ISSN 1009-3079 (print)
ISSN 2219-2859 (online)

世界华人消化杂志®

WORLD CHINESE JOURNAL OF DIGESTOLOGY

Shijie Huaren Xiaohua Zazhi

2022 年 8 月 28 日　　第 30 卷　　第 16 期　　(Volume 30 Number 16)

16/2022

《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、中国知网《中国期刊全文数据库(CNKI)》、《中文科技期刊数据库(CSTJ)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录.

ISSN 1009-3079
16>
9 771009 307056

世界华人消化杂志
https://www.wjgnet.com
二零二二年八月二十八日
第三十卷
第十六期

WCJD 世界华人消化杂志®

目　次

2022年8月28日 第30卷 第16期 (总第708期)

述评

693　中医脾气虚证现代实质研究进展
刘婧, 乔波, 谭周进

临床研究

701　NLRC5基因多态性与胃癌易感性的关系
倪栋琼, 谭惠城, 张欣怡, 邵欢, 黄宣

710　Meta分析评估BISAP评分对HLAP严重性的预测价值
吕永才, 姚燕华, 吴德彪, 雷静静

文献综述

718　铁死亡抑癌机制及其在消化系统肿瘤中的研究进展
李佳佳, 夏宣平, 吴利敏, 朱正, 史宇宁, 张徐昭, 夏豫珊, 卢光荣

729　特发性非肝硬化门脉高压症的肝脏病理及影像特征
谭明洁, 刘晖, 丁惠国

735　脂肪生成抑制剂治疗非酒精性脂肪性肝病的研究进展
杨柳, 李锦忠, 李敏然

目次

消　　息

700　《代谢相关脂肪性肝病肝外并发症》书讯
709　《世界华人消化杂志》栏目设置
717　《世界华人消化杂志》参考文献要求
734　《世界华人消化杂志》性质、刊登内容及目标

封面故事

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本期责任人

编务 张砚梁; 送审编辑 张砚梁; 组版编辑 张砚梁; 英文编辑 王天奇;
形式规范审核编辑部主任 郭旭; 最终清样审核总编辑 马连生

世界華人消化雜志

Shijie Huaren Xiaohua Zazhi

吴阶平　题写封面刊名
陈可冀　题写版权刊名
(半月刊)
创　刊 1993-01-15
改　刊 1998-01-25
出　版 2022-08-28
原刊名 新消化病学杂志

期刊名称
世界华人消化杂志

国际标准连续出版物号
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

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7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: wcjd@wjgnet.com
http://www.wjgnet.com

出版
百世登出版集团有限公司
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

制作
北京百世登生物医学科技有限公司
100025, 北京市朝阳区东四环中路62号, 远洋国际中心D座903室
电话: +86-10-85381901

《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、中国知网《中国期刊全文数据库(CNKI)》、《中文科技期刊数据库(CSTJ)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录.

《世界华人消化杂志》正式开通了在线办公系统(https://www.baishideng.com), 所有办公流程一律可以在线进行, 包括投稿、审稿、编辑、审读, 以及作者、读者和编者之间的信息反馈交流.

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定价
每期136.00元 全年24期3264.00元

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Contents

Volume 30 Number 16 August 28, 2022

EDITORIAL

693 Progress in modern research on substance of spleen qi deficiency in Chinese medicine
Liu J, Qiao B, Tan ZJ

CLINICAL RESEARCH

701 Relationship between *NLRC5* gene polymorphisms and gastric cancer susceptibility
Ni DQ, Tan HC, Zhang XY, Shao H, Huang X

710 Value of BISAP score for predicting severity of hyperlipidemic acute pancreatitis: A meta-analysis
Lv YC, Yao YH, Wu DB, Lei JJ

REVIEW

718 Cancer suppression by ferroptosis and its role in digestive system tumors
Li JJ, Xia XP, Wu LM, Zhu Z, Shi YN, Zhang XC, Xia YS, Lu GR

729 Pathological and imaging features of idiopathic non-cirrhotic portal hypertension
Tan MJ, Liu H, Ding HG

735 Progress in research of lipogenesis inhibitors for treatment of nonalcoholic fatty liver disease
Yang L, Li JZ, Li MR

Contents

World Chinese Journal of Digestology
Volume 30 Number 16 August 28, 2022

COVER

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Indexed/Abstracted by

Chemical Abstracts, EMBASE/Excerpta Medica, Abstract Journals, Scopus, CNKI, CSTJ and Superstar Journals Database.

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Shijie Huaren Xiaohua Zazhi

Founded on January 15, 1993
Renamed on January 25, 1998
Publication date August 28, 2022

NAME OF JOURNAL
World Chinese Journal of Digestology

ISSN
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

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7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: wcjd@wjgnet.com
https://www.wjgnet.com

PUBLISHER

Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PRODUCTION CENTER

Beijing Baishideng BioMed Scientific Co., Limited Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381901

PRINT SUBSCRIPTION

RMB 136 Yuan for each issue
RMB 3264 Yuan for one year

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WCJD 世界华人消化杂志®

在线投稿: https://www.baishideng.com

世界华人消化杂志 2022年8月28日; 30(16): 718-728

DOI: 10.11569/wcjd.v30.i16.718

ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

铁死亡抑癌机制及其在消化系统肿瘤中的研究进展

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收稿日期: 2022-03-31
修回日期: 2022-05-02
接受日期: 2022-08-18
在线出版日期: 2022-08-28

Cancer suppression by ferroptosis and its role in digestive system tumors

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Received: 2022-03-31
Revised: 2022-05-02
Accepted: 2022-08-18
Published online: 2022-08-28

Abstract

Cancer is the second leading cause of death worldwide, and digestive system tumors remain the leading malignancy in China, seriously endangering national health and imposing a huge economic burden. Ferroptosis is a form of cell death characterized by increased intracellular reduced iron and accumulated lipid peroxide. Recent studies have revealed that ferroptosis is closely related to the occurrence and treatment of cancer. Therefore, this paper reviews the studies on ferroptosis and cancer to explore the potential of ferroptosis in the treatment of malignant tumors, especially digestive system tumors, and to provide a new direction for developing treatment options.

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Key Words: Malignancy; Ferroptosis; Digestive system tumor; Cancer therapy; Resistance

Citation: Li JJ, Xia XP, Wu LM, Zhu Z, Shi YN, Zhang XC, Xia YS, Lu GR. Cancer suppression by ferroptosis and its role in digestive system tumors. Shijie Huaren Xiaohua Zazhi 2022; 30(16): 718-728
URL: https://www.wjgnet.com/1009-3079/full/v30/i16/718.htm
DOI: https://dx.doi.org/10.11569/wcjd.v30.i16.718

摘要

癌症是全球第二大死亡原因, 而消化系统的癌症仍是我国主要的恶性肿瘤, 严重危害国民健康, 带来巨大的经济负担. 铁死亡是以细胞内还原铁增加和脂质过氧化物蓄积为特点的细胞死亡方式, 近年来的研究揭示铁死亡与癌症发生及治疗有着密切联系. 因此本文回顾铁死亡与癌症相关研究, 探讨铁死亡在恶性肿瘤尤其是消化系统肿瘤治疗中的潜力, 为研发新的治疗方案提供新思路.

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关键词: 恶性肿瘤; 铁死亡; 消化系统肿瘤; 肿瘤治疗; 耐药

核心提要: 铁死亡通过促进肿瘤细胞死亡、增强肿瘤对放化疗敏感性、调节肿瘤对免疫治疗的反应等方式发挥抗癌作用, 在消化系统肿瘤中, 铁死亡参与癌症相关基因以及索拉非尼、顺铂等药物调控肿瘤发生发展的过程.

文献来源: 李佳佳, 夏宣平, 吴利敏, 朱正, 史宇宁, 张徐弼, 夏豫珊, 卢光荣. 铁死亡抑癌机制及其在消化系统肿瘤中的研究进展. 世界华人消化杂志 2022; 30(16): 718–728

URL: https://www.wjgnet.com/1009-3079/full/v30/i16/718.htm

DOI: https://dx.doi.org/10.11569/wcjd.v30.i16.718

0 引言

癌症是第二大死亡原因, 是严重威胁人类生命健康的主要疾病之一, 2020年全球估计有1930万新发癌症病例, 近1000万人死于癌症[1]. 我国癌症中心公布的数据显示, 恶性肿瘤死亡占居民全部死因的23.91%, 而其中肝癌、胃癌等起源消化系统的癌症仍是我国主要的恶性肿瘤, 严重危害国民健康, 带来巨大的经济负担[2]. 铁死亡(Ferroptosis)2012年首次由Brent R. Stockwell提出, 以细胞内还原铁蓄积和脂质过氧化物蓄积为特点, 是不同于凋亡、自噬的新型细胞程序性死亡(regulated cell death, RCD)方式[3]. 研究表明[4-6], 铁死亡参与神经病变、缺血再灌注损伤、急性肾功能不全和恶性肿瘤等多种疾病的发生发展, 但其确切的调控机制和生物学功能尚不明确, 现就铁死亡的抑癌机制作一综述, 探讨铁死亡在恶性肿瘤尤其是消化系统肿瘤治疗中的潜力.

1 铁死亡概述

1.1 铁死亡的特点 铁死亡的主要特点是细胞内Fe^{2+}与过氧化物发生芬顿反应(Fenton chemistry)生成羟基自由基或烷氧基自由基等活性氧(reactive oxygen species, ROS), ROS在细胞内蓄积与不饱和脂肪酸(polyunsaturated fatty acids, PUFAs)发生反应形成脂质过氧化物, 而脂质过氧化物又能够在Fe^{2+}催化下生成脂质自由基, 最终导致细胞膜损伤从而诱发细胞死亡. 不同于凋亡、自噬等坏死模式铁死亡具有其独特的表现, 在形态学方面可以观察到线粒体萎缩, 线粒体膜皱缩、破裂, 细胞核正常但缺乏染色质凝集; 细胞代谢方面表现为细胞内亚铁离子和ROS聚集, 发生显著的磷脂过氧化(phospholipid peroxidation, pLPO)、脂质过氧化物修复功能受损[3,7].

1.2 铁死亡的调控机制

1.2.1 System XC--GSH-GPX4通路: 谷氨酸/胱氨酸逆向转运体(glutamate/cystine antiporter, System X_C^-)是位于细胞膜的转运蛋白, 由轻链SLC7A11和重链SLC3A2组成的异二聚体, 其中SLC7A11(又名xCT)是其催化亚基, 能够实现细胞内谷氨酸与细胞外胱氨酸的相互置换[8]. 胱氨酸在细胞内转换为半胱氨酸, 半胱氨酸是内源性谷胱甘肽(glutathione, GSH)合成的原材料之一, 而GSH是一种重要的细胞抗氧化剂, 起到维持细胞氧化平衡的作用, 同时也是激活谷胱甘肽过氧化物酶4(glutathione peroxidase 4, GPX4)所必需的辅助因子[9]. GPX4是一种重要的过氧化物还原酶, 能够清除细胞内蓄积的ROS, 将有毒的脂质过氧化物(LOOH)还原为无毒的脂质醇(L-OH), 保护细胞免受氧化应激反应的伤害[10]. GPX4的功能缺失则会导致细胞内蓄积的ROS无法得到有效的清除, 使蓄积的脂质过氧化物损伤细胞, 最终引起铁死亡. 当System X_C^-受到抑制, 细胞摄取胱氨酸减少, 导致GSH合成减少, 降低细胞内GSH水平, 进而使GPX4失活, 最终引起铁死亡.

1.2.2 NADH-FSP1-CoQ10通路: Conrad团队和Olzmann团队分别通过基因抑制剂和CRISPR-Cas9技术筛选出线粒体相关凋亡诱导因子2(apoptosis-inducing factor mitochondria-associated 2, *AIFM2*)基因, 鉴定为非GPX4依赖的内源性铁死亡抑制因子, 并将其重命名为铁死亡抑制蛋白1(ferroptosis suppressor protein 1, FSP1)[11]. AIFM2最初描述为促凋亡基因, 研究发现FSP1具有NADH依赖的泛醌氧化还原酶活性, 能够利用NADH将泛醌(CoQ_{10})还原为二氢泛醌(CoQ_{10}-H2), 而CoQ_{10}-H2是一种亲脂氧自由基清除剂[12], 进而终止脂质过氧化反应, 在GPX4缺失的情况下抑制铁死亡[11,13].

1.2.3 GCH1-BH4-DHFR通路: Kraft等人[14]通过基因技术筛选出鸟苷三磷酸环水解酶1(GTP cyclohydrolase-1, GCH1), 发现过表达GCH1的细胞株能够抵御GPX4缺失所诱发的铁死亡, 鉴定为独立于GXP4的铁死亡负调控因子. 进一步研究发现作为四氢生物蝶呤(tetrahydrobiopterin, BH4)合成的限速酶, GCH1过表达能够促进内源性BH4的合成, 而BH4本身是一种强效的亲脂氧自由基清除剂, 同时还参与CoQ_{10}前体的合成, 可以促进可以抑制细胞内脂质过氧化, 进而阻止铁死亡发生. 另一团队研究发现[15], 除GCH1外二氢叶酸还原酶(dihydrofolate reductase, DHFR)作为二氢叶酸(dihydrofolate, BH2)合成BH4的关键酶, 能够使氧化的BH4再生, 同样是重要的铁死亡负调控因子.

1.2.4 DHODH-CoQH2通路: 二氢乳清酸脱氢酶(dihydroorotate dehydrogenase, DHODH)是线粒体内膜上的黄素依赖性酶, 参与催化二氢乳清酸氧化为乳清酸.

Mao等人发现[16], 抑制DHODH能够在GPX4低表达的细胞系中诱发线粒体脂质过氧化和铁死亡, 深入研究发现, DHODH能够催化线粒体膜上的CoQ_{10}还原为抗氧化剂CoQH2, 进而抑制铁死亡. 因此, 将DHODH鉴定为独立于GXP4的另一个铁死亡防御因子.

1.3 铁死亡的诱导剂及抑制剂

1.3.1 铁死亡诱导剂: I类诱导剂: 通过抑制System X_C^-减少摄取胱氨酸, 导致GSH合成减少, 细胞内GSH水平下降进而抑制GPX4活性, 诱发铁死亡, 代表药物为Erastin、柳氮磺胺吡啶(sulfasalazine)和索拉非尼(sorafenib). Ⅱ类诱导剂: 是一类小分子物质, 通过与GPX4活性位点结合直接抑制GPX4活性, 导致细胞内脂质过氧化物蓄积, 最终诱发铁死亡, 包括RAS选择性致死蛋白3(RAS-selective lethality protein 3, RSL3)、altretamine等[3,17].

1.3.2 铁死亡抑制剂: 常见的铁死亡抑制剂可分为以下几类: 第一类以去铁胺(deferoxamine, DFO)为代表的铁螯合剂, 通过与细胞内Fe2+结合, 降低细胞内Fe2+水平抑制Fenton反应; 第二类包括Ferrostatin-1(Fer-1)和Liproxstatins, 通过抑制脂质过氧化, 减少细胞内ROS生成, 从而抑制铁死亡发生[18].

2 铁死亡抑制肿瘤的机制研究进展

2.1 铁死亡与肿瘤细胞死亡 正常细胞死亡对维持机体生理平衡和预防过度细胞增殖是至关重要的, 而恶性肿瘤常表现为转化细胞的不受控制地生长和增殖[19], 因此诱发肿瘤细胞死亡是首先被考虑的癌症治疗策略. 目前临床上使用的抗癌药物大多基于凋亡通路诱导癌细胞死亡[20], 但在使用过程中出现的药物抗性性限制了相应药物的使用, 使我们需要寻求新机制诱发癌细胞死亡. 铁死亡作为新发现的细胞程序性死亡模式, 近年来被证实在杀伤肿瘤细胞方面起着关键性作用.

青蒿素是从青蒿中提取的天然化合物, 是一种耐受性良好的抗疟疾药物, 近年来青蒿素及其衍生物在肿瘤治疗方面的应用受到广泛关注, 并被证实对多种肿瘤细胞均具有细胞毒性作用[21]. Ooko等人[22]报道青蒿素衍生物能够在非小细胞肺癌、白血病等多种肿瘤中诱导细胞死亡, 而铁死亡抑制剂能够显著降低青蒿素衍生物的细胞毒性. 青蒿琥酯(artesunate, ART)是青蒿素的半合成衍生物, 有文献报道青蒿琥酯处理后卵巢癌HEY1和HEY2细胞增殖受到抑制, 细胞中ROS水平明显升高, 而铁死亡抑制剂能够降低青蒿琥酯介导的细胞毒性[23]. Markowitsch和Wang团队[24,25]则分别证实ART能够通过诱导铁死亡抑制舒尼替尼耐药的肾细胞癌细胞和Burkitt淋巴瘤细胞的生长, 双氢青蒿素 (dihydroartemisinin, DHA)作为青蒿素衍生物同样被证实能够在胶质瘤细胞中诱导铁死亡依赖的细胞死亡[26].

转录激活因子-4(activating transcription factor 4, ATF4)在氨基酸消耗、氧化应激等因素刺激下表达增加, 研究发现ATF4在肿瘤组织中高表达, 并且能够改善肿瘤细胞在缺氧和营养缺乏的肿瘤微环境中的生存[27,28]. Chen等人[29]发现在胶质瘤细胞中ATF4高表达促进细胞增殖, 而诱导铁死亡可以减弱ATF4促进增殖的效果, 进一步研究发现, 在过表达ATF4的胶质瘤细胞中通过siRNA技术沉默xCT可以抑制细胞增殖, 在敲低ATF的胶质瘤细胞中过表达xCT则能够有效促进细胞增殖, 推测ATF4正是通过靶向调控xCT进而抑制铁死亡从而达到促进胶质瘤细胞的增殖的作用. Bai等人[30]报道MicroRNA-214-3p能够靶向抑制ATF4表达, 进而诱导肝癌细胞发生铁死亡依赖的细胞死亡. 除此之外, Alvarez等[31]证实缺氧环境能够上调铁硫簇生物合成酶(NFS1)的表达, 而NFS1能够保护细胞免于氧化损伤所诱发的铁死亡, 帮助肺腺癌细胞在低氧环境下存活. 上述研究展示了铁死亡在药物、基因调控肿瘤细胞死亡中的作用, 进一步阐释铁死亡调控细胞死亡的机制, 对于研发新的抗癌药物有重大意义.

2.2 铁死亡与肿瘤化学治疗 化疗药物是无法手术的肿瘤病人的主要治疗方式之一, 为改善病人预后做出巨大贡献, 然而在化学治疗过程中肿瘤细胞会对化疗药物产生抵抗性, 这种现象被称为肿瘤的多药耐药性(multidrug resistance, MDR)[32] . MDR的形成可以大致分为两种情况: (1)肿瘤在接受化学治疗之前对该种化疗药物就具有抵抗性, 称为固有抵抗; (2)在有效的化学治疗后, 肿瘤对化疗药物产生了抵抗, 称为获得性抵抗[33]. MDR的发生使得化疗的临床疗效十分受限, 因此研究肿瘤耐药性的产生机制, 寻求减弱药物耐药的方法对提高化疗疗效具有重要意义.

三磷酸腺苷结合基因(ATP-binding cassette subfamily B member 1, *ABCB1*)基因可以编码多种转运蛋白和通道蛋白, 将细胞内的底物主动泵出至细胞外, 从而降低细胞内药物的蓄积[34], 研究表明ABCB1的过表达可以减少细胞内化疗药物的积累, 并导致蒽环类(阿霉素), 长春花生物碱(长春碱)等多种常用化疗药物产生耐药性[35,36]. Zhou[37]等人发现ABCB1的过表达导致卵巢癌对多烯紫杉醇产生耐药性, 而Erastin能够抑制ABCB1的药物外排活性增强过表达ABCB1的卵巢癌细胞对多烯紫杉醇的敏感性. 另外, 研究表明作为铁死亡的关键分子谷胱甘肽(GSH)能够与顺铂的结合形成Pt(GS)2偶联物, 并通过多药耐药相关蛋白(multidrug-resistant-associated proteins, MRPs)转运至细胞外, 降低细胞内顺铂浓度, 从而使细胞

获得顺铂耐药性[38,39]. 在急性白血病、非小细胞肺癌等多种肿瘤中所展开的研究也证实了GSH水平升高是产生顺铂耐药的主要因素[40-42]. Roh团队[43]和Zhang团队[44]通过体内和体外实验同样证实Erastin、柳氮磺吡啶等铁死亡诱导剂或基因敲除xCT能有效诱导细胞发生铁死亡, 增强耐药头颈癌细胞系和舌鳞状细胞癌对顺铂的敏感性, 进一步证实铁死亡与肿瘤耐药之间的潜在联系.

调节细胞内ROS水平也是逆转药物MDR的策略之一[45], Gentric等人[46]通过蛋白质组学、代谢组学和生物遗传分析等技术将高度浆液性卵巢癌(High-grade serous ovarian cancer, HGSOC)分为高氧化磷酸化(high-OXPHOS)和低氧化磷酸化(low-OXPHOS)两个亚群, 并报道high-OXPHOS亚群能够通过增加细胞内ROS和Fe^{2+}水平, 促进脂质过氧化, 增强细胞对卡铂和紫杉醇敏感性, 提示铁死亡可能起到关键作用. 针对多形性胶质母细胞瘤(glioblastoma multiforme, GBM)的研究表明过表达xCT能够调节细胞氧化还原反应, 降低细胞内ROS水平, 从而使GBM细胞对替莫唑胺敏感性下降[47], 而通过铁死亡诱导剂Erastin或基因敲除抑制xCT表达均能够促进细胞ROS生成和谷胱甘肽(GSH)消耗, 从而增强GBM细胞对替莫唑胺的敏感性[47,48], 提示增强铁死亡是克服肿瘤MDR的潜在机制.

2.3 铁死亡与肿瘤放射治疗 放射治疗是癌症治疗的重要方式之一, 广泛应用于肺癌、食管癌、鼻咽癌等多种实体肿瘤的治疗[49], 辐射造成的DNA损伤被认为是放疗的主要作用机制, 而DNA损伤程度和修复速度被认为是决定受辐射细胞死亡的关键因素2, 因此过往放疗抗性的研究主要涉及DNA修复激活和细胞凋亡抑制[50-52]. 除DNA损伤外, 辐射还会引起细胞中的脂质过氧化[53], 随着铁死亡被人们所知, 铁死亡是否介导辐射诱导的细胞死亡, 能否参与放疗抗性调节也引起了广泛关注.

Pan等人[54]发现Erastin联合放疗能够增强放疗对放疗抗性的非小细胞肺癌细胞(non-small cell lung cancer, NSCLC)细胞的杀伤效果, 而铁死亡抑制剂去铁胺(deferoxamine)可以缓解联合治疗诱导细胞死亡, 而凋亡抑制剂和坏死抑制剂则没有这样的效果. Lei等人[55]的研究进一步揭示放射治疗可以通过上调ACSL4表达诱导非小细胞肺癌细胞发生铁死亡依赖的细胞死亡, 同时也能够调控SLC7A11和GPX4表达并抑制放疗所诱导的铁死亡, 进而导致放疗抵抗. 而铁死亡诱导剂(Erastin和RSL3)能够提高耐辐射的癌细胞对放疗的敏感性, 并在动物模型中证实铁死亡诱导剂能够有效增强非小细胞肺癌的放疗敏感性. Ling的团队[56]同样发现铁死亡抑制剂而不是凋亡或坏死抑制剂能够拮抗放疗诱导的细胞死亡, 而铁死亡诱导剂与放疗协同治疗能够增强细胞内脂质过氧化却不增加细胞DNA损伤, 并通过体外细胞模型和体内小鼠移植瘤模型证实铁死亡诱导剂能够增强肺腺癌和神经胶质瘤对放疗的敏感性. 除此之外, Erastin、RSL3和柳氮磺胺吡啶等铁死亡诱导剂还被证实能够增强黑色素瘤、乳腺癌等恶性肿瘤对放疗的敏感性[57-59], 进一步揭示了铁死亡有望成增强放疗敏感性、改善放疗疗效的新方向.

2.4 铁死亡与肿瘤免疫治疗 肿瘤发展的过程中肿瘤细胞能够通过多种方式使人体免疫系统无法正常识别并清除肿瘤细胞, 从而保障肿瘤的生存发展, 这个过程被称为肿瘤免疫逃逸[60]. 免疫治疗就是通过调节免疫系统关键分子, 以恢复免疫系统对肿瘤的正常监视和清除功能[61], 而程序性细胞死亡1(programmed death 1, PD-1)/程序性死亡配体1(programmed death ligand 1, PD-L1)是最经典的免疫治疗靶点[61].

肿瘤免疫治疗可以激活肿瘤微环境的$CD8^+$ T细胞, 并通过穿孔素-颗粒酶和Fas-Fas配体途径诱导细胞死亡来清除肿瘤[62,63]. Wang等人[64]研究表明免疫疗法激活的$CD8^+$T细胞可以通过释放干扰素-γ(Interferon-γ, IFN-γ)下调 SLC3A2和SLC7A11表达, 抑制System X_C^-活性并诱导肿瘤细胞发生铁死亡, 而所诱导的铁死亡又能够增强$CD8^+$ T细胞对肿瘤细胞的损伤. 同时, 他们通过回顾性分析发现xCT表达情况与$CD8^+$ T细胞、IFN-γ水平、免疫治疗疗效等呈负相关, 进一步证实免疫治疗期间$CD8^+$ T细胞促进的肿瘤铁死亡是一种抗肿瘤机制, 是改善肿瘤免疫疗法的潜在靶点[64]. Lang等发现[65]放射治疗诱导的共济失调毛细血管扩张突变基因(ataxia telangiectasia-mutated, ATM)及免疫治疗激活的$CD8^+$T细胞能够协同抑制SLC7A11表达诱导铁死亡发生, 而抑制铁死亡会减低放射治疗及免疫治疗的疗效, 提示铁死亡诱导剂可以增强肿瘤细胞对放射治疗和免疫治疗的敏感性, 同时能够作为两者协同作用的“桥梁”.

3 铁死亡在消化系统肿瘤中的研究进展

根据国际癌症研究结构公布的数据, 来源消化系统的结直肠癌、肝癌、胃癌是2020年全球癌症相关死亡的主要原因, 分别是位于全球癌症死亡病因的第二、第三、第四位[1]. 而在我国, 肝癌、胃癌等起源消化系统的恶性肿瘤仍是主要的恶性肿瘤[2], 研究消化系统肿瘤的发病机制, 寻找新的治疗方案有重大意义. 本文对铁死亡在消化系统肿瘤中的研究进展进行概述(表1), 探讨铁死亡在消化系统肿瘤治疗中的潜力, 为研发新的治疗方案提供新思路.

3.1 肝癌 肝癌是世界范围内癌症相关死亡的前几位原因, 由于慢性丙型肝炎病毒感染、非酒精性脂肪性肝

表 1 铁死亡在消化系统肿瘤中的作用机制

肿瘤类型	作用机制	参考文献
肝癌	Rb可以调节索拉非尼在人肝细胞癌中诱发的铁死亡	[69]
	TP53S47突变使P53对SLC7A11的抑制的作用减弱, 进而抑制铁死亡发生	[70]
	索拉非尼诱导人肝细胞癌发生铁死亡依赖的细胞死亡	[74]
	MT-1G通过抑制铁死亡促进人肝癌细胞产生索拉非尼耐药	[77]
	氟哌啶醇通过促进铁死亡增强索拉非尼对肝癌细胞的细胞毒性作用	[78]
	LDL-DHA处理后人干细胞癌发生铁死亡依赖的细胞死亡	[79,80]
胰腺癌	高表达xCT可以促进胰腺癌增殖和吉西他滨耐药性	[83,84]
	HSPA5通过与GPX4结合抑制铁死亡导致胰腺癌细胞对吉西他滨耐药	[85]
	荜拨酰胺诱导胰腺癌细胞铁死亡依赖的细胞死亡	[86]
	CN-A联合PEITC诱导胰腺癌细胞发生铁死亡依赖的细胞死亡	[87]
胃癌	CAF分泌的miR-522通过抑制铁死亡促进胃癌细胞获得性化疗耐药性	[89]
	线粒体功能障碍通过调节xCT表达增强胃癌细胞对顺铂的耐药	[90]
	过表达CDO1可以增强Erastin诱导的铁死亡	[93]
	SCD1通过抑制铁死亡促进胃癌细胞的增殖能力	[96]
结直肠癌	TP53通过调控SLC7A11转录表达和阻断DPP4抑制结直肠癌细胞发生铁死亡	[98]
	柳氮磺胺吡啶通过抑制xCT增强结直肠癌对顺铂的敏感性	[100]
	RSL3通过抑制GPX4增强顺铂抗结直肠癌的作用	[103]
食管癌	Ori通过抑制GGT1和GCLC诱导食管癌细胞发生铁死亡依赖的细胞死亡	[105]
	异土木香内酯诱导食管癌细胞发生铁死亡依赖的细胞死亡	[106]
	IDH1 R132C突变能够通过靶向调节GPX4增强食管癌细胞对铁死亡的敏感性	[109]

病、饮酒等事件的增多, 肝癌的发病率正在上升, 虽然近年来肝动脉靶向化疗等治疗的开展为肝癌治疗带来显著的变化, 但目前仍缺乏有效的肝癌治疗方案[66].

肝癌的发生发展与抑癌基因失活息息相关, 视网膜母细胞瘤蛋白(retinoblastoma protein, Rb)功能缺失是肝细胞癌(hepatocellular carcinoma, HCC)发生发展过程中的一个重要事件[67,68], Louandre等人[69]发现索拉非尼在低表达Rb的HCC细胞表现出更强的细胞杀伤效果, 同时也诱导更强的铁死亡反应, 提示铁死亡或与低表达Rb的肝癌细胞对索拉非尼更敏感有关. p53是最重要的肿瘤抑制基因之一, Jennis等报道[70]P53密码子第47位丝氨酸(TP53S47)在非洲人中存在多样性, 而S47突变可能增加非裔个体的患癌风险. 与野生型P53相比S47变体表现出显著的顺铂耐药性, 并增加小鼠模型患肝癌的风险, 进一步研究发现S47突变会减弱P53靶向抑制SLC7A11的能力, 进而抑制铁死亡. 上述研究提示, 铁死亡可能是Rb、P53等抑癌基因调控肝癌发生发展的潜在机制.

索拉非尼是一种新型多靶向性抗癌药物, 能够抑制多种激酶的活性, 从而发挥广泛的抗癌作用, 被批准用于晚期肝细胞肝癌的治疗. Lachaier[71]发现索拉非尼能诱导肝癌、胰腺癌等多种癌细胞发生铁死亡且索拉非尼的细胞毒性与铁死亡呈正相关, 而吉非替尼、伊马替尼等10种其他激酶抑制剂却没有显示出铁死亡诱导效应, 进一步研究发现, 索拉非尼可能通过抑制System X_C^-、促进ROS生成发挥独特的诱导铁死亡效应[72,73]. Louandre等[74]使用去铁胺 (deferoxamine, DFX) 消耗细胞内铁储存发现可以通过抑制氧化应激反应保护HCC 细胞免受索拉非尼的细胞毒性作用, 但却不会抑制索拉非尼诱导的细胞凋亡、自噬和激酶阻断活性, 由此证实索拉非尼能够诱导HCC发生铁死亡依赖的细胞死亡. 金属硫蛋白(metallothionein, MT)是一类广泛表达的金属结合蛋白, 近年来被证实与多种癌症的发生发展及耐药性相关, 常作为肿瘤的分子标志物进行研究[75,76]. Sun团队发现[77]索拉非尼同样可以特异性上调MT-1G表达, 而通过基因技术敲低MT-1G, 可以促进HCC细胞内谷胱甘肽消耗和脂质过氧化, 增强索拉非尼诱导的铁死亡, 同时增强HCC细胞以及移植瘤模型对索拉非尼的敏感性. 上述研究提示铁死亡有望成为改善索拉非尼疗效的潜在靶点.

Bai等人报道[78], 氟哌啶醇可以促进Fe2+的积累、脂质过氧化和谷胱甘肽的消耗, 进而增强索拉非尼所诱导的细胞死亡, 而铁死亡抑制剂(ferrostatin-1)可以阻断氟哌啶醇所增强的细胞死亡, 但凋亡和坏死的抑制剂(ZVAD-FMK和necrosulfonamide)却不能, 证明氟哌啶醇能够促进HCC细胞发生铁死亡, 却不会促进细胞凋亡和坏死. Wen和Moss的研究团队报道[79,80]天然omega-3脂肪酸二十二碳六烯酸(LDL-DHA)重组的低密度脂蛋白纳米颗粒可选择性地杀死肝癌细胞并减少大鼠原位肝肿瘤的生长, 而凋亡、自噬和坏死抑制剂都不能阻止LDL-

DHA介导的肝癌细胞死亡. 进一步研究发现, LDH-DHA处理后的HCC细胞中可以捕捉到显著的脂质过氧化物增加、谷胱甘肽消耗和GPX4失活, 提示肿瘤细胞经历了铁死亡依赖的细胞死亡[81], 提示诱导铁死亡是研发新的抗肝癌药物的新思路.

3.2 胰腺癌 胰腺癌是最具侵袭性的恶性肿瘤之一, 因其高侵袭性, 早期转移, 对放化疗反应不佳的特点, 胰腺癌的5年生存率仅有5%左右. 手术和以吉西他滨为主的化学治疗是目前胰腺癌的主要治疗方式, 近年来虽有新的药物用于胰腺癌治疗, 但均不能收获良好的临床疗效[82].

Lo等[83]报道xCT在胰腺癌中表达水平高于正常胰腺组织, 进一步研究发现, 过表达xCT的胰腺癌细胞表现出更强的吉西他滨耐药性, 而xCT特异性抑制剂处理后胰腺癌细胞的生长受到显著抑制, 提示xCT与胰腺癌的增殖能力和耐药性相关. Daher等[84]同样证实不论是通过基因技术敲低还是Erastin等抑制剂预处理来抑制xCT均可以增强胰腺癌细胞对吉西他滨和顺铂的敏感性. Zhu的团队报导[85]热休克蛋白家族A成员5(heat shock 70kDa protein 5, HSPA5)能够与GPX4蛋白结合并抑制其降解, 从而抑制铁死亡的发生. HSPA5或GPX4敲低的PDAC细胞中, 吉西他滨能够诱导更显著的细胞死亡, 而铁死亡抑制剂能够抑制吉西他滨诱导的细胞死亡, 而凋亡和坏死抑制剂则没有这样的效果.

荜拔酰胺(piperlongumine, PL)是一种天然产物, 能够在胰腺癌细胞中能发挥显著的杀伤效果, 且铁死亡抑制剂和铁螯合剂能够抑制PL的细胞毒性, 但不受凋亡抑制剂和坏死抑制剂的影响, 提示PL主要通过增强铁死亡诱导胰腺癌细胞死亡[86]. Cotylenin A(CN-A)是一种髓系白血病细胞分化诱导剂, 在多种癌细胞中均表现出抑癌活性, Takashi等人报道CN-A联合异硫氰酸苯乙酯(PEITC)能够有效抑制胰腺癌细胞增殖, 而ferrostatin-1、liproxstatin和去铁胺作为铁死亡抑制剂均能有效消除了这种协同作用, 自噬抑制能够部分消除, 而凋亡和坏死的抑制剂没有这种效果, 提示CN-A与PEITC主要通过诱导铁死亡发挥抗胰腺癌作用[87]. 上述研究提示, 铁死亡能够在改善吉西他滨等现役药物的疗效或是研发新的抗胰腺癌药物方面作出贡献.

3.3 胃癌 胃癌是全球最常见的癌症之一, 在东亚、东欧和南美洲胃癌的发病率最高, 手术是唯一有可能根治胃癌的方式, 而基于5-氟尿嘧啶(5-FU)或顺铂的化疗是晚期胃癌的患者最有效的治疗方式, 但化疗毒性, 肿瘤耐药性等因素限制了最终疗效[88].

Zhang等[89]报道顺铂和紫杉醇能够激活肿瘤相关成纤维细胞(cancer associated fibro-blasts, CAFs)并分泌外泌体miR-522抑制花生四烯酸脂氧合酶15(ALOX15)活性, 减少细胞内脂质ROS积累, 从而抑制胃癌细胞发生铁死亡, 最终导致化疗敏感性下降. Wang[90]等发现顺铂耐药的胃癌细胞具有xCT高表达, 并通过Kaplan-Meier生存分析发现xCT高表达是胃癌患者辅助化疗的不良预后因素, 进一步研究发现线粒体功能障碍能够增强顺铂耐药性和促进xCT表达, 而抑制xCT活性能够部分逆转胃癌细胞因线粒体功能障碍导致的顺铂耐药性, 进一步证实提示铁死亡可能是胃癌获得性化疗耐药的新机制.

半胱氨酸双加氧酶1(cysteine dioxygenase 1, CDO1)是一种含铁金属酶, 参与半胱氨酸向牛磺酸的转换, 在结直肠癌、胃癌等多种肿瘤中发现CDO1启动子甲基化是肿瘤预后的独立危险因素, 被认为是新发现的抑癌基因[91,92]. Hao[93]等人发现铁死亡诱导剂Erastin在胃癌细胞中能够有效触发铁死亡依赖的细胞死亡, 而敲低CDO1能够有效抑制Erastin诱导的铁死亡和细胞毒性, 而过表达CDO1则有相反的结果, 提示CDO1介导胃癌细胞中铁死亡的调控. 硬脂酰辅酶A去饱和酶1(stearoyl-CoA desaturase 1, SCD1)是一种重要的内质网相关脂肪合酶, 可以促进肺癌、卵巢癌多种癌症的肿瘤发生[94,95]. Wang等[96]报道SCD1在胃癌中高表达, 且是胃癌的独立预后危险因素, 高表达 SCD1提示患者预后不佳, 进一步研究发现SCD1能够促进胃癌在体内、体外的生长和能力并保护胃癌细胞免于铁死亡. 上述研究提示铁死亡可能是CDO1、SCD1等分子的潜在作用机制.

3.4 结直肠癌 结直肠癌(colorectal cancer, CRC)是消化道常见肿瘤之一, 根据国际癌症研究机构公布的数据, 结直肠癌是2020年癌症相关死亡的第二大病因, 甚至超过了肝癌和胃癌, 寻找有效的治疗方案迫在眉睫.

结直肠癌常发生TP53缺失或突变[97], Xie等报道[98] TP53缺失使CRC细胞对Erastin诱发的铁死亡更敏感, 提示TP53能够抑制Erastin所诱导的铁死亡依赖的细胞死亡, 进一步研究发现TP53能够通过调控SLC7A11转录表达和促进二肽基肽酶-4(dipeptidyl peptidase-4, DPP4)入核的双层机制抑制CRC发生铁死亡, 提示抑癌基因TP53可能通过铁死亡参与调控结直肠癌的发生发展.

以铂为基础的化疗广泛应用于各种恶性肿瘤的治疗, 但是耐药性的产生却极大限制了顺铂等药物在临床上的应用, 过去的研究已经证实, 细胞内GSH高水平是产生顺铂耐药的主要因素[40-42]. System X_C^-能够调节胱氨酸的摄取对GSH合成至关重要, 抑制System X_C^-可以抑制细胞内GSH的合成. Sugano等人[99]检测了304例结直肠癌组织标本中xCT蛋白的表达水平, 发现其中208例组织中xCT表达呈阳性, 而这部分患者术后复发风险显著高于xCT表达阴性的患者, 提示xCT表达增加是结直肠癌复发的独立预测因子. 另一研究团队[100] 同样报道了xCT

高表达于结直肠癌组织, 同时他们还发现柳氮磺胺吡啶(Sulfasalazine, SSZ)-xCT的有效抑制剂[101,102], 能够有效消耗CRC细胞内GSH并诱导ROS积累, 但在正常结肠组织中却没有如此显著的效果. 进一步研究发现, SSZ联合顺铂能够显著提高CRC细胞内铂浓度, 与顺铂产生协同的细胞毒性作用. GPX4作为铁死亡的关键调节分子, 同样被发现在结直肠癌等癌组织中的表达高于正常组织, 并且与患者的预后呈负相关, 通过RSL3抑制GPX4可以增强顺铂在体外和体内的抗癌作用[103]. 上述研究揭示, 铁死亡可能是结直肠癌耐药的潜在机制.

3.5 食管癌 食管癌是最具侵袭性的胃肠道恶性肿瘤之一, 尽管目前有手术、放化疗等方式可用于食管癌治疗, 但由于药物副作用等原因上述治疗方式未能收获很好的疗效, 食管癌的5年总生存率仍然很低[104].

萜类化合物是一类具有抗癌作用的天然化合物, Zhang等人报道[105]冬凌草甲素(oridonin, Ori)能够诱导食管癌细胞发生显著的细胞死亡, 同时检测到细胞内Fe^{2+}、丙二醛和ROS水平升高, 而铁死亡抑制剂能够干扰Ori的作用, 说明Ori在食管癌细胞中诱导铁死亡依赖的细胞死亡. 深入研究发现Ori能够抑制γ-谷酰胺转酞酶(gamma-glutamyl transpeptidase 1, GGT1)和谷氨酸半胱氨酸连接酶催化亚基(glutamate cysteine ligase catalytic subunit, GCLC)的活性, 导致GHS合成减少, 降低细胞内GSH水平, 进而抑制GPX4活性, 最终触发铁死亡发挥抗癌活性. 异土木香内酯(Isoalantolactone)同属于萜类化合物, Lu等人[106] 报道异土木香内酯处理后食管癌细胞可以观察到显著的细胞内ROS升高和细胞增殖受抑, 而异土木香内酯对食管癌细胞的细胞毒性能够被凋亡和铁死亡抑制剂逆转. 上述研究提示, 萜类化合物在食管癌中发挥铁死亡依赖的杀伤效果.

异柠檬酸脱氢酶1(isocitrate dehydrogenase 1, IDH1)是三羧酸循环的关键酶, 近年来在胆管癌、骨肉瘤[107,108]等多种恶性肿瘤中均有报道IDH1突变. Wang等人[109]发现$IDH1^{R132C}$突变可以增强Erastin在食管癌细胞中诱导的铁死亡, 进一步研究发现$IDH1^{R132C}$突变能够通过靶向调节GPX4的蛋白质水平增强细胞对铁死亡的敏感性, 提示铁死亡可能是IDH1突变的潜在作用机制.

4 展望

自铁死亡被报道以来就受到了广泛的关注, 并被证实与多种疾病的发生发展具有相关性, 但其确切的调控机制和生物学功能尚不明确, 本文通过回顾铁死亡与肿瘤相关研究, 对铁死亡抑制恶性肿瘤尤其是消化系统肿瘤的机制作一综述. 本如本文所述, 诱导铁死亡能够通过促进肿瘤细胞死亡、增强肿瘤对放化疗敏感性、调节肿瘤对免疫治疗的反应等方式发挥抗癌作用, 然而铁死亡在肿瘤侵袭性、肿瘤能量代谢、肿瘤微环境等方面中的作用还鲜为人知, 有待进一步完善相关研究. 在消化系统肿瘤中, 铁死亡参与TP53、Rb、CDO1等癌症相关基因以及索拉非尼、顺铂、苹拔酰胺等药物调控肿瘤发生发展的过程, 但是上述基因和药物调控铁死亡的具体靶点仍是未知数, 有待从基因突变、表观遗传学等角度进一步研究分析. 总的来说, 作为新发现的细胞程序性死亡方式, 铁死亡展示出强大的抗癌潜力, 深入研究消化道肿瘤中铁死亡的分子机制, 有助于研发新的治疗方式以改善消化道肿瘤的预后.

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科学编辑: 张砚梁 制作编辑: 张砚梁

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton,
CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
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ISSN 1009-3079
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