

【专论】

脂肪生成影响恶性肿瘤发展与转移机制的研究进展

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摘要: 正常组织中用于供能的脂肪酸主要来自饮食中的游离脂质,但在生长旺盛的肿瘤组织中,能量却来自于脂质的重新合成,所以在不同来源的肿瘤组织见到脂质合成相关基因的变化,在原发肿瘤中和肿瘤发生相关的生脂基因功能已经基本明确。研究表明在肿瘤细胞中脂肪酸合成酶,硬脂酰辅酶A脱氢酶1、乙酰辅酶A羧化酶在肿瘤的生成和发展起非常重要的作用。脂肪酸的功能与能量贮存、生物膜的结构、信号转导和蛋白质的乙酰化有关,但是现在对脂肪重新生成进程在肿瘤转移中的作用尚不明确。由于耐药性的产生和化疗药物的毒副作用,恶性肿瘤的化疗效果一直不满意,为了寻找新的、选择性抗肿瘤方法,以脂代谢催化酶为靶点的抗肿瘤药物亟待进一步研究和应用。

关键词: 脂肪生成; 脂肪酸; 脂肪酸合酶; 上皮间质转化; 硬脂酰辅酶A脱氢酶1; 胆固醇调节元件结合蛋白

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Research progress on mechanism of lipogenesis in cancer progression and metastasis

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Abstract: The fatty acids in normal tissues for energy supply are mainly from dietary free lipid. However, in fast-developing tumor tissues, energy is supplied by lipid resynthesis, which explains why resynthesis-related genes are spotted in tumors of various origins. And the functions of the lipogenesis genes concerning the onset of primary tumors have been basically clear. A great number of studies have indicated that intracellular fatty acid synthase (FAS), stearoyl-CoA desaturase-1 (SCD1), and acetyl-CoA carboxylase (ACC) all play important roles in the genesis and development of tumors. The functions of fatty acids regard energy reserve, biomembrane structure, signal transduction, and protein acetylation. But unfortunately, the effect of lipid resynthesis on tumor metastasis remains unclear. The curative effect of chemotherapy in malignant tumors has been unsatisfactory because of drug resistance and the toxicity of chemotherapeutic drugs. In order to find new and selective antitumor methods, anticancer drugs targeting lipid metabolism catalyzing enzyme are urgently to be further studied and applied.

Key words: lipogenesis; fatty acid; epithelial-mesenchymal transition; fatty acid synthase; stearoyl-CoA desaturase-1; sterol regulatory element binding protein

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实体肿瘤需要很高的能量以供应其生长和膜结构合成,这种能量的来源就是脂肪。健康个体正常细胞优先利用饮食来源的游离脂肪酸,很少利用重新合成的脂肪酸,但是在生长旺盛的肿瘤组织中,却绝大多数依赖脂质的重新合成^[1],于是脂肪生成率也被明显诱导增加^[2]。脂肪的生成过程发生在肝和脂肪组织中,并使糖酵解来的乙酰辅酶A开始生成脂肪,乙酰辅酶A随即被乙酰辅酶A羧化酶(Acetyl CoA carboxylase, ACC)羧化生成丙二酰辅酶A,丙二酰辅酶A和乙酰辅酶A由脂肪酸合成酶(fatty acid synthase, FAS)进一步处理生成棕榈酸,然后再转化生成硬脂酸^[3]。脂肪生成率被明显诱导增加^[4],并以脂滴的形式储存在细胞内,为肿瘤细胞提供充分的内源性脂肪酸,恶性肿瘤也因此得以实现其生物学功能。

选择性抑制内源性脂肪酸的合成,从而切断肿瘤增殖的能量来源已成为肿瘤治疗和抗肿瘤新药研发的新思路。抑制脂肪酸的合成必须抑制指导脂肪酸合成的关键酶,有研究发现^[5]利用靶向抗血管生成药物舒尼替尼或索拉非尼治疗肿瘤,停药后复发的肿瘤细胞恶性程度增加,并且脂肪酸合成显著增强。在动物实验中,再利用FAS抑制剂可明显抑制肿瘤的复发和转移。这提示阻断表达FAS可以抑制肿瘤的侵袭和浸润。同样道理,抑制了SCD1的表达也可抑制肿瘤的生长和代谢,Mason等^[6]通过RNAi干扰技术,分别降低结肠癌细胞系(HCT116)中FAS、SCD1、ACC的表达,导致细胞毒性增加,而这种毒性可以通过加入外源性的脂肪酸逆转。FAS抑制剂浅蓝菌素、C75均可抑制HCT116细胞的活性,且这两种药物对棕榈酸、硬脂酸及油酸的刺激无反应。而ACC抑制剂TOFA的细胞毒性仅被油酸逆转,实验发现TOFA可以作为一个强有力的SCD1抑制剂。该研究为脂肪酸合成关键酶作为切断癌细胞营养供应的潜在有效靶点提供了证据,对癌症的治疗具有重要的理论和临床意义。本文综述脂肪生成影响恶性肿瘤发展与转移机制的研究进展,为寻找新的、选择性抗肿瘤方法,以脂代谢催化酶为靶点的抗肿瘤药物奠定基础。

1 恶性肿瘤转移进程

为了更好地了解脂肪生成对恶性肿瘤的影响,使研究成果更多地应用于使患者受益上,首先需要着眼于癌症中脂肪生成的各个环节。转移进程是一个复杂的多步骤过程,肿瘤细胞需要从原发肿瘤逃

逸,进入血液和淋巴系统。大多数循环中的细胞会最终凋亡^[7],但有一些能够生存并侵犯新的组织^[8]。上皮间充质转化(epithelial-mesenchymal transition, EMT)与肿瘤进展和转移有关^[9-10]。它能打开上皮细胞间的紧密联接、细胞外基质以及基底部联接,导致形成失去正常组织关联的活动的间充质细胞群^[10]。在EMT中首先发生的事件是钙黏附蛋白(E-cadherin)表达缺失,E-cadherin是一种跨膜蛋白,与紧密结合联接形成有关^[11]。其中E-cadherin表达缺失与转录遏制蛋白表达增加有关^[12-13]。正常情况下糖原合成激酶(glycogen synthase kinase, GSK3 β)可以磷酸化E-cadherin的转录抑制子使其经蛋白酶体降解,并允许E-cadherin转录^[14]。患癌症时TGF- β 、Wnt、RTK和整合蛋白(integrin)途径活化^[15-16],导致GSK3 β 受抑^[17],并且造成E-cadherin的转录抑制子不能磷酸化也不能降解,最终使E-cadherin表达缺失^[18]。另一个途径是连环素(β -catenin)磷酸化缺失,导致其不能进入蛋白酶体和胞浆中累积,而是转位进入细胞核,进而活化转录基因如c-myc,后者是重要的细胞周期调节因子^[19-20]。E-cadherin也在肌动蛋白骨架结构中发挥作用,它直接与肌动蛋白微丝结合或 β -catenin结合,维持细胞极性和组织结构^[21]。在癌细胞中,一旦E-cadherin/ β -catenin复合物消失,激动蛋白网络系统就中断了调节细胞迁移的功能^[22-23],并且核 β -catenin也增加了一些间充质蛋白表达^[24-25]。

FAS表达上调是肿瘤发生EMT的一个关键因素。Jiang等^[26]发现在发生EMT的细胞中FAS表达上调,相反沉默FAS可逆转EMT的表型。Wnt信号通路通过抑制GSK3 β 进而抑制细胞质中 β -catenin降解,最终诱发EMT。FAS可通过两个途径调节肿瘤EMT:一是通过调控脂筏的组成和稳定性,进而影响定位于脂筏的蛋白,最终对EMT进行调控;二是FAS通过调控Wnt的棕榈酰化水平,激活Wnt/ β -catenin信号通路,进而诱导EMT^[27]。另外TGF β 和EGF介导SCD1的表达,有证据表明SCD1能活化GSK3 β 以及调整细胞黏附与迁移的下游信号,从而在转移癌细胞中发挥作用。

2 胆固醇调节原件结合蛋白(SREBPs)和核转录因子肝X受体(LXR)的作用

生脂酶FAS、SCD1和ACC的表达受核转录因子肝X受体(liver X receptor, LXR)和胆固醇调节原件结合蛋白(sterol regulatory element-binding

proteins, SREBPs)的控制^[2]。其中 SREBPs 对 FAS 基因表达调控相比 LXR 起主要作用。SREBPs 是调节脂肪酸和胆固醇合成的反式作用因子,属于碱性-螺旋-环-螺旋亮氨酸拉链家族,是脂肪酸和胆固醇合成的关键酶。SREBPs 前体固定在胞内内质网和核膜上,当被活化后易位到核内,并和目的基因的增强子结合从而激活转录。SREBPs 共有 3 种亚型 SREBP-1a、SREBP-1c 和 SREBP-2^[26-29]。作为 SREBP-1 在肝脏中表达的主要亚型, SREBP-1c 是众多脂质合成基因的表达调控枢纽。SREBP-1 和 SREBP-2 有不同的效应, SREBP-1 优先活化脂肪酸合成相关酶,如 FAS、ACC,而 SREBP-2 则优先活化胆固醇合成的相关基因,如羟甲基戊二酸单酰 CoA 合酶(hydroxymethylglutaryl CoA synthase, HMG CoA synthase)和羟甲基戊二酸单酰 CoA 还原酶(hydroxymethylglutaryl CoA reductase, HMGCoA reductase)等。Viollet 等^[30-31]研究还发现腺苷酸活化酶(5' AMP-activated protein kinase, AMPK)可以失活 ACC 和 SREBP-1c 而参与肝脏内脂肪生成过程。ACC 和 FAS 在大量癌细胞中都有过度表达,而在一些肿瘤中 SCD1 的表达增加和活性增加往往使这些肿瘤组织中单不饱和脂肪酸(MUFA)表达大幅增加^[32],同时 SREBP1 也参与肿瘤生长^[33],由此可见高脂生成率可能与肿瘤发生有关。生脂活性增高也与癌症进展和转移有关, SREBP1 高表达可能至少部分解释生脂基因表达增加与恶性肿瘤分层有关^[34]。然而生脂酶的表达是与恶性肿瘤相关却并不依赖于 SREBP1 的表达。最近的研究也证实了脂肪生成在癌症进展和转移中的作用。

肝 X 受体 LXR 是转录因子核激素受体超家族成员,现已知其配体主要是胆固醇及其衍生物。LXR 分两种亚型——LXR α 和 LXR β , LXR α 在肝脏、小肠、肾、脂肪组织高表达, LXR β 几乎表达于所有组织是配体调节的核受体,在脂肪酸合成、葡萄糖、胆固醇代谢的过程中起重要作用^[35-36]。LXR 和视黄酸 X 受体(retinoid X receptor, RXR)一起结合于 DNA 调控元件,参与诱导多基因转录,如脂肪合成、胆汁酸生成、胆固醇和葡萄糖代谢。LXR 影响脂肪酸合成主要包括 LXR/RXR 二聚体直接结合在脂肪合成相关酶的启动子区;或者间接地通过激活 SREBP-1c 来调节脂肪酸的生成^[36]。Repa 等^[37]和 Yoshikawa 等^[38]证实 LXR 可直接作用于 SREBP-1c 进行调控。

3 癌症进程中脂生成调控及影响

癌细胞中脂生成由 EGF 介导,可以通过活化人表皮生长因子受体 2(human epidermal growth factor receptor-2, HER2)^[39]和靶向 SREBP-1^[40-41]的 PI3k/Akt 途径^[40, 42, 43]来诱导完成。PI3K 属于磷脂酰肌醇 3-激酶(PI3Ks)蛋白家族,因结构和功能的差异又分为 PI3K1、PI3K2 和 PI3K3 亚型,参与增殖、分化、凋亡和葡萄糖转运等多种细胞功能的调节。蛋白激酶 B(Protein kinase B, PKB/Akt)是 PI3K 的下游分子,活化的 AKT 通过磷酸化多种酶、激酶和转录因子等下游因子,进而调节细胞的功能。其作用主要表现为抗凋亡,细胞增殖和细胞生长。它也参与胰岛素介导的代谢效应(如脂肪生成),葡萄糖摄取和转换为糖原并转化为脂肪酸和胆固醇等进程^[40]。而 AKT 与其重要下游分子哺乳动物雷帕霉素靶蛋白(mTOR)组成了 PI3K/Akt/mTOR 信号通路,该通路细胞增殖及肿瘤血管形成密切相关。另外一条和 mTOR 相关的通路是 LKB1/AMPK/mTOR 通路, LKB1 通过磷酸化激活腺苷酸活化蛋白激酶(adenosine monophosphate activated protein kinase, AMPK),进而实现对 mTOR 的负性调控。LKB1 基因又称 Serine-Threonine11、STK11,作为 AMPK 底物其活性调节可以通过多位点水平磷酸化激活 AMPK 来调节细胞的能量代谢、细胞周期和增值凋亡等进程^[44]。

AMPK 是生物能量代谢调节的关键分子,它在代谢相关的器官中均有表达,当体内能量耗竭时,如缺氧、运动、缺血等状态,细胞内 ATP 下降, AMP 增加,均能够激活 AMPK 对线粒体功能进行调控,维持能量稳态,直接或间接调节 mTORC1 的活性,在抗肿瘤、抗感染、预激综合征等治疗中发挥重要作用^[45]。乙酰辅酶 A 羧化酶(ACC)和 3-羟基-3-甲基戊二酸单酰辅酶 A 还原酶(3-hydroxy-3-methylglutaryl coenzyme A reductase, HMGCR)均是 AMPK 的重要底物,分别调节脂肪酸和胆固醇的合成代谢过程^[46]。ACC 是催化长链脂肪酸合成的关键酶,糖代谢生成的乙酰辅酶 A 可在其作用下合成丙二酰辅酶 A,丙二酰辅酶 A 是脂肪酸合成的产物,通过负反馈抑制肉毒碱棕榈酸转移酶-1(carnitine palmitoyl transferase-1, CPT-1)的活性,从而对线粒体的脂肪酸氧化和酮体的生成起到抑制作用。激活 AMPK 可以使其底物磷酸化而失去活性,抑制脂肪酸和胆固醇的合成,从而减少脂供应、

阻滞细胞周期、减少细胞分裂和肿瘤生长^[47]。在早期乳癌能看到 ACC 表达增加^[48]，并且沉默 ACC 表达可以使生长抑制、癌细胞凋亡^[49-51]。相对于 HMGR 来说，ACC 对 AMPK 更敏感，更容易受到 AMPK 活化水平的影响。所以脂肪酸相对于胆固醇更容易受到 AMPK 活化程度的影响，更说明脂肪酸的合成可能为癌细胞提供能量供应，刺激细胞分裂和生存，导致肿瘤生长。另外 FAS 表达增加诱导癌细胞进入 S 期^[52]；相反，抑制 FAS 表达降低肿瘤生长并诱导癌细胞凋亡^[53]。SCD1 的高表达与癌细胞增殖有关，并且可以降低细胞死亡率^[54-57]。SREBP1c 在正常细胞转化中也发挥作用^[58]。

4 脂肪酸合成酶的作用

毋庸置疑，肿瘤的恶性程度与肿瘤相关的能量代谢密不可分，而出现代谢异常又与控制代谢的关键酶异常表达有关，因此研究调控这些关键酶表达的调控基因就变得尤为重要。与癌转移有关的生脂酶中，FAS 是研究最多的蛋白。FAS 广泛存在于动物、植物组织细胞中，是内源性脂肪酸合成的限速酶，脂肪酸的功能与能量贮存、生物膜的结构、信号转导和蛋白质的乙酰化有关。FAS 较高表达基本上集中分布于脂质代谢程度高的细胞，如脂肪细胞、黄体、肝细胞；对激素敏感的细胞，如乳腺、子宫内膜、前列腺、肾上腺皮质；处于增殖状态的细胞，如胃十二指肠上皮细胞、结肠吸收细胞、胎儿消化呼吸系统增殖上皮。FAS 表达上升是对内源性脂肪酸合成和细胞增殖的适应。FAS 的主要产物软脂酸既是细胞膜结构的主要成分，也是细胞能量代谢的重要底物。

肿瘤患者的预后与生存期主要与转移和 FAS 过度表达有关，这个机制也与几种激素依赖型癌症的不良预后有关^[59-63]。FAS 高表达和转移的直接关系在前列腺癌^[64]和乳癌中^[60]可以观察到。转基因小鼠前列腺癌模型能密切反映人类前列腺癌进展，这种模型中 FAS 表达和活性明显增高^[65]。给免疫缺陷小鼠注入高表达 FAS 和雄激素受体（androgen receptor, AR）的人前列腺癌细胞导致侵袭性腺癌，雄激素通过增加核的 SREBP 水平刺激前列腺癌中 FAS 高表达^[66]。这最可能是激活蛋白（Srebp Cleavage Activating Protein, SCAP）表达增加的结果，SCAP 能从内质网输送 SREBP 到高尔基体，并在那里裂解活化。随后 SREBP 被雄激素刺激激活，生脂基因表达亦增加^[67-68]。如前介绍 AR 下游

PI3K/Akt 途径与 FAS 活性有关^[69]。前列腺癌中，异肽酶 USP2a 通过抑制蛋白酶体降解参与 FAS 表达活化^[70]。

卵巢癌细胞中 FAS 和局部黏附激酶（focal adherinkinase, FAK）的蛋白水解导致血管内皮生长因子（vascular endothelial growth factor, VEGF）介导的细胞迁移和侵袭明显减少^[71]，同时在相同的研究中，异肽酶 USP2a 表现出能稳定 FAS 的能力。另一个研究证明绿茶提取物 EGCG 在乳腺癌细胞中通过调节 FAS 和 EGFR 信号途径来干扰细胞黏附，原因是 EGCG 可以使 β -catenin 在胞浆中累积，从而减少 E-cadherin 表达^[72]。

FAS 通过影响 EGFR 表达参与乳癌细胞转化^[73]。HER2 是癌基因，与乳癌转移和发展有关^[74]。在 HER2 阳性细胞中，FAS 表达增加能稳定脂筏结构 rafts，结果 HER2 表达的增加活化了下游通路^[75]。同时 EGF 也增加 FAS 转录，从而建立起 FAS 和 EGF 间的正反馈调节^[76-78]。

在乳腺癌和子宫内膜癌中 FAS 的表达受雌激素的刺激^[62]。FAS 的表达增加可能与原发性肿瘤的建立有关，因为肿瘤内存在雌激素和孕激素受体的患者预后好于有 HER2 表达的病人^[74, 79]。FAS 表达和预后差的相关性在非激素依赖的肿瘤^[80-82]和其转移中也可以观察到^[83]。

转移性肾癌中，FAS 表达明显强于非恶化的肿瘤^[84]。人类胰腺癌细胞的侵袭性可被人工合成的 FAS 抑制剂 C75 所遏制，后者可能通过下调 HER2 和/STAT3 磷酸化来实现这一过程^[83]。在一个小鼠自发黑色素瘤转移的模型中，腹腔直接注入一种天然的 FAS 抑制剂 Orlistat，也可以半数抑制淋巴结转移^[85]。

进展期结肠癌的异种移植模型中，抑制 FAS 可减少肝转移^[86-87]，这与 FAS 下游的 AKT 有关。抑制 FAS 也能削弱 MET 受体和 FAK 的活性，MET 是肝细胞生长因子的受体，由原癌基因 c-Met 编码，是一种赖氨酸激酶受体。这两种蛋白都与黏附、迁移和癌细胞侵袭有关^[71]。

上述研究指出癌症进展中 FAS 的关键作用，可能通过调节脂筏结构形成进而活化 EGFR、HER2 和 MET。下游信号活化增加 SREBP1c 活化 FAS 的核定位，并且与其他生脂基因完成正反馈。

5 硬脂酰辅酶 A 脱氢酶 1

SCD1 是催化饱和脂肪酸（saturated fatty acid，

SFA) 向单不饱和脂肪酸 (monounsaturated fatty acid, MUFA) 转变的限速酶, 与肥胖、脂肪性肝病、胰岛素敏感性调节等一系列的代谢综合征及癌症的发生、发展密切相关。SCD1 的活性受到发育、饮食、激素、温度等多种途径的调节。目前较为清楚的是多不饱和脂肪酸 (polyunsaturated fatty acid, PUFA) 主要通过 SREBP-1c 依赖途径抑制 SCD1 的活性。

MUFA 在恶变的癌细胞中增加, 这暗示 SCD1 在肿瘤发生中发挥作用。脂肪酸的表达特性特别是 SFA 和 MUFA 的平衡可以用于预测乳腺癌^[88-90]。最近证实沉默乳腺癌细胞 SCD1 不影响细胞存活能力, 但可以抑制细胞周期^[91], 导致参与细胞周期进展的关键蛋白的表达下降。SCD1 表达受抑制的程度直接与抑制癌细胞增殖相关^[55], 并且减少 ACC 的主要抑制物 SFA (SCD1 的底物) 的表达^[92]。

其他研究也指出了 SCD1 与癌症进展和转移中的作用。胆固醇酯中 MUFA 含量与癌症患者的高死亡率有关^[93], 转移性乳腺癌中油酸增加, 这都意味着 SCD1 活性增加^[94]。乳腺癌磷脂酰胆碱中低含量硬脂酸 (SCD1 底物) 也与后续的转移相关。乳腺脂肪组织中, MUFA 在良性肿瘤组织和正常组织中没有区别, 但 MUFA 的浓度却和转移正相关^[95]。乳腺癌中 SFA/MUFA 比例的改变不能反映患者的饮食摄入, 但却能反映细胞中脂肪酸代谢的变化^[96], 是新合成 MUFA 和 SCD1 的潜在基础。

众所周知 AKT 与癌症进展有关^[97], 一个研究在肺腺癌细胞中敲除 SCD1 可以抑制 AKT 的磷酸化和活性^[56], 延缓其进展。SV40 转化肺成纤维细胞和乳腺癌细胞中沉默 SCD1 可以抑制 GSK3 β 磷酸化^[56]。核内 β -catenin 转运减少导致细胞周期蛋白 D1 (cyclin D1) 和波形蛋白 (vimentin) 表达降低, 这二种蛋白都与间充质细胞表型有关^[98]。在 MCF7 和 MDA-MB-231 乳腺癌细胞中沉默 SCD1 增加 E-cadherin 表达, 这与细胞形态学变化和细胞迁移减少有关^[91]。Wnt 通路蛋白表达修饰时需要棕榈酸 (SCD1 产物) 参与, 也能导致 Wnt 信号途径活化而促进癌症进展^[99]。

在乳腺癌细胞中, 如果终止沉默 SCD1, 观察到转化生长因子- β (transforming growth factor- β , TGF- β) 诱导 β -catenin 核转运会减少, TGF- β 作为肿瘤抑制子, 但当癌细胞对其作用拮抗时, 它的作用就转为刺激恶性转化^[10]。TGF- β 通过 Smad 依赖

途径活化 SCD1 表达^[98]。通过 ErbB 受体活化 EGF 信号途径与转移和预后差有关^[100]。但矛盾的是, 乳腺癌细胞与油酸共同孵育后抑制 HER2 表达, 这意味着 SCD1 产物的抗转移作用^[101]。

6 其他生脂基因的作用

在癌症进展中调节脂的表达与几个参与脂代谢的基因表达增加有关^[94], 并且除了 FAS 和 SCD1, 其他基因的表达如 ACC、胰岛素诱导基因抗体 1 (insulin-induced gene 1, INSIG1)、SCAP 和甲状腺激素反应基因 (thyroid hormone-responsive protein) 都可以不同程度地调节脂代谢。

THRSP 也称作 Spot14, 是核蛋白, 能够活化生脂基因^[102]。Spot14 低表达与延长侵袭性乳腺癌生存有关, 这暗示 Spot14 可能在 EMT 中起关键作用^[102]。另一项研究也表明乳腺癌细胞不表达脂蛋白酶, 脂必需由局部微环境如乳腺脂肪供给, 这就解释了为什么癌细胞低表达 Spot14 不能在低脂表达的环境 (如淋巴结) 中生存^[103]。以上结论也暗示癌细胞中 Spot14 表达增加是唯一能解释癌细胞中脂生成增加的原因。

ACC 作为 AMPK 的重要底物能被其磷酸化, 也与恶性肿瘤有关, 并可以为癌细胞提供能量^[47]。增加的 ACC 表达也与乳腺癌细胞更易浸润有关^[60]。ACC 基因拷贝扩增可以使乳癌生存率降低^[104]。BCRA1 与遗传易感性癌症有关, 突变后不能与失活的磷酸化的 ACC 相互作用, 使 ACC 去磷酸化而活化^[105]。脂联素 (adiponectin) 是一种脂肪细胞因子, 被认为具有抗转移作用, 能够增加 AMPK 活性而抑制 ACC 的表达^[106]。在乳腺癌细胞中, ACC 通过与 AKR1B10 (aldoketo reductase family 1 B10) 作用后被泛素降解^[48]。癌细胞中使用药物抑制 ACC 能够抑制伪足形成, 伪足是突出细胞表面的膜结构, 帮助基质降解和细胞侵袭^[107], 但在伪足形成中不需要 SCD1 参与, 这意味着和 SCD1 遵循不同的途径。丙二酰 CoA 能减少 HER2 基因表达, 提示 ACC 的抗转移作用^[108]。这是因为 FAS 能减少细胞中丙二酰 CoA 含量, 并且强调了 FAS 在 EMT 中的作用。前列腺癌的出现与进展依赖雄激素, 证据显示雄激素活化 SREBP 途径可能解释了大多数雄激素在脂生成中的作用^[109]。雄激素通过增加 SCAP 和 INSIG 的表达增加 SREBP 的分裂激活^[68]。雄激素通过增加活性氧 (reactive oxygen species, ROS) 产生, 活化裂解 SREBP 而诱导肿瘤进展^[110-111]。一些研究观

察到在乳癌中孕激素和 EGF 对 SREBP 同样有裂解作用^[58, 76, 78]。

7 结语

脂质生成增多和生脂酶的表达变化是癌症进展和转移的重要标志, 这些作用一部分是通过 SREBP1 介导的, 但证据指出生脂酶的作用并不依赖 SREBP1。在癌细胞中 ACC 活性通过 AMPK 磷酸化或与 BCRA1 相互作用而调节。ACC 的产物丙二酰 CoA 具有抗转移作用, 这暗示 FAS 对 EMT 的更直接作用。棕榈酸酯对膜形成和脂筏形成中的作用使得脂筏招募稳定受体如 EGF、HER2 和 MET 来促进癌症进展。与 FAS 相反, SCD1 可以直接参与 EMT 但与伪足形成并不相关, 这就揭示了这两个酶都与 EMT 有关, 但调节机制各不同。增加 SCD1 活性可以减少 SFA 的水平, SFA 抑制 ACC 的表达从而活化癌细胞中的脂生成。

以上证据表明研究生脂酶 FAS 和 SCD1 可能成为治疗转移性癌症最有价值的靶点而具有深远意义。肿瘤因为其异质性, 免疫逃逸等特点, 仅仅是孤立地作用于肿瘤相关信号通路的靶向治疗效果比较局限, 而相对于基因水平的改变, 肿瘤能量代谢的改变是下游事件, 并且不同来源的肿瘤在代谢层面拥有基本类似的通路和特征, 因此以肿瘤代谢特征为靶标的抗肿瘤新药研发及治疗有其独特的优势。总之, 深入了解肿瘤细胞脂代谢调节的具体机制, 抑制恶性肿瘤细胞维持代谢需要的内源性脂肪酸合成, 研究及开发脂肪酸合成酶(如 FAS、SCD1)的抑制剂, 为恶性肿瘤的生物学治疗开拓了新的思路与方法。

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