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·综述·

双硫死亡的分子调控与靶向治疗研究进展

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摘要 双硫死亡(disulfidptosis)是近年来发现的由细胞内二硫键应激触发的新型程序性细胞死亡(programmed cell death, PCD)方式, 其分子机制独立于凋亡、焦亡、铁死亡等经典程序性细胞死亡方式。该死亡方式的核心级联反应为: 在溶质载体家族7成员11(solute carrier family 7 member 11, SLC7A11)高表达细胞中, 葡萄糖缺乏会引发还原型烟酰胺腺嘌呤二核苷酸磷酸(NADPH)耗竭, 进而导致以肌动蛋白为主的细胞骨架蛋白异常二硫键交联与网络崩解。该通路在疾病发生发展中扮演着重要角色: 相关研究不仅阐明了高表达SLC7A11的肿瘤存在全新的代谢脆弱性, 还证实了靶向双硫死亡通路与内质网应激(endoplasmic reticulum stress, ERS)抑制剂联合使用能够产生协同治疗效应; 此外, 该通路还参与非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)的发生与进展, 同时为阐释肿瘤微环境中乳酸脱氢酶B(lactate dehydrogenase B, LDHB)介导的$CD8^+$ T细胞功能耗竭的新型免疫逃逸机制提供了全新理论依据。目前, 靶向该通路的治疗策略及相关预测工具的研究已取得一定进展, 未来可围绕疾病谱拓展、与其他细胞死亡方式的交互作用、精准靶向药物开发等方向进行深入研究, 为相关领域基础研究与临床转化提供系统的理论参考。

关键词 双硫死亡; SLC7A11; NADPH; 肿瘤代谢; 免疫调节; 靶向治疗

Research Progress on Molecular Regulation and Targeted Therapy of Disulfidptosis

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Abstract Disulfidptosis is a newly identified form of PCD (programmed cell death) caused by intracellular disulfide stress, with a unique molecular mechanism distinct from other PCD modalities such as apoptosis, pyroptosis, and ferroptosis. In this form of PCD, glucose deprivation in cells with high SLC7A11 expression leads to the depletion of NADPH. The resulting NADPH deficiency triggers abnormal disulfide cross-linking and collapse of

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the actin-dominated cytoskeletal network. The disulfidptosis pathway plays a pivotal role in disease pathogenesis and progression. Relevant studies have not only clarified that SLC7A11-high tumors exhibit a novel metabolic vulnerability, but also confirmed that targeting the disulfidptosis pathway in combination with ERS (endoplasmic reticulum stress) inhibitors exerts synergistic therapeutic effects. In addition, this pathway contributes to the progression of NAFLD (non-alcoholic fatty liver disease), and provides a novel theoretical basis for elucidating the immune escape mechanism of $CD8^+$ T cell functional exhaustion mediated by LDHB (lactate dehydrogenase B) in the tumor microenvironment. Currently, various therapeutic strategies targeting this pathway have been proposed. Future research will further clarify its disease relevance and crosstalk with other types of programmed cell death, thereby laying a systematic theoretical foundation for the development of precision targeted therapies.

Keywords disulfidptosis; SLC7A11; NADPH; tumor metabolism; immune regulation; targeted therapy

程序性细胞死亡(programmed cell death, PCD)是维持生物体稳态的核心生理过程, 是阐明发育障碍、衰老及重大疾病发病机制的关键, 更是肿瘤、神经退行性疾病靶向治疗的重要突破口, 已成为转化医学研究热点[1]。除经典凋亡外, 坏死性凋亡(necroptosis)、焦亡(pyroptosis)、铁死亡(ferroptosis)、铜死亡(cuproptosis)、双硫死亡(disulfidptosis)等新型亚型被陆续发现, 各类死亡方式在形态、分子机制及病理功能上存在显著差异[2-3]。为明确双硫死亡与其他主要PCD亚型的核心区别, 本文对各亚型关键特征进行整理对比(表1)。

表1 双硫死亡与其他主要程序性细胞死亡亚型的关键特征对比

Table 1 Comparison of key characteristics between disulfidptosis and other major programmed cell death subtypes

程序性细胞死亡类型 Type of programmed cell death	触发因素 Triggers	关键分子 Key molecules	形态特征 Morphological features	核心通路 Core pathways	特异性抑制剂 Specific inhibitors
Disulfidptosis	Glucose deprivation, disulfide stress, inhibition of SLC7A11 function	SLC7A11, NADPH, G6PD, actin, Rac1	Cytoskeletal collapse, plasma membrane rupture, disulfide accumulation	Imbalanced glucose metabolism, NADPH depletion, disulfide stress, cytoskeletal collapse	DTT (dithiothreitol) and other disulfide-reducing agents, SLC7A11 activators
Necroptosis	Death receptor stimulation (e.g., TNF-α), viral infection, caspase-8 inhibition	RIPK1, RIPK3, MLKL, caspase-8	Cell swelling, plasma membrane rupture, organelle swelling, necrotic morphology	RIPK1/RIPK3 necrosome formation, MLKL phosphorylation and membrane disruption	Necrostatin-1 (RIPK1 inhibitor), GSK'872 (RIPK3 inhibitor), necrosulfonamide (MLKL inhibitor)
Apoptosis	Apoptotic stimuli, DNA damage, oxidative stress	Caspase family, Bcl-2 family, p53	Cell shrinkage, chromatin condensation, apoptotic body formation	Extrinsic death receptor pathway, intrinsic mitochondrial pathway	Z-VAD-FMK (pan-Caspase inhibitor)
Pyroptosis	Inflammatory stimuli, pathogen infection	Caspase-1/4/5/11, GSDMD	Membrane pore formation, inflammatory cytokine release, cell swelling	Inflammasome activation, GSDMD cleavage, membrane pore formation	VX-765 (Caspase-1 inhibitor)
Ferroptosis	Iron accumulation, lipid peroxidation, GSH depletion	GPX4, SLC7A11, ACSL4	Lipid peroxidation of cellular membranes, mitochondrial damage, iron accumulation	GSH depletion, lipid peroxidation, dysregulated iron metabolism	Ferrostatin-1, Liproxstatin-1
Cuproptosis	Copper accumulation, abnormal protein lipoylation	FDX1, DLAT, LIAS	Mitochondrial damage, protein misfolding, cell swelling	Abnormal copper ion transport, protein lipoylation, mitochondrial dysfunction	TTM (tetrathiomolybdate)

双硫死亡是甘波谊团队[4]于2023年在*Nature Cell Biology*首次报道的新型程序性细胞死亡亚型，其发现背景源于对SLC7A11高表达肿瘤细胞代谢脆弱性的研究。该团队在体外培养的溶质载体家族7成员11(solute carrier family 7 member 11, SLC7A11)高表达肺腺癌细胞模型中发现，在葡萄糖缺乏条件下，细胞会出现一种不同于凋亡、铁死亡等的新型细胞死亡形态，表现为细胞骨架急剧崩解、细胞膜破裂，进一步研究证实该死亡方式由细胞内二硫键应激触发，故将其命名为双硫死亡[4]。这一发现突破了传统程序性细胞死亡的认知局限，揭示了代谢、氧化还原与细胞骨架之间的新型关联，为SLC7A11高表达肿瘤的治疗提供了全新靶点。双硫死亡不受经典死亡通路抑制剂调控，仅被二硫键还原剂逆转，具备独立的生物学特征[4]，也为SLC7A11高表达肿瘤的代谢干预提供了新思路[5-6]。本文系统综述双硫死亡分子机制、病理作用及靶向治疗研究进展，为该领域研究提供参考。

1 双硫死亡的核心分子机制

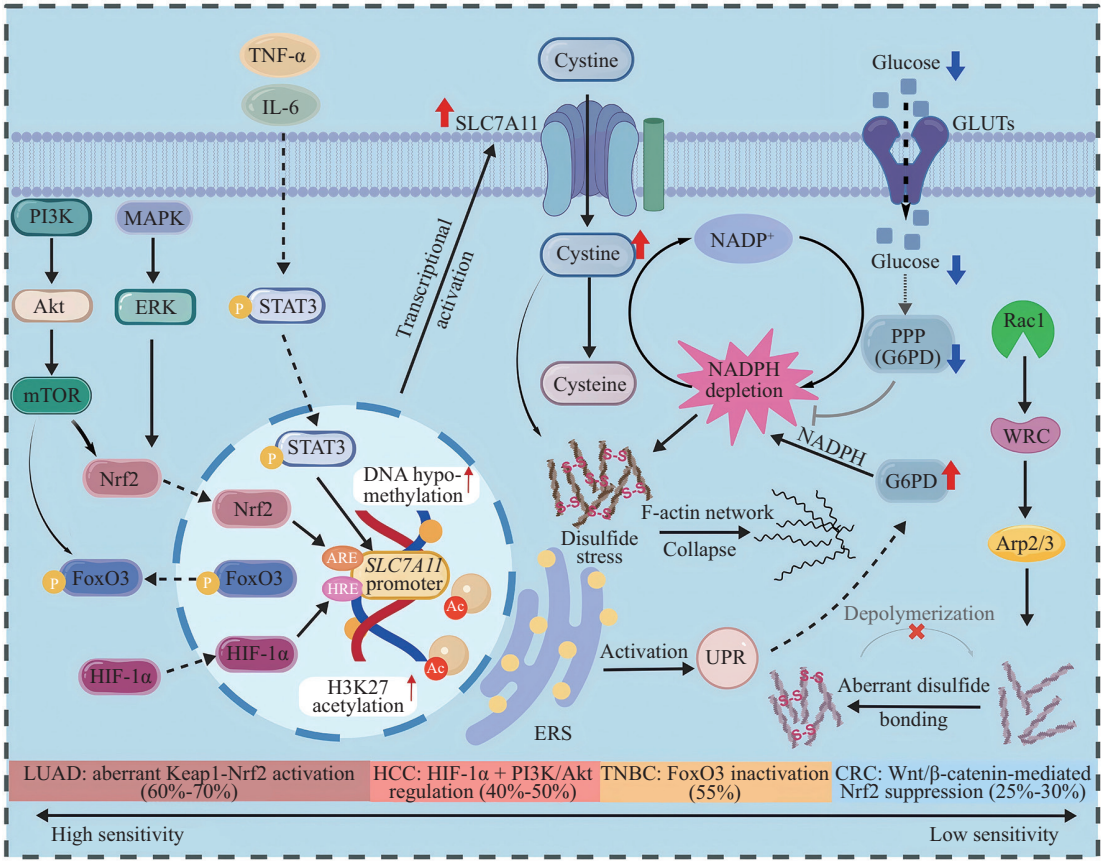
双硫死亡以代谢失衡-NADPH耗竭–二硫键应激–细胞骨架崩解为核心信号轴，同时涵盖Rac1-WAVE调节复合物(WAVE regulatory complex, WRC)通路、内质网应激代偿等调控网络，核心机制如图1所示。

1.1 代谢触发与失衡

1.1.1 SLC7A11表达与代谢转换 SLC7A11是双硫死亡的关键分子开关，其表达水平与代谢状态共同决定细胞死亡命运。SLC7A11表达并非恒定，可受多种转录因子、表观遗传修饰调控，这也是不同肿瘤间其表达水平差异显著的核心原因。肿瘤微环境中的特定信号通路同样会诱导其异常高表达。

核因子E2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)是转录调控层面的核心转录因子，可直接结合*SLC7A11*启动子的抗氧化反应元件(antioxidant response element, ARE)以促进其转录。肿瘤中*Nrf2*常因基因突变、Keap1降解异常而被激活，进而导致SLC7A11持续高表达[7]；缺氧诱导因子1α(hypoxia-inducible factor-1α, HIF-1α)可结合*SLC7A11*启动子的缺氧响应元件(hypoxia response element, HRE)上调其表达[8]；叉头框蛋白O3(forkhead box O3, FoxO3)则发挥转录抑制作用，其失活会解除对SLC7A11的抑制[9]。在表观遗传调控方面，DNA甲基化、组蛋白修饰均可调控*SLC7A11*表达，*SLC7A11*启动子低甲基化可增强该基因的转录活性，在肺癌、肝癌中，DNA甲基转移酶抑制剂可诱导其表达上调[10]；组蛋白H3K27乙酰化可促进*SLC7A11*转录，组蛋白去乙酰化酶(histone deacetylase, HDAC)抑制剂则能通过增加H3K27乙酰化水平，进一步上调其表达[11]。在肿瘤微环境中，PI3K/Akt/mTOR通路作为主要调控通路，持续激活可磷酸化FoxO3使其失活，同时促进Nrf2核转移，协同上调SLC7A11[12]；MAPK/ERK通路通过激活Nrf2促进*SLC7A11*转录[13]；TNF-α、IL-6等炎症因子可激活STAT3信号通路，间接上调SLC7A11表达，以帮助肿瘤适应炎症应激[14]。SLC7A11的上游调控网络复杂，核心调控因子包括Nrf2、HIF-1α、FoxO3等转录因子及DNA甲基化、组蛋白乙酰化等表观遗传修饰。在肿瘤中，*SLC7A11*高表达的核心原因可分为三个层面：一是转录层面，*Nrf2*、*HIF-1α*等异常激活持续驱动*SLC7A11*转录；二是表观遗传层面，*SLC7A11*启动子甲基化水平低、H3K27乙酰化水平高从而增强其转录活性；三是肿瘤微环境层面，PI3K/Akt/mTOR等信号通路持续激活协同上调其表达[15]，最终使肿瘤细胞获得抗氧化优势，同时也形成了对双硫死亡的代谢脆弱性。在生理状态下，SLC7A11介导胱氨酸摄取，维持谷胱甘肽(glutathione, GSH)合成与氧化还原稳态；当葡萄糖缺乏时，磷酸戊糖途径(pentose phosphate pathway, PPP)受阻导致NADPH生成减少，SLC7A11持续驱动胱氨酸还原进一步消耗NADPH，供需失衡引发NADPH耗竭并启动双硫死亡[16]。SLC7A11异常高表达使肿瘤细胞的抗氧化优势转化为可被靶向干预的代谢脆弱性，这也解释了此类肿瘤对葡萄糖剥夺的高度敏感性，为靶向肿瘤代谢脆弱性提供了理论依据[6]。

不同癌种中的SLC7A11的表达水平存在显著差异，且直接影响肿瘤细胞对双硫死亡的敏感性：肺腺癌中SLC7A11高表达比例最高(60%~70%)，主要与Keap1-Nrf2通路异常激活相关，因此肺腺癌细胞对葡萄糖剥夺或葡萄糖转运/PPP通路抑制所诱导的双硫死亡敏感性最强，肺腺癌也是双硫死亡靶向治疗的优先适应证[17-18]；肝癌中SLC7A11高表达比例为40%~50%，受HIF-1α和PI3K/Akt通路共同调控，其高表达肝癌细胞对双硫死亡诱导剂的敏感



SLC7A11是双硫死亡的重要分子开关, 其表达受Nrf2、HIF-1α、FoxO3等转录因子及DNA甲基化、H3K27乙酰化等表观遗传修饰调控。在肿瘤微环境中, PI3K/Akt/mTOR、MAPK/ERK及TNF-α、IL-6激活的STAT3信号通路可协同上调SLC7A11表达, 增强肿瘤细胞抗氧化能力并形成双硫死亡相关代谢脆弱性。当葡萄糖缺乏时, SLC7A11高表达细胞PPP受阻、NADPH生成减少, 而胱氨酸还原持续消耗NADPH, 最终导致其耗竭; 继而细胞骨架蛋白发生异常二硫键交联, 诱导骨架崩解并触发双硫死亡。Rac1-WRC通路可促进该进程, 而ERS可通过上调G6PD产生代偿性保护作用。SLC7A11: 溶质载体家族7成员11; Nrf2: 核因子E2相关因子2; HIF-1α: 缺氧诱导因子1α; FoxO3: 叉头框蛋白O3; PI3K: 磷酸肌醇3-激酶; Akt: 蛋白激酶B; mTOR: 哺乳动物雷帕霉素靶蛋白; MAPK: 丝裂原活化蛋白激酶; ERK: 细胞外信号调节激酶; STAT3: 信号转导与转录激活因子3; PPP: 磷酸戊糖途径; F-actin: F-肌动蛋白; Rac1: Ras相关C3肉毒素底物1; WRC: WAVE调节复合物; Arp2/3: 肌动蛋白相关蛋白2/3复合物; UPR: 未折叠蛋白反应; G6PD: 葡萄糖-6-磷酸脱氢酶。

SLC7A11 is an important molecular switch of disulfidptosis. Its expression is regulated by transcription factors including Nrf2, HIF-1α, and FoxO3, as well as epigenetic modifications such as DNA methylation and H3K27 acetylation. In the tumor microenvironment, the PI3K/Akt/mTOR and MAPK/ERK pathways, together with the STAT3 signaling pathway activated by TNF-α and IL-6, coordinately upregulate SLC7A11 expression, thereby enhancing the antioxidant capacity of tumor cells and creating a metabolic vulnerability associated with disulfidptosis. Under glucose deprivation, the pentose phosphate pathway is suppressed in cells with high SLC7A11 expression, resulting in reduced NADPH production, while continuous cystine reduction further consumes NADPH and eventually causes its depletion. This in turn leads to aberrant disulfide bond crosslinking of cytoskeletal proteins, cytoskeletal collapse, and subsequent disulfidptosis. The Rac1-WRC pathway promotes this process, whereas endoplasmic reticulum stress exerts a compensatory protective effect through upregulation of G6PD. SLC7A11: solute carrier family 7 member 11; Nrf2: nuclear factor erythroid 2-related factor 2; HIF-1α: hypoxia-inducible factor-1α; FoxO3: forkhead box O3; PI3K: phosphoinositide 3-kinase; Akt: protein kinase B; mTOR: mechanistic target of rapamycin; MAPK: mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase; STAT3: signal transducer and activator of transcription 3; PPP: pentose phosphate pathway; F-actin: filamentous actin; Rac1: Ras-related C3 botulinum toxin substrate 1; WRC: WAVE regulatory complex; Arp2/3: actin-related protein 2/3 complex; UPR: unfolded protein response; G6PD: glucose-6-phosphate dehydrogenase.

图1 双硫死亡的核心分子机制及调控网络示意图(本图由BioGDP绘制)

Fig.1 Schematic diagram of the core molecular mechanism and regulatory network of disulfidptosis (created by BioGDP)

性显著高于低表达细胞, 且与肝癌侵袭转移能力呈正相关[19-20]; 三阴性乳腺癌中SLC7A11高表达比例约为55%, 与FoxO3失活相关, 双硫死亡敏感性高于激素受体阳性乳腺癌[21-22]; 结直肠癌中SLC7A11高表达比例较低(25%~30%), 与Wnt/β-catenin通路抑制Nrf2活性有关, 因此结直肠癌细胞对双硫死亡的敏感性相对较弱[23-24]。这种癌种差异为双硫死亡靶向治疗的个体化分层提供了重要依据, 也为后续临床研究的患者筛选提供了参考。

1.1.2 NADPH耗竭与氧化还原失衡 NADPH耗

竭是双硫死亡的不可逆核心环节[5]。NADPH主要由PPP通路合成，葡萄糖-6-磷酸脱氢酶(glucose-6-phosphate dehydrogenase, G6PD)为该通路限速酶，其活性决定NADPH生成效率[25]。当葡萄糖缺乏或G6PD表达受到抑制时，NADPH生成中断，叠加SLC7A11介导的NADPH持续消耗，细胞内氧化还原稳态迅速失衡[26]。NADPH耗竭导致蛋白质二硫键还原能力丧失，肌动蛋白等骨架蛋白半胱氨酸残基异常氧化交联，破坏骨架动态稳定性，最终引发细胞死亡[4]。

1.2 下游执行通路：从二硫键应激到细胞骨架崩解

1.2.1 *蛋白质异常二硫键积聚* 异常二硫键积聚是衔接NADPH耗竭与细胞骨架崩解的核心生化事件，也是双硫死亡的标志性特征[27]。蛋白质组学证实，在葡萄糖剥夺下，SLC7A11高表达细胞的二硫键水平显著升高，且异常增多的二硫键富集于肌动蛋白(β-actin)、细丝蛋白A(filamin A, FLNA)、肌球蛋白重链9(myosin heavy chain 9, MYH9)等骨架蛋白，分子内/间交联直接破坏骨架可塑性[28-29]。敲除*SLC7A11*可完全阻断该过程，从反面证实其核心驱动作用[4]。

1.2.2 *细胞骨架崩解* 广泛的蛋白质异常二硫键交联会导致细胞骨架网络发生物理性僵化，进而引发F-肌动蛋白(F-actin)纤维的不可逆收缩与聚集，破坏其正常的丝状网状结构，最终导致F-actin网络崩解[30]。在显微镜下可观察到，发生双硫死亡的细胞会出现应力纤维解体、皮层肌动蛋白网络崩解及细胞急剧回缩等形态学变化；随着细胞骨架系统的进一步物理性塌陷，细胞膜失去必要的结构支撑而发生破裂，引发细胞质渗漏，呈现出典型的坏死样死亡形态[31]。

值得注意的是，这种不可逆化学交联和细胞骨架物理崩解的终末过程，是双硫死亡区别于凋亡、铁死亡等其他程序性细胞死亡方式的独特形态学特征，也是双硫死亡命名的重要依据[32]。

1.2.3 *Rac1-WRC通路的调控作用* Rac1-WRC通路是双硫死亡的重要调控开关[5]。全基因组CRISPR/Cas9筛选证实，抑制WRC关键组分的表达可显著阻断双硫死亡过程。Rac1持续活化激活WRC，在二硫键应激下病理性驱动肌动蛋白过度组装，加速骨架崩解，成为靶向干预的潜在节点[6,33]。

1.3 新兴的调控网络

内质网应激(endoplasmic reticulum stress, ERS)在双硫死亡背景下被激活，发挥适应性保护反应，可通过启动代谢救援机制，帮助细胞抵抗二硫键应激，延缓双硫死亡的发生[26]。当双硫死亡启动时，细胞内的ERS及其下游的未折叠蛋白反应(unfolded protein response, UPR)会被激活，通过上调G6PD的表达水平，增加NADPH的生成，补充细胞内耗竭的NADPH，从而缓解二硫键应激，实现细胞的代谢救援[34-35]。

这一机制为肿瘤治疗提供了重要的转化启示，抑制ERS介导的这种代偿性保护通路[如使用蛋白激酶R样内质网激酶(protein kinase R-like endoplasmic reticulum kinase, PERK)抑制剂]，可削弱细胞的代谢代偿能力，使其对葡萄糖缺乏或NADPH生成受限更为敏感，从而促进双硫死亡的发生。这种联合诱导双硫死亡并抑制代偿保护的策略，有望协同削弱肿瘤细胞的适应性保护机制。已有体内实验证实，将双硫死亡诱导剂与ERS抑制剂联用，可有效诱导肿瘤细胞发生二硫键应激并抑制肿瘤生长，为靶向代谢压力的抗肿瘤治疗提供新的思路[36]。

2 双硫死亡在疾病中的作用

2.1 肿瘤

在肿瘤领域，双硫死亡的核心研究价值在于其揭示了SLC7A11高表达肿瘤细胞的一个可被精准干预的代谢脆弱性。多种实体瘤(如肺癌、肝癌、乳腺癌等)中普遍存在SLC7A11高表达现象[37]，在葡萄糖充足的生理条件下，SLC7A11的高表达可通过增强细胞抗氧化能力，帮助肿瘤细胞逃避氧化应激损伤，获得生存优势；但在葡萄糖供应受限的肿瘤微环境中，SLC7A11的高表达会成为肿瘤细胞的代谢负担，主要是因为SLC7A11介导的胱氨酸还原过程持续消耗NADPH，而PPP通路因葡萄糖底物不足无法有效补充NADPH，最终导致NADPH耗竭并触发双硫死亡[38-39]。

基于这一机制，靶向诱导肿瘤细胞发生双硫死亡已成为一种极具前景的抗癌治疗策略。例如，葡萄糖转运蛋白抑制剂可通过模拟葡萄糖剥夺状态，选择性杀伤SLC7A11高表达的肿瘤细胞。WANG等[26]进一步发现，联合使用ERS抑制剂可阻断肿瘤细胞在双硫死亡过程中的代偿性保护反应，显著增强葡萄糖限制条件下双硫死亡的诱导作用，为针对SLC7A11高表达肿瘤的联合治疗策略提供了进一步的实验依据。

2.2 代谢性疾病

双硫死亡在代谢性疾病中的作用近年来受到越来越多的关注, 其中在非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)中的研究最为深入[40]。临床研究证据显示, NAFLD患者肝脏组织中双硫死亡相关基因(disulfidptosis-related genes, DRGs)的表达谱发生显著改变, 且这种表达改变与肝脏免疫微环境重塑密切相关[41]。例如, 肌球蛋白轻链6(myosin light chain 6, *MYL6*)等DRGs在NAFLD患者肝脏中的表达水平显著升高, 且其表达量与肝脏炎症程度、氧化应激水平及疾病严重程度呈正相关, 提示这些DRGs有望成为NAFLD诊断的生物标志物及潜在治疗靶点[42]。

在分子机制上, NAFLD患者常伴随胰岛素抵抗, 肝细胞可能通过代偿性上调SLC7A11的表达水平, 应对胰岛素抵抗引发的氧化应激损伤; 但当肝细胞同时面临能量代谢障碍或PPP通路受阻时, SLC7A11介导的NADPH消耗与NADPH生成不足之间的矛盾会被激化, 从而触发肝细胞发生双硫死亡。肝细胞的异常双硫死亡会导致细胞内异常二硫键积累, 进一步加剧肝脏炎症反应, 并促进肝纤维化, 推动疾病从单纯性脂肪肝向非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)进展[40]。尽管双硫死亡在NAFLD中的具体分子调控机制仍需更多实验研究阐明, 但现有研究已为NAFLD的机制解析与干预靶点探索开辟了全新方向。

2.3 免疫细胞功能失调

双硫死亡在免疫学领域的研究进展, 主要集中在其对$CD8^+$ T细胞功能的调控上, 揭示了$CD8^+$ T细胞耗竭的新机制, 为肿瘤免疫治疗及其他免疫相关疾病的治疗提供了新思路。其中乳酸脱氢酶B(lactate dehydrogenase B, LDHB)介导的$CD8^+$ T细胞功能耗竭是近年来发现的一种全新免疫逃逸机制, 亦是双硫死亡调控$CD8^+$ T细胞功能的核心机制[43]。LDHB与SLC7A11存在间接调控关系, SLC7A11高表达引发的NADPH耗竭, 可间接诱导肿瘤微环境中$CD8^+$ T细胞内LDHB代偿性高表达, 提示SLC7A11、NADPH失衡与LDHB异常表达之间存在功能关联, 可加剧$CD8^+$ T细胞双硫死亡及功能耗竭。

在肿瘤微环境中, 葡萄糖缺乏是普遍存在的代谢特征, 该代谢压力不仅可诱导肿瘤细胞发生双硫死亡, 同时也会直接扰乱$CD8^+$ T细胞的代谢稳态及效应功能。作为抗肿瘤免疫的核心效应细胞, $CD8^+$ T细胞在活化后主要依赖糖酵解供能, 以维持自身增殖与细胞毒性功能; 而当肿瘤微环境中的葡萄糖匮乏时, 其糖酵解过程受限导致NADPH供给不足, 同时LDHB出现代偿性上调, 进而引发乳酸堆积、氧化应激加重, 最终触发双硫死亡, 伴随IFN-γ、TNF-α等细胞因子分泌减少, 形成功能受损表型[43], 这一过程中LDHB的异常表达被认为是重要的调控节点。

LDHB介导的$CD8^+$ T细胞耗竭, 本质是肿瘤细胞借助代谢重编程实现免疫逃逸的关键途径。肿瘤细胞自身高表达SLC7A11, 虽在葡萄糖充足条件下可增强抗氧化能力, 但在葡萄糖受限的肿瘤微环境中也使其更易暴露出双硫死亡相关的代谢脆弱性, 同时通过消耗微环境中的葡萄糖, 间接加剧$CD8^+$ T细胞的代谢紊乱与双硫死亡, 最终削弱机体抗肿瘤免疫应答能力[43]。这一机制的发现, 为肿瘤免疫治疗提供了新的干预思路, 即靶向LDHB可有效抑制$CD8^+$ T细胞双硫死亡, 恢复其细胞毒性功能, 与PD-1/PD-L1抑制剂联用更能显著增强抗肿瘤免疫效果, 该联合策略目前已在肺腺癌小鼠模型中获得了初步阳性结果[44]。

3 靶向双硫死亡的治疗策略与研究技术

3.1 直接靶向核心代谢通路

直接靶向双硫死亡核心代谢通路, 是目前最成熟、最具转化潜力的治疗策略, 主要包括诱导双硫死亡与抑制双硫死亡两类, 分别用于肿瘤治疗与正常细胞保护, 已报道的诱导剂/抑制剂及其靶点总结如下(表2)。

3.1.1 靶向SLC7A11 SLC7A11作为双硫死亡的关键开关, 是靶向诱导双硫死亡的核心靶点。目前已开发多种SLC7A11抑制剂, 其中柳氮磺吡啶(sulfasalazine, SAS)是临床常用的抗炎药物, 可通过抑制SLC7A11介导的胱氨酸摄取, 减少GSH合成, 加剧NADPH耗竭, 诱导SLC7A11高表达肿瘤细胞发生双硫死亡, 已在急性髓系白血病等模型中证实其抗肿瘤效果[4,45]。此外, HG106是一种特异性SLC7A11抑制剂, 可直接结合SLC7A11的胱氨酸结合位点, 抑制其活性, 在肺腺癌临床前模型中表现出显著的抗肿瘤活性, 且对正常细胞毒性较低[46]。

3.1.2 靶向葡萄糖代谢与PPP通路 靶向葡萄糖代谢与PPP通路, 可通过减少NADPH生成, 间接诱

表2 已报道的双硫死亡诱导剂/抑制剂及其靶点总结

Table 2 Summary of reported disulfidptosis inducers/inhibitors and their targets

类别 Category	药物/化合物 Drug/compound	靶点 Target	作用机制 Mechanism of action	研究应用模型 Research model/application	参考文献 References
Disulfidptosis inducers	SAS (sulfasalazine)	SLC7A11	Inhibits cystine uptake, reduces GSH synthesis, and aggravates NADPH depletion	Acute myeloid leukemia	[45]
	HG106	SLC7A11	Specifically inhibits SLC7A11 activity and induces disulfide stress	Lung adenocarcinoma (pre-clinical)	[46]
	BAY-876	GLUT1	Inhibits glucose uptake, blocks the PPP pathway, and reduces NADPH production	Multiple solid tumors	[47-48]
	G6PDi-1	G6PD	Inhibits the activity of G6PD, the rate-limiting enzyme of the PPP, thereby blocking NADPH synthesis	Tumors (preclinical)	[49]
	6-AN (6-aminonicotin-amide)	G6PD	Inhibits G6PD activity and reduces NADPH production	Mechanistic studies in tumors	[50]
	GSK2656157	PERK	Inhibits the compensatory ERS (endoplasmic reticulum stress) pathway and indirectly enhances disulfidptosis (in combination)	Tumors (combination therapy, preclinical)	[26]
Disulfidptosis inhibitors	DTT (dithiothreitol)	Disulfide bonds	Reduces aberrant disulfide bonds and alleviates disulfide stress	General cell-based experi-ments	[51]
	TTM (tetrathiomolyb-date)	Copper ions	When used alone, inhibits copper ion accumulation and indirectly suppresses disulfidptosis, thereby protecting normal cells	Cell-based experiments	[52]

导双硫死亡。葡萄糖转运蛋白1(glucose transporter type 1, GLUT1)抑制剂BAY-876, 可抑制肿瘤细胞葡萄糖摄取, 阻断PPP通路, 减少NADPH生成, 在多种实体瘤模型中可有效诱导SLC7A11高表达肿瘤细胞发生双硫死亡[47-48]; G6PD作为PPP通路的限速酶, 其抑制剂G6PDi-1、6-氨基烟酰胺(6-aminonicotinamide, 6-AN)等, 可直接抑制NADPH生成, 协同SLC7A11高表达诱导双硫死亡, 目前主要用于肿瘤机制研究, 未来有望开发为新型抗肿瘤药物[49-50]。

3.1.3 *靶向二硫键应激与细胞骨架* 靶向二硫键应激与细胞骨架, 可直接促进双硫死亡的终末执行过程。二硫键氧化剂可直接提高细胞内二硫键水平, 加剧二硫键应激, 协同诱导双硫死亡; 而细胞骨架抑制剂(如细胞松弛素D)可破坏肌动蛋白网络, 加速细胞骨架崩解, 增强双硫死亡效应[5]。此外, Rac1抑制剂(如NSC23766)可通过抑制Rac1-WRC通路, 阻断肌动蛋白过度组装过程, 抑制双硫死亡, 主要用于保护正常细胞免受双硫死亡损伤[4]。

3.2 联合治疗策略

单一靶向双硫死亡的治疗效果有限, 联合其他治疗方式可显著提升疗效, 目前主要的联合策略包括以下两类。

3.2.1 *双硫死亡诱导剂与ERS抑制剂联用* 如1.3.1小节所述, ERS抑制剂可阻断肿瘤细胞的代偿性保护反应, 增强双硫死亡诱导剂的杀伤效果。已有研究证实, PERK抑制剂GSK2656157与SLC7A11抑制剂HG106联用, 可显著提升肺腺癌细胞的双硫死亡水平, 抑制肿瘤生长, 且联用组的抗肿瘤效果显著优于单一用药组[26]; 此外, ERS抑制剂与葡萄糖剥夺策略联用, 也可通过双重阻断NADPH生成, 协同诱导肿瘤细胞双硫死亡, 为肿瘤治疗提供新的联合治疗思路[26]。

3.2.2 *双硫死亡诱导剂与免疫治疗联用* 双硫死亡诱导剂可通过诱导肿瘤细胞死亡, 释放肿瘤相关抗原, 激活机体抗肿瘤免疫应答, 与免疫治疗联用可实现协同增效。例如, SLC7A11抑制剂SAS与PD-1

抑制剂联用, 可在抑制肿瘤细胞生长的同时, 恢复$CD8^+$ T细胞的功能, 增强抗肿瘤免疫效果, 已在黑色素瘤小鼠模型中取得初步成果[53]; 此外, 靶向LDHB的抑制剂与PD-L1抑制剂联用, 可通过保护$CD8^+$ T细胞免受双硫死亡损伤, 增强免疫治疗的疗效, 为肿瘤免疫治疗的优化提供新方向[43]。

3.3 双硫死亡相关研究技术

3.3.1 *单细胞与空间多组学技术的应用* 单细胞与空间多组学技术为双硫死亡的精准研究提供了技术支撑, 且已在肿瘤、NAFLD等疾病模型中获得了明确研究成果。在肿瘤模型中, 单细胞转录组测序发现肺腺癌中SLC7A11高表达的肿瘤细胞亚群(尤其是Keap1-Nrf2通路异常激活的亚群)最易发生双硫死亡, 且该亚群与肿瘤侵袭转移能力呈正相关, 这一发现为肺腺癌个体化双硫死亡靶向治疗提供了细胞层面的筛选依据[25,54]。在肝癌中, 肝实质癌细胞亚群(尤其是HIF-1α高表达亚群) SLC7A11表达水平显著高于间质细胞, 其双硫死亡敏感性也显著增强, 为肝癌代谢靶向治疗的细胞精准定位提供了参考[25,55]。在NAFLD模型中, 单细胞代谢组学证实肝星状细胞与肝细胞亚群是双硫死亡的主要发生细胞, 这些细胞中SLC7A11、G6PD表达水平异常升高, 且双硫死亡程度与肝脏纤维化程度呈正相关, 揭示了双硫死亡在NAFLD进展中的核心作用, 为NAFLD的分期诊断与靶点筛选提供了新线索[41-42]。空间代谢组学与质谱成像技术则可在肿瘤、肝脏组织原位可视化NADPH、乳酸等双硫死亡相关代谢物的分布, 定位双硫死亡热点区域(如肿瘤中心缺氧区、NAFLD肝脏炎症区), 明确双硫死亡与疾病病理分区的关联, 为治疗靶点的精准定位提供可视化支撑[56-57]。

3.3.2 *双硫死亡相关预测模型与生物标志物* 随着双硫死亡研究的深入, 一系列预测模型与生物标志物被开发, 为疾病诊断、预后评估及治疗方案选择提供了重要工具。在肿瘤领域, 基于双硫死亡相关基因(DRGs)构建的预后风险模型, 科研人员已在肺腺癌、肝癌等多种肿瘤中证实其有效性, 可有效预测患者的总生存期、无进展生存期, 为患者分层与个体化治疗提供参考[58]。在NAFLD领域, *MYL6*、*G6PD*等DRGs可作为NAFLD诊断与病情进展的潜在生物标志物, 其表达水平与疾病严重程度密切相关[42,59]。

此外, 借助蛋白质组学与代谢组学技术, 科研人员也发现了一系列双硫死亡相关的特征性标志物, 如异常二硫键修饰的肌动蛋白、NADPH代谢物、乳酸等。这些标志物不仅可用于双硫死亡的检测与鉴定, 也可为靶向治疗的疗效评估提供参考[4,60]。

4 总结与展望

双硫死亡作为一种新型程序性细胞死亡方式, 其核心机制为SLC7A11高表达状态下葡萄糖缺乏引发的NADPH耗竭、二硫键应激与细胞骨架崩解, 其调控网络涵盖转录调控、表观遗传调控、代谢调控及免疫调控等多个层面。另外, 双硫死亡在肿瘤、NAFLD等疾病的发生发展中具有核心作用, 不仅揭示了SLC7A11高表达肿瘤的代谢脆弱性, 为肿瘤治疗提供了全新靶点, 也为代谢性疾病、免疫相关疾病的机制解析与治疗策略开发开辟了新方向。

目前, 双硫死亡的研究仍处于快速发展阶段。尽管已取得一系列重要成果, 但仍存在诸多不足。首先, 双硫死亡的分子调控网络尚未完全明确, 如SLC7A11上游调控的具体分子机制、双硫死亡与其他程序性细胞死亡方式的交互作用等仍需进一步深入研究, 不同癌种、不同细胞类型中的双硫死亡的调控差异及这种差异对靶向治疗效果的影响仍需更多临床样本与实验数据支撑, 双硫死亡靶向药物的开发仍处于临床前阶段, 缺乏高效、特异性的靶向药物, 且联合治疗策略的优化与临床转化仍面临挑战。未来, 双硫死亡的研究可聚焦于多个方向: 深入解析双硫死亡的分子调控网络, 明确SLC7A11的上游调控机制、双硫死亡与其他细胞死亡方式的交互作用, 为靶向治疗提供更多潜在靶点; 扩大疾病研究范围, 探索双硫死亡在神经退行性疾病、心血管疾病等其他疾病中的作用, 拓展其临床应用场景; 加快双硫死亡靶向药物的研发与临床转化, 优化联合治疗策略, 提高治疗效果, 减少不良反应; 结合单细胞与空间多组学等先进技术, 进一步阐明双硫死亡在不同疾病、不同细胞类型中的异质性, 为个体化治疗提供更精准的依据。

随着研究的不断深入, 双硫死亡的分子机制将被进一步阐明, 其在疾病治疗中的应用价值也将得到充分发挥。双硫死亡有望为相关疾病的基础研究与临床转化提供全新的思路与策略。

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