靶向铁死亡信号通路抗肝纤维化机制与药物研究进展

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摘要: 铁死亡 (ferroptosis) 是一种以铁依赖性、脂质过氧化物累积为核心特征的新型程序性细胞死亡方式, 其发生受细胞内铁代谢、脂质过氧化及抗氧化系统等多重信号通路精密调控。近年来研究表明, 铁死亡在肝星状细胞 (hepatic stellate cells, HSCs) 与肝细胞命运抉择中扮演双重角色, 与肝纤维化发生发展密切相关。本文阐述了铁死亡关键分子机制, 铁死亡抗肝纤维化的双重作用, 系统综述了以铁死亡关键分子为靶点的天然产物与人工合成化合物在抗肝纤维化研究的最新进展。旨在为基于调控铁死亡通路抗肝纤维化创新药物研发提供坚实的理论依据与策略方向。

关键词: 铁死亡; 肝纤维化; 肝星状细胞; 信号通路; 脂质过氧化

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Targeting the ferroptosis signaling pathway for liver fibrosis: Mechanisms and pharmaceutical research advances

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Abstract: Ferroptosis, a novel programmed cell death mechanism characterized by the iron-dependent accumulation of lipid peroxides, is precisely regulated by multiple signaling pathways, including intracellular iron metabolism, lipid peroxidation, and antioxidant systems. Recent studies have highlighted the dual role of ferroptosis in the fate determination of hepatic stellate cells (HSCs) and hepatocytes, indicating its significant involvement in the progression of hepatic fibrosis. This is corroborated by ongoing research that explores the molecular mechanisms of ferroptosis and its potential as a therapeutic target in various liver diseases, including liver fibrosis. This article elucidates the key molecular mechanisms of ferroptosis and its dual role in liver fibrosis, while systematically reviewing the latest progress in anti-fibrotic research using natural products and synthetic compounds targeting key ferroptosis molecules. The study aims to offer a solid theoretical basis and strategic guidance for the development of innovative anti-fibrotic drugs by regulating ferroptosis pathways.

Key words: ferroptosis; liver fibrosis; hepatic stellate cell; signal pathway; lipid peroxidation

肝脏作为人体重要的代谢和解毒器官, 在维持机体正常生理功能中发挥着关键作用。肝纤维化是多种慢性肝脏疾病发展过程中的关键病理阶段, 其特征为细胞外基质 (extracellular matrix, ECM) 的过度沉积, 进而破坏肝脏的正常结构与功能[1]。目前, 针对肝纤维化的治疗手段较为有限, 尚无特效药物获批用于临

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床, 因此深入探究肝纤维化的发病机制并寻找有效的治疗靶点十分紧迫。近年来, 铁死亡 (ferroptosis) 作为一种新型程序性细胞死亡方式, 受到了广泛关注。铁死亡具有独特的生物学特征, 主要表现为铁离子依赖性的脂质过氧化反应过度激活, 导致细胞内活性氧 (reactive oxygen species, ROS) 大量积累, 最终引发细胞死亡[2]。多项研究揭示了铁死亡与肝纤维化之间存在着密切的联系, 其在肝纤维化中的作用机制和治疗潜力正逐渐被揭示。在肝纤维化发生发展过程中, 铁死亡异常调控发挥着重要作用, 其不仅影响肝细胞、肝星状细胞 (hepatic stellate cells, HSCs) 等肝脏细胞的命运, 还与炎症反应、氧化应激等病理过程相互交织[3]。深入研究铁死亡信号通路在肝纤维化治疗中的分子机制, 有望为肝纤维化的防治提供新的策略和靶点。近年来的研究表明, 铁死亡在肝纤维化中发挥重要作用, 特别是在HSCs的活化过程中。通过调节铁代谢和相关信号通路, 铁死亡可能成为肝纤维化治疗的新靶点。本文将系统综述靶向铁死亡信号通路在抗肝纤维化中的作用机制及药物研究进展, 阐释铁死亡信号通路于肝纤维化治疗中的效用, 旨在为肝纤维化的临床治疗提供理论支撑与新的研究方向。

1 肝纤维化的发生机制

肝纤维化的发生是一个复杂的病理过程 (图1), 涉及多种细胞和信号通路异常激活, 其中HSCs活化为增殖性纤维化肌成纤维细胞是实验性和病理性肝损伤中肝纤维化发生的关键事件[2]。活化的HSCs (activated HSCs, aHSCs) 失去其原有特征, 获得增殖能力并大量合成和分泌ECM, 导致ECM在肝脏组织中过度沉积, 破坏肝脏正常结构和功能。在肝纤维化进程中, 多种细胞因子如转化生长因子 β (transforming growth factor β, TGF-β) 是已知最强促纤维化细胞因子, TGF-β通过与细胞表面受体结合, 激活下游Smad信号通路, 促进HSCs激活、增殖及ECM合成[4]。此外, 血小板衍生生长因子 (platelet-derived growth factor, PDGF)、肿瘤坏死因子 α (tumor necrosis factor α, TNF-α)、白细胞介素 1β (interleukin 1β, IL1-β) 等细胞因子也参与其中, 其通过旁分泌、自分泌等方式相互作用形成复杂细胞因子网络, 共同推动肝纤维化进展[5]。除细胞因子外, 氧化应激在肝纤维化进程中也起着关键作用。当肝脏受到损伤时, 细胞内抗氧化防御系统失衡, 导致大量ROS生成, 直接损伤胞内生物大分子, 如脂质、蛋白质和DNA, 引发细胞损伤和死亡。同时, ROS还可激活多条信号通路, 如丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK)、核因子-κB (nuclear factor κB, NF-κB) 等通路, 进一步促进HSCs激活和炎症反应, 加速肝纤维化进程。同时, 肝纤维化的发生还与肝脏内的免疫细胞密切相关, 如巨噬细胞在肝损伤时被激活, 释放多种炎症因子和趋化因子, 吸引其他免疫细胞聚集, 加剧炎症反应, 其还可分泌TGF-β等直接促进HSCs激活和纤维化进程。此外, T淋巴细胞、B淋巴细胞等免疫细胞也可通过调节免疫反应和细胞因子分泌, 影响肝纤维化发展。

2 铁死亡抗纤维化调控机制与信号通路

2.1 System Xc^--GSH-GPX4 System Xc^-是一种位于细胞膜上的胱氨酸/谷氨酸逆向转运体, 由溶质载体家族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) 两个亚基组成[6]。System Xc^-主要功能是将胞外胱氨酸 (cystine) 转运至胞内, 同时把胞内谷氨酸排至胞外, 胱氨酸进入细胞后被还原成半胱氨酸 (cysteine, Cys), Cys是合成谷胱甘肽 (glutathione, GSH) 限速氨基酸。System Xc^--GSH-GPX4调控铁死亡: 当system Xc^-功能受到抑制时, 细胞外胱氨酸无法正常进入细胞内, 导致细胞内半胱氨酸供应不足, 进而使GSH合成减少, 使得谷胱甘肽过氧化物酶4 (glutathione peroxidase 4, GPX4) 活性受到抑制, 无法有效清除细胞内脂质过氧化物, 脂质过氧化物积累引发细胞膜氧化损伤, 最终导致细胞铁死亡发生。当前, 如柳氮磺胺吡啶 (sulfasalazine, SAS)、艾拉斯汀 (erastin, Era) 等抑制剂通过抑制system Xc^-功能, 诱导细胞发生铁死亡。此外, p53蛋白通过抑制SLC7A11表达, 降低system Xc^-功能, 从而增加细胞对铁死亡的敏感性, 这一机制为p53介导的肿瘤抑制提供了新的解释。此外, 研究表明, p53介导的铁死亡还可能通过脂质加氧酶如花生四烯酸12-脂氧合酶 (arachidonate 12-lipoxygenase, ALOX12) 和钙离子非依赖性磷脂酶A2β (calcium-independent phospholipase A2 beta, iPLA2β) 等途径实现。p53直接上调ALOX12表达并激活iPLA2β酶活性, 后者水解膜磷脂释放多不饱和脂肪酸 (如花生四烯酸), 为ALOX12提供底物, 二者协同驱动脂质过氧化链式反应, 加速铁死亡进程。该通路在肝细胞与肝星状细胞中可能存在差异调控, 为选择性诱导HSCs铁死亡提供了新思路。相反, 核因子E2相关因子2 (nuclear factor erythroid 2-related factor 2, Nrf2) 等可激活一系列抗氧化基因表达, 从而增强细胞抗氧化能力, 抑制铁死亡发生[7]。

2.2 铁代谢调控通路 细胞内铁代谢在铁死亡的发生中起着核心作用。细胞外铁主要以Fe^{3+}形式存在, 其摄取主要经由转铁蛋白受体1 (transferrin receptor 1, TFR1) 介导的内吞作用完成。具体过程: 转铁蛋白

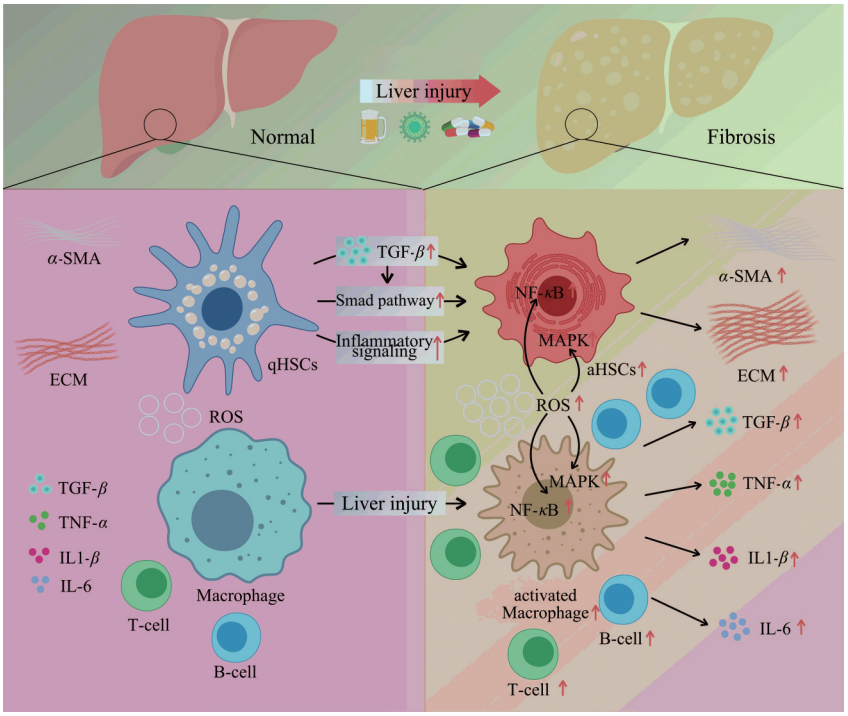


Figure 1 Mechanism of hepatic fibrosis. HSCs: Hepatic stellate cells; qHSCs: Quiescent hepatic stellate cells; aHSCs: Activated hepatic stellate cells; α-SMA: α-Smooth muscle actin; TGF-β: Transforming growth factor β; NF-κB: Nuclear factor kappa B; MAPK: Mitogen-activated protein kinase; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor α; IL1-β: Interleukin 1β; IL6: Interleukin 6; ECM: Extracellular matrix; B-cell: B lymphocyte; T-cell: T lymphocyte

(transferrin, TF) 与血浆中的 Fe^{3+} 结合形成 TF-Fe^{3+} 复合物, 该复合物与 TFR1 特异性结合, 通过网格蛋白依赖的内吞途径进入细胞, 形成内吞小体; 在内吞小体内, 六跨膜上皮抗原 3 (six-transmembrane epithelial antigen of the prostate 3, STEAP3) 等还原酶将 Fe^{3+} 还原为 Fe^{2+}。随后, 二价金属离子转运体 1 (divalent metal transporter 1, DMT1) 将 Fe^{2+} 从小体内转运至细胞质不稳定铁池 (labile iron pool, LIP) 中, 供细胞利用[8]。在细胞内, 过量的 Fe^{2+} 可被储存于铁蛋白 (ferritin) 中。在铁死亡过程中, 通过铁蛋白自噬 (ferritinophagy) 等机制, 铁蛋白被降解, Fe^{2+} 被释放至 LIP 中, 导致胞内游离 Fe^{2+} 浓度升高。升高的 Fe^{2+} 通过 Fenton 反应 ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^-$) 产生大量高活性的羟基自由基 (·OH), 攻击细胞膜上富含的多不饱和脂肪酸 (PUFAs), 引发脂质过氧化, 最终导致细胞铁死亡[9]。相反, 铁离子螯合剂可通过与 Fe^{2+} 结合, 降低细胞内 LIP 水平, 从而抑制铁死亡发生。此外, 铁调节蛋白 1 (iron regulatory protein 1, IRP1) 和铁调节蛋白 2 (iron regulatory protein 2, IRP2) 可通过感应细胞内铁离子水平, 与铁反应元件 (iron response element, IRE) 结合, 通过动态调节 TFR1 和铁蛋白的 mRNA 稳定性与翻译, 实现精细调控铁的摄取与储存, 维持细胞内铁稳态[10]。

2.3 脂质代谢调控通路 脂质过氧化是铁死亡的执行环节, 脂代谢的重编程直接决定了细胞对铁死亡的敏感性。并非所有脂质都容易发生过氧化。多不饱和脂肪酸 (polyunsaturated fatty acids, PUFAs) 作为铁死亡发生的重要底物, 其中含有双烯丙基氢原子的长链 PUFAs 是最为关键的底物。长链脂酰辅酶 A 合成酶 4 (acyl-CoA synthetase long chain family member 4, ACSL4) 是铁死亡的关键决定因子, ACSL4 特异性催化长链 PUFAs 与辅酶 A (coenzyme A, CoA) 结合, 生成脂酰辅酶 A (PUFA-CoA)[11]; 溶血磷脂酰胆碱酰基转移酶 3 (lysophosphatidylcholine acyltransferase 3, LPCAT3) 将 PUFA-CoA 酯化到溶血磷脂酰乙醇胺上, 合成完整的富含 PUFAs 的磷脂酰乙醇胺 (phosphatidyl ethanolamine, PE) 并整合到细胞膜 (尤其是质膜和线粒体膜) 中; 当富含 PUFAs 的磷脂在细胞膜上形成后, 它们就成为脂质过氧化的目标, 游离铁离子通过 Fenton 反应产生大量羟基自由基 (·OH), 高活性自由基会从 PUFAs 的双烯丙基位置夺取氢原子, 引发脂质自由基 (L·) 链式反应, 最终生成脂质过氧化物 (LOOH)。此外, 脂氧合酶 (lipoxygenases, LOXs) 能直接、特异性催化 PUFAs 过氧化, 如花生四烯酸 15-脂氧合酶 (arachidonate 15-lipoxygenase, ALOX15)、ALOX12 和花生四烯酸脂氧合酶 3 (arachidonate lipoxygenase 3, ALOXE3) 等已被证明在多种细胞环境中促进铁死亡[12]。

2.4 线粒体调控通路 线粒体在铁死亡中扮演着复杂而重要的角色, 不仅是细胞的代谢中心, 而且直接参与了铁死亡的执行过程。在铁死亡初期, 由其他原因(如GPX4抑制等)产生的少量脂质过氧化物会破坏线粒体功能, 导致电子传递链 (electron transport chain, ETC) 功能障碍, 发生电子"泄漏", 将氧气 (O_2) 不完全还原生成超氧化物阴离子($O_2^{-}\cdot$), 产生大量ROS[13]。这形成了一个正反馈循环, 进一步加剧脂质过氧化, 显著放大铁死亡信号。同时, 线粒体是细胞铁代谢的重要节点, 其拥有独立的铁池, 也是血红素和铁硫簇 (Fe-S cluster) 生物合成的场所。当细胞铁水平升高时, 线粒体会大量摄取铁, 导致线粒体内游离铁离子过度累积, 高浓度的 Fe^{2+} 与线粒体产生的 H_2O_2 发生Fenton反应, 产生毒性极强的羟基自由基 (·OH) 攻击线粒体膜脂, 尤其是富含PUFAs的磷脂膜更易被氧化, 加速脂质过氧化。此外, 有研究表明, 线粒体外膜上的电压依赖性阴离子通道 (voltage-dependent anion channel, VDAC) 在线粒体铁死亡中起作用。一个名为VSTM2L的蛋白通过与VDAC1和己糖激酶2 (hexokinase 2, HK2) 相互作用, 抑制VDAC1的寡聚化, 从而维持线粒体稳态并抑制铁死亡[14]。当这种相互作用被破坏时, 会促进铁死亡的发生。相反, 线粒体也存在防御机制, 线粒体GPX4 (mitochondria GPX4, mtGPX4) 可直接清除线粒体内产生的脂质过氧化物, 是保护线粒体免受氧化损伤的第一道防线, 当mtGPX4失效时, 二氢乳清酸脱氢酶 (dihydroorotate dehydrogenase, DHODH) 可以通过其结合的电子辅酶 $CoQH_2$ (泛醇) 直接还原线粒体内的脂质过氧化物, 从而抑制铁死亡[15]。

2.5 其他新兴调控通路 FSP1-CoQ10-NAD(P)H通路: 铁死亡抑制蛋白1 (ferroptosis inhibitory protein 1, FSP1) 是独立于GPX4的铁死亡抑制系统。在质膜上FSP1将氧化型辅酶Q10 (CoQ10) 还原为抗氧化形式的CoQ10(H2), 后者捕获脂质自由基, 从而抑制脂质过氧化, 保护细胞免受铁死亡影响[15]。GCH1-BH4通路: GTP环化水解酶1 (GTP cyclase hydrolase 1, GCH1) 是合成四氢生物蝶呤 (tetrahydrobiopterin, BH4) 的关键限速酶, 而BH4是一种强自由基捕获抗氧化剂, 其抗氧化循环与CoQ10系统相关联, 可维持CoQ10还原态CoQ10(H2), CoQ10(H2)本身也是一种重要的脂溶性抗氧化剂, 能独立于GPX4系统抑制铁死亡[16]。MAPK通路: 活化的p38 MAPK磷酸化并激活转录因子 (如ATF2、CHOP), 这些转录因子会结合*SLC7A11*基因的启动子区域, 抑制SLC7A11表达, 抑制system Xc^- 功能, 诱发铁死亡[17]; 与p38类似, 活化的c-Jun氨基末端激酶 (c-Jun N-terminal kinase, JNK) 磷酸化转录因子c-Jun, 形成激活蛋白1 (activated protein 1, AP-1) 复合物, 上调ACSL4蛋白表达, 增加细胞对脂质过氧化敏感性[18]; JNK磷酸化Bcl-2解除其对自噬相关蛋白Beclin-1的抑制, 激活选择性自噬 (如铁蛋白自噬) 功能, 增加细胞内游离铁水平, 促进Fenton反应[19]; 此外, 激活的细胞外信号调节激酶 (extracellular signal-regulated kinase, ERK) 上调ACSL4表达或增强p53活性来促进铁死亡。PI3K-AKT-mTOR通路: 激活的哺乳动物雷帕霉素靶蛋白复合物1 (mammalian target of rapamycin complex 1, mTORC1) 促进固醇调节元件结合蛋白 (sterol regulatory element-binding protein, SREBPs) 活化和核转位, mTORC1-SREBP促进单不饱和脂肪酸 (monounsaturated fatty acid, MUFAs) 合成, 其通过酯化竞争方式减少PUFAs整合到细胞膜磷脂中, 显著降低细胞膜对脂质过氧化敏感性, 抵抗铁死亡; 此外, 激活的mTORC1能抑制自噬体形成, 减少细胞内游离铁水平, 限制Fenton反应发生, 抑制铁死亡的核心驱动因素; 阿克转鼠科胸腺瘤病毒致癌基因同源物 (Ak strain transforming thymoma viral oncogene homolog, AKT), 常称为蛋白激酶B, 其通过磷酸化Nrf2, 负调控Kelch样ECH相关蛋白1 (kelch-like ECH-associated protein 1, Keap1), 促进Nrf2稳定及核转位, 启动一系列抗氧化和细胞保护基因的转录, 如血红素加氧酶-1 (heme oxygenase 1, HO-1)、醌氧化还原酶-1 (quinone oxidoreductase 1, NQO1) 等[20]。

2.6 铁死亡关键分子在肝细胞与HSCs中的差异表达与调控 铁死亡通路在肝纤维化治疗中的潜力, 很大程度上取决于其关键调控分子在肝细胞与HSCs, 特别是aHSCs中是否存在差异性的表达、活性或调控网络[21]。这种差异是开发选择性药物, 实现保肝细胞、杀aHSCs治疗目标的分子基础。目前研究表明, 多个核心分子在两类细胞中存在显著差异 (图2)。① System Xc^--GSH-GPX4轴: SLC7A11/GPX4在静息态HSCs中表达较低。在aHSCs中, 其表达常因促纤维化信号(如TGF-β)而进一步受到抑制, 导致aHSCs的基础抗氧化能力较弱, 对system Xc^- 抑制剂 (如erastin) 或GPX4抑制剂 (如RSL3) 更为敏感。相反, 正常肝细胞通常维持较高的SLC7A11/GPX4表达以应对代谢压力, 但长期损伤下其表达也可能下调。② 脂质代谢相关分子: ACSL4、FSP1。ACSL4作为铁死亡的正向调控因子, ACSL4在aHSCs中的表达通常显著上调。这与aHSCs需要大量合成细胞外基质、膜重塑活跃有关, 导致其膜磷脂中PUFAs比例升高, 对脂质过氧化更敏感。肝细胞中ACSL4表达水平相对较低且更稳定[22]; FSP1作为GPX4平行的铁死亡抑制系统, FSP1在

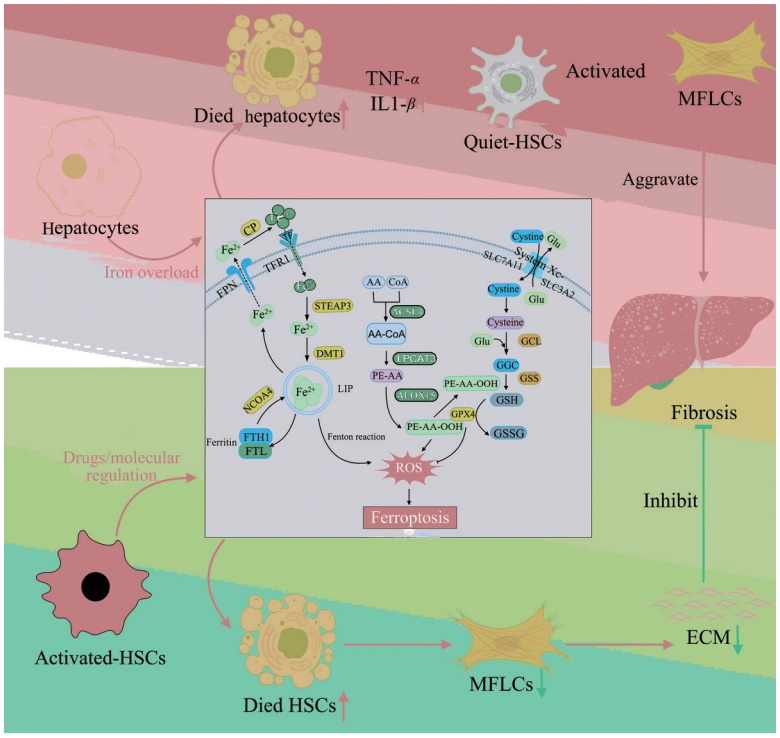


Figure 2 Molecular pathway mechanism of ferroptosis in hepatocytes and hepatic stellate cells. MFLCs: Myofibroblast-like cells; FTH1: Ferritin heavy chain 1; FTL: Ferritin light chain; CP: Ceruloplasmin; STEAP3: Six-transmembrane epithelial antigen of the prostate 3; DMT1: Divalent metal transporter 1; SCD1: Stearoyl-CoA desaturase 1; GPX4: Glutathione peroxidase 4; ALOX15: Arachidonate 15-lipoxygenase; DPP4: Dipeptidyl peptidase 4; GSSG: Glutathione (*S*-*S*-glutathione, oxidized form); GSH: Glutathione (sulfhydryl form); GCLC: Glutamate-cysteine ligase, catalytic subunit; PE-AA: Phosphatidylethanolamine-arachidonic acid; PE-AA-OOH: Phosphatidylethanolamine-arachidonic acid-oxygenated derivatives; SLC7A11: Solute linker carrier family 7, member 11; SLC3A2: Solute linker carrier family 3, member 2; GLU: Glucose; Gly: Glycine; Glu: Glutamate; Cys: Cysteine; LIP: Labile iron pool; AA: Arachidonic acid; AA-CoA: Arachidonoyl-coenzyme A; NCOA4: Nuclear receptor coactivator 4; LPCAT3: Lysophosphatidylcholine acyltransferase 3

aHSCs中的表达可能下调或功能受损, 进一步削弱了aHSCs的抗铁死亡防御。而在部分肝细胞中, FSP1可作为重要的补偿性保护机制。③ 铁代谢相关分子: TFR1/铁蛋白。aHSCs处于增殖状态, 对铁的需求增加, 常表现为TFR1表达上调, 同时铁蛋白储存能力可能相对不足, 导致其不稳定铁池更易波动, 在应激下更快累积游离Fe^{2+}。肝细胞铁代谢则更侧重于稳态维持。④ 调控网络与微环境: aHSCs处于高度氧化应激和富含促纤维化细胞因子 (如TGF-β、PDGF) 的微环境中。这些因素能协同下调SLC7A11/GPX4, 上调ACSL4, 共同将aHSCs推向铁死亡敏感状态。而肝细胞在相同微环境中可能激活不同的适应性应答 (如Nrf2通路)。

3 调控铁死亡肝纤维化中的双重作用及机制

铁死亡在肝纤维化进程中扮演着复杂且具有双重性的角色, 这一特性与肝纤维化发病机制紧密相连 (图3)。一方面, 在正常肝细胞中铁死亡促进肝纤维化发展。当肝细胞遭受铁过载、氧化应激等损伤时, 胞内铁离子浓度显著升高, 进而发生Fenton反应, 产生大量ROS, 诱发脂质过氧化链式反应, 产生过多的脂质过氧化产物, 破坏细胞膜的完整性和功能, 最终致使肝细胞死亡。肝细胞持续死亡会触发肝脏修复反应, 巨噬细胞、中性粒细胞等大量浸润, 释放TNF-α、IL1-β等细胞因子和趋化因子, 激活HSCs转化为肌成纤维细胞样细胞 (myofibroblast-like cells, MFLCs) 分泌大量ECM加速肝纤维化进程。另一方面, 研究显示, 在HSCs中诱导铁死亡, 可以有效抑制肝纤维化的进展。静息HSCs主要储存维生素A和参与肝脏细胞外基质的更新与维持, 在肝纤维化过程中, HSCs被持续激活转化为MFLCs。研究发现, 诱导HSCs发生铁死亡能够有效减少其数量, 降低ECM的合成与分泌, 进而缓解肝纤维化[23]。

3.1 氧化应激调控铁死亡作用 氧化应激作为肝纤维化过程中的关键因素, 与铁死亡之间存在复杂的相互调控关系。如受体相互作用丝氨酸/苏氨酸蛋白激酶4 (receptor-interacting serine/threonine-protein kinase

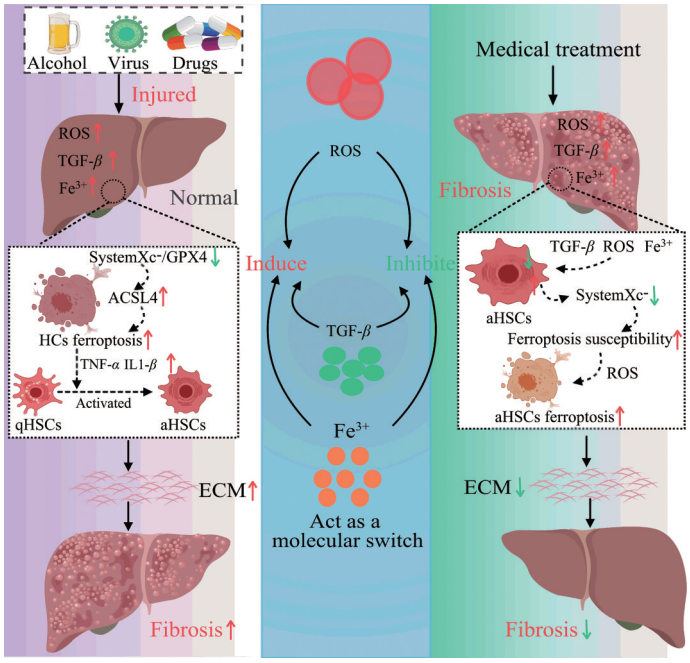


Figure 3 The dual role of ferroptosis in liver fibrosis and its differential regulatory mechanisms. TGF-*β*: Transforming growth factor *β*; ACSL4: Acyl-CoA synthetase long chain family member 4

4, RIPK4) 通过调控酰基辅酶 A 合成酶中链家族成员 1 (acyl-CoA synthetase medium chain family member 1, ACSM1) 的表达, 影响铁死亡发生, 这揭示了氧化应激和铁死亡之间的新机制。在肝纤维化发生发展过程中, 多种致病因素如病毒感染、酒精刺激、药物损伤等会导致肝脏内氧化还原平衡失调, 产生大量 ROS 直接损伤肝细胞和 HSCs, 同时还能经由多种信号通路影响铁死亡发生。一方面, ROS 可促进铁离子从铁蛋白中释放, 增加细胞内游离铁离子浓度, 为 Fenton 反应提供更多底物, 加剧脂质过氧化, 诱导铁死亡发生; 另一方面, 铁死亡过程中产生大量脂质过氧化产物会进一步加重氧化应激, 形成恶性循环, 共同推动肝纤维化进展。在氧化应激条件下, 一些抗氧化防御系统的关键成分会发生变化, 进而影响铁死亡调控。如 Nrf2 是细胞内重要抗氧化转录因子, 在正常情况下, Nrf2 与 Keap1 结合时处于失活状态, 当细胞受到氧化应激刺激时, Nrf2 脱离 Keap1, 进入细胞核结合到抗氧化反应元件 (antioxidant response element, ARE) 上, 激活如 HO-1、NQO1 等抗氧化基因表达, 清除 ROS 抑制脂质过氧化, 发挥抑制铁死亡作用。然而, 在肝纤维化过程中, Nrf2 信号通路常受到抑制, 导致其抗氧化能力降低, 无法有效抑制铁死亡和氧化应激, 进而加重肝脏损伤。在乙肝病毒感染所致的肝纤维化患者中, 肝组织内 Nrf2 表达水平显著降低, 同时铁死亡相关指标升高, 这提示 Nrf2 信号通路的抑制可能促进了铁死亡和肝纤维化发展。

3.2 细胞因子调控铁死亡作用 细胞因子在肝纤维化进程中发挥着重要的调节作用, 同时对铁死亡的发生和发展也产生显著影响。多种细胞因子如 TGF-*β*、PDGF、TNF-*α* 等在肝纤维化过程中异常表达, 它们通过与细胞表面相应受体结合, 激活下游信号通路, 不仅参与 HSCs 激活和 ECM 合成, 还能调控铁死亡相关分子表达和活性[5]。研究发现, TGF-*β* 是目前已知最强促纤维化细胞因子, 在肝纤维化过程中, TGF-*β* 表达显著上调, 其通过激活 Smad 信号通路, 抑制 HSCs 中 system Xc^- 功能, 减少胱氨酸摄取, 降低胞内 GSH 合成, 降低 GPX4 活性, 无法有效清除脂质过氧化物, 增加 HSCs 对铁死亡敏感性[4]。此外, TGF-*β* 通过调节铁代谢相关蛋白的表达, 如增加 TFR1 表达, 促进铁离子的摄取, 加剧 HSCs 铁死亡。TNF-*α* 是一种具有多种生物学功能的细胞因子, 在肝纤维化过程中, 其表达也明显增加。TNF-*α* 通过激活受体相互作用调节性诱导蛋白 1 (regulatory induced protein 1, RIP1) 和 RIP3, 诱导细胞发生坏死性凋亡, 同时促进铁死亡发生。研究表明, TNF-*α* 通过上调 NADPH 氧化酶 4 (nicotinamide adenine dinucleotide phosphate oxidase 4, NOX4) 表达, 增加 ROS 产生促进铁死亡[24]。此外, TNF-*α* 还通过调节铁代谢相关蛋白, 如铁蛋白重链 (ferritin heavy chain, FTH)、铁蛋白轻链 (ferritin light chain, FTL) 等, 影响细胞内铁离子的储存和释放, 参与铁死亡的调

控[25]。在酒精性肝纤维化小鼠模型中, 给予TNF-α抑制剂后, 观察到肝组织内铁死亡相关指标MDA含量、铁离子浓度等明显降低, 同时肝纤维化程度也得到缓解。这与虎葛颗粒 (Hu-Ge granules, HGG) 对肝纤维化大鼠肝脏GSH、丙二醛 (malondialdehyde, MDA) 及血清TNF-α含量的影响相一致, 进一步提示TNF-α在酒精性肝纤维化过程中对铁死亡具有促进作用[26]。

4 调控铁死亡抗肝纤维化药物及作用机制

4.1 天然产物药物方面 天然产物是抗肝纤维化药物研发的重要来源, 其可通过调控铁死亡的关键通路发挥治疗作用 (表1)。一是诱导HSCs铁死亡类。此类天然产物通过抑制抗氧化防御体系, 选择性清除活化的HSCs, 如姜黄素 (curcumin, CUR) 源自姜科植物姜黄根茎, 通过抑制Nrf2/ARE通路增加ROS生成, 诱导HSCs铁死亡[27]; 辣椒素 (capsaicin, CAP) 源自辣椒, 通过激活瞬时受体电位香草酸亚型1 (transient receptor potential vanilloid subtype 1, TRPV1) 通道引发钙内流和氧化应激, 抑制system Xc^-/GPX4通路, 诱导HSCs铁死亡[28]; 汉黄芩素 (wogonin, WOG) 源自黄芩, 直接抑制Nrf2信号通路, 下调GPX4和SLC7A11表达, 削弱抗氧化能力, 触发脂质过氧化累积[29]; 蒿甲醚 (artemether, ART) 源自青蒿素, 脂溶性更易进入aHSCs, 其过氧桥(-O-O-) 与Fe^{2+}反应发生裂解, 产生大量活性碳中心自由基, 攻击细胞膜上的PUFAs, 启动脂质过氧化链式反应, 诱导aHSCs铁死亡[30]。二是抑制肝细胞铁死亡类。此类天然产物通过螯合铁或增强抗氧化能力, 保护肝细胞免受损伤, 如乳铁蛋白 (lactoferrin, LF), 源自乳汁, 通过强力螯合游离铁, 抑制Fenton反应和脂质过氧化, 保护肝细胞[31]; 甘草酸镁 (magnesium isoglycyrrhizinate, MgIG) 源自天然甘草, 通过激活Nrf2信号通路, 减轻肝细胞损伤, 抑制肝细胞发生铁死亡, 从源头阻断HSCs活化, 间接实现抗纤维化效果[32]。三是多机制协同作用。此类天然产物同时作用于多条通路, 兼具诱导HSCs死亡和保护肝细胞的双重作用, 如黄芩苷 (baicalin, BA), 源自黄芩, 抑制GPX4活性并诱发线粒体功能障碍, 增加ROS产生促进HSCs铁死亡, 还可激活Nrf2信号通路, 诱导HO-1和GPX4表达, 增强肝细胞抗氧化能力, 清除过多脂质过氧化物, 保护肝细胞免受铁死亡[3]; 白藜芦醇 (resveratrol, RSV)[33]、芹菜素 (apigenin, API)[34]、槲皮素 (quercetin, QUE)[35]等通过激活Nrf2, 上调GPX4和SLC7A11表达, 抑制肝细胞铁死亡, 亦可通过抑制TGF-β1/Smad通路, 下调HSCs活化标志物合成, 诱导aHSCs凋亡和自噬。

Table 1 Drugs for treating liver fibrosis by regulating ferroptosis with natural products

Drug source	Representative drug	Mechanisms of action	Pre-clinical/clinical progress	Advantage	Limitation
Turmeric rhizome	Curcumin (CUR)	Inhibit Nrf2/ARE pathway, increase ROS generation, induce HSCs ferroptosis	Cell and animal experiments showed anti-fibrotic effects	Anti-inflammatory and antioxidant polypharmacism	Fast metabolism *in vivo*, low bioavailability, poor cellular selectivity, potential hepatotoxicity risk
Chili pepper	Capsaicin (CAP)	CAP activates TRPV1, causing Ca^{2+} influx, calcium overload, and mitochondrial dysfunction. This leads to ROS production, inducing HSCs apoptosis	Animal studies have confirmed the effectiveness of CAP against liver fibrosis	Strong targeting, anti-inflammatory, antioxidant and multi-effect of regulating lipid metabolism	Fast metabolism *in vivo*, low bioavailability, poor cellular selectivity
Scutellaria baicalensis	Wogonin (WOG)	Inhibit Nrf2/ARE pathway, downregulate GPX4 and SLC7A11 expression to weaken cells' antioxidant defense capacity; then promote ROS production to induce HSCs ferroptosis	Cell and animal experiments showed that WOG had anti-fibrotic effect	Multiple targets, anti-inflammatory and antioxidant multi-effect	Fast metabolism *in vivo*, low bioavailability, poor cellular selectivity
Artemisinin	Artemether (ART)	ART peroxide bridge bond is cleaved by Fe^{2+}, resulting in a large amount of ROS and inducing ferroptosis of aHSCs	Accurate aHSCs ferroptosis was triggered in cell and animal models. Meanwhile, ART was used to treat drug-resistant malignant malaria	Highly fat-soluble, it easily passes through cell membranes and blood-brain barrier, and has higher bioavailability	Potential neurotoxicity at high doses, poor cellular selectivity
Mammalian milk	Lactoferrin (LF)	Chelate-free Fe^{2+}, inhibit Fenton reaction, reduce oxidative stress, protect hepatocytes from ferroptosis	Animal experiments support LF's anti-liver fibrosis effect. Moreover, LF has been used as an adjuvant therapy and nutritional supplement	High safety, as an oral preparation, good patient compliance, no need for injection	Moderate effect, low bioavailability, limited cellular selectivity

Continued

Drug source	Representative drug	Mechanisms of action	Pre-clinical/clinical progress	Advantage	Limitation
Glycocholic acid and derivatives	Magnesium isoglycyrrhizinate (MgIG)	Activate Nrf2 signaling pathway, reduce hepatocyte injury and ferroptosis, block HSCs activation signal, and achieve anti-fibrosis effect	MgIG is used in clinical liver injury treatment, and its anti-fibrosis effect is key to its overall liver protection	Water soluble, suitable for preparation of injectables, easy to metabolize	Extremely limited capacity to directly reverse severe fibrosis, limited selectivity for HSCs over hepatocytes in pro-ferroptotic contexts
Scutellaria baicalensis	Baicalin (BA)	Activate Nrf2, upregulate GPX4 and SLC7A11 to inhibit hepatocyte ferroptosis. Inhibit GPX4, induce mitochondrial dysfunction and increase ROS to promote HSCs ferroptosis	BA protects against erastin-induced ferroptosis in cell and animal models, reducing liver inflammation and fibrosis	Unique bidirectional regulatory effect, multi-effect synergy	Difficult to absorb orally, fast metabolism, low bioavailability, complex bidirectional effects challenging selectivity control
Grapes, peanuts, *etc*.	Resveratrol (RSV)	Activate Nrf2, upregulate GPX4 and SLC7A11 expression to inhibit hepatocytes ferroptosis. Inhibit TGF-β1/Smad pathway, downregulate HSCs activation markers synthesis, and induce aHSCs apoptosis and autophagy	RSV has been shown to be effective against liver fibrosis in cell and animal models	Broad mechanism, including antioxidant, anti-inflammatory, anti-apoptosis (hepatocytes), pro-apoptosis (HSCs), and autophagy regulation	Fast metabolism *in vivo*, low bioavailability, poor cellular selectivity for ferroptosis induction
Celery, cilantro, *etc*.	Apigenin (API)	Activate Nrf2, upregulate GPX4 and SLC7A11, inhibit hepatocyte ferroptosis. Meanwhile, inhibit TGF-β1/Smad pathway, downregulate HSCs activation marker synthesis, and induce aHSCs apoptosis and autophagy	API has been shown to be effective against liver fibrosis in cell and animal models	Multiple target characteristics, high safety	Fast metabolism *in vivo*, low bioavailability, poor cellular selectivity
Flavonols in fruits, vegetables, *etc.*	Quercetin (QUE)	Activate Nrf2, upregulate GPX4 and SLC7A11 to inhibit hepatocyte ferroptosis. Meanwhile, inhibit TGF-β1/Smad pathway, downregulate HSCs activation marker synthesis, and induce aHSCs apoptosis and autophagy	QUE has been shown to be effective against liver fibrosis in cell and animal models	High safety, anti-inflammatory and antioxidant polypharmacy	Fast metabolism *in vivo*, low bioavailability, poor cellular selectivity

4.2 人工合成药物方面 人工合成物质通过精确靶向铁死亡通路, 为抗肝纤维化治疗提供了新策略 (表2)。一是诱导HSCs铁死亡类。此类物质通过抑制system Xc^- – GPX4抗氧化轴, 选择性清除aHSCs。如索拉非尼 (sorafenib, Sora) 作为多激酶抑制剂, 临床用于晚期肝癌治疗, 通过直接抑制system Xc^-功能, 阻断胱氨酸摄取, 耗竭GSH间接失活GPX4, 诱导aHSCs铁死亡, 减轻肝纤维化, 但临床应用中出现手足皮肤反应、腹泻等不良反应, 限制了其在肝纤维化治疗中的推广[7]。SAS和Era等能直接抑制system Xc^-功能, SAS是已上市抗炎药, 但缺乏选择性和潜在肝毒性限制了其应用, 而Era是作为铁死亡的首个发现工具药, 缺乏临床适用性; RAS选择性致死分子3 (RAS selective lethal molecule 3, RSL3) 则直接共价抑制GPX4活性, 绕过上游通路, 快速诱发铁死亡, 在动物模型中证实可特异性清除HSCs减轻纤维化, 是重要科研工具[36]; 青蒿琥酯 (artesunate, AS) 通过铁依赖性反应产生ROS, 下调GPX4表达, 协同诱导HSCs铁死亡[37]。二是抑制肝细胞铁死亡类的物质。这类物质通过增强抗氧化防御能力或减少铁依赖性氧化损伤, 保护肝细胞, 从源头上阻止纤维化的启动。如铁螯合剂去铁胺 (deferoxamine, DFO) 通过结合游离铁离子, 减少Fenton反应阻断脂质过氧化启动, 适用于铁过载相关肝病, 但需肠胃外给药, 不便长期使用[38]; 脂质抗氧化剂利普斯塔-1 (liproxstatin-1, Lip-1) 和铁死亡抑制剂-1 (ferrostatin-1, Fer-1), 作为脂溶性抗氧化剂直接中和脂质过氧自由基, 稳定细胞膜, 在多种肝损伤模型中保护肝细胞, 减轻纤维化, 是验证铁死亡机制的关键工具药, 但成药性差[39]。三是多机制协同作用。此类物质通过多重通路协同作用, 兼具诱导HSCs死亡和保护肝细胞的效果。如瑞戈非尼 (regorafenib), 拜耳公司开发的索拉非尼衍生物, 是一种口服多激酶抑制剂, 有

效抑制 system Xc⁻, 阻断胱氨酸摄取, 耗竭 GSH, 进而诱导 GPX4 失活, 且能靶向血管内皮生长因子受体 1～3 (vascular endothelial growth factor receptor 1－3, VEGFR1－3)、血小板衍生生长因子受体 (platelet-derived growth factor receptor, PDGFR)、成纤维细胞生长因子受体 (fibroblast growth factor receptor, FGFR) 等激酶, 抑制 HSCs 活化和病理性血管生成[40]。

4.3 实现 HSCs 选择性铁死亡诱导的策略 尽管铁死亡为肝纤维化治疗提供了新思路, 但实现肝星状细胞 (尤其是 aHSCs) 选择性铁死亡诱导仍是当前转化的核心挑战。现有大多数铁死亡诱导剂 (如 erastin、RSL3、CUR 等) 缺乏细胞类型选择性, 可同时损伤肝细胞, 反而加剧纤维化。因此, 未来研究应聚焦于: ① 解析 HSCs 特异性铁死亡调控网络。系统比较静息态 HSCs、aHSCs 与肝细胞在 system Xc⁻、GPX4、ACSL4、FSP1 等关键分子上的表达差异、翻译后修饰状态及表观遗传调控特征, 寻找可靶向 HSCs 或 aHSCs 特异性脆弱点[41]; ② 开发细胞选择性递送系统。利用纳米载

Table 2 Artificially synthesized drugs for regulating ferroptosis to treat liver fibrosis

Representative drug	Mechanisms of action	Pre-clinical/clinical progress	Advantage	Limitation
Sorafenib (Sora)	Inhibit system Xc^- function, block cystine uptake, deplete GSH, inactivate GPX4, induce HSCs ferroptosis	Cell and animal experiments confirmed Sora can reduce liver fibrosis, and it has been used in clinical liver cancer treatment	The potential of "old medicine with new use", multi-target and multi-mechanism coordination	Lack of clinical data for fibrosis, side effects, poor cellular selectivity, potential hepatotoxicity risk
Sulfasalazine (SAS)	Highly inhibit system Xc^- function, block cystine uptake, deplete GSH, and indirectly inactivate GPX4	The anti-liver fibrosis effect of SAS has been confirmed *in vitro* and animal models	As an oral drug, patients have good compliance and convenient administration	Lack of cellular selectivity, potential hepatotoxicity
Erastin (Era)	Inhibit system Xc^- function, block cystine uptake, deplete GSH, inactivate GPX4, induce HSCs ferroptosis	The anti-liver fibrosis effect of SAS has been confirmed *in vitro* and animal models	Preclinical research tool compounds	Lack of clinical applicability, poor cellular selectivity
Ras-selective lethal small molecule 3 (RSL3)	Inhibit GPX4 activity, leads to the failure of lipid peroxides cannot be reduced, specifically induced ferroptosis in aHSCs	The anti-fibrotic effect of RSL3 on ferroptosis has been confirmed in cell and animal models	Preclinical research tool compounds	Lack of clinical applicability, poor cellular selectivity
Artesunate (AS)	AS hydrolyzed to dihydroartemisinin (DHA), the peroxide bridge of DHA is cleaved by Fe^{2+}, produces a large amount of ROS and induces ferroptosis in aHSCs	AS can induce ferroptosis of aHSCs to achieve anti-liver fibrosis has been confirmed *in vitro* and animal models	Anti-inflammatory and antioxidant multi-effect; precise mechanism of action	Lack of clinical data, unknown long-term safety, contraindicated for pregnant women, poor cellular selectivity
Deferoxamine (DFO)	Chelate-free Fe^{2+}, inhibit Fenton reaction, reduce oxidative stress, protect hepatocytes from ferroptosis	DFO has been approved by the FDA for the treatment of iron overload	Mechanism and safety are clear and approved for marketing	Oral absorption extremely poor, must be infused, lacks cellular specificity, may systemically chelate iron
Liproxstatin-1 (Lip-1)	Neutralize lipid peroxide free radicals, inhibit lipid peroxidation, block hepatocyte ferroptosis, protect hepatocytes from damage, and prevent HSCs activation	*In vitro* and animal models have confirmed that Lip-1 protects hepatocytes from damage by inhibiting ferroptosis	Preclinical research tool compounds	Lack of clinical applicability, poor cellular selectivity as a protective agent
Ferrostatin-1 (Fer-1)	Neutralize lipid peroxide free radicals, inhibit lipid peroxidation, block the process of hepatocyte ferroptosis, protect hepatocytes from damage, and prevent HSCs activation	In animal models, Fer-1 can effectively reduce liver injury and secondary fibrosis caused by alcohol and drugs	Preclinical research tool compounds	Poor pharmacokinetic properties, poor cellular selectivity as a protective agent
Regorafenib	Inhibit system Xc^- function, block cystine uptake, deplete GSH, inactivate GPX4, and induce HSCs ferroptosis. Meanwhile, target VEGFR1−3, TIE2, PDGFR *etc*. to inhibit HSCs activation and pathological angiogenesis	Rigobinib is a marketed drug approved for treating metastatic colorectal cancer, gastrointestinal stromal tumor, and hepatocellular carcinoma (HCC)	The potential of "old medicine with new use", multi-target and multi-mechanism coordination	Side effects limit use for liver fibrosis treatment, poor cellular selectivity

体、抗体偶联药物 (antibody-drug conjugate, ADC) 或配体导向递送技术, 将铁死亡诱导剂特异性递送至aHSCs。如基于aHSCs高表达血小板衍生生长因子受体β (platelet-derived growth factor receptor β, PDGFRβ)或整合素$\alpha v\beta 3$的特性设计靶向载体[42,43]; ③ 利用微环境调控实现选择性。aHSCs处于高度氧化应激和铁富集的微环境中, 其对铁死亡的阈值可能低于肝细胞。可通过设计前药, 使其仅在aHSCs特有的高ROS或高铁环境下被激活, 从而实现选择性杀伤; ④ 结合基因治疗与蛋白质药物。如本课题组构建的细胞穿膜肽TAT与胞红蛋白 (cytoglobin, Cygb) 的融合蛋白TAT-Cygb, 通过穿膜肽递送胞红蛋白, 特异性地在LX2细胞中触发铁死亡[2]; ⑤ 多通路协同调控。联合使用低剂量铁死亡诱导剂与HSCs活化抑制剂 (如TGF-β受体抑制剂), 在降低全身毒性的同时增强对aHSCs的清除效果。

5 展望

铁死亡在肝纤维化的治疗中显示出巨大的潜力, 有望成为突破现有治疗困境的关键方向。实现aHSCs选择性铁死亡诱导并非单一学科可以完成, 它需要分子生物学、药物化学、材料科学和临床医学的深度融合。未来的研究应更加注重: ① 利用单细胞测序等技术, 进一步精细绘制aHSCs与肝细胞在铁死亡通路上的全景差异图谱; ② 发展更先进的生物材料, 实现药物的时空可控释放; ③ 在类器官或更接近人体的动物模型中, 系统性评估选择性策略的有效性与安全性。此外, 在现有的研究基础上, 加快靶向铁死亡通路的药物研发和临床转化进程至关重要。因此, 研究人员需拓宽靶向药物来源, 开拓新型治疗方式, 如开发蛋白药物及其基因治疗手段。本课题组致力于抗肝纤维化机制及相关蛋白药物 (如TAT-Cygb) 研究[2,44,45], 后续课题组将继续探索对这类大分子药物进一步工程化改造 (如添加HSCs靶向肽), 提高其细胞选择性, 并探索通过基因治疗方式解决药物递送、靶向性和生物利用度等困扰临床应用转化问题。

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利益冲突: 作者之间无利益冲突。

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