

doi: 10.13241/j.cnki.pmb.2020.12.003

# 肉毒碱棕榈酰基转移酶 CPT2 促进肝癌细胞迁移侵袭的作用研究 \*

耿西林<sup>1</sup> 常虎林<sup>1</sup> 高淑娟<sup>2</sup> 张 煜<sup>1</sup> 杜立学<sup>1△</sup>

(1 陕西省人民医院肝胆外科 陕西 西安 710068; 2 陕西省人民医院消化内科 陕西 西安 710068)

**摘要目的:**探讨肉毒碱棕榈酰基转移酶 2(CarnitinePalmitoyltransferase2, CPT2)在肝癌细胞迁移侵袭中的调控作用。**方法:**1).用免疫组化实验,检测 62 对肝癌组织与癌周组织中 CPT2 表达,以明确肝癌组织细胞中 CPT2 表达是否发生异常改变。2).细胞划痕实验,在人肝癌细胞 HLE 中分析干涉 CPT2 表达对肝癌细胞迁移能力的影响。3).Transwell 侵袭实验,在人肝癌细胞 HLE 中分析干涉 CPT2 表达对肝癌细胞侵袭能力的影响。**结果:**1).CPT2 主要为胞浆染色且染色呈线粒体蛋白染色典型的颗粒状分布;与癌周组织相比,肝癌组织中 CPT2 表达显著升高。2).细胞划痕实验证实,干涉人肝癌细胞 HLE 中 CPT2 表达后,细胞的相对迁移距离显著变短(siCtrl VS siCPT2#1 VS siCPT2#2=1.00±0.8 VS 0.67±0.42 VS 0.64±0.31)。3).Transwell 侵袭实验证实,干涉人肝癌细胞 HLE 中 CPT2 表达后,侵袭至小室底部的细胞数目显著变少(siCtrl VS siCPT2#1 VS siCPT2#2 = 23.34±3.51 VS 8.00±2.00 VS 8.67±1.53)。**结论:**CPT2 在肝癌细胞中表达显著上调,CPT2 表达上调促进了肝癌细胞的迁移与侵袭。

**关键词:**CPT2; 脂代谢; 迁移; 侵袭; 肝癌**中图分类号:**R-33; R735.7 **文献标识码:**A **文章编号:**1673-6273(2020)12-2214-05

## The Role of CPT2 in the Migration and Invasion of Liver Cancer Cells\*

GENG Xi-lin<sup>1</sup>, CHANG Hu-lin<sup>1</sup>, GAO Shu-juan<sup>2</sup>, ZHANG Yu<sup>1</sup>, DU Li-xue<sup>1△</sup>

(1 Department of Hepatobiliary Surgery, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi, 710068, China;

2 Department of Gastroenterology, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi, 710068, China)

**ABSTRACT Objective:** To explore the biological functions of CPT2 (Carnitine Palmitoyltransferase2) in the migration and invasion abilities of liver cancer cells. **Methods:** 1). Immunohistochemistry analysis was applied to evaluate the expression of CPT2 in tumor and adjacent non-tumor cells from 62 patients with liver cancer. 2). Effect of CPT2 knockdown by siRNA on the migration ability in HLE cells. 3). Effect of CPT2 knockdown by siRNA on the invasion ability in HLE cells. **Results:** 1). CPT2 positive staining is mainly localized in cytoplasm with a granular distribution similar to other of mitochondrial protein. The expression of CPT2 was significantly over-expressed in tumor tissues of liver cancer when compared with their adjacent non-tumor tissues. 2). CPT2 knockdown significantly reduced the distance of the migration of HLE cells (siCtrl VS siCPT2#1 VS siCPT2#2 = 1.00±0.8 VS 0.67±0.42 VS 0.64±0.31). 3). CPT2 knockdown significantly reduced the number of invaded liver cancer cells in HLE cells (siCtrl VS siCPT2#1 VS siCPT2#2 = 23.34±3.51 VS 8.00±2.00 VS 8.67±1.53). **Conclusions:** CPT2 is significantly up-regulated in liver cancer, which promoted both migration and invasion abilities of liver cancer cells.

**Key words:** CPT2; Lipid metabolism; Migration; Invasion; Liver cancer**Chinese Library Classification(CLC):** R-33; R735.7 **Document code:** A**Article ID:**1673-6273(2020)12-2214-05

### 前言

肿瘤细胞最显著的特征之一便是代谢的异常改变,研究表明代谢异常改变在肿瘤发生发展的各个环节均发挥重要的促进作用<sup>[1,2]</sup>。肿瘤细胞通过改变自身原有的代谢特点,一方面更好的适应外界环境的改变,另一方面为自身快速增殖及转移提供物质与能量基础<sup>[3,4]</sup>。

人肉毒碱棕榈酰基转移酶 (Carnitine Palmitoyltransferase,

CPT)是调控细胞脂肪酸氧化的关键酶,定位于线粒体膜,负责转运胞浆中的脂酰辅酶 A 进入线粒体进行β- 氧化<sup>[5]</sup>。CPT 包含两个成员分别为 CPT1 与 CPT2,其中 CPT1 又含 3 个亚型,分别为 CPT1A、CPT1B 与 CPT1C。以往在卵巢癌中研究证实,CPT1A 通过参与卵巢癌细胞的脂肪酸氧化而促进卵巢癌细胞的转移<sup>[6]</sup>。此外,肺癌中研究也表明 CPT1A 可促进肺癌转移。与 CPT1 相比,CPT2 的研究相对较少。以往在肝癌中研究发现 CPT2 与肝癌进展及顺铂耐药性显著相关<sup>[7-9]</sup>。此外,CPT2 还可

\* 基金项目:国家自然科学基金面上项目(81670557)

作者简介:耿西林(1981-),男,硕士,副主任医师,主要从事肝胆疾病临床诊治与肝癌发病分子机理研究,

E-mail:gengxilin001@163.com,电话:15529519125

△ 通讯作者:杜立学(1963-),男,博士,主任医师,主要从事肝胆疾病临床诊治与慢性肝疾病发病分子机理研究,

E-mail:lixuedu\_xa@163.com,电话:(029)85251331

(收稿日期:2019-12-23 接受日期:2020-01-18)

通过降低脂毒性而促进肥胖相关肝癌的进展<sup>[10]</sup>。但目前,CPT2在肝癌细胞中表达及其在肝癌细胞迁移侵袭中的调控作用均尚不十分清楚。进而,本项目将首次分析CPT2在肝癌细胞中的表达及其在肝癌侵袭迁移中的调控作用,从而为肝癌的治疗提供潜在的分子靶标。

## 1 材料与方法

### 1.1 肝癌临床组织标本与肝癌细胞系

收集62例于2015-2016年间在陕西省人民医院肝胆外科进行肝癌根治手术病人的癌与癌旁,所有患者均签署了知情同意书并经病理确诊为原发性肝细胞肝癌,患者在术前无放疗与化疗等辅助治疗,患者临床资料统计见表1。

表1 62例肝癌患者临床资料

Table 1 The clinical pathological characteristics of 62 HCC patients

Variables	No. of cases(%)
All	62
Age	
<55	26 (41.9%)
≥55	36 (58.1%)
Gender	
Female	14 (22.6%)
Male	48 (77.4%)
HBV infection	
Negative	11(17.7%)
Positive	51(82.3%)
AFP (μg/mL)	
<200	33 (53.2%)
≥200	29 (46.8%)
Tumor maximum diameter	
<5	49 (79.0%)
≥5	13 (21.0%)
Portal vein tumor thrombosis	
No	56 (90.3%)
Yes	6 (9.7%)
Differentiation grade	
I+ II	14 (22.6%)
III	48 (77.4%)
TNM stage	
I+ II	47 (75.8%)
III+ IV	15 (24.2%)

人肝癌细胞HLE购于ATCC细胞库,细胞培养于含10%胎牛血清的DMEM培养基中(上海生工生物有限公司),孵箱温度为37℃,CO<sub>2</sub>浓度为5%。

### 1.2 实验方法

#### 1.2.1 免疫组织化学染色

首先,第一时间将手术切除的肿瘤

组织迅速置于液氮中,福尔马林固定24 h后将组织切块并进行石蜡包埋与切片(厚度为4 μm)。切片置于65℃的温箱中进行2 h的烤片后即可进行二甲苯脱蜡与梯度酒精水化。随后切片依次经历高压柠檬酸抗原修复、双氧水去除内源性过氧化物酶后即可进行一抗CPT2(武汉三鹰生物有限公司,货号26555-1-AP,1:200浓度)、二抗与三抗孵育(福建迈新生物科技有限公司,货号KIT-9902)。加入底物DAB显色与苏木素复染后即可对切片进行脱水、透明与封片处理。最后将切片置于显微镜下进行结果观察与拍照。

**1.2.2 qRT-PCR** 用细胞RNA提取试剂盒(OMEGA,R6688)对不同处理后肝癌细胞中总RNA进行提取。随后用反转录试剂盒(TAKARA,RR037A)将所提RNA反转录合成cDNA。CPT2引物序列:上游5'-CATACAAGCTACATTCGGGACC-3',下游5'-AGCCCGGAGTGTCTTCAGAA-3'。将β-actin作为内参基因对各组上样进行平衡,β-actin引物序列为:5'-TCGCCTTGCCGATCCG-3',5'-ATGATCTGGGTATCCTCTCG-3'。qRT-PCR的反应体系为:cDNA(体积1 μL)+上下游引物各(1 μL)+SYBR Premix EX Taq酶(Takara公司,体积10 μL)+双蒸水,先后在95℃和58℃各反应30 s,之后72℃反应30 s,共进行40个循环,最后在72℃反应10 min。最后,用 $2^{-\Delta \Delta Ct}$ 相对定量法对各组细胞中CPT2的相对表达进行分析。

**1.2.3 Western Blot** 用含蛋白酶与磷酸酶抑制剂的RIPA裂解液裂解不同处理后肝癌细胞提取细胞总蛋白,加入上样缓冲液后煮5 min,蛋白自然冷却后即可上样进行电泳。初始电泳采用90V恒压,待蛋白电泳进入分离胶后采用120V恒压,溴酚蓝电泳至底部即将进入电泳液中时停止电泳。采用“三明治”法蛋白转至PVDF膜,BSA室温封闭1 h后加入CPT2(武汉三鹰生物有限公司,货号26555-1-AP,稀释比为1:1000)与β-actin(武汉三鹰生物有限公司,货号20536-1-AP,稀释比为1:3000)抗体,置于4℃冰箱孵育过夜后用TPBS洗膜3次(每次5分钟),随后加入二抗并在室温孵育2 h,TPBS洗3次(每次5分钟)后用ECL化学发光系统对结果进行拍照。

**1.2.4 siRNA转染细胞** 合成特异性靶向CPT2与无关对照的小RNA干扰片段(吉玛基因生物公司),随后即可对肝癌细胞进行siRNA转染,大致过程为:将 $2 \times 10^5$ 个不同处理的肝癌细胞接种至6孔板内,次日待细胞生长至底面积85%左右时进行转染,转染采用lip2000为介质。分别用不含血清的DMEM培养液稀释siRNA片段与lip2000,将两种稀释液均静置5 min后混合,继续静置25 min,随后吸去100 μL上步中所得混合液并加入6孔板细胞中,置于孵箱中常规培养6 h,更换新鲜含血清的DMEM培养液继续培养24 h即可进行RNA与蛋白提取。

**1.2.5 划痕实验** 首先,对肝癌细胞中CPT2表达进行siRNA干涉,消化收集细胞并进行计数,随后将细胞接种至6孔板中,次日待细胞长至铺满底面85%时即可进行划痕处理。采用黄枪头于孔中央垂直划线,用培养基洗去划线处脱落细胞后将细胞置于显微镜下拍照,随后将细胞于培养箱中继续培养24 h后再次进行拍照,拍照均采用400倍放大。最后,在电脑上用测量图像测量软件(Digimizer,V4.2.6版本)对各组细胞的相对迁移距离(0 h的划痕宽度减去24 h的划痕宽度)进行计算。将对照组细胞的相对迁移距离定义为“1”并据此计算其它处理细胞

的相对迁移距离。

**1.2.6 Transwell 侵袭实验** 首先,对肝癌细胞中CPT2表达进行siRNA 干涉,消化收集细胞并进行计数,随后将细胞以 $2 \times 10^5$ /孔接种至事先用基质胶包被过的24孔小室内。小室底部加入含血清的DMEM培养基,而小室内则加入无血清培养基。将细胞置于培养箱中培养48 h,随后取出小室并用棉签擦去小室底部内侧未穿膜细胞,用结晶紫对穿至小室底部外侧细胞进行染色,自来水冲洗、晾干后即可置于显微镜下进行观察拍照,于400倍镜下随机选取5个视野进行拍照与细胞计数,最后进行统计分析。

**1.2.7 统计分析** 数据采用均数±标准差 (Mean±SD) 进行展

示,利用SPSS 17.0软件对结果进行统计分析,分别用t检验与方差分析进行两组或两组以上数据差异分析,当 $P<0.05$ 时认为组间差异具有统计学意义。

## 2 结果

### 2.1 肝癌组织中CPT2表达显著上调

首先,利用免疫组化实验,对62例肝癌患者癌组织与癌旁组织中CPT2表达进行检测,结果如图1所示:CPT2染色主要位于细胞浆中并呈明显的颗粒状分布,提示CPT2主要定位线粒体膜;CPT2表达在肝癌癌组织中表达显著高于癌旁组织。

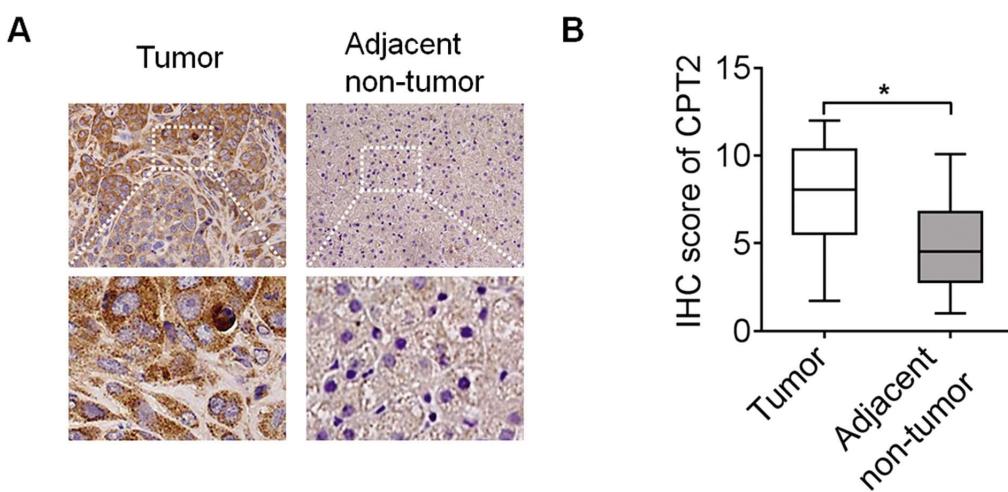


图1 免疫组化检测肝癌癌组织与癌旁组织中CPT2表达  
(A. 典型CPT2组化染色结果(上图,400×;下图,1600×); B.统计结果,\*代表 $P<0.05$ )

Fig. 1 Immunohistochemistry analysis for expression of CPT2 in tumor and adjacent non-tumor tissues of HCC

(A. Representative IHC staining results of CPT2 (upper panel, 400×; down panel, 1600×); B. Statistical results, \* represents  $P<0.05$ )

### 2.2 干涉CPT2可显著抑制肝癌细胞的迁移

首先,合成靶向CPT2表达的siRNA 干涉片段并对其进行下调肝癌下拨CPT2表达的效率进行qRT-PCR与western blot检测,结果如图2A与2B所示:该siRNA 可明显下调肝癌细胞中CPT2的表达。

明确设计合成的siRNA 可显著下调肝癌细胞中CPT2表达,下一步即可在下调CPT2表达后分析对肝癌细胞迁移与侵

袭能力的影响。利用划痕实验检测肝癌细胞迁移后发现(图3):干涉CPT2表达后,肝癌细胞向划痕处的相对迁移距离明显缩短 (siCtrl VS siCPT2#1 VS siCPT2#2 = 1.00±0.8 VS 0.67±0.42 VS 0.64±0.31),表明干涉CPT2可显著降低肝癌细胞的迁移能力。

### 2.3 干涉CPT2可显著抑制肝癌细胞的侵袭

进一步利用Transwell侵袭实验检测肝癌细胞侵袭后发现

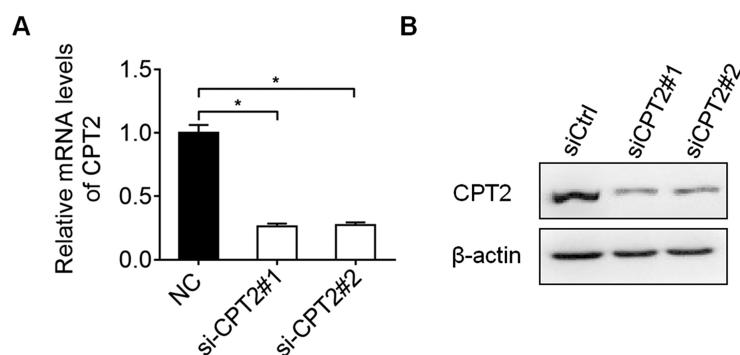


图2 siRNA对肝癌细胞中CPT2表达的干扰效率分析  
(A: 实时荧光定量PCR检测,\*代表 $P<0.05$ ;B: Western Blot检测)  
Fig. 2 Determination of knockdown efficiency of CPT2 in HCC cells  
(A. qRT-PCR analysis,\* represents  $P<0.05$ ; B. Western blot analysis)

(图4): 干涉 CPT2 表达后, 侵袭至 Transwell 小室底部另一侧细胞数明显减少 (siCtrl VS siCPT2#1 VS siCPT2#2 = 23.34±

3.51 VS 8.00± 2.00 VS 8.67±1.53), 表明干涉 CPT1A 可显著抑制肝癌细胞的侵袭能力。

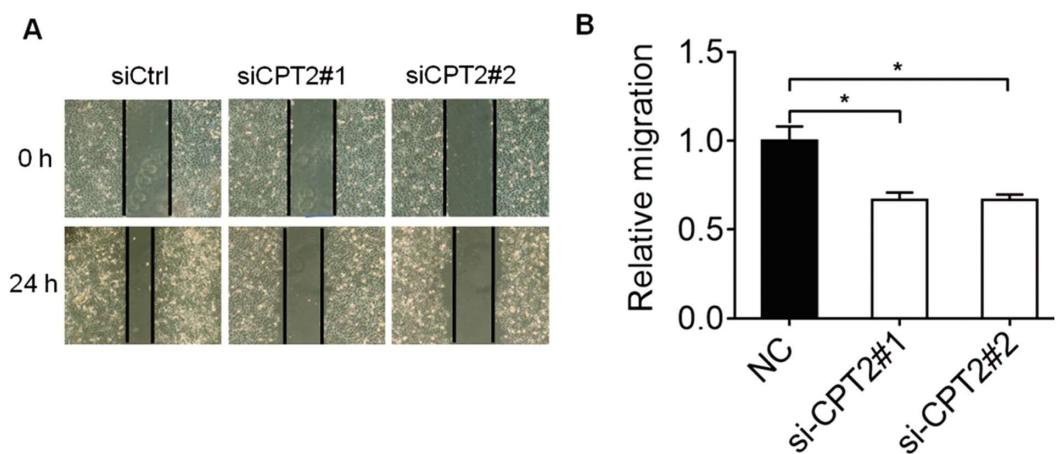


图 3 划痕实验分析干涉 CPT2 对肝癌细胞迁移能力的影响(24 h)

(A: 划痕拍照结果; B: 统计结果, \* 代表  $P<0.05$ )

Fig. 3 Scratch assay for the effect of CPT2 knockdown on the migration of HCC cells (24 h)

(A. Scratch photography results; B. Statistical results, \* represents  $P<0.05$ )

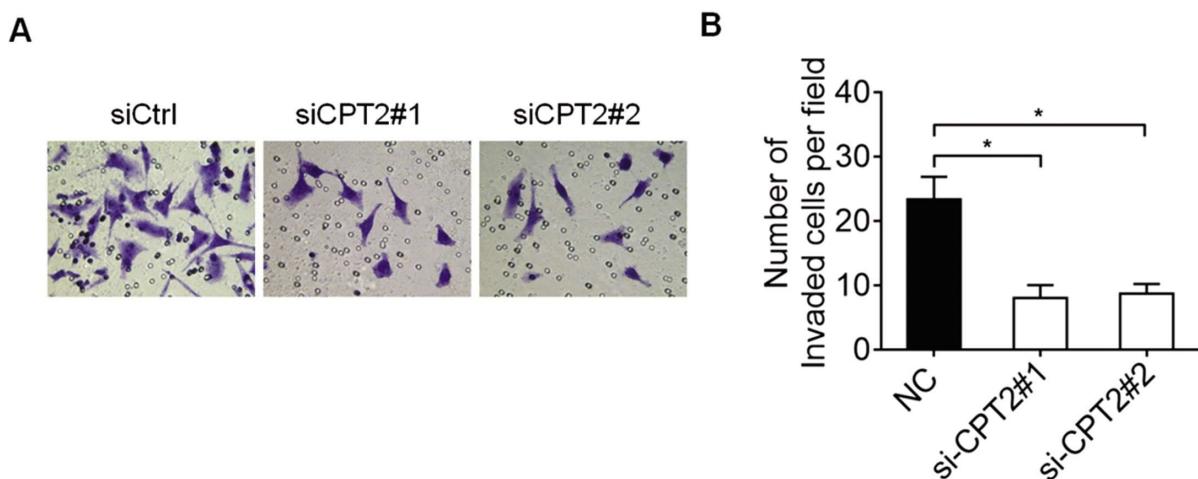


图 4 Transwell 侵袭实验分析干涉 CPT2 对肝癌细胞侵袭能力的影响(48 h)

(A: 侵袭细胞拍照结果; B: 统计结果, \* 代表  $P<0.05$ )

Fig. 4 Transwell invasion assay for the effect of CPT2 knockdown on the invasion ability of HCC cells (48 h)

(A. Invaded cell photography results; B. Statistical results, \* represents  $P<0.05$ )

### 3 讨论

代谢重编程是目前公认的肿瘤十大特征之一, 在促进肿瘤发生与进展的各个环节均发挥重要的促进作用<sup>[1,11,12]</sup>。因而, 探寻驱动肿瘤细胞代谢重编程发生背后的分子机理是目前肿瘤研究领域的热点问题之一<sup>[1,13-15]</sup>。肿瘤细胞代谢重编程主要体现在糖、脂与氨基酸代谢三个方面, 其中糖代谢与氨基酸代谢研究相对较多, 肿瘤细胞脂肪酸代谢受到的关注相对较少<sup>[16,17]</sup>。但近年来越来越多的研究表明, 脂肪酸代谢异常与肿瘤的发生进展高度相关<sup>[18-21]</sup>。肿瘤细胞脂肪酸氧化可通过产生还原性辅酶 NADPH (nicotinamide adenine dinucleotide phosphate) 而帮助肿瘤细胞抵抗氧化损伤<sup>[22]</sup>。此外, 脂肪酸氧化还可通过产生 ATP 而促进肿瘤在营养缺乏等不利环境的存活<sup>[23,24]</sup>。

CPT 是位于线粒体内膜上参与脂肪酸氧化调控的关键分

子, 包括 CPT1 与 CPT2 两个成员, 其中 CPT1 又分 CPT1A、CPT1B 与 CPT1C 三个亚型<sup>[25,26]</sup>。以往肿瘤中研究主要集中在 CPT1, 尤其是 CPT1A 在肿瘤发生进展中的作用。如以往在白血病中的研究表明, CPT1A 分子高表达与患者较差预后显著相关<sup>[27]</sup>。结直肠癌中研究表明, CPT1A 调控的脂肪酸氧化在结直肠癌细胞的侵袭与转移中发挥重要的促进作用<sup>[28]</sup>。下调鼻咽癌细胞中 CPT1A 表达可增强肿瘤对放射治疗的敏感性<sup>[29]</sup>。此外, 乳腺癌中 CPT1A 被证实参与 VEGF 介导的淋巴管生成<sup>[30]</sup>, CPT1A 是乳腺癌潜在的特异性治疗靶点<sup>[31]</sup>。卵巢癌中 CPT1A 也被证实可通过抑制 FoxO 转录因子而促进细胞周期与细胞增殖<sup>[32]</sup>。与 CPT1A 相比, CPT2 仅在肝癌中有少量研究。Lin 等在 41 对肝癌癌与癌旁组织中检测发现, 大多数肝癌组织中 CPT2 的表达显著低于癌旁组织 (59.7%, 24/41)<sup>[7]</sup>。此外, Lu 等也在 8 对肝癌癌与癌旁组织中检测 CPT2 表达后同样发现

CPT2 在多数肝癌组织中表达低于癌旁组织<sup>[8]</sup>。与上述两项研究结论相反，我们在 62 对肝癌与癌旁组织中研究发现，CPT2 在多数肝癌组织中的表达高于癌旁组织(59.7%，37/62)。出现上述研究 CPT2 表达趋势不一致的原因可能有：一方面，本研究与 Lin 等与 Lu 等的研究样本量均不大，尤其 Lu 等的研究样本量更小，所得结论均有待大样本的进一步验证。另一方面，三项研究所采用实验方法及检测 CPT2 所用抗体来源不同也可能是导致最终研究结果不一致的原因。肝癌中 CPT2 表达趋势究竟如何，仍有待未来在更大样本量中进行验证。有趣的是，Lin 等在肝母细胞系 HepG2 中研究证实，CPT2 发挥抑制肿瘤细胞生长与侵袭转移的作用<sup>[7]</sup>，而我们在肝癌细胞系 HLE 中研究发现，CPT2 发挥促进细胞侵袭与转移的作用。提示 CPT2 可能在不同肝癌亚型(如肝母细胞瘤与肝细胞肝癌)中发挥不同甚至相反的作用。

本研究首次在肝癌细胞中证实 CPT2 表达上调促进了肝癌细胞的迁移与侵袭。但肝癌中 CPT2 表达上调及 CPT2 促进肝癌迁移侵袭背后的分子机理仍有待未来研究进一步阐明。

#### 参 考 文 献(References)

- [1] Pavlova NN, Thompson CB. The Emerging Hallmarks of Cancer Metabolism[J]. *Cell metabolism*, 2016, 23(1): 27-47
- [2] DeBerardinis RJ, Chandel NS. Fundamentals of cancer metabolism[J]. *Science advances*, 2016, 2(5): e1600200
- [3] Boroughs LK, DeBerardinis RJ. Metabolic pathways promoting cancer cell survival and growth[J]. *Nature cell biology*, 2015, 17(4): 351-9
- [4] Valcarcel-Jimenez L, Gaude E, Torrano V, et al. Mitochondrial Metabolism: Yin and Yang for Tumor Progression [J]. *Trends in endocrinology and metabolism: TEM*, 2017, 28(10): 748-57
- [5] Bonnefont JP, Djouadi F, Prip-Buus C, et al. Carnitine palmitoyltransferases 1 and 2: biochemical, molecular and medical aspects[J]. *Molecular aspects of medicine*, 2004, 25(5-6): 495-520
- [6] Miranda F, Mannion D, Liu S, et al. Salt-Inducible Kinase 2 Couples Ovarian Cancer Cell Metabolism with Survival at the Adipocyte-Rich Metastatic Niche[J]. *Cancer cell*, 2016, 30(2): 273-89
- [7] Lin M, Lv D, Zheng Y, et al. Downregulation of CPT2 promotes tumorigenesis and chemoresistance to cisplatin in hepatocellular carcinoma[J]. *Onco Targets Ther*, 2018, 11(1): 3101-3110
- [8] Lu X, Zhang X, Zhang Y, et al. Metabolic profiling analysis upon acylcarnitines in tissues of hepatocellular carcinoma revealed the inhibited carnitine shuttle system caused by the downregulated carnitine palmitoyltransferase 2[J]. *Mol Carcinog*, 2019, 58(5): 749-759
- [9] Enooku K, Nakagawa H, Fujiwara N, et al. Altered serum acylcarnitine profile is associated with the status of nonalcoholic fatty liver disease (NAFLD) and NAFLD-related hepatocellular carcinoma [J]. *Sci Rep*, 2019, 9(1): 106-113
- [10] Fujiwara N, Nakagawa H, Enooku K, et al. CPT2 downregulation adapts HCC to lipid-rich environment and promotes carcinogenesis via acylcarnitine accumulation in obesity[J]. *Gut*, 2018, 67(8): 1493-1504
- [11] Sotgia F, Whitaker-Menezes D, Martinez-Outschoorn UE, et al. Mitochondrial metabolism in cancer metastasis: visualizing tumor cell mitochondria and the "reverse Warburg effect" in positive lymph node tissue[J]. *Cell cycle*, 2012, 11(7): 1445-54
- [12] Vander Heiden MG, DeBerardinis RJ. Understanding the Intersections between Metabolism and Cancer Biology[J]. *Cell*, 2017, 168(4): 657-69
- [13] Singh SR, Tan M, Rameshwar P. Cancer Metabolism: Targeting metabolic pathways in cancer therapy[J]. *Cancer Lett*, 2015, 356(2): 147-8
- [14] Jeon SM, Hay N. Expanding the concepts of cancer metabolism[J]. *Exp Mol Med* 2018, 50. Epub ahead of print]
- [15] Snyder V, Reed-Newman TC, Arnold L, et al. Cancer Stem Cell Metabolism and Potential Therapeutic Targets [J]. *Frontiers in Oncology*, 2018, 8(1): 49-54
- [16] Choi YK, Park KG. Targeting Glutamine Metabolism for Cancer Treatment[J]. *Biomol Ther*, 2018, 26(1): 19-28
- [17] Li Z, Zhang H. Reprogramming of glucose, fatty acid and amino acid metabolism for cancer progression [J]. *Cellular and molecular life sciences: CMLS*, 2016, 73(2): 377-92
- [18] Pakiet A, Kobiela J, Stepnowski P, et al. Changes in lipids composition and metabolism in colorectal cancer: a review[J]. *Lipids Health Dis*, 2019, 18(1): 208-217
- [19] Liu QP, Luo Q, Halim A, et al. Targeting lipid metabolism of cancer cells: A promising therapeutic strategy for cancer [J]. *Cancer Letters*, 2017, 401(1): 39-45
- [20] Munir R, Lisec J, Swinnen JV, et al. Lipid metabolism in cancer cells under metabolic stress[J]. *Brit J Cancer*, 2019, 120(12): 1090-1098
- [21] Iwamoto H, Abe M, Yang YL, et al. Cancer Lipid Metabolism Confers Antiangiogenic Drug Resistance[J]. *Cell Metabolism*, 2018, 28(1): 104-116
- [22] Pike LS, Smift AL, Croteau NJ, et al. Inhibition of fatty acid oxidation by etomoxir impairs NADPH production and increases reactive oxygen species resulting in ATP depletion and cell death in human glioblastoma cells [J]. *Biochimica et biophysica acta*, 2011, 1807(6): 726-34
- [23] Jeon SM, Chandel NS, Hay N. AMPK regulates NADPH homeostasis to promote tumour cell survival during energy stress[J]. *Nature*, 2012, 485(7400): 661-5
- [24] Carracedo A, Cantley LC, Pandolfi PP. Cancer metabolism: fatty acid oxidation in the limelight [J]. *Nature reviews Cancer*, 2013, 13(4): 227-32
- [25] Melone MAB, Valentino A, Margarucci S, Galderisi U, et al. The carnitine system and cancer metabolic plasticity [J]. *Cell Death Dis*, 2018, 9(2): 86-98
- [26] Guan LH, Chen YX, Wang YT, et al. Effects of carnitine palmitoyltransferases on cancer cellular senescence[J]. *J Cell Physiol*, 2019, 234(2): 1707-1719
- [27] Shi J, Fu H, Jia Z, et al. High Expression of CPT1A Predicts Adverse Outcomes: A Potential Therapeutic Target for Acute Myeloid Leukemia[J]. *EBioMedicine*, 2016, 14: 55-64
- [28] Wang YN, Zeng ZL, Lu J, et al. CPT1A-mediated fatty acid oxidation promotes colorectal cancer cell metastasis by inhibiting anoikis [J]. *Oncogene*, 2018, 37(46): 6025-6040

- invasive potential of breast cancer cells and sensitizes cells to DNA damages by targeting histone methyltransferase SET8 [J]. *J Biol Chem*, 2013, 288(27): 19633-42
- [17] Takawa M, Cho HS, Hayami S, et al. Histone lysine methyltransferase SETD8 promotes carcinogenesis by deregulating PCNA expression[J]. *Cancer Res*, 2012, 72(13): 3217-27
- [18] Lin Z-Z, Ming D-S, Chen Y-B, et al. KMT5A promotes metastasis of clear cell renal cell carcinoma through reducing cadherin-1 expression[J]. *Oncology letters*, 2019, 17(6): 4907-13
- [19] Veo B, Danis E, Pierce A, et al. Combined functional genomic and chemical screens identify SETD8 as a therapeutic target in MYC-driven medulloblastoma[J]. *JCI insight*, 2019, 4(1)
- [20] Liu B, Zhang X, Song F, et al. A functional single nucleotide polymorphism of SET8 is prognostic for breast cancer[J]. *Oncotarget*, 2016, 7(23): 34277-87
- [21] Shih CT, Chang YF, Chen YT, et al. The PPAR $\gamma$ -SETD8 axis constitutes an epigenetic, p53-independent checkpoint on p21-mediated cellular senescence[J]. *Aging cell*, 2017, 16(4): 797-813
- [22] Veschi V, Liu Z, Voss TC, et al. Epigenetic siRNA and Chemical Screens Identify SETD8 Inhibition as a Therapeutic Strategy for p53 Activation in High-Risk Neuroblastoma [J]. *Cancer cell*, 2017, 31(1): 50-63
- [23] Veo B, Danis E, Pierce A, et al. Combined functional genomic and chemical screens identify SETD8 as a therapeutic target in
- MYC-driven medulloblastoma[J]. *JCI insight*, 2019, 4(1): e122933
- [24] Dhami GK, Liu H, Galka M, et al. Dynamic methylation of Numb by Set8 regulates its binding to p53 and apoptosis [J]. *Molecular cell*, 2013, 50(4): 565-76
- [25] Houston SI, McManus KJ, Adams MM, et al. Catalytic function of the PR-Set7 histone H4 lysine 20 monomethyltransferase is essential for mitotic entry and genomic stability [J]. *The Journal of biological chemistry*, 2008, 283(28): 19478-88
- [26] Nikolaou KC, Moulous P, Harokopos V, et al. Kmt5a Controls Hepatic Metabolic Pathways by Facilitating RNA Pol II Release from Promoter-Proximal Regions[J]. *Cell reports*, 2017, 20(4): 909-22
- [27] Cruz-Bermúdez A, Laza-Briviesca R, Vicente-Blanco RJ, et al. Cisplatin resistance involves a metabolic reprogramming through ROS and PGC-1 $\alpha$  in NSCLC which can be overcome by OXPHOS inhibition[J]. *Free radical biology & medicine*, 2019, 135: 167-81
- [28] Liao T, Wang Y-J, Hu J-Q, et al. Histone methyltransferase KMT5A gene modulates oncogenesis and lipid metabolism of papillary thyroid cancer in vitro[J]. *Oncology reports*, 2018, 39(5): 2185-92
- [29] Karaman EF, Zeybel M, Ozden S. Evaluation of the epigenetic alterations and gene expression levels of HepG2 cells exposed to zearalenone and  $\alpha$ -zearalenol [J]. *Toxicol Lett*, 2020 [Epub ahead of print]
- [30] Blum G, Ibáñez G, Rao X, et al. Small-molecule inhibitors of SETD8 with cellular activity[J]. *ACS Chem Biol*, 2014, 9(11): 2471-2476

---

(上接第 2218 页)

- [29] Tan Z, Xiao L, Tang M, et al. Targeting CPT1A-mediated fatty acid oxidation sensitizes nasopharyngeal carcinoma to radiation therapy [J]. *Theranostics*, 2018, 8(9): 2329-47
- [30] Xiong Y, Liu Z, Zhao X, et al. CPT1A regulates breast cancer-associated lymphangiogenesis via VEGF signaling [J]. *Biomed Pharmacother*, 2018, 106: 1-7
- [31] Pucci S, Zonetti MJ, Fisco T, et al. Carnitine palmitoyl transferase-1A (CPT1A): a new tumor specific target in human breast cancer [J]. *Oncotarget*, 2016, 7(15): 19982-96
- [32] Shao H, Mohamed EM, Xu GG, et al. Carnitine palmitoyltransferase 1A functions to repress FoxO transcription factors to allow cell cycle progression in ovarian cancer[J]. *Oncotarget*, 2016, 7(4): 3832-46