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Cullin-Ring Ligase泛素连接酶在肿瘤脂代谢调控中的研究进展

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［**摘要**］ 脂质代谢重编程是肿瘤的核心代谢特征之一。肿瘤细胞通过增强外源性脂质摄取、内源性脂质转化与合成，满足其快速增殖的能量与膜结构需求。近年来，CRL（Cullin-RING Ligase）泛素连接酶作为调控肿瘤脂质代谢的关键酶类，已有大量研究探讨CRL泛素连接酶与肿瘤之间的作用机制，但目前尚缺乏针对脂质代谢调控的系统总结，本文系统综述CRL泛素连接酶调控肿瘤脂质代谢的研究进展及靶向治疗策略，旨在阐明（1）CRL泛素连接酶调控肿瘤脂质代谢的分子机制；（2）靶向CRL-脂质代谢轴的治疗策略；（3）现有研究的局限性与未来方向。我们在PubMed数据库中检索了截至2026年的文献，检索词包括“Cullin-RING Ligase”，“tumor lipid metabolism”，“lipid metabolism”，“targeted therapy”等，筛选原则为：（1）筛选时间为2020-2025，纳入少许2020以前的高分文章；（2）分区限定为Q1、Q2；（3）文献类型为Article，纳入少许高分review。CRL泛素连接酶通过介导关键底物蛋白泛素化降解，广泛参与脂肪酸合成与氧化、胆固醇代谢及多种脂质代谢相关信号通路的调控。研究表明，$CRL1^{FBXW7}$、$CRL4^{COP1}$、$CRL4^{DCAF1}$、$CRL1^{SKP2}$、$CRL2^{VHL}$等泛素连接酶通过调控脂代谢关键分子，影响肿瘤细胞脂质合成、储存与氧化过程，从而促进肿瘤发生、发展。基于上述机制，目前靶向CRL-脂质代谢轴的抗肿瘤治疗策略已取得重要进展。在靶向$CRL1^{FBXW7}$方面，抑制剂BI2536、BI6727和Entinostat分别通过抑制Polo样激酶1（Polo-like kinase 1，PLK1）和组蛋白去乙酰化酶（Histone Deacetylase，HDAC）间接稳定含F-box和WD重复结构域（F-box and WD repeat domain containing 7，FBXW7）7从而促进其底物降解；在靶向$CRL1^{SKP2}$方面，DT204和Compound 25通过阻断S期激酶相关蛋白2（S-phase kinase associated protein 2，SKP2）与骨架蛋白结合抑制其泛素连接酶活性；MLN4924作为NEDD8活化酶（NEDD8-activating enzyme，NAE）的抑制剂，通过阻断Cullin蛋白neddylation修饰抑制CRL活性，目前已展现联合用药价值。此外，靶向下游脂质代谢因子的药物如抑制剂Fatostatin、拮抗剂GW9662和T0070907等亦显示出一定抗肿瘤潜力。尽管靶向CRL-脂质代谢轴展现广阔应用前景，但仍面临单靶点治疗易致代谢代偿、个体脂质代谢异质性显著及长期抑制CRL的脱靶毒性等挑战。未来研究应着重于：解析CRL-脂质代谢轴在肿瘤微环境与免疫代谢中的交互作用；开发高选择性降解技术以降低脱靶效应；整合多组学技术指导个体化精准用药；探索CRL抑制剂与免疫检查点抑制剂的联合治疗方案等。随着对CRL调控机制认识的不断深入及新型靶向技术的开发，精准干预CRL-脂质代谢轴有望成为肿瘤代谢治疗的重要策略。

［**关键词**］ CRL泛素连接酶；肿瘤；脂代谢；代谢调控；靶向治疗

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Research progress of Cullin-Ring Ligase ubiquitin ligase in the regulation of tumor lipid metabolism　Wang Junyan, Zhu Feng, Wang　Shiwen　(Huadong Hospital, Fudan University, Laboratory Department, Shanghai 200040)

［**Abstract**］ Lipid metabolic reprogramming is one of the core metabolic features of tumors. Tumor cells satisfy the energy and membrane structure demands required for rapid proliferation by enhancing exogenous lipid uptake, endogenous lipid transformation,

and synthesis. In recent years, CRL (Cullin-RING Ligase) ubiquitin ligases have emerged as key enzymes regulating tumor lipid metabolism. A substantial number of studies have explored the mechanisms between CRL ubiquitin ligases and tumors; however, a systematic summary specifically addressing lipid metabolic regulation is still lacking. Therefore, this article provides a systematic review of the research progress and targeted therapeutic strategies concerning CRL ubiquitin ligase regulation of tumor lipid metabolism, aiming to elucidate: (1) the molecular mechanisms by which CRL ubiquitin ligases regulate tumor lipid metabolism; (2) therapeutic strategies targeting the CRL-lipid metabolism axis; and (3) current research limitations and future directions. We retrieved literature from the PubMed database up to 2026, using search terms including "Cullin-RING Ligase, " "tumor lipid metabolism," "lipid metabolism," and "targeted therapy." The inclusion criteria were: (1) articles published between 2020 and 2025, with a few highly cited articles from before 2020 also included; (2) journals classified as Q1、Q2; and (3) primarily research articles, with a few high-impact reviews included. CRL ubiquitin ligases widely participate in the regulation of fatty acid synthesis and oxidation, cholesterol metabolism, and various lipid metabolism-related signaling pathways by mediating ubiquitin-dependent degradation of key substrate proteins. Studies indicate that ubiquitin ligases such as $CRL1^{FBXW7}$, $CRL4^{COP1}$, $CRL4^{DCAF1}$, $CRL1^{SKP2}$, and $CRL2^{VHL}$ influence tumor cell lipid synthesis, storage, and oxidation processes by regulating key lipid metabolism molecules, thereby promoting tumorigenesis and progression. Based on these mechanisms, significant progress has been made in antitumor therapeutic strategies targeting the CRL-lipid metabolism axis. Regarding $CRL1^{FBXW7}$, inhibitors BI2536, BI6727, and Entinostat indirectly stabilize FBXW7 by inhibiting PLK1 and HDAC, respectively, thereby promoting substrate degradation. For $CRL1^{SKP2}$, DT204 and Compound 25 inhibit its ubiquitin ligase activity by blocking the interaction between SKP2 and scaffold proteins. MLN4924, an inhibitor of NAE, suppresses CRL activity by blocking Cullin protein neddylation modification and has demonstrated potential for combination therapy. Additionally, drugs targeting downstream lipid metabolism factors, such as the inhibitor fatostatin and antagonists GW9662 and T0070907, have also shown certain antitumor potential.

［**Key words**］Cullin-RING Ligase; Tumor; Lipid metabolism; Metabolic regulation; Targeted therapy

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脂质是合成质膜等结构的物质基础和细胞活动主要的能量来源，同时参与细胞内外信号转导[1]。脂质代谢失调是肿瘤发生、发展过程中的重要代谢特征之一。高度增殖的肿瘤细胞通过促进外源脂质/脂蛋白摄取、内源性脂质转化与合成水平以获得强脂质亲和力、能量以及合成生物膜所需的脂质组分，合成并释放信号调控分子，从而支持其持续增殖与转移以适应肿瘤微环境的变化[2]。过剩胆固醇以脂滴形式储存，其高含量已成为结肠癌干细胞等侵袭性亚群的标志性特征，且赋予肿瘤细胞化疗耐药性[3]。研究发现，低密度脂蛋白水平升高时，胰腺癌细胞可动员脂滴内胆固醇酯维持肿瘤细胞致癌活性，抑制低密度脂蛋白摄取则削弱其恶性表型[3]。此外，肿瘤细胞存活与转移还依靠脂肪酸β-氧化供能，如β-氧化是前列腺腺癌和弥漫性大B细胞淋巴瘤等非糖酵解肿瘤的主要生物能量途径[3]。在肿瘤脂代谢重编程中，肿瘤细胞将合成的脂质优先供给PI3K-AKT-mTOR-SREBP脂质合成轴和Hippo-YAP/TAZ脂质代谢轴等相关促癌代谢途径，从而加速肿瘤进展[4]。此外，脂质代谢重编程还可抑制免疫细胞的功能且脂质代谢关键酶在肿瘤发生、发展中常发生功能失调，从而促进肿瘤发生、发展[5-6]。

CRL泛素连接酶是一类多亚基E3泛素连接酶超家族，主要由骨架蛋白Cullin家族、RING-finger蛋白、接头蛋白和底物识别蛋白四部分组成[7]。CRL泛素连接酶通过介导底物蛋白泛素化降解影响多种生物学进程，而其功能失调可以促进肿瘤的发生、发展[7]。既往研究报道，CRL泛素连接酶通过泛素-蛋白酶体系统调控肿瘤脂质代谢，通过调控脂肪酸合成酶（Fatty Acid Synthase，FASN）、乙酰辅酶A羧化酶（acetyl-CoA carboxylase，ACC）等脂质合成限速酶以及固醇调节元件结合蛋白（Sterol Regulatory Element-Binding Protein，SREBP）等转录因子的稳定性及活性来影响脂肪酸与胆固醇合成水平[7]。部分CRL泛素连接酶例如RING型E3泛素连接酶TRIM28和$CRL1^{FBXW7}$也可分别靶向腺苷酸活化蛋白激酶（AMP-activated protein kinase，AMPK）和β-catenin等信号通路关键分子，从而调控能量代谢和信号通路[8]。总的来说，E3泛素连接酶在维持肿瘤脂质代谢重编程、支持膜生物合成、调控信号通路中发挥重要作用[9]。鉴于CRL泛素连接酶在调控肿瘤脂质代谢中发挥的关键作用，目前靶向CRL-脂质代谢轴已成为一种极具潜力的抗肿瘤治疗策略[10]。本文将对CRL泛素连接酶在肿瘤脂质代谢调控中的研究进展作一综述。

1 CRL泛素连接酶在肿瘤脂代谢调控中的作用

1.1 脂肪酸合成与氧化

脂肪酸合成为肿瘤细胞生物膜等结构的合成提供所需脂质组分，CRL泛素连接酶通过介导多种脂肪酸合成关键酶泛素化降解发挥关键调控作用[11]。例如，FBXW7β作为CRL1泛素连接酶底物识别蛋白可介导脂肪酸合酶FASN的泛素化降解，但在结直肠癌（Colorectal Cancer，CRC）中FBXW7β常发生突变，导致FASN降解受阻，从而促进CRC细胞中脂质的过度合成，加速肿瘤生长[12]。又如，促癌蛋白COP9信号体亚基6（COP9 signalosome subunit 6，CSN6）可通过增强FBXW7β自泛素化降解上调FASN表达，从而增强CRC细胞中脂质合成水平，促进肿瘤进展[12-13]。此外，CRL泛素连接酶在肿瘤脂肪酸氧化中也发挥重要作用[14]。XY等人发现，肉碱棕榈酰转移酶2（Carnitine palmitoyl-transferase 2，CPT2）通过诱导长链脂肪酸进入线粒体进行β-氧化为细胞供能，而定位于线粒体外膜的RING型E3泛素连接酶MUL1可介导CPT2泛素化降解，从而使CPT2无法转移长链脂肪酸进入线粒体进行β-氧化，导致细胞中脂质堆积进而促进三阴性乳腺癌的生长与转移[14，15]。

1.2 胆固醇代谢与合成

胆固醇合成为快速增殖的肿瘤细胞提供膜成分，驱动肿瘤持续增殖[16]。既往研究发现，脂质代谢中的关键转录因子SREBP-1a促进胆固醇合成所需多种关键酶的表达[17]，FBXW7可识别磷酸化的SREBP-1a并介导其泛素化降解[18，19]。OI等发现，在CRC中FBXW7常失活导致SREBP-1a蛋白水平上调，增加脂质合成从而促进CRC的发生、发展[11]。此外，当高糖信号传入时，乙酰化酶p300乙酰化$CRL4^{COP1}$并激活其泛素连接酶活性，通过介导p53的泛素化降解，从而激活SREBP-2导致胆固醇合成增强，促进肿瘤发生、发展[20，21]。且SREBP-1在前列腺癌细胞中高表达，诱导脂肪酸合酶FASN和NADPH氧化酶5表达增加，从而导致脂肪酸和脂滴积累，进而促进前列腺癌细胞生长和侵袭进展，且SREBP-1高表达与患者预后不良相关[22]。

1.3 CRL泛素连接酶调控多种肿瘤脂质代谢相关信号通路

1.3.1 CRL泛素连接酶调控Hippo-YAP/TAZ-SREBP/ PPARγ脂质代谢轴

Hippo信号通路通过参与调控脂代谢、增殖及转移等多种生物学过程在肿瘤发生、发展中发挥重要作用[23]。哺乳动物Sterile20样激酶1/2和大肿瘤抑制因子激酶（Large Tumor Suppressor kinase，LATS）1/2能够磷酸化Yes相关蛋白（Yes-associated protein，YAP）和含PDZ结合基序的转录共激活因子（Transcriptional co-Activator with PDZ-binding motif，TAZ），从而被E3泛素连接酶识别并降解[23]。YAP/TAZ可与SREBP结合，促进其成熟和核转位，从而激活FASN等脂质合成相关基因[24]。研究发现，$CRL4^{DCAF1}$能够直接与LATS1和LATS2结合并介导LATS1泛素化降解，同时非降解性泛素化LATS2使其激酶活性丧失，导致YAP/TAZ去磷酸化并与SREBP结合，诱导脂质合成增加，增强肿瘤细胞自我更新、增殖、迁移和侵袭能力[25，26]。此外，磷酸化后的YAP/TAZ会招募$CRL1^{β\text{-}TrCP1}$复合物并识别其磷酸化降解位点，从而导致YAP/TAZ被$CRL1^{β\text{-}TrCP1}$泛素化降解，进而抑制脂质合成[27-30]。

1.3.2 CRL泛素连接酶调控AMPK-脂质氧化轴

AMPK作为细胞能量稳态的核心调控组分，其激活后会磷酸化脂肪酸合成的关键限速酶ACC并抑制其活性，从而促进长链脂肪酸进入线粒体进行β-氧化[9，31]。肝激酶B1（Liver kinase B1，LKB1）是AMPK的上游激酶，其活性依赖于与假激酶STE20相关适配器α（STE20 related adaptor alpha，STRAD）和支架蛋白钙结合蛋白39（scaffolding protein calcium binding protein 39，CAB39）形成的异源三聚体复合体的稳定[32]。既往研究发现，$CRL1^{SKP2}$能够介导LKB1非降解性泛素化，增强其与STRAD和CAB39的结合，增强AMPK磷酸化活化并促进长链脂肪酸进入线粒体进行β-氧化，从而促进肝细胞癌等肿瘤进展[22，33]。此外，促癌蛋白TRIM28作为RING型E3泛素连接酶可介导AMPKα的泛素化降解，抑制长链脂肪酸的β-氧化[34，35]，导致细胞被迫依赖Warburg效应和谷氨酰胺分解供能，促进肿瘤能量代谢重编程，加速肿瘤生长与转移[36]。作为检测指标，AMPK高表达在胃癌、妇科肿瘤和其他类型肿瘤中与患者良好预后正相关[37]。

1.3.3 CRL泛素连接酶调控PPARγ介导的脂质合成与储存

过氧化物酶体增殖物激活受体γ（Peroxisome Proliferator-Activated Receptor γ，

PPARγ）作为脂质代谢和脂肪细胞分化的转录因子，驱动脂质储存与脂肪细胞分化，其受CRL泛素连接酶关键调控[38，39]。既往研究报道，$CRL2^{VHL}$通过介导缺氧诱导因子1α（Hypoxia-inducible factor-1 alpha，HIF-1α）泛素化降解进而参与肿瘤脂代谢调控[40，41]。正常情况下，HIF-1α在核内与PPARγ竞争性结合共激活因子p300/CBP，并招HDAC3，使PPARγ靶基因（SREBP-1c、FASN、SCD1、CD36）启动子保持低乙酰化从而抑制脂质合成与摄取[40]。而在肾透明细胞癌中，肿瘤细胞因VHL突变或缺失而导致HIF-1α持续高表达，从而抑制PPARγ及下游脂质氧化基因，使脂肪酸无法被β-氧化，从而导致脂滴大量聚集于肿瘤细胞内，最终加速肿瘤进展[22，42]。另有研究表明，PPARγ表达水平可作为CRC筛查与预后评估的候选指标，但仍需进一步临床验证[43]。

1.3.4 CRL调控Wnt/β-catenin-SREBP/PPARγ介导的脂质代谢

Wnt/β-catenin-SREBP/PPARγ代谢通路通过多种机制参与调控脂质代谢[44]。既往研究表明，β-catenin能够直接结合SREBP-1c等脂质合成相关启动子，驱动脂肪酸从头合成[44，45]；此外，β-catenin还能激活PPARγ的表达，进而促进脂质合成与储存[46]。研究报道，$CRL1^{FBXW7}$调控Wnt/β-catenin-SREBP/ PPARγ通路并在肿瘤发生、发展中发挥关键作用[47-50]。当Wnt信号被抑制时，糖原合成酶激酶-3β（Glycogen Synthase Kinase-3β，GSK-3β）/酪蛋白激酶1δ（Casein Kinase 1δ，CK-1δ）会磷酸化β-catenin，使其可被$CRL1^{FBXW7}$识别并泛素化降解，抑制脂肪酸从头合成，脂质合成与储存受阻，脂肪酸氧化增强[50，51]。而在三阴性乳腺癌中，FBXW7常缺失或发生突变导致β-catenin积聚，促进脂质沉积，肿瘤负荷显著增加[48，50]。研究表明，Wnt/β-Catenin-SREBP/PPARγ通路促进骨肉瘤、肺癌及CRC等多种恶性肿瘤的发生、发展，是潜在的肿瘤治疗靶点[52]。

2 靶向CRL-脂质代谢轴和关键脂质代谢因子的肿瘤治疗策略

2.1 靶向CRL–脂质代谢轴的肿瘤治疗策略

2.1.1 靶向$CRL1^{FBXW7}$-FASN/SREBP/β-catenin轴：具有一定潜力

目前已有多种药物被证实可靶向FBXW7，抑制其泛素连接酶活性[56-57]。既往研究发现，

表1 不同CRL泛素连接酶在不同肿瘤中的作用

Table 1 The roles of different CRL ubiquitin ligases in different tumors

CRL ubiquitin ligase	Type	Mechanism	References
FBXW7β	Colorectal cancer	The FBXW7β gene often undergoes mutations, which results in the obstruction of FASN degradation and subsequently facilitates the excessive synthesis of lipids in CRC cells, thereby accelerating tumor growth.	[12]
FBXW7β	Colorectal cancer	The frequent inactivation of FBXW7 leads to an increase in the protein level of SREBP-1a, which enhances lipid synthesis and thereby promotes the occurrence and development of colorectal cancer.	[12]
MUL1	Triple-negative breast cancer	MUL1 can mediate the ubiquitination and degradation of CPT2, thereby preventing CPT2 from transferring long-chain fatty acids into mitochondria for β-oxidation. This leads to lipid accumulation in the cells and promotes the growth and metastasis of triple-negative breast cancer.	[14, 15]
COP1	Glioma	COP1 mediates the ubiquitination and degradation of p53, thereby upregulating SREBP-2, leading to enhanced cholesterol synthesis and promoting tumor occurrence and development.	[53]
DCAF1	Mesothelioma	This leads to the dephosphorylation of YAP/TAZ and their binding to SREBP, thereby inducing an increase in lipid synthesis and enhancing the self-renewal, proliferation, migration and invasion capabilities of tumor cells.	[26]
β-TrCP1	HEK293T	β-TrCP1 ubiquitination and degradation of YAP/TAZ downregulating lipid synthesis.	[27-30]
SKP2	Hepatocellular carcinoma	SKP2 mediates the non-degradative ubiquitination of LKB1, enhances its binding to STRAD and the anchoring protein MO25, upregulating the phosphorylation and activation of AMPK, and promotes the entry of long-chain fatty acids into mitochondria for β-oxidation, thereby promoting the progression of tumors such as Hepatocellular carcinoma.	[22, 33]
VHL	Renal clear cell carcinoma	The VHL mutation or deletion leads to the continuous high expression of HIF-1α, which inhibits PPARγ and downstream lipid oxidation genes, preventing fatty acids from undergoing β-oxidation. As a result, lipid droplets accumulate in large quantities within tumor cells, ultimately accelerating tumor progression.	[42][54]
FBXW7	Triple-negative breast cancer	The frequent absence or mutation of FBXW7 leads to the accumulation of β-catenin, promoting lipid deposition and significantly increasing the tumor burden.	[48, 50]
TRIM28	Colorectal and breast cancer	TRIM28, as a RING-type ubiquitin ligase, can mediate the ubiquitination and degradation of AMPKα, promoting the reprogramming of tumor energy metabolism and accelerating tumor growth and metastasis.	[55]

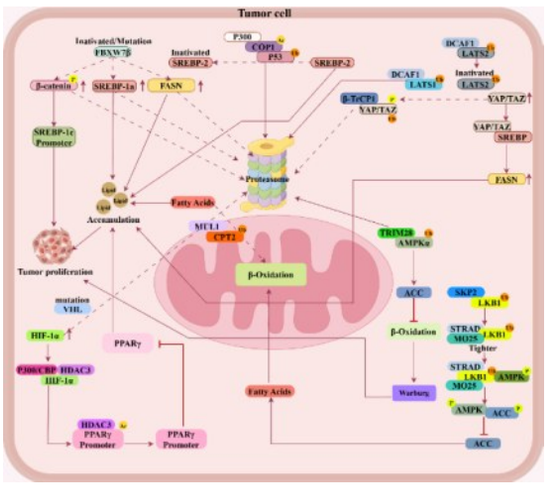


图1 CRL泛素连接酶在肿瘤脂代谢调控中的机制示意图

Figure1 Schematic diagram of the mechanism of CRL ubiquitin ligases in the regulation of tumor lipid metabolism

本图由Figdraw绘制

PLK1可直接磷酸化FBXW7并诱导其被泛素化降解[58]，PLK1抑制剂（如BI2536、BI6727）可通过抑制PLK1活性并诱导FBXW7积聚，从而加速FASN/SREBP/β-catenin的降解，进而抑制肿瘤进展[56]。此外，HDAC抑制剂（如Entinostat MS-275）通过阻断HDAC的去乙酰化活性，使FBXW7启动子区域染色质保持高乙酰化开放状态，激活FBXW7转录从而促进FASN/SREBP/β-catenin的降解，在非小细胞肺癌治疗中展现一定潜力[56，59]。

2.1.2 靶向$CRL1^{SKP2}$-AMPK轴：种类丰富，尚处早期

目前已开发多种SKP2抑制剂，但大部分仍停留在临床前阶段[60-62]。DT204通过抑制Skp2与Cullin-1的结合从而抑制其非降解性泛素化底物LKB1与STRAD和锚定蛋白MO25的结合，进而抑制该复合物对AMPK的激活，且DT204可增加SKP2底物如p27蛋白表达水平，发挥抑制脂质合成和促凋亡的功能[63，64]。另一研究发现，Compound 25（C25）通过竞争性阻断SKP2与SKP1的结合，导致$CRL1^{SKP2}$泛素连接酶活性被抑制，进而抑制AMPK活性；并可导致p27等抑癌蛋白累积，从而抑制肿瘤细胞增殖[65]。另有研究报道，AAA237通过与Skp2结合，抑制Skp2表达从而抑制p21和p27的降解，进而抑制胶质母细胞瘤细胞的增殖[66]。

2.1.3 靶向抑制CRL泛素连接酶：研究深入，仍存局限

目前靶向抑制CRL泛素连接酶的主要策略是阻断Cullin蛋白neddylation修饰，例如MLN4924可靶向NAE1抑制CRL泛素连接酶活性，通过抑制Cullin蛋白neddylation修饰，MLN4924可抑制泛素连接酶$CRL4^{COP1}$对P53的泛素化降解从而抑制SREBP-2，进而抑制胆固醇合成[20，29]；还可抑制泛素连接酶$CRL4^{DCAF1}$泛素化降解LATS1/2从而抑制SREBP成熟和脂质合成，进而抑制肿瘤细胞自我更新、增殖、迁移和侵袭能力[25]。最新临床研究发现，在针对高风险骨髓增生综合征、慢性骨髓单核细胞白血病、低原始细胞急性骨髓性白血病，样本量为227的Ⅱ/Ⅲ期临床试验中MLN4924与azacitidine联用对患者治疗有一定价值，但并未达到预期研究终点，仍存在局限性[67]。

2.2 靶向关键脂质代谢因子

2.2.1 SREBP拮抗剂：潜力尚可，仍存局限

SREBP通路作为肿瘤脂代谢的重要调控组分，目前已有多种靶向抑制SREBP通路的药物被开发[68]。L X等研究报道，fatostatin可通过阻断SREBP核转位和抑制SREBP-1/2激活来抑制脂质合成，于前列腺癌治疗前景尚可，但该药物并未进入临床试验，其临床潜力亟待验证[69，70]。此外，ACC抑制剂（如firsocostat）也可通过抑制ACC活性来抑制丙二酰辅酶A间接抑制SREBP，达到抑制脂质合成并限制肿瘤生长的目的[49，71]。另一研究报道，SREBP抑制剂betulin能提高前列腺癌治疗效果和增强患者的化疗敏感性，显示出该药在前列腺癌治疗中的良好前景[72]。但目前靶向药物仍存在局限性：fatostain同时抑制SREBP-1与SREBP-2，导致胆固醇及必需脂肪酸合成受阻，高剂量时可出现皮炎、体重下降及肝功能异常等不良作用[73]。

2.2.2 PPARγ拮抗剂：机制丰富，具有价值

GW9662、T0070907是目前研究相对成熟的小分子PPARγ拮抗剂[74]。研究发现，GW9662通过不可逆结合PPARγ的配体结合域中的Cys285，进而阻断其配体结合和共激活因子招募，抑制其驱动脂质储存与脂肪细胞分化的功能从而抑制肿瘤进展，目前已在乳腺癌模型中得到验证[74，75]。L G等研究发现，T0070907通过与PPARγ的配体结合域中的Cys313共价结合，招募协同抑制因子NCoR，进而抑制PPARγ活性，现已在CRC、前列腺癌等肿瘤模型验证[76]。SR1664等新一代可逆共价抑制剂通过阻断PPARγ磷酸化发挥作用，现已在前列腺癌模型中被证实有效[77，78]。另一研究发现，cinobufotalin促进PPARγ被蛋白酶体降解，从而显著抑制

PPARγ及其下游靶点以及RT112细胞中的脂滴形成和游离脂肪酸水平，其在治疗腔内型膀胱癌上具有一定前景[79]。

3 总结与展望

肿瘤脂质代谢在肿瘤发生、发展中发挥重要作用。CRL泛素连接酶通过介导多种底物降解参与调控脂肪酸合成与氧化、胆固醇代谢及多种脂质代谢相关信号通路，进而影响肿瘤发生、发展。目前靶向CRL泛素连接酶及脂代谢轴关键分子已成为新的肿瘤治疗策略，且已有多种药物显示出较好疗效。然而，目前靶向CRL泛素连接酶-脂代谢轴仍存在诸多难题，如单靶点治疗有限、个体脂代谢差异大、药物毒副作用不明确等。因此亟待探索肿瘤脂质代谢的详细机制和相关靶点，进一步发掘新的安全高效的靶向药物，并针对个体差异提出更精准的治疗策略。未来研究可着重于：（1）阐明药物诱导脂质重编程和耐药发生的机制，设计联合用药策略和个体精准用药策略，以改善患者预后；（2）发展高选择性技术如蛋白水解靶向嵌合体（Proteolysis-Targeting Chimeras，PROTAC）以精准招募CRL降解关键脂质代谢酶，从而减少脱靶毒性并提高治疗效果[80]；（3）探索脂代谢网络相联系的CRL泛素连接酶新底物，阐明不同CRL泛素连接酶在肿瘤脂代谢中的作用和功能，探究调控CRL泛素连接酶活性重要分子如NAE如何在肿瘤脂代谢过程中动态调控CRL泛素连接酶活性与脂代谢平衡；（4）探究肿瘤脂代谢过程中肿瘤微环境的动态变化，系统性阐明肿瘤进展过程中的多细胞代谢互作过程。

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