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心力衰竭治疗药物与铁死亡调控关系的研究进展

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摘 要

本文综述了治疗心力衰竭常用药物与铁死亡调控之间的联系与相关研究进展，旨在为改善心力衰竭患者心脏功能提供新的策略和思路。

关键词

心力衰竭，铁死亡，达格列净，沙库巴曲缬沙坦，维利西呱，伊伐布雷定

Research Progress of Ferroptosis and Its Role in the Medication for Heart Failure

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Abstract

This article sums up the relationship between the medication for heart failure and the ferroptosis and its role. It provides a new way of thinking for improving cardiac function in those with heart failure.

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Keywords

Heart Failure, Ferroptosis, Dapagliflozin, Sacubitril Valsartan Sodium Tablets, Vericiguat, Ivabradine

1. 引言

心力衰竭是临床中常见的心血管疾病之一，25 岁及以上人群中，HF 标准化患病率是 1.1%，发病率每年约 100,000 人中就有 275 人患病，估算现有心衰患者达 1205 万，每年新发心衰患者 297 万[1]。心衰是一种临床综合征，是由于心脏结构和/或功能异常而引起的症状和/或体征(EF < 50%，心脏异常变大，E/E′ > 15，中度/重度心室肥大或者中度/重度瓣膜梗阻或反流)，同时至少有以下一种情况：利钠肽水平升高，心肺或全身循环充血的客观证据例如影像学诊断(如胸部 X 线或超声心动图提示心室充盈压升高)或静止或运动等刺激时的血流动力学测定(如右心导管，肺动脉导管) [2]。

铁死亡是 2003 年由 Sonam 等[3]命名，它一种细胞程序性死亡方式，其标志是铁超载诱导产生大量活性氧(ROS)并导致脂质过氧化物的积累[4]。研究表明铁死亡在肿瘤、神经退行性病变等疾病中发挥重要的作用[5] [6]。Chen X.等发现在心衰中发生了心肌细胞的铁死亡，并且铁死亡促进心衰的发生[7]。研究发现铁死亡在心血管疾病的发病机制中起着至关重要的作用，靶向调控铁死亡可能为减少心肌细胞死亡和改善心血管疾病提供新策略[8] [9]。

本文旨在探讨治疗心力衰竭的几种常用药物在铁死亡调控方面所起到的作用，为改善心力衰竭患者心脏功能提供策略和思路。

2. 铁死亡的调控机制

2.1. 铁代谢

铁是细胞发生铁死亡所必需的元素，铁死亡的发生与细胞中铁的转运和储存有关。Yan N.等发现细胞内的脂质过氧化反应程度随着细胞内铁离子浓度的升高而剧烈，从而促进铁死亡的进程[10]。Cai Z.等发现降低体内铁离子水平，可以有效预防铁死亡引发的心力衰竭[11]。在降低体内铁离子浓度的同时也要防止机体发生铁缺乏，缺铁造成的线粒体功能障碍会造成心肌细胞的进一步损伤，从而导致心力衰竭的进行性发展[12]。

2.2. 氨基酸代谢

部分氨基酸在铁死亡过程中起到重要的调节作用，研究显示，细胞内的半胱氨酸起到抑制铁死亡的作用，细胞膜系统 Xc-由催化亚基 SLC7A11 和伴侣亚基 SLC3A2 组成，细胞外的胱氨酸通过细胞膜 XC 系统与细胞内的谷氨酸 1:1 交换，进入细胞后在细胞质内被还原成半胱氨酸，随后进一步合成谷胱甘肽(glutathione, GSH)，谷胱甘肽通过抑制 ROS 的氧化作用对抗细胞的铁死亡[13]。研究表明在抑制细胞膜 XC 系统时，细胞内缺少半胱氨酸，影响 GSH 的合成，从而促进了细胞的铁死亡[14]。另有研究显示，可以产生 β-巯基乙醇的细胞可以通过 β-巯基乙醇完成胱氨酸到半胱氨酸的转换。(可以产生 β-巯基乙醇的

细胞) Hayano M.等的研究表明，敲除半胱氨酸 tRNA 合成酶的细胞可以将蛋氨酸转化为半胱氨酸，从而抑制细胞的铁死亡[15]。氧化型谷胱甘肽(GSSH)可以由谷胱甘肽过氧化物酶 4 (glutathione peroxidase 4, GPX4)氧化形成，GSSH 可以促进细胞内脂质醇的合成，从而抑制铁代谢相关的脂质过氧化过程，达到维持细胞膜稳态的效果[16]。因此在细胞内 GPX4 减少或失活时会促进细胞的铁死亡进程。

2.3. 脂质代谢

各类膜损伤是细胞铁死亡的重要标志，损伤的本质是铁离子依赖的脂质过氧化，具体表现为线粒体内的游离铁和氧气通过芬顿反应生成 ROS [17]，铁死亡过程中产生的大量 ROS 可以与 PUFAs 发生反应，PUFAs 被催化生成脂质过氧化物，破坏细胞形态及功能，如细胞膜缺陷及线粒体收缩功能障碍，最终诱发铁死亡[18] [19]。又有研究显示，外源性不饱和脂肪酸可以降低细胞对铁死亡的易感性，同时减轻细胞膜脂质双分子层的过氧化损伤,从而抑制细胞膜破裂和细胞的死亡[20]。

3. 常用治疗药物与铁死亡

3.1. 达格列净

达格列净是一种新型钠—葡萄糖共转运体抑制剂，其作用可有效的抑制钠氢离子交换，从而抑制钠葡萄糖共转运蛋白 2 (Sodium Glucose Transporter-2, SGLT2)酶的活性，促进葡萄糖以尿糖排泄，达到降糖的目的[21]。Kieran F Docherty 等在临床试验中发现，使用达格列净患者的转铁蛋白(TRF)饱和度、铁蛋白和铁调素(Hepcidin, Hepc)降低，其可溶性转铁蛋白受体(TfR)和总铁结合力(TIBC)增加，从而起到缓解心肌细胞的铁死亡进程的作用[22]。Huang Bin 等发现达格列净可以和 SLC40A1 相互结合，从而达到抑制铁死亡的效果[23]。

3.2. 沙库巴曲缬沙坦

沙库巴曲缬沙坦口服给药后可在体内被 1:1 的分解为沙库巴曲(AHU377)和缬沙坦(Valsartan)，其中沙库巴曲为脑啡肽酶(Neprilysin, NEP)抑制剂，缬沙坦为血管紧张素受体拮抗剂[24]。AHU377 作为脑啡肽酶(Neprilysin, NEP)抑制剂的前体，可有效抑制醛固酮的活性，从而抑制 RAAS 系统，同时也降低了细胞内 ROS 水平，达到减缓细胞的铁死亡进程的作用[25]。

3.3. 维利西呱

一氧化氮生物利用度低是造成心衰患者心室重构机制之一，其影响的是 NO-sGC-cGMP 通路，该通路异常导致溶酶体铁或一氧化氮的积累，从而造成细胞铁死亡[26]。在 NO-sGC-cGMP 通路中，维利西呱可以直接作用作用在 sGC 上以刺激 cGMP 的生成，同时它可以增加 sGC 对 NO 的敏感度，促进细胞内 cGMP 的增加，从而起到改善血管张力的作用[27]。

3.4. 伊伐布雷定

β-受体阻滞剂通过降低心率缓解心衰患者的心肌耗氧高及心肌灌注不足的情况，伊伐布雷定是治疗慢性心衰的常见该类药物[28]。铁死亡可以激活 NK/p38 信号通路抑制胰岛样细胞簇的分化和成熟，同时上调 NOX4 的表达促进生成细胞内 ROS [29]。Zuo 等发现伊伐布雷定抑制 JNK/p38MAPK 通路介导的炎症和细胞凋亡，以此保护链脲佐菌素诱导的糖尿病小鼠心脏功能[30]。TIMP1 的表达可直接影响细胞内的铁离子浓度，有实验表明沉默 TIMP1 可明显降低细胞内铁离子浓度，ROS、MDA 水平，以及 ptgs2 mRNA 的表达[31]。白延平等发现冠心病大鼠心肌组织中 TIMP1 出现异常高表达，经过伊伐布雷定治疗后抑制了 TIMP1 的表达[32]。

4. 结语

近年来，随着各种新型心力衰竭治疗药物不断被开发，各类药物的治疗机制研究逐渐深入，铁死亡作为一种新被发现的细胞死亡方式，与心力衰竭的治疗相关的研究也同样被更多人关注，但目前铁死亡在心力衰竭药物治疗中的相关作用研究较少，其相关信号通路尚不完善，因此，进一步探究心衰治疗药物与心肌细胞铁死亡的关系，将为心衰治疗提供新的思路。

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