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表观遗传调控在肿瘤细胞铁死亡中的作用

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摘要 表观遗传(epigenetics)是指在DNA序列不发生改变的前提下, 通过DNA甲基化、组蛋白修饰、非编码RNA等机制调控基因表达与生物性状的可逆性变化, 并具有遗传性。近年来, 随着对其在生命活动中的广泛参与及在药物开发中的潜在价值的认识, 表观遗传调控逐渐成为研究的热点。铁死亡(ferroptosis)是一种依赖于脂质过氧化和铁离子的新型细胞死亡形式。研究表明, 恶性肿瘤细胞对铁死亡极为敏感, 显示出其肿瘤治疗新策略的潜力。最近研究发现, 包括DNA甲基化、RNA甲基化、组蛋白修饰及非编码RNA在内的多种表观遗传机制在调控肿瘤细胞铁死亡中发挥重要作用。它们影响铁死亡相关基因的表达, 调节细胞对铁死亡诱导的敏感性, 从而影响肿瘤的发生发展。同时, 表观遗传调控的异常也是肿瘤细胞抗药性产生的重要原因。该综述旨在总结近年来铁死亡相关的表观遗传调控研究进展, 期望为理解铁死亡的表观遗传机制、开发新型靶向药物提供理论依据, 并为肿瘤治疗策略的创新提供新的思路。

关键词 表观遗传; 铁死亡; 肿瘤发生

Roles of Epigenetics in Regulating Ferroptosis in Tumor Cells

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Abstract Epigenetics refers to the reversible and heritable regulation of gene expression and phenotypic traits without altering the underlying DNA sequence. This regulation is mediated through mechanisms such as DNA methylation, histone modifications, and non-coding RNAs. In recent years, as their broad involvement in biological processes and potential in drug development have been increasingly recognized, epigenetic regulation has become a research hotspot. Ferroptosis is a novel form of cell death dependent on lipid peroxidation and iron ions. Recent research indicates that various epigenetic mechanisms—including DNA methylation, RNA methylation, histone modifications, and non-coding RNAs—play critical roles in regulating ferroptosis in tumor cells. They affect the expression of ferroptosis-related genes, modulate cellular sensitivity to ferroptotic induction, and consequently influence tumor development and progression. Furthermore, abnormal epigenetic regulation is an important factor contributing to drug resistance in tumor cells. This review aims to summarize recent advances in the epigenetic regulation of ferroptosis,

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providing a theoretical basis for understanding its mechanisms, exploring new targeted therapies, and inspiring innovative approaches in tumor treatment.

Keywords epigenetics; ferroptosis; tumorigenesis

表观遗传修饰是指在不改变DNA碱基序列的情况下，通过DNA甲基化、组蛋白修饰、染色质结构改变及非编码RNA调控等机制调控基因表达的现象[1]。这一调控机制不仅贯穿生命全过程，也极易受到环境因素的影响，与肿瘤的发生与发展密切相关[2]。研究表明，几乎在所有已知的人类癌症中都存在着表观遗传调控的异常，其与基因的突变共同作用，驱动肿瘤发生[3]。

铁死亡(ferroptosis)是一种铁依赖性的脂质过氧化引发的细胞死亡方式，其本质是细胞结构和功能的损伤[4-8]。本质上说，铁死亡是一种铁依赖性的程序性坏死，其核心机制是细胞内脂质过氧化物(尤其是磷脂过氧化物)的不可控累积，导致细胞膜完整性破坏。该过程由代谢副产物(如活性氧和活性铁)驱动，并受谷胱甘肽过氧化物酶4(glutathione peroxidase 4, GPX4)、胱氨酸/谷氨酸反向转运体(System Xc^-)等抗氧化系统的严密调控。其在癌症、神经退行性疾病及缺血再灌注损伤等过程中具有重要病理意义[5-6]。与传统的细胞死亡方式不同，铁死亡不伴随典型的染色质凝聚和细胞质膜破裂，而表现为线粒体体积缩小，膜密度增加、嵴减少甚至完全丧失以及外膜破裂等特征[9]。

自铁死亡概念被提出以来，相关研究迅速增长，尤其铁死亡在肿瘤治疗方面的作用成为研究的热点。肿瘤细胞对凋亡诱导剂表现出抗性，甚至产生耐药性，而铁死亡则提供了一条新的治疗途径[10]。多个实验已经证实，单独使用铁死亡诱导剂或者将其与传统抗癌药物联合使用，均能有效杀灭癌细胞[11-14]。值得注意的是，越来越多的证据表明，表观遗传机制能够通过调节铁死亡过程中的关键基因表达，影响细胞对铁死亡的敏感性[15]。因此，探索表观遗传调控铁死亡的机制，不仅丰富了我们对肿瘤生物学的理解，也为开发基于铁死亡的新型肿瘤治疗策略提供了潜在的靶点。深入研究表观遗传调控铁死亡的机制，将利用其可逆性与可继承性特征，为肿瘤药物研发和相关疾病的干预提供全新的思路。

1 铁死亡的发生机制

铁死亡的发生密切依赖于脂质过氧化和铁离子的异常积累，其机制复杂且精细调控。脂质过氧化是铁死亡的关键驱动因素[16]，主要由多不饱和脂肪酸磷脂(polyunsaturated-fatty-acid-containing phospholipid, PUFA-PLs)在脂氧合酶(lipoxygenase, LOX)的催化下反应生成PUFA-PL-OOH过氧化物[17]。在这一过程中，多不饱和脂肪酸(PUFA)需要被激活并整合到细胞膜磷脂中，才能通过氧化反应产生活性毒性物质。相关的酶包括长链脂酰辅酶A合成酶4(acyl-CoA synthetase long-chain family 4, ACSL4)和溶血磷脂酰胆碱酰基转移酶3(lysophosphatidylcholine acyltransferase 3, LPCAT3)，ACSL4将PUFA激活生成PUFA-CoA，随后由LPCAT3酯化到膜磷脂中，形成易于被氧化的PUFA-PLs[17]。

另外，细胞内铁离子水平升高和抗氧化能力下降为脂质过氧化提供了有利条件[18]。铁离子通过转铁蛋白受体(transferrin receptor, TFR)进入细胞，在铁还原酶的作用下还原为二价铁(Fe^{2+})。Fe^{2+}在细胞内不稳定的铁池和铁蛋白中储存，也可由铁转运蛋白[如SLC40A1(solute carrier family 40 member 1)]排出细胞。铁水平的动态平衡在正常细胞中维持稳定，而在铁死亡发生时，Fe^{2+}积累显著增加。Fe^{2+}可与过氧化氢(H_2O_2)反应，形成自由基和活性氧(reactive oxygen species, ROS)，这一过程被称为Fenton反应，为脂质过氧化提供底物，同时铁还是LOX的辅助因子，进一步促进脂质过氧化的过程。

GPX4在抵抗铁死亡中发挥重要作用。作为一种硒蛋白，GPX4能够将有毒性的PUFA-PL-OOH还原为无毒的磷脂醇(PUFA-PL-OH)，以防止脂质过氧化的积累，保护细胞免受氧化损伤[19]。谷胱甘肽(GSH)作为GPX4的必备辅因子，通过由System Xc^-[由SLC7A11(solute carrier family 7 member 11)和SLC3A2(solute carrier family 3 member 2)组成]介导的谷氨酸/胱氨酸逆向转运被输送到细胞内[20]。诱导铁死亡的发生则可通过直接抑制GPX4活性或间接抑制System Xc^-的功能，降低GSH水平，从而促进

脂质过氧化, 诱发细胞死亡[21]。

值得注意的是, 最新研究表明, 表观遗传调控能够影响铁死亡的关键基因表达, 调节细胞对羟基自由基和脂质过氧化物的敏感性。这一调控机制为理解肿瘤细胞铁死亡的细胞机制提供了新的视角, 也为开发基于表观遗传的抗肿瘤策略提供了潜在的靶点。

2 DNA/RNA甲基化修饰对肿瘤细胞铁死亡的调控

作为表观遗传学的重要修饰形式, DNA甲基化(DNA methylation)和RNA甲基化(RNA methylation)在调控细胞的生长、代谢和铁死亡过程中的作用日益受到关注。这些修饰可通过影响关键基因的表达, 调节肿瘤细胞对铁死亡的敏感性, 使其成为潜在的治疗靶点。

2.1 DNA甲基化

DNA甲基化主要发生在基因组的CpG岛上, 由DNA甲基化转移酶(DNA methyltransferase, DNMT)催化, 将甲基基团加入到胞嘧啶的5′碳原子上[22]。该修饰通常会导致目标基因沉默, 尤其是在启动子区域的高甲基化状态会抑制转录。肿瘤细胞通过异常的DNA甲基化调控影响癌基因或抑癌基因的表达, 从而促进肿瘤的发生[23]。

研究发现, 在上胃肠腺癌细胞(upper gastrointestinal adenocarcinoma, UGC)中, DNA甲基化调控铁死亡关键因子GPX4的表达[24]。例如, miR-4715-3p上游的CpG位点甲基化导致其表达水平下降, 而使用DNA甲基转移酶抑制剂如5-aza(5-aza-2’deoxycytidine)处理或外源过表达miR-4715-3p, 能够逆转这一状态, 抑制极光激酶A(Aurora kinase A, AURKA)表达, 从而降低GPX4水平, 促进UGC细胞的铁死亡[24]。此外, DCAF8/WDR76/LSH轴的调控也受到DNA羟甲基化(DNA hydroxymethylation)的影响。研究表明, DNA羟甲基化破坏了DCAF8与LSH的相互作用, 增加了LSH的稳定性, 抑制了铁死亡发生[25]。另外, DNA去甲基化在肿瘤铁死亡调控中也具有重要的作用。例如, 在胰腺癌细胞中, DNA去甲基化酶TET3通过非催化机制招募组蛋白去乙酰酶(histone deacetylase, HDAC)至*GATA6*启动子区, 介导H3K27去乙酰化, 抑制GATA6表达的同时, 诱导脂质代谢酶[如SCD(stearoyl-CoA desaturase)、ACSL3(acyl-CoA synthetase long chain family member 3)]的上调, 从而增强肿瘤细胞抵抗铁死亡的能力[26]。

2.2 RNA甲基化

RNA甲基化, 特别是N^6-甲基腺嘌呤(N^6-methyladenosine, m^6A), 作为一种富集于mRNA的转录后修饰, 调控mRNA的稳定性、翻译效率和核输出。由m^6A甲基转移酶(writers)、去甲基化酶(erasers)及m^6A识别蛋白(readers)共同调控, 具有高度的动态可逆性[27]。

在调节肿瘤细胞铁死亡中, SLC7A11作为关键靶点受到m^6A修饰的调控。研究发现, 甲基转移酶METTL3在不同肿瘤中对SLC7A11的调控作用存在差异: 在肺腺癌(lung adenocarcinoma, LUAD)中, METTL3通过m^6A修饰稳定*SLC7A11*的mRNA, 促进其翻译, 从而抑制铁死亡, 促进细胞增殖[28]; 在肝母细胞瘤(hepatoblastoma, HB)中, METTL3介导的m^6A修饰通过识别*IGF2* mRNA结合蛋白1(YTH N^6-methyladenosine RNA binding protein F1, YTHDF1)增强SLC7A11的稳定性, 亦表现出抑制铁死亡的作用[29]。相反, 在人主动脉平滑肌细胞中, METTL3则表现出抑制SLC7A11的作用[30]。此外, YTH家族蛋白在不同组织中的作用也有所不同, 例如在肝细胞癌(hepatocellularcarcinoma, HCC)中, METTL14诱导*SLC7A11* mRNA的5′非翻译区(5′ untranslated region, 5′UTR)发生m^6A修饰, 通过YTHDF2介导的降解机制, 降低SLC7A11的表达水平, 促进HCC细胞的铁死亡[31]。与此同时, YTHDF1在LUAD中被METTL3募集, 增强SLC7A11的m^6A修饰能力, 从而稳定其mRNA, 抑制铁死亡, 促进肿瘤细胞存活[28]。

除了m^6A修饰外, 去甲基化酶FTO(fat mass and obesity-associated)在甲状腺乳头状癌中表达下调, 过表达FTO可通过减少SLC7A11的m^6A修饰释放, 促进细胞增殖、迁移与侵袭, 同时降低铁死亡的敏感性[32]。此外, m^6A修饰还直接调控GPX4的表达。在肺泡上皮细胞中, METTL3过表达导致GPX4的m^6A修饰水平升高, 表达水平相应降低; 而在乳腺癌细胞中, METTL16调控的GPX4 m^6A修饰能促进其表达[33-34]。LI等[35]发现, 线粒体特异性甲基转移酶METTL17通过多种RNA甲基化修饰(包括m^4C、m^5C、m^7G和m^6A)影响线粒体蛋白的翻译, 从而增强结肠癌细胞对铁死亡的抗性。这些研究提示, RNA

m^6A甲基化作为表观遗传调控的一种形式, 显著影响肿瘤细胞铁死亡的调控网络, 为揭示肿瘤发生发展机制提供了新的分子靶点, 也为抗肿瘤药物研发提供了潜在的理论基础。

3 组蛋白修饰对肿瘤细胞铁死亡的调控

在真核细胞中, 组蛋白(histone)是染色质的核心组成部分, 由H2A、H2B、H3、H4组成八聚体, 与DNA共同构成基本的核小体结构。组蛋白在转录调控中发挥关键作用, 其可发生甲基化、乙酰化、泛素化等多种可逆性翻译后修饰, 从而动态调节染色质结构和基因表达, 参与肿瘤的发生与发展[36]。

3.1 组蛋白甲基化在调控铁死亡中的作用

组蛋白甲基化作为重要的表观遗传调控机制, 主要发生在组蛋白H3和H4 N-端的赖氨酸和精氨酸残基上, 由组蛋白甲基转移酶(histone methyltransferases, HMTs)和组蛋白去甲基化酶(histone demethylases, HDMs)调控, 精确控制目标基因的表达, 影响细胞的铁死亡敏感性[37]。

在肾透明癌细胞(clear cell renal cell carcinoma, ccRCC)中, 研究发现, 抑制组蛋白甲基化酶SUV39H1(suppressor of variegation 3-9 homolog 1)可以显著抑制铁死亡相关蛋白DPP4(dipeptidyl peptidase 4)启动子区域的H3K9me3修饰, 导致*DPP4*转录上调, DPP4与NADPH氧化酶1(NADPH oxidase 1, NOX1)形成复合物, 促进脂质过氧化, 诱导铁死亡, 从而抑制肿瘤生长[38]。此外, SETD2(SET domain containing 2)的低表达通过减少亚铁螯合酶(ferrochelatase, *FECH*)启动子上的H3K36me3修饰, 增加脂质过氧化和Fe^{2+}水平, 促进铁死亡, 为ccRCC提供潜在的治疗靶点[39]。

在肝细胞癌(hepatocellular carcinoma, HCC)中, EZH2(enhancer of zeste 2)过表达通过双重途径抑制铁死亡。一方面, EZH2在*TFR2*启动子区域沉积H3K27me3修饰, 下调TFR2表达[40]; 另一方面, EZH2促进*ATOH8*(atonal BHLH transcription factor 8)启动子DNA甲基化与H3K27me3双重修饰, 进一步沉默ATOH8, 抑制铁死亡[41]。临床前研究显示, EZH2抑制剂联合铁死亡诱导剂具有协同抗肿瘤效果[42]。

在神经系统疾病背景中, 组蛋白甲基转移酶G9a通过增加H3K9me2修饰, 抑制抗铁死亡基因表达, 降低谷胱甘肽(glutathione, GSH)水平, 促使细胞发生铁死亡[43]。G9a抑制剂则可以逆转这一过程[43]。在食管鳞状细胞癌(esophageal squamous cell cancer, ESCC)中, 斯钙素2(stanniocalcin 2, STC2)激活组蛋白甲基转移酶5(protein arginine methyltransferase 5, PRMT5), 促进H4R3me2修饰, 激活ATF4、SLC7A11和SLC3A2通路, 抑制铁死亡, 增强放疗抵抗性[44]。

此外, 在肝脏修复和干细胞移植研究中发现, 支持修复的间充质基质细胞(mesenchymal stem cell, MSC)在受损肝组织中易发生铁死亡, 其机制涉及支链氨基酸转氨酶-1(branched chain amino acid transaminase 1, *BCAT1*)基因启动子区域的H3K9me3修饰的减少, 从而减少GPX4的表达, 促进铁死亡[45]。

除了上述在特定肿瘤中存在的调控机制外, 赖氨酸去甲基化酶(lysine-specific demethylase 1/2, LSD1/2)也被证实为跨越多类疾病调控铁死亡的重要因子[46-47]。抑制LSD1表达可提升H3K9me2的修饰水平, 抑制ATF4及system Xc^-的表达, 减少GSH的合成, 进而促进铁死亡。此外, LSD2通过募集CNC转录因子BACH1(BTB and CNC homology 1), 解除对SLC7A11的抑制, 从而抑制铁死亡[47]; 在HER2阳性乳腺癌中, 曲妥珠单抗(trastuzumab)耐药细胞表现出H3K4me3修饰水平升高和DNA甲基化水平下降的协同作用, 增强SLC7A11表达能力, 阻碍铁死亡, 靶向该调控通路可恢复药物敏感性[48]。

3.2 组蛋白乙酰化在肿瘤细胞铁死亡中的调控作用

组蛋白乙酰化由组蛋白乙酰基转移酶(histone acetyltransferases, HAT)和去乙酰化酶(HDAC)共同调控, 主要靶向组蛋白H3和H4赖氨酸残基, 通常伴随基因转录的激活[49]。在肿瘤中, 组蛋白乙酰化修饰常常发生异常, 从而影响铁死亡相关基因的表达[50]。

研究显示, ZHANG等[51]在肝癌细胞中系统解析了铁死亡的转录调控网络, 发现了HNF4α(hepatocyte nuclear factor 4 alpha)和HIC1(hypermethylated in cancer 1)两种转录因子对铁死亡基因表现出拮抗调控作用。具体而言, 组蛋白乙酰基转移酶KAT2B(K/lysine acetyltransferase 2B)通过与这两者竞争结合, 调节其对铁死亡相关基因的调控, 从而影响细胞对铁死亡

的敏感性。此外，RB1的诱导的线粒体蛋白复合物(RB1 inducible coiled-coil 1, RB1CC1)与延伸乙酰转移酶复合物3(elongator acetyltransferase complex subunit 3, ELP3)相互作用，可提升H4K12ac水平，激活*CHCHD3*(coiled-coil-helix-coiled-coil-helix domain containing 3)等铁死亡促进基因，增强线粒体ROS产生，诱导铁死亡[52]。此外，羟甲基戊二酰辅酶A裂解酶(3-hydroxy-3-methylglutaryl-CoA lyase, HMGCL)通过促进DPP4的H3K9ac修饰，增加其表达量，从而提高肿瘤细胞的铁死亡敏感性[53]。另外，HDAC抑制剂可通过抑制system Xc^-和GPX4的表达，诱导铁死亡[54-55]。值得注意的是，不同类别的HDAC抑制剂在神经系统疾病与肿瘤细胞中的作用可能存在差异，其具体机制尚需进一步研究[56]。

3.3 组蛋白泛素化在肿瘤铁死亡中的调控作用

组蛋白的泛素化是一种关键的翻译后修饰，通过泛素–蛋白酶体系统调节蛋白质降解和基因的转录活动[57]。在肿瘤中，组蛋白的泛素化稳态失衡常促进驱动癌变的基因激活或抑制抗肿瘤基因的表达，从而影响铁死亡过程[58]。

BRCA1相关蛋白1(BRCA1 associated deubiquitinase 1, BAP1)作为去泛素化酶，能通过减少H2A泛素化(H2Aub)在*SLC7A11*启动子区的丰度，抑制SLC7A11的表达，促进铁死亡，进而抑制肿瘤生长[59]。类似地，H2B泛素化(H2Bub)水平的降低也可抑制SLC7A11的表达，促进铁死亡[60]。p53通过募集泛素特异性肽酶7(ubiquitin specific peptidase 7, USP7)降低H2Bub在*SLC7A11*调控区的丰度，从而以非转录依赖的方式抑制SLC7A11表达[60]。在肝癌中，USP22(ubiquitin specific peptidase 22)通过降低在*TFRC*(transferrin receptor)启动子区的H2B-K120ub修饰的富集水平，抑制铁死亡，为索拉非尼(sorafenib)耐药提供潜在机制[61]。此外，组蛋白去泛素酶MYSM1(Myb like, SWIRM and MPN domains 1)的缺失会导致铁死亡关键蛋白GPX4、SLC7A11和FTH1(ferritin heavy chain 1)水平降低，增加肿瘤细胞的铁死亡敏感性[62]。ZMYND8(zinc finger MYND-type containing 8)通过稳定NRF2(nuclear factor erythroid 2-related factor 2)表达，可增强抗氧化反应，抑制乳腺癌干细胞的铁死亡，从而促进肿瘤的发生[63]。

4 非编码RNA在肿瘤细胞铁死亡的调控作用

非编码RNA(non-coding RNA, ncRNA)是指能够转录但不编码蛋白质的RNA分子。近年来的研究发现，特定类型的ncRNA，包括微小RNA(microRNA, miRNA)、长链非编码RNA(long non-coding RNA, lncRNA)和环状RNA(circular RNA, circRNA)，通过调控铁死亡过程，影响肿瘤生长和发展[64]。深入揭示这些调控机制对于肿瘤的早期诊断和靶向治疗具有重要指导意义。

4.1 MicroRNA在铁死亡调控中的作用

微小RNA(miRNA)是一类长度约22核苷酸的单链非编码RNA，主要通过特异性结合靶基因mRNA的3′非翻译区(3′UTR)，调控其表达：完全互补配对促使mRNA降解，而不完全互补则抑制翻译。

研究表明，miRNA通过多种途径调控铁死亡。在铁代谢方面，miR-302a-3p和miR-335靶向铁转运蛋白和铁蛋白，升高胞内的Fe^{2+}浓度，从而促进铁死亡[65-66]；相反，miR-137和miR-7-5p通过抑制谷氨酸转运蛋白SLC1A5及线粒体铁蛋白的表达，可降低细胞内的Fe^{2+}水平，抑制铁死亡[67-68]。在抗氧化途径中，多个miRNAs靶向GPX4(如miR-182-5p、miR-324-3p和miR-15a-5p)及SLC7A11(如miR-378a-3p、miR-375、miR-5096、miR-125b-5p、miR-1261和miR-520d-5p)，发挥负调控作用，调控铁死亡[69-76]。在脂质过氧化调控中，miR-424-5p和miR-670-3p分别通过靶向ACSL4抑制铁死亡[77-78]；此外，miR-18a和miR-522通过调控ALOXE3(arachidonate epidermal lipoxygenase 3)和ALOX15(arachidonate 15-lipoxygenase)，参与铁死亡的调节[79-80]。在肝癌中，miR-339-5p高表达通过促进铁蛋白重链1(ferritin heavy chain 1, FTH1)的自噬降解，抑制铁死亡[81]。值得一提的是，已有利用miRNA纳米药物靶向铁死亡在体内治疗的案例[82]，表明调控miRNA水平可能是抑制肿瘤增殖的有效策略。

4.2 LncRNA在铁死亡调控中的作用

长链非编码RNA(lncRNA)是一类长度大于200个核苷酸的非编码RNA，通过与蛋白质、mRNAs、转录因子结合，或作为miRNA的海绵，发挥表观遗传调控功能。在铁死亡中，lncRNA主要通过竞争性内源RNA(competing endogenous RNA, ceRNA)机制与miRNA相互作用，调控铁死亡过程[83-84]。

具体而言，lncRNA在铁死亡调控中多种途径发

挥作用, 例如调节细胞内Fe^{2+}、SCL7A11、GPX4的表达水平。在铁代谢方面, LncRNA NEAT1通过结合miR-9-5p上调转铁蛋白受体(transferrin receptor, TFR)和GOT1(glutamate oxaloacetate transaminase 1)的表达, 增加Fe^{2+}的积累, 促使铁死亡[83]; 而PR11-89则通过miR-129-5p和prom2通路, 抑制铁死亡发生[84]。在调控抗氧化因子方面, lncRNA还发挥重要作用。例如, LncPVT1通过结合miR-214-3p, 抑制其与*GPX4* 3′UTR的结合, 从而抑制肝癌细胞中的铁死亡[85]。在对SLC7A11的调控过程中, 主要参与者包括LncRNA OIP5-AS1/miR-128-3p、SLC16A1-AS1/miR-143-3p, 作用于前列腺癌及肾癌等多种肿瘤类型[86-87]; 此外, LINC00618通过降低LSH表达水平, 抑制*SLC7A11*启动子活性, 降低细胞铁死亡发生的风险[88]。有趣的是, 单个lncRNA可以调控多个铁死亡途径。例如, 肺癌中LncRNA LINC00336不仅通过结合ELAV样RNA结合蛋白1(ELAV like RNA-binding protein 1, ELAVL1), 减少细胞内Fe^{2+}浓度和脂质ROS的产生[89], 还可作为ceRNA影响GSH合成, 从而抑制铁死亡。另外, LncRNA MT1DP通过miR-365a-3p/NRF2通路, 增强细胞对铁死亡的敏感性。此类机制的结合应用, 包括与铁死亡诱导药物(如erastin)的靶向共递送, 为非小细胞肺癌(non-small cell lung cancer, NCSLC)等肿瘤的治疗提供了新思路[90]。

4.3 环状RNA(circRNA)在铁死亡调控中的作用

CircRNA是一类由线性RNA经过反向剪接形成的环状非编码RNA, 具有抗降解的特性。作为内源性竞争性RNA(ceRNA)可通过miRNA“海绵”(miRNA sponge)机制结合特定miRNA, 解除其对靶基因的抑制作用, 从而在肿瘤铁死亡中发挥作用[91]。类似于miRNA, circRNA也可通过调控SLC7A11和GPX4等关键因子影响铁死亡。研究发现, circ-0097009与circFNDC3B可以结合miR-1261和miR-520d-5p, 解除对SLC7A11的抑制, 促进其表达, 抑制铁死亡[92]; 此外, circ0067934通过miR-545-3p/SLC7A11通路抑制甲状腺癌细胞的铁死亡[93]。CircKIF4A、hsacirc0048179和circIL4R作为miR-1231、miR-188-3p、miR-541-3p的海绵, 可促进GPX4的表达[94-96]。

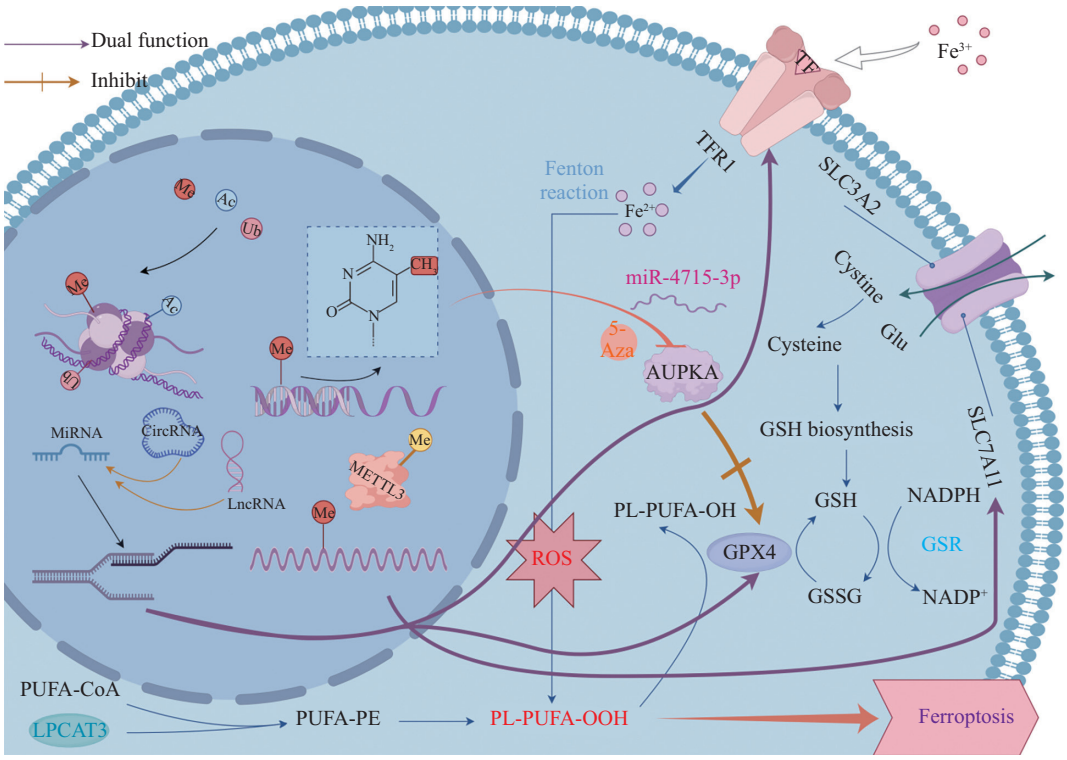
值得注意的是, 某些circRNA可同时结合多种miRNA, 形成复杂的调控网络。例如circ-EPSTI1通过结合miR-375、miR-409-3p和miR-515-5p, 上调SLC7A11的表达, 抑制宫颈癌细胞的铁死亡[97]。此外, circRNA还可能结合RNA结合蛋白(RNA-binding protein, RBP), 调控铁死亡机制[98]。例如, cIARS在肝细胞癌(HCC)中高表达, 通过与RNA结合蛋白ALKBH5相互作用, 促进铁死亡的发生[99]。最新研究还显示, circ-CCDC719-13在前列腺癌中通过靶向热休克蛋白90(heat shock protein90, HSP90), 调控巨噬细胞铁死亡和极化状态, 其过表达可以抑制M2型肿瘤相关巨噬细胞(tumor associated macrophages, TAMs)的促癌功能, 减缓肿瘤的生长和抑制肿瘤的转移[100]。针对目前的研究进展, 我们总结如图1。

5 问题与展望

铁死亡是一种由脂质过氧化驱动的新型的细胞死亡形式。肿瘤细胞常通过逃逸铁死亡机制促进其发展和转移, 而有针对性地诱导铁死亡则为克服抗凋亡治疗中的耐药性提供了新的策略。表观遗传调控机制(包括DNA甲基化和RNA甲基化、非编码RNA及组蛋白修饰等)具有易于调控、可遗传和可逆的优势, 已成为诱导肿瘤铁死亡的重要潜在手段。

当前研究表明, 表观遗传机制通过调控关键铁死亡调控因子(如SLC7A11、GPX4等)的表达, 影响细胞对铁死亡的敏感性。然而, 令人关注的是, 铁死亡的核心特征——脂质过氧化的积累及膜脂结构与流动性的剧变——这些发生在核外部的事件如何被精确调控, 以及细胞内的核内基因表达如何反馈调节到这些核外的过程, 是未来研究的关键方向。此外, 基于肿瘤细胞特有的表观遗传异常, 结合表观遗传药物与铁死亡诱导剂的联合应用, 显示出具有潜力的治疗前景, 或许能显著提高靶向性并降低副作用。

目前的研究多聚焦于铁代谢和脂质过氧化相关分子, 然而其他调控铁死亡的因子和在不同疾病模型中的作用尚未得到充分阐明。另外, 尚不清楚多种表观遗传途径是如何协同调控铁死亡的, 以及相同修饰在不同类型肿瘤中的差异性机制[29-30]。这些细胞特异性的生物学效应可能受多种因素的影响, 但目前仍缺乏系统性认识。深入探索利用表观遗传调控手段调节肿瘤细胞铁死亡的机理, 具有巨大的潜力, 有望为肿瘤的防治提供新思路和治疗策略, 为临床应用开辟新的途径。



表观遗传修饰通过DNA/RNA甲基化动态调控、组蛋白修饰及非编码RNA网络等多重调节机制，精准调节铁死亡关键基因(如*GPX4*、*ACSL4*等)的表达水平与其相关蛋白酶活性，从而影响肿瘤细胞脂质过氧化的进程。这种表观遗传–铁死亡的交叉调控不仅揭示了肿瘤发生发展的新机制，还为开发双靶向疗法(如表观遗传药物联合铁死亡诱导剂)提供了创新干预策略。

Epigenetic modifications precisely regulate the expression levels of ferroptosis-related key genes such as *GPX4* and *ACSL4* and associated enzyme activities through multiple regulatory mechanisms, including dynamic regulation of DNA/RNA methylation, histone modifications, and non-coding RNA networks, thereby influencing the lipid peroxidation progression in tumor cells. This epigenetic-ferroptosis cross-regulation not only reveals novel mechanisms underlying tumorigenesis and development, but also provides innovative intervention strategies for developing dual-targeted therapies (e.g. epigenetic drugs combined with ferroptosis inducers).

图1 表观遗传调控铁死亡机制(本图由Figdraw绘制)

Fig.1 Epigenetic regulation of ferroptosis mechanisms (by Figdraw)

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