

脂滴在肿瘤、心血管疾病和肝病中调控细胞程序性死亡的进展

金超凡 刘星燕 崔清华 钟雨婷 余涵 宋昊凌 丁磊*
(云南大学生命科学学院, 昆明 650500)

摘要 脂滴(lipid droplets, LDs)作为细胞内核心的脂质储存与代谢细胞器, 已突破单一的储存脂质的功能范畴, 成为调控脂质稳态、信号转导及细胞命运的关键枢纽。脂代谢紊乱是肿瘤、心血管疾病、肝病等重大疾病的共同病理基础。脂滴调控脂质合成、分解与转运的动态平衡, 脂代谢紊乱导致细胞凋亡、焦亡、铁死亡及自噬依赖性细胞死亡等细胞程序性死亡, 参与疾病的病理进程。靶向脂滴纠正脂代谢紊乱或调控其下游细胞死亡通路, 已成为疾病干预的潜在策略。该文系统阐述了脂滴介导的脂质代谢紊乱在疾病中特异性的调控机制, 深入解析了疾病状态下脂滴与细胞程序性死亡的交叉网络, 并总结了靶向脂滴的小分子药物、核酸药物及天然化合物等策略的研究进展, 旨在为相关疾病的病理机制解析及精准治疗提供全新视角与策略支撑。

关键词 脂滴; 脂代谢紊乱; 细胞程序性死亡; 肿瘤; 心血管疾病; 肝病; 靶向治疗

Progress of Lipid Droplets in Regulating Programmed Cell Death in Tumors, Cardiovascular Diseases, and Liver Diseases

JIN Chaofan, LIU Xingyan, CUI Qinghua, ZHONG Yuting, YU Han, SONG Haoling, DING Lei*
(School of Life Sciences, Yunnan University, Kunming 650500, China)

Abstract LDs (lipid droplets), as core intracellular organelles for lipid storage and metabolism, have functions that go beyond merely storing lipids, becoming key hubs of regulating lipid homeostasis, signal transduction, and cell fate. Disrupted lipid metabolism is a common pathological basis of major diseases such as tumors, cardiovascular diseases, and liver diseases. LDs regulate the dynamic balance of lipid synthesis, breakdown, and transport, and lipid metabolism disorders lead to programmed cell death, including apoptosis, pyroptosis, ferroptosis, and autophagy-dependent cell death, contributing to disease progression. Targeting LDs to correct lipid metabolism disorders or regulate their downstream cell death pathways has become a potential strategy for disease intervention. This article systematically summarizes the specific regulatory mechanisms of lipid droplet-mediated lipid metabolism disorders in diseases, provides an in-depth analysis of the crosstalk network between lipid droplets and programmed cell death under disease conditions, and summarizes research progress on strategies including small molecule drugs, nucleic acid drugs, and natural compounds targeting LDs, aiming to offer new perspectives and strategic references for the understanding of disease pathogenesis and precise therapy.

Keywords lipid droplets; lipid metabolism disorder; programmed cell death; tumor; cardiovascular disease; liver disease; targeted therapy

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*通信作者。Tel: 0871-65031412, E-mail: dingleiynu@ynu.edu.cn

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*Corresponding author. Tel: +86-871-65031412, E-mail: dingleiynu@ynu.edu.cn

脂滴(lipid droplets, LDs)是具有独特结构组成和多种细胞功能的动态细胞器,由单层磷脂膜及各种蛋白质分子包裹,内部含有甘油三酯(triglyceride, TG)和胆固醇酯等中性脂质,广泛存在于原核生物和真核生物细胞中,在脂质储存与代谢中起着核心作用。脂滴功能不仅局限于储存脂质,它还通过自身或表面蛋白与细胞质膜、线粒体膜及溶酶体膜等各种细胞器膜结合,广泛参与脂质代谢、信号转导及应激应答等关键生理过程^[1-2]。脂代谢紊乱(lipid metabolism disorder)是指脂质合成、分解、转运或代谢产物利用失衡的病理状态,其核心特征为TG、胆固醇及游离脂肪酸(free fatty acid, FFA)等脂质在细胞内异常累积,是多种疾病发生发展的共同驱动因素^[3]。

细胞程序性死亡(programmed cell death, PCD)是由基因调控的主动有序的细胞死亡方式,是维持机体稳态的重要程序性过程,其调控失衡与疾病进展密切相关。根据形态学与分子机制差异,PCD可分为凋亡、焦亡、铁死亡及自噬依赖性细胞死亡等多种类型^[4]。脂滴介导的脂代谢紊乱可通过改变细胞内脂质组成、活性氧(reactive oxygen species, ROS)水平及信号分子释放水平,选择性激活或抑制不同PCD通路,形成疾病特异性的调控网络。本文围绕脂滴在肿瘤、心血管疾病、肝病中的作用机制及靶向治疗展开综述,以期为该领域研究提供参考。

1 脂滴在脂代谢中的核心作用及其异质性

1.1 脂滴的结构组成与代谢功能

近年来研究表明,脂滴并非单纯的脂质储存仓库,而是脂代谢的核心调控者。脂滴的代谢功能依赖于其表面的脂滴相关蛋白如脂滴包被蛋白(perilipin, PLIN)及各类脂代谢酶等,同时依靠与线粒体、内质网(endoplasmic reticulum, ER)等细胞器形成的膜接触位点(membrane contact site, MCS)协同发挥作用,共同构成复杂的脂代谢调控网络^[5]。当机体能量充足时,脂滴通过脂肪合成酶(fatty acid synthase, FASN)、二酰甘油O-酰基转移酶1(diacylglycerol O-acyltransferase 1, DGAT1)等调控中性脂质合成,将过量FFA转化为TG储存于脂滴内核,避免FFA累积引发的脂毒性^[6]。当能量匮乏时,脂滴通过脂肪甘油三酯脂肪酶(adipose triglyceride lipase, ATGL)、激素

敏感性脂肪酶(hormone-sensitive lipase, HSL)介导的脂解作用按需释放FFA,为细胞供能或用于膜脂合成^[7]。

1.2 脂滴在细胞器中的定位及互作

脂滴起源于ER,中性脂质首先在ER膜双层间积累,随后以“出芽”方式形成具有单层磷脂膜的脂滴,并被释放至胞质中。因此,ER不仅是脂滴生物发生的起始场所,也是脂滴扩增、生长和表面蛋白装配的重要平台。除ER外,脂滴还可与多种细胞器形成MCS,从而实现脂质转运、代谢偶联和信号整合^[1,5]。

脂滴-线粒体接触位点是调控脂肪酸氧化和能量代谢的重要结构基础。脂滴释放的FFA可在接触位点被高效转运至线粒体进行 β -氧化,从而为细胞供能。这一接触异常易造成FFA利用障碍、脂质堆积和ROS生成量增加,进而诱发氧化应激及PCD^[8]。脂滴与溶酶体的互作主要通过脂噬(lipophagy)实现。脂噬是溶酶体对脂滴的选择性自噬降解,可分为巨脂噬(macrolipophagy,依赖于自噬体包裹)和微脂噬(microlipophagy,脂滴直接被溶酶体吞噬),是细胞清除过量脂质、维持代谢稳态的核心途径^[9]。脂滴还可与过氧化物酶体协同参与极长链脂肪酸代谢和脂质解毒,并与细胞膜、高尔基体及内体系统发生功能联系,影响膜脂更新、炎症信号转导和脂质输出^[5]。

脂滴不仅存在于胞质中,还可形成核脂滴(nuclear lipid droplets)。核脂滴与胞质脂滴在脂质组成、相关蛋白招募及生物学功能上均存在差异,可能与核膜稳态、脂质信号和基因表达调控相关^[10]。这说明,脂滴在细胞内具有明显的空间异质性,其功能并非完全一致,而是受到亚细胞定位和微环境的共同影响。

1.3 不同器官和组织中脂滴的状态差异

脂滴具有显著的组织特异性,不同器官中其数量、大小、脂质组成、包被蛋白谱和代谢活性均存在差异,这些差异决定了脂滴在生理和病理条件下的不同功能^[11]。

在肿瘤组织中,脂滴具有更强的异质性。多数恶性肿瘤细胞可通过促进脂质摄取、合成和储存形成大量脂滴,以适应快速增殖、缺氧、氧化应激和治疗压力。在不同肿瘤类型、不同分化阶段及不同微环境下,脂滴积累程度和功能差异明显,其既可为

肿瘤细胞提供能量和膜脂前体,也可通过隔离多不饱和脂肪酸(polyunsaturated fatty acid, PUFA)、缓冲脂质过氧化应激改变细胞对PCD的敏感性^[12]。

肝脏作为全身脂质合成、分配和氧化的核心枢纽,肝细胞脂滴的数量、大小和组成受营养状态、胰岛素信号和氧化应激的精细调控。肝细胞脂滴过度堆积导致的脂代谢紊乱,是代谢相关脂肪性肝病(metabolic associated fatty liver disease, MASLD)从单纯脂肪变性向肝纤维化进展的关键驱动力^[13]。

在心脏中,心肌细胞脂滴数量通常较少但周转迅速,其主要作用是持续收缩活动提供脂肪酸底物。心肌细胞脂滴通常与线粒体紧密邻接,以适应高水平氧化代谢需求;当脂滴积累过多或分解失衡时,该病理状态则可能诱发脂毒性、线粒体损伤和心肌细胞死亡^[14]。

总体而言,脂滴并非均一静态结构,而是在不

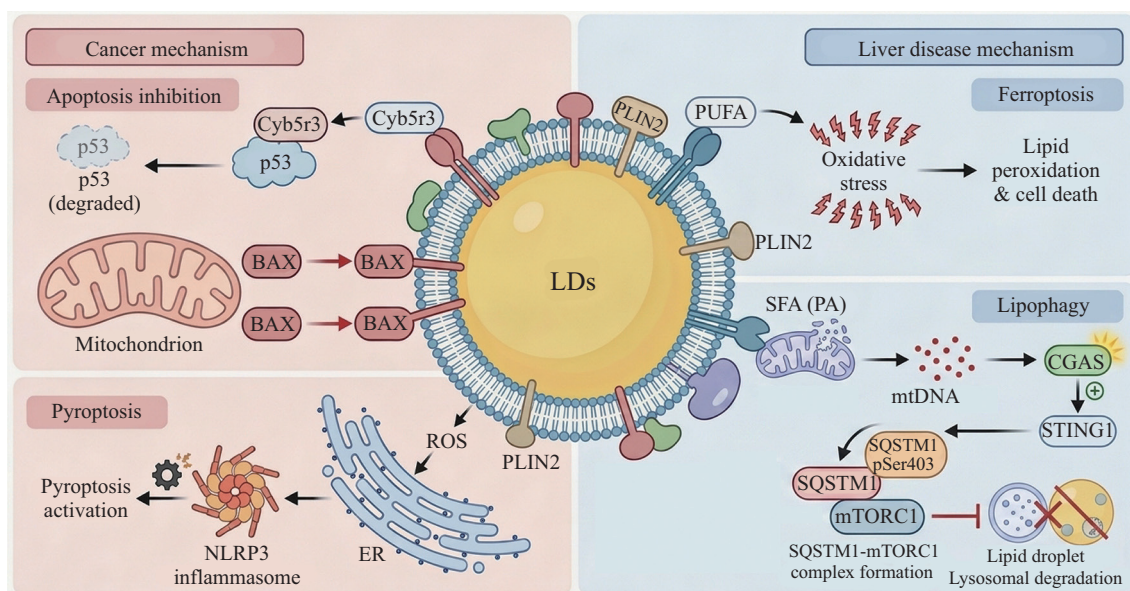
同细胞器定位和不同器官背景下呈现出明显异质性。这种“空间-组织”双重异质性,是脂滴参与重大疾病发生发展的重要基础。

2 脂滴介导脂代谢紊乱及细胞程序性死亡在重大疾病中的作用机制

脂滴作为脂代谢稳态的核心调控枢纽,其功能异常可直接诱发或加剧脂代谢紊乱,导致脂质代谢重编程。在不同疾病中,脂滴调控脂代谢紊乱的分子机制存在共性与特异性(图1),但其核心机制均为脂滴介导的脂质稳态失衡,这种失衡进一步通过调控细胞增殖、炎症反应及细胞程序性死亡等过程,促进疾病的发展^[3,15](表1)。

2.1 脂滴在肿瘤中的作用及其调控机制

越来越多的证据表明,脂质代谢在肿瘤转移进程中发挥关键调控作用,而脂代谢重编程是肿瘤细



脂滴(lipid droplets)通过表面蛋白Cyb5r3捕获细胞质中的p53,并通过表面蛋白MDM2介导p53的泛素化降解,进而抑制细胞凋亡。脂滴还可将凋亡蛋白如BAX从线粒体招募并隔离到自身,从而阻断凋亡进程,促进肿瘤增殖。脂滴通过将PUFA酯化为中性甘油三酯并储存于脂滴核心,有效减少了游离PUFA与铁的接触机会,从而抑制了铁死亡。ROS会引发脂滴内的脂质过氧化,随后这些过氧化脂质被转运至内质网激活NLRP3,进而通过Caspase-3/GSDME通路触发细胞焦亡。饱和脂肪酸可通过损伤线粒体,释放线粒体DNA,进而通过cGAS/STING通路激活mTORC1信号,阻碍脂滴自噬的正常进行,从而加剧肝脏脂肪积累和炎症。↑:促进作用;⊕:强促进作用;⊥:抑制作用。

LDs (lipid droplets) capture p53 from cellular lipids through the surface protein Cyb5r3, and the ubiquitination degradation of p53 is mediated via the surface protein MDM2, leading to inhibit apoptosis. LDs can also recruit apoptotic related proteins, such as BAX, from mitochondria and sequester them within LDs to block the apoptotic process, promoting tumor proliferation. LDs reduce the exposure of free PUFAs to iron by esterifying PUFAs into neutral triglycerides and storing them in the core of LDs, thereby inhibiting ferroptosis. ROS can trigger lipid peroxidation within LDs, and these peroxidized lipids are subsequently transported to the endoplasmic reticulum to activate NLRP3, which in turn initiates pyroptosis through the activation of Caspase-3/GSDME pathway. Saturated fatty acids can damage mitochondria, releasing mitochondrial DNA that activates STING via cGAS, thereby activating mTORC1 signaling pathway and impeding normal lipophagy, ultimately exacerbating hepatic lipid accumulation and inflammation. ↑: promotion; ⊕: strong promotion; ⊥: inhibition.

图1 脂滴在肿瘤、心血管疾病和肝病中的部分调控机制

Fig.1 Partial regulation mechanism of lipid droplets in tumors, cardiovascular diseases and liver diseases

表 1 脂滴介导细胞程序性死亡参与肿瘤、心血管疾病及肝病的主要机制
Table 1 The main mechanisms by which lipid droplet-mediated programmed cell death
in tumors, cardiovascular diseases and liver diseases

疾病 Disease	死亡通路 Death pathway	脂滴的关键作用 Key roles of lipid droplet	参考文献 References
Cancer	Apoptosis	Isolating apoptotic proteins, maintaining metabolic balance, resisting oxidative stress in ER, and promoting tumor cell survival, growth and therapy resistance	[16-17]
	Pyroptosis and ferroptosis	Dual roles of lipid droplet affect the tumor immune microenvironment and therapeutic response. Storing PUFA reduces lipid peroxidation and inflammasome activation, while targeting lipid peroxidation trigger ferroptosis and pyroptosis	[18-19]
	Autophagy	Autophagy-derived fatty acids are stored in lipid droplets to avoid lipotoxicity and maintain mitochondrial health, which helps tumor cells adapt to stress microenvironments, such as acidosis, to promote survival	[20]
Cardiovascular disease	Pyroptosis	ox-LDL triggers NLRP3 inflammasome activation resulting in the release of IL-1 β and other cytokines, thereby inducing pyroptosis and aggravating plaque inflammation	[21-22]
	Apoptosis	The loss of PLIN5 disrupts the integrity of lipid droplets, leading to more severe intracellular oxidative stress, which in turn activates the classical mitochondrial apoptosis pathway	[23]
	Ferroptosis	In cardiomyocytes of MIRI model mice, inhibiting lipid droplet degradation significantly reduced lipid peroxidation and suppressed ferroptosis, thereby alleviating MIRI in mice	[24]
Liver disease	Ferroptosis	Lipid droplet can inhibit ferroptosis due to lipid storage, while it also can act as a driver of ferroptosis under certain conditions	[25-26]
	Autophagy	Lipotoxicity can activate innate immune pathways, such as the STING pathway, which in turn activates mTORC1 signaling, thereby inhibiting lipophagy and exacerbating hepatic fat accumulation and inflammation	[27]

胞的核心病理特征, 其中脂滴异常累积尤为典型。基础研究与临床实践证实, 脂滴积累这一病理表型可作为多种癌症不良预后的重要标志物^[28-29]。

在脂质合成层面, 肿瘤细胞通过上调脂代谢关键酶, 显著提升内源性脂肪酸与TG的合成效率。例如, 在肺癌细胞中, JAK2/p-STAT3信号通路通过调节FASN表达, 促进脂质沉积和脂滴堆积, 从而增强肺癌细胞的辐射抗性和增殖能力^[30]。PLIN2依赖性脂滴的积累通过激活PI3K/AKT/mTOR通路, 诱导口腔鳞状细胞癌(oral squamous cell carcinoma, OSCC)细胞发生上皮-间质转化(epithelial-mesenchymal transition, EMT), 促进癌细胞的迁移和侵袭^[31]。抑制DGAT1的表达则会降低脂滴密度并影响前列腺癌细胞迁移^[32]。临床研究表明, 在肿瘤组织中FASN、DGAT1的高表达水平与肿瘤分期进展及患者不良预后呈显著正相关, 提示脂合成通路可作为肿瘤恶性进展的潜在标志物^[33-35]。

脂滴还可通过影响多种细胞程序性死亡调控肿瘤细胞命运。在凋亡方面, 高脂饮食诱导的肿瘤细胞脂滴积累可通过脂滴表面的Cyb5r3(cytochrome

b5 reductase 3)特异性捕获细胞质中的p53/Myh9复合物, 将其招募至脂滴表面, 随后通过鼠双微体同源基因2(murine double minute 2, MDM2)介导的泛素化修饰促进p53降解, 使其丧失抑癌功能, 促进肿瘤增殖并抑制细胞凋亡^[36]。定位于线粒体的凋亡蛋白如BAX含有“V”结构域, 该结构域使其能在线粒体和脂滴之间穿梭, 且对脂滴的亲合力高于线粒体。当细胞质中的脂滴含量增加时, 这些凋亡蛋白会从线粒体清除并重新定位到脂滴中, 从而中断凋亡程序^[17]。此外, 脂解过程也参与凋亡调控, ABHD5(abhydrolase domain containing 5)是脂肪酶的共激活因子, 参与TG降解(类似于ATGL), 负责维持脂质稳态^[37]。在前列腺癌细胞中, ABHD5有助于细胞生长, 抑制ABHD5会引起腺苷酸活化蛋白激酶(adenosine 5'-monophosphate-activated protein kinase, AMPK)磷酸化水平升高和p70S6K磷酸化水平降低, 导致蛋白质合成阻断和细胞凋亡^[38]。

在焦亡调控方面, 脂滴的衍生脂质是调控炎症小体的重要信号分子。脂滴内储存的PUFA在氧化应激条件下可生成4-羟基壬烯醛(4-hydroxynonenal,

4-HNE)、丙二醛(malondialdehyde, MDA)、8-异前列腺素(8-isoprostanes)等活性脂质分子。这些脂质过氧化产物通过与蛋白质形成共价加合物^[39]影响抗氧化系统和炎症系统及相关的信号通路^[40]。在肿瘤细胞中高表达的PLIN2蛋白可稳定脂滴膜,抑制PUFA泄漏,避免PUFA氧化生成4-HNE^[41],最终抑制NLRP3(NOD-like receptor protein 3)炎症小体的活化^[42-43]。研究发现,一类能够特异性聚集在肿瘤细胞脂滴中的光敏剂,在光照下会产生ROS,引发脂滴内的脂质过氧化,随后这些过氧化脂质被转运至ER激活NLRP3,进而通过Caspase-3/GSDME通路触发细胞焦亡,为抗肿瘤治疗提供了一种有效策略^[19]。

在铁死亡调控方面,脂滴通过储存与释放脂质双向调控肿瘤细胞敏感性。如在三阴性乳腺癌(triple-negative breast cancer, TNBC)细胞中脂肪酸脱饱和酶1/2(fatty acid desaturases 1/2, FADS1/2)驱动了细胞内PUFA的生物合成,PUFA的存在促进铁死亡;基因干扰和药物方法靶向FADS1/2可以使肿瘤对铁死亡产生抗性,而补充外源性PUFA使PUFA/MUFA比例失衡,则使耐药肿瘤重新对铁死亡诱导敏感^[44]。在肺癌模型中,细胞周期停滞的细胞通过DGAT介导的脂滴生成量增加来储存PUFA,从而抵抗铁死亡^[45]。

脂滴作为缓冲系统,储存自噬产生的脂肪酸。研究表明,脂滴可保护结直肠癌细胞中的线粒体免受脂毒性。阻断脂滴生物合成会导致线粒体功能障碍,这种障碍可以通过抑制肉碱棕榈酰转移酶1 α (carnitine palmitoyltransferase 1 α , CPT1 α)来挽救。因此,自噬通量和脂滴形成的级联反应在维持线粒体健康以促进癌细胞在慢性酸中毒条件下的存活中起着至关重要的作用^[20]。

因此,脂滴在肿瘤中的功能并不限于提供能量和膜脂原料,而是深度参与肿瘤细胞死亡调控、微环境重塑和治疗应答。围绕脂滴相关通路开展靶向干预,可能为克服肿瘤侵袭转移与治疗耐药提供新策略。

2.2 脂滴在心血管疾病中的作用及调控机制

脂代谢紊乱是动脉粥样硬化(atherosclerosis, AS)、缺血性心脏病(ischemic heart disease, IHD)等心血管疾病的**核心因素。近年来研究表明,脂滴不仅通过调控脂质代谢加速血管内皮损伤、泡沫细胞形成及斑块进展,还通过介导多种细胞程序性死亡

途径,驱动疾病的发生与发展。

血管内皮细胞中的脂滴积累是驱动AS起始的关键事件。高脂环境可诱导内皮细胞脂滴形成,从而特异性隔离细胞质中的棕榈酸(palmitic acid, PA),导致ARL13B(ARF-like GTPase 13B)等纤毛相关蛋白的S-棕榈酰化修饰不足,这一变化破坏了内皮细胞纤毛的稳态^[46]。同时,脂毒性物质如溶血磷脂酰胆碱能激活NLRP3炎症小体,直接诱导血管内皮细胞和单核细胞发生焦亡,释放大量白细胞介素-1 β (interleukin-1 β , IL-1 β),形成持续性的炎症刺激^[22],推动AS的发展。

AS的核心病理过程为泡沫细胞形成,而脂滴异常累积是泡沫细胞的典型特征。血液中过量低密度脂蛋白(low-density lipoprotein, LDL)被血管内皮细胞摄取后,经氧化修饰形成氧化型LDL(oxidized low-density lipoprotein, ox-LDL)。ox-LDL可诱导巨噬细胞脂质摄取量增加,同时抑制脂质分解,这导致TG和胆固醇酯在巨噬细胞内大量累积形成脂滴,促使巨噬细胞转化为泡沫细胞^[47]。泡沫细胞内脂滴通过PLIN2、PLIN3蛋白稳定结构并抑制脂解酶活性,加剧脂代谢紊乱^[48]。此外,脂滴中储存的TAG可经ATGL介导的脂解过程释放FFA,并促进PGE2等炎症性脂质介质的生成,从而参与巨噬细胞炎症反应的调控^[49]。值得注意的是,饱和脂肪酸作为脂解的重要产物之一,能够激活TLR4相关炎症信号通路,显著上调肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白细胞介素-6(IL-6)等促炎因子的表达^[50]。这些释放的炎症因子又能够进一步上调巨噬细胞表面的清道夫受体,极大地增强细胞对ox-LDL的摄取能力,导致脂质堆积和炎症反应同步加剧,促进AS斑块的形成和进展。

除调控炎症反应外,脂滴还通过调控凋亡影响AS进程。研究表明,PLIN5的缺失会破坏脂滴的完整性,导致更严重的细胞内氧化应激,进而激活经典的线粒体凋亡通路,主要表现为细胞色素C释放量增加,以及下游凋亡执行蛋白Caspase-3和PARP(poly ADP-ribose polymerase)的切割活化作用增强,直接加速AS的进程^[23]。

脂滴的动态变化同样在IHD和心肌缺血/再灌注(myocardial ischemic reperfusion injury, MIRI)中发挥重要作用。在IHD的心肌细胞中,脂滴代谢异常可通过激活凋亡通路加剧损伤。如在脂毒性应

激下, PA上调CD36(cluster of differentiation 36)等脂质转运蛋白的表达, 同时显著降低ATGL、HSL等酶以及PLIN5的表达水平, 导致脂滴积累和线粒体功能障碍, 最终引发心肌细胞凋亡^[51]。这一机制揭示了调控脂滴动态平衡是保护心肌细胞的关键节点。而MIRI的核心机制之一是铁死亡, 利用新型荧光探针的研究揭示, 在MIRI小鼠模型中, 在再灌注早期(0~9 h), 心肌细胞内的脂滴会迅速累积; 而在晚期(>24 h), 这些脂滴通过自噬过程被选择性降解。抑制脂滴的分解可以显著降低心肌细胞内的脂质过氧化水平, 减轻铁死亡。这表明靶向脂滴代谢与自噬通路可能是保护心肌、减轻再灌注损伤的潜在策略^[24]。此外, PLIN家族蛋白在氧化应激条件下起到内源性保护的作用^[52], 进一步凸显了脂滴调控在心血管疾病防治中的重要价值。

综上, 脂滴通过调控血管内皮稳态与心肌细胞的死亡信号, 在心血管疾病的发生发展中发挥多重、动态的调控作用, 使其成为一个极具潜力的治疗靶标。

2.3 脂滴在肝病中的作用及调控机制

代谢相关脂肪性肝病是全球发病率最高的慢性肝病, 其核心病理特征为肝细胞脂滴异常累积引发的脂代谢紊乱, 疾病进展过程为单纯脂肪变性到脂肪性肝炎再到肝纤维化、肝硬化最后发展为肝癌^[53-54]。脂滴介导的死亡通路贯穿MASLD全程, 其核心机制之一为铁死亡与铁稳态失衡^[45], 同时伴随凋亡与自噬等通路共同构成了MASLD复杂的病理网络。

单纯脂肪变性本质上是肝细胞面对脂质输入超过输出能力时的一种适应性保护反应, 主要由高脂饮食和全身性胰岛素抵抗(insulin resistance, IR)等因素驱动, 这种失衡导致肝脏脂肪酸摄取水平升高和脂肪从头合成(*de novo* lipogenesis, DNL)增加^[55]。同时, 肝细胞膜上脂肪酸转运蛋白CD36表达上调, 显著促进FFA摄取, 过量FFA储存于脂滴, 以减轻脂毒性^[56]。然而, 当脂质输入持续不断时, 这种适应性机制便崩塌, 标志着疾病向代谢功能障碍相关脂肪性肝炎(metabolic dysfunction associated steatohepatitis, MASH)的恶性转变。在此阶段, 脂滴稳定性下降引发脂代谢紊乱加剧, 肝细胞内过量脂滴使PLIN5上调而PLIN2下调, 导致脂滴膜完整性遭到破坏, 释放大量的FFA^[57], 推动脂肪变性向肝炎进展。

肝星状细胞(hepatic stellate cell, HSC)的激活是肝纤维化的主要因素^[58], 脂滴介导的脂代谢紊乱通过激活HSC加速纤维化进程^[59]。有研究揭示, 调节HSC的脂质代谢和能量状态可以影响其活化和产生细胞外基质的能力^[60]。HSC的活化在传统上被认为伴随细胞内脂滴的消耗, 然而研究表明, 通过干预手段(如上调PLIN5表达)促使已活化的HSC重新积累脂滴, 可诱导其向静止态部分逆转, 这为靶向脂代谢以抗纤维化提供了新思路^[61]。

脂滴在MASLD中可双向调控铁死亡。它既能因脂质储存而抑制铁死亡, 又在特定条件下成为铁死亡信号的驱动者。在MASLD中, 过量脂肪酸(尤其是PUFA)在细胞内堆积会诱发脂质过氧化链式反应, 而脂滴通过将PUFAs酯化为中性甘油三酯并储存于核心, 有效减少了游离PUFAs与铁的接触机会, 从而抑制了铁死亡。这一保护机制在cGAS-ALDH2调控轴中有精确的阐释。cGAS结合并抑制ALDH2, 当cGAS缺失时, ALDH2被激活, 乙醛转化为乙酰辅酶A, 促进组蛋白乙酰化和脂质合成基因转录, 驱动脂滴大量积累。而这些异常堆积的脂滴赋予了肝细胞对铁死亡的抵抗能力, 但同时诱导内质网应激, 抑制STING激活。这一发现揭示了脂滴虽赋予铁死亡抵抗, 却以内质网应激和代谢紊乱为代价^[26]。PLIN5在正常生理条件下介导线粒体-脂滴接触以促进脂肪酸氧化, 但在MASLD中, PLIN5的过度表达反而促进脂质积累和铁死亡。研究发现, 敲低PLIN5可能靶向ATF3/CHOP/CHAC1信号轴, 从而减轻肝细胞中的铁死亡, 最终缓解MASLD, 提示PLIN5可能是连接脂滴稳态与铁死亡敏感性的关键分子开关^[25]。

此外, 作为脂质清除的关键途径, 自噬的功能受损是MASLD恶化的重要环节。例如, PA会导致线粒体损伤并促使线粒体DNA释放。cGAS检测到线粒体DNA后, 促进SQSTM1在Ser403位点的磷酸化, 磷酸化的SQSTM1促进mTORC1的复合物形成, 这增强了mTORC1信号, 使脂滴自噬的正常进行受到阻碍, 从而加剧肝脏脂肪积累和炎症^[27]。Rab GTP酶(如Rab10)与动力蛋白发动蛋白-2(dynamin-2)构成了复杂的调控网络, 精确指导自噬体对脂滴的识别、包裹、运输及与溶酶体的融合^[62]。多种肝损伤因素可破坏此网络, 例如乙醇等肝毒性物质可通过特异性抑制Rab7活性来阻碍自噬^[63]。除上述经

典自噬通路外,脂滴的稳态还可受非自噬性脂质重塑机制调控。ATG9A(autophagy-related 9A)通过与PLA2G6(phospholipase A2 group VI)结合,以不依赖经典自噬的方式驱动磷脂代谢重编程和线粒体损伤,推动代谢性肝病及肝癌的发展^[64]。

随着MASH和纤维化的持续进展,长期的炎症、氧化应激和遗传不稳定性最终将部分患者引向肝硬化和肝癌。因此,针对脂滴代谢的关键节点进行干预,已成为极具前景的治疗新策略。未来研究不仅需进一步阐明脂滴蛋白组在疾病各阶段的精确调控网络,还需探索如何特异性靶向肝脏不同细胞内的脂滴,从而实现对MASLD安全有效的逆转。

3 靶向脂滴的疾病干预策略

基于脂滴在脂代谢紊乱及疾病进展中的核心作用,靶向脂滴纠正脂代谢失衡或调控其下游细胞死亡通路,已成为疾病干预的关键方向。目前,已开发出小分子药物、核酸药物、天然化合物等多种干预策略,部分已进入临床前或临床试验阶段,展现出良好的疾病治疗潜力。

3.1 小分子药物

小分子药物通过靶向脂滴相关脂代谢关键酶或细胞死亡通路核心分子,纠正脂滴介导的脂代谢紊乱,调控细胞死亡,发挥疾病治疗作用。FASN抑制剂(如cerulenin^[65]、C75^[66])通过抑制脂肪酸合成,降低肿瘤细胞、肝细胞脂滴累积水平,纠正脂代谢紊乱。TVB-2640作为临床阶段FASN抑制剂,已在乳腺癌临床前模型中展现出显著的抗肿瘤活性,且耐受性良好^[67]。ATGL抑制剂ATGLi(atglistatin)在MASH小鼠模型中,能抑制过氧化物酶体增殖物激活受体 α (peroxisome proliferator-activated receptor α , PPAR α)信号通路,减轻肝脏脂肪变性、炎症和纤维化,该机制在人类细胞模型中同样有效^[68]。DGAT1抑制剂(如A922500)可抑制TG合成,减少肝细胞脂滴累积量,缓解肝损伤与炎症反应^[69]。

靶向炎症小体的小分子药物可直接阻断其激活来缓解脂代谢紊乱引发的损伤。如NLRP3小分子拮抗剂通过直接结合NLRP3,抑制其激活,从而抑制下游促炎因子(如IL-1 β)成熟和细胞焦亡。该抑制剂在包括MASH在内的多种疾病中进入II期临床试验^[70]。MCC950可以直接与NLRP3的NACHT结

构域中的Walker B基序相互作用,从而阻断ATP水解,进而抑制NLRP3的激活和炎症小体的形成^[71]。因此,MCC950治疗有可能减轻肝脏炎症反应和纤维化程度,进而减轻MASLD病理状况^[72]。

3.2 核酸药物

核酸药物在MASLD/MASH中展现出了良好的治疗效果。核酸药物通过靶向脂滴相关蛋白,精准调控脂滴功能,纠正脂代谢紊乱,具有特异性高、副作用小的优势,而脂滴靶向递送系统的优化进一步提升了核酸药物的疗效与安全性。

靶向PLIN2的siRNA通过肝脏靶向递送系统(如GalNAc修饰的脂质纳米颗粒),可特异性下调肝细胞PLIN2表达,促进脂滴分解和脂质外排,显著缓解MASLD/MASH小鼠的肝脏脂肪变性、炎症和纤维化^[73]。PNPLA3(patatin-like phospholipase domain-containing protein 3)蛋白的I148M(第148位异亮氨酸由蛋氨酸取代^[74])与MASH严重程度、肝纤维化和肝细胞癌相关^[75]。AZD2693是一种靶向肝脏的PNPLA3的反义寡核苷酸,降低了PNPLA3 mRNA和蛋白水平,并呈剂量依赖性地减少了肝脏脂肪含量,表明AZD2693可作为MASH潜在精准治疗药物^[76]。ION224是一种靶向肝脏的DGAT2的反义寡核苷酸抑制剂,能够抑制脂肪从头生成,II期临床试验显示出良好的安全性和耐受性,可缓解MASH中的潜在炎症、肝细胞损伤和纤维化^[77]。

3.3 天然化合物

天然化合物通过温和调控脂滴合成、分解或自噬,缓解脂代谢紊乱,具有安全性高、耐受性好的优势,为疾病防治提供了新选择。

植物提取物与膳食多酚展现出良好的脂滴调控能力。矢车菊素-3-葡萄糖苷(cyanidin-3-O-glucoside, C3G)可纠正脂代谢紊乱^[78]。在MASLD模型中,C3G能通过促进PINK1(PTEN-induced putative kinase 1)介导的线粒体自噬、缓解氧化应激和抑制NLRP3炎症小体激活来抑制肝脏脂肪变性和减轻炎症^[79]。柚皮苷(naringin)通过激活转录因子EB(transcription factor EB, TFEB)介导的溶酶体生物合成和脂噬减轻肝脂肪变性和MASLD症状^[80]。山柰酚(kaempferide)靶向线粒体蛋白TUFM,在不干扰mTOR通路的情况下激活TFEB,促进自噬和脂滴降解,改善饮食诱导肥胖小鼠的代谢状况^[81]。

4 总结与展望

脂滴作为细胞内脂质代谢的核心枢纽, 已从传统认知中的脂质储存仓库重新定义为整合代谢信号与细胞命运决策的关键平台。本文系统阐述了脂滴驱动的脂代谢紊乱通过调控细胞程序性死亡通路, 在肿瘤、心血管疾病和肝病中发挥的核心病理作用, 并揭示了其在不同疾病中的共性与特异性机制。

近年来, 学界在脂滴研究方面虽取得显著进展, 但领域内仍面临诸多亟待解决的关键问题。脂滴与胞内多数细胞器如线粒体、ER等的MCS是脂质转运和代谢协作的关键平台, 但其发生接触的具体条件仍不完全明确。此外, 脂滴结构和功能的异质性是新兴的研究方向。异质性可在细胞或器官水平上发生, 同一细胞内的脂滴可以具有不同的脂质和蛋白质组成, 并可作为与其他细胞器相互作用的亚群存在。在许多情况下, 这些差异究竟是代表稳定的脂滴亚群, 还是仅为暂时的中间状态, 仍需要进一步的探索。近期研究已经明确了核脂滴与细胞质脂滴存在差异, 这提示细胞内脂滴在空间上存在进一步的功能划分。

在临床转化层面, 靶向脂滴代谢的药物已在临床前或早期临床研究中展现出潜力, 但如何实现精准递送、克服代偿机制及规避脱靶毒性仍是重大挑战。当前的研究大多忽视了代谢靶点之间复杂的相互作用。鉴于脂质代谢通路具有内在代谢可塑性, 过度干预单一通路可能导致替代通路的代谢紊乱, 损害网络稳定性和整体脂质稳态。此外, 长期使用脂质代谢靶向药物可能损害正常免疫细胞和肝功能, 引发代谢紊乱和免疫相关不良反应。因此, 安全问题依然是限制当前研究临床转化的主要瓶颈。同时, 脂质代谢受众多因素影响, 包括遗传易感性、环境因素和生活方式, 这些因素导致治疗反应差异显著。遗传多样性、药物代谢个体差异和饮食习惯可能显著影响治疗结果, 从而增加治疗策略的复杂性。

综上, 未来研究需要在深入解析脂滴复杂调控网络的基础上, 整合分子机制、细胞异质性与整体代谢稳态的多维度视角, 以推动脂滴相关疾病的诊疗突破。

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