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铁死亡

·专题报道·

铁死亡调控肝细胞癌及其肿瘤免疫研究进展

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［摘　要］ 铁死亡是一种依赖铁代谢失衡并以脂质过氧化为特征的调控性细胞死亡形式，在多种病理过程中发挥关键作用。研究表明，铁死亡的发生与肝细胞癌（HCC）的进展密切相关。铁死亡参与调控HCC的脂质代谢、铁离子稳态、线粒体代谢和氧化还原过程，在HCC肿瘤免疫中发挥着关键作用。铁死亡通过调节免疫微环境中不同细胞的表型和功能影响肿瘤的免疫逃逸和进展；铁死亡诱导的脂质过氧化物和氧化应激能促进M1型巨噬细胞的极化，增强肿瘤的促炎反应，同时抑制髓源性抑制细胞和调节性T细胞等免疫抑制细胞的功能，从而破坏免疫抑制；铁死亡相关分子如谷胱甘肽过氧化物酶4、溶质载体家族7成员11等的表达调控不仅影响肿瘤细胞对免疫治疗的敏感性，也直接作用于T淋巴细胞、树突状细胞等效应细胞的活性和生存，进一步增强或减弱抗肿瘤免疫反应。靶向铁死亡在HCC治疗中展现了重要的临床潜力，通过纳米医学和分子靶向策略诱导铁死亡，不仅直接杀伤肿瘤细胞，还能增强抗肿瘤免疫反应。结合免疫治疗的多模式疗法进一步拓展了铁死亡的应用。本文尝试从代谢调控和免疫细胞调节角度，探讨铁死亡在HCC进展中的作用，以期为开发基于铁死亡调控的综合抗肿瘤治疗策略提供新思路。

［关键词］ 肝细胞癌；铁死亡；肿瘤免疫；免疫微环境；免疫疗法；综述
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Research progress on ferroptosis regulation in tumor immunity of hepatocellular carcinoma

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[**Abstract**] Ferroptosis is a form of regulated cell death, which is dependent on iron metabolism imbalance and characterized by lipid peroxidation. Ferroptosis plays a crucial role in various pathological processes. Studies have shown that the occurrence of ferroptosis is closely associated with the progression of hepatocellular carcinoma (HCC). Ferroptosis is involved in regulating the lipid metabolism, iron homeostasis, mitochondrial metabolism, and redox processes in HCC. Additionally, ferroptosis plays a key role in HCC tumor immunity by modulating the phenotype and function of various immune cells in the tumor microenvironment, affecting tumor immune escape and progression. Ferroptosis-induced lipid peroxidation and oxidative stress can promote the polarization of M1 macrophages and enhance the pro-inflammatory response in tumors, inhibiting immune suppressive cells such as myeloid-derived suppressor cells and regulatory T cells to disrupt their immune suppression function. The regulation of expression of ferroptosis-related molecules such as GPX4 and SLC7A11 not only affects the sensitivity of tumor cells to immunotherapy but also directly influences the activity and survival of effector cells such as T cells and dendritic cells, further enhancing or weakening host antitumor immune response. Targeting ferroptosis has demonstrated significant clinical potential in HCC treatment. Induction of ferroptosis by nanomedicines and molecular targeting strategies can directly kill tumor cells or enhance antitumor immune responses. The integration of multimodal therapies with immunotherapy further expands the application of ferroptosis targeting as a cancer therapy. This article reviews the relationship between ferroptosis and antitumor immune responses and the role of ferroptosis in HCC progression from the perspective of tumor immune microenvironment, to provide insights for the development of antitumor immune therapies targeting ferroptosis.

[**Key words**] Hepatocellular carcinoma; Ferroptosis; Tumor immunity; Immune microenvironment; Immunotherapy; Review

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[**缩略语**] 肝细胞癌(hepatocellular carcinoma, HCC);程序性死亡配体(programmed death-ligand, PD-L);谷胱甘肽过氧化物酶(glutathione peroxidase, GPX);核富集非编码转录本(nuclear paraspeckle assembly transcript, NEAT);钙黏附蛋白β14(protocadherin beta 14, PCDHB14);溶质载体家族(solute carrier family, SLC);3-羟基-3-甲基戊二酰辅酶A裂解酶(3-hydroxy-3-methylglutaryl-coA lyase, HMGCL);信号转导及转录激活因子(signal transducer and activator of transcription, STAT);激活STAT蛋白抑制因子(protein inhibitor of activated STAT, PIAS);转化生

长因子（transforming growth factor，TGF）；硬脂酰辅酶A去饱和酶（stearoyl-CoA desaturase，SCD）；白血病抑制因子受体（leukemia inhibitory factor receptor，LIFR）；乙型肝炎病毒X交互蛋白（hepatitis B virus X interacting protein，HBXIP）；无精子症相关蛋白（deleted in azoospermia associated protein，DAZAP）；乙型肝炎病毒X蛋白（hepatitis B virus X protein，HBx）；分化抗原（cluster of differentiation，CD）；酰基辅酶A合成酶长链家族（acyl-CoA synthetase long-chain family，ACSL）；程序性死亡（programmed death，PD）；跨膜蛋白（transmembrane protein，TMEM）；髓源抑制性细胞（myeloid-derived suppressor cell，MDSC）；多形核-髓源性抑制细胞（polymorphonuclear-myeloid-derived suppressor cell，PMN-MDSC）；Mer酪氨酸激酶受体（Mer tyrosine kinase，MerTK）；激活转录因子（activating transcription factor，ATF）；三结构域蛋白（tripartite motif，TRIM）

HCC是最常见的原发性肝癌类型，占肝癌病例的75%~85%[1]。早期HCC可通过手术切除、肝移植和局部消融等治疗获益[2-3]，晚期HCC可采用经导管动脉化疗栓塞、肝动脉灌注化疗和介入治疗，但治疗后复发率仍较高[4-9]。近年来，靶向治疗联合免疫疗法在改善HCC患者预后方面取得一定进展[10-11]，目前已获批的药物有PD-L1和表皮生长因子受体抑制剂[12-13]。

HCC肿瘤微环境的复杂性对治疗效果有一定影响[14-15]。研究表明，铁死亡与肿瘤发展密切相关，对其进行调控可抑制HCC细胞增殖，并可在一定程度上增强免疫治疗、化学治疗和放射治疗的效果[16-19]。但HCC细胞可通过强化抗氧化机制逃避铁死亡，以维持其增殖和治疗耐受性[20-23]。本文从代谢调控和免疫细胞调节角度探讨了铁死亡在HCC肿瘤进展中的作用及临床应用潜力，为开发基于铁死亡调控的HCC治疗策略提供理论支持。

1 铁死亡在肿瘤中的分子生物学过程及其在肝细胞癌进展中的作用

铁死亡在肿瘤中的分子生物学过程分为通过抑制胱氨酸/谷氨酸转运蛋白或激活运铁蛋白启动的外源性途径[24-26]和通过抑制抗氧化酶（如GPX4）激活的内源性途径[27]。其发生源于驱动因素（如多不饱和脂肪酸-磷脂过氧化、铁及线粒体代谢）与防御系统（如GPX4-谷胱甘肽、铁死亡抑制蛋白1-二氢辅酶Q、二氢乳酸脱氢酶-二氢辅酶Q和鸟苷三磷酸环化酶1-四氢生物蝶呤系统）之间的失衡[28-31]。当驱动因素超过防御系统的解毒能力时，铁死亡即被触发。

在HCC中，铁死亡相关基因在肿瘤与邻近非肿瘤组织中表达差异显著，并与患者临床特征密切相关[32-34]。基于这些基因表达谱构建的模型能够独立预测HCC患者的预后[34-35]。其中，P53通过调控NEAT1/miR-362-3p/MIOX轴，增加亚铁离子、谷胱甘肽和还原型烟酰胺腺嘌呤二核苷酸磷酸水平，诱导脂质过氧化，从而引发铁死亡，抑制肝癌细胞生长[36]；PCDHB14通过抑制SLC7A11增强铁死亡效应，从而抑制肿瘤作用[37]；氯转运蛋白CLTRN表达下调与较差预后相关，但其上游因子核转录因子红系2相关因子1通过激活铁死亡从而抑制HCC发展[38]；谷氨酰胺酶2通过调节铁死亡机制在HCC中发挥保护作用[39]；HMGCL通过调控二肽基肽酶4的表达促进铁死亡，抑制肿瘤细胞的增殖及转移[40]；PIAS3通过PIAS3/TGF-β/TXNIP轴驱动铁死亡信号，限制HCC的进展[41]。

另一方面，肝癌细胞也通过多种途径抑制铁死亡。在脂质代谢中，乳酸通过HCAR1/MCT1-SREBP1-SCD1途径促进单不饱和脂肪酸合成，抵抗脂质过氧化的影响[42]。在铁稳态方面，LIFR表达下调通过激活NF-κB信号通路上调铁螯合因子脂质运载蛋白2，减少亚铁离子的积累，降低铁死亡的敏感性[43]；TEA域转录因子2上调抑制亚铁离子积累和脂质过氧化反应[44]。在线粒体代谢与氧化还原调控中，烯醇化酶1通过抑制铁调节蛋白1 mRNA降解阻止铁死亡发生，促进肿瘤发展[45]。而铁死亡抑制分子HBXIP的下调导致谷胱甘肽耗竭，调节铁死亡发生[46]。此外，DAZAP1调控铁死亡相关SLC7A11/GPX4通路抑制铁死亡[47]。HBx蛋白通过HBx/PRMT9/HSPA8/CD44

轴抑制铁死亡,加速HCC恶化[48]。

综上,在HCC的铁死亡调控中,不同因子构成复杂的网络,发挥促进或抑制作用,见表1。铁死亡相关分子的多维度调控为HCC的病理机制研究提供了重要线索,同时为HCC提供了潜在的治疗策略。

表1 肝细胞癌中的铁死亡调控分子及其调控机制

Table 1 Ferroptosis-regulating molecules in hepatocellular carcinoma

分 子	调控下游分子与通路的机制	促进或抑制铁死亡
NEAT1[36]	p53/NEAT1/miR-362-3p/MIOX/Fe^{2+}	促进
PCDHB14[37]	RNF182/p65/SLC7A11	促进
CLTRN[38]	NRF1/CLTRN/SLC7A11	促进
GLS2[39]	SLC7A11	促进
HMGCL[40]	β-OHB/H3K9/DPP4	促进
PIAS3[41]	PIAS3/TGF-β/TXNIP	促进
乳酸[42]	HCAR1/MCT1-SREBP1-SCD1	抑制
LIFR[43]	NF-κB/LCN2/Fe^{2+}	抑制
TEAD2[44]	Hippo/TEAD2/Fe^{2+}	抑制
ENO1[45]	ENO1/IRP1/Mfrn1	抑制
HBXIP[46]	谷胱甘肽	抑制
DAZAP1[47]	SLC7A11/GPX4	抑制
HBx[48]	HBx/PRMT9/HSPA8/CD44	抑制

NEAT:核富集非编码转录本;miR:微RNA;MIOX:髓质肾髓醇氧化酶;PCDHB14:钙黏附蛋白β14;RNF:环指蛋白;SLC7A11:溶质载体家族7成员11;CLTRN:阳离子样转运蛋白;Nrf:核转录因子红系2相关因子;GLS:谷氨酰胺酶;HMGCL:3-羟基-3-甲基戊二酰辅酶A裂解酶;OHB:羟基丁酸;H3K9:组蛋白3赖氨酸9;DPP:二肽基肽酶;PIAS:激活STAT蛋白抑制因子;TGF:转化生长因子;TXNIP:硫氧还蛋白相互作用蛋白;HCAR:羟基羧酸受体;MCT:单羧酸转运蛋白;SREBP:固醇调节元件结合蛋白;SCD:硬脂酰辅酶A去饱和酶;LIFR:白血病抑制因子受体;NF-κB:核因子κB;LCN:脂质运载蛋白;TEAD:TEA域转录因子;ENO:烯醇化酶;IRP:铁调节蛋白;Mfrn:线粒体铁转运蛋白;HBXIP:乙型肝炎病毒X交互蛋白;DAZAP:无精子症相关蛋白;HBx:乙型肝炎病毒X蛋白;PRMT:蛋白质精氨酸甲基转移酶;HSP:热休克蛋白;CD:分化抗原.

2 免疫细胞铁死亡在肝细胞癌进展中的作用

2.1 $CD8^+$ T细胞通过铁死亡增强抗肿瘤活性

作为主要的抗肿瘤免疫效应细胞,$CD8^+$ T细胞通过释放穿孔素、颗粒酶B和激活Fas/FasL通路诱导肿瘤细胞程序性死亡,从而抑制肿瘤进展[14]。在HCC患者中,免疫检查点抑制剂通过激活$CD8^+$ T细胞发挥抗肿瘤效应,其疗效与$CD8^+$ T细胞功能密切相关,因此解析其机制对优化疗效至关重要[49]。研究显示,当铁死亡通路被阻断时,肿瘤对免疫治疗的敏感性降低[50]。进一步研究发现,活化的$CD8^+$ T细胞能够释放γ干扰素,进而通过JAK/STAT通路下调肿瘤细胞膜上胱氨酸转运系统Xc^-的关键亚基SLC3A2和SLC7A11的表达,使肿瘤细胞对铁死亡更为敏感[51];γ干扰素还能与花生四烯酸发生协同作用,通过上调ACSL4促进肿瘤细胞膜脂质重新编程,进一步增强肿瘤细胞的铁死亡反应[52]。此外,活化的$CD8^+$ T细胞还能通过提高肿瘤细胞内脂质过氧化水平来诱导铁死亡[50]。

但是,肿瘤微环境中的高脂环境可能导致$CD8^+$ T细胞本身铁死亡易感性增加,从而影响其抗肿瘤活性。$CD8^+$ T细胞表面CD36吸收氧化低密度脂蛋白,激活脂质过氧化过程,导致铁死亡发生并削弱其效应功能。阻断CD36或直接抑制T淋巴细胞铁死亡有助于提高其功能,特别是与PD-1抑制剂联合使用时能显著增强抗肿瘤效果[53]。此外,过表达GPX4能有效抑制脂质过氧化,减轻铁死亡发生,从而部分恢复$CD8^+$ T细胞的抗肿瘤功能[54]。

2.2 调节性T细胞通过自身铁死亡机制调节肿瘤免疫逃逸

调节性T细胞是$CD4^+$ T细胞的免疫抑制亚群,负责维持免疫稳态和自身耐受[55]。但在HCC中,调节性T细胞通过抑制肿瘤特异性免疫反应支持肿瘤进展,呈现出“双刃剑”效应。STAT3调控PD-L1,并对调节性T细胞的铁死亡保护基因*GPX4*进行调节[56-57]。GPX4缺失会导致调节性T细胞内脂质过氧化和铁死亡,在抑制肿瘤生长的同时避免诱发自身免疫,为癌症治疗提供新的策略[56]。另外,调节性T细胞的铁死亡调控还涉及SLC7A11、铁蛋白重链1等STAT3通路中的重要分子[58],并在低氧条件下受到*EGLN1*等基因的调节[59]。长链非编码RNA LINC00942通过增强SLC7A11 mRNA稳定性抑制铁死亡,进一步促进调节性T细胞的免疫抑制功能[60]。

2.3 肿瘤相关巨噬细胞通过铁死亡调控促炎和抗炎反应

肿瘤相关巨噬细胞主要由外周血单个核细胞分化而来,进入肿瘤后在特定微环境信号的引导下呈现不同表型[61]。根据功能和分泌的细胞

因子，肿瘤相关巨噬细胞通常分为M1型（激活型）和M2型（抑制型）巨噬细胞，分别在促进或抑制炎症反应中发挥作用[62]。研究表明，铁死亡能够提高M1型巨噬细胞标志物的表达、降低M2型巨噬细胞标志物的水平，从而促进M1型巨噬细胞极化，加剧肝脏的炎症反应和纤维化过程[63]。这种极化转变与铁死亡诱导的活性氧生成及P53乙酰化有关[64]。此外，抑制载脂蛋白C1可以通过铁死亡途径促进M2型巨噬细胞向M1型转化，重塑肿瘤免疫微环境，进而增强抗PD-1免疫疗法的效果[65]。单细胞测序进一步揭示了铁死亡相关分子SLC40A1高表达与肿瘤相关巨噬细胞的促炎和免疫调节功能之间的关联，敲低*SLC40A1*水平会影响巨噬细胞分泌的细胞因子谱，尤其是通过调节IL-1β生成来调控肿瘤炎症状态[66]。此外，有研究显示HCC患者的内质网膜中TMEM147表达上调与患者低存活率和免疫浸润相关，提示TMEM147可以作为HCC潜在的预后标志物[67-68]。进一步研究发现，TMEM147通过与7-脱氢胆固醇还原酶相互作用诱导铁死亡抵抗和M2型极化，促进肿瘤进展[69]。

2.4 MDSC通过铁死亡诱导免疫抑制

MDSC可通过产生血管内皮生长因子、TGF-β和精氨酸酶等因子有效抑制T淋巴细胞的活化[70]，还可通过与NKp30受体相互作用抑制NK细胞的功能[71]。在肿瘤微环境中，PMN-MDSC是抗肿瘤免疫的主要负调节因子，铁死亡诱导PMN-MDSC自发性死亡的同时释放氧合脂质，直接抑制T淋巴细胞的活性，从而增加免疫抑制[72]。在HCC患者中，MDSC增多与患者预后差和免疫治疗耐药紧密相关[73]。Pam3CSK4（Toll样受体1/2激动剂）靶向Runx1等铁死亡通路，促使MDSC向树突状细胞和巨噬细胞转变，从而抑制肝癌细胞的生长[74]。此外，MerTK通过整合糖酵解和氧化磷酸化调控HCC生长，其上调SLC7A11抑制肿瘤铁死亡，同时通过招募MDSC增强免疫抑制，导致抗PD-L1治疗耐药性[75-76]。

2.5 NK细胞铁死亡的抗肿瘤潜力

NK细胞是先天免疫系统的关键组成部分，是抵御病毒感染和肿瘤细胞的第一道防线[77]。与传统的T淋巴细胞不同，NK细胞无需识别特定抗原即可被肿瘤细胞表面的配体激活，具备广谱杀伤肿瘤细胞的能力，同时对自身正常细胞无害。研究显示，NK细胞通过释放大量穿孔素和颗粒酶等细胞因子，促进肿瘤坏死因子α等促凋亡因子的表达，从而引起肿瘤细胞的凋亡和坏死[77]。肝脏中含有大量低反应性NK细胞，这是肝脏耐受性的基础，使肝脏能够暴露于肠道来源的外源性抗原而不引发炎症。而驻留在肝脏的NK细胞以记忆细胞群形式存在，并通过产生γ干扰素发挥细胞毒性作用[78]。在HCC中，肿瘤相关巨噬细胞通过高表达CD48与NK细胞的2B4受体相互作用，导致NK细胞快速激活后迅速衰竭和死亡，这可能是肝癌逃避免疫监视的一种机制[79]。尽管尚未明确NK细胞是否会直接经历铁死亡，但在脓毒症相关研究中发现，铁死亡相关基因在肝衰竭模型中高表达，并可能通过B淋巴细胞和NK细胞促使肝衰竭的发展[80]。

2.6 树突状细胞在铁死亡影响下的抗原提呈作用

树突状细胞是体内功能最强的抗原提呈细胞，能刺激初始T细胞增殖，是免疫应答的始动者，在免疫诱导中占据独特地位[81]。在HCC中，缺氧诱导因子-1α高表达帮助肿瘤适应低氧环境，同时伴随一系列免疫调节变化，如CD47过表达。CD47过表达与$CD103^+$树突状细胞数和NK细胞数减少相关，通常预示不良预后，提示树突状细胞在HCC发展中占据重要作用[82]。此外，肿瘤细胞早期铁死亡阶段会影响树突状细胞的成熟和功能。树突状细胞吞噬铁死亡的肿瘤细胞后，其在适应性免疫应答中的作用尤其是抗原交叉提呈功能可能受到抑制，这对于激活有效的抗肿瘤免疫反应至关重要[83]。

综上所述，铁死亡可通过调节免疫微环境中不同细胞的表型和功能影响肿瘤的免疫逃逸和进展。一方面，铁死亡诱导的脂质过氧化物和氧化应激不仅能促进M1型巨噬细胞的极化，增强抗肿瘤的促炎反应，还可能抑制MDSC和调节性T细胞等免疫抑制细胞的功能，从而打破免疫抑制。另一方面，铁死亡相关分子如GPX4、SLC7A11等表达调控不仅影响肿瘤细胞对免疫治疗的敏感性，也直接影响T淋巴细胞、树突状细胞等效应细胞的活性，进一步增强或减弱抗肿瘤免疫反应。这些机制揭示了铁死亡在调节HCC肿瘤免疫中的多层次作用，为优化免疫治疗策略、克服治疗耐药性提供了新的研究方向。

3 靶向铁死亡在肝细胞癌治疗中的应用

靶向铁死亡在HCC治疗中具有重要的临床应用前景(表2)。纳米医学方面,碳量子点通过耗竭谷胱甘肽和增加活性氧诱导铁死亡不仅直接杀死肿瘤细胞,还能招募免疫细胞激活抗肿瘤免疫[84,89]。另一种纳米粒则结合了氯化血红素和免疫抑制阻断剂,通过诱导铁死亡并减少免疫抑制效应,增强免疫反应[90]。基于铁死亡/焦亡双感应的纳米系统Tf-LipoMof@PL通过降低谷胱甘肽水平和抑制GPX4进一步推动了联合免疫治疗的发展[85]。肝癌恶性腹水的治疗效果并不理想,一种基于氧化葡聚糖CH-OD的载柳氮磺吡啶水凝胶可在腹水模型中显著抑制HCC进展,并在PD-1抗体的联合下显著提升治疗效果[86,91]。

在分子靶向药物和多靶治疗方面,由铁死亡、细胞凋亡和免疫激活驱动的HCC多模式疗法揭示了铁死亡协同癌症治疗的巨大潜力[92]。Fe-MnO_2/DHA纳米药物结合免疫治疗可诱导铁死亡、刺激肿瘤坏死并增强T淋巴细胞浸润,展现了协同抗肿瘤效果[87];酪氨酸激酶抑制剂联合SCD1抑制剂在野生型p53的HCC中表现出潜力,通过调节脂质代谢提高了对铁死亡的敏感性[93];ATF4通过调控谷胱甘肽生成抑制铁死亡,联合免疫治疗抑制ATF4可减少HCC发生[76],揭示了针对铁死亡的免疫治疗策略的可能性[94]。此外,抑制磷酸甘油酸变位酶1[95]或高效成分多苷酚Ⅰ[96]通过不同途径诱导铁死亡,为HCC提供了新的治疗靶点及中医治疗HCC的新思路[88];MerTK抑制剂Sitravatinib与免疫检查点抑制剂结合使用也能通过促进铁死亡,增强对PD-L1抗体的疗效[75]。

以上研究为结合铁死亡与免疫治疗策略的制订提供了新思路,或将提高HCC治疗效果并为患者带来更大希望。

4 结 语

近年来,铁死亡在癌症治疗中的作用日益凸显,为HCC治疗策略的创新提供了新的思路。本文阐述了铁死亡的分子机制及其在HCC进展中的作用、免疫细胞铁死亡在HCC进展中的作用以及靶向铁死亡在HCC治疗中的应用,探讨通过以下途径诱导铁死亡以开发针对HCC的新型治疗可能的方法:一是通过调整铁死亡相关分子的表达水平,影响癌细胞对铁死亡的敏感性;二是通过调控肿瘤免疫微环境中与铁死亡相关的关键基因激活免疫细胞对癌细胞的杀伤作用,并逆转普遍存在的免疫抑制状态,从而显著增强免疫治疗效果。

目前已发现铁死亡在调节肿瘤靶向与免疫治疗响应中具有众多潜力靶点,仍需进一步临床验证。在HCC进展中,铁死亡相关分子(如LIFR、PCDHB14、NEAT1等)通过调控癌细胞对铁死亡的敏感性显著影响肿瘤进展。此外,ACSL4等分子通过重编程脂肪酸代谢诱导铁死亡,为改善耐药性提供了潜在靶点[97]。TRIM34/UPF1/GPX4轴介导HCC的铁死亡抗性,从而促进恶性表型。靶向TRIM34的HCC细胞对抗PD-1治疗表现出更好的反应[98]。在HCC肿瘤免疫调控方面,铁死亡通过调节免疫细胞活化、逆转免疫抑制状态显著增强免疫治疗效果。将铁死亡诱导剂与免疫检查点抑制剂(如PD-1/PD-L1抗体)联合使用不仅有效诱导免疫原性细胞死亡,还能促进免疫细胞

表2 现有诱导肝细胞癌铁死亡药物一览

Table 2 Overview of ferroptosis-inducing drugs in hepatocellular carcinoma

药 物	作用机制	药物研发阶段
碳量子点[84]	谷胱甘肽耗竭和活性氧产生机制诱导铁死亡	细胞实验
Tf-LipoMof@PL[85]	清除谷胱甘肽,下调GPX4,诱导铁死亡	细胞实验
CH-OD-SSZ[86]	搭载SSZ诱导铁死亡	动物实验
Fe-MnO_2/DHA[87]	释放Fe^{2+}和DHA,活性氧积累诱导铁死亡	动物实验
多苷酚Ⅰ[88]	Nrf2/HO-1/GPX4轴增强线粒体破坏和诱导铁死亡	动物实验
Sitravatinib[75]	MerTK抑制剂,联合免疫检查点抑制剂提升PD-L1耐药的肿瘤细胞铁死亡	临床试验(NCT03941873)

Tf-LipoMof@PL:转铁蛋白修饰的脂质体与金属有机框架复合物;GPX:谷胱甘肽过氧化物酶;CH-OD-SSZ:载有柳氮磺吡啶的化合物;SSZ:柳氮磺吡啶;Fe-MnO_2:铁锰氧化物;DHA:二氢黄酮酸;Nrf:核转录因子红系2相关因子;HO:血红素加氧酶;MerTK:巨噬细胞诱导受体激酶;PD-L:程序性死亡配体.

的抗肿瘤反应,改善HCC患者的治疗效果。靶向受各种代谢和免疫元件调节的铁死亡可能成为抗肿瘤治疗的新策略[99]。

靶向铁死亡的临床转化应用为HCC治疗展示出广阔前景。如基因递送系统G-LPQDEA/shSLC7A11和TRIM34靶向治疗等均展现出抑制肿瘤进展的潜力[100]。联合治疗策略如mTOR抑制剂与抗PD-L1抗体的组合为P53野生型HCC的新型精准治疗提供了新思路[101]。此外,针对线粒体功能和免疫反应的联合治疗在癌症治疗中具有重要潜力[102]。同时,氧化葡聚糖水凝胶、纳米粒等靶向系统的开发也为克服HCC耐药性提供了新的治疗选择。尽管靶向铁死亡在HCC治疗中展现出良好的前景,但将基于铁死亡的疗法转化为临床实践仍存在挑战。目前,许多铁死亡诱导剂在正常细胞和肿瘤细胞中缺乏足够的选择性,可能导致严重副作用;肝癌的高度异质性使得单一的治疗策略难以全面奏效;虽然铁死亡可以增强免疫治疗的效果,但肿瘤细胞可能通过其他途径实现免疫逃逸。

综上所述,靶向铁死亡作为一种创新治疗策略,在HCC治疗中展现了良好前景。未来,通过更深入的研究和临床验证,有望开发出更安全、高效的个体化精准治疗方案,为HCC患者带来切实的治疗获益。

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医学伦理 研究不涉及人体或动物实验

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors

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· 学术动态 ·

Atg1介导的Cct2磷酸化与Cct2-Atg11的结合通过调控Cct2与Atg8的互作启动固态聚集体自噬

2024年9月25日,浙江大学医学院易聪研究员团队在《欧洲分子生物学组织报告》(*EMBO Reports*)发表了题为“Two distinct regulatory pathways govern Cct2-Atg8 binding in the process of solid aggrephagy”的研究论文(DOI:10.1038/s44319-024-00275-7)。该研究发现两种不同的分子途径调控了含伴侣蛋白的无尾复合多肽(Cct)2-自噬相关基因(Atg)8的互作——Atg1介导的Cct2磷酸化以及Atg11与Cct2的直接结合。研究人员发现Cct2是磷酸激酶Atg1的底物,其Ser412和Ser470两个氨基酸残基是Atg1的磷酸化位点,其突变会抑制Cct2与Atg8的结合。同时,Atg11通过其CC4结构域直接与Cct2结合。缺乏这种相互作用会显著削弱Cct2与Atg8的结合。这些发现为固体聚集体自噬过程中Cct2与Atg8互作的调控提供了新的见解,也为筛选影响CCT2-Atg8/LC3C互作的调节剂或药物提供参考。

陈禹亭和张毅博士研究生、刘钊杰助理研究员为论文第一作者。研究工作得到国家科技重大专项、国家自然科学基金、浙江省自然科学基金等资助。

王本教授团队发现肿瘤钙化可促进糖脂代谢转换从而逆转化疗耐药

2024年10月10日,浙江大学转化医学研究院/浙江大学医学院附属第二医院王本教授团队在《生物材料》(*Biomaterials*)发表题为“Cell calcification reverses the chemoresistance of cancer cells via the conversion of glycolipid metabolism”的研究论文(DOI:10.1016/j.biomaterials.2024.122886)。研究人员设计了一种能诱导顺铂耐药的宫颈癌细胞发生微钙化的大分子药物——folate-polySia(FpSA)。在生理条件下,一定浓度的FpSA能靶向耐药细胞并富集血钙离子至细胞膜,促使细胞表面发生自发钙化——微钙化。微钙化依赖糖酵解代谢途径,对耐药细胞并不会产生直接的杀伤力,但会使肿瘤细胞内线粒体功能紊乱、脂肪酸摄取减少和脂肪酸β-氧化障碍。体内外实验结果显示,顺铂和FpSA联合治疗能有效抑制顺铂耐药肿瘤的生长,提高荷瘤小鼠的存活率。研究表明,微钙化肿瘤中,FpSA将脂肪酸代谢转换为糖酵解,增加顺铂耐药细胞的化疗敏感性。FpSA诱导癌细胞钙化为化疗耐药肿瘤的治疗提供了一种代谢重编程的新策略。

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