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综 述

铁死亡在缺氧相关脑损伤中的研究进展

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摘 要：脑部缺氧经常带来不可逆的中枢神经系统损伤，严重危害着人类健康，对缺氧相关脑损伤机制的深入探索具有重要意义。铁死亡作为一种程序性细胞死亡，主要表现为铁依赖性脂质过氧化物过量积累导致的细胞死亡，与谷胱甘肽代谢、脂质过氧化和铁代谢异常相关，参与多种疾病的发生和发展。研究发现铁死亡在缺氧相关脑损伤中发挥重要作用。本文总结了铁死亡的发生机制，并阐述了其在脑缺血再灌注损伤、新生儿缺氧缺血性脑损伤、阻塞性睡眠呼吸暂停所致脑损伤及高原低氧脑损伤中的研究进展。

关键词：铁死亡；高原低氧；缺血再灌注；新生儿缺氧缺血性脑损伤；阻塞性睡眠呼吸暂停；间歇性低氧

Research progress of ferroptosis in hypoxia-associated brain injury

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Abstract: Cerebral hypoxia often brings irreversible damage to the central nervous system, which seriously endangers human health. It is of great significance to further explore the mechanism of hypoxia-associated brain injury. As a programmed cell death, ferroptosis mainly manifests as cell death caused by excessive accumulation of iron-dependent lipid peroxides. It is associated with abnormal glutathione metabolism, lipid peroxidation and iron metabolism, and is involved in the occurrence and development of various diseases. Studies have found that ferroptosis plays an important role in hypoxia-associated brain injury. This review summarizes the mechanism of ferroptosis, and describes its research progress in cerebral ischemia reperfusion injury, neonatal hypoxic-ischemic brain damage, obstructive sleep apnea-induced brain injury and high-altitude hypoxic brain injury.

Key words: ferroptosis; high-altitude hypoxia; ischemia-reperfusion; hypoxic-ischemic brain damage; obstructive sleep apnea; intermittent hypoxia

缺氧相关脑损伤是一类由于各种原因导致脑部缺氧形成脑损伤的疾病，如缺血性脑卒中、新生儿缺血缺氧、阻塞性睡眠呼吸暂停 (obstructive sleep apnea, OSA) 及高原低气压低氧环境暴露等，轻则暂时影响人们的记忆、认知功能，重则给患者留下严重的中枢神经系统后遗症，甚至威胁生命，严重危害着人类健康。神经元是执行维持脑功能的基本单元，同时也是对缺氧最为敏感的细胞，短暂的缺氧有可能造成神经元的永久性死亡 [1–3]，因此，当前研究认为缺氧相关脑损伤与神经元死亡关系密切，神经元死亡的机制研究及相应保护策略开发对于此类疾病的治疗具有重要意义。

铁死亡作为一种程序性细胞死亡，主要表现为铁依赖性脂质过氧化物 (lipid peroxide, LPO) 过量积累导致细胞死亡 [4]，其发生机制涉及氨基酸和谷胱甘肽 (glutathione, GSH) 代谢、脂质过氧化和铁过量

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蓄积等。细胞铁死亡与癌症、脑卒中、创伤性脑损伤、缺血再灌注 (ischemia-reperfusion, I/R) 损伤、心肌梗死和神经退行性疾病等多种疾病的病理密切相关 [4, 5]。最新研究表明，缺氧可以增加新生动物脑铁含量而导致神经变性，同时通过谷胱甘肽过氧化酶 4 (glutathione peroxidase 4, GPx4) 和溶质载体家族 7 成员 11 (solute carrier family 7 number 11, SLC7A11) 和影响神经细胞代谢导致氧自由基过剩和超氧化物歧化酶 (superoxide dismutase, SOD) 活性下降，细胞膜多元不饱和脂肪酸 (polyunsaturated fatty acids, PUFAs) 发生脂质过氧化反应生成大量脂质活性氧 (reactive oxygen species, ROS)，进而引发铁死亡 [4, 6–8]。因此，铁死亡可能是除凋亡、坏死、自噬、焦亡外，缺氧诱导神经细胞损伤的又一重要原因，并成为缺氧相关脑损伤的潜在干预靶点。

在基础研究层面，铁死亡在一些缺氧相关脑损伤中的重要作用已经逐步被发现，抑制铁死亡也表现出了治疗效果。在另一部分缺氧相关脑损伤中，铁死亡的作用虽然尚未证实，但已有的研究资料也提示了铁死亡在其中的潜在发生机制。本文将对铁死亡在脑 I/R 损伤、新生儿缺氧缺血性脑损伤 (hypoxic-ischemic brain damage, HIBD)、OSA 和高原低氧所致脑损伤中研究进展进行综述，旨在为缺氧相关脑损伤的防治提供新思路。

1 铁死亡

1.1 铁死亡概述

铁死亡是一种由铁依赖性的 LPO 过量蓄积所触发的程序性细胞死亡方式，于 2012 年发现并命名、确定 [9]，其典型形态特征为细胞线粒体超微结构发生改变，即线粒体嵴消失、线粒体膜凝聚以及线粒体外膜破裂，但不伴随凋亡中细胞皱缩、染色质凝集、凋亡小体形成等形态学特征 [10, 11]，常伴随细胞内铁离子过量、LPO 及相关代谢产物蓄积，并导致质膜 PUFAs 的过氧化反应 [12]。

1.2 铁死亡发生机制

1.2.1 铁代谢紊乱

铁是过氧化脂质积聚和铁死亡发生的关键，铁的输入、输出、储存和转运等代谢过程对铁死亡的发生均有一定影响。当参与铁代谢的基因或蛋白质功能失调导致铁代谢紊乱时，细胞内铁的输入、输出、储存和转运等环节出现异常，同时过量的游离 Fe^{2+} 与过氧化氢发生 Fenton 反应可导致 LPO 过量蓄积，最终引发细胞铁死亡。因此，使用去铁胺、去铁酮、环吡酮胺和 2,2- 联吡啶等铁螯合剂可以有效减少细胞内游离 Fe^{2+}，抑制细胞铁死亡的发生 [9]。进一步研究发现，铁蛋白的选择性自噬也可以通过影响铁代谢调节对铁死亡的敏感性，热休克蛋白家族成员 B1 (heat shock protein B1, HSPB1) 和 CDGSH 铁硫结构域 1 (CDGSH iron-sulfur domain 1, CISD1) 等铁代谢相关蛋白也可以影响铁死亡的敏感性 [4]。综上所述，铁代谢的调节和铁蛋白是控制铁死亡的一个潜在的控制点，细胞内 Fe^{2+} 水平异常增加和由于铁超载引发 LPO 过量蓄积均可导致细胞发生铁死亡，使用药物降低 Fe^{2+} 水平可抑制铁死亡的发生 (图 1)。

1.2.2 脂质过氧化

研究证明，脂质代谢与铁死亡密切相关，细胞膜上 PUFAs 过氧化导致的 LPO 蓄积是铁死亡的重要驱动因素 [5]。在正常情况下，细胞内可以维持氧化还原稳态，避免 LPO 蓄积从而保持氧化还原平衡；当细胞内氧化还原失衡时，位于细胞膜上的 PUFAs 经氧化反应生成大量 LPO，导致 LPO 异常积累，严重破坏细胞膜结构完整性而导致细胞发生铁死亡 [9]。研究发现，长链脂酰辅酶 A 合成酶 4 (acyl-CoA synthetase long chain family member 4, ACSL4) 和脂氧合酶亚型 5 (lipoxygenase 5, LOX-5) 是调节细胞铁死亡的重要蛋白，调节其活性可以有效抑制脂质过氧化的发生进而抑制细胞铁死亡 [13]。因此，脂质过氧化引发 LPO 的异常积累是导致细胞铁死亡发生的关键环节，通过药物或基因敲除等方法降低 LPO 的异常蓄积可有效抑制细胞铁死亡 (图 1)。

1.2.3 GSH代谢

研究证明，氨基酸和 GSH 代谢与铁死亡密切相关。还原型 GSH 是以谷氨酸、半胱氨酸和甘氨酸作为原料，在三磷酸腺苷 (adenosine triphosphate, ATP) 依赖性谷氨酸 - 半胱氨酸连接酶和 GSH 合成酶作用下两步合成得到的，GSH 的合成速度与半胱氨酸密切相关。半胱氨酸是人体的非必需氨基酸，在细胞生长和防止细胞死亡中发挥重要作用，由胱氨酸氧化还原得到。System xc^- 是一种细胞表面的氨基酸逆向转运系统，具有溶质载体家族 3 成员 2 (solute carrier family 3 number 2, SLC3A2) 和 SLC7A11 两个亚基，前者起调节作用，后者介导细胞外胱氨酸和细胞内谷氨酸的等量转运 [9]。细胞外谷氨酸水平异常增加和抑制 SLC7A11 表达水平 [14] 均可导致

System xc⁻ 功能无法正常发挥，谷氨酸和胱氨酸转运异常并抑制 GSH 的合成。GSH 是细胞内 Fe^{2+} 配体和 GPx4 活性必需物，GSH 水平的降低可以促进 Fe^{2+} 生成高毒性羟基自由基，进而导致铁死亡 [15]，同时影响 GPx4 发挥清除有害 LPO 的作用，导致 LPO 过量蓄积而发生细胞铁死亡。已有研究证明，GPx4 可以催化过氧化氢的还原进而保护细胞免受脂质过氧化的危害，其功能由于共价抑制而直接丧失 (如 RSL3) 和由于 GSH 耗尽而间接丧失 (如 Erastin) 均可导致铁死亡的发生 [16, 17]，并且 Chen 等 [18] 研究发现 p53 通过与位于 GPx4 启动子上的特定位点结合可以直接抑制 GPx4 转录，进而诱导铁死亡发生，提示 GPx4 是调节细胞铁死亡的重要蛋白，增强其表达或活性能够抑制脂质过氧化进而抑制铁死亡的发生。另有研究发现，核因子 E2 相关因子 2 (NF-E2-related factor 2, Nrf2) 可以抑制细胞铁死亡，其机制与促进 GSH 和 GPx4 表达有关 [19–23]。因此，降低细胞外谷氨酸水平、保护 System xc⁻ 转运功能、促进 GSH 合成以及增强 Nrf2 和 GPx4 表达、活性能够有效抑制铁死亡的发生 (图 1)。

1.2.4 其他机制

最新研究表明，铁死亡抑制蛋白 1 (ferroptosis suppressor protein 1, FSP1) 是一种有效的铁死亡抑制因子，也是 Nrf2 的转录靶点，其表达受 keap1-Nrf2 通路的调控，keap1 缺乏将通过上调 Nrf2 介导 FSP1 表达上调，利用还原型辅酶 II (nicotinamide

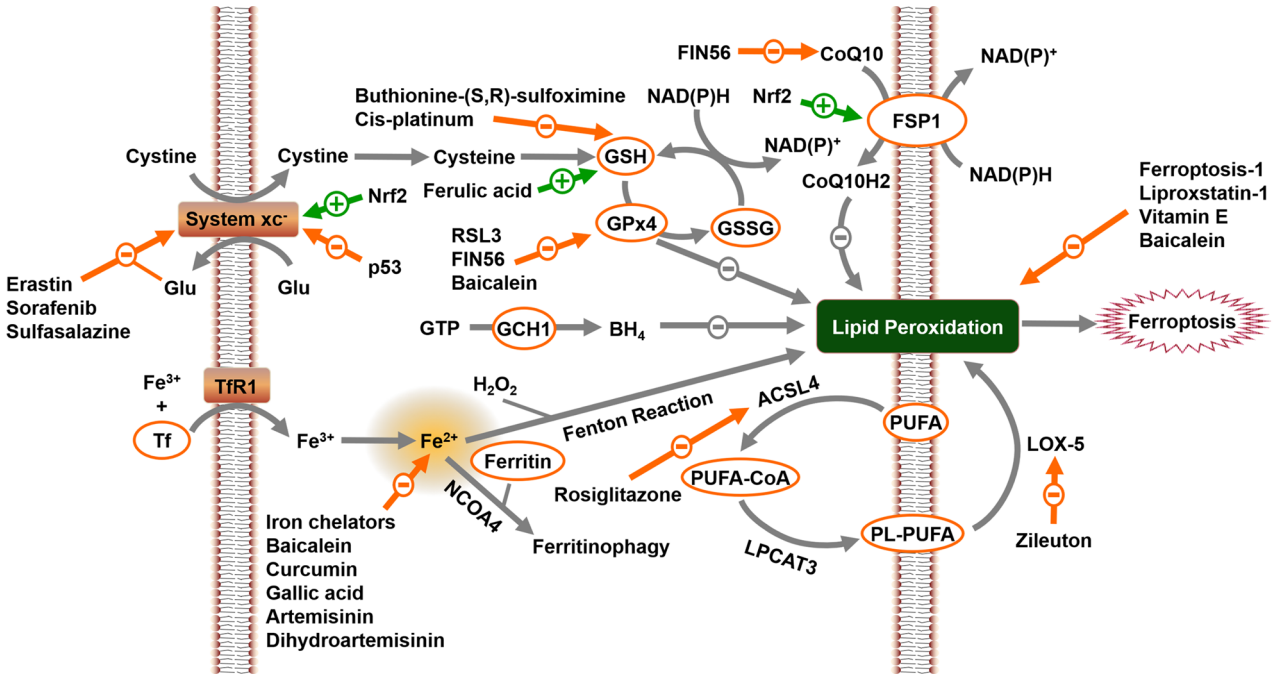

图 1. 铁死亡的发生机制

Fig. 1. Mechanisms of ferroptosis. The mechanism of ferroptosis mainly involves three aspects: lipid peroxidation, abnormal GSH and iron metabolism. Lipid peroxidation: when the intracellular redox is unbalanced, the PUFAs located on the cell membrane undergo an oxidation reaction to generate a large amount of LPO, and the abnormally accumulated LPO seriously damages the structural integrity of the cell membrane and leads to cell ferroptosis. Regulation of the activity of ACSL4 and LOX-5 can effectively inhibit ferroptosis. Abnormal GSH metabolism: the dysfunction of System xc⁻ inhibits the synthesis of GSH, affects the role of GPx4 and leads to ferroptosis. Reducing the level of extracellular glutamate, protecting the function of System xc⁻, promoting the synthesis of GSH, and enhancing the expression and activity of Nrf2 and GPx4 can effectively inhibit the occurrence of ferroptosis. Abnormal iron metabolism: when the iron metabolism process is abnormal, the Fenton reaction of excess free Fe^{2+} can lead to excessive accumulation of LPO and cause ferroptosis. Selective autophagy of ferritin can also modulate the sensitivity to ferroptosis. The use of iron chelators can effectively inhibit ferroptosis. Furthermore, the FSP1-CoQ10-NAD(P) pathway, the DHODH-CoQH2 pathway and the GCH1-BH_4 pathway also have potential roles in ferroptosis. The orange and green arrows indicate inhibition and promotion respectively, and point to potential targets of ferroptosis. GSH: glutathione; PUFAs: polyunsaturated fatty acids; LPO: lipid peroxide; ACSL4: acyl-CoA synthetase long chain family member 4; LOX-5: lipoxygenase 5; GPx4: glutathione peroxidase 4; FSP1: ferroptosis suppressor protein 1; CoQ10: coenzyme Q10; DHODH: dihydroorotate dehydrogenase; CoQH2: panthenol; GSSG: glutathione disulfide.

adenine dinucleotide phosphate, NADPH) 将质膜上的辅酶 Q_{10} (coenzyme Q10, CoQ10) 还原为还原型辅酶 Q10 (ubiquinol, CoQ10H2) [24–27]。作为一种有效的脂溶抗氧化剂，CoQ10H2 可以与膜上的自由基直接反应，防止脂质过氧化进而抑制铁死亡的发生 [28]。FSP1 抗铁死亡的作用与细胞 GSH 水平、GPx4 活性、ACSL4 表达等无关，即 FSP1-CoQ10-NADPH 通路独立于典型的 GSH-GPx4 通路，并可以与后者协同作用抑制脂质过氧化和铁死亡 [29, 30]。此外，二氢乳清酸脱氢酶 (dihydroorotate dehydrogenase, DHODH) 能够调节线粒体内膜还原型辅酶 Q (panthenol, CoQH2) 生成进而抑制铁死亡，因此 DHODH-CoQH2 通路在抑制铁死亡中具有重要作用 [31]。另有研究发现 GTP 环水解酶 -1 (GTP cyclohydrolase-1, GCH1)- 四氢生物蝶呤 (tetrahydrobiopterin, BH_4) 通路能够有效抑制脂质过氧化、重塑脂膜环境并增加 CoQ10H2 水平，最终抑制铁死亡的发生 [5, 32] (图 1)。

1.3 铁死亡调节剂

细胞铁死亡与癌症、脑卒中、创伤性脑损伤、I/R、心肌梗死和神经退行性疾病等多种疾病的病理密切相关 [4]，通过铁死亡调节剂诱导或抑制细胞铁死亡有望成为癌症和损伤相关疾病的潜在治疗策略。

1.3.1 铁死亡抑制剂

研究发现，去铁胺、去铁酮、环吡酮胺和 2,2-联吡啶等铁络合剂能够有效抑制细胞铁死亡，其机制与螯合细胞内 Fe^{2+} 从而降低游离 Fe^{2+} 水平有关 [11]；作为脂溶性抗氧化剂，Ferrostatin-1、Liproxstatin-1 和维生素 E 等可以特异性减少 ROS 的产生，进而抑制 RSL3 诱导的细胞铁死亡 [13, 33, 34]；罗格列酮可在体内外调节 ACSL4 活性从而抑制脂质过氧化的发生，进而抑制细胞铁死亡，齐留通则可以通过下调 LOX-5 活性从而抑制脂质过氧化和细胞铁死亡的发生 [13]。此外，许多天然药物成分已被证明能够有效抑制铁死亡发生。Xie 等 [35] 研究发现，黄芩素可以抑制细胞内 Fe^{2+} 生成和 GPx4 降解，进而抑制脂质过氧化，提示黄芩素可以增强细胞抗铁死亡的能力，有望成为治疗铁死亡相关组织损伤的潜在药物；Guerrero-Hue 等 [36] 研究发现，姜黄素可以抑制细胞内游离 Fe^{2+} 水平的增加和 LPO 的异常蓄积，提示姜黄素也可以抗细胞铁死亡，可作为铁死亡相关组织损伤的潜在治疗药物；Liu 等 [37] 研究发现，阿魏酸可以促进 GSH 生成，抑制 ROS 过量生成和 Fe^{2+} 累积，具有抗铁死亡活性 (表 1)。

1.3.2 铁死亡诱导剂

研究发现，Erastin、柳氮磺胺吡啶和谷氨酸等可以抑制 System xc^- 对胱氨酸的摄取，使 GSH 耗竭进而导致 GPx4 失活，最终引发细胞铁死亡 [9, 17]；索拉非尼作为经美国食品药品监督管理局批准的多激酶抑制剂可以阻断 System xc^- 功能，导致 GSH 耗竭，最终导致细胞铁死亡 [11]；丁硫氨酸 - 亚砜亚胺和顺铂可以抑制 GSH 合成，导致 GSH 耗竭，最终导致细胞铁死亡 [11, 38]；研究发现，RSL3 在没有 GSH 耗竭的情况下直接抑制 GPx4，FIN56 可以诱导 GPx4 降解并降低 CoQ10 水平，导致细胞内氧化还原稳态失衡而引发铁死亡 [17, 39]；另有研究发现，FINO2 直接与 Fe^{2+} 发生 Fenton 反应引发脂质过氧化 [5]。此外，许多天然药物成分在铁死亡发生和发展中具有重要作用。Ooko 等 [40] 研究发现没食子酸作为一种天然的抗癌化合物可以增加细胞内 Fe^{2+}、ROS，进而诱导细胞铁死亡，发挥抗癌作用；Ooko 等 [40]、Chen 等 [41] 研究发现，青蒿素及其衍生物双氢青蒿素能够诱导细胞铁死亡的发生 (表 1)。

2 铁死亡与缺氧相关脑损伤

2.1 铁死亡与脑I/R损伤

I/R 损伤多发于心肌梗死、卒中、器官移植等临床状况，导致心 [42–46]、肺 [47]、肝 [48]、肠 [49]、肾 [50–52] 和脑等多种器官细胞死亡，最终导致器官衰竭。研究发现，I/R 诱导的组织及细胞损伤涉及调节性细胞死亡，如自噬、细胞焦亡和铁死亡等 [53]。

脑 I/R 损伤是在脑卒中所致脑缺血后，因灌注和氧气输送不足造成神经元损伤，当低灌注缺血缺氧脑组织恢复血液供给时，缺血性损伤及代谢功能障碍进一步加重所导致的 [54]。研究发现，脑 I/R 损伤中出现脂质过氧化增多和细胞内铁超载等与铁死亡发生机制相同的表现 [55–58]，并且铁死亡已被证明发生在再灌注期 [59]。Zille 等 [60] 研究发现实验性脑出血具有细胞铁死亡特征；Li 等 [61] 研究发现在 C57/BL6 小鼠脑出血模型和海马组织型切片培养中，脑出血后通过上调谷氨酸水平和耗竭 GSH 可影响 GPx4 活性，此外通过上调环氧合酶 -2 (cyclo-oxygenase, COX-2) 表达水平介导神经元铁死亡；Tuo 等 [62] 研究发现，I/R 诱导的脑损伤发生时，细胞内通过运输淀粉样前体蛋白 (amyloid precursor protein, APP) 来稳定转铁蛋白 (ferroportin, FPN) 的 tau 蛋白减少，不利于细胞内铁转运至细胞外，细

表1. 铁死亡调节剂

Table 1. Ferroptosis regulators

Regulator	Name	Link	Mechanism	Reference
Inhibitor	Deferoxamine	Iron metabolism	Decrease free Fe^{2+}	[11]
	Deferiprone	Iron metabolism	Decrease free Fe^{2+}	[11]
	Ciclopirox	Iron metabolism	Decrease free Fe^{2+}	[11]
	2,2-bipyridyl	Iron metabolism	Decrease free Fe^{2+}	[11]
	Ferrostatin-1	Lipid peroxidation	Decrease ROS	[13, 33, 34]
	Liproxstatin-1	Lipid peroxidation	Decrease ROS	[13, 33, 34]
	Vitamin E	Lipid peroxidation	Decrease ROS	[13, 33, 34]
	Rosiglitazone	Lipid peroxidation	Regulate the activity of ACSL4 and inhibit lipid peroxidation	[13]
	Zileuton	Lipid peroxidation	Regulate the activity of LOX-5 and inhibit lipid peroxidation	[13]
	Baicalein	Lipid peroxidation Iron metabolism GSH metabolism	Decrease LPO and free Fe^{2+} and inhibit the degradation of GPx4	[35]
	Curcumin	Lipid peroxidation Iron metabolism	Decrease LPO and free Fe^{2+}	[36]
	Ferulic acid	GSH metabolism Lipid peroxidation Iron metabolism	Increase the synthesis of GSH , decrease ROS and free Fe^{2+}	[37]
Inducer	Erastin	GSH metabolism	Inhibit the uptake of cystine	[9, 17]
	Sulfasalazine	GSH metabolism	Inhibit the uptake of cystine	[9, 17]
	Glutamate	GSH metabolism	Inhibit the uptake of cystine	[9, 17]
	Sorafenib	GSH metabolism	Inhibit the uptake of cystine	[11]
	Buthionine-(S,R)-sulfoximine	GSH metabolism	Inhibit the synthesis of GSH	[11, 38]
	Cisplatin	GSH metabolism	Inhibit the synthesis of GSH	[11, 38]
	RSL3	GSH metabolism	Inactivate GPx4	[11, 38]
	FIN56	GSH metabolism	Inactivate GPx4 and make CoQ10 deficient	[17, 39]
	FINO2	Lipid peroxidation	Oxidize Fe^{2+} and increase LPO	[5]
	Gallic acid	Iron metabolism	Increase free Fe^{2+} and ROS	[40]
	Artemisinin	Iron metabolism	Increase free Fe^{2+} and ROS	[40, 41]
	Dihydroartemisinin	Iron metabolism	Increase free Fe^{2+} and ROS	[40, 41]

ROS: reactive oxygen species; ACSL4: acyl-CoA synthetase long chain family member 4; LOX-5: lipoxygenase 5; GSH: glutathione; GPx4: glutathione peroxidase 4; LPO: lipid peroxide; CoQ10: coenzyme Q10.

胞内游离 Fe^{2+} 增加进而引发铁死亡；Lan 等 [14] 研究发现在 SD 大鼠大脑中动脉阻塞 (middle cerebral artery occlusion, MCAO) 模型中，急性脑缺血通过高浓度谷氨酸抑制 SLC7A11 表达影响 GSH 合成，进而导致 GPx4 活性下降，此外通过调节转铁蛋白受体 1 (transferrin receptor 1, TfR1) 和二价金属转运蛋白 1 (divalent metal transporter 1, DMT1) 表达导致缺血坏死脑组织海马区、CA2 区和皮质区铁沉积，最终通过诱导铁代谢失衡和氧化还原紊乱导致神经元铁死亡；Jin 等 [3] 研究发现在 C57BL/6 小鼠 MCAO 和原代细胞氧糖剥夺 / 复氧模型中，脑组织 I/R 损伤可通过缺氧诱导因子 1α (hypoxia-inducible factor 1α, HIF-1α) 和信号传导及转录激活因子 3 (signal transducer and activator of transcription 3, STAT3) 上调神经元聚合酶 I 和转录释放因子 (polymerase I and transcript release factor, PTRF) 表达，进而激活磷脂酶 A2-IVA (phospholipase A2, group IVA [cytosolic, calcium-dependent], PLA2G4A)，促进神经细胞脂质代谢重塑，最终导致脂质过氧化和铁死亡；Huang 等 [63] 研究发现在 SD 大鼠 MCAO 和原代皮质神经元细胞氧糖剥夺与再灌注模型中，脑组织 I/R 可以降低含 UbiA 异戊烯基转移酶结构域 1 (UbiA pren-

yltransferase domain containing 1, UBIAD1) 水平，影响神经元中非线粒体 CoQ10 的产生，进而导致脂质过氧化和铁死亡的发生。已有研究发现，使用特异性铁死亡抑制剂 Ferrostatin-1 [61, 64]、铁螯合剂 [65]、CoQ10 [66–69]、香芹酚 [70]、山奈酚 [71]、红花黄色素 [72]、高良姜素 [73]、补充硒 [74–76]、跑台训练 [77] 和电针预适应 [78] 等方式抑制铁死亡可逆转神经功能损伤并改善预后，这些有望成为 I/R 损伤的重要潜在治疗药物和方法，但分子机制尚不明确，有待进一步研究证实。

上述研究表明，脑组织 I/R 可导致丙二醛 (malonyldialdehyde, MDA) 水平升高，而 GSH 含量和 SOD 活性显著降低，显著提高海马区脂质过氧化水平；I/R 显著提高海马铁含量，调节 TfR1、DMT1 等铁代谢相关蛋白表达导致铁代谢紊乱和海马区铁蓄积；I/R 发生时海马区 System xc^-、GSH 和 GPx4 水平均显著降低，铁死亡相关标志物 COX-2 的表达显著增加，抗氧化功能降低导致 LPO 累积；此外，I/R 显著降低海马区 Nrf2 及其下游 GPx4 等抗氧化蛋白水平，导致 System xc^-、GSH 和 GPx4 等调节障碍，进而影响铁摄取、储存和抗脂质过氧化能力，促进铁死亡发生。因此，铁死亡介导脑 I/R 损伤，抑制铁死亡能够减轻 I/R 诱导的脑组织神经元损伤，提示铁死亡是 I/R 诱导的脑组织神经元损伤干预的重要潜在靶点 (图 2)。

2.2 铁死亡与新生儿HIBD

HIBD 严重影响新生儿发育甚至可能造成永久性神经缺陷甚至死亡，其病理机制与围产期窒息有关 [79]。新生儿 HIBD 后神经元早期死亡形式是缺血性坏死，但是持续的神经细胞死亡可能导致长期神经损伤 [80]。

Rathnasamy 等 [81] 研究发现在 1 日龄 Wistar 大鼠混合胶质细胞培养模型中，缺氧、缺血通过显著降低原代小胶质细胞内 GSH 水平、增加铁调节蛋白 (iron regulatory proteins, IRPs) 和 TfR 的表达导致铁蓄积和脂质过氧化增强进而诱导铁死亡的发生；El Bana 等 [82] 研究发现在足月围产期窒息新生儿的脐带血中 MDA 浓度与相关脑损伤程度呈正相关，提示新生儿 HIBD 与脂质过氧化有关；进一步研究证实，新生儿 HIBD 时血清 LPO 浓度与相关脑损伤程度呈正相关，具有神经毒性 [83, 84]；Zhu 等 [85] 研究发现缺氧、缺血可显著上调 Toll 样受体 4 (Toll-like receptor 4, TLR4)，提高 p53 水平，降低 SLC7A11 和 GPx4 水平并导致线粒体损伤，进而诱导海马神经元铁死亡，抑制 TLR4 能够通过减轻氧化应激和线粒体损伤有效改善铁死亡；新生儿缺血缺氧时导致基底节和丘脑等部位谷氨酸升高 [86]，不利于 System xc^- 功能的正常发挥，可能导致谷氨酸和胱氨酸转运异常，影响 GSH 代谢，最终导致 LPO 过量蓄积并发生细胞铁死亡。整体研究表明，香芹酚可以有效抑制海马神经元铁死亡而改善脑缺血导致的学习和记忆障碍，其保护作用与抑制脂质过氧化有关 [70]；褪黑素可以有效改善 HIBD 的病理损害、抑制神经元铁死亡、促进海马神经元存活并改善 HIBD 大鼠的学习和记忆能力，使用 RSL3 抑制 GPx4 可阻断其改善作用，提示褪黑素通过抑制神经元铁死亡而发挥神经保护作用 [87]；最新的研究表明，甘草酸可以通过调节高迁移率族蛋白 B1 (high mobility group box 1 protein, HMGB1) 和 GPx4 的表达，改善氧化应激失衡和线粒体损伤，抑制 HIBD 大鼠神经元铁死亡 [88]。体外研究表明，铁死亡特异性抑制剂 Ferrostatin-1 可以有效抑制神经元铁死亡，其机制与抑制脂质过氧化和 COX-2 表达有关 [61]；此外，天麻素可通过 Nrf2 和血红素氧合酶 1 (heme oxygenase-1, HO-1) 通路拮抗谷氨酸诱导性 HT-22 细胞铁死亡的发生 [89]，提示抑制铁死亡具有神经保护作用。

上述研究表明，新生儿缺氧缺血导致脑组织 GPx4、GSH 和 SLC7A11 表达降低，抗氧化能力降低，ROS 表达升高，导致 PUFAs 发生脂质过氧化；缺血、缺氧所致酸性环境可能导致游离 Fe^{2+} 的积累，TfR 等铁代谢相关蛋白的表达增强，导致脑细胞对铁的输入和储存障碍，进而导致脑组织游离 Fe^{2+} 的增加和铁超载。因此，HIBD 的发生过程涉及 ROS 和 LPO 产生、GSH 耗竭、铁沉积和谷氨酸升高等，这与铁死亡表现基本一致，铁死亡可能是 HIBD 发病机制中的关键环节 (图 2)。

2.3 铁死亡与OSA所致脑损伤

OSA 是指在睡眠过程中因上呼吸道狭窄或阻塞导致的反复性呼吸浅慢或暂停，引起氧化应激、交感神经激活、炎症增强、内皮功能障碍及代谢功能失调等生理变化，是高血压、缺血性脑卒中、心力衰竭、冠心病等疾病的独立危险因素，还会加重缺血性脑卒中所致记忆力、学习能力等认知功能障碍 [90]。间歇性低氧作为 OSA 的核心病理基础和特征，是心血管系统、自主神经系统损伤病理机制的主要因素 [91]。OSA 患者通常产生记忆力、执行能力

减退和运动功能障碍等多种认知功能损伤[92]，其机制与长期间歇性低氧导致海马神经元氧化应激[93–95]和脑组织血流灌注不足[96–98]等有关。

已有研究发现，间歇性低氧可诱导 ROS 增加，通过内质网应激导致 GSH 耗竭，影响 GPx4 活性进而导致铁死亡和空间学习、记忆障碍[95]。Yadav 等[99]和 Sarma 等[100]先后研究发现 OSA 患者脑中细胞外谷氨酸水平升高，可诱导兴奋性毒性进而导致神经元功能障碍和认知功能障碍[101]，而细胞外谷氨酸水平的异常升高可通过抑制 System xc^- 转运功能进而抑制 GSH 的合成，提示铁死亡可能存在于 OSA 所致脑损伤的发生、发展中；Tauman 等[102]研究发现，间歇性低氧可诱导脂质过氧化，增加 MDA 等 LPO 含量，且脂质过氧化程度与间歇性缺氧程度呈正相关，提示铁死亡可能是慢性间歇性低氧所致脑损伤和神经认知障碍中的潜在机制。另有研究发现，中重度的 OSA 患者外周血中 HO-1、SOD、NADPH 和 GPx 等 Nrf2-ARE 通路相关抗氧化物酶水平显著降低，影响中枢神经系统抗氧化能力进而导致氧化与抗氧化失衡，最终引起神经元损伤和信号转导异常，逐渐导致记忆及执行功能损伤[103, 104]，而 GSH 和 GPx4 表达水平调节障碍可能诱导细胞铁死亡。

上述研究表明，间歇性低氧可能通过 Nrf2-ARE 通路导致脑组织 GPx4 和 GSH 表达降低，抗氧化能力降低，ROS 和 MDA 表达升高，导致 PUFAs 发生脂质过氧化；细胞外谷氨酸水平的异常升高可能导致 System xc^- 转运功能障碍，进一步抑制 GSH 的合成，影响抗脂质过氧化能力进而促进铁死亡发生。因此，铁死亡可能在 OSA 和间歇性低氧所致脑损伤和神经认知障碍中发挥重要作用，其机制可能与脂质过氧化和谷氨酸水平异常升高和 Nrf2 调节障碍导致的 GSH 耗竭相关，仍有待进一步研究（图 2）。

2.4 铁死亡与高原低氧脑损伤

高原低氧脑损伤是由低氧等多种高原环境因素对脑组织造成的一系列损伤综合征。Zhou 等[105]研

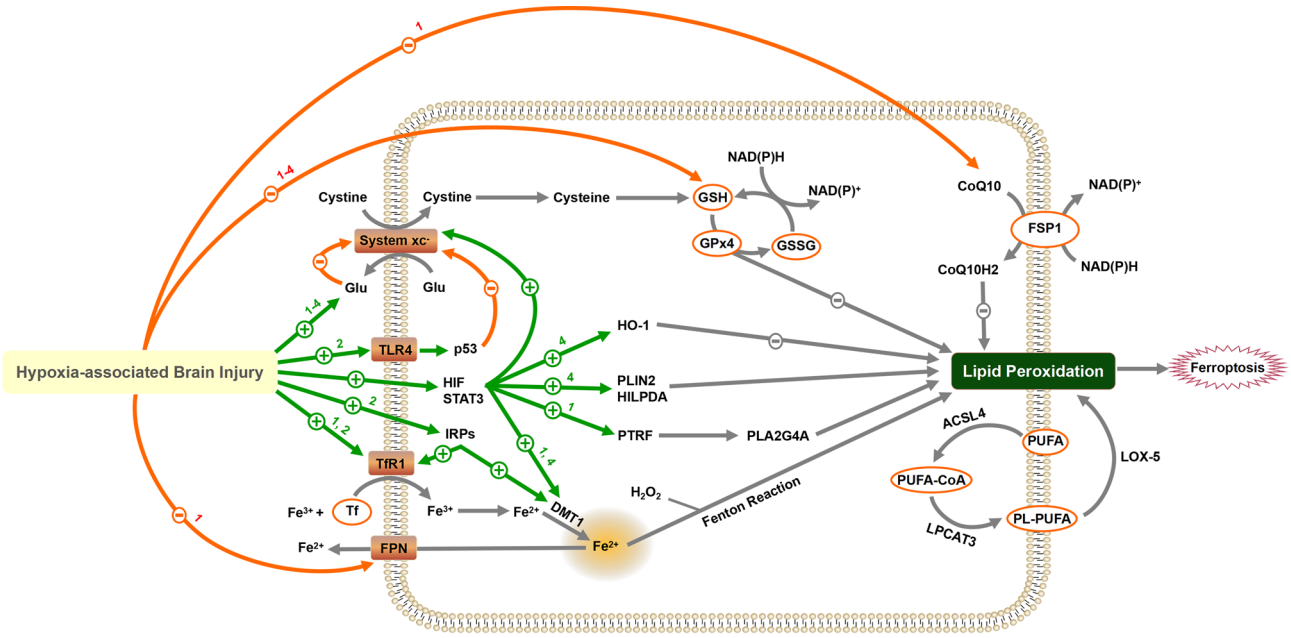

图 2. 铁死亡在缺氧相关脑损伤中的潜在发生机制

Fig. 2. The underlying mechanisms of ferroptosis in hypoxia-associated brain injury. Hypoxia-associated brain injury mainly includes cerebral ischemia-reperfusion injury, neonatal hypoxic-ischemic brain damage, brain injury caused by obstructive sleep apnea, and high-altitude hypoxic brain injury. Ferroptosis may play a key role in the occurrence and development of hypoxia-associated brain injury, and the mechanism of ferroptosis mainly involves three aspects: lipid peroxidation, abnormal GSH and iron metabolism. The orange and green arrows indicate inhibition and promotion respectively, and point to potential targets of ferroptosis in hypoxia-related diseases. Numbers on the lines indicate that the mechanism occurs in the corresponding diseases. 1: cerebral ischemia-reperfusion injury; 2: neonatal hypoxic-ischemic brain damage; 3: brain injury caused by obstructive sleep apnea; 4: high-altitude hypoxic brain injury.

究发现，高原低氧环境发生氧化应激可诱导神经细胞凋亡、变性；Zhong 等 [106] 进一步研究发现，长期暴露在高原会导致学习、记忆以及执行功能等认知障碍，提示高原低氧脑损伤与神经元损伤密切相关，而神经元损伤是学习、记忆和认知功能损伤的重要发生机制。目前，高原低氧脑损伤的发病机制研究主要包括氧化应激学说 [107–109]、神经递质释放 [110]、神经细胞损伤 [111] 以及炎性介质的活化 [112, 113] 等，但铁死亡在高原低氧脑损伤中的作用尚不明确。

大量研究证实，高原低氧会导致机体重要脏器缺氧缺血，干扰机体抗氧化系统，表现为 MDA 含量增加、SOD 活力和 GSH 含量降低 [114]；随着机体暴露于缺氧条件下时间的延长，LPO 过量蓄积可引起脂质过氧化损伤 [115]。此外，高原低氧环境可通过触发 HIF 信号诱导 DMT1 的表达和抑制肠道铁调素促进肠道铁的吸收并导致铁超载，细胞内铁含量的增加有可能触发神经元铁死亡，同时 Fe^{2+} 通过 Fenton 反应促进 ROS 生成，使 MDA 含量显著升高，而 GSH 水平和总抗氧化能力显著降低 [116]，可能通过影响 GPx4 活性和脂质过氧化导致铁死亡的发生。已有研究表明，在慢性低氧环境暴露下谷氨酸合成和释放增多，神经兴奋性毒性可能引发铁死亡进而介导神经元损伤和认知损伤 [110, 117]，其机制可能是细胞外谷氨酸水平的异常增加不利于 System xc^- 功能的正常发挥，导致谷氨酸和胱氨酸转运异常，影响 GSH 代谢，最终导致 LPO 过量蓄积并发生细胞铁死亡。MDA 是脂质过氧化的最终产物，在高原低氧环境中，海马区 ROS 的积累可直接导致神经细胞损伤，提高 GSH 水平可显著抑制海马区和脑组织中 ROS 水平的升高 [105, 108]，提示抑制脂质过氧化反应能够有效减少海马区神经元损伤数量而发挥神经保护作用；Hou 等 [109] 研究发现，在 9 000 m 高海拔低氧环境下暴露 24 h 可导致大鼠血浆 MDA 水平显著增加，进而导致海马区神经元损伤和认知功能障碍；最新的研究发现，高原低氧条件下小鼠脑组织 MDA 含量增加、GSH 含量降低，谷氨酸含量显著增高，导致学习记忆功能损伤 [114]，提示高原低氧会增加细胞内铁含量，抑制 System xc^- 功能并降低 GSH 水平，导致 LPO 过量蓄积，最终发生细胞铁死亡。

另有研究表明，缺氧可以引起 HIF 转录因子水平增加，HIF-1 可以促进 SLC7A11 和 HO-1 的转录进而抑制铁死亡的发生，而 HIF-2 可以增加脂肪分化相关蛋白 (perilipin2, PLIN2) 和低氧诱导脂滴相关蛋白 (hypoxia-inducible lipid droplet-associated protein, HILPDA) 的表达，进而增加脂质堆积和氧化应激，最终增强铁死亡 [118]。因此，铁死亡在高原低氧脑组织和神经元损伤中是否发挥重要作用，以及铁死亡在高原低氧脑损伤发生、发展中的作用及具体病理机制尚未阐明，仍有待进一步研究 (图 2)。

3 总结与展望

铁死亡是一种新型可调控性细胞死亡形式，与细胞内铁代谢异常、LPO 异常积累及 GSH 相关氧化还原平衡紊乱密切相关 [9, 12, 15, 16]。其发生机制虽然独立于其他细胞程序性死亡方式，但该过程常伴随炎症反应、氧化应激的过度激活 [2]。当前研究显示，铁死亡在脑 I/R 损伤、新生儿 HIBD 和 OSA 所致脑损伤中发挥重要作用，铁死亡在这些疾病中的潜在发生机制主要包括：(1) Fe^{2+} 水平异常升高和铁超载引发的 LPO 过量蓄积，其原因与铁离子转运相关蛋白 TfR1、DMT1 的上调及 FPN 的抑制有关；(2) GSH 含量减少抑制了 GPx4 发挥清除有害 LPO 的作用，其原因包括 ROS 导致的 GSH 过度消耗，细胞外谷氨酸过量及 p53 激活导致的 GSH 合成减少；(3) FSP1 介导的脂溶抗氧化剂 CoQ10H2 生成减少导致 LPO 清除能力的下降，其原因与非线粒体 CoQ10 的生成受损有关。抑制铁死亡能够减轻脑 I/R 损伤、脑组织缺血缺氧性损伤和慢性间歇性低氧所致脑损伤，提示铁死亡可能是干预缺氧相关中枢神经系统损伤的重要靶点。

从高原低氧环境下机体铁吸收增加，神经元脂质过氧化水平升高，GSH 水平降低，以及炎症反应和氧化应激上调的大量研究成果中可以推断，高原低氧暴露可能诱导神经元铁死亡的发生，介导高原低氧认知功能障碍的发生，严重影响高原人群作业能力 [105, 108, 115, 116]。但是，铁死亡在高原低氧暴露所致脑损伤中的作用及机制尚未得到证实，并且已有研究证明缺氧可能抑制铁死亡的发生 [119–121]。因此，进一步研究铁死亡在低氧暴露所致脑损伤中的作用以及机制有望为高原低氧认知障碍的治疗提供重要方向和靶点。

综上所述，铁死亡在缺氧相关脑损伤中的研究尚处于初始阶段，对于其具体机制、关键因子及相关信号通路的深入探索，并以此为靶点进行的药物开发将有利于这类疾病的预防和治疗。

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