

胃癌疾病治疗的新策略: 自噬、焦亡、铁死亡 及肿瘤免疫

郭崇元^{1#} 宋冰^{1,2#} 李红恩³ 汪永锋^{1,3} 张琪琪¹ 何锦^{4*}

(¹甘肃中医药大学科研实验中心, 兰州 730000; ²甘肃省实验动物行业技术中心, 兰州 730000;

³甘肃医学院临床医学院, 平凉 744000; ⁴甘肃省人民医院重症医学科, 兰州 730000)

摘要 胃癌作为全球最常见的致死癌之一, 早期诊断率低, 晚期预后较差。尽管化疗有助于改善胃癌患者的生活质量, 但其无法根治疾病。近年来研究发现, 肿瘤微环境(tumor microenvironment, TME)对于胃癌的发展至关重要。而自噬、焦亡、铁死亡与TME中的肿瘤免疫相互作用参与免疫治疗, 其诱导剂能够以与免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)协同作用的方式增强抗肿瘤活性, 因此调节性细胞死亡(regulated cell death, RCD)有望成为胃癌疾病治疗的新靶点。该文先就自噬、焦亡、铁死亡模式进行梳理, 后对自噬、焦亡、铁死亡参与胃癌疾病的内容进行详细的阐述, 最后列举自噬、焦亡、铁死亡相关诱导剂与ICIs协同作用, 以期达到胃癌免疫治疗的目的。

关键词 胃癌; 自噬; 焦亡; 铁死亡; 肿瘤免疫

New Strategies for the Treatment of Gastric Cancer: Autophagy, Pyroptosis, Ferroptosis and Tumor Immunity

GUO Chongyuan^{1#}, SONG Bing^{1,2#}, LI Hongen³, WANG Yongfeng^{1,3}, ZHANG Qiqi¹, HE Jin^{4*}

(¹Gansu University of Chinese Medicine Research and Experiment Center, Lanzhou 730000, China;

²Gansu Provincial Laboratory Animal Industry Technology Center, Lanzhou 730000, China;

³Clinical Medical College of Gansu Medical University, Pingliang 744000, China;

⁴Department of Critical Care Medicine, Gansu Provincial People's Hospital, Lanzhou 730000, China)

Abstract Gastric cancer, as one of the most common fatal cancers worldwide, has a low rate of early diagnosis and a poor prognosis in the advanced stage. Although chemotherapy can improve the quality of life of patients with gastric cancer to some extent, it still cannot completely cure the disease. Recent studies have found that the TME (tumor microenvironment) is crucial for the development of gastric cancer. Autophagy, pyroptosis, ferroptosis and tumor immunity in the TME interact with each other and participate in immunotherapy. Their inducers

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[#]共同第一作者

^{*}通信作者。Tel: 13919219341, E-mail: hejin1978@163.com

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[#]These authors contributed equally to this work

^{*}Corresponding author. Tel: +86-13919219341, E-mail: hejin1978@163.com

can enhance anti-tumor activity in a way that synergizes with ICIs (immune checkpoint inhibitors). Therefore, the combination of RCD (regulated cell death) inducers and ICIs are expected to become new targets for the treatment of gastric cancer. This article first reviews the autophagy, pyroptosis and ferroptosis pathways. Then, it elaborates in detail on the roles of autophagy, pyroptosis and ferroptosis in the progression of gastric cancer. Finally, it lists the synergistic effects of autophagy, pyroptosis and ferroptosis inducers with ICIs, aiming to achieve the goal of gastric cancer immunotherapy.

Keywords gastric cancer; autophagy; pyroptosis; ferroptosis; tumor immunity

胃癌是消化道最常见的恶性肿瘤之一, 2022年全球癌症统计(GLOBOCAN)的最新数据显示, 近年来胃癌的发病率和死亡率虽呈稳步下降趋势, 但其发病率和死亡率都仍居全球常见癌症第5位^[1]。幽门螺杆菌感染、不良饮食习惯、吸烟、喝酒等都可引起慢性非萎缩性胃炎, 进而引起慢性萎缩性胃炎, 随后易出现肠上皮化生、异型增生, 最后发展成为胃癌。对于大多数早期胃癌患者, 最有效的治疗方法就是内镜切除术, 包括内镜黏膜切除术(endoscopic mucosal resection, EMR)和内镜黏膜下剥离术(endoscopic submucosal dissection, ESD); 而对于胃癌晚期患者则通过化疗以及免疫治疗以提高生活质量和延长生存时间, 但少有长期存活者^[2]。

近年来, 随着免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)的出现, 免疫反应作为抗肿瘤治疗的靶点, 肿瘤免疫治疗取得了前所未有的突破。通过封锁免疫检查点的治疗策略近来已兴起, 包括抑制程序性细胞死亡蛋白1(programmed cell death protein 1, PD-1)、PD-L1和细胞毒性T淋巴细胞抗原4(cytotoxic T lymphocyte antigen-4, CTLA-4)等^[3]。根据2018年细胞死亡命名委员会(Nomenclature Committee on Cell Death, NCCD)的建议, 将细胞死亡方式分为调节性细胞死亡(regulated cell death, RCD)和意外细胞死亡(accidental cell death, ACD)^[4]。RCD也称为程序性细胞死亡(programmed cell death, PCD), 包括自噬、焦亡、铁死亡等。近来的研究发现, 诱导RCD是一种新兴的抗癌策略, 能够与肿瘤微环境(tumor microenvironment, TME)中的肿瘤免疫相互作用, 表现出强烈的抗肿瘤免疫反应, 包括自噬、焦亡、铁死亡等^[5-6]。基于此, 本文回顾了自噬、焦亡、铁死亡的分子机制, 以及它们在胃癌中调节肿瘤免疫的作用, 并阐述了靶向诱导剂与ICIs在免疫治疗中的协同作用如何极大增强

抗肿瘤活性, 以期达到治疗胃癌的目的。

1 自噬

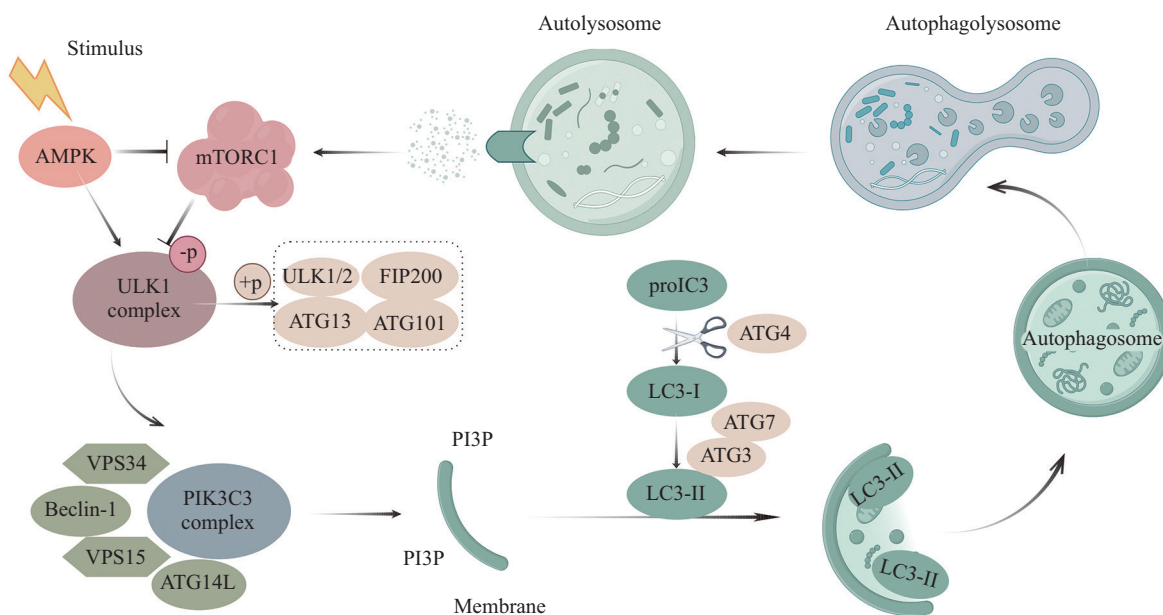
1.1 自噬的概述

自噬是一种进化上高度保守的稳态机制, 受自噬相关基因(autophagy-related gene, ATG)严格调控, 哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)逆向调控自噬^[7]。自噬的起始是由丝氨酸/苏氨酸unc-51样自噬活化激酶(serine/threonine UNC-51-like kinase, ULK)复合物介导的。当细胞缺乏生长因子和氨基酸时, 或是被雷帕霉素刺激的情况下, ULK1能够从mTOR中迅速分离出来并进行去磷酸化。当mTOR复合物1(mTORC1)被抑制或5'-AMP激活的蛋白激酶(5'-AMP-activated protein kinase, AMPK)被激活时, ULK1复合物会进入活性状态^[8]。ULK1复合物由ULK1/2、ATG13、ATG101和FIP200组成, 通过激活III类磷脂酰肌醇3-激酶(class III phosphatidylinositol 3-kinase, PIK3C3)复合物调节自噬体的形成, PIK3C3复合物包括VPS34、Beclin-1、ATG14L和VPS15, 进而生成磷脂酰肌醇3-磷酸(phosphatidylinositol 3-phosphate, PI3P)以作为支架招募PI3P结合分子, 促进吞噬体的成核。在微管相关蛋白轻链3(microtubule-associated protein light chain 3, LC3)修饰过程中, ATG4将前LC3剪切成可溶形式LC3-I, 再在ATG7和ATG3的共同作用下将其共价链与磷脂酰乙醇胺偶联形成脂溶性LC3-II, 进而参与膜的延伸。延伸后, 自噬体的外膜与溶酶体融合, 形成自噬溶酶体, 自噬体内的成分降解后被循环利用^[9]。自噬是一种普遍存在于所有真核细胞中的生物现象, 已被证实人类疾病(包括癌症、心血管疾病、神经退行性疾病等)中发挥重要作用(图1)^[10]。

1.2 自噬在胃癌免疫调节中的作用

自噬作为一把“双刃剑”, 对肿瘤起正向或负向

Autophagy



当AMPK活跃或mTORC1被抑制时, ULK1复合物会转变为活跃状态, 随后激活PIK3C3复合物。通过生成PI3P来募集结合分子, 然后LC3形成LC3-II, 它会整合到自噬体膜上并促进其伸长。最后自噬体的外膜与溶酶体结合, 形成自噬溶酶体。AMPK: 5'-AMP激活的蛋白激酶; mTOR: 哺乳动物雷帕霉素靶蛋白; ULK1: unc-51样自噬活化激酶1; PI3P: 磷脂酰肌醇3-磷酸; LC3: 微管相关蛋白轻链3。-p: 去磷酸化; +p: 磷酸化。

When AMPK is active or mTORC1 is inhibited, the ULK1 complex transitions to an active state, then activate PIK3C3 complex. Binding molecules are recruited by generating PI3P, then LC3 forms LC3-II, which integrates into autophagosomal membranes and promotes their elongation. Finally, the outer membrane of the autophagosome combines with the lysosome, creating an autophagolysosome. AMPK: 5'-AMP-activated protein kinase; mTOR: mammalian target of rapamycin; ULK1: UNC-51-like kinase 1; PI3P: phosphatidylinositol 3-phosphate; LC3: microtubule-associated protein light chain 3. -p: dephosphorylation; +p: phosphorylation.

图1 自噬的分子机制概述(本图由Figdraw绘制, 导出ID: AYPAS3dda4)

Fig.1 Overview of the molecular mechanisms of autophagy (by Figdraw, export ID: AYPAS3dda4)

调节作用, 目前以自噬为目的的肿瘤免疫疗法及其抗肿瘤作用已成为一种前瞻性治疗肿瘤的策略。自噬除了在TME中能够调控肿瘤免疫外, 自噬相关基因已被证实与胃癌的发生发展密切相关。已有研究表明, 自噬相关基因C-X-C趋化因子受体4(C-X-C chemokine receptor type 4, CXCR4)在幽门螺杆菌感染后的胃黏膜组织中表达量增加。CXCR4的表达与巨噬细胞、B细胞显著相关, 而高表达CXCR4诱导胃癌细胞增殖, 使胃癌患者预后不良, 因此CXCR4可以作为预测胃癌患者预后的生物标志物^[11-12]。在一组细胞毒性T淋巴细胞(cytotoxic T lymphocytes, CTL)培养的具有遗传多样化的小鼠癌症模型中筛选了182个核心基因, 发现自噬途径是肿瘤细胞逃避CTL以及对抗细胞因子IFN γ 和肿瘤坏死因子(tumor necrosis factor, TNF)诱导的细胞毒性必要的保守介质。因此, 诱导自噬能够使肿瘤细胞逃避CTL杀伤, 是TME中肿瘤细胞的重要免疫逃避机制^[13]。

一项研究发现, 在胃癌患者中, 微卫星不稳定

性(microsatellite instability, MSI)型胃癌患者生存期优于微卫星稳定性(microsatellite stability, MSS)型患者, PD-L1表达阳性的胃癌患者预后优于PD-L1阴性患者; 并且将自噬诱导剂(PARA)与PD-1/PDL1免疫抑制剂联合使用, 也可以在免疫治疗的基础上通过自噬调节影响肿瘤及免疫细胞代谢, 改变TME以提高临床疗效, 为胃癌临床免疫治疗提供新的靶点^[14]。通过对癌症基因组图谱(the cancer genome atlas, TCGA)中的胃癌基因进行Cox回归分析, 构建自噬相关lncRNA(autophagy-related long non-coding RNA, ARL)预后特征, 发现高危组中单核细胞、M2巨噬细胞、树突状细胞静息和自然杀伤细胞静息的浸润显著增多, 且高危组胃癌患者中的PD-1、PD-L1和PD-L2等免疫检查点基因表达水平明显高于低危组, 证明ARL风险特征是一个独立的预后因素, 能够有效预测胃癌患者的生存率^[15]。由于ICIs的广泛应用, ALEXANDRA等^[16]将FLOT化疗与ICIs联合使用, 发现其对PD-L1阳性的胃癌患者有效, 而PD-L1阳性胃肿瘤表现出自噬激活

和PD-1表达水平降低的状态。因此,结合ARL风险特征与自噬相关分子标志物,有望为胃癌患者提供更有有效的免疫治疗策略。

2 焦亡

2.1 焦亡的概述

焦亡是用来形容促炎程序性细胞死亡的,通常通过激活caspase-1来完成^[4]。在经典焦亡途径和非经典焦亡途径中,caspase-1/4/5/11参与GSDMD(gasdermin D)的切割,在焦亡中发挥着重要的生物学功能^[17-18]。经典焦亡途径依赖被炎性小体激活的caspase-1,当细胞受到不同细菌或蛋白质的刺激时,由病原体相关的分子模式(pathogen-associated molecular patterns, PAMPs)和内源性应激诱导的损伤相关分子模式(damage-associated molecular patterns, DAMPs)启动,形成炎性小体^[19]。炎性小体是应对细胞感染、毒性损伤或细胞内应激而被激活的分子平台,释放白细胞介素-1(interleukin-1, IL-1)家族成员,目前已经鉴定出五种类型的炎性小体: NLRP1、NLRP3、NLRC4、IPAF和AIM2,它们都激活caspase-1^[20]。Caspase-1首先切割GSDMD释放N末端,从而导致焦亡;继而切割和激活促炎细胞因子IL-1 β 和IL-18的前体,这些活性IL-1 β 和IL-18招募炎症细胞,从而放大炎症反应,促进IL-1 β 和IL-18的成熟,并通过焦亡诱导细胞死亡^[21]。此外,在阻断TAK1后,caspase-8-GSDMD也能促使IL-1 β 和IL-18释放到细胞外环境,以浸润免疫细胞炎症微环境^[22]。在非经典焦亡途径中,小鼠的caspase-11和人类的caspase-4/5在细胞质中被激活后,直接与细胞内脂多糖(lipopolysaccharide, LPS)结合,与CARD结构域直接相互作用,激活的caspase-4/5/11切割GSDMD的N-端和C-端结构域,裂解GSDMD,释放HMGB1和K⁺,介导细胞焦亡^[23]。除了GSDMD外,gasdermin家族还有许多其他蛋白质,如GSDMA、GSDMB、GSDMC、GSDME/DFNA5、PJVK/DFNB59/GSDMF。除PJVK外,Gasdermin家族的其他成员,如GSDME,也具有在细胞膜破坏和细胞毒性方面类似的功能,可以通过焦亡引起细胞死亡(图2)^[24-25]。

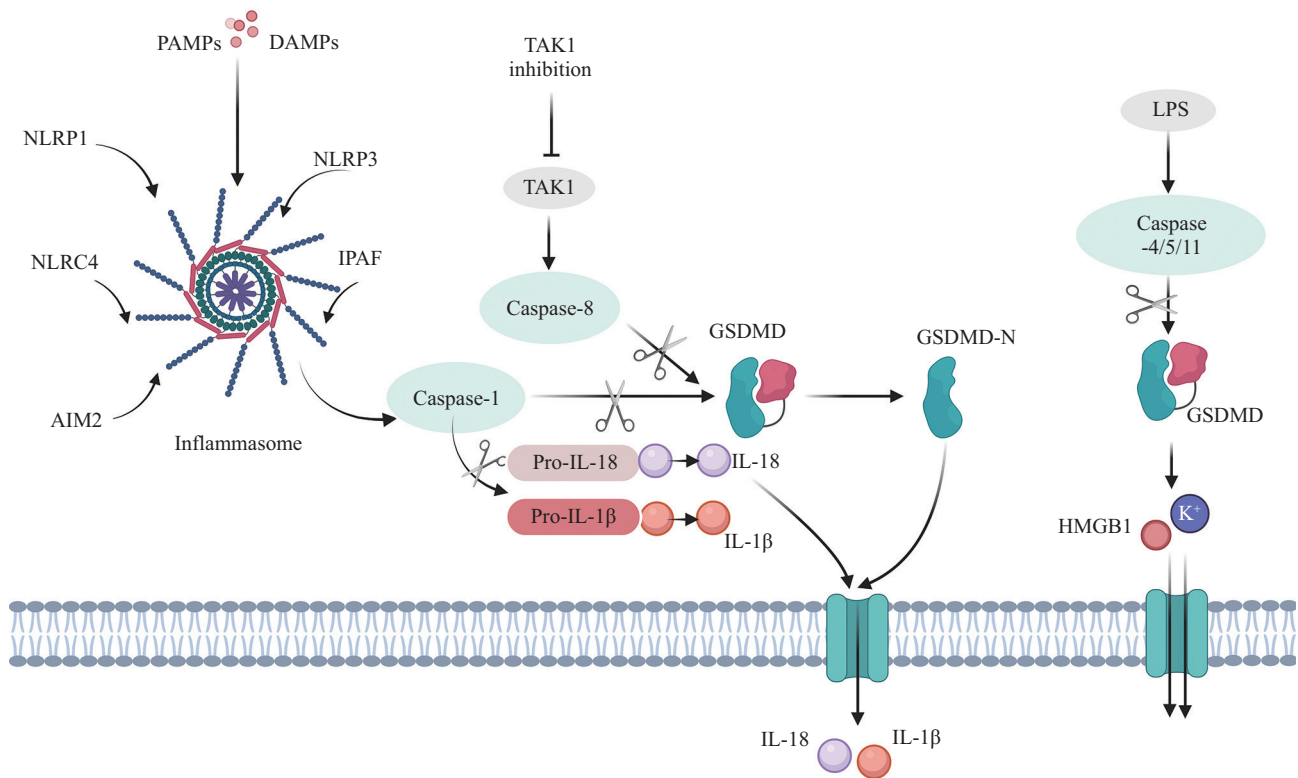
2.2 焦亡在胃癌免疫调节中的作用

焦亡作为一种高度炎症的PCD方式,诱导细胞焦亡可以增强抗肿瘤活性,为胃癌的治疗提供了促进免疫反应的治疗靶点^[26]。幽门螺杆菌感染是胃

癌发病的主要原因。在幽门螺杆菌感染下,NLRP3炎性小体诱导IL-1 β 在巨噬细胞、中性粒细胞和树突状细胞中发育成熟,使得IL-1 β 高度表达,抑制胃酸,从而导致胃萎缩,进一步发展成为胃癌^[27]。此外,十二指肠胃反流也是胃癌的发病原因之一。在人和小鼠DGR模型中,巨噬细胞使泛素特异性肽酶50(ubiquitin-specific peptidase 50, USP50)表达显著上调,USP50与凋亡相关蛋白协同作用以激活NLRP3炎性小体,这为预防十二指肠胃反流相关胃癌提供了新的思路^[28]。研究表明,焦亡风险评分(pyroptosis risk score, PRS)能够作为独立的胃癌生物标志物。对48例接受新辅助免疫治疗和49例接受新辅助化疗的胃癌患者进行PRS,证实低PRS与诱导的焦亡活性增加和CD4⁺T细胞浸润增多相关,并且与肿瘤相关巨噬细胞极化相关,使胃癌患者预后得到改善。焦亡能够诱导TME中的免疫反应,为胃癌患者提供可靠治疗策略^[29]。而对于胃癌中焦亡相关基因的预后进行单因素Cox分析发现,在胃癌高危患者中,巨噬细胞、中性粒细胞和树突状细胞显著浸润,且总生存期更差,证明焦亡相关风险基因能够显著预测胃癌患者预后,已成为胃癌患者预后的独立预测指标^[30]。在胃癌荟萃队列(GSE15459、GSE62254、GSE84437、GSE26253和TCGA-STAD)中提取与预后相关的焦亡基因后,1 275例胃癌患者共建立了三种不同的焦亡表型,根据焦亡评分将患者分为高、低焦亡评分组,发现低焦亡评分患者联合抗PD-1在临床中的获益更多,生存时间更长。这揭示了胃癌中焦亡在TME和免疫调节中的重要作用^[31]。

通过设计碳酸酐酶IX(carbonic anhydrase IX, CAIX)锚定的铈(II)光敏剂(CA-Re),使得在缺氧条件下能够进行光动力疗法,且诱导GSDMD介导的焦亡,提高TME的免疫原性。CA-Re还能促进树突状细胞成熟以及增强其抗原呈递能力,并彻底激活T细胞诱导的适应性免疫反应,从而破坏原发肿瘤以及清除远处肿瘤^[32]。将模拟多酶的共价有机框架(covalent organic frameworks, COFs)用来诱导GADME介导的焦亡,能够重塑TME以促进抗肿瘤免疫,进而促进 α PD-1检查点抑制的反应,防止肿瘤发生转移和复发^[33]。IBI315作为一种靶向PD-1和表皮生长因子受体2(human epidermal growth factor receptor 2, Her2)的双抗体,抗肿瘤作用显著。IBI315能够引起

Pyroptosis



经典的细胞焦亡途径依赖于caspases-1, 并且需要炎症小体的激活。在非经典的细胞焦亡途径中, 脂多糖会直接在细胞质中激活caspases-1/4/5/11。激活后的caspases-1/4/5/11会切割GSDMD-N, 最终引发细胞焦亡。DAMPs: 损伤相关分子模式; PAMPs: 病原体相关的分子模式; IL-1 β : 白细胞介素-1 β ; IL-18: 白细胞介素-18; LPS: 脂多糖。

The classical pyroptosis pathway is caspase-1 dependent and relies on the activation of inflammasomes. In the non-classical pyroptosis pathway, caspases-1/4/5/11 are directly activated in the cytoplasm by LPS. Activated caspase-1/4/5/11 cleave GSDMD-N, finally inducing pyroptosis. DAMPs: damage-associated molecular patterns; PAMPs: pathogen-associated molecular patterns; IL-1 β : interleukin-1 β ; IL-18: interleukin-18; LPS: lipopolysaccharide.

图2 焦亡的分子机制概述(本图由BioRender绘制, 授权码: AP28XYQBEX)

Fig.2 Overview of the molecular mechanisms of pyroptosis (by BioRender, agreement number: AP28XYQBEX)

肿瘤细胞中GSDMB介导的焦亡, 诱导T细胞活化, 进而产生IFN γ , 使GSDMB表达能力增强。GSDMB在Her2阳性胃癌细胞中表达上调, 从而为IBI315治疗Her2阳性胃癌提供基本原理, 疗效显著^[34]。由此可见, ICIs在胃癌患者中的治疗前景显著。KANG等^[35]的研究表明, 高甲基化1(hypermethylated in cancer 1, HIC1)的表达水平在胃癌中显著降低, 而高表达的HIC1能够诱导细胞焦亡。具体来说, GSDMD作为HIC1的下游靶标, HIC1激活后使GSDMD裂解诱发焦亡, 且促进CD8⁺ T细胞的浸润以抵消免疫逃逸反应。研究发现, HIC1过表达与PD-L1抗体联合使用显示出胃癌的协同治疗效果。因此, 焦亡诱导剂与ICIs协同使用具有作为治疗胃癌免疫治疗靶点的潜力。

3 铁死亡

3.1 铁死亡的概述

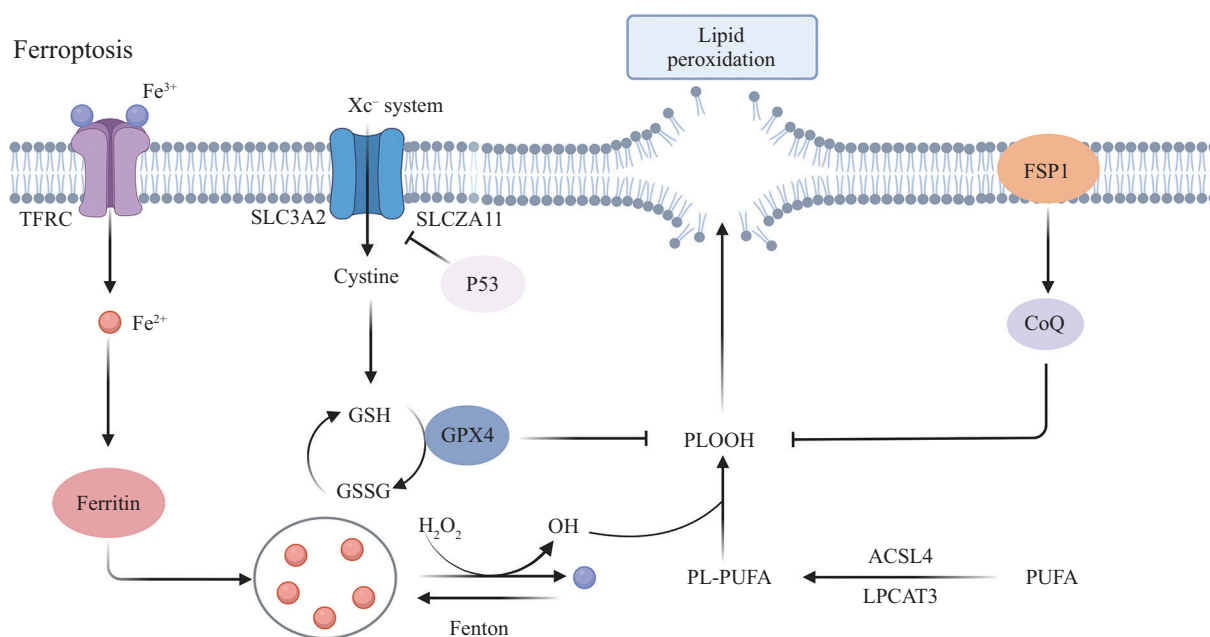
铁死亡是一种铁依赖性细胞死亡方式, 在生物学上表现为脂质过氧化和氧化还原的动态失衡。在生理条件下, 铁以三价铁离子(Fe^{3+})的形式存在, 与转铁蛋白结合后通过其受体(transferrin receptors, TFRC)进入细胞。进入细胞之后的 Fe^{3+} 被迅速还原成二价铁离子(Fe^{2+}), 除形成铁蛋白外, 多余的 Fe^{2+} 在细胞质中大量积累, 形成不稳定铁池(labile iron pool, LIP)。铁池中游离的 Fe^{2+} 通过芬顿反应与 H_2O_2 相互作用将 Fe^{2+} 氧化回 Fe^{3+} , 形成活性氧(reactive oxygen species, ROS)中最具化学活性的物质羟基自由基($\text{OH}\cdot$)。ROS的过度积累, 导致脂质过氧化, 进而诱发铁死亡^[36]。 $\text{OH}\cdot$ 还可以与含细胞膜内磷脂(phos-

pholipid, PL)的多不饱和脂肪酸(polyunsaturated fatty acid, PUFA)的自氧化自由基发生连锁反应,将PL转化为碳中心的脂质自由基(PL[•]),形成连锁反应,继而与Fe²⁺相互作用,引入下一轮PL[•]生成^[37]。谷胱甘肽(glutathione, GSH)和谷胱甘肽过氧化物酶4(glutathione peroxidase 4, GPX4)作为铁死亡的主要调节因子,其抗氧化系统能够阻止脂质过氧化,在抑制铁死亡过程中起到重要作用。铁死亡可以通过抑制GPX4的激活来引发,依赖其还原辅因子GSH和胱氨酸/谷氨酸反向转运蛋白系统Xc⁻^[38]。系统Xc⁻包含两个亚基,即重链溶质载体家族3成员2(heavy chain solute carrier family 3 member 2, SLC3A2)和轻链溶质载体家族7成员11(light chain solute carrier family 7 member 11, SLC7A11)。当系统Xc⁻被破坏时,GSH的合成受限,细胞内抗氧化能力减弱,GPX4不能正常运作,加速脂质过氧化,促进铁死亡^[39-40]。除GPX4外,铁死亡抑制蛋白1(ferroptosis suppressor protein 1, FSP1)也被发现为是一种抗铁氧化因子。FSP1通过肉豆蔻酰化被募集到质膜上,作为氧化还原酶发挥作用,从而还原泛醌-10(coenzyme Q10, CoQ10),辅

酶Q10作为一种亲脂性自由基捕获抗氧化剂,能够阻止脂质过氧化。它作为非线粒体辅酶Q10抗氧化系统,与GPX4的经典通道平行发挥抑制铁死亡的作用^[41]。最近的研究强调,P53在肿瘤抑制中起着重要作用,可抑制SLC7A11和GPX4的表达,从而在肿瘤细胞中诱导铁死亡^[42]。此外,GTP环水合酶1(GTP cyclohydrolase 1, GCH1)通过其代谢衍生物四氢生物蝶呤(tetrahydrobiopterin, BH4)和二氢生物蝶呤(BH2)以调控铁死亡,这是一种独立于GPX4的抗氧化机制(图3)^[43]。

3.2 铁死亡在胃癌免疫调节中的作用

免疫细胞诱导肿瘤细胞铁死亡可提高免疫治疗的抗肿瘤免疫功能,与胃癌之间也有着密切联系,是一种新兴的抗癌机制。一些包括M2型巨噬细胞、髓源性抑制细胞和Tregs细胞在内的免疫抑制细胞,能够通过GPX4高表达拮抗铁死亡,从而来维持细胞的活化。而GPX4缺乏则会导致脂质过氧化物过度积累以及发生铁死亡,IL-1 β 释放增多,以诱导辅助性T细胞17(T helper cell 17, Th17)的抗肿瘤免疫^[44-45]。故诱导铁死亡能够使这些细胞死亡并抑制肿瘤进展。



铁离子通过TFRC进入细胞,并经历一系列反应生成活性氧物质。系统Xc⁻受到抑制,从而抑制了GSH的合成,随后GPX4失去了功能。最终,脂质过氧化加速,诱导铁死亡。GSH: 谷胱甘肽; GPX4: 谷胱甘肽过氧化物酶4; PUFA: 多不饱和脂肪酸; PL: 磷脂。

Fe³⁺ enter the cell through TFRC and undergo a series of reactions to produce ROS. The system Xc⁻ is inhibited, thus limiting GSH synthesis, then GPX4 loses functionality. As a result, lipid peroxidation accelerates, and ferroptosis is promoted. GSH: glutathione; GPX4: glutathione peroxidase 4; PUFA: polyunsaturated fatty acid; PL: phospholipid.

图3 铁死亡的分子机制概述(本图由BioRender绘制,授权码: PA28XR0XTJ)

Fig.3 Overview of the molecular mechanisms of ferroptosis (by BioRender, agreement number: PA28XR0XTJ)

表1 自噬、焦亡、铁死亡的诱导剂综述

Table 1 Summary of inducers of autophagy, pyroptosis and ferroptosis

诱导剂 Inducers	细胞死亡方式 Forms of cell deaths	与ICIs协同作用机制 The mechanism of synergistic action with ICIs	参考文献 References
PARA	Autophagy	In combination with PD-1/PDL1 immune checkpoint inhibitors, change TME	[14]
FLOT	Autophagy	Enhanced expression of LC3B, decreased expression of PD-1; related to PD-L1 positivity	[16]
COF	Pyroptosis	GSDME expression; reconstructing TME and promoting αPD-1 checkpoint inhibition	[33]
IBI315	Pyroptosis	GSDMB expression; inducing T cell activation, combined with PD-1 checkpoint inhibition	[34]
HIC1	Pyroptosis	GSDMD expression; CD8 ⁺ T cell infiltration, combined with PD-L1 checkpoint inhibition	[35]
Simvastatin	Ferroptosis	CD8 ⁺ T cell infiltration; PD-1 and PD-L1 co-immunotherapy	[49-50]

将NK-92细胞株用以人源化异种移植肿瘤小鼠模型中,发现胃癌细胞的IDO产生的L-KYN能够促进NK细胞铁死亡,从而抑制TME中NK细胞的活性,进而发现GPX4水平较高的NK细胞对L-KYN所致铁死亡显示出耐药反应,GPX4高表达的NK-92细胞株或能治疗胃癌,成为胃癌免疫治疗新策略^[46]。分析胃癌样本中铁死亡相关基因TCGA-STAD数据集显示,有效干预lncRNAs和铁死亡相关基因能够诱导胃癌患者的CD4⁺ T细胞活化,进而促进肿瘤免疫治疗,是胃癌的免疫治疗的新靶点^[47]。将406例胃癌患者根据风险评分分为高风险组和低风险组各203例,并基于12个铁死亡相关可变剪接事件预测风险评分,结果显示,在PD-1阴性CTLA-4阳性、PD-1阳性CTLA-4阴性和PD-1阴性CTLA-4阴性组别中,低风险组呈现免疫激活特征,预后显著改善,在免疫治疗中更能获益^[48]。

在胃癌的治疗中,免疫疗法作为有前景的治疗方法仍然充满挑战。研究表明,他汀类药物可以降低胃癌患者体内白细胞介素增强结合因子3(interleukin enhancer binding factor 3, ILF3)和PD-L1水平。Simvastatin通过抑制胃癌细胞中的ILF3以诱导铁死亡,具体来说,使ILF3的残基位点H3K14的乙酰化水平下调从而抑制ILF3。ILF3还可以通过DEPTOR/mTOR信号通路调节PD-L1表达,从而促进协同免疫治疗^[49]。Simvastatin作为一种胆固醇合成抑制剂,能够抑制胃癌细胞生长和转移,以及诱导铁死亡。在荷瘤小鼠中, simvastatin能够使CD8⁺ T细胞数量增加以调节TME, 诱导MSS胃癌患者铁死亡,同时与PD-1免疫检查点阻断治疗协同发挥抗肿瘤作用,成为免疫检

查点阻断治疗的新兴疗法^[50]。表1总结了自噬、焦亡、铁死亡诱导剂与ICIs的协同作用机制。

4 自噬、焦亡和铁死亡之间的交互作用

研究发现, ATG5介导的自噬可以通过降解NLRP3以抑制NLRP3炎性小体的激活,从而逆向调控焦亡,防止发生过度的炎症反应^[51]。在ROS依赖性铁死亡中,自噬由ROS触发,导致铁积累和脂质过氧化,进而诱导自噬性细胞死亡^[52]。铁死亡细胞释放的DAMPs是启动炎症反应的关键介质,其引发的氧化微环境还可以激活免疫细胞中的NLRP3炎性小体,进而激活caspase-1,促进IL-1β等细胞因子的成熟、释放,协同放大炎症^[53]。

镓镁层状双氢氧化物(MG-LAAO)通过启动caspase-1/GSDMD和caspase-3/GSDME通路诱导肿瘤细胞焦亡,释放Ga³⁺诱导线粒体铁超载,导致铁死亡。此外, MG-LAAO还可以抑制肿瘤细胞自噬,重塑免疫抑制TME,从而避免免疫逃逸,产生强大的抗肿瘤免疫反应,为自噬、焦亡、铁死亡和肿瘤免疫多网络协同调节提高肿瘤免疫治疗提供了新思路^[54]。

5 小结与展望

本文基于实验室研究和临床研究,介绍了RCD的分子机制及其与胃癌之间的相互作用。胃癌作为难治性恶性肿瘤,与肿瘤免疫关系密切, ICIs作为一种免疫治疗方法在癌症中广泛应用,而自噬、焦亡、铁死亡等作为广泛的RCD形式,被认为是胃癌的潜在治疗策略。在胃癌治疗中,诱导细胞死亡可以增

强TME抗肿瘤免疫反应,以及在胃癌的发展、侵袭、转移与免疫逃逸方面都发挥重要作用。随着越来越多的细胞死亡诱导剂被开发出来,其抗肿瘤作用极大增强,将RCD诱导剂与ICIs联合使用成为一个新兴治疗靶点,从而提高临床疗效,为胃癌免疫治疗提供了新思路。此外,TME中不同的细胞类型,如巨噬细胞、NK细胞、T细胞等与自噬、焦亡、铁死亡等相互作用,能够通过肿瘤免疫调控肿瘤进展。自噬、焦亡、铁死亡在胃癌TME中的具体机制尚不清楚,因此,后续应积极开展联合治疗的临床试验,确保其治疗效果和安全性,为今后更深的研究提供更好的参考价值,以阐明RCD形式在胃癌中的意义、深入发展胃癌免疫治疗,改善更多胃癌患者的预后。

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