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综 述

铁死亡在呼吸系统疾病中的研究进展及应用

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摘 要：铁死亡(ferroptosis)是一种新发现的细胞死亡调控方式，依赖于铁和活性氧簇，主要特征是细胞内脂质过氧化物堆积。与其他细胞死亡方式相比，铁死亡在形态、生物化学、遗传学等方面有自身的特点。铁死亡的发生机制与非酶促反应或者酶促反应触发铁催化的脂质过氧化物堆积有关。近年来的研究显示铁死亡与血液系统、心脑血管、肝肾系统等多种疾病相关，然而在呼吸系统疾病中的研究相对较少。本文就铁死亡的定义、机制、诱导剂、病理生理状态下的铁死亡以及铁死亡在呼吸系统疾病中的相关研究展开综述，以期为呼吸系统疾病的临床防治提供新思路、新靶点。

关键词：铁死亡；呼吸系统疾病；铁死亡诱导剂；脂质过氧化物
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Ferroptosis in respiratory diseases

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Abstract: Ferroptosis is a novel form of regulated cell death which is dependent on iron and reactive oxygen species (ROS) and associated with the accumulation of lipid peroxides. It is obviously different from other cell death types in terms of morphology, biochemistry, genetics, *etc*. Also, it is related to the production of iron catalyzed lipid peroxides which is triggered by non-enzymatic or enzymatic reactions. Ferroptosis has been proved to be involved in hematological diseases, cardio-cerebrovascular diseases, liver and kidney diseases. This paper will review the definition, mechanism, inducers of ferroptosis, as well as the function of ferroptosis in respiratory system. We expect to present a new concept for respiratory research and suggest potential targets for clinical prevention and treatment of respiratory diseases.

Key words: ferroptosis; respiratory diseases; ferroptosis inducers; lipid peroxides

1 引言

铁死亡 (ferroptosis) 是新近定义的一种铁依赖的、脂质过氧化物不断堆积导致的死亡方式，其死亡方式与凋亡、坏死皆不同，形态学上主要表现为线粒体皱缩。近年来，关于铁死亡诱导剂与抑制剂的研究越来越多，同时更多的研究开始关注铁死亡在疾病中的作用和机制，然而其在呼吸系统疾病中的研究相对较少。本文首先总结了铁死亡的定义、机制、诱导剂以及研究现状等，随后就铁死亡在呼吸系统疾病中的相关研究展开综述与展望。

2 铁死亡的定义

2003 年 Dolma 等在 Ras 突变的肿瘤细胞中筛选选择性致死抗肿瘤药物时，意外发现经小分子抑

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制剂 erastin 处理过的细胞并未出现凋亡的经典特征 [1]。Yang 等在随后的实验中发现 RSL3——Ras 选择性致死 (Ras-selective lethal, RSL) 化合物也引起了同样的表型 [2]。进一步实验表明，RSL3 诱导的死亡与细胞内活性氧 (reactive oxygen species, ROS) 升高有关，并且能够通过铁螯合剂来预防 [2]。2012 年，Dixon 等 [3] 通过研究将这一类死亡方式命名为铁死亡，是一种铁依赖的非凋亡的细胞死亡。2017 年，Dixon 等在 *Cell* 发表综述，正式将铁死亡定义为铁依赖的、细胞内脂质过氧化物堆积所导致的死亡方式 [4]。

铁死亡在细胞形态、生物化学、遗传等方面与凋亡、程序性坏死、自噬存在明显不同，电镜下主要表现为线粒体外膜破坏、线粒体皱缩，而没有染色体的浓缩 (凋亡)、细胞器的肿胀 (坏死) 及双层膜囊泡的形成 (自噬)[3]。

铁死亡最初被认为是一种必须排除其他死亡方式，如凋亡、程序性坏死的死亡形式 [4]。但也有研究显示，铁死亡与程序性坏死存在交叉途径，如热休克蛋白 90 (heat shock protein 90, HSP90) 同时参与坏死和铁死亡 [5]。同样的，后续研究显示自噬也参与铁死亡过程，自噬通过降解铁蛋白促进铁死亡 [6, 7]，自噬相关蛋白 BECN1 可以通过调节癌细胞中胱氨酸和谷氨酸逆转运系统 (cystine/glutamate antiporter system, System XC^-) 的活性促进铁死亡 [8]。钟表性吞噬 (clockophagy)，即昼夜节律调节器核心生物钟蛋白 ARNTL/BMAL1 的选择性降解对铁死亡至关重要 [9, 10]。越来越多的研究表明，铁死亡与多种死亡途径存在交叉，铁死亡的机制也将逐步明朗。

3 铁死亡的发生机制及诱导剂

铁死亡表现为典型的线粒体外膜破坏与线粒体皱缩，可能是由于 BCL2 (B-cell lymphoma 2) 家族，如 BH3 结构域凋亡诱导蛋白 BID (BH3-interacting domain death agonist) [11]、BCL2 绑定组件 3 (BCL2 binding component 3, BBC3) [12]，而不是 BAX (BCL2-associated X protein) 或者 BAK1 (BCL2-antagonist/killer 1) 的活化 [3]。但是线粒体究竟在其中起何种作用，目前仍没有定论。

铁死亡没有任何凋亡的标志，并且敲低程序性坏死相关分子受体相互作用丝氨酸苏氨酸蛋白激酶 1 (receptor-interacting serine-threonine protein kinase 1, RIPK1) 和 3 (RIPK3) 也不能保护细胞免受铁死亡的影响 [13]。相反，铁死亡通过非酶促反应 —— 芬顿反应 (Fenton 反应) 或者酶促反应 —— 脂氧合酶 (lipoxygenases, Lox) 触发铁催化的脂质过氧化物产生 [14]，Lox 通过磷酸化酶激酶 γ2 (phosphorylase kinase, gamma 2, PHKG2) 依赖的铁池氧化多不饱和脂肪酸 (polyunsaturated fatty acid, PUFA) 对于铁死亡是必需的，并且共价抑制谷胱甘肽过氧化物酶 4 (glutathione peroxidase 4, GPX4) 中的催化硒代半胱氨酸 (selenocysteine, Sec) 活性位点可防止 PUFA 氢过氧化物的消除，进而诱发铁死亡 [14]。PUFA 是膜脂质过氧化的主要底物，产生的脂质过氧化物被认为是铁死亡中脂质过氧化物的来源。

因此，常见的铁死亡抑制剂可以分为铁螯合剂或者脂质过氧化物清除剂。多种铁螯合剂，如 DFO (deferoxamine) 和 CPX (ciclopirox) 可以通过减少铁的利用从而抑制铁死亡的发生。而脂质过氧化物清除剂，如 Vitamin E、ferrostatin-1 和 liproxstatin-1 可以通过亲脂性自由基捕获脂质过氧化物抑制铁死亡的发生 [3, 13]。此外，抑制脂质代谢途径，如下调 / 抑制 ACSL4 (acyl-CoA synthetase long-chain family member 4)、LPCAT3 (lysophosphatidylcholine acyl-transferase 3) 或抑制 Lox 参与的脂质过氧化，也可以抑制铁死亡的发生 (图 1)。

虽然铁死亡的上游通路逐渐清晰，但是脂质过氧化物堆积究竟如何导致细胞死亡仍然是一个未知数。通常的分子动力学模型假设是，持续的氧化反应与 PUFA 的消耗，降低了膜的流动性结构，膜通透性增加，完整性丧失，从而使膜不断变薄，同时曲率增加，抗氧化物质进入变得困难，从而导致了膜的孔洞形成和胶束化 [15]。

几类常见的铁死亡诱导剂通过 GPX4 失活、细胞内谷胱甘肽 (glutathione, GSH) 耗竭、胞内可变铁池 (labile iron pool, LIP) 增加等方式诱导铁死亡 (图 1)。

3.1 GPX4失活

GPX4 占据了铁死亡的核心位置，可以通过失活 GPX4 的方式来诱导铁死亡。在细胞中过表达 GPX4 能增加铁死亡抗性，而敲低 GPX4 则促进了铁死亡 [16]。铁死亡诱导剂 RSL3 能与 GPX4 的活性位点 Sec 共价结合，从而直接抑制 GPX4 的磷脂 - 过氧化物酶活性 [14]。$FINO_2$、ML162、withaferin A (WA) 和抗癌药 altretamine 也有此作用 [17–20]。由于 GPX4 的活性位点受 Sec 影响 [21]，其特定转运体 RNA (Sec-tRNA) 经过异戊烯基转移酶进行修饰，

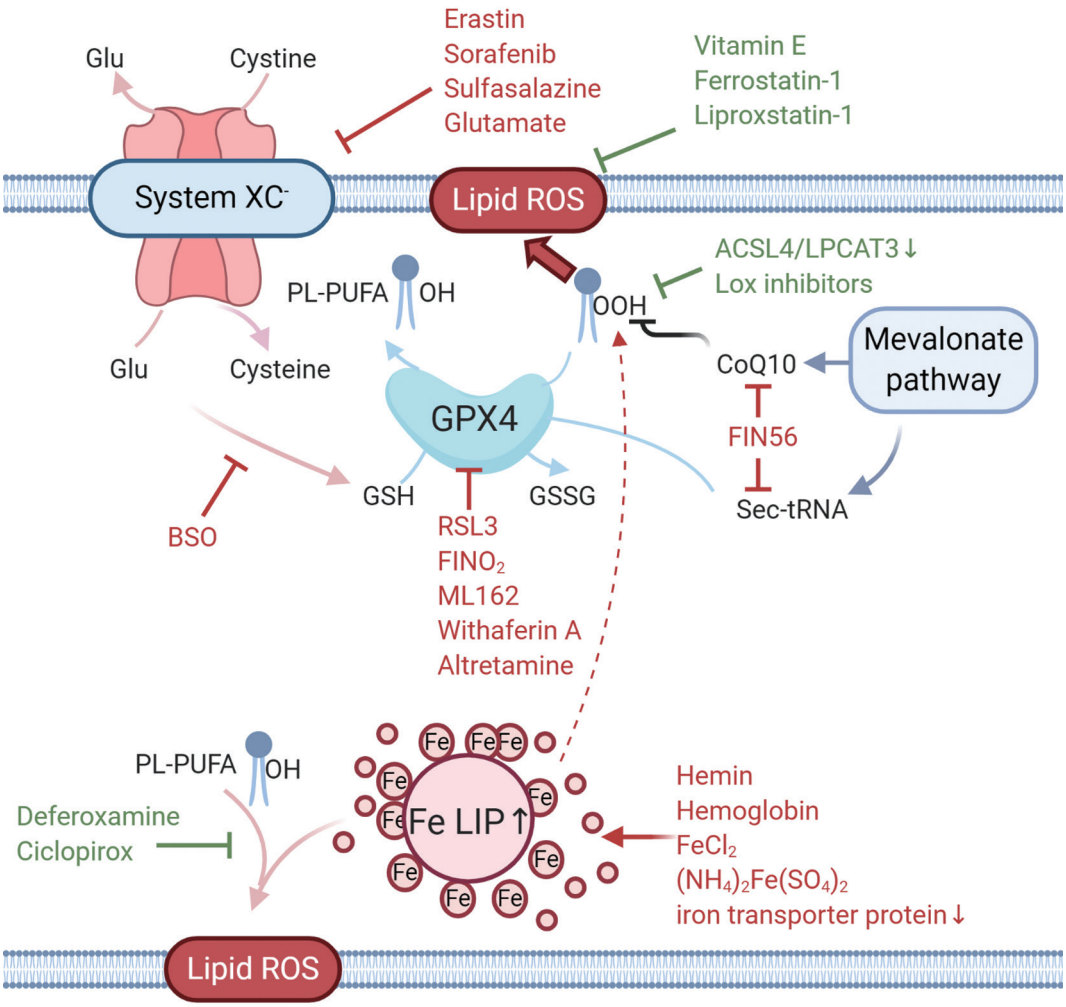

图 1. 几类常见的铁死亡诱导剂及抑制剂

Fig. 1. Several common ferroptosis inducers and inhibitors. System XC^- is used for transporting Glu and cystine, which will generate GSH. GSH is served as a cofactor for GPX4 to deplete lipid hydroperoxides which is catalyzed by ACSL4, LPCAT3 or Lox. The LIP can catalyze free radical formation to propagate lipid hydroperoxides, and mediate the activity of ROS-producing enzymes. Accumulation of lipid hydroperoxides will induce ferroptosis later. System XC^-, cystine/glutamate antiporter system; Glu, glutamic acid; GSH, glutathione; GSSG, glutathione disulfide; GPX4, glutathione peroxidase 4; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; Lox, lipoxygenases; ROS, reactive oxygen species; BSO, buthionine sulfoximine; LIP, labile iron pool; PUFA, polyunsaturated fatty acid.

而作为供体的异戊烯焦磷酸盐是甲羟戊酸 (Mevalonate, MVA) 通路的重要产物，因此可通过他汀类药物抑制 Sec-tRNA 的形成，抑制 GPX4 合成，从而诱导铁死亡 [22]。FIN56 通过结合和激活角鲨烯合酶 (squalene synthase, SQS)，进而抑制脂溶性抗氧化剂辅酶 Q10 (coenzyme Q10, CoQ10) 和 Sec-tRNA，导致 GPX4 的消耗 / 失活来促进铁死亡 [23]。

3.2 细胞内GSH耗竭

System XC^-由调节性亚基溶质转运家族 SLC3A2 和催化亚基溶质转运家族 SLC7A11 组成 [24]，交换胞内的谷氨酸盐与胞外的胱氨酸 [25]，胱氨酸在体内被还原为半胱氨酸，进而生成 GSH。GPX4 利用 GSH 来清除产生的磷脂过氧化物 (phospholipid hydroperoxides, PLOOH)，减少胞内的 GSH 导致 GPX4 催化脂质过氧化物底物的作用减弱，从而诱发铁死亡。System XC^-抑制剂 erastin、sulfasalazine、sorafenib 和 glutamate 通过直接或间接抑制转运体功能，导致胞内 GSH 合成受阻，触发脂质过氧化物堆积，发生铁死亡 [3, 26–28]。对 GSH 合成的直接抑制也足以在某些细胞中诱导铁死亡。例如，丁硫氨

酸硫酸亚胺 (L-buthionine-sulfoximine, BSO) 抑制谷氨酸 - 半胱氨酸连接酶 (glutamate-cysteine ligase, GCL) 引起铁死亡 [16]。

3.3 胞内LIP增加

铁在铁死亡的过程中扮演着重要的作用，胞内大部分铁都以亚铁离子 (Fe^{2+}) 存在于铁池中，被称为 LIP，铁通过 Fenton 反应催化自由基产生，进一步促进脂质过氧化。同样，铁及其衍生物对体内抗氧化相关蛋白的活性也至关重要。如 IκBα 抑制剂 (BAY 11-7085) 通过上调血红素加氧酶 -1 (heme oxygenase-1, HO-1) 的表达，导致 HO-1 进入细胞核和线粒体，造成线粒体失活，线粒体自噬，引起铁死亡 [29]。使用硫酸亚铁铵、氯化铁、血红蛋白、血红素、敲低铁转运蛋白等使胞内铁超载都可以引起铁死亡或增加对铁死亡的敏感性 [20, 30–33]。

4 病理生理状态下的铁死亡

随着铁死亡研究的不断进展，我们有理由相信，铁死亡作为一种新型的细胞死亡方式，应当不仅仅局限于干预铁死亡的诱导剂使用后发生，自然的病理生理状态下也可能存在铁死亡。

这方面的研究主要集中于 GPX4 这一铁死亡过程中的明星蛋白。虽然全身性敲除 GPX4 小鼠胚胎致死 [34]，人们构建了一系列条件敲除小鼠来明确组织细胞对铁死亡的敏感性，如感光细胞 [35]、T 细胞 [36]、肝细胞 [37]、神经细胞 [38]、肾脏上皮细胞 [13] 等。

随后的研究显示，血液系统疾病、心脑血管疾病、肝肾疾病等的发生和发展均与铁死亡相关。红细胞含有大量铁元素，每产生 20 mL 血液需包含 6 g 血红蛋白和 20 mg 铁 [39]。因此，溶血、出血或嗜红作用容易发生铁死亡。在溶血过程中，血红素通过铁素体调节作用介导人血小板的活化和铁死亡 [33]。在小鼠输血模型中，输入长期库存的红细胞会导致红髓巨噬细胞的红细胞吞噬作用增加，引起细胞铁死亡 [40]。肠道局部缺血通过活化 ACSL4 促进铁死亡的发生，从而引起缺血再灌注损伤 [41]。

铁离子对于维持心脏功能具有重要作用，而铁离子作为大脑中最丰富的过渡金属参与神经递质合成、神经元发育等。此外，人们发现大脑中铁元素含量随年龄不断增加 [42, 43]。因而，在心脑血管方面的铁死亡研究主要集中在缺血、出血、神经系统损伤等方面。研究显示，小鼠心脏移植后心肌细胞发生铁死亡，并引起炎症反应 [44]。高铁饮食的条件性铁蛋白敲除小鼠患有严重的具有铁死亡典型特征的心肌损伤与肥大性心肌病，而铁蛋白能有效地预防心肌肥大和随后发生的心肌损伤 [45]。小鼠脑出血时，血红蛋白和裂解的红细胞氧化产物会引起铁死亡与程序性坏死相关的继发性损伤 [46, 47]。而颅脑外伤小鼠体内多种铁死亡生物标志物明显增加，降低磷脂酰乙醇胺氧化能有效改善预后，提示铁死亡参与其中 [48, 49]。Pelizaeus-Merzbacher 病 (Pelizaeus-Merzbacher disease, PMD) 在接受诱导多能干细胞 (induced pluripotent stem cells, iPSC) 和基因矫正治疗过程中，患者来源的少突胶质细胞可以发展到髓鞘形成前期，但随后即发生死亡，这种死亡方式呈现铁死亡的特征形态，但同时不能排除凋亡 [50]。在帕金森病研究中发现多巴胺能神经元会发生铁死亡，而使用铁死亡抑制剂 ferrostatin-1 在体内和体外都能减少神经元死亡 [51, 52]。此外，阿尔茨海默症 [52, 53]、亨廷顿舞蹈症 [54, 55] 等与铁死亡也息息相关。

铁代谢的主要调节者铁调素、转铁蛋白、铜蓝蛋白等主要由肝脏合成，而肾脏可以回收滤过的铁 [56–58]，因而在肝肾疾病中主要集中于铁增加引起组织及细胞铁死亡方面。高铁饮食可以诱导小鼠出现铁死亡相关的血色素沉着症 [59]。而高铁饮食喂养转铁蛋白敲除小鼠会导致其易患由铁死亡引起的肝纤维化，同时在肝硬化患者血清中发现转铁蛋白水平显著降低 [60]。在叶酸诱导的小鼠急性肾损伤模型中，脂质过氧化物清除剂而不是其他细胞死亡方式的抑制剂能有效地保护细胞 [61]。剧烈运动引起的横纹肌溶解会进一步诱发急性肾衰竭，其可能机制为肌红蛋白代谢产生的铁离子诱发肾小管上皮脂质过氧化，进而引起铁死亡，参与肾损伤 [62, 63]。GPX4 失活能触发小鼠急性肾衰竭 [13]。

此外，还有一些研究显示，铁死亡的敏感性与其他通路有关。例如 $CD8^+$ T 细胞释放的干扰素 γ (interferon-γ, IFN-γ) 会下调细胞 SLC3A2 和 SLC7A11 水平，减少体内 GSH 产生，促进脂质过氧化物产生，增加了细胞对铁死亡的敏感性，临床研究也表明 SLC3A2 的表达减少与 IFN-γ 和 $CD8^+$ T 细胞的增加有关 [64, 65]。此外上皮细胞间通过 E- 钙黏蛋白活化胞内 NF2-YAP 信号通路增强铁死亡抗性 [66]。

从 2012 年人们第一次发现铁死亡这一新型细胞死亡方式以来，越来越多的研究显示，在病理生理状态下同样也存在着铁死亡，成为今后研究的热点之一。目前的研究通常关注于过量的铁引起的铁

死亡，而对脂质过氧化在病理生理状态下引起铁死亡的研究较少。同时，诱导铁死亡与免疫疗法、放射疗法的协同使用，为癌症治疗提供了新的思路。

5 铁死亡与呼吸系统疾病

呼吸系统中铁死亡的研究主要集中在慢性气道疾病与肺部肿瘤方面，同时也涉及感染、肺纤维化等。由于细胞特异性，铁死亡对呼吸系统疾病可能存在不同的作用，然而系统性与全方面的研究还没有深入展开。目前的研究结果表明，呼吸系统疾病与铁死亡密切相关 (表 1)。

5.1 慢性气道疾病

铁死亡在慢性气道疾病中的研究目前较少，主要集中在慢性阻塞性肺病 (慢阻肺) 与哮喘方面。香烟烟雾能诱导人支气管上皮细胞发生铁死亡，同时在慢阻肺小鼠模型中可以检测到不稳定铁增加，GPX4 敲除小鼠构建的慢阻肺小鼠较正常小鼠脂质过氧化物水平增加、小气道厚度增加，在吸烟者的

表1. 铁死亡和呼吸系统疾病

Table 1. Ferroptosis and respiratory diseases

Respiratory disease		*In vitro*	*In vivo*
Chronic airway disease	Induce	CSE induces ferroptosis in human bronchial epithelial cells (HBECs) [67, 68]	GPX4 regulates cell death during COPD [68]
		PM2.5 leads to endothelial cells ferroptosis [69]	/
		FINs cause eosinophils ferroptosis-like death [70]	FINs alleviate the allergic airway inflammation [70]
Lung cancer	Induce	Erastin and APAP cotreatment promote ferroptosis and apoptosis [71]	Erastin and APAP act synergistically on xenograft of lung cancer [71]
		Erastin decreases radio-resistance by inducing NSCLC cell ferroptosis [72]	/
		Zinc intoxication leads to human lung cells (A549) ferroptosis [73]	/
		SLC7A11 is downregulated in XAV939-treated NSCLC cells [74]	/
		P53RRA causes A549, SPCA1, and H522 cells cell cycle arrest, apoptosis, and ferroptosis [75]	P53RRA overexpression decreases tumor size and weight [75]
	Inhibit	LINC00336 inhibits ferroptosis in lung cancer cell lines [76]	LINC00336 overexpression increases tumor size, volume, and weight and vice versa [76]
		Overexpressed STYK1 suppresses SW900 cell ferroptosis [77]	/
		LSH inhibits ferroptosis [78]	LSH depletion reduces the tumor volume, weight and formation [78]
		Cancer cells tend to ferroptosis by suppressing NFS1 [79]	Xenografts expressing NFS1 shRNA and FINs have synthetic effect on inhibiting tumor growth [79]
Infection	Induce	*Pseudomonas aeruginosa* without AA-PE can oxidize host AA-PE to trigger ferroptosis in HBECs [80]	*P. aeruginosa* isolated from patients with persistent respiratory infection can induce HBE cells ferroptosis and have high prevalence of pLoxA [80]
		Mtb-induced macrophage necrosis is associated with ferroptosis [81]	Fer-1 can inhibit Mtb-induced tissue necrosis as well as bacterial burden [81]
Lung injury			RILF and RILI are associated with ferroptosis [82, 83]
	Induce	LPS causes ferroptosis in BEAS-2B [84]	Fer-1 alleviates LPS-induced ALI [84]

CSE, cigarette smoke extract; GPX4, glutathione peroxidase 4; PM2.5, particulate matter 2.5; COPD, chronic obstructive pulmonary disease; FINs, ferroptosis inducers; APAP, acetaminophen; NSCLC, non-small cell lung cancer; SLC7A11, solute carrier 7A11; STYK1, serine/threonine/tyrosine kinase 1; LSH, lymphoid-specific helicase; NFS1, iron-sulfur cluster biosynthetic enzyme; AA-PE, arachidonic acid-phosphatidylethanolamines; Mtb, *Mycobacterium tuberculosis*; RILF, radiation-induced lung fibrosis; RILI, radiation-induced lung injury; LPS, lipopolysaccharide; Fer-1, ferrostatin-1; ALI, acute lung injury.

肺组织中也检测到相应表型 [67, 68]。PM2.5 导致内皮细胞发生铁死亡，其中铁超载、脂质过氧化和氧化还原失衡在其中起了重要作用 [69]。

本研究组最近研究显示，三种类型铁死亡诱导剂 ——erastin、RSL3、青蒿琥酯 (artesunate, ART) 都能诱导小鼠嗜酸性粒细胞和人外周血嗜酸性粒细胞死亡，在电镜下呈现典型的铁死亡形态，铁死亡诱导剂诱导的死亡能被铁螯合剂 DFO 所缓解，但不能被脂质过氧化物清除剂 ferrostation-1、凋亡抑制剂 Z-VAD-FMK、坏死抑制剂 necrostatin-1 所缓解。进一步的研究显示，脂质 ROS 虽随着时间不断累积，但是胞质 ROS 而不是脂质 ROS 对嗜酸性粒细胞的死亡起主要调控作用。因此，我们认为，铁死亡诱导剂引起的嗜酸性粒细胞呈非典型的铁死亡。同时，我们构建了小鼠卵清白蛋白 (ovalbumin, OVA) 哮喘模型，发现铁死亡诱导剂能诱导小鼠肺泡灌洗液中嗜酸性粒细胞发生铁死亡。此外我们进一步研究显示，铁死亡诱导剂诱导的嗜酸性粒细胞铁死亡与激素地塞米松诱导的嗜酸性粒细胞凋亡存在显著的协同效应，其联合使用能更进一步诱导嗜酸性粒细胞死亡，并在体内进一步保护哮喘气道 [70]。

5.2 肺癌

铁死亡在肺癌方面的研究尚在起步阶段，主要集中在治疗非小细胞肺癌 (non-small cell lung cancer, NSCLC) 与肺腺癌抗铁死亡方面。

研究显示，erastin 与乙酰氨基酚 (acetaminophen, APAP) 联用协同促进了 NSCLC 细胞的死亡。Erastin 与 APAP 联用促进了细胞的铁死亡与凋亡，不仅表现为细胞内 GSH 减少与脂质过氧化物异常增加，也表现为红系衍生的核因子 2 相关因子 2 (nuclear factor E2-related factor 2, Nrf2) 和 HO-1 表达下降，在小鼠移植瘤模型中也有同样的协同作用 [71]。在放射抗性亚型的 NSCLC 细胞中，erastin 不仅能诱导细胞铁死亡，同时部分降低了细胞对放射的抗性 [72]。潜在性治疗方式之一 —— 锌的使用被认为促进了肿瘤细胞的铁死亡 [73]。长链非编码 RNA (long non-coding RNA, lncRNA) 网络，如 LINC00336、LINC00973、lncRNA P53RRA 等也参与了肺癌的发生与细胞对铁死亡的敏感性 [74–76]。

同时，针对相关靶点蛋白开发一系列药物靶向诱导肿瘤铁死亡也成为了新的研究进展。对临床标本和细胞的研究表明，NSCLC 肺组织与细胞系中 GPX4 上调，GPX4 高表达预后不良，而丝氨酸苏氨酸酪氨酸激酶 1 (serine/threonine/tyrosine kinase 1, STYK1) 调控 GPX4 表达可能是其癌变机制之一 [77]。淋巴样特异性解旋酶 (lymphoid specific helicase, LSH) 在肺癌的体内和体外模型中都起着癌基因作用，EGLN1/c-Myc 通过抑制低氧诱导因子 -1α (hypoxia inducible factor-1α, HIF-1α) 激活 LSH 的表达，激活脂质代谢相关基因与铁死亡相关基因 (SCD1、FADS2) 表达，抑制肿瘤铁死亡 [78, 85]。针对以上相关蛋白可以开发一系列靶点药物诱导肿瘤细胞铁死亡，从而治疗肺癌。

此外，基于肿瘤对铁硫簇生物合成酶 (iron-sulfur cluster biosynthetic enzyme, NFS1) 的需求取决于环境中的氧浓度，而 NFS1 在肺腺癌中经历阳性选择，是肿瘤形成所必须的。抑制 NFS1 或其下游效应物能诱使肿瘤细胞吸收大量铁并释放细胞内存储的铁，增加细胞对铁死亡敏感性，与抑制胱氨酸转运能协同促进肿瘤细胞铁死亡 [79]。

5.3 感染

从细菌本身特性与铁死亡机制方面入手，人们发现了如下几种引起细胞铁死亡的细菌。

15- 脂氧合酶对花生四烯酸 - 磷脂酰乙醇胺 (arochidonic acid-phosphatidyl ethanolamine, AA-PE) 进行选择性氧化进而发生铁死亡 [14, 86]。绿脓杆菌 —— 一种不含 AA-PE 但能表达脂氧合酶 (pLoxA) 的细菌，能氧化人支气管上皮的 AA-PE 成为 15- 氢化氧化 -AA-PE，引起细胞铁死亡。在绿脓杆菌引起的持续性下呼吸道感染的病人中分离这部分绿脓杆菌，发现其高表达 pLoxA，引起人支气管上皮细胞发生铁死亡 [80]。铁水平升高与患者活动性肺结核风险增加相关 [87]，同时结核杆菌 (*Mycobacterium tuberculosis*, Mtb) 感染上调 HO-1 表达 [88]。基于此研究，人们进一步发现 Mtb 诱导巨噬细胞死亡与 GSH、GPX4 水平降低，游离铁、线粒体超氧化物、脂质过氧化物增加有关，可以被脂质过氧化物清除剂 ferrostatin-1 所缓解。在 Mtb 诱导的急性肺损伤模型中也发现了 GPX4 低表达与脂质过氧化物增加，应用 ferrostatin-1 能有效降低细菌载量与肺部炎症 [81]。

5.4 其他呼吸系统疾病

放射疗法中不可避免会发生放射诱导的肺纤维化 (radiation-induced lung fibrosis, RILF) 与放射诱导的急性肺损伤 (radiation-induced lung injury, RILI)。细胞死亡是 RILF 与 RILI 发生的关键点。GPX4 水平在 RILF 小鼠模型组明显下调，铁死亡抑制剂

liproxstatin-1 可以通过激活 Nrf2 途径下调 TGF-β1 来减轻 RILF [82]。小鼠急性 RILI 模型中也观察到 GPX4 水平下降，电镜下肺组织线粒体呈铁死亡形态，铁死亡抑制剂同样能有效缓解小鼠肺部组织病理变化 [83]。在脂多糖 (lipopolysaccharide, LPS) 诱导的急性肺损伤 (acute lung injury, ALI) 中，LPS 处理能增加人支气管上皮丙二醛 (malondialdehyde, MDA)、4- 羟基壬醛 (4-hydroxynonenal, 4-HNE)、总铁水平，体内模型也表明 ferrostatin-1 能有效缓解小鼠 ALI [84]。

6 总结与展望

自 2012 年 Dixon 等提出铁死亡概念以来，铁死亡的相关通路与诱导剂、抑制剂不断被发现。虽然相关机制在被不断完善当中，如最初的研究认为，铁死亡不发生线粒体 ROS 水平的增高、自噬不参与铁死亡过程 [3]，但随后的研究逐渐显示，线粒体及线粒体 ROS 在铁死亡中起重要作用 [11, 89, 90]，自噬促进铁死亡的发生 [6–8]，但铁死亡的核心定义 (铁依赖与脂质过氧化物堆积) 从未被撼动，脂质过氧化物清除剂与铁螯合剂，尤其是脂质过氧化物清除剂能保护细胞一直是铁死亡定义的金标准。

随着研究的不断进展，人们发现铁死亡这种新型的细胞死亡方式在病理生理过程当中同样存在，诱导细胞发生铁死亡将成为新的治疗手段与新药开发靶点。但该领域仍有诸多问题亟待解决：脂质过氧化物如何导致细胞发生死亡？铁死亡与凋亡、程序性坏死等是否存在其他交叉通路？不同细胞发生铁死亡途径是否相同？细胞在进化过程中进化出铁死亡是否有更深层次的意义？铁死亡诱导剂与抑制剂的临床应用如何？

铁死亡在呼吸系统中的研究和应用尚处于萌芽阶段，目前主要集中在铁死亡诱导剂治疗肿瘤，铁死亡参与病理过程，如 LPS、绿脓杆菌诱导上皮细胞铁死亡、PM2.5 诱导内皮细胞铁死亡等。然而值得注意的是，铁死亡 (或者应用铁死亡诱导剂) 存在细胞特异性的问题。针对结构细胞在疾病发生和发展过程中可能存在的铁死亡，我们需要抑制；然而我们的前期研究表明，铁死亡诱导剂能选择性地诱导嗜酸性粒细胞铁死亡 [70]，提示靶向诱导炎症细胞的铁死亡可以有效缓解相关疾病。因此，关于铁死亡在不同的疾病、不同的细胞、不同的诱导剂或抑制剂、不同的应用剂量等方面的作用，都需要更进一步的探索。

随着越来越多的研究去探索铁死亡在呼吸系统疾病中的作用，靶向诱导炎症细胞的铁死亡或者靶向抑制结构细胞的铁死亡，将为某一类呼吸系统疾病的临床防治提供新靶点和新思路。

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