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铁死亡在心血管疾病中作用机制的研究进展

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摘　要

铁死亡是不同于细胞凋亡，坏死的新型细胞死亡方式。研究表明铁死亡参与心血管疾病的发生发展，铁死亡在心肌病，心肌梗死，缺血再灌注损伤和心力衰竭中起关键作用。中国患有心血管疾病的总人数超过了肿瘤和其他慢性病，疾病负担重。然而铁死亡在心血管疾病中的作用机制，治疗靶点仍需进一步阐明。本文概述了铁死亡的分子机制及其在心血管疾病中的作用，强调靶向铁死亡可能是未来心血管疾病的潜在治疗策略。

关键词

铁死亡，心血管疾病，脂质过氧化

Advances in Mechanisms of Ferroptosis in Cardiovascular Disease

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Abstract

Ferroptosis is a novel form of cell death distinct from apoptosis and necrosis. Studies have shown that Ferroptosis is involved in the development of cardiovascular disease and plays a key role in

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cardiomyopathy, myocardial infarction, ischemia-reperfusion injury and heart failure. The total number of people suffering from cardiovascular disease in China exceeds that of oncology and other chronic diseases, and the burden of disease is high. However, the mechanism of Ferroptosis in cardiovascular diseases and therapeutic targets still need to be further elucidated. This article provides an overview of the molecular mechanisms of Ferroptosis and its role in cardiovascular disease, emphasising that targeting Ferroptosis may be a potential therapeutic strategy for cardiovascular disease.

Keywords

Ferroptosis, Cardiovascular Disease, Lipid Peroxidation

1. 引言

心血管疾病(Cardiovascular disease, CVD)是全球疾病负担和过早死亡的主要原因[1]。截至 2018 年，中国患有 CVD 的总人数为 2.9 亿，占疾病相关死亡人数的 40%，超过了肿瘤和其他慢性病，疾病负担重[2]。慢性全身炎症，氧化应激，细胞死亡等在心血管疾病发病机制起着核心作用[3]。无论机制如何，各种氧化应激等损伤导致心肌细胞的最终结局都是细胞死亡。心肌细胞因不可逆损伤和细胞死亡而急性丢失，是各种心脏病、心室重构和心力衰竭的重要原因[4]。作为终末分化的细胞，成体心肌细胞的自我更新能力有限。在大多数不利情况下，心肌细胞和血管细胞主要死于调节性细胞死亡[5] [6]。细胞死亡是多细胞生物在发育过程中必要的过程，对于预防心肌疾病至关重要，了解心血管疾病中的细胞死亡有利于心血管疾病的治疗[7]。

铁死亡是一种新型的细胞死亡，起源于拉丁语“ferrum”和希腊语“ptosis”，分别表示“铁”和“坠落”[8]。与坏死、细胞凋亡、自噬和坏死性凋亡不同，铁死亡是一种铁依赖性脂质过氧化物积累引起的新型细胞死亡方式，其形态学特征线粒体萎缩、外膜破裂、线粒体膜密度增加、线粒体嵴减少或消失[9]。最近的研究揭示了铁死亡与心血管疾病之间密切相关。已知铁死亡在心肌病[10]、心肌梗死[11]、缺血再灌注损伤[12]和心力衰竭[13]中起关键作用。抑制铁死亡，从而防止心脏细胞死亡可能成为心血管疾病的有效治疗策略[14]。

在这篇综述中，介绍了铁死亡的机制与各 CVD 相关的当前研究，提供了靶向铁死亡治疗心血管疾病的新视角。

2. 铁死亡机制

2.1. 铁代谢

铁是电子传递、氧气的运输和储存、线粒体呼吸和氧化还原反应等一系列重要生物过程所必需的[15]。体内，Fe^{2+}可以通过铜蓝蛋白转化为 Fe^{3+}，Fe^{3+}与转铁蛋白结合形成复合物通过转铁蛋白受体 1 被细胞摄取。细胞内 Fe^{3+}还原为 Fe^{2+}，用于组成铁依赖性酶或储存在不稳定的铁池和铁蛋白中。哺乳动物铁蛋白由铁蛋白重链(Ferritin Heavy Chain 1, FTH1)和轻链的 24 个亚基组成，形成一个能够储存 4500 个铁原子的保护笼[16]。冗余的铁也可以通过铁转运蛋白(ferroportin, FPN)释放到细胞外空间[17]。铁离子的过度积累通过芬顿反应增加了 ROS 的产生，其中亚铁与过氧化氢在非酶促过程中形成产物三价铁和羟基自由

基，促进细胞对于铁死亡的敏感性[18]。

2.2. 氨基酸代谢

谷胱甘肽(Glutathione GSH)是由谷氨酸、半胱氨酸和甘氨酸组成的三肽化合物。GSH 可以将细胞代谢产生的有害脂质氢过氧化物还原为无害的脂质醇，这是决定细胞是否发生铁死亡的关键[19]。GSH 在催化酶的催化下由细胞内半胱氨酸，谷氨酸和甘氨酸合成。胱氨酸由谷氨酸胱氨酸逆向转运蛋白系统 Xc−(systemic Xc−)运输。GSH 是 GPX4 (glutathione peroxidase 4, GPX4)功能的重要辅助因子，胱氨酸水平降低最终会消耗 GSH 使 GPX4 失活，erastin、柳氮磺吡啶和索拉非尼可以通过抑制系统 Xc−来消耗细胞内胱氨酸引发铁死亡，GPX4 的直接抑制剂可以通过灭活 GPX4 来启动铁死亡。

2.3. 脂类代谢

脂质过氧化是细胞膜中的脂质电子被自由基物质去除的过程。这个过程产生过量的活性氧(reactive oxygen species, ROS)，导致膜脂质多不饱和脂肪酸(polyunsaturated fatty acids, PUFAs)氧化。PUFAs 对 ROS 极为敏感，容易受损导致细胞膜破坏，细胞死亡[6]。过氧化氢与亚铁离子通过芬顿反应产生羟基自由基，随后去除 PUFA 双烯丙基氢以产生多不饱和脂肪酸自由基。这些不稳定的自由基迅速与氧气反应最终产生多不饱和酸氢过氧化物[20]。

脂氧合酶(lipoxygenases, LOXs)是催化 PUFA 脱氧的含铁酶家族，在铁死亡的脂质过氧化中起核心作用。人类有 6 种 LOX 亚型，其中 12 和 15-LOX 广泛分布在多种组织中发挥主要作用[21]。15-LOX 的过表达会促进脂质过氧化，而 15-LOX 抑制剂会抑制铁死亡。酰基辅酶 A 合酶长链家族成员 4 (Acyl-coenzyme A synthetase long chain family member 4, ACSL4)是一种参与磷脂代谢的酶，ACSL4 催化辅酶 A 添加到花生四烯酸的长链多不饱和键中，导致 PUFA 酯化形成磷脂。ACSL4 激活后，溶血磷脂酰胆碱酰基转移酶 3 将酰基插入溶血磷脂中，并将游离 PUFA 掺入磷脂中，参与铁死亡脂质信号传导[22]。

3. 铁死亡在心血管疾病中的作用

3.1. 心肌缺血再灌注与铁死亡

在缺血性心脏中，快速恢复血流(再灌注)对于氧气和营养供应是必要的，但缺血一段时间后再灌注导致心肌损伤，心功能恶化，这种现象被称为心肌缺血再灌注损伤(myocardial ischemia-reperfusion injury, MI/RI) [23] [24]。心肌缺血再灌注阶段导致氧气突然重新进入导致组织暴露于 ROS [25]缺血心肌中铁超载[26]等触发氧化应激诱导细胞死亡。

已有研究报道抑制铁死亡可以保护心肌缺血再灌注损伤。研究表明铁死亡相关 circRNA 参与心肌细胞铁死亡的调节并改善心肌 I/R 损伤。铁死亡抑制剂以及铁螯合剂可以通过抑制铁死亡来减轻心肌缺血再灌注期间心肌梗死的大小[4] [25]。除了铁死亡抑制剂等，其它药理治疗如中成药人参皂甙[27]、棉酚乙酸[28]、川陈皮素[29]，免疫抑制剂环孢菌素 A [30]，纳米药物聚多巴胺[31]抑制心肌细胞铁死亡保护心肌缺血再灌注损伤。基于临床前研究已经进行了几项临床研究，以证明铁螯合疗法对冠状动脉疾病患者的益处。在 Paraskevaidis 等人的研究中，在冠状动脉旁路移植手术期间施用铁螯合剂，这种干预保护了心肌免受再灌注损伤，减少了患者在重症监护病房的住院时间，还减少了脂质过氧化[32]。

综上所述，铁死亡是缺血性心脏病治疗中的新治疗靶点，目前在心肌缺血再灌注治疗中大多采取抗氧化(中成药等)，或者铁螯合剂靶向铁死亡减少心肌细胞损伤。值得注意的是大多数细胞死亡发生在再灌注的最初几分钟内。对于药物，通常最好在缺血期间尽早给药，以确保在再灌注开始时有足够的心肌浓度[33] [34]。

3.2. 心力衰竭

心力衰竭特征是心脏肥大和纤维化。心力衰竭的原因很多，糖尿病、高血压、肥胖和炎症可能是诱发因素。根据研究，已经确定了铁死亡在心肌梗死和心肌病引起的心力衰竭的发生和进展中的重要作用，这可能为心力衰竭提供更好的治疗靶点[13] [35]。射血分数保留的心力衰竭小鼠的心脏中确实存在铁死亡的异常激活，铁死亡被抑制后射血分数保留心力衰竭关键基因表达水平的改变和表型的缓解[36]。一项研究发现在心肌细胞中过表达 ACSL4 会加剧压力超负荷，通过铁死亡诱导心功能障碍。ACSL4 的药理学抑制和基因缺失均显著减小了心力衰竭小鼠的左心室大小并改善了心脏功能[37]。钠－葡萄糖协同转运蛋白 2 (Sodium-glucose cotransporter 2, SGLT2)抑制剂可降低心力衰竭患者因心力衰竭而死亡和住院的风险[38]。在实验模型中，SGLT2 抑制剂可抑制铁死亡，保留射血心力衰竭的心脏功能[39]。在主动脉缩窄心力衰竭小鼠模型中，白藜芦醇通过激活心力衰竭中的 Sirt1/p53 通路，减少了 SLC7A11 的耗竭，抑制了铁死亡，并改善了心脏功能[40]。除了心肌细胞外，肌成纤维细胞的死亡是心脏纤维化的关键驱动因素。最新的研究发现肌成纤维细胞中 Sirtuin 3/乙酰化 p53 通路诱导的铁死亡，作为抑制心脏纤维化进一步发展的潜在治疗靶点[41]。目前铁死亡在心力衰竭中的研究大多与一些信号通路激活发挥抗氧化机制发挥抗铁死亡作用，这为心力衰竭治疗提供了新的思路。

3.3. 心脏移植

心力衰竭是大多数原发性心血管疾病的最终临床结果，对于终末期心脏病患者心脏移植是最有效的策略。然而，移植物缺血再灌注损伤在临床上会引起严重的无菌性炎症，导致原发性移植物功能障碍甚至死亡[42]。Li 等人研究发现心脏移植后的炎症反应是通过移植物内皮细胞中的铁死亡和 TLR4/Tif 依赖性信号传导启动的。铁死亡的特异性抑制剂 ferrostatin-1 可降低促铁死亡的氢过氧－花生四烯酰－磷脂酰乙醇胺的水平，减少心肌细胞死亡，并阻断心脏移植后中性粒细胞的募集[43]。Kreisel D 等人报告称，用铁蛋白酶抑制剂-1 治疗接受者可以抑制缺血再灌注损伤的心脏移植物中成纤维细胞的铁死亡，铁抑制剂-1 治疗强烈抑制了中性粒细胞对冠状血管内皮细胞的粘附，这表明铁死亡对于心脏移植后的炎症反应至关重要。因此，建议在移植前用铁死亡抑制剂治疗供体移植物，以减轻心脏损伤中的炎症反应，从而可能改善心脏移植后的预后。

3.4. 心肌病

心肌病是一种心肌结构和功能异常的心肌疾病，其中心肌在结构和功能上都异常，而没有观察到足以引起心肌异常的冠状动脉疾病、高血压、瓣膜病和先天性心脏病[20]。糖尿病心肌病是一种独立于高血压和冠状动脉疾病的特定形式的心肌病，可增加氧化应激并激活多种炎症途径，导致细胞损伤、心脏重塑以及收缩和舒张功能障碍，最终导致心肌细胞死亡。铁死亡参与糖尿病心肌病的证据来自以下事实：1) 在糖尿病中，晚期糖基化终末产物增加、脂质过氧化和氧化应激，这也是细胞铁过载和铁死亡的触发因素[43]。2) 线粒体磷脂氢过氧化物谷胱甘肽过氧化物酶 4 的过表达在链脲佐菌素诱导的 DCM 模型中提供心脏保护[44]。3) 糖尿病性心肌病会增加 MDA，这是一种与铁死亡相关的典型标志物，糖尿病性心肌病会降低 SLC7A11 和 GSH，这是铁死亡调节关键因子[39]。4) 使用 Liproxstatin-1 治疗可改善糖尿病小鼠模型的心脏舒张功能[45]。迄今为止铁死亡在糖尿病心肌病中作用的可用证据主要来自在高葡萄糖中培养的细胞研究和少许糖尿病模型的动物研究。因此，虽然现有研究支持糖尿病心肌病中可能存在铁死亡，但仍需要更可靠的实验和临床证据。

肥厚型心肌病是最常见的原发性心肌病，特点是存在左心室肥厚，并与心源性猝死有关。目前对肥厚性心肌病的治疗主要包括药物治疗、肌切除术和酒精间隔消融术[46]。铁死亡在肥厚性心肌病中发挥作

用主要与以下证据有关 1) Wang 等人通过基因表达综合数据库筛选了肥厚性心肌病的差异表达基因和枢纽基因后分析肥厚性心肌病和铁死亡之间的关联，发现差异表达基因与铁死亡调控有关，包括 ATF3、LPCAT3 和 SLC1A5 [47]。2) 肥厚型心肌病心肌细胞中 L 型钙离子通道活性增强，已经证明 L 型钙离子通道的激活不仅使细胞外 Ca^{2+}进入，但也增加了细胞内铁积累[48] [49]。因此，肥厚型心肌病中细胞内铁浓度升高，这会促进 ROS 的过度产生和脂质过氧化、抗氧化剂的耗竭，最后导致铁死亡。3) 肥厚型心肌病的特征是葡萄糖利用改变和普遍存在糖酵解，产生丙酮酸和乳酸，从而促进铁死亡。Fang 等人最近报道，喂食高铁饮食的铁蛋白缺乏小鼠中 SLC7A11 下调，SLC7A11 是 GSH 产生的关键调节因子，因此可能导致铁死亡相关的左心室肥大[16]。

值得注意的是相比于铁死亡在糖尿病心肌病[45] [50]，阿奇霉素诱导的心肌病[51]-[53]机制研究相比，心肌肥厚性心肌病相关的研究较少，关于铁死亡在肥厚性心肌病中是否发挥作用以及具体机制，治疗靶点需要进一步的基础以及临床研究探索。

4. 总结与展望

在全球范围内，CVD 是导致死亡、高发病率和残疾的主要原因，了解心肌细胞损伤的病理过程是制定心血管治疗的关键。研究表明铁死亡发生在心肌病、心肌梗死和心力衰竭的不同阶段，有望通过抑制心肌细胞的铁死亡来预防这些疾病的发生发展恶化，这为心血管疾病治疗提供了新的治疗靶点。

尽管已经进行了一些铁死亡与心血管疾病的相关研究，但相关的基础和临床研究仍存在一些问题需要探索。铁死亡治疗有时是一把双刃剑，铁死亡中的 ROS 一方面作为第二信使在信号转导中发挥生理益处，另一方面在过量产生时会诱导氧化应激和细胞死亡。针对铁代谢的干预措施也可能诱发不良反应，例如贫血。某些心血管疾病如急性心肌梗死，由于心脏血流减少，药物可能无法在心脏中达到有效治疗浓度。未来关于铁死亡治疗方向将会集中三个方面：1) 铁死亡分子机制如 ROS，铁蓄积可能展开更加深入的病理机制研究以减少铁死亡治疗相关的不良反应。2) 铁死亡相关的调控通路如抗氧化通路 Nrf2 及其下游调控因子将会展开更加深入研究以探索更多治疗靶点。3) 通过对药物进行纳米修饰等改善已有的铁死亡治疗药物药代动力学，靶向性，使其精准靶向病变部位。例如在肿瘤的治疗中将特异性单克隆抗体与细胞毒性药物相结合提高肿瘤部位药物浓度等，或者将铁死亡诱导化合物载入稳定的纳米颗粒中来提高其代谢稳定性，以及器官靶向性。

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