

谷胱甘肽在调控代谢相关脂肪性肝病铁死亡和铜死亡中的作用

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[摘要] 代谢相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease, MASLD)是以代谢功能障碍为核心特征的脂肪肝病, 是全球肝病最常见的原因之一, 可带来严重的疾病负担。异常的细胞死亡方式参与MASLD的发生与发展, 铁死亡和铜死亡诱发并加重 MASLD, 成为新近研究热点。谷胱甘肽(glutathione, GSH)作为调节氧化还原过程最重要的还原剂, 其含量下降或耗竭会促进肝脏脂质蓄积与氧化损伤, 推动 MASLD 进展。GSH 是铁死亡和铜死亡的共同枢纽: 一方面, GSH 作为谷胱甘肽过氧化物酶 4(glutathione peroxidase 4, GPX4)的必需还原底物, 通过清除有毒脂质过氧化物来抑制铁死亡; 另一方面, GSH 能整合细胞内过量的亚铜离子(Cu^+), 降低 Cu^+ 在细胞内的毒性, 从而抑制铜死亡。因此, GSH 是调控 MASLD 铁死亡与铜死亡的关键, 靶向 GSH 代谢通路有望成为预防、诊断与治疗 MASLD 的潜在新策略。未来可深入解析 GSH 调控铁死亡与铜死亡串扰的分子网络, 并结合纳米靶向递送、基因编辑等新技术, 开发安全高效的 GSH 靶向调节剂, 推动基础研究成果向临床转化。

[关键词] 谷胱甘肽; 代谢相关脂肪性肝病; 铁死亡; 铜死亡; 串扰; 氧化应激; 脂质过氧化

Role of glutathione in regulating ferroptosis and cuproptosis in metabolic dysfunction-associated steatotic liver disease

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a fatty liver disease characterized by metabolic dysfunction as its core feature. It represents one of the most common causes of liver disease worldwide and imposes a substantial disease burden. Abnormal cell death patterns are involved in the initiation and progression of MASLD, and

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ferroptosis and cuproptosis have recently emerged as research hotspots due to their roles in triggering and exacerbating MASLD. Glutathione (GSH), the most important reductant in redox regulation, can promote hepatic lipid accumulation and oxidative injury when its levels decline or become depleted, thereby driving the progression of MASLD. GSH serves as a common hub linking ferroptosis and cuproptosis: on the one hand, GSH acts as an essential reducing substrate for glutathione peroxidase 4 (GPX4) and suppresses ferroptosis by eliminating toxic lipid peroxides; On the other hand, GSH chelates excessive intracellular cuprous ions (Cu^+), reducing the cytotoxicity of Cu^+ and thus inhibiting cuproptosis. Therefore, GSH is a key regulator of ferroptosis and cuproptosis in MASLD, and targeting the GSH metabolic pathway holds promise as a potential novel strategy for the prevention, diagnosis, and treatment of MASLD. Future investigations should focus on dissecting the molecular network of GSH-mediated crosstalk between ferroptosis and cuproptosis and integrating advanced approaches such as nano-targeted delivery and gene editing to develop safe and potent GSH-directed modulators, thereby expediting the translation of basic research findings into clinical practice.

KEY WORDS glutathione; metabolic dysfunction-associated steatotic liver disease; ferroptosis; cuproptosis; crosstalk; oxidative stress; lipid peroxidation

代谢相关脂肪性肝病 (metabolic dysfunction-associated steatotic liver disease, MASLD) 过去被称为非酒精性脂肪肝病 (nonalcoholic fatty liver disease, NAFLD), 是肝脏脂肪堆积与代谢功能障碍共存的疾病, 其代谢异常表现为超重或肥胖及胰岛素抵抗。MASLD 的特征是肝脏脂肪堆积 (进而表现为肝脂肪变性), 伴有不同程度的炎症和纤维化^[1]。研究^[2]显示, MASLD 全球患病率为 30.2%, 已成为全球公共卫生负担。如不及时治疗, MASLD 常发展为代谢相关脂肪性肝炎 (metabolic dysfunction-associated steatohepatitis, MASH)、肝纤维化甚至肝细胞癌 (hepatocellular carcinoma, HCC)^[2], 严重危害患者健康。

MASLD 的发病涉及多种病理机制, 其中氧化应激、脂质过氧化被认为是推动疾病进展的重要机制^[3]。谷胱甘肽 (glutathione, GSH) 是细胞内最重要的抗氧化分子之一, 不仅参与清除活性氧 (reactive oxygen species, ROS), 还是谷胱甘肽过氧化物酶 (glutathione peroxidase, GPX) 的必需辅因子, GSH 将脂质过氧化物还原为无毒脂质醇, 从而抑制脂质过氧化累积、减轻氧化损伤, 促进内源性及外源性有害物质的解毒^[4]。近年研究^[5]表明, GSH 缺失诱导肝细胞应激、损伤和死亡, 造成肝脏纤维化, 导致肝硬化和 HCC。新近研究^[6-7]发现, 铁死亡和铜死亡均与氧化还原失衡、脂质过氧化积累及金属离子稳态

异常密切相关, 参与 MASLD 进展。GSH 含量降低会增加 ROS 和脂质过氧化, 继而促进铁死亡和铜死亡, 参与 MASLD 的发生与发展^[4, 6-7]。本文旨在总结 MASLD 中 GSH 调控铁死亡和铜死亡的进展, 为探究 MASLD 新的治疗靶点提供证据。

1 GSH 在 MASLD 中的作用

GSH 由谷氨酸、半胱氨酸和甘氨酸组成, 是真核细胞中最丰富的天然活性肽, 也是哺乳动物细胞中最常见的非蛋白硫醇^[8]。维持细胞内氧化还原平衡状态的抗氧化系统主要分为 3 类: 还原型谷胱甘肽/氧化型谷胱甘肽 (oxidized glutathione, GSSG) 系统、谷还蛋白 (glutaredoxin, Grx) 系统及硫氧化蛋白 (thioredoxin, Trx)/Trx 还原酶系统。前 2 个系统均需要 GSH 提供电子供体, 因此 GSH 是维持生物体内氧化还原稳态最重要的小分子活性物质^[9]。

细胞内 GSH 的稳态依赖于一个由合成酶、再生酶、结合酶及降解酶精密调控的网络, 该网络常被称为 GSH 抗氧化系统^[10]。其核心包括 2 个方面: 合成与再生循环。GSH 的合成主要分为 2 步, 由腺苷三磷酸 (adenosine triphosphate, ATP) 驱动的酶促反应: 首先, 谷氨酸和半胱氨酸在谷氨酸半胱氨酸连接酶 (glutamate-cysteine ligase, GCL) 的催化下生成 γ -谷氨

酰半胱氨酸,这是GSH合成的限速步骤;随后,谷胱甘肽合成酶(glutathione synthetase, GS)催化甘氨酸与 γ -谷氨酰半胱氨酸结合生成GSH^[11]。在发挥抗氧化作用时,GSH在GPX的催化下,将电子提供给过氧化物(如脂质过氧化物),自身被氧化为GSSG。随后,GSSG在谷胱甘肽还原酶(glutathione reductase, GR)和还原型烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate hydrogen, NADPH)的作用下被还原再生为GSH,从而维持细胞内极高的GSH/GSSG比值。这一循环是维持细胞氧化还原稳态的核心机制^[10]。

抗氧化系统在MASLD发病机制和疾病进展中发挥关键作用,作为抵抗氧化应激的主要防御物质,GSH主要集中在肝脏,对肝脏健康至关重要^[12]。研

究^[13]发现,GSH能有效抑制大鼠体内抗坏血酸诱导的肝微粒体和线粒体不饱和脂肪酸发生脂质过氧化。GSH含量下调、GSH依赖性抗氧化剂活性降低是MASLD恶化的机制^[14]。在MASLD早期,代谢改变限制了甘氨酸的可用性,损害了GSH的合成,从而加剧了急性肝毒性^[15]。随着疾病加重,GSH/GSSG比值下降,这提示氧化应激和GSH耗竭存在于MASLD整个过程中^[16]。鉴于GSH耗竭在MASLD进展中的重要作用,通过外源性物质靶向调控GSH代谢已成为潜在的干预策略。例如,黄芩苷可通过影响GSH的从头合成途径有效缓解MASLD^[17];对肝脂肪变性小鼠补充甘氨酸,可通过支持GSH的从头合成来减轻对乙酰氨基酚诱导的肝毒性^[15]。肝脏GSH氧化还原系统及其在MASLD进展中的失代偿过程见图1。

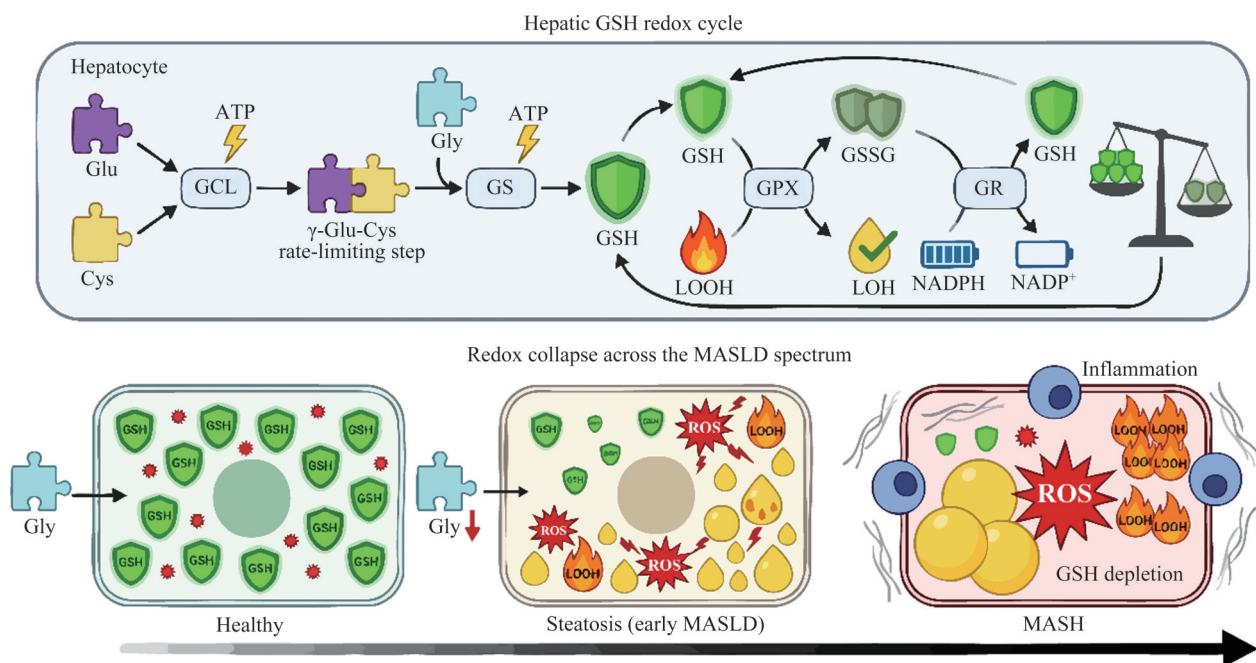


图1 肝脏GSH氧化还原系统及其在MASLD进展中的失代偿

Figure 1 Hepatic GSH redox system and its decompensation during MASLD progression

De novo GSH synthesis is catalyzed in 2 steps by GCL and GS. In the redox cycle, GSH reduces lipid peroxides to lipid alcohols via GPX, generating GSSG; GSSG is then regenerated to GSH by GR using NADPH, thereby maintaining a high GSH/GSSG ratio. Healthy hepatocytes are rich in GSH and contain very low levels of ROS. In early MASLD, decreased Gly availability impairs GSH synthesis, leading to the accumulation of ROS and lipid peroxides and the initiation of lipid peroxidation. Upon progression to MASH, GSH is nearly depleted, and hepatocytes experience severe oxidative stress, massive lipid peroxide accumulation, inflammatory infiltration, and fibrosis. ATP: Adenosine triphosphate; Cys: Cysteine; GSH: Glutathione; Glu: Glutamate; GCL: Glutamate-cysteine ligase; Gly: Glycine; GS: Glutathione synthetase; GPX: Glutathione peroxidase; GSSG: Oxidized glutathione; GR: Glutathione reductase; LOOH: Lipid hydroperoxide; LOH: Lipid alcohol; MASLD: Metabolic dysfunction-associated steatotic liver disease; MASH: Metabolic dysfunction-associated steatohepatitis; NADPH: Nicotinamide adenine dinucleotide phosphate hydrogen; NADP⁺: Nicotinamide adenine dinucleotide phosphate; ROS: Reactive oxygen species; γ -Glu-Cys: Gamma-glutamylcysteine.

2 GSH调控MASLD铁死亡和铜死亡

2.1 GSH调控肝细胞铁死亡

2012年, Dixon等^[18]首次提出铁死亡, 这是一种依赖于细胞内铁, 在形态学、生化和遗传学上不同于凋亡、坏死和自噬的细胞死亡方式。铁过载、脂质过氧化和GSH耗竭是铁死亡的特征^[18]。铁过载由细胞内 Fe^{2+} 积聚引起, Fe^{2+} 通过芬顿反应产生大量羟基自由基, 参与脂质过氧化, 造成氧化应激损伤, 导致细胞发生铁死亡。同时, 含铁脂氧合酶也通过产生脂质氢过氧化物, 成为促进脂质氧化的关键物质, 这一过程依赖于脂酰辅酶A合成酶长链家族成员4(acyl-CoA synthetase long-chain family member 4, ACSL4)介导的脂质生物合成^[19]。在抗氧化防御层面, GSH是GPX4(铁死亡的核心抑制因子)清除脂质过氧化物必需的还原底物, 当GSH耗竭或GPX4失活时, 细胞清除有毒脂质过氧化物的能力下降, 导致脂质过氧化物在膜磷脂中大量积累, 最终诱发铁死亡^[20]。而GPX4的活性又依赖于由溶质载体家族7成员11(solute carrier family 7 member 11, SLC7A11)摄取胱氨酸后合成的GSH^[19]。铁死亡主要由细胞抗氧化系统的失活引起, 尤其是胱氨酸/谷氨酸反向转运体(系统Xc⁻)-GSH-GPX4这一关键轴线的功能崩溃, 系统Xc⁻是质膜上由SLC7A11和溶质载体家族3成员2(solute carrier family 3 member 2, SLC3A2)组成的异二聚体蛋白复合物, 通过反向转运胱氨酸和谷氨酸, 负责摄取胱氨酸以合成GSH, 从而维系GPX4的活性, 在保护细胞免受铁死亡损害中发挥关键作用^[19]。此外, 核因子-E2相关因子2(nuclear factor-E2-related factor 2, Nrf2)是抗氧化基因和铁调节基因的关键转录因子, Nrf2不仅能调节抗氧化能力, 还通过其下游靶标(包括GPX4、SLC7A11)减轻脂质过氧化, 从而直接限制铁死亡。因此, Nrf2-脂质过氧化-铁死亡轴在氧化还原敏感性疾病中发挥重要作用^[21]。

铁死亡是MASLD的病理特征之一^[22]。铁过载、脂质过氧化及抗氧化防御失衡共同参与MASLD的发生与发展。研究^[23-24]发现, 肝脂肪变性通常由铁过载引起, 且肝脏铁的过度积累促进MASH的进展。GPX4上调可通过抑制ROS积累和脂质过氧化抑制铁死亡, 从而缓解肝脂肪变性^[25-26]。铁死亡诱导剂RAS合成致死分子3(RAS-selective lethal small molecule 3, RSL-3)的应用导致小鼠肝脏GPX4含量降低, 加重肝脂肪变性, 使丙氨酸氨基转移酶(alanine aminotransferase, ALT)含量升高并导致组织炎症^[27]。铁死亡抑制剂的应用可阻断ACSL4的表达, 从而改

善脂肪变性和脂肪性肝炎^[28]。脱氢枞酸通过抑制脂质过氧化减少铁死亡并改善MASLD^[25], 银杏内酯B通过Nrf2信号通路阻断氧化应激和脂质过氧化引起的铁死亡, 从而治疗MASLD^[26], 玉米黄质、褪黑素和熊果苷通过增加GPX4的表达水平减少肝细胞脂质过氧化, 从而防止铁死亡, 缓解肝脂肪变性^[29-31]。

GSH能抵抗铁死亡过程中的氧化损伤^[32]。研究^[33]发现, 苍术素可增加GSH的含量, 从而抑制MASLD中的铁死亡。小檗碱可激活SLC7A11/GSH/GPX4信号通路抑制铁死亡, 改善MASLD诱导的骨质流失^[34]。褪黑素通过增加GSH水平保护细胞免受氧化应激的影响, 从而抑制MASLD中的铁死亡^[30]。抑制GSH的生物合成能诱导铁死亡^[35], 多种原因导致的GSH耗竭及随后的GPX4失活可导致大量脂质过氧化物积累, 从而引起铁死亡^[36]。RSL-3在抑制GPX4的同时, 可通过抑制Nrf2/GSH通路, 诱导肺腺癌细胞铁死亡^[37]。环境污染物, 特别是重金属, 可干扰细胞内抗氧化系统, 特别是Nrf2、GSH和GPX4通路, 通过积累有毒脂质过氧化物来诱导铁死亡^[38]。Bai等^[39]发现, 氟哌啶醇治疗加速了肝细胞的GSH耗竭, 从而引起肝细胞铁死亡。GSH调控细胞铁死亡的作用见图2。

2.2 GSH调控肝细胞铜死亡

2022年3月, Tsvetkov等^[40]首次揭示了铜诱导的细胞死亡机制——铜死亡。铜死亡的特征是细胞内 Cu^+ 异常积累, 并进一步与线粒体呼吸中三羧酸循环中的硫辛酰化成分直接结合, 导致硫辛酰化蛋白质聚集和随后的铁硫(Fe-S)簇蛋白下调, 从而导致蛋白质毒性应激并最终导致细胞死亡。其中, 铁氧还蛋白1(ferredoxin 1, FDX1)是蛋白质硫辛酰化的上游调节因子和铜死亡的关键调节因子^[41], 丙酮酸脱氢酶复合体[由丙酮酸脱氢酶E1 α 亚基1(pyruvate dehydrogenase E1 alpha 1, PDHA1)、丙酮酸脱氢酶E1 β 亚基(pyruvate dehydrogenase E1 beta subunit, PDHB)、二氢硫辛酰胺转乙酰酶(dihydrolipoyl transacetylase, DLAT)、二氢硫辛酰胺脱氢酶(dihydrolipoyl dehydrogenase, DLD)组成]是硫辛酰化蛋白靶标^[42]。

铜死亡是MASLD发病的重要因素^[7]。在MASLD中, 铜死亡被激活, 导致非酒精性脂肪肝(nonalcoholic fatty liver, NAFL)发展为MASH^[43]。Zhao等^[44]发现, MASH患者肝脏中FDX1显著上调, FDX1在MASH进展为HCC的过程中发挥着核心作用。研究^[43]显示, DLD和PDHB与MASLD患者预后有关。DLD和DLAT是MASLD发病机制中关键的生

物标志物^[45]。研究^[46]发现,铜过量诱导肝脏产生脂毒性,促进MASLD的发展。Zhang等^[47]指出,血清铜水平和可能导致MASLD发生的危险因素(体重指数、瘦素以及胰岛素抵抗)呈正相关。Li等^[48]发现,血清铜水平与MASLD呈正相关,血清铜水平升高的个体对MASLD的易感性增加。循环铜的增加促进MASLD向肝硬化甚至肝癌发展,高铜浓度的细胞微环境在促进肝脏肿瘤的发生与发展中起主要作用^[49]。铜死亡是MASLD的重要发病机制,为MASLD等疾病防治提供了新的研究方向。

GSH是重要的内源性铜螯合剂,GSH分子中的半胱氨酸残基含有一个巯基(-SH),该巯基对Cu⁺具有高亲和力,能螯合Cu⁺,形成稳定的Cu⁺-GSH复合物,进而清除细胞内过量的Cu⁺^[50-51]。这一螯合作用不仅抑制了游离Cu⁺参与芬顿反应产生ROS的能力,而且阻止了游离Cu⁺与必需蛋白结合,从而降低Cu⁺在细胞内的毒性,发挥抑制铜死亡的作用^[52]。AmeliMojarad等^[53]发现,华蟾素毒基可消耗GSH,诱导HepG2细胞的铜死亡。Li等^[54]发现一种新型纳米颗粒可减少GSH,诱导HCC中的铜死亡。Tao等^[55]发现,肝豆状核变性患者体内GSH含量下降,诱导肝细胞发生铜死亡。Xue等^[56]发现,在非小细胞肺癌细胞中GSH含量下降,细胞表现出铜死亡的特征。铁死亡诱导剂通过激活蛋白质硫辛酰化和抑制GSH合成增强铜死亡^[57]。GSH的耗竭使癌细胞对复合材料GOx@[Cu(tz)]诱导的铜死亡敏感^[58]。研究^[59]表明,GSH可防止铁-硫簇蛋白的丢失,阻断铜死亡过程。肿瘤蛋白p53能抑制SLC7A11转运体功能,从而抑制GSH合成,加重铜死亡,p53还能作用于细胞周期蛋白依赖性激酶抑制剂促进GSH合成,进而加强螯合铜的作用,抑制铜死亡^[60]。GSH调控细胞铜死亡的作用见图2。

3 铁死亡和铜死亡之间的串扰

研究^[61]表明,在响应网络中,多个输入信号通过整合,共同调节某个生物学输出的过程,即为串扰。若2条通路同时符合以下2个条件,即可判定它们之间存在串扰:1)2条通路联合产生的组合信号,应引发与各自单独作用时不同的响应;2)这2条通路之间必须有直接或间接的连接。当2条或2条以上信号通路共有特定的信号组分时,即构成直接串扰;若一条通路的组分被其他信号通路中的酶直接修饰,也可归为直接串扰。在更广义的层面上,研究者也用“串扰”来描述一条信号通路对另一条通路的间接影响。间接串扰常被用来表示不同信号通路的顺序性

作用,尤其是当第一条通路的活性是观察到第二条通路活性的必要条件时。此外,“串扰”有时也用于描述2种不同信号共同汇聚于共调控基因启动子时所引发的响应(如转录响应)^[61]。

铁死亡与铜死亡的串扰主要体现在以下方面:第一,共享细胞死亡发生机制。铁死亡以脂质过氧化为核心^[18],脂质过氧化也是铜死亡的具体机制之一,Cu⁺可被Cu⁺载体运送至细胞内,从而使细胞内Cu⁺含量增加,通过芬顿反应产生过量ROS,诱导细胞死亡^[62]。过量铜可诱导抗氧化酶中GPX4的自噬降解,促进铁死亡^[63],提示在氧化应激方面,铁死亡和铜死亡存在密切联系。第二,共享上游调控分子。SLC7A11通过介导胱氨酸摄取和谷氨酸释放促进GSH合成,以抵抗氧化应激诱导的细胞死亡^[64]。SLC7A11是铁死亡和铜死亡的关键调节因子之一,是靶向铁死亡和铜死亡的有效靶标^[65]。在结直肠癌细胞中,Elesclomol(铜死亡诱导剂)使铜离子保留在线粒体中,导致ROS积累,促进SLC7A11降解,增加细胞对铁死亡的易感性^[66]。第三,三羧酸循环是双向的。线粒体三羧酸循环产生的ROS参与铁死亡的过程^[67],铜死亡的重要成分硫辛酰化蛋白也来自三羧酸循环,因此推测铁死亡与铜死亡可能通过三羧酸循环发生串扰^[62]。第四,均受铁-硫簇稳态影响。铁-硫簇稳态与线粒体代谢及ROS的产生密切相关。Fe-S依赖性酶受到破坏,会影响三羧酸循环的活性和电子传输的效率,从而调节线粒体产生的ROS水平,影响铁死亡。在铜死亡中,铁-硫簇扰动是蛋白质毒性损伤和代谢紊乱的次要结果^[68]。第五,线粒体功能障碍与脂质过氧化之间可能存在相互影响。在铁死亡过程中,线粒体ROS有助于脂质过氧化的启动和扩散,而由此生成的活性脂质亲电体有可能修饰线粒体蛋白,进而加剧线粒体应激。这种反馈交互作用可能降低铜胁迫下蛋白质毒性崩溃的阈值,但目前尚缺乏直接证据^[68]。第六,相互调控基因表达。在肺癌相关研究^[69]中,敲除铁死亡调节因子使铜死亡调节因子的表达发生显著变化,如敲除磷酸酶和张力蛋白同源物(phosphatase and tensin homolog, *PTEN*)后溶质载体家族31成员1(solute carrier family 31 member 1, *SLC31A1*)的表达增加,敲除线粒体转录因子A(mitochondrial transcription factor A, *TFAM*)后铜转运ATP酶 α 肽(copper-transporting ATPase alpha peptide, *ATP7A*)的表达上调,敲除激活转录因子2(activating transcription factor 2, *ATF2*)后脂酰转移酶1(lipoyltransferase 1, *LIPT1*)的表达下调。而铜死亡是否能反向影响铁死亡相关基因的表达,仍待进一步探索。

在MASLD中,铜的累积会调节铁代谢,影响铁死亡的进程,间接地调控MASLD的进程^[70]。Wang等^[71]指出,间歇性缺氧可导致肝脏铜储备减少和继发性铁沉积,从而诱发铁死亡并导致MASLD。线粒体铜缺乏是MASLD的一个驱动因素,可促进肝脏及其

他器官的生物能量衰竭、铁死亡、衰老以及纤维炎症性损伤^[72]。上述研究表明,铁-铜稳态的相互失衡可能构成MASLD中2种死亡方式串扰的病理基础,但目前相关研究仍较少,有待深入探讨。

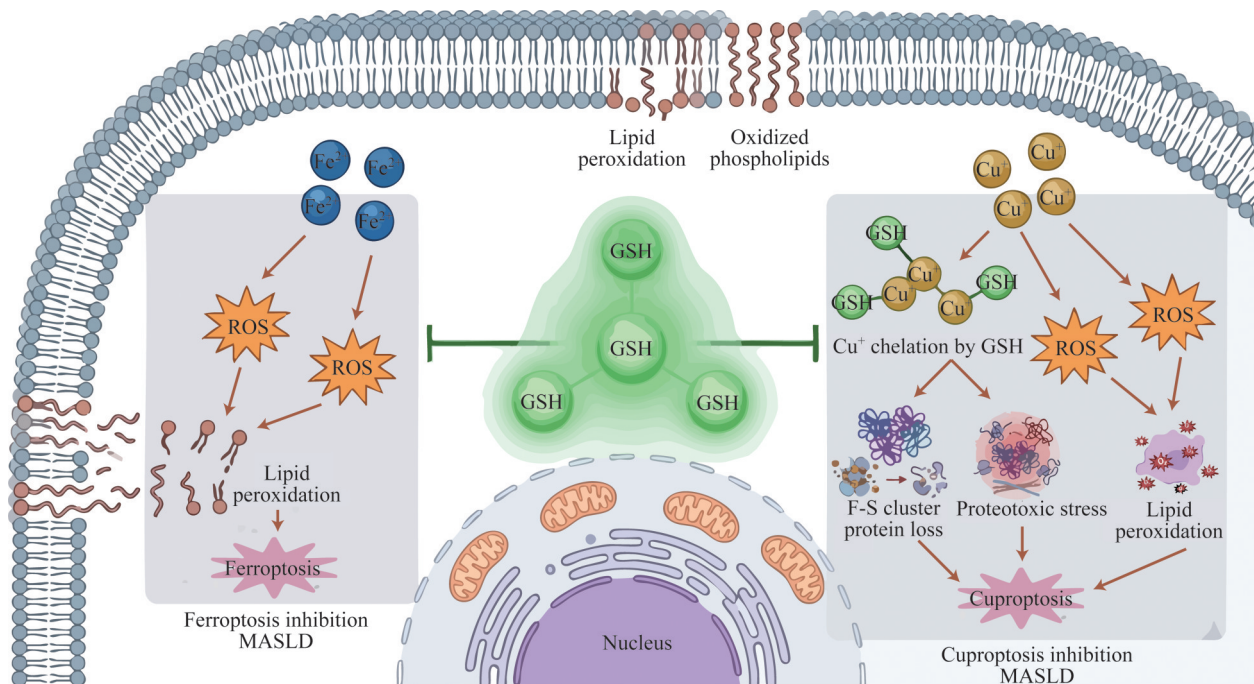


图2 GSH调节肝细胞中的铁死亡和铜死亡

Figure 2 GSH regulates both ferroptosis and cuproptosis in hepatocytes

In MASLD, excessive accumulation of Fe^{2+} induces ROS generation and leads to lipid peroxidation, thereby triggering ferroptosis. GSH suppresses ferroptosis in MASLD by inhibiting ROS production and lipid peroxidation. In parallel, excess Cu^+ in MASLD directly binds to lipoylated proteins in the mitochondrial tricarboxylic acid cycle, inducing their aberrant aggregation, which results in the loss of Fe-S cluster proteins and proteotoxic stress, ultimately driving cuproptosis. GSH can chelate excess Cu^+ to form stable Cu^+ -GSH complexes, thereby clearing surplus intracellular Cu^+ . This chelation not only abolishes the ability of free Cu^+ to generate ROS through the Fenton reaction but also prevents free Cu^+ from binding to essential proteins, consequently reducing the intracellular toxicity of Cu^+ and exerting an inhibitory effect on cuproptosis.

4 GSH在铁死亡和铜死亡中的串扰

GSH是铁死亡和铜死亡的共同枢纽,对铁死亡和铜死亡均有抑制作用^[73]。在铁死亡中,GSH发挥抗氧化剂的作用,阻止脂质过氧化;在铜死亡中,GSH充当铜伴侣蛋白,与 Cu^+ 结合以减少硫辛酰化蛋白的聚集^[40]。在肿瘤细胞中,GSH耗竭同时与GPX4抑制和DLAT寡聚化有关,从而触发铁死亡和铜死亡^[74]。Zhang等^[51]发现,铁死亡调控通路中的Xc-转运体会影响GSH对铜的螯合作用,促进铜死亡。研究发现,铁死亡诱导剂sorafenib和erastin抑制FDX1

蛋白降解并抑制细胞内GSH合成,从而增加铜依赖性硫辛酰化蛋白聚集来增强原发性肝癌细胞中的铜死亡^[58]。基于GSH耗竭的机制,Bai等^[75]合成了具有谷胱甘肽氧化酶样活性的(3-羧丙基)三苯基溴化磷衍生的透明质酸修饰的氧化铜纳米棒(MitCuOHA),MitCuOHA可催化GSH消耗并诱导铁死亡,同时阻止细胞内铜水平的减少,诱导蛋白毒性应激,引起铜死亡,从而通过铁死亡和铜死亡协同治疗癌症。Jiang等^[76]发现,基于聚多巴胺的GSH响应型杂化纳米颗粒(CACuPDA)通过诱导GSH/GPX4耗竭的铁死亡和铜死亡,引发广泛的细胞裂解,最终实现免疫

抑制性肿瘤微环境的重编程。Cheng等^[77]开发了一种pH/GSH双响应型非晶态双金属有机框架材料(Fe/CuP5H),通过铁死亡、铜死亡和细胞凋亡协同治疗癌症。然而,目前有关MASLD中GSH调控铁死亡与铜死亡交互作用的研究较少,有待深入探讨。

5 靶向GSH代谢治疗MASLD的潜在策略

鉴于GSH在MASLD铁死亡与铜死亡交互作用中的重要调控作用,靶向GSH代谢通路开发干预策略具有一定的临床转化潜力。研究^[78]表明,给予丝氨酸和甘氨酸(合成GSH的前体物)会抑制人类和动物模型中的MASLD。Irie等^[79]发现,每日服用300 mg GSH可防止MASLD发展为MASH。Honda等^[80]评估了口服GSH(300 mg/d)对MASLD患者的治疗效果,证明GSH在控制肝损伤方面具有潜在治疗作用。一项研究^[81]发现,口服GSH增强剂S-腺苷甲硫氨酸(S-adenosylmethionine, SAM)和2-正丙基噻唑烷-4-羧酸(2-n-propylthiazolidine-4-carboxylic acid, PTCA)在MASH患者中具有治疗前景。N-乙酰半胱氨酸(N-acetylcysteine, NAC)是临床常用的抗氧化剂,能有效提供半胱氨酸,迅速提升肝内GSH水平。最近一项随机对照试验^[82]表明,NAC对MASLD具有潜在的抗氧化和抗炎效果。但未来仍需采用更高剂量和更长疗程开展进一步研究,以全面阐明其在肝脏健康中的治疗作用。新型GSH前体L-半胱氨酸-谷胱甘肽混合二硫化物(L-cysteine-glutathione mixed disulfide, L-CySSG)可通过提升线粒体GSH水平保护肝脏免受MASLD引起的损伤,口服GSH补充剂通常因 γ -谷氨酰转肽酶的酶解作用而效果不佳,但L-CySSG在小鼠中经口服后具有生物利用度,这种能够在体内被吸收并有效利用、且不会经历同样降解的特性,可能使L-CySSG成为一种有前景的治疗替代品^[83]。

靶向激活Nrf2以增强GSH合成是另一项关键策略,利用奥替普拉和富马酸二甲酯(dimethyl fumarate, DMF)等Nrf2激动剂来治疗MASLD可能成为未来研究的方向。随着纳米医学的发展,基于MASLD病灶区氧化应激和微环境特征,开发靶向GSH代谢的纳米载体,将抗氧化药物或靶向基因精准递送至肝脏以减少非靶位点毒性,同样值得关注。

6 结语与展望

铁死亡和铜死亡是MASLD发生与发展过程中的重要机制。GSH作为细胞内主要的抗氧化分子之一,在调控MASLD铁死亡和铜死亡中发挥着重要作用。

激活GSH合成通路可能为MASLD提供一种新的有效的治疗策略。未来研究应深入探讨GSH调控MASLD铁死亡和铜死亡的具体作用机制(如进一步阐明GSH调控铁死亡和铜死亡的具体信号通路及其相互作用,特别是在不同病理条件下这些通路的变化);探索GSH与其他细胞死亡方式的串扰,全面解析MASLD的分子病理网络;探究GSH合成相关基因(如*SLC7A11*、*Nrf2*等)在MASLD中的表达调控机制,探索如何调节这些基因来增强GSH的保护作用;将纳米材料技术、基因编辑与表观遗传调控以及多组学技术等应用于MASLD的治疗,寻找更加安全、有效的治疗措施,以减少MASLD带来的公共卫生问题。

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