靶向脂质–铁死亡轴: 天然活性化合物干预结直肠癌的研究进展与临床前景

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摘要: 结直肠癌 (colorectal cancer, CRC) 是全球高发的消化系统恶性肿瘤, 化疗与免疫治疗耐药是其临床治疗的主要困境。脂质代谢重编程在支持肿瘤增殖的同时, 也赋予CRC细胞对铁死亡的特定代谢易感性, 铁死亡是一种铁依赖的、由脂质过氧化物积累驱动的程序性细胞死亡。CRC细胞通过上调酰基辅酶A合成酶长链家族成员4 (acyl-CoA synthetase long-chain family member 4, ACSL4) 促进多不饱和脂肪酸 (polyunsaturated fatty acids, PUFAs) 膜整合, 激活硬脂酰辅酶A去饱和酶1 (stearoyl-CoA desaturase 1, SCD1) 降低膜脂不饱和度, 并依赖溶质载体家族7成员11 (solute carrier family 7 member 11, SLC7A11)/谷胱甘肽过氧化物酶4 (glutathione peroxidase 4, GPX4) 抗氧化系统及铁死亡抑制蛋白1 (ferroptosis suppressor protein 1, FSP1)、二氢乳清酸脱氢酶 (dihydroorotate dehydrogenase, DHODH) 等平行通路清除过氧化物, 维持“脂质–铁死亡轴”的动态平衡。天然活性化合物通过多靶点调节优势, 抑制脂肪酸去饱和化、诱导脂噬性底物动员、阻断抗氧化防御及破坏铁稳态特异性干预该轴, 触发CRC细胞铁死亡。此外, 天然产物与化疗药物或免疫检查点抑制剂联用, 能有效逆转代谢适应性耐药, 并通过诱导免疫原性铁死亡激活抗肿瘤免疫。由于临床转化仍面临成药性不足及疗效预测模型缺失等问题, 因此, 笔者系统解析了天然活性化合物干预脂质–铁死亡轴的药效物质基础与分子机制, 旨在为开发靶向代谢重塑药物及优化联合治疗方案提供理论依据。

关键词: 结直肠癌; 脂质代谢重编程; 铁死亡; 天然活性化合物; 脂噬; 耐药逆转

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Targeting the lipid-ferroptosis axis: Research progress and clinical prospects of natural bioactive compounds in the intervention of colorectal cancer

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Abstract: Colorectal cancer (CRC) is a highly prevalent malignant tumor of the digestive system worldwide, and resistance to chemotherapy and immunotherapy constitutes a major challenge in its clinical management. While lipid metabolic reprogramming supports tumor proliferation, it also confers a specific metabolic susceptibility of CRC cells to ferroptosis, an iron-dependent form of programmed cell death driven by the accumulation of lipid peroxides. CRC cells promote the membrane incorporation of polyunsaturated fatty acids (PUFAs) by upregulating acyl-CoA synthetase long-chain family member 4 (ACSL4), reduce membrane lipid unsaturation by activating stearoyl-CoA desaturase 1 (SCD1), and rely on the solute carrier family 7 member 11

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(SLC7A11)/glutathione peroxidase 4 (GPX4) antioxidant system, together with parallel pathways such as ferroptosis suppressor protein 1 (FSP1) and dihydroorotate dehydrogenase (DHODH), to eliminate peroxides and maintain the dynamic balance of the "lipid-ferroptosis axis". Owing to their multi-target regulatory advantages, natural bioactive compounds specifically intervene in this axis by inhibiting fatty acid desaturation, inducing lipophagic substrate mobilization, blocking antioxidant defenses, and disrupting iron homeostasis, thereby triggering ferroptosis in CRC cells. In addition, the combination of natural products with chemotherapeutic agents or immune checkpoint inhibitors can effectively reverse metabolism-adaptive resistance and activate antitumor immunity by inducing immunogenic ferroptosis. Given that clinical translation still faces challenges such as poor druggability and the lack of predictive models for therapeutic efficacy, the authors systematically analyzed the pharmacodynamic material basis and molecular mechanisms by which natural bioactive compounds modulate the lipid-ferroptosis axis, with the aim of providing a theoretical foundation for the development of drugs targeting metabolic remodeling and for the optimization of combination therapeutic strategies.

Key words: colorectal cancer; lipid metabolism reprogramming; ferroptosis; natural bioactive compounds; lipophagy; drug resistance reversal

结直肠癌 (colorectal cancer, CRC) 是全球范围内高发的消化系统恶性肿瘤, 其发病率位居恶性肿瘤第三位, 死亡率居第二位[1]。尽管以氟尿嘧啶、奥沙利铂为基础的联合化疗及靶向治疗改善了早期患者的预后, 但转移性CRC的五年生存率仍低于15%[2]。临床研究表明, 微卫星稳定型 (microsatellite stable, MSS) CRC约占全部CRC的85%, 该类患者对免疫检查点抑制剂具有固有耐药性, 且传统化疗在应用过程中常发生继发性耐药[3]。因此, 深入探讨CRC的恶性生物学特征并识别新的代谢调节位点, 对于开发新型治疗策略具有重要意义。代谢重编程是肿瘤恶性进展的基本生物学特征[4]。在CRC进展过程中, 肿瘤细胞通过重塑代谢网络以适应快速增殖及缺氧微环境的需求, 其中脂质代谢重编程尤为突出。CRC细胞通过上调脂肪酸合酶 (fatty acid synthase, FASN) 等关键酶促进脂肪酸从头合成 (*de novo* lipogenesis, DNL), 以满足膜磷脂合成的需求, 并调节脂质种类与分布以影响信号转导与抗氧化水平[5]。然而, 这种代谢适应性同时赋予肿瘤细胞特定的代谢易感性。研究表明, CRC细胞膜中富集的多不饱和脂肪酸 (polyunsaturated fatty acids, PUFAs) 及醚脂对活性氧 (reactive oxygen species, ROS) 介导的氧化损伤表现出高度易感性。为维持氧化还原稳态, 肿瘤细胞通过上调谷胱甘肽过氧化物酶4 (glutathione peroxidase 4, GPX4) 等抗氧化防御系统进行代偿性调控, 形成了脂质底物积累与抗氧化防御之间的动态平衡, 即“脂质–铁死亡轴”[6,7]。

铁死亡是一种铁依赖的、以脂质过氧化物积累为特征的程序性细胞死亡方式, 受脂质底物供应、铁催化与抗氧化防御系统的动态调控[8]。研究表明, CRC细胞通过增强硬脂酰辅酶A去饱和酶1 (stearoyl-CoA desaturase 1, SCD1) 的表达以降低膜脂不饱和度, 上调溶质载体家族7成员11 (solute carrier family 7 member 11, SLC7A11) 以促进胱氨酸摄取, 并激活铁死亡抑制蛋白1 (ferroptosis suppressor protein 1, FSP1) 等平行通路[9]。上述代谢适应性变化与肿瘤增殖、化疗耐药及免疫逃逸的发生密切相关。因此, 通过干预脂质–铁死亡轴, 破坏脂质代谢与抗氧化防御系统之间的动态平衡, 已成为CRC新型治疗策略的研究重点[10,11]。天然活性化合物具有结构多样与多靶点调节的特点, 在干预肿瘤代谢方面具有巨大的应用潜力[12]。近年来研究发现, 青蒿素衍生物及知母皂苷等天然产物可通过抑制脂肪酸去饱和化、诱导脂噬、抑制GPX4活性及干扰铁稳态等途径靶向脂质–铁死亡轴, 进而诱导肿瘤细胞死亡[13,14]。此外, 这些化合物与化疗药物或免疫治疗联合使用时, 在逆转化疗耐药与提高免疫治疗敏感性方面均表现出显著的协同效应[15]。然而, 现有研究多关注单一成分的药理作用, 尚缺乏对作用机制的系统性分类、构效关系的综合总结及临床转化路径的深入探讨。因此, 本文旨在从底物供应、铁催化与抗氧化防御3个维度阐述CRC“脂质–铁死亡轴”的分子基础, 归纳天然活性化合物的干预机制与构效关系, 并探讨其在逆转耐药与免疫增敏中的应用前景, 以期为CRC的精准治疗提供理论依据。

1 结直肠癌中的脂质–铁死亡轴

1.1 脂质底物代谢特征 铁死亡的发生以细胞膜磷脂层发生致死性脂质过氧化为特征, 其敏感性主要取决于膜组分中PUFAs的丰度及脂质种类。在CRC的发病进展过程中, 肿瘤细胞通过脂质代谢重编程改变膜脂构成, 从而调节其对铁死亡信号的响应。酰基辅酶A合成酶长链家族成员4 (acyl-CoA synthetase long-chain family member 4, ACSL4) 与溶血磷脂酰胆碱酰基转移酶3 (lysophosphatidylcholine acyltransferase 3,

LPCAT3) 介导的PUFAs膜整合是决定细胞铁死亡敏感性的核心限速步骤[16]。在CRC细胞内, ACSL4催化花生四烯酸或肾上腺酸的脂酰辅酶A活化, 继而由LPCAT3将其酰基化至溶血磷脂, 形成富含PUFAs的磷脂酰乙醇胺 (polyunsaturated fatty acid-containing phosphatidylethanolamines, PE-PUFAs)[17]。现有研究表明, CRC组织中ACSL4的表达水平与肿瘤恶性程度呈正相关, 这种富含PUFAs的膜脂构成提高了细胞脂质过氧化的易感性[18]。此外, 由过氧化物酶体中磷酸二羟丙酮酰基转移酶 (glyceronephosphate *O*-acyltransferase, GNPAT) 与烷基甘油酮磷酸合酶 (alkylglycerone phosphate synthase, AGPS) 催化合成的醚脂, 被确定为调控CRC铁死亡的重要促氧化组分[19]。在过氧化物酶体中, AGPS催化醚脂合成的关键限速步骤, 与GNPAT协同将磷酸二羟丙酮 (dihydroxyacetone phosphate, DHAP) 逐步转化为缩醛磷脂等醚脂亚类; CRC组织中AGPS与GNPAT的表达量显著高于正常结肠黏膜。缩醛磷脂整合至细胞膜磷脂层 (*sn*-1 醚键位点) 后, 经15-脂氧合酶氧化生成plasmalogen-OOH, 其促铁死亡效能高于等量的双酯型PE-PUFAs, 与ACSL4/LPCAT3通路共同构成膜脂过氧化的双重底物供给机制, 协同增强CRC细胞铁死亡易感性[20,21]。缩醛磷脂因其*sn*-1位的化学结构对ROS攻击表现出高度易感性, 该路径与ACSL4/PUFAs路径在分子机制层面相互协同。为规避氧化损伤, CRC细胞常代偿性上调SCD1以促进单不饱和脂肪酸 (monounsaturated fatty acids, MUFAs) 的生物合成[22]。MUFAs的化学性质相对稳定, 通过与PUFAs竞争膜磷脂的整合位点, SCD1的激活显著提升了膜上MUFA/PUFAs的分子比率, 使细胞形成铁死亡抵抗表型[23]。综上所述, CRC细胞通过精确调控ACSL4、LPCAT3及SCD1等关键酶的表达, 介导了膜脂中促氧化组分与抗氧化组分的比例调控, 为天然活性化合物干预CRC铁死亡提供了明确的分子靶点。

1.2 亚细胞区室化抗氧化网络 CRC细胞通过亚细胞区室化的抗氧化系统清除脂质过氧化物, 从而维持膜磷脂的氧化还原稳态。该调控网络主要由GPX4介导的还原途径以及定位在质膜与线粒体膜的平行途径组成。SLC7A11催化的胱氨酸摄取是该系统的前提, 摄入的胱氨酸经还原生成半胱氨酸, 进而参与还原型谷胱甘肽 (glutathione, GSH) 的生物合成[7]。GPX4作为催化磷脂氢过氧化物 (phospholipid hydroperoxide, PL-OOH) 还原的关键酶, 利用GSH作为供氢辅因子将PL-OOH还原为无毒的磷脂醇 (phospholipid alcohol, PL-OH), 从而终止脂质过氧化链式反应[24]。在CRC细胞中, 核因子E2相关因子2 (nuclear factor erythroid 2-related factor 2, Nrf2) 或细胞癌基因 (c-Myc cellular myelocytomatosis oncogene, c-Myc) 等转录因子常正向调控SLC7A11与GPX4的表达, 显著增强了细胞的抗氧化能力[25]。除上述途径外, FSP1在质膜处发挥还原酶功能, 通过将辅酶Q10转化为泛醇 (ubiquinol, $CoQH_2$) 以直接清除磷脂自由基[26]。同时, 线粒体内膜定位的二氢乳清酸脱氢酶 (dihydroorotate dehydrogenase, DHODH) 在催化嘧啶合成的同时, 介导线粒体内CoQ向$CoQH_2$的还原转化, 实现了对线粒体膜脂过氧化的特异性抑制[27]。在线粒体局部, Fe^{2+}通过Fenton反应持续催化ROS生成, 驱动L•→LOO•→LOOH脂质过氧化链式反应, 导致线粒体膜脂损伤信号持续放大; DHODH介导的$CoQH_2$生成是对抗上述线粒体氧化损伤的核心代谢防线。此外, SLC25A39负责将胞质GSH转运至线粒体基质, 维持线粒体内GSH池的底物供给, 保障线粒体抗氧化容量[28]。在线粒体质量控制层面, PINK1/Parkin通路通过感知线粒体损伤信号, 启动线粒体自噬, 主动清除持续产生ROS的受损线粒体, 从而阻断铁死亡损伤信号的进一步扩增; CRC细胞中该通路功能的下调可削弱上述保护机制, 进而影响细胞铁死亡敏感性[29]。综上, CRC细胞通过SLC7A11/GPX4、FSP1及DHODH等通路在不同亚细胞位点的协同表达, 实现了对脂质过氧化物的高效清除。这种多通路协同的抗氧化调控网络使CRC细胞形成了稳固的铁死亡抵抗, 同时也为联合阻断多个抗氧化节点的治疗策略提供了分子依据。

1.3 脂滴稳态与脂噬调节 脂滴 (lipid droplets, LDs) 通过将中性脂质区室化储存于细胞内, 在调控CRC细胞铁死亡敏感性中发挥重要作用。CRC细胞内PUFAs在二酰甘油酰基转移酶 (diacylglycerol acyltransferase, DGAT) 催化下酯化形成甘油三酯 (triglycerides, TGs), 并储存于LDs中, 从而限制PUFAs作为膜磷脂合成底物的可利用性, 降低膜脂过氧化底物水平[30]。在氧化应激和代谢重编程等条件下, CRC细胞可通过脂噬动员LDs中的脂质储备[31]。脂噬属于选择性自噬过程, 其起始依赖Unc-51样自噬激活激酶1复合体激活及III类磷脂酰肌醇3-激酶复合体介导的隔离膜形成。随后, 微管相关蛋白1轻链3经自噬相关蛋白7和自噬相关蛋白3介导脂质化形成LC3-II, 并锚定于自噬膜表面, 促进脂滴被包裹形成自噬体。成熟自噬体并不直接完成降解, 而是在Rab7 GTPase和同型融合与蛋白分选复合体 (homotypic fusion and protein sorting complex, HOPS) 的介导下与溶酶体接触, 并由syntaxin 17、突触体相关蛋白29和囊泡相关膜

蛋白8构成的SNARE复合体驱动膜融合, 最终形成自溶酶体。自溶酶体内TG经溶酶体酸性水解酶降解后释放游离脂肪酸 (free fatty acids, FFAs), 尤其是PUFAs, 这些脂质分子可在ACSL4活化后重新进入膜磷脂重塑及脂质过氧化过程, 从而提高细胞对铁依赖性氧化损伤及铁死亡的敏感性[32]。与此同时, LDs中α-生育酚等脂溶性抗氧化成分的再分布也会影响胞内氧化还原稳态[33]。因此, LDs的合成、储存与脂噬降解共同决定了胞内脂质底物的空间分布与代谢去向, 而自噬体–溶酶体融合所维持的自噬流完整性, 则是影响脂质动员效率和CRC细胞铁死亡易感性的关键环节。

1.4 转录调控与环境应激 CRC对铁死亡的敏感性取决于遗传变异与微环境应激信号的共同调控。在转录水平, 肿瘤抑制蛋白p53 (tumor protein p53, p53) 的基因状态对铁死亡通路具有双向调节作用; 野生型p53通过转录抑制SLC7A11的表达增加细胞对铁死亡的敏感性, 而功能缺失型p53常伴随SLC7A11表达水平的上调, 从而提升胞内还原能力[34,35]。Nrf2在CRC细胞中表现为组成性激活, 通过调控SLC7A11、GPX4及血红素加氧酶-1 (heme oxygenase-1, HO-1) 等基因的转录, 维持胞内氧化还原平衡[36,37]。在能量应激状态下, 细胞通过单磷酸腺苷激活的蛋白激酶 (AMP-activated protein kinase, AMPK) 通路调节铁死亡进程。葡萄糖匮乏激活的AMPK可通过磷酸化抑制乙酰辅酶A羧化酶 (acetyl-CoA carboxylase, ACC), 降低脂肪酸合成速率, 进而减少脂质过氧化底物的生物利用度。此外, 在特定刺激条件下, AMPK亦可通过调控Beclin1介导的自噬进程影响铁死亡[38]。综上, CRC细胞通过整合转录因子活性与能量代谢状态, 实现对铁死亡通路的精细调节, 该调控过程是肿瘤细胞在复杂微环境中维持铁死亡抵抗的重要机制 (图1)。

2 天然活性化合物靶向脂质–铁死亡轴的作用机制

天然活性化合物通过干预脂质代谢、氧化还原平衡及铁稳态等多个调控节点, 破坏CRC细胞的代谢稳

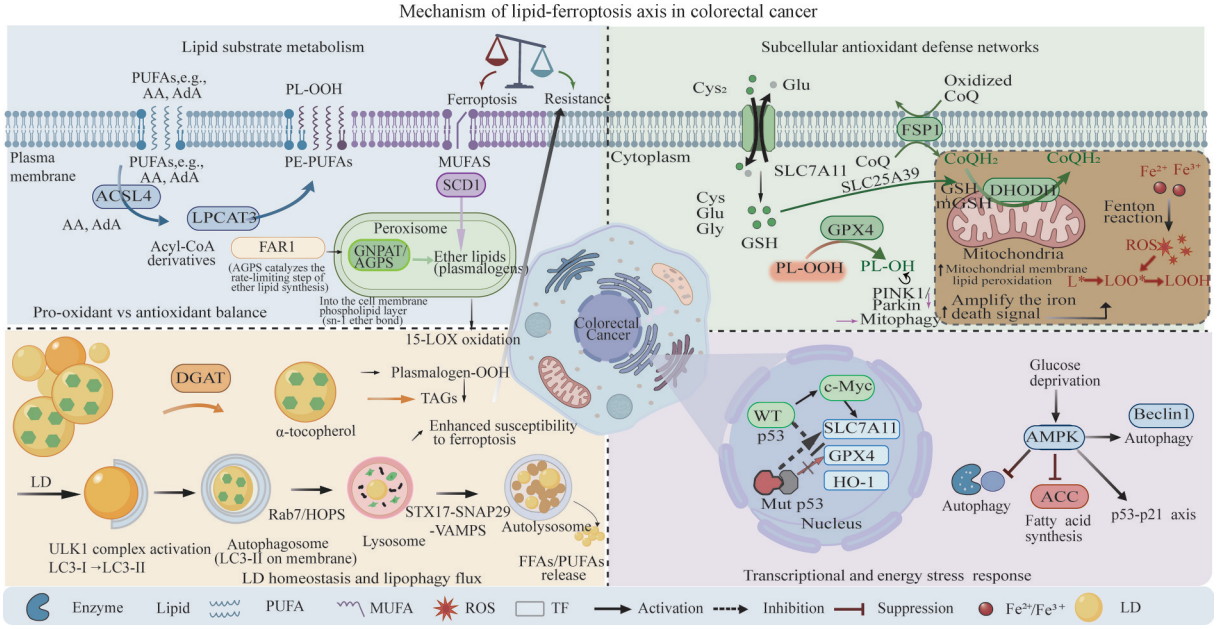


Figure 1 Mechanism of lipid-ferroptosis axis in colorectal cancer. 15-LOX: 15-Lipoxygenase; AA: Arachidonic acid; ACC: Acetyl-CoA carboxylase; ACSL4: Acyl-CoA synthetase long-chain family member 4; AdA: Adrenic acid; AGPS: Alkylglycerone phosphate synthase; AMPK: AMP-activated protein kinase; CoA: Coenzyme A; CoQ: Coenzyme Q; $CoQH_2$: Ubiquinol; Cys: Cysteine; Cys_2: Cystine; DGAT: Diacylglycerol *O*-acyltransferase; DHODH: Dihydroorotate dehydrogenase; FAR1: Fatty acyl-CoA reductase 1; Fe^{2+}: Ferrous ion; Fe^{3+}: Ferric ion; FFAs: Free fatty acids; FSP1: Ferroptosis suppressor protein 1; Glu: Glutamate; Gly: Glycine; GNPAT: Glyceronephosphate *O*-acyltransferase; GPX4: Glutathione peroxidase 4; GSH: Glutathione; HO-1: Heme oxygenase 1; HOPS: Homotypic fusion and protein sorting complex; L•: Lipid radical; LC3: Microtubule-associated protein 1 light chain 3; LD: Lipid droplet; LOO•: Lipid peroxyl radical; LOOH: Lipid hydroperoxide; LPCAT3: Lysophosphatidylcholine acyltransferase 3; mGSH: Mitochondrial glutathione; MUFAs: Monounsaturated fatty acids; Mut: Mutant; p21: Cyclin-dependent kinase inhibitor 1A; p53: Tumor protein p53; Parkin: Parkin RBR E3 ubiquitin protein ligase; PE-PUFAs: Phosphatidylethanolamine-polyunsaturated fatty acids; PINK1: PTEN-induced kinase 1; PL-OH: Phospholipid alcohol; PL-OOH: Phospholipid hydroperoxide; PUFAs: Polyunsaturated fatty acids; Rab7: Ras-related protein Rab-7; ROS: Reactive oxygen species; SCD1: Stearoyl-CoA desaturase 1; SLC7A11: Solute carrier family 7 member 11; SLC25A39: Solute carrier family 25 member 39; SNAP29: Synaptosomal-associated protein 29; STX17: Syntaxin 17; TAGs: Triacylglycerols; TF: Transcription factor; ULK1: Unc-51-like autophagy activating kinase 1; VAMPs: Vesicle-associated membrane proteins; WT: Wild type

态。根据作用靶点, 可将其分为4类: 抑制脂肪酸去饱和化与重塑膜脂构成、诱导脂质底物动员、抑制抗氧化防御系统以及破坏铁代谢稳态 (图2)。

2.1 抑制脂肪酸去饱和化与重塑膜脂构成 天然活性化合物通过多层次调控脂质代谢网络, 干扰CRC细胞的膜脂稳态, 从而发挥抗肿瘤作用。抑制脂肪酸去饱和化是关键机制之一。青蒿素衍生物可共价修饰染色质重塑因子淋巴特异性解旋酶 (lymphoid-specific helicase, LSH), 破坏LSH与尤文肉瘤断裂点区域1 (Ewing sarcoma breakpoint region 1, EWSR1)的复合物并抑制细胞色素P450家族成员 (cytochrome P450 family 24 subfamily A member 1, CYP24A1)转录, 进而通过钙离子−单磷酸腺苷激活的蛋白激酶信号轴下调SCD1, 提高膜脂中PUFAs/MUFAs比率; 该机制抑制了肿瘤生长及细胞增殖[14]。除直接抑制代谢酶外, 调节上游转录网络亦可限制底物供应。如木蝴蝶苷A通过抑制缺氧诱导因子-1α (hypoxia-inducible factor-1α, HIF-1α), 同时下调固醇调节元件结合蛋白1 (sterol regulatory element-binding protein 1, SREBP1)与FASN介导的脂质合成, 并上调肉碱棕榈酰转移酶1 (carnitine palmitoyltransferase 1, CPT1)促进β-氧化, 导致细胞内脂肪酸水平下降并诱发代谢应激, 进而诱导G2/M期阻滞并减轻肿瘤负荷[39]。此外, 调节膜物理性质与胆固醇稳态亦是有效途径: 白藜芦醇通过激活丙酮酸脱氢酶磷酸酶1 (pyruvate dehydrogenase phosphatase 1, PDP1)重定向葡萄糖代谢流以减少脂质合成, 并促进脂筏形成与Piezo1通道募集, 改变膜力学特性, 从而提升肿瘤细胞对肿瘤坏死因子相关凋亡诱导配体诱导凋亡的敏感性[40,41]; 青藤碱衍生物则通过激活固醇调节元件结合转录因子2 (sterol regulatory element binding transcription factor 2, SREBF2)导致胆固醇过量积聚, 引发严重的内质网应激与脂质过氧化, 表现出良好的安全性与抑瘤活性[42]。这些研究表明, 从转录调控到代谢酶活性的多靶点干预, 能有效阻断CRC的脂质代谢重编程。

2.2 诱导脂噬、自噬与应激介导的底物积累 除了直接调控脂质合成, 通过诱导脂噬、调节自噬流或激活细胞器应激以激活胞内脂质底物, 是诱导铁死亡的重要策略。知母皂苷A III通过上调Ras相关蛋白Rab-7a (Ras-related protein Rab-7a, Rab7)介导的脂噬作用, 促进LDs内TGs水解及PUFAs释放, 这种底物再分配导致脂质过氧化水平升高, 从而在体内实验中显著抑制肿瘤生长[13]。与之机制不同, 独脚金内酯类似物通过阻断自噬体−溶酶体融合, 导致受损线粒体累积并诱导线粒体活性氧 (mitochondrial reactive oxygen species, mtROS)产生, 这种氧化应激削弱了耐药细胞的代谢适应性, 并显著增强了奥沙利铂的抑瘤活性[43]。此外, 利用外源性脂质过载诱导内质网应激亦是有效途径: 棕榈酸经白细胞分化抗原36 (cluster of differentiation 36, CD36)摄取后激活蛋白激酶R样内质网激酶 (protein kinase R-like endoplasmic reticulum kinase, PERK)-真核翻译起始因子2α (eukaryotic translation initiation

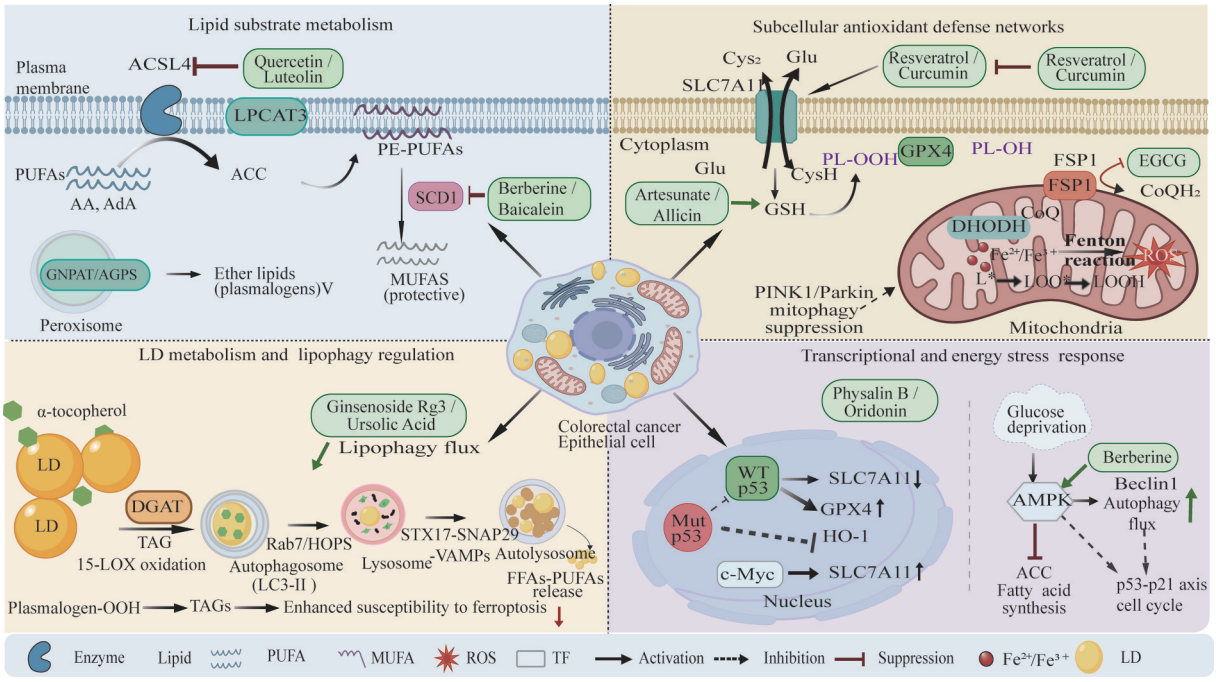


Figure 2 Natural active compounds targeting the lipid-ferroptosis axis in colorectal cancer. c-Myc: MYC proto-oncogene; EGCG: Epigallocatechin-3-gallate; LC3-II: Lipidated microtubule-associated protein 1 light chain 3

factor 2α, eIF2α)-激活转录因子4 (activating transcription factor 4, ATF4) 信号轴, 干扰胞内钙–铁稳态并驱动铁依赖性氧化损伤, 且对CD36高表达肿瘤组织表现出更高的敏感性[44]。黄酮类化合物芹菜素则通过抑制沉默调节蛋白3 (sirtuin 3, SIRT3)/锰超氧化物歧化酶 (manganese superoxide dismutase, MnSOD) 轴增强ROS信号, 并激活c-Jun氨基末端激酶 (c-Jun N-terminal kinase, JNK)/高迁移率族蛋白B1 (high mobility group box 1, HMGB1)/Beclin-1通路, 有效改善结肠病理损伤并降低肿瘤负荷[45]。上述研究表明, 利用天然产物干扰细胞器稳态, 促进代谢储备转化为氧化底物, 是干预CRC“脂质–铁死亡轴”的有效机制。

2.3 抑制GPX4/SLC7A11抗氧化系统 阻断SLC7A11/GPX4抗氧化轴是诱导CRC细胞发生铁死亡的关键策略。针对核心酶GPX4, 木犀草素被证实能直接结合其酶活性中心并抑制其催化功能, 导致脂质过氧化物无法被有效清除, 从而在体内实验中显著抑制肿瘤生长[46]; 而毛兰素则通过促进GPX4的泛素化–蛋白酶体降解途径, 降低胞内GPX4蛋白水平, 在原位癌模型中有效降低了肿瘤负荷[47]。针对上游胱氨酸转运体SLC7A11的转录调控亦是关键切入点: 穿心莲内酯与姜黄素通过激活p53信号通路, 转录抑制SLC7A11表达, 导致胞内GSH耗竭及氧化还原失衡, 其抗肿瘤活性在多种体内模型中得到验证[48,49]; 丹参酮IIA则通过阻断磷脂酰肌醇3-激酶 (phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B (protein kinase B, AKT)/哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 信号轴下调SLC7A11, 诱发铁依赖性细胞死亡[50]。此外, 干扰上游代谢前体策略同样有效: 齐墩果酸通过靶向磷酸丝氨酸转氨酶1 (phosphoserine aminotransferase 1, PSAT1) 阻断丝氨酸及GSH的生物合成路径, 削弱细胞抗氧化能力[51]; 而青蒿素–硒杂化物则表现出对SystemXc$^-$/GPX4轴的双重抑制作用[52]。这些研究证实, 通过不同机制阻断抗氧化系统, 能有效破坏CRC细胞的氧化还原稳态并诱导肿瘤消退。

2.4 破坏铁稳态与诱导铁蛋白自噬 破坏细胞内铁稳态以扩增不稳定铁池并催化芬顿反应, 是启动脂质过氧化链式反应的关键环节。诱导铁蛋白自噬是铁动员的主要机制之一, 蒽醌类化合物大黄素通过抑制核因子-κB (nuclear factor kappa B, NF-κB) 信号通路显著上调核受体共激活因子4 (nuclear receptor coactivator 4, NCOA4), 促进铁蛋白的自噬性降解及铁离子的释放; 这种铁过载状态加剧了细胞内的氧化损伤, 从而在体内模型中有效抑制了肿瘤生长[53]。除了动员储存铁, 促进血红素降解亦能导致游离铁水平升高, 龙血素高氯酸盐直接激活HO-1, 加速血红素分解与铁释放, 同时伴随SLC7A11的表达抑制, 这种促氧化与抗氧化能力的失衡显著阻遏了肿瘤进展[54]; 秦皮苷则通过诱发内质网应激并激活PERK-Nrf2轴, 引起HO-1的异常高表达与铁依赖性氧化损伤, 表现出抑瘤效力[55]。此外, 阻断铁转运过程同样能破坏铁稳态, acevaltrate通过特异性结合并下调铁伴侣蛋白多聚C结合蛋白1/2 [poly(rC)-binding protein 1/2, PCBP1/2], 阻碍铁离子向铁蛋白的正常转运, 导致胞浆内游离铁异常蓄积与ROS生成, 进而触发铁死亡并抑制肿瘤细胞增殖[56]。这些研究表明, 通过多途径破坏胞内铁代谢平衡, 提升不稳定铁池水平, 是利用天然产物干预CRC脂质–铁死亡轴的有效策略 (表1)[13,14,39-56]。

Table 1 Major mechanisms and experimental evidence for natural bioactive compounds targeting the lipid-ferroptosis axis in CRC. CRC: Colorectal cancer; LSH: Lymphoid-specific helicase; EWSR1: Ewing sarcoma breakpoint region 1; HIF-1α: Hypoxia-inducible factor-1α; FASN: Fatty acid synthase; CaMKKβ: Ca^{2+}/calmodulin-dependent protein kinase kinase β; AOM-DSS: Azoxymethane-dextran sulfate sodium; OXA: Oxaliplatin; mtROS: Mitochondrial reactive oxygen species; CD36: Cluster of differentiation 36; PERK: Protein kinase R-like endoplasmic reticulum kinase; DMH: 1, 2-Dimethylhydrazine; SIRT3: Sirtuin 3; MnSOD: Manganese superoxide dismutase; PDX: Patient-derived xenograft; PI3K: Phosphatidylinositol 3-kinase; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; System Xc^-: Cystine/glutamate antiporter; NCOA4: Nuclear receptor coactivator 4; Nrf2: Nuclear factor erythroid 2-related factor 2; ER: Endoplasmic reticulum; PCBP1/2: Poly(rC)-binding protein 1/2; i.p.: Intraperitoneal injection; *p.o.*: Per os; i.g.: Intragastric administration

Classification of mechanism	Compound	Experimental model and treatment	Core molecular target/pathway	Mechanism and anti-tumor effect	Reference
Inhibition of fatty acid desaturation and membrane lipid remodeling	Artemisinin derivatives	*In vitro*: HCT116, HT29, HCT-8 cells (0, 5, 10, 20 μmol·L^{-1}); *In vivo*: BALB/c nude mice bearing HCT116 xenografts (10, 20, 40 mg·kg^{-1}, i.p.)	LSH-EWSR1/SCD1	Disruption of the complex downregulates SCD1, elevates the PUFA ratio, and inhibits tumor proliferation	[14]
	Oroxylin A	*In vitro*: HCT116 cells (25, 50, 100, 150 μmol·L^{-1}); *In vivo*: BALB/c nude mice bearing HCT116 xenografts and AOM-DSS-induced C57BL/6 mice (150, 300 mg·kg^{-1}, *p.o.*; 200 mg·kg^{-1}, *p.o.*)	HIF-1α/FASN	Inhibition of lipid synthesis and promotion of β-oxidation; induction of G2/M arrest and reduction of tumor burden	[39]

Continued

Classification of mechanism	Compound	Experimental model and treatment	Core molecular target/pathway	Mechanism and anti-tumor effect	Reference
	Resveratrol	*In vitro*: Caco-2, HCT116 cells (10 μmol·L^{-1}); *In vivo*: -	CaMKK*β*/AMPK	Inhibition of cell proliferation and reversal of the Warburg effect	[40]
	Resveratrol	*In vitro*: SW480, SW620 cells (50 μmol·L^{-1}) *In vivo*: -	Lipid rafts/Piezo1	Induction of apoptotic phenotype and enhancement of mechanosensitivity	[41]
	Artemisinin derivatives	*In vitro*: HCT116, RKO cells (0, 1.25, 2.5, 5, 10, 20 μmol·L^{-1}); *In vivo*: BALB/c nude mice bearing HCT116 xenografts (30, 50 mg·kg^{-1}, i.p.)	SREBF2	Activation of SREBF2 leads to cholesterol accumulation and inhibits tumor activity	[42]
Induction of lipophagy, autophagy, and accumulation of stress substrates	Timosaponin AIII	*In vitro*: SW480, HCT116 cells (10 μmol·L^{-1}); *In vivo*: BALB/c nude mice bearing HCT116 xenografts (3, 6 mg·kg^{-1}, i.p.)	Rab7/lipophagy	Upregulation of Rab7 mediates lipophagy to release PUFAs and inhibits tumor activity	[13]
	Strigolactone analogues	*In vitro*: HCT116, OXA-resistant HCT116R, SW620, SW480, HT29, RKO, LOVO, DLD-1, COLO205 cells (0.01−100 μmol·L^{-1}); *In vivo*: BALB/c nude mice bearing HCT116 xenografts (30 mg·kg^{-1}, i.p.)	Autophagosome-lysosome fusion	Blockade of autophagic flux induces mtROS and enhances oxaliplatin efficacy	[43]
	Palmitic acid	*In vitro*: HT29, HCT116, SW480, SW620 cells (120 μmol·L^{-1}); *In vivo*: BALB/c nude mice bearing HT29 or SW620 xenografts (10 mg·kg^{-1}, i.p.)	CD36/PERK	Activation of the PERK axis disrupts Ca^{2+}-Fe homeostasis and specifically kills tumor cells	[44]
	Apigenin	*In vitro*: - *In vivo*: DMH-induced C57BL/6 mice (25, 50 mg·kg^{-1}, i.g.)	SIRT3/MnSOD	Inhibition of the SIRT3/MnSOD axis enhances ROS levels, improves histopathology, and reduces tumor burden	[45]
Inhibition of the GPX4/SLC7A11 antioxidant system	Luteolin	*In vitro*: MC38, CT26 cells (10, 20, 40 μmol·L^{-1}); *In vivo*: C57BL/6 mice bearing MC38 xenografts (15, 30, 60 mg·kg^{-1}, i.p.)	GPX4	Direct inhibition of GPX4 enzymatic activity and suppression of tumor growth	[46]
	Erianin	*In vitro*: HCT116, SW480 cells (25, 50, 100 μmol·L^{-1}); *In vivo*: AOM-DSS-induced C57BL/6 male mice (20, 40, 80 mg·kg^{-1}, i.g., six times per week)	GPX4	Promotion of GPX4 ubiquitination and degradation, reducing orthotopic tumor burden	[47]
	Andrographolide	*In vitro*: LoVo, HCT8 cells (0−80 μmol·L^{-1}); *In vivo*: Nude mouse PDX model (5, 10, 20 mg·kg^{-1}, i.p.)	p53/SLC7A11	Transcriptional repression of SLC7A11 leads to GSH depletion and inhibits cancer activity	[48]
	Curcumin	*In vitro*: SW620, LoVo, NCM460 cells (10, 20, 40, 80 μmol·L^{-1}); *In vivo*: BALB/c nude mice bearing SW620 xenografts (50, 100, 200 mg·kg^{-1}, i.g.)	p53/SLC7A11	Transcriptional repression of SLC7A11 leads to GSH depletion and inhibits cancer activity	[49]
	Tanshinone IIA	*In vitro*: OUMS23 cells (0, 5, 10, 20 μmol·L^{-1}); *In vivo*: BALB/c nude mice bearing OUMS23 xenografts (50 mg·kg^{-1}, i.p.)	PI3K/AKT/mTOR	Blockade of the PI3K/AKT/mTOR axis downregulates SLC7A11 and triggers ferroptosis	[50]
	Oleanolic acid	*In vitro*: HCT116, SW480, LoVo, SW620 cells (100 nmol·L^{-1}); *In vivo*: -	PSAT1	Targeting PSAT1 blocks GSH synthesis, weakens antioxidant capacity, and induces ferroptosis	[51]
	Artesunate-Se	*In vitro*: HCT116, SW480 cells (3.3, 6.6, 13.2 μmol·L^{-1}); *In vivo*: -	System Xc^-/GPX4	Dual inhibition of the System Xc^-/GPX4 axis induces ferroptosis	[52]
Disruption of iron homeostasis and induction of ferritinophagy	Emodin	*In vitro*: HCT-15, SW620 cells (40, 80, 120 μmol·L^{-1}); *In vivo*: BALB/c nude mice bearing SW620 xenografts (10, 20 mg·kg^{-1}, i.p.)	NCOA4/ferritin	Induction of ferritinophagy releases labile iron and inhibits tumor growth	[53]
	Dracorhodin perchlorate	*In vitro*: HCT116, SW480 cells (0, 5, 10, 20, 40, 80, 160 μmol·L^{-1}); *In vivo*: BALB/c nude mice bearing HCT116 xenografts (20, 40 mg·kg^{-1}, i.p.)	HO-1/SLC7A11	Activation of HO-1 accelerates heme degradation and inhibits tumor progression	[54]

Continued

Classification of mechanism	Compound	Experimental model and treatment	Core molecular target/pathway	Mechanism and anti-tumor effect	Reference
	Esculin	*In vitro*: HCT116, HCT8, HT29, Caco-2, SW480 cells (20, 40, 80 μmol·L^{-1}); *In vivo*: AOM-DSS-induced C57BL/6 mice (20, 40 mg·kg^{-1}, *p.o.*)	PERK-Nrf2/HO-1	Induction of ER stress upregulates HO-1 expression and causes iron overload, thereby inhibiting tumor growth	[55]
	Acevaltrate	*In vitro*: RKO, HCT116 cells (0.1, 0.5, 1, 2, 5 μmol·L^{-1}); *In vivo*: BALB/c nude mice bearing HCT116 or RKO xenografts (0, 10, 25, 50 mg·kg^{-1}, *p.o.*)	PCBP1/2	Downregulation of PCBP1/2 leads to accumulation of labile iron and inhibits cell proliferation	[56]

3 临床转化的治疗前景

化疗耐药和免疫逃逸是CRC治疗失败的重要原因。天然活性化合物通过调控脂质–铁死亡轴, 在逆转代谢适应性耐药、增强化疗及免疫治疗敏感性方面显示出潜在应用价值。

3.1 逆转多药耐药 化疗耐药是CRC治疗失败的主要因素, 其机制涉及肿瘤细胞的脂质代谢重编程及对微环境的适应性改变, 而靶向脂质–铁死亡轴已成为逆转多药耐药 (multidrug resistance, MDR) 的有效策略。针对由脂肪细胞微环境诱导的获得性耐药, 6-姜烯酚被证实能激活AMPK信号通路, 抑制AKT/mTOR/SREBP-1信号轴介导的脂质合成代谢适应, 从而显著逆转耐药细胞对5-氟尿嘧啶的敏感性[57]。对于固有或获得性化疗耐药, 天然铁死亡诱导剂与化疗药物的联合应用显示出显著的增效作用: 盐霉素与5-氟尿嘧啶联用, 能协同抑制SLC7A11/GPX4抗氧化系统, 通过促进脂质过氧化物的积累, 在体内外模型中发挥协同抗肿瘤效应[58]; 西南凤尾蕨提取物则通过耗竭胞内GSH并抑制SLC7A11, 降低了顺铂耐药细胞清除氧化应激产物的能力, 实现了化疗增效[59]。此外, 白术内酯I通过靶向网格蛋白重链 (clathrin heavy chain, CLTC) 与X射线修复交叉互补蛋白5 (X-ray repair cross-complementing protein 5, XRCC5), 重编程脂肪酸氧化代谢网络并诱导代谢应激, 在患者来源类器官模型中显著增强了奥沙利铂的抗肿瘤活性[60]。这些研究表明, 干预脂质代谢与氧化还原稳态是克服CRC化疗耐药的有效途径。

3.2 联合治疗 对于单一疗法的临床局限性, 天然产物的多靶点联合干预策略已成为提升CRC临床疗效的重要方向。在药物协同方面, 姜黄素与二甲双胍联用, 通过协同下调二价金属离子转运体1 (divalent metal transporter 1, DMT1)、阻断pAKT/mTOR信号转导并抑制KEAP1-Nrf2抗氧化通路, 导致胞内ROS积聚、SLC7A11表达抑制及脂质过氧化水平升高, 在体内模型中抑制肿瘤生长且未见明显毒性[61]。在免疫联合增效方面, 天然产物经脂质–铁死亡轴诱导的免疫原性铁死亡是其与免疫治疗协同增效的核心机制。铁死亡过程中积累的PL-OOH驱动肿瘤细胞膜裂解, 释放HMGB1、钙网蛋白及ATP等损伤相关分子模式, 促进树突状细胞成熟并激活肿瘤特异性CD8$^+$ T细胞应答; 浸润的CD8$^+$ T细胞分泌IFN-γ, 经JAK1/2-STAT1轴转录抑制SLC7A11, 降低肿瘤细胞半胱氨酸摄取与GSH合成, 进一步削弱其脂质过氧化防御能力[62,63]。如淫羊藿苷通过靶向HMGA2/STAT3/HIF-1α轴下调SLC7A11/GPX4、诱导脂质过氧化并促进DAMPs释放, 显著增强CD8$^+$ T细胞浸润及IFN-γ分泌, 有效增强了PD-1抑制剂对MSS型CRC的疗效[64]。在重塑肿瘤免疫微环境方面, 天然产物可通过抑制IL-10/TGF-β分泌促进肿瘤相关巨噬细胞由M2向M1表型转变, 并经下调肿瘤细胞PD-L1表达与免疫检查点抑制剂形成靶点互补, 为MSS型患者克服免疫耐受提供新策略[65]。在减毒方面, CRC细胞与正常肠上皮细胞在代谢特征上的差异构成了天然产物选择性的分子基础。CRC细胞因高ACSL4表达驱动PUFAs膜整合, 伴随SCD1活化及低GPX4/GSH储备, 对铁死亡高度敏感; 而正常肠上皮细胞因ACSL4活性低且抗氧化防御充足, 对该干预天然抵抗, 从而赋予天然铁死亡诱导剂较佳的治疗指数[66]。此外, 小檗碱等天然产物具有肠道抗炎、菌群调节及黏膜屏障保护作用, 理论上有助于降低免疫检查点抑制剂相关肠炎等胃肠道免疫相关不良事件的风险; 但目前该结论主要基于肠炎模型、菌群–免疫机制研究及联合治疗安全性观察, 尚缺乏CRC免疫联合治疗中的直接临床证据[67,68]。综上所述, 天然活性化合物通过靶向脂质–铁死亡轴, 在增效层面经免疫原性铁死亡激活抗肿瘤免疫, 在减毒层面依靠肿瘤与正常组织的代谢差异实现选择性杀伤, 为优化CRC联合治疗方案、克服MSS型患者免疫耐受提供了理论依据与转化潜力 (表2)[57-61,64]。

3.3 临床研究现状 尽管多种天然活性化合物在临床前模型中展现出精准靶向脂质–铁死亡轴的抗肿瘤

Table 2 Summary of natural bioactive compounds in reversing drug resistance and combination therapy. SREBP-1: Sterol regulatory element-binding protein 1; CLTC: Clathrin heavy chain; XRCC5: X-ray repair cross-complementing protein 5; DMT1: Divalent metal transporter 1; HMGA2: High mobility group AT-hook 2; STAT3: Signal transducer and activator of transcription 3; DAMPs: Damage-associated molecular patterns; PD-1: Programmed cell death protein 1

Application strategy	Compound	Experimental model and treatment	Target/pathway	Mechanism and efficacy	Reference
Reversal of multidrug resistance	6-Shogaol	*In vitro*: DLD-1, SW480 cells (5, 10, 20 μmol·L^{-1}) *In vivo*: -	AMPK/SREBP-1	Activation of AMPK to inhibit lipid synthesis; reversal of adipose microenvironment-induced 5-fluorouracil resistance	[57]
	Salinomycin	*In vitro*: SW480, HCT116 cells (2.5, 5, 10, 40, 80 μmol·L^{-1}) *In vivo*: BALB/c nude mice bearing SW480, HCT116 xenografts (5 mg·kg^{-1}, i.p.)	SLC7A11/GPX4	Synergistic pro-oxidative effect in combination with 5-fluorouracil; enhancement of chemosensitivity	[58]
	Pteris wallichiana	*In vitro*: SW480, HCT116 cells (5, 10 μmol·L^{-1}) *In vivo*: AOM-DSS-induced C57BL/6 mice; BALB/c nude mice bearing SW480, HCT116 xenografts (10, 30 mg·kg^{-1}, i.g.)	SLC7A11/GSH	Depletion of GSH to impair antioxidant capacity; reversal of cisplatin resistance	[59]
	Atractylenolide I	*In vitro*: CRC5, CRC11, CRC107, CRC118 cells (0, 10, 20, 40, 80, 100, 160, 320 μmol·L^{-1}) *In vivo*: BALB/c nude mice bearing CRC5 xenografts (25, 50 mg·kg^{-1}, i.p.)	CLTC/XRCC5	Targeting DNA repair and metabolism; enhancement of oxaliplatin efficacy in patient-derived organoid models	[60]
Combination of multi-drug and immunotherapy	Curcumin + metformin	*In vitro*: HCT116, CT26 cells (15, 50 μmol·L^{-1}) *In vivo*: BALB/c nude mice bearing CT26, HCT116 xenografts (20 mg·kg^{-1}, i.p.)	DMT1/Nrf2	Synergistic blockade of iron uptake and antioxidant defense; tumor suppression without significant toxicity	[61]
	Icariin	*In vitro*: HCT116, SW620, MC38, CT26 cells (0, 10, 20, 40, 60, 80, 100, 120, 140 μmol·L^{-1}) *In vivo*: C57BL/6 nude mice bearing MC38 xenografts (10, 20, 40 mg·kg^{-1}, i.g.)	HMGA2-STAT3/DAMPs	Induction of ferroptosis to release DAMPs, thereby activating CD8$^+$ T cells; enhancement of anti-PD-1 inhibitor efficacy	[64]

潜力, 但其临床转化进程相对缓慢。目前的临床探索主要集中于少数经典化合物, 并侧重于化学预防。小檗碱提供了具有代表性的临床证据, 一项纳入1 108例受试者的大规模随机对照试验证实, 给予小檗碱0.3 g每日两次口服2年, 以结肠镜复查确认的腺瘤复发为主要终点, 其抗腺瘤机制与阻断SREBP-1介导的DNL密切相关。结果显示, 小檗碱组2年腺瘤复发率 (36%) 较安慰剂组 (47%) 降低 ($P < 0.001$), 晚期腺瘤的抑制效果尤为突出; 伴随的转化分析提示, 基线肿瘤SREBP-1高表达患者的临床获益更显著, 初步支持以脂质代谢表型指导患者分层的可行性; 不良反应以轻度一过性胃肠道不适为主, 耐受性良好, 为化学预防领域提供了证据[69,70]。在晚期CRC治疗探索方面, Howells等[71]开展的IIa期开放标签随机对照试验纳入28例转移性CRC患者, 按1∶2随机分配至FOLFOX组或CUFOX组, 后者在FOLFOX方案基础上联合口服姜黄素2 g·d^{-1}, 进行12个化疗周期。治疗分析表明, CUFOX组中位无进展生存期为291天, 中位总生存期约16.5个月, 总生存期 (overall survival, OS) 风险比为0.34 ($P = 0.02$), 提示姜黄素联合化疗具有潜在生存获益。两组不良事件谱相近, 姜黄素联合FOLFOX安全性及耐受性良好。临床前研究表明, 肿瘤活检标本中SLC7A11相关抗氧化标志物下调、铁死亡敏感性通路活性升高, 为姜黄素干预脂质−铁死亡轴的增效机制提供了初步的患者组织层面证据[48,49]; 但上述结果仅属2b级证据, 尚需大样本III期临床试验加以确证, 口服生物利用度不足的问题也需要解决。白藜芦醇的两项I期探索性研究着眼于靶组织活性确认: Nguyen等[72]对8例CRC患者进行葡萄源白藜芦醇干预, 结肠黏膜活检证实Wnt/*β*-连环蛋白信号通路靶基因表达下调; Patel等[73]则在20例术前CRC患者中给予白藜芦醇1.0 g·d^{-1}口服8天, 病理分析显示肿瘤组织Ki67增殖指数下降约5%, 血浆脂质过氧化终产物4-HNE同步升高, 提示靶组织局部脂质氧化损伤被激活; 但两项研究的共同局限在于样本量偏小与系统生物利用度不足, 效应量有限。然而, 临床转化仍面临客观挑战。首先是基础研究与临床实践的脱节, 现有的临床试验多缺乏对关键代谢酶FASN、ACSL4及脂质组学特征的

直接检测, 导致难以确证临床获益是否源于脂质–铁死亡重编程机制。其次是药代动力学与安全性的限制, 白藜芦醇的I期试验表明, 其低生物利用度限制了肿瘤局部的有效药物浓度[72]; 同时, 铁死亡诱导的非特异性氧化应激可能损伤正常肠上皮, 限制了其临床应用剂量的提升, 亟需明确精确的治疗窗口以平衡疗效与潜在毒性。上述两方面构成天然活性化合物转化研究的首要瓶颈, 亦指明了未来开展以代谢生物标志物为核心的精准临床试验的迫切方向。

3.4 临床转化策略 成药性不足与疗效预测模型缺失是天然活性化合物靶向脂质–铁死亡轴临床转化的两大核心制约因素。针对成药性问题, 活性成分固有的药代动力学缺陷是根本原因, 姜黄素因低吸收率、首过代谢显著及消除迅速, 口服生物利用度不足1%[74]; 白藜芦醇I期临床研究证实, 结肠黏膜局部暴露量远低于体外诱导铁死亡的有效浓度[73], 上述缺陷直接限制了体内靶向效应的实现。针对上述问题, TME响应型纳米载体是目前具有转化价值的优化策略, 利用CRC微环境中高ROS与高GSH并存的特征, 硫缩酮键型与二硫键型载体可分别在氧化或还原条件下触发药物释放, 并通过消耗H_2O_2或GSH降低胞内抗氧化水平, 增强铁死亡诱导效率; 借助结肠菌群来源的偶氮还原酶或β-葡糖醛酸苷酶将前药在靶部位选择性活化, 可进一步提升局部药物浓度并降低系统毒性, 减少对正常肠上皮的非特异性损伤[75,76]。分子结构改造层面, 引入聚乙二醇化修饰或以氟原子替换易代谢酚羟基, 可在保留药效团的前提下改善水溶性与代谢稳定性[42]。就疗效预测问题而言, 现有临床试验普遍未纳入基于脂质–铁死亡代谢表型的患者分层, 致使临床获益与靶轴干预的因果关系难以确证。为此, 建议构建基线分层、动态监测与功能验证3个层次的预测体系。基线层面以ACSL4、GPX4、SLC7A11免疫组化联合评分整合PE-PUFAs/PE-MUFA磷脂组学比值及铁代谢标志物, 建立脂质–铁死亡易感性评分[77], 用于筛选高代谢易感亚群并指导富集入组, 小檗碱随机对照试验转化分析所示的基线SREBP-1高表达与临床获益的相关性为该策略提供了初步依据[69]。动态监测层面以血浆丙二醛 (malondialdehyde, MDA)、4-羟基壬烯醛 (4-hydroxynonenal, 4-HNE) 及氧化磷脂酰乙醇胺 (oxidized phosphatidylethanolamine, ox-PE) 定量反映铁死亡诱导程度[78], 同步结合循环肿瘤DNA (circulating tumor DNA, ctDNA) 检测追踪SLC7A11、GPX4体细胞变异以识别获得性耐药[79]。功能验证层面以患者来源类器官体外评估铁死亡应答, 对患者进行功能性预分层[80], 补充静态标志物在个体预测方面的不足。将上述体系与多组学铁死亡敏感性评分整合, 建立以生物标志物为依据的适应性富集临床设计, 有望系统明确天然产物靶向铁死亡干预在特定CRC亚群中的适用范围, 为该领域精准临床转化提供方法学支持 (表3)[69,71-73]。

4 总结与展望

CRC的代谢重编程赋予其特定的代谢依赖性, 脂质–铁死亡轴作为连接脂质代谢与细胞死亡的调节网络, 是CRC治疗的潜在靶点。本文阐述了CRC细胞通过ACSL4/LPCAT3介导的膜脂重塑、SCD1调控的去饱和化、SLC7A11/GPX4系统及FSP1/DHODH通路构建的铁死亡抵抗机制, 指出脂质底物、铁催化与抗氧化防御间的动态平衡决定了铁死亡敏感性。天然活性化合物通过多靶点调节干预该轴: 青蒿素衍生物抑制SCD1, 知母皂苷A III诱导脂噬, 木犀草素与毛兰素阻断GPX4, 大黄素调节铁稳态。这些化合物可特异性调节CRC代谢重编程的关键节点。此外, 天然产物与化疗或免疫检查点抑制剂联用, 不仅能逆转代谢适应性介导的耐药, 还可通过诱导免疫原性铁死亡增强抗肿瘤免疫, 为克服MSS型CRC的治疗抵抗提供策略。

然而, 临床转化仍面临挑战: 现有研究多限于单一化合物, 缺乏基于代谢特征的疗效预测模型; 部分天然产物存在水溶性差、生物利用度低等成药性问题; 铁死

Table 3 Clinical trials of natural bioactive compounds in the prevention and treatment of CRC. Levels of evidence are graded according to the Oxford Centre for Evidence-Based Medicine criteria: 1b denotes a single high-quality randomized controlled trial; 2b denotes a single cohort study or a low-quality randomized controlled trial; 4 denotes a case series or single-arm study

Compound	Trial phase/type	Sample size	Primary clinical outcomes	Registration number	Level of evidence	Reference
Berberine	Randomized, double-blind randomized controlled trial	1 108	Reduction in adenoma recurrence rate	NCT02226185	1b	[69]
Curcumin	Phase IIa	28	Improved survival with no significant adverse effects	NCT01490996	2b	[71]
Resveratrol	Phase I (open-label)	8	No significant histological changes observed in cancerous tissue	NCT00256334	2b	[72]
Resveratrol	Prospective clinical study	20	Reduction in tumor cell proliferation index by 5%	NCT00433576	4	[73]

亡诱导可能引起正常肠上皮的非特异性损伤; 且缺乏针对晚期患者的高质量临床证据; 同时, 目前尚无研究在同一实验体系内, 系统验证天然活性化合物通过靶向脂质–铁死亡轴在CRC免疫联合治疗中同步实现增效与减毒的双重效应, 这一空白构成未来研究的重要方向。鉴于此, 未来研究应聚焦于: ① 深化机制解析, 阐明天然产物对醚脂代谢及线粒体防御系统的调控, 探索代谢与免疫的交互作用; ② 优化递送系统, 利用纳米技术改善药代动力学特性, 开发微环境响应型载体; ③ 构建分子分型, 基于ACSL4、Nrf2等标志物及脂质组学特征建立敏感性分型标准, 筛选获益人群; ④ 开展临床研究, 评估联合治疗获益, 建立包含脂质过氧化与铁代谢指标的疗效监测体系。综上, 随着机制阐明、递送优化及分型建立, 靶向脂质–铁死亡轴的天然活性化合物有望成为逆转耐药、增强免疫治疗的辅助手段。

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