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·综　述·

# 胃癌治疗的新靶点：铁死亡

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［摘要］ 胃癌是我国人口死亡的主要原因之一，近年来确诊为早期胃癌的患者数量逐年上升，然而肿瘤细胞耐药性的产生严重限制了手术和化学治疗的效果，极有必要探索胃癌治疗的新靶点。铁死亡是一种铁依赖性细胞程序性死亡方式，其显著特征是细胞内脂质过氧化。胃癌细胞对细胞内铁代谢水平非常敏感，铁死亡在胃癌的发生、进展、治疗及耐药机制中发挥着至关重要的作用。胃癌细胞内铁死亡相关基因和非编码 RNA 与胃癌转移、耐药和预后密切相关，近年来关于铁死亡对胃癌细胞增殖的调节作用研究已获得一定的进展，因此，靶向铁死亡可能是胃癌的有效治疗策略。本文通过阐述铁死亡在胃癌细胞增殖、侵袭、转移及耐药机制中的作用，总结与铁死亡相关的靶点基因，并对靶向调节铁死亡在胃癌治疗中的前景进行展望。

［关键词］ 胃肿瘤；铁死亡；肿瘤侵袭；肿瘤转移；细胞增殖；肿瘤抗药性；预后
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## Ferroptosis: a new therapeutic target for gastric cancer

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［Abstract］ Gastric cancer (GC) is one of the main causes of death in China. Recently, the patients diagnosed with early GC has increased year by year. However, drug resistance has seriously limited the effects of surgery and chemotherapy. Therefore, it is urgent to explore new therapeutic targets for GC. Ferroptosis is an iron-dependent programmed cell death, and it is characterized by intracellular lipid peroxidation. GC cells are very sensitive to the level of intracellular iron metabolism. Ferroptosis plays an important role in the development, progression, treatment and drug resistance of GC. Ferroptosis-related genes and non-coding RNAs in GC cells are closely related to metastasis, drug resistance and prognosis of GC. In recent years, research on the regulatory effect of ferroptosis on the proliferation of GC cells has made some progress, and targeted ferroptosis may be an effective treatment for GC. This article describes the role of ferroptosis in the proliferation, invasion, metastasis and drug resistance of GC cells, summarizes the target genes related to ferroptosis, and prospects the application of targeted regulation of ferroptosis in the treatment of GC.

［Key words］ stomach neoplasms; ferroptosis; tumor invasion; tumor metastasis; cell proliferation; neoplasm drug resistance; prognosis
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胃癌是消化道的主要恶性肿瘤之一，东亚国家胃癌发病率极高，新发病例数占全球胃癌新发病数的 40% 以上[1]。在中国，2015 年男性胃癌发病率为 26.54/10 万，女性发病率为 11.09/10 万[2]。近年来，鉴于诊断技术的进步，早期胃癌总发病率在全球范围内呈上升趋势[3-4]。手术治疗联合化疗是胃癌主要的治疗方法[5]，其中手术切除是胃癌唯一可能根治的方法，但这种治疗仅限于Ⅰ期胃癌患者[6]。

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中晚期胃癌的治疗方案较为有限，预后也较差[7]。为提高胃癌患者生存率，探索胃癌治疗的新靶点已逐渐成为研究的焦点。

缺氧条件下的代谢紊乱是胃癌最重要的特征之一，代谢紊乱引起的生化特性改变与胃癌细胞增殖、程序性死亡、营养物质运输和耐药性的产生有密切联系[8]。然而，肿瘤细胞免疫逃逸机制限制了程序性细胞死亡的发生[9]，因此，通过药物诱导胃癌细胞程序性死亡在其治疗中具有重要的意义。药物诱导癌细胞死亡的方式包括细胞凋亡、自噬、坏死等[10]，它们都依赖于高水平的活性氧（reactive oxygen species，ROS）对程序性细胞死亡的调节作用[11]。线粒体是ROS的主要来源，受损的线粒体将产生更多的ROS[12]，其原因在于ROS可破坏线粒体酶，导致铁硫簇释放铁，引起细胞内铁代谢障碍[13]。因此，铁死亡这一概念被提出来，它不同于上述各类死亡方式，其核心为铁依赖的ROS堆积导致细胞膜脂质过氧化、通透性发生改变，特征是谷胱甘肽（glutathione，GSH）耗竭、谷胱甘肽过氧化物酶4（glutathione peroxidase 4，GPX4）氧化还原防御中断和有害的脂质ROS形成，在形态学上表现为线粒体缩小与线粒体嵴减少[14-15]。

铁死亡的调节主要取决于ROS的产生，细胞内的ROS水平决定了脂质过氧化程度[16-18]。GPX4是调节ROS氧化还原反应的核心因子，过量的ROS在GPX4的催化下与GSH中和，因此，抑制GPX4途径可以有效促进铁死亡[19-20]。大量ROS会在花生四烯酸5-脂氧合酶（arachidonate 5-lipoxygenase，ALOX5）催化下与脂质膜反应形成脂质过氧化物，因此任何影响ALOX5表达或活性的因素都会调控铁死亡[18]。本文总结了胃癌中铁死亡的调节机制，并阐述铁死亡在胃癌发生、发展、侵袭与耐药中的作用，为胃癌的诊断和治疗提供参考。

## 1　铁死亡与胃癌细胞代谢

1.1　*能量代谢*　能量代谢是肿瘤生物学研究的热点[21]，糖代谢、脂肪酸代谢、氨基酸代谢和核苷酸合成代谢增强是肿瘤细胞的重要标志[22]。与正常细胞相比，癌细胞对能量的需求更高[23]，因此癌细胞经常在缺氧条件下增殖并重编程其能量代谢[24]。胃癌的肿瘤微环境（tumor micro-environment，TME）是一个复杂的综合系统，具有缺氧、酸中毒、间质高压和免疫炎症反应等特点[25]，缺氧条件下诱导生成的ROS对肿瘤细胞的生存而言是一柄双刃剑。一方面，缺氧诱导的ROS有利于缺氧诱导因子（hypoxia inducible factor，HIF）-1α的表达[26]，它通过促进线粒体自噬来限制ROS，从而去除受损的线粒体[27]，甚至可以通过上调磷酸化Akt促进胃癌细胞增殖[28]；另一方面，药物能通过进一步提高胃癌细胞内ROS水平促进细胞程序性死亡[29]。Chen等[30]认为，ROS生成进一步增加是导致胃癌细胞活力降低的关键因素。因此，提高细胞内ROS水平是胃癌治疗的重要切入点。

线粒体在铁代谢、物质和能量代谢中不可或缺，因为它是铁利用、分解代谢和合成代谢途径的主要细胞器[31]。相关证据表明，线粒体需要铁才能发挥作用，并在铁代谢中发挥核心作用[32]。铁代谢对许多细胞过程至关重要，包括氧气运输、呼吸和DNA合成等，许多癌细胞表现出铁代谢失调[33]。在细胞代谢过程中，铁与过氧化氢通过芬顿（Fenton）反应产生ROS，过量的ROS促进脂质过氧化，从而使细胞发生铁死亡[34]。因此，通过调节铁代谢各环节都可以调节铁死亡。膳食铁在十二指肠和空肠细胞通过二价金属离子转运体1（divalent metal transporter 1，DMT1）进入细胞，而基底膜的铁转运蛋白1（ferroportin 1，FPN1）将铁转运到血液中，血浆转铁蛋白（transferrin，TF）将铁输送到各组织，与转铁蛋白受体1（transferrin receptor 1，TFR1）结合将铁从细胞外向细胞内运输[35]。补充外源性铁离子但不补充其他金属离子可以加速erastin诱导的铁死亡[14]。NFS1（一种半胱氨酸脱硫酶）可通过增加TFR1水平和降低铁蛋白（ferritin，FTH）水平使细胞对铁死亡敏感[36]。利拉鲁肽通过降低TFR1表达和增加铁转运蛋白1（ferroportin 1，FPN1）表达减少铁在细胞内沉积，抑制铁死亡[37]。自噬也可以通过影响铁代谢来调节细胞对铁死亡的敏感性[17]。核受体共激活因子4（nuclear receptor coactivator 4，NCOA4）通过将FTH招募到溶酶体进行降解来调节铁含量，因此抑制溶酶体活性或破坏NCOA4蛋白可抑制铁死亡，而NCOA4的过表达增加了FTH的降解并促进了铁死亡[38-39]。

1.2　*物质代谢*　胃癌细胞主要通过有氧糖酵解获取能量，相比于氧化磷酸化，有氧糖酵解虽然获取的ATP量少，但是速率更快。在此过程中，肿瘤细胞中积累的乳酸是形成酸性微环境的关键因素[40]，在此环境中，Myc、Ras及Akt等癌基因表达活跃，

致使肿瘤细胞中糖酵解酶的表达增多，以增强ATP的供应，抵抗肿瘤细胞凋亡并促进其转移。相关证据表明，肿瘤细胞在有氧糖酵解过程中可引起ROS积累和谷氨酰胺摄入增强[41]，前者是诱发铁死亡的关键性细胞内因素，而后者是铁死亡的细胞外调节剂[42]。相关研究表明谷氨酰胺代谢能够抑制GSH合成并诱导铁死亡，而细胞内积累的ROS可直接与质膜多不饱和脂肪酸反应，将其氧化为脂质过氧化物，引发铁死亡[43]。有研究者发现异常脂肪酸代谢也是推动胃癌细胞增殖的重要危险因素，进一步研究发现脂滴可降低ROS毒性，从而提高肿瘤细胞存活率[44]。然而，有氧糖酵解引起的有害物质的蓄积并不足以引起细胞毒效应，肿瘤细胞可通过自噬反应从有氧糖酵解产生的少量ROS中获益[45]。有研究表明通过抑制胃癌细胞自噬能有效促进肿瘤细胞凋亡[46]；深入研究发现，抑制自噬能促进ROS蓄积，引起细胞内脂质过氧化物堆积，诱发铁依赖性细胞程序性死亡[47]。

1.3　铁离子稳态　细胞的能量代谢和物质代谢发生改变后，线粒体的功能异常将进一步影响线粒体中间代谢、离子稳态及细胞凋亡[48]。细胞代谢生成的脂质过氧化物主要由GPX4进行还原，研究发现，铁离子水平升高通常抑制GPX4和脂酰CoA合成酶长链家族成员4（acyl-CoA synthetase long chain family member 4，ACSL4）的表达，脂质过氧化物的堆积是诱发铁死亡的关键因素，因此GPX4下调可诱导铁依赖性细胞死亡[49]。虽然从生物学角度分析，铁与胃癌的发生可能存在关系，但是仍需大量证据支持。有学者发现胃癌与FTH和转铁蛋白饱和度指数之间呈显著负相关[50]，这意味着铁离子稳态与胃癌的发生、发展存在密切联系。有证据表明GPX4参与调节肿瘤细胞对12种铁死亡诱导剂的敏感性[13]，其中RSL3、DPI7、DPI12、DPI17、DPI10、DPI13、FIN56等小分子通过抑制GPX4活性发挥调节铁死亡的作用[51]。因此，GPX4活性反映了肿瘤细胞铁死亡水平。

GPX4发挥作用需要利用硒和GSH[52]，GSH中存在易于氧化和脱氢的活性巯基基团，是体内自由基清除的有力武器。GSH的合成需要半胱氨酸作为起始材料，并依赖胱氨酸/谷氨酸反转运体系统（system $Xc^-$）将胱氨酸转运至细胞内，而system $Xc^-$由2个亚基组成，分别为溶质载体家族7成员11（solute carrier family 7 member 11，SLC7A11）和溶质载体家族3成员2（solute carrier family 3 member 2，SLC3A2）。当system $Xc^-$功能被抑制时，易诱发细胞铁死亡。相关证据表明，二甲双胍通过抑制SLC7A11来诱导铁死亡[53]。柳氮磺吡啶、索拉非尼、erastin等则通过抑制system $Xc^-$来诱导铁死亡[51]。

综上所述，胃癌细胞在进行能量和/或物质代谢时，低浓度ROS可能通过诱导HIF发挥促进细胞增殖的作用，通过促进自噬保持细胞增殖状态；然而高浓度ROS状态下，会引起细胞内铁离子水平改变，这将引起相关酶的活性发生改变，特别是氧化还原系统功能被抑制，引起细胞内脂质过氧化物的堆积，这是诱发细胞铁死亡的关键因素。

## 2　铁死亡与胃癌细胞增殖、侵袭和转移

胃癌细胞代谢过程中ROS、细胞内铁、GPX4及GSH等一系列氧化代谢相关物质水平的改变，将会在不同层次引起细胞内脂质过氧化物的堆积，进而改变细胞铁死亡水平。ROS是铁死亡的关键性特征之一[54]。相关研究表明，生理状况下ROS是细胞代谢过程中产生的分子，促进细胞增殖和存活[55]。由于癌细胞的细胞代谢和增殖，ROS的产生增加[56]。近年来有研究者发现低浓度ROS通过调节自噬促进细胞适应应激条件帮助细胞存活[56]，因此小范围内ROS波动可能有利于胃癌细胞的增殖，甚至有利于胃癌细胞迁移[57]。然而，高浓度的ROS及抗氧化酶的消耗将导致细胞凋亡[58]。研究表明ROS会攻击线粒体，高浓度ROS状态下，线粒体耗竭引起严重的ATP缺乏，或将引起线粒体损伤依赖性细胞凋亡[59]。在胃癌细胞中，外界因素诱导的ROS进一步升高能显著抑制肿瘤细胞的增殖[60]。有研究发现，ROS的累积可以提高胃癌细胞中铁死亡的水平[61]。根据分子亚型，铁死亡相关基因被分为3个簇，具有与DNA修复、基础转录因子和P53信号通路相关的簇的胃癌患者生存率最高，而富集在基质激活途径，包括转化生长因子信号通路、黏附斑块、细胞外基质受体相互作用、MAPK信号通路、细胞黏附分子和白细胞跨上皮迁移的簇的胃癌患者预后最差[62]。虽然尚不清楚造成这种差异的原因，但是这种现象对于将铁死亡用于诱导胃癌细胞凋亡、提高患者生存质量的医疗实践具有较强的指导意义。

## 3　铁死亡与胃癌的耐药

肿瘤细胞的耐药是目前药物治疗失败的主要

原因。研究发现，肿瘤的耐药性与铁死亡密切相关，诱导肿瘤细胞铁死亡有助于克服耐药性。由于遗传改变和异常生长，癌细胞比正常细胞经历更高水平的ROS氧化应激，因此，维持抗氧化剂GSH对于它们的生存和增殖至关重要[63]。化疗仍然是胃癌治疗的主要方法之一，抑制STAT3可阻抑铁死亡负调节轴，并遏制胃癌生长、减轻化疗耐药性[64]。激活转录因子3（activating transcription factor 3，ATF3）可减轻胃癌的顺铂耐药性[65]。ADP核糖基化因子6（ADP ribosylation factor 6，ARF6）能够调控erastin诱导的脂质过氧化反应，抑制ARF6可减轻胃癌细胞对卡培他滨的耐药性[66]。这些研究表明，调节铁死亡可能成为靶向耐药肿瘤细胞的有效策略。

## 4　铁死亡与胃癌的诊断和预后

尽管胃癌的诊治取得了显著的临床进展，但早期诊断率低和治疗受限两大瓶颈导致晚期胃癌患者的5年生存率不足10%[67]；相反，通过早期诊断获得有效治疗的患者5年生存率可高达95%[68]。因此早期诊断和治疗对于胃癌患者来说极为重要。然而，早期胃癌患者通常没有任何症状，尽管早期癌症筛查正在不断普及，已有的胃癌诊断生物标志物仍不能用于早期诊断。因此，寻找可用于胃癌早期诊断和预后的可靠分子标志物具有重要意义。

胃癌细胞与正常细胞最显著的区别之一是新陈代谢，靶向代谢已成为癌症诊断和治疗的一个有吸引力的靶点[69]。胃癌细胞的糖代谢、脂肪代谢、氨基酸代谢和离子代谢均异于正常组织细胞，其共同点在于胃癌细胞代谢过程中蓄积的ROS更多[70]，这成为早期胃癌诊断壁垒的突破口。

烟酰胺腺嘌呤二核苷酸磷酸氧化酶4（nicotinamide adenine dinucleotide phosphate oxidase 4，NOX4）是NOX家族中唯一能将分子氧还原为$H_2O_2$的酶[71]，它也是介导ROS生成的促进胃癌细胞转移的关键性分子之一[70]。值得注意的是，NOX4也能通过提高NADPH活性增加ROS的产生并破坏线粒体完整性，从而促进铁死亡[72]。因此，在胃癌的早期，NOX4可以用来检测肿瘤转移；在化疗期间，NOX4可能用于检测内环境，特别是肿瘤铁死亡水平，用以预测胃癌预后。此外，基因转录调节因子MYB也被认为是胃癌的重要危险因素[73]，相关证据指出MYB表达能驱动胃癌细胞增殖、迁移和侵袭[74]。从机制上讲，MYB能抑制半胱氨酸双加氧酶1（cysteine dioxygenase 1，CDO1）表达，而后者具有抑制GPX4表达的能力，因此MYB高表达能抑制肿瘤细胞内铁死亡水平[75]。MYB的高表达既能促进胃癌细胞增殖，也能增强细胞的耐药性，有望成为早期诊断及治疗随访的重要检测分子。在基因表达层次，其他研究也筛选出一些可用来预测胃癌预后的铁死亡相关基因（表1）[76-80]。

**表1　胃癌预后相关的铁死亡基因**

| 相关研究 | 基因 |
|---|---|
| Shao等[76] | *TCFBR1*, *MYB*, *NFE2L2*, *ZFP36*, *TF*, *SLC1A5*, *NF2*, *NOX4* |
| Liu等[77] | *SP1*, *MYB*, *ALDH3A2*, *KEAP1*, *AIFM2*, *ITGB4*, *TGFBR1*, *MAP1LC3B*, *NOX4*, *ZFP36* |
| Liu等[78] | *NOX5*, *ZFP36*, *DUSP1*, *TSC22D3*, *TXNIP*, *GABARAPL1*, *CDO1*, *TGFBR1*, *HAMP*, *NOX4*, *NNMT*, *CXCL2*, *AIFM2*, *SLC1A4*, *NF2*, *SP1*, *GLS2*, *MYB*, *PSAT1* |
| Zheng等[79] | *GABARAPL1*, *ZFP36*, *DUSP1*, *TXNIP*, *NNMT*, *MYB*, *PSAT1*, *CXCL2* |
| Huang等[80] | *ANGPTL7*, *CDKN2A*, *FADS2*, *GCH1*, *GDF15*, *IL6*, *LINC00472*, *MAPK3*, *NNMT*, *NOX4*, *PTGS2*, *RGS4*, *SCD*, *SLC1A4*, *SLC2A3*, *SOCS1*, *TAZ*, *TF*, *TP63*, *VLDLR* |

TCFBR1：转录因子T细胞因子受体1；MYB：MYB转录因子；NFE2L2：红细胞衍生核因子2样蛋白2；ZFP36：锌指蛋白36；TF：转铁蛋白；SLC1A5：溶质载体家族1成员5；NF2：神经纤维瘤蛋白2；NOX4：烟酰胺腺嘌呤二核苷酸磷酸氧化酶4；SP1：特异性蛋白1；ALDH3A2：醛脱氢酶3家族成员A2；KEAP1：Kelch样ECH关联蛋白1；AIFM2：线粒体凋亡诱导因子2；ITGB4：整合素β4重组蛋白；TGFBR1：转化生长因子β受体1；MAP1LC3B：微管关联蛋白1轻链3β；NOX5：烟酰胺腺嘌呤二核苷酸磷酸氧化酶5；DUSP1：双特异性磷酸酶1；TSC22D3：TSC22结构域家族成员3；TXNIP：硫氧还蛋白互作蛋白；GABARAPL1：γ-氨基丁酸受体相关蛋白样蛋白1；CDO1：半胱氨酸双加氧酶1；HAMP：铁调素重组蛋白；NNMT：烟酰胺*N*-甲基转移酶；CXCL2：趋化因子CXC配体2；GLS2：谷氨酰胺酶2；PSAT1：磷酸丝氨酸转氨酶1；ANGPTL7：血管生成素样蛋白7；CDKN2A：周期素依赖性激酶抑制因子2A；FADS2：脂肪酸去饱和酶2；GCH1：鸟苷三磷酸环化水解酶1；GDF15：生长分化因子15；IL6：白细胞介素6；LINC00472：基因间长链非编码RNA 00472；MAPK3：丝裂原活化蛋白激酶3；PTGS2：前列腺素内过氧化物合酶2；RGS4：G蛋白信号调节因子4；SCD：硬脂酰辅酶A去饱和酶；SLC2A3：溶质载体家族2成员3；SOCS1：细胞因子信号转导抑制因子1；TAZ：Tafazzin蛋白；TP63：肿瘤蛋白P63；VLDLR：极低密度脂蛋白受体.

## 5　铁死亡与胃癌的治疗

目前应用于消化道肿瘤的化疗药物主要有铂类制剂、氟尿嘧啶类和紫杉醇类。临床化疗药物应用的主要难点在于耐药性，长期及过高的ROS含量均可诱发胃癌细胞对化疗药物的耐药性。肿瘤细胞暴露于奥沙利铂或伊立替康会导致ROS含量显著增加，但可通过增加其谷氨酰胺代谢以进行补偿，这是肿瘤化疗耐药机制之一[81]。目前相对应的治疗策略主要从3个方面着手：通过靶向脂加氧酶阻断脂质ROS的积聚，以促进胃癌细胞铁死亡[82]；通过抑制ROS激活的相关信号通路，逆转其所导致的线粒体功能障碍引发的顺铂抵抗[83]；通过调节ROS水平诱导铁死亡，如过氧化物还原蛋白2（peroxiredoxin-2）可通过调节ROS含量扰乱细胞内氧化环境并诱导铁死亡[84]。

## 6　小　结

胃癌与铁死亡关系密切。在细胞代谢层次上，能量代谢和物质代谢都能不同程度引起胃癌细胞内氧化应激水平升高，这些氧化代谢产物将在不同维度引起肿瘤细胞内细胞器功能紊乱，其中最主要的是铁及铁代谢相关产物，因为这些物质的少量堆积可能是促进肿瘤发生的危险因素。线粒体是维持ROS和抗氧化剂平衡的关键性细胞器，主要通过自噬维持其结构、数量和功能的完整性，因此当线粒体自噬受限而铁死亡水平较高时，细胞易发生铁依赖性程序性死亡。因此，基于细胞代谢层面的特定分子可能有助于胃癌的早期诊断、治疗随访及病情进展的预测。此外，通过激活胃癌细胞内铁死亡或抑制具有杀伤能力免疫细胞内的铁死亡水平有望成为未来疾病治疗的新策略。

尽管铁死亡在胃癌领域已经取得了一些研究进展，但仍然有许多不清楚的机制，例如有关FSP1途径、甲羟戊酸途径、二氢乳清酸脱氢酶途径的调控机制研究较少，铁死亡相关lncRNA的生成、选择和降解的机制尚不清楚，阐明这些机制可能对铁死亡未来的应用意义重大。另外，关于胃癌铁死亡靶向治疗的研究仍处于实验阶段，尚未开发出能应用于临床的药物。铁死亡的临床应用依然面临很多问题，例如：什么样肿瘤类型的患者适合铁死亡疗法？应该从什么角度来考虑对患者施行铁死亡疗法？哪些指标可以用来评价铁死亡疗法在肿瘤中的应用？这些问题都有待未来的研究阐明。

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