiple roles and therapeutic potential of HSP60 in cancer. Biochem Pharmacol, 2022, 201: 115096.

[20] Morizono MA, McGuire KL, Birouty NI, et al. Structural insights into GrpEL1-mediated nucleotide and substrate release of human mitochondrial Hsp70. Nat Commun, 2024, 15: 10815.

[21] Wang W, Liu Q, Liu Q, et al. Conformational equilibria in allosteric control of Hsp70 chaperones. Mol Cell, 2021, 81: 3919–33.

[22] Modrzejewska M, Zdanowska O. The role of heat shock protein 70 (HSP70) in the pathogenesis of ocular diseases-current literature review. J Clin Med, 2024, 13: 3851.

[23] Finci LI, Chakrabarti M, Gulten G, et al. Structural dynamics of RAF1-HSP90-CDC37 and HSP90 complexesreveal asymmetric client interactions and key structural elements. Commun Biol, 2024, 7: 260.
[24] Sager RA, Backe SJ, Neckers L, et al. Detecting posttranslational modifications of Hsp90 isoforms. Methods Mol Biol, 2023, 2693: 125–39.
[25] Wickner S, Nguyen TL, Genest O. The bacterial Hsp90 chaperone: cellular functions and mechanism of action. Annu Rev Microbiol, 2021, 75: 719–39.
[26] Zuo WF, Pang Q, Zhu X, et al. Heat shock proteins as hallmarks of cancer: insights from molecular mechanisms to therapeutic strategies. J Hematol Oncol, 2024, 17: 81.
[27] Riedl S, Bilgen E, Agam G, et al. Evolution of the conformational dynamics of the molecular chaperone Hsp90. Nat Commun, 2024, 15: 8627.
[28] Maiti S, Picard D. Cytosolic Hsp90 isoform-specific functions and clinical significance. Biomolecules, 2022, 12: 1166.
[29] Hoter A, El-Sabban ME, Naim HY. The HSP90 family: structure, regulation, function, and implications in health and disease. Int J Mol Sci, 2018, 19: 2560.
[30] Zhang M, Bi X. Heat shock proteins and breast cancer. Int J Mol Sci, 2024, 25: 876.
[31] Horwitz J. Alpha-crystallin can function as a molecular chaperone. Proc Natl Acad Sci U S A, 1992, 89: 10449–53.
[32] Louros N, Schymkowitz J, Rousseau F. Mechanisms and pathology of protein misfolding and aggregation. Nat Rev Mol Cell Biol, 2023, 24: 912–33.
[33] Dupuy E, Van der Verren SE, Lin J, et al. A molecular device for the redox quality control of GroEL/ES substrates. Cell, 2023, 186: 1039–49.
[34] Lee GJ, Roseman AM, Saibil HR, et al. A small heat shock protein stably binds heat-denatured model substrates and can maintain a substrate in a folding-competent state. EMBO J, 1997, 16: 659–71.
[35] Javed A, Johnson OT, Balana AT, et al. O-GlcNAc modification of HSP27 alters its protein interactions and promotes refolding of proteins through the BAG3/HSP70 co-chaperone. Protein Sci, 2024, 33: e5173.
[36] Zhang XH, Wu JX, Sha JZ, et al. Heat shock protein 90 relieves heat stress damage of myocardial cells by regulating Akt and PKM2 signaling *in vivo*. Int J Mol Med, 2020, 45: 1888–908.
[37] Li Y, Li S, Wu H. Ubiquitination-proteasome system (UPS) and autophagy two main protein degradation machineries in response to cell stress. Cells, 2022, 11: 851.
[38] Rehman A, Yousuf S, Maken GR, et al. Cardiac troponin-I, a biomarker for predicting COVID-induced myocardial damage prognosis. J Coll Physicians Surg Pak, 2023, 33: 498–503.
[39] Zhou X, Fang X, Ithychanda SS, et al. Interaction of filamin C with actin is essential for cardiac development and function. Circ Res, 2023, 133: 400–11.
[40] Graceffa P. Hsp27-actin interaction. Biochem Res Int, 2011, 2011: 901572.
[41] Saleh A, Srinivasula SM, Balkir L, et al. Negative regulation of the Apaf-1 apoptosome by Hsp70. Nat Cell Biol, 2000, 2: 476–83.
[42] Ravagnan L, Gurbuxani S, Susin SA, et al. Heat-shock protein 70 antagonizes apoptosis-inducing factor. Nat Cell Biol, 2001, 3: 839–43.
[43] Ruchalski K, Mao H, Li Z, et al. Distinct Hsp70 domains mediate apoptosis-inducing factor release and nuclear accumulation. J Biol Chem, 2006, 281: 7873–80.
[44] Bonvini P, Zorzi E, Mussolin L, et al. The effect of the cyclin-dependent kinase inhibitor flavopiridol on anaplastic large cell lymphoma cells and relationship with NPM-ALK kinase expression and activity. Haematologica, 2009, 94: 944–55.
[45] Dubaniewicz A. Mycobacterial heat shock proteins in sarcoidosis and tuberculosis. Int J Mol Sci, 2023, 24: 5084.
[46] Bhadra K. A mini review on molecules inducing caspase-independent cell death: a new route to cancer therapy. Molecules, 2022, 27: 6401.
[47] Reinle K, Mogk A, Bukau B. The diverse functions of small heat shock proteins in the proteostasis network. J Mol Biol, 2022, 434: 167157.
[48] Shan R, Liu N, Yan Y, et al. Apoptosis, autophagy and atherosclerosis: relationships and the role of Hsp27. Pharmacol Res, 2021, 166: 105169.
[49] Roufayel R, Kadry S. Molecular chaperone HSP70 and key regulators of apoptosis. Curr Mol Med, 2019, 19: 315–25.
[50] Qing Y, Guo Y, Zhao Q, et al. Targeting lysosomal HSP70 induces acid sphingomyelinase-mediated disturbance of lipid metabolism and leads to cell death in T cell malignancies. Clin Transl Med, 2023, 13: e1229.
[51] Marber MS, Mestril R, Chi SH, et al. Overexpression of the rat inducible 70-kD heat stress protein in a transgenic mouse increases the resistance of the heart to ischemic injury. J Clin Invest, 1995, 95: 1446–56.
[52] Bruns AF, Yuldasheva N, Latham AM, et al. A heat-shock protein axis regulates VEGFR2 proteolysis, blood vessel development and repair. PLoS One, 2012, 7: e48539.

[53] Chen DX, Lu CH, Na N, et al. Endothelial progenitor cell-derived extracellular vesicles: the world of potential prospects for the treatment of cardiovascular diseases. Cell Biosci, 2024, 14: 72.
[54] Tanimoto T, Parseghian MH, Nakahara T, et al. Cardioprotective effects of HSP72 administration on ischemia-reperfusion injury. J Am Coll Cardiol, 2017, 70: 1479–92.
[55] Ye W, Meng X, Xu S. Research progress on collagen secretion mechanisms in scarring. Zhejiang Da Xue Xue Bao Yi Xue Ban, 2025, 54: 266–78.
[56] Huang D, Zhao D, Li M, et al. Crosstalk between PML and p53 in response to TGF-β1: a new mechanism of cardiac fibroblast activation. Int J Biol Sci, 2023, 19: 994–1006.
[57] Kleinbongard P, Dejam A, Lauer T, et al. Plasma nitrite reflects constitutive nitric oxide synthase activity in mammals. Free Radic Biol Med, 2003, 35: 790–6.
[58] Szyller J, Bil-Lula I. Heat shock proteins in oxidative stress and ischemia/reperfusion injury and benefits from physical exercises: a review to the current knowledge. Oxid Med Cell Longev, 2021, 2021: 6678457.
[59] Szyller J, Kozakiewicz M, Siermontowski P, et al. Oxidative stress, HSP70/HSP90 and eNOS/iNOS serum levels in professional divers during hyperbaric exposition. Antioxidants (Basel), 2022, 11: 1008.
[60] Martínez-Laorden E, Navarro-Zaragoza J, Milanés MV, et al. Cardiac protective role of heat shock protein 27 in the stress induced by drugs of abuse. Int J Mol Sci, 2020, 21: 3623.
[61] Zhang H, Gong W, Wu S, et al. Hsp70 in redox homeostasis. Cells, 2022, 11: 829.
[62] Xu NW, Chen Y, Liu W, et al. Inhibition of JAK2/STAT3 signaling pathway suppresses proliferation of burkitt′s lymphoma raji cells via cell cycle progression, apoptosis, and oxidative stress by modulating HSP70. Med Sci Monit, 2018, 24: 6255–63.
[63] Paladino L, Rappa F, Barone R, et al. NF-kB regulation and the chaperone system mediate restorative effects of the probiotic lactobacillus fermentum LF31 in the small intestine and cerebellum of mice with ethanol-induced damage. Biology (Basel), 2023, 12: 1394.
[64] Kovár J, Stýbrová H, Novák P, et al. Heat shock protein 90 recognized as an iron-binding protein associated with the plasma membrane of HeLa cells. Cell Physiol Biochem, 2004, 14: 41–6.
[65] Zhang M, Wang D, Geng Z, et al. Effect of heat shock protein 90 against ROS-induced phospholipid oxidation. Food Chem, 2018, 240: 642–47.
[66] Zhang M, Wang D, Xu X, et al. Evaluation of antioxidant property of heat shock protein 90 from duck muscle. Anim Biosci, 2021, 34: 724–33.
[67] Balogi Z, Multhoff G, Jensen TK, et al. Hsp70 interactions with membrane lipids regulate cellular functions in health and disease. Prog Lipid Res, 2019, 74: 18–30.
[68] Wang B, Pratt MR. Potential for targeting small heat shock protein modifications. Trends Pharmacol Sci, 2024, 45: 583–85.
[69] Han X, Jiang Z, Hou Y, et al. Myocardial ischemia-reperfusion injury upregulates nucleostemin expression via HIF-1α and c-Jun pathways and alleviates apoptosis by promoting autophagy. Cell Death Discov, 2024, 10: 461.
[70] Ahmed K, Zaidi SF, Mati Ur R, et al. Hyperthermia and protein homeostasis: cytoprotection and cell death. J Therm Biol, 2020, 91: 102615.
[71] Fan GC, Kranias EG. Small heat shock protein 20 (HspB6) in cardiac hypertrophy and failure. J Mol Cell Cardiol, 2011, 51: 574–7.
[72] Chen Y, Li M, Wu Y. Heat shock protein 22: a new direction for cardiovascular disease. Mol Med Rep, 2025, 31: 82.
[73] Shi P, Wu J, Li M, et al. Upregulation of Hsp27 via further inhibition of histone H2A ubiquitination confers protection against myocardial ischemia/reperfusion injury by promoting glycolysis and enhancing mitochondrial function. Cell Death Discov, 2023, 9: 466.
[74] Xin BR, Li P, Liu XL, et al. Visfatin relieves myocardial ischemia-reperfusion injury through activation of PI3K/Akt/HSP70 signaling axis. Eur Rev Med Pharmacol Sci, 2020, 24: 10779–89.
[75] Zhao LL, Gu JN, Zhu XF, et al. HSC70-JNK-BAG3 complex is critical for cardiomyocyte protection of BAG3 through its PXXP and BAG structural domains. Front Biosci (Landmark Ed), 2021, 26: 102–13.
[76] Hazra J, Vijayakumar A, Mahapatra NR. Emerging role of heat shock proteins in cardiovascular diseases. Adv Protein Chem Struct Biol, 2023, 134: 271–306.
[77] Lin KM, Lin B, Lian IY, et al. Combined and individual mitochondrial HSP60 and HSP10 expression in cardiac myocytes protects mitochondrial function and prevents apoptotic cell deaths induced by simulated ischemia-reoxygenation. Circulation, 2001, 103: 1787–92.
[78] Lv F, Qi F, Zhang Z, et al. An amphipathic Bax core dimer forms part of the apoptotic pore wall in the mitochondrial membrane. EMBO J, 2021, 40:

e106438.

[79] Fan F, Duan Y, Yang F, et al. Deletion of heat shock protein 60 in adult mouse cardiomyocytes perturbs mitochondrial protein homeostasis and causes heart failure. Cell Death Differ, 2020, 27: 587–600.

[80] Havasi A, Li Z, Wang Z, et al. Hsp27 inhibits Bax activation and apoptosis via a phosphatidylinositol 3-kinase-dependent mechanism. J Biol Chem, 2008, 283: 12305–13.

[81] Kotler JLM, Street TO. Mechanisms of protein quality control in the endoplasmic reticulum by a coordinated Hsp40-Hsp70-Hsp90 system. Annu Rev Biophys, 2023, 52: 509–24.

[82] Ghosh R, Pattison JS. Chaperone-mediated autophagy regulates hypoxic pathology in cardiomyocytes. Autophagy Rep, 2023, 2: 2174337.

[83] Torrente MP, Shorter J. The metazoan protein disaggregase and amyloid depolymerase system: Hsp110, Hsp70, Hsp40, and small heat shock proteins. Prion, 2013, 7: 457–63.

[84] Roberts RJ, Hallee L, Lam CK. The potential of Hsp90 in targeting pathological pathways in cardiac diseases. J Pers Med, 2021, 11: 1373.

[85] Dabravolski SA, Sukhorukov VN, Kalmykov VA, et al. Heat shock protein 90 as therapeutic target for CVDs and heart ageing. Int J Mol Sci, 2022, 23: 649.

[86] Lanneau D, Brunet M, Frisan E, et al. Heat shock proteins: essential proteins for apoptosis regulation. J Cell Mol Med, 2008, 12: 743–61.

[87] Vidyasagar A, Wilson NA, Djamali A. Heat shock protein 27 (HSP27): biomarker of disease and therapeutic target. Fibrogenesis Tissue Repair, 2012, 5: 7.

[88] Wang B, Moon SP, Cutolo G, et al. HSP27 inhibitory activity against caspase-3 cleavage and activation by caspase-9 is enhanced by chaperone O-GlcNAc modification *in vitro*. ACS Chem Biol, 2023, 18: 1698–704.

[89] Lan Y, Wang Y, Huang K, et al. Heat shock protein 22 attenuates doxorubicin-induced cardiotoxicity via regulating inflammation and apoptosis. Front Pharmacol, 2020, 11: 257.

[90] Li W, Li Y, Guan S, et al. Extracellular heat shock protein-90alpha: linking hypoxia to skin cell motility and wound healing. EMBO J, 2007, 26: 1221–33.

[91] Meng F, Xie B, Martin JF. Targeting the Hippo pathway in heart repair. Cardiovasc Res, 2022, 118: 2402–14.

[92] Wang J, Huang L, Yu H, et al. Role of Hippo-YAP/TAZ signaling pathway in organ fibrosis. Zhong Nan Da Xue Xue Bao Yi Xue Ban, 2024, 49: 1509–16.

[93] Shu J, Yan S, Ju C, et al. PARP1 promotes heart regeneration and cardiomyocyte proliferation. Int J Biol Sci, 2024, 20: 1602–16.

[94] Ryter SW. Heme oxygenase-1: an anti-inflammatory effector in cardiovascular, lung, and related metabolic disorders. Antioxidants (Basel), 2022, 11: 555.

[95] Deng B, He X, Wang Z, et al. HSP70 protects PC12 cells against TBHP-induced apoptosis and oxidative stress by activating the Nrf2/HO-1 signaling pathway. In Vitro Cell Dev Biol Anim, 2024, 60: 868–78.

[96] Song JA, Lee E, Choi YU, et al. Influence of temperature changes on oxidative stress and antioxidant defense system in the bay scallop, *Argopecten irradians*. Comp Biochem Physiol A Mol Integr Physiol, 2025, 299: 111775.

[97] Amata E, Pittalà V, Marrazzo A, et al. Role of the Nrf2/HO-1 axis in bronchopulmonary dysplasia and hyperoxic lung injuries. Clin Sci (Lond), 2017, 131: 1701–12.

[98] Hu J, Wang Q, Liu Y. Research progress on proteasome subunits in regulating occurrence and development of hepatocellular carcinoma. Zhejiang Da Xue Xue Bao Yi Xue Ban, 2021, 50: 396–402.

[99] Wang N, Liu X, Liu K, et al. Homo-oxidized HSPB1 protects H9c2 cells against oxidative stress via activation of KEAP1/NRF2 signaling pathway. iScience, 2023, 26: 107443.

[100] Currie RW, Karmazyn M, Kloc M, et al. Heat-shock response is associated with enhanced postischemic ventricular recovery. Circ Res, 1988, 63: 543–9.

[101] Song N, Ma J, Meng XW, et al. Heat shock protein 70 protects the heart from ischemia/reperfusion injury through inhibition of p38 MAPK signaling. Oxid Med Cell Longev, 2020, 2020: 3908641.

[102] Liu T, Juan Z, Xia B, et al. HSP70 protects H9C2 cells from hypoxia and reoxygenation injury through STIM1/IP3R. Cell Stress Chaperones, 2022, 27: 535–44.

[103] Zou Y, Shi H, Liu N, et al. Mechanistic insights into heat shock protein 27, a potential therapeutic target for cardiovascular diseases. Front Cardiovasc Med, 2023, 10: 1195464.

[104] Duan Y, Tang H, Mitchell-Silbaugh K, et al. Heat shock protein 60 in cardiovascular physiology and diseases. Front Mol Biosci, 2020, 7: 73.

[105] Melnick J, Aviel S, Argon Y. The endoplasmic reticulum stress protein GRP94, in addition to BiP, associates with unassembled immunoglobulin chains. J Biol Chem, 1992, 267: 21303–6.

[106] Yan Z, Liu Y, Yang B, et al. Endoplasmic reticulum stress

caused by traumatic injury promotes cardiomyocyte apoptosis through acetylation modification of GRP78. Acta Biochim Biophys Sin, 2024, 56: 96–105.

[107] Chen X, Shi C, He M, et al. Endoplasmic reticulum stress: molecular mechanism and therapeutic targets. Signal Transduct Target Ther, 2023, 8: 352.

[108] Dybdahl B, Slørdahl SA, Waage A, et al. Myocardial ischaemia and the inflammatory response: release of heat shock protein 70 after myocardial infarction. Heart, 2005, 91: 299–304.

[109] Hamilton KL, Staib JL, Phillips T, et al. Exercise, antioxidants, and HSP72: protection against myocardial ischemia/reperfusion. Free Radic Biol Med, 2003, 34: 800–9.

[110] Zhang Y, Wang X, Wang S, et al. Heat shock protein 27 regulates the inflammatory response of intestinal epithelial cells by the nuclear factor-κB pathway. Dig Dis Sci, 2020, 65: 3514–20.

[111] Fang H, Wu Y, Huang X, et al. Toll-like receptor 4 (TLR4) is essential for Hsp70-like protein 1 (HSP70L1) to activate dendritic cells and induce Th1 response. J Biol Chem, 2011, 286: 30393–400.

[112] Locke M, Noble EG, Atkinson BG. Exercising mammals synthesize stress proteins. Am J Physiol, 1990, 258: C723–9.

[113] 陈佩杰, 魏勇, 杨德洪. 不同强度运动后大鼠心肌细胞热休克蛋白72mRNA的表达. 中国运动医学杂志, 2004, 23: 624–8.
Chen PJ, Wei Y, Yang DH. Effects of different exercise intensities on the expression of heat shock protein72 mRNA in myocardium of rats. Chinese Journal of Sports Medicine, 2004, 23: 624–8.

[114] 曹桂霞. 耐力训练对大鼠心肌Hsp72 mRNA表达及急性运动耐受性的影响[D]. 上海: 华东师范大学, 2007.
Cao GX. Effects of endurance training on Hsp72 mRNA expression in rat myocardium and acute exercise tolerance [D]. Shanghai: East China Normal University, 2007.

[115] Jiang L, Shen X, Dun Y, et al. Exercise combined with trimetazidine improves anti-fatal stress capacity through enhancing autophagy and heat shock protein 70 of myocardium in mice. Int J Med Sci, 2021, 18: 1680–86.

[116] 申毓军. 运动预适应对力竭运动大鼠心肌损伤保护效应中蛋白激酶C的作用及其机制[D]. 上海: 上海体育学院, 2011.
Shen YJ. Role and mechanism of protein kinase C in exercise preconditioning-mediated protection against myocardial injury in exhaustion-exercised rats [D]. Shanghai: Shanghai University of Sport, 2011.

[117] 张丽琴, 王蕴红, 赵明华, 等. 运动对大鼠心肌FOS和HSP70表达的影响. 北京体育大学学报, 2010, 33: 64–6+70.
Zhang LQ, Wang YH, Zhao MH, et al. Effect of exercise on the expression of cardiac FOS and heat shock protein 70 in rats. Journal of Beijing Sport University, 2010, 33: 64–6+70.

[118] Boluyt MO, Brevick JL, Rogers DS, et al. Changes in the rat heart proteome induced by exercise training: increased abundance of heat shock protein Hsp20. Proteomics, 2006, 6: 3154–69.