

肝细胞癌脂质代谢重编程及中药干预的研究进展

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[摘要] 肝细胞癌(HCC)被认为是最具侵袭性的肿瘤之一,常发生于慢性肝病和肝硬化患者。尽管目前的治疗方法有所进步,但由于其进展不明显,直到晚期才有明显症状,在诊断时已失去根治性肝切除术或经肝动脉化疗栓塞术等局限性治疗的机会,预后较差。与正常细胞比较,肿瘤细胞对能量的需求更大,通过进行代谢重编程的方式以维持其生长增殖及转移,因此代谢重编程是肿瘤发生的标志之一。糖代谢、脂质代谢、氨基酸代谢和核苷酸代谢是几种常见的细胞代谢方式,由于肝脏是脂质代谢的主要器官,因此HCC的发生发展过程多伴有异常的脂质代谢。在HCC脂质代谢重编程中涉及多种酶、蛋白、基因、信号通路及代谢产物,他们的异常表达可通过多种机制促进脂质合成和脂滴累积,进一步影响HCC细胞的增殖、迁移、侵袭、自噬、凋亡及血管生成等过程。近年来,中药在肿瘤治疗方面表现出巨大潜力,引起学者们的广泛关注。研究发现,中药有效成分和中药复方可以通过调控脂质代谢相关酶、蛋白及信号通路,抑制HCC中脂质的从头合成、减少脂质累积水平,进而抑制HCC的发生发展过程。本文总结了HCC中脂质代谢相关调节因子的作用机制及中药通过调控脂质代谢重编程抑制HCC的相关研究,并展望脂质代谢作为中药治疗HCC新靶点的应用前景,以期HCC的临床治疗提供参考。

[关键词] 中药; 肝细胞癌; 脂质代谢; 作用机制

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Lipid Metabolism Reprogramming and Chinese Medicine Intervention in Hepatocellular Carcinoma: A Review

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[Abstract] Hepatocellular carcinoma (HCC) is considered to be one of the most aggressive tumors. It often occurs in patients with chronic liver disease and liver cirrhosis. Although research achievements have been attained in the current treatment methods, the opportunity of radical hepatectomy or transcatheter arterial chemoembolization has been lost due to the unobvious progression and no obvious symptoms until the late stage, which results in the poor prognosis. Tumor cells need more energy than normal cells. They maintain their growth, proliferation, and metastasis through metabolic reprogramming. Therefore, metabolic reprogramming is one of the signs of tumorigenesis. Glucose metabolism, lipid metabolism, amino acid metabolism, and nucleotide metabolism are several common cellular metabolism modes. Because the liver is the main organ of lipid metabolism, the occurrence and development of HCC is often accompanied by abnormal lipid metabolism.

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A variety of enzymes, proteins, genes, signaling pathways, and metabolites are involved in the lipid metabolism reprogramming of HCC. Their abnormal expression can promote lipid synthesis and lipid droplet accumulation through a variety of mechanisms, and further affect the proliferation, migration, invasion, autophagy, apoptosis, and angiogenesis of HCC cells. In recent years, traditional Chinese medicine (TCM) has demonstrated great potential in the treatment of tumors, which has attracted wide attention of scholars. The effective components in Chinese herbal medicines and Chinese medicine compound prescriptions can inhibit the de novo synthesis of lipids, lower the level of lipid accumulation, and then inhibit the occurrence and development of HCC by regulating the lipid metabolism-related enzymes, proteins, and signaling pathways. This review summarizes the mechanism of the factors regulating lipid metabolism in HCC and the research progress in the TCM inhibition of HCC by regulating lipid metabolism reprogramming, and makes an outlook on the application prospect of lipid metabolism as a new target of TCM in the treatment of HCC, aiming to provide reference for the clinical treatment of HCC.

[Keywords] traditional Chinese medicine; hepatocellular carcinoma; lipid metabolism; mechanism

肝细胞癌(HCC)是全球癌症相关死亡的主要原因之一,其中占原发性肝癌的75%~85%^[1]。晚期HCC患者往往预后较差,严重影响患者的生存质量。研究肿瘤的发生发展机制对于HCC的防治有着重要意义。代谢重编程是肿瘤的重要标志之一,主要通过改变肿瘤细胞中碳水化合物、氨基酸、和脂质的代谢途径,以维持并促进其生长和增殖^[2-3]。其中研究最多的代谢特性是Warburg效应,肿瘤细胞通过有氧糖酵解而不是线粒体氧化磷酸化,导致乳酸生成增加,进而在细胞生长中发挥作用^[4]。虽然肿瘤的发生发展在一定程度上依赖于糖酵解,但糖酵解抑制剂对肿瘤生长抑制的作用较小^[5]。因此,其他代谢途径对肿瘤细胞存活同样至关重要。脂质代谢是细胞能量代谢的主要方式之一,脂质代谢重编程可促进肿瘤进展,通过调节肿瘤的特征在多种癌变过程中发挥重要作用,如肿瘤细胞的增殖、迁移、侵袭、自噬、凋亡及血管生成等^[6]。肝脏可以维持脂质稳态和能量平衡,是脂质代谢的主要代谢中枢,因此HCC多伴有高度的脂质代谢异常^[4]。靶向代谢是一种全新的肿瘤治疗策略,研究表明,中药可以通过调控脂质代谢相关酶、蛋白及信号通路,干预HCC细胞的脂质代谢重编程,进而发挥抗肿瘤作用。本文主要就HCC中脂质代谢重编程的作用机制及中药通过调控脂质代谢对HCC的治疗作用进行综述。

1 脂质代谢概述

脂质是一类疏水性或两亲性分子,主要分为8大类:脂肪酸类、甘油酯类、甘油磷脂类、鞘脂类、固醇脂类、异戊烯醇脂类、糖脂类和聚酮类,不仅可作为营养物质提供和储存能量,还可作为细胞和信号

分子的主要成分^[4,7]。脂质代谢是维持生命的基本条件,其改变可以直接影响细胞膜的合成和增殖,作为维持细胞生存的先决条件,脂质内稳态由综合系统协调,以快速响应代谢变化^[8]。脂质代谢过程主要包括脂质摄取、从头合成、运输和降解。脂肪酸(FA)是脂质的主要组成部分,在正常细胞中,多倾向于从食物摄取外源性FA,只有小部分FA由细胞内源性合成。脂肪酸由脂肪酸合成酶(FASN)、在三磷酸腺苷(ATP)-柠檬酸裂解酶(ACLY)、乙酰辅酶A羧化酶(ACC)等酶从头合成,在正常情况下,FASN将过量的碳水化合物转化为脂肪酸,一部分用于肝脏合成胆固醇,或在脂肪组织中酯化为甘油三酯,以脂滴的形式储存能量,必要时通过 β 氧化进一步产生热量;另一部分可以组成生物膜或作为信号分子,帮助调节多种信号通路,控制细胞生长、增殖、分化、凋亡、运动、炎症、生存和膜稳态^[9-13]。在正常细胞中,脂质合成、脂滴储存和脂肪酸氧化(FAO)处于动态平衡状态,然而在肿瘤细胞中,随着其代谢需求的增加,过量的脂质和胆固醇被储存在脂滴中,肿瘤细胞通过激活FA的从头合成,为生物膜形成、能量生产和蛋白质修饰提供持续的FA供应^[14-15]。肝脏是脂质代谢的主要器官,因此HCC的发生发展过程多伴随异常的脂质代谢,并涉及多个连续的生物过程,这些过程可以由许多调节因子和不同的关键酶控制,进而在HCC细胞的增殖、迁移、侵袭、凋亡和铁死亡等发生发展过程中发挥作用。

2 HCC脂质代谢重编程的相关分子

2.1 HCC脂质代谢相关酶 脂质生物合成和去饱和是HCC发生发展的必要条件,在HCC脂质代谢重编程的过程中,多伴有相关酶的异常过表达,如

硬脂酰辅酶A-去饱和酶1(SCD1)、FASN、ACLY、ACC等^[16],其中最常见的是SCD1表达异常。SCD1是一种含铁的内质网结合酶,仅定位于内质网,SCD1是其主要亚型,在脂肪组织、心脏、大脑、肝脏和肺中普遍存在,其表达对FA和碳水化合物敏感,并受激素和各种生长因子的调控,是细胞脂质代谢的重要调节因子^[17-18]。在肿瘤细胞中,SCD1的表达上调,通过增加FA的从头合成,为快速分裂的癌细胞提供结构、信号和能量储存的脂质生物分子,其已被证实可促进肿瘤细胞的增殖、迁移和侵袭等过程^[19]。研究发现,SCD1在手术切除的肝癌组织和多种HCC细胞系(HepG2、Hep3B和PLC5)中高表达,且其水平与肿瘤分化程度呈负相关;SCD1表达的上调依赖于核定位和固醇调节元件结合蛋白(SREBP)-1,并由Jun氨基末端激酶(JNK)1/2和磷脂酰肌醇3-激酶(PI3K)介导,下调SCD1的表达可以抑制HCC细胞的增殖,并促进HCC细胞对化疗药物的敏感性^[20]。同时,SCD1的表达水平还与HCC自噬呈负相关,抑制SCD1的表达可激活腺苷酸活化蛋白激酶(AMPK)信号通路,进而诱导HCC自噬依赖性凋亡^[21]。此外,下调SCD1的表达还可抑制HCC细胞的侵袭、迁移、成瘤能力及化疗耐药性,SCD1敲低后分化标志物的表达增加,表明SCD1通过引导分化过程调控肝脏肿瘤源起细胞(T-ICs),进一步研究发现SCD1通过抑制内质网应激调控肝脏T-ICs和索拉非尼耐药性^[22]。由于SCD1对HCC的发生发展具有促进作用,因此使用SCD1抑制剂或其他化疗药物联用或将成为HCC新的治疗策略。

FASN是FA从头合成的关键酶,其可催化乙酰辅酶A和丙二酰辅酶A生成棕榈酸酯和16碳长脂肪酸;FASN的表达在具有临床侵袭性、预后差和治疗耐药性的肿瘤中显著上调;相反,其在癌旁非肿瘤组织通常低水平表达,同时FASN也可在一些良性和癌前病变中被检测到^[23]。研究发现,FASN在HCC组织中高表达,且其表达在高转移性MHCC97H和SK-Hep-1细胞系中高于低转移性HCC细胞系,敲低FASN可抑制HCC细胞的增殖、迁移和侵袭能力^[24]。在肝脏中,FASN本身不致癌,但受多种因素影响,在其他基因诱导的HCC中发挥作用。间充质-上皮转化因子(c-Met)已被证明参与多种细胞过程,包括细胞增殖、生存、恶性转化和转移,蛋白激酶B(Akt)活化和Akt/c-Met的共同激活可诱导HCC的发生,而FASN失活可抑制Akt活化,这一过程受哺乳动物雷帕霉素靶蛋白复合物

(mTORC)1和mTORC2调控,表明FASN失活可抑制Akt和Akt/c-Met原癌基因驱动的HCC的发生^[25-27]。此外,在c-核蛋白类基因(c-Myc)诱导的HCC中,FASN同样是mTORC1的重要下游效应因子^[28]。此外,下调FASN可通过抑制 β -连环蛋白(β -catenin)/c-Myc通路,进而抑制HepG2细胞增殖并诱导其凋亡^[29]。另有研究发现,环氧合酶-2(COX-2)抑制剂塞来昔布通过抑制Akt/c-Met驱动的HCC中COX-2/Akt/FASN级联,延缓了肝癌的发生;体外实验表明,塞来昔布可抑制HCC细胞内源性Akt/FASN轴和脂质积累^[30]。FASN失活还可触发胆固醇生成的代偿增加。CHE等^[31]研究发现FASN的失活会延迟HCC的起始,且FASN的缺失会引发体内外3-羟基-3-甲基戊二酰辅酶A还原酶(HMGCR)代偿性上调,促进了SREBP2的激活,从而触发了胆固醇生成,而抑制FASN和HMGCR可能会阻止这种代谢适应,导致抑制HCC肿瘤生长。

ACLY定位于细胞质和细胞核,催化胞质乙酰辅酶A的产生,用于脂肪酸和胆固醇从头合成,同时为细胞质和核蛋白的乙酰化提供乙酰辅酶A,从而将代谢与基因表达的表观遗传调控联系起来;ACLY在许多类型的肿瘤细胞中高度表达,通过脂肪从头合成促进细胞增殖^[32]。ACLY可与不含POU结构的八聚体结合蛋白(NONO)相互作用,促进FA的生物合成,从而促进HCC的发展^[33]。ACLY抑制剂BMS-303141可诱导内质网应激,激活磷酸化真核细胞起始因子(p-eIF2 α)/转录活化因子4(ATF4)/C/EBP同源蛋白(CHOP)轴促进肝癌细胞凋亡,并与索拉非尼协同治疗HCC^[34]。另有研究表明,ACLY是分泌性糖蛋白(Wnt)/ β -catenin信号通路的有效调控因子,可调控肝脏T-ICs的干性和转移^[35]。下调ACLY表达可有效逆转HCC索拉非尼耐药^[36]。

ACC可将乙酰辅酶A转化为丙二酰辅酶A,包含2种亚型,ACC1和ACC2,其中ACC1定位于胞浆中,是FA从头合成的一种限速酶;ACC2定位于线粒体外膜,产生丙二酰辅酶A,进而调节参与FA β -氧化的肉碱棕榈酰转移酶1(CPT1)的活性^[37]。ACC在HCC发生发展的相关机制中发挥作用。研究发现,糖松酸(LA)可通过活性氧(ROS)依赖的肝激酶B1(LKB1)/AMPK/ACC信号通路磷酸化,进而诱导HCC细胞凋亡^[38]。此外,ND-654可通过降低ACC磷酸化水平,抑制肝脏FA从头合成和HCC细胞增殖,进而提高荷瘤大鼠生存^[39]。以上研究表明,ACC可作为药物治疗HCC的新靶点。

2.2 HCC 脂质代谢相关蛋白 SREBPs 和脂肪酸结合蛋白(FABPs)是脂质代谢过程中重要的蛋白质。SREBPs 属于膜结合蛋白的一个小家族,是一种内质网结合的转录因子,调控与脂质合成和摄取相关基因的表达,介导大量脂质产生,尤其是胆固醇的生成,在脂质代谢中起核心作用,并通过增加低密度脂蛋白的摄入和胆固醇的合成来增加肿瘤细胞中的胆固醇水平^[40-41]。在肝脏中 SREBPs 受转化生长因子(TGF)- β 活化激酶 1(TAK1)调控,其调控有助于维持肝脏稳态,防止脂肪变性^[42]。此外,抑制 SREBP 表达可抑制脂质从头合成,下调包括白细胞介素(IL)-6、肿瘤坏死因子- α (TNF- α)和 IL-1 β 在内的促肿瘤细胞因子,抑制 HCC 进展^[43]。SREBPs 包括 SREBP-1 和 SREBP-2, SREBP-1 基因可以产生 SREBP-1a 和 SREBP-1c 两种由不同启动子衍生的蛋白^[44]。研究发现, SREBP-1 在 HCC 组织中的表达高于癌旁组织,下调 SREBP-1 的表达可抑制 HepG2 和 MHCC97L 细胞增殖并诱导凋亡; SREBP-1 敲除可显著抑制 HepG2 和 MHCC97L 细胞的迁移和侵袭^[45]。SREBP-1 还可介导其他因子促进 HCC 的发生发展。MIN 等^[46]研究发现肝癌衍生生长因子(HDGF)通过激活 SREBP-1 介导的成脂基因转录进而促进脂肪从头生成,且 HDGF 和 SREBP-1 高表达与 HCC 患者的预后不良显著相关。另有研究表明,TD26 可与 SREBP1 相互作用,从而阻断 AMPK 介导的对 SREBP1 活性的抑制,增加脂肪生成,促进 HCC 细胞增殖^[47]。射频消融术(RFA)是治疗晚期 HCC 的重要手段,而抑制 SREBP-1 活化可增强 RFA 对异种移植瘤的治疗作用^[48]。以上研究表明, SREBPs 在 HCC 中发挥重要作用,不仅可调控脂质代谢,还可调节 RFA 对 HCC 的疗效。

FABPs 是一组低分子量的蛋白质,存在于各种组织中,其包含多种亚型,在脂肪酸代谢中发挥重要作用^[49]。研究发现, FABP1 在 HCC 组织中高表达,其在膜筏上与血管内皮生长因子受体 2(VEGFR2)相关,并激活 Akt/哺乳动物雷帕霉素靶蛋白(mTOR)/P70S6 激酶(P70S6K)/真核细胞翻译起始因子 4E 结合蛋白 1(4EBP1)和酪氨酸激酶(Src)/黏着斑激酶(FAK)/细胞周期蛋白 42(CDC42)通路,导致血管内皮生长因子(VEGF)-A 上调,同时促进 HCC 迁移和血管生成^[50]。OHATA 等^[51]研究发现过表达 FABP5 可上调 HepG2 细胞中锌指转录因子 1(SNAI1)的表达,而敲除 FABP5 后, E-钙黏蛋白(E-cadherin)和闭锁小带蛋白-1(ZO-1)

的表达显著升高, SNAI1 表达降低, β -catenin 核转位降低,表明 FABP5 通过诱导上皮间质转化(EMT),进而促进 HCC 进展和转移。此外, FABP5 还可激活 IL-6/转录因子激活因子 3(STAT3)/VEGF-A 通路,促进 HCC 血管生成^[52]。

2.3 HCC 脂质代谢相关信号通路 在肿瘤脂质代谢重编程中最常见的代谢途径是 PI3K/Akt 信号通路^[17]。该信号通路受多种因素调控,参与 HCC 脂质代谢重编程过程。8u 是吡啶衍生物,已被证实具有抗肝癌的作用,可通过阻断 PI3K/Akt 通路,降低 FASN 的表达,扰乱脂质代谢,抑制 HCC 细胞侵袭转移^[53]。溶酶体相关膜蛋白 3(LAMP3)被证实可通过激活 PI3K/Akt 信号通路,上调 HepG2 细胞中 FASN 和 SCD-1 的表达,导致细胞内脂滴和甘油三酯积聚^[54]。此外,下调染色质重构复合物核心催化亚基 1(Brg1)可通过上调糖基化溶酶体膜蛋白(GLMP),改变 PI3K/Akt 通路,减少 HCC 细胞内脂滴沉积^[55]。

AMPK 是一种适应性酶复合体,参与多种能量和氧化还原稳态所需的过程,包括自噬、糖代谢和脂质代谢,是细胞能量状态的传感器^[56]。LI 等^[57]研究发现细胞内色素上皮衍生因子(PEDF)通过泛素蛋白酶体介导的降解抑制 AMPK 的活化,增加脂肪酸从头合成,降低游离脂肪酸(FFAs)氧化,从而导致 FFA 的积累,最终促进 HCC 细胞的增殖。另有研究表明, HCC 细胞耐药性的产生与脂质代谢异常相关, CXC 趋化因子受体 3(CXCR3)通过下调 AMPK 通路活性和脂质过氧化,及上调脂肪细胞因子水平,增强 HCC 细胞对索拉非尼的耐药性^[58]。LI 等^[59]发现敲除低密度脂蛋白受体相关蛋白 1B(LRP1B)后,细胞内脂质含量降低,脂质合成相关酶表达下调, β -氧化相关酶表达上调,激活 AMPK 信号通路,表明 AMPK 信号通路参与了 LRP1B 对 HCC 脂质代谢重编程的调控。脂肪酸转运蛋白 5(FATP5)参与 FA 运转途径,其表达在 HCC 组织中下调, FATP5 可促进细胞糖酵解通量和 ATP 的产生,从而抑制 AMPK 活性并激活其下游信号靶点 mTOR,促进 HCC 的进展和转移,表明 FATP5 可通过调控 AMPK/mTOR 通路成为 HCC 新的抑制因子^[60]。此外, AMPK 还参与丝/苏氨酸蛋白激酶 25(STK25)介导的脂质代谢异常, STK25 通过激活纹蛋白(STRN)抑制 AMPK 磷酸化,进而上调 ACC1,促进 HCC 脂质代谢重编程能量储备和 EMT^[61]。

其他信号通路也可以在 HCC 脂质代谢重编程

过程中发挥作用。LI等^[62]研究发现细胞外基质金属蛋白酶诱导物(CD147)可通过调控多种信号通路及与肝癌细胞脂肪酸代谢的重编程;一方面,CD147通过激活Akt/mTOR信号通路上调SREBP1c的表达,进而直接激活主要成脂基因FASN和ACC1的转录,促进脂肪重新生成;另一方面,CD147通过激活p38丝裂原活化蛋白激酶(MAPK)信号通路下调过氧化物酶体增殖物激活受体 α (PPAR α)及其转录靶基因肉碱棕榈酰转移酶1A(CPT1A)和酰基辅酶A氧化酶1(ACOX1),抑制脂肪酸 β -氧化,进而在HCC细胞的增殖和转移中发挥作用。YIN等^[63]发现下调Tat结合蛋白30(TIP30)可激活Akt/mTOR信号通路,并上调SREBP1的表达,通过激活FASN、SCD等脂质生成基因转录促进HCC脂质代谢。WANG等^[64]分析了Janus激酶(JAK)/STAT信号通路主要成分在HCC中可能的分子机制,其中STAT6在HCC中可能通过影响细胞周期、细胞分裂和脂质代谢进而发挥作用。此外,mTORC1与STAT5通路交叉对话可上调SREBP1、ACC1和FASN的表达,促进脂质从头合成,诱导HCC^[65]。

2.4 HCC脂质代谢相关非编码RNA 根据RNA的编码能力可将其分为编码RNA和非编码RNA,其中非编码RNA包含多种类型,如微小RNA(miRNA)、长链非编码RNA(lncRNA)、环状RNA(circRNA)、小干扰RNA(siRNA)等^[66]。研究显示,miRNAs和lncRNAs参与了HCC脂质代谢重编程过程。miRNA一种是由18~22个核苷酸组成的非编码RNA,在体内生物机制的调节中发挥重要作用,其表达高度依赖于组织类型、疾病和代谢状态^[67]。研究发现,抑制miR-122的表达可降低正常小鼠的血浆胆固醇水平,增加其肝脏脂肪酸氧化,并降低肝脏脂肪酸和胆固醇合成率^[68]。miR-205与乙酰辅酶A合成酶1(ACSL1)和ACSL4的表达水平呈负相关,低水平的miR-205可通过上调ACSL1的表达,从而加速HCC细胞中的脂肪生成和甘油三酯的积累;此外,乙型肝炎X病毒(HBx)可通过抑制miR-205导致ACSL4过表达,在HCC细胞中积累胆固醇并引起脂质代谢异常^[69-70]。ZHANG等^[71]研究发现miR-449可通过抑制沉默信息调节因子1(SIRT1)、SREBP-1c及其下游靶基因的表达,包括FASN和HMGCR,对HCC细胞中脂肪生成和胆固醇生成进行重编程。另有研究发现,miR-1207-5p过表达可通过直接抑制FASN进而调控Akt/mTOR信号通路,抑制HCC细胞的增殖和侵袭,表明miR-

1207-5p可以作为FASN的内源性抑制剂干预HCC的治疗^[72]。CHENG等^[73]研究发现敲除miR-148a可直接上调HMGCR、过氧化物酶体增殖物激活受体 γ 共激活因子1 α (PGC1 α)、SIRT7和Y-盒结合蛋白1(YBX1)的表达,进而促进脂肪生成和胆固醇生物合成,导致肝脏脂质积累并升高血清和肝脏的总胆固醇水平。此外,IL-6可诱导miR-603的表达,进而抑制FABP1的表达,促进脂质代谢和合成相关蛋白,包括CPT1A、PPAR α 和SREBP1,最终增加细胞氧化应激水平,导致HCC细胞转移^[74]。miR-4310可通过抑制SCD1和FASN介导的脂质合成,在体外抑制肝癌细胞增殖、迁移和侵袭,在体内抑制肝癌肿瘤的生长和转移^[75]。另有研究发现miR-377-3p通过抑制CPT1C,阻止FA进入线粒体,减少HCC细胞中ATP的生成,从而抑制FAO,降低miR-377-3p/CPT1C通路调控体内外HCC增殖、迁移和侵袭的能力^[76]。

lncRNA是一种长度>200个核苷酸的非编码RNA,其可通过作为致癌基因或肿瘤抑制因子,在肿瘤发生和发展过程中发挥作用^[77]。研究表明,lncRNA可通过调控脂质代谢在HCC发生发展过程中发挥作用。lncRNA肝癌高表达转录本(HULC)可引发miR-9启动子中CpG岛的甲基化,抑制miR-9的表达,进而导致PPAR α 的表达上调和ACSL1的转活化,从而促进HCC细胞的脂肪生成,造成细胞内甘油三酯和胆固醇累积;此外,ACSL1的胆固醇产物通过激活转录因子核受体视黄酸X受体 α (RXR α)上调HULC的表达,形成HULC/miR-9/PPAR α /ACSL1/胆固醇/RXRA/HULC正反馈环路^[78]。lncRNA核富集转录本1(NEAT1)通过miR-124-3p/脂肪甘油三酯脂肪酶(ATGL)/甘油二酯(DAG)+FFA/PPAR α 通路破坏HCC细胞的脂肪分解,进而促进HCC细胞的增殖^[79]。lncRNA还可通过调控脂质代谢相关信号通路促进HCC进展。WANG等^[80]发现肺腺癌转录本1(MALAT1)可降低AMPK信号通路和不饱和脂肪酸生物合成通路中多个基因的表达,抑制葡萄糖摄取和脂肪生成,从而促进HCC细胞的增殖和侵袭。此外,含TCP1的伴侣蛋白亚基3(CCT3)/LINC00326可以减少HCC细胞内脂质积聚、增加脂质降解并减少体内肿瘤生长^[81]。以上研究进一步完善了HCC脂质代谢重编程的作用机制,为HCC的治疗提供了新靶点。

2.5 HCC脂质代谢产物 代谢物是细胞状态的最佳分子指标,因为与mRNA和蛋白质比较,代谢物

的快速通量是一种对细胞表型极其敏感的测量^[82]。HCC脂质代谢重编程可通过其代谢物水平反映,通过代谢组学分析HCC脂质代谢物水平对其鉴别诊断、预后及药物治疗效果具有重要作用。在HCC鉴别诊断方面,研究发现与肝硬化患者相比,HCC患者血清中参与鞘脂代谢和磷脂分解代谢的代谢物,如鞘脂苷-1-磷酸(S-1-P)和溶血磷脂酰胆碱(lysoPC 17:0)表达上调。参与胆汁酸生物合成,尤其是胆固醇代谢的代谢物,如甘氨酸去氧胆酸3-硫酸盐(3-sulfo-GCDCA)、甘氨酸胆酸(GCA)、甘氨酸去氧胆酸(GDCA)、牛磺胆酸(TCA)和牛磺胆酸去氧胆酸(TCDCA)的表达下调^[83]。另有研究发现,SCD的活性脂质代谢物单不饱和棕榈酸(MUPA)水平在侵袭性HCC组织样本中升高^[82]。CAI等^[84]发现从慢性乙型肝炎(CHB)到肝硬化(LC)再到HCC,随着肝损伤的加重,患者血液中亚油酸含量降低。此外,在HCC预后方面,高浓度的总胆固醇、低密度脂蛋白胆固醇和低密度脂蛋白颗粒(LDL-p)与HCC患者总生存率下降相关^[85]。以上研究表明,脂质代谢产物具有诊断HCC和预测HCC预后的潜力,同时其代谢物水平还可用于反映药物治疗效果。

3 中药在HCC脂质代谢中的作用机制

3.1 调控HCC脂质代谢相关酶和蛋白 YANG等^[86]研究发现大黄素可诱导肝癌Bel-7402细胞凋亡,同时减少Bel-7402细胞甘油三酯和脂肪酸的去饱和水平,并降低SREBP1及其下游信号通路的蛋白表达水平,以及降低脂肪酸代谢相关蛋白如ACLY、ACC α 、FASN和SCD的表达水平;而敲除SREBP1可减少大黄素诱导的内在凋亡,表明大黄素可通过SREBP1依赖性和SREBP1非依赖性的方式诱导肝癌细胞凋亡。此外,大黄素还可通过调节脂质代谢增强肝癌细胞对化疗药物的敏感性。研究发现,大黄素可抑制SREBP-2的转录活性,从而抑制胆固醇生物合成和Akt信号传导,并导致STAT3失活,协同增强索拉非尼的抗肿瘤作用,减少体内外胆固醇的生物合成,诱导HCC细胞周期阻滞及凋亡^[87]。SREBP裂解激活蛋白(SCAP)是重要的脂代谢因子,大黄素可通过下调SCAP信号抑制移植瘤脂质代谢,或可通过抑制胱天蛋白酶(Caspase)-2进而降低位点1蛋白酶(S1P)的表达,阻滞SREBP1被剪切从而阻断脂质代谢,诱导肝癌移植瘤细胞内源性凋亡^[88]。

此外,制何首乌醇提物作用于肝癌Bel-7402细胞后,可下调SREBP1 mRNA及蛋白的表达水平,同

时,抑制脂肪酸合成相关因子ACC、ACLY mRNA的表达,以及脂肪酸去饱和化因子SCD1、脂肪酸转运因子FABP3的mRNA和蛋白的表达水平,进而抑制肝癌细胞的脂肪酸合成及脂肪酸的去饱和化,调节脂质代谢,诱导肝癌细胞的内源性凋亡^[89]。

KIM等^[90]研究发现熊果酸可激活肝癌细胞SK-HEP-1、Huh7及Hep3B中的SREBP2,同时增加胆固醇生物合成相关基因和酶的表达,如羟甲基戊二酸单酰辅酶A合成酶1(HMGCS1)、HMGCR、甲基戊酸焦磷酸脱羧酶(MVD)、法尼基焦磷酸合酶(FDPS);进一步研究发现,熊果酸可抑制肝癌细胞中Akt、MAPK和细胞外调节蛋白激酶(ERK)1/2的磷酸化,而补充水溶性胆固醇可逆转这一作用,表明熊果酸的降胆固醇作用可能是其抑制HCC细胞肿瘤生长信号转导的一种调控机制。另有研究表明,小檗碱除可激活AMPK通路外,还可调控相关蛋白抑制脂质代谢。发现小檗碱及其4种代谢产物均可上调肝癌HepG2细胞中低密度脂蛋白受体(LDLR) mRNA和蛋白的表达水平,进而抑制HepG2细胞脂质积累,发挥降脂作用^[91]。

3.2 调控HCC脂质代谢相关信号通路 研究发现,小檗碱及其代谢产物非洲防己碱可能通过激活肝癌HepG2细胞中AMPK信号通路,上调脂质分解基因中链酰基辅酶A脱氢酶(mCAD)的表达,下调脂质生成基因ACC、FASN、甘油3-磷酸酰基转移酶(GPAT)和HMGCR的表达,从而发挥降甘油三酯作用^[92]。罗汉果醇可以激活AMPK信号通路,上调SREBP-1c、FASN mRNA和蛋白的表达水平,进而抑制脂肪酸从头合成,减少肝癌HepG2细胞中脂质累积,降低甘油三酯和总胆固醇含量,调节肝癌脂质代谢^[93]。雷公藤红素可以激活HepG2细胞中的p-AMPK α 并抑制SREBP-1、FASN、ACC等脂肪酸从头合成关键蛋白的表达,通过激活AMPK信号通路抑制脂代谢及增殖相关蛋白表达,进而抑制肝癌HepG2细胞的增殖^[94]。人参皂苷CK通过激活LKB1和AMPK的磷酸化,在体外和体内调节与脂质合成和代谢相关因子的表达,进而减少肝癌HepG2细胞的脂质累积水平^[95]。以上研究表明,AMPK信号通路在肝癌脂质代谢中发挥重要作用,是中药治疗肝癌的潜在靶点。

肝X受体(LXRs)的激活与PI3K/Akt信号通路相关,同时可维持脂质稳态,研究发现,佛手柑内酯可上调HCC中LXR α 、LXR β 、ATP结合盒转运体A1(ABCA1)、LDLR诱导型降解子(IDOL)mRNA和蛋

白表达,下调SREBP1、LDLR、FASN、SCD1、PI3K、Akt mRNA和蛋白的表达,通过调控LXR/PI3K/Akt和IDOL/LDLR通路降低肝癌细胞脂滴水平,维持脂质稳态,发挥抗HCC作用^[96]。蛇床子素可抑制Akt/c-Met诱导的HCC小鼠肝脏脂肪变性,并通过抑制Akt/核糖体蛋白S6(RPS6)/FASN信号通路和ERK磷酸化发挥抗HCC增殖的作用,延缓HCC的发生^[97]。

3.3 调控HCC脂质代谢相关物质 PAN等^[98]研究发现薯蓣皂苷呈浓度依赖性抑制肝癌Hep3B和HCCLM3细胞的增殖和迁移,并可通过抑制脂质代谢物的合成,如乙酸、癸酸、甘油和L-脯氨酸,干扰HCC细胞的脂质代谢途径,进而发挥抗HCC作用。

另有研究发现,中药复方同样可以调节肝癌模型小鼠的脂质代谢。成欣等^[99]使用青蒿鳖甲汤对H22荷瘤小鼠进行灌胃给药,结果显示其可降低肿瘤质量,抑瘤率为15.01%;进一步检测小鼠血浆中代谢物的变化,经过筛选确定了15种显著差异的代谢物,如1-磷酸-鞘氨醇、磷酸鞘氨醇、溶血磷脂酰胆碱、胆酸等,表明青蒿鳖甲汤对肝癌的抑制作用可能与调节体内鞘酯代谢、甘油磷脂代谢、胆汁分泌、类固醇激素生物合成、色氨酸代谢、 α -亚麻酸代谢、花生四烯酸代谢、赖氨酸降解、亚油酸代谢等代谢通路中的相关代谢产物的表达有关。以上研究表明,中药有效成分或中药复方可通过调节HCC的脂质代谢,进而对其发挥治疗作用,为中药治疗肝癌提供新思路。

4 总结与展望

综上所述,脂质代谢重编程在HCC中发挥重要作用,其相关酶、蛋白、基因、信号通路及代谢产物在HCC细胞中异常表达,通过多种作用机制,促进细胞增殖、迁移、侵袭、血管生成及耐药性的产生,并抑制其自噬和凋亡。而中药可以靶向脂质代谢相关酶、蛋白及信号通路,调控脂质代谢,进一步抑制HCC的发生发展过程。因此,脂质代谢的相关分子或将成为中药治疗HCC的新靶点。

但研究尚存在一些问题,在肿瘤脂质代谢重编程相关研究方面,目前有关HCC脂质代谢作用机制的研究多集中在脂质从头合成方面,而在脂质运输和降解方面的研究相对较少;已证实相关分子在HCC中发挥作用,但其具体作用机制尚未阐明;同时有关代谢产物在HCC诊断和预后中研究也有待开展。在中药调控脂质代谢治疗HCC方面,缺少中药复方调控HCC脂质代谢的相关研究,且现有研究

中中药作用的靶点不够全面,多为不同药物靶向同样的调控因子或信号通路,如PI3K/Akt是肿瘤脂质代谢重编程中最主要的信号通路,但有关中药靶向该通路抑制HCC的研究相对较少;同时还缺少中药通过靶向非编码RNA调控HCC脂质代谢的相关研究。总而言之,HCC中药靶向脂质代谢治疗HCC的研究相对较少,在今后的研究中还需不断深入,随着其作用机制的阐明,脂质代谢重编程会成为HCC新的治疗角度,为将来相关药物应用于临床打下基础。

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