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综 述

胆固醇代谢重编程在胰腺癌中的作用及靶向胆固醇代谢药物的应用

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摘 要：胰腺癌起病隐匿，缺乏有效的治疗方法，是预后最差的实体肿瘤之一，亟需探索新的治疗方向。代谢重编程是肿瘤的重要标志之一，处于恶劣肿瘤微环境中的胰腺癌细胞为了维持旺盛的代谢需求将胆固醇代谢全面上调，肿瘤相关成纤维细胞为癌细胞提供大量的脂质。胆固醇代谢重编程涉及胆固醇的合成、摄取、酯化、以及胆固醇相关代谢产物的一系列调整，与胰腺癌的增殖、侵袭、转移、耐药、免疫抑制等表型密切相关，抑制胆固醇代谢具有明显的抗肿瘤作用。本文从胰腺癌的高危因素、肿瘤相关成纤维细胞与癌细胞间的能量交互、细胞胆固醇代谢关键靶点的作用机制及其靶向药物，综述了胰腺癌胆固醇代谢的复杂性与重要性。胆固醇代谢具有严格的调控与反馈机制，单一靶点药物在临床应用中的效果并不明确，因此胆固醇代谢的多靶点疗法是胰腺癌治疗的新方向。

关键词：胰腺癌；胆固醇；脂代谢；代谢重编程

The role of cholesterol metabolism reprogramming in pancreatic cancer and the application of cholesterol-targeted metabolism drugs

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Abstract: Pancreatic cancer has an insidious onset and lacks effective treatment methods, which is one of the tumors with the worst prognosis, so it is urgent to explore new treatment directions. Metabolic reprogramming is one of the important hallmarks of tumors. Pancreatic cancer cells in the harsh tumor microenvironment have comprehensively increased cholesterol metabolism in order to maintain strong metabolic needs, and cancer associated fibroblasts also provide cancer cells with a large amount of lipids. Cholesterol metabolism reprogramming involves the changes in the synthesis, uptake, esterification and metabolites of cholesterol, which are closely related to the proliferation, invasion, metastasis, drug resistance, and immunosuppression of pancreatic cancer. Inhibition of cholesterol metabolism has obvious anti-tumor effect. In this paper, the important effects and complexity of cholesterol metabolism in pancreatic cancer were comprehensively reviewed from perspectives of risk factors for pancreatic cancer, energy interaction between tumor-related cells, key targets of cholesterol metabolism and its targeted drugs. Cholesterol metabolism has a strict regulation and feedback mechanism, and the effect of single-target drugs in clinical application is not clear. Therefore, multi-target therapy of cholesterol metabolism is a new direction for pancreatic cancer treatment.

Key words: pancreatic cancer; cholesterol; lipid metabolism; metabolic reprogramming

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胰腺癌是 5 年生存率最低的恶性肿瘤，90% 的患者确诊时已处于中晚期，胰腺癌 5 年生存率为 3%，中位生存期 3.5 个月，仅 11% 胰腺癌患者有机会手术治疗 [1]。且术后中位生存期仅 17~23 个月，近 10 年间国内外胰腺癌发病率、死亡率均呈持续增长趋势 [2, 3]。胰腺癌对放疗不敏感，对化疗易耐药，对新兴靶向药物、抗血管生成药物、免疫治疗药物均不敏感，缺乏有效的治疗手段导致其患者生存期短暂 [4]，亟需探索新的治疗方向。

能量代谢重编程是癌症的基本标志 [5]，是肿瘤细胞维持快速增殖的必要手段。胆固醇代谢重编程通过促进胰腺癌增殖、侵袭、转移、耐药、免疫抑制等多个方面为胰腺癌的发生与发展提供助力。越来越多研究表明抑制胆固醇代谢具有良好的抗胰腺癌效果，深入了解胆固醇代谢重编程对胰腺癌的影响及作用机制或许可以为我们提供新的治疗方向。本文综述了胆固醇代谢重编程对胰腺癌的重要影响，总结了胆固醇代谢重编程的关键靶点及相关药物。

1 肥胖与高脂、高胆固醇饮食是胰腺癌的危险因素

《柳叶刀公共卫生》数据显示，1995 年至 2014 年间，包括胰腺癌在内的 6 种肥胖相关的肿瘤 (胰腺癌、多发性骨髓瘤、结直肠癌、子宫体癌、胆囊癌和肾癌) 发病率显著上升，这在年轻人群中的表现尤为明显 [6]。美国国立卫生研究院的大型队列研究发现，超重或肥胖 [体重指数 (BMI) ≥ 30 kg/m²] 群体相较于 BMI 正常 (BMI = 18.5~22.4 kg/m²) 人群，罹患胰腺癌的风险更高 [7]。深度加工食品往往含有大量饱和脂肪酸与胆固醇，这种不健康的饮食不仅是肥胖的重要原因，也是恶性肿瘤的危险因素。流行病学研究发现高脂 [8]、高胆固醇饮食 [9] 与高胆固醇血症 [2] 是胰腺癌发病危险因素。实验研究显示，高脂饮食喂养的小鼠无论是原发性胰腺肿瘤的大小还是远期器官转移率都明显超过标准饮食的小鼠 [10]。高脂饮食可增强胰腺脂肪浸润 [11]，促进胰腺癌的转移、提高致死率 [12]。高胆固醇摄入可增加罹患胰腺癌的风险 [13]。高胆固醇饮食促进肿瘤生长 [14] 与转移 [15]，增加癌症死亡率 [16]，低胆固醇饮食则可降低癌症风险 [17]。

胆固醇稳态的改变可能触发或支持了肿瘤的发生 [18]。血清总胆固醇 (total cholesterol, TC) 与胰腺癌风险存在相关趋势，但 TC 水平升高是保护因素 [19] 还是危险因素 [20] 仍存在争议，TC 水平尚未被列为胰腺癌发病风险的预测因子。细胞内胆固醇水平似乎比血清胆固醇水平对癌症有着更大的影响 [21]。靶向胆固醇代谢具有预防和抗胰腺癌作用，后文将对此详细论述。

2 胆固醇代谢重编程影响多种表型、促进胰腺癌进展

胆固醇代谢重编程是肿瘤细胞在恶劣的肿瘤微环境中为获取大量胆固醇而对正常胆固醇代谢做出的一系列调整，例如胆固醇及其衍生物的合成增加，脂筏中胆固醇含量与分布的变化等。胆固醇代谢重编程通过促进癌细胞的增殖、侵袭、转移、耐药、免疫抑制、衰老等方面促进胰腺癌进展。

胆固醇作为细胞膜的主要组成部分，是满足细胞增殖的必要原料 [22]。胰腺癌细胞为维持迅速增殖的特性，需大量摄取胆固醇 [23]。切断胆固醇供给，细胞会进入周期阻滞状态 [24]。癌细胞对胆固醇消耗的敏感性高于正常细胞 [25]，抑制胆固醇合成可抑制肿瘤细胞增殖 [22]。胆固醇生物合成抑制剂如普伐他汀、洛伐他汀、西立伐他汀，胆固醇吸收抑制剂如依折麦布，均可显著降低胆固醇水平，抑制肿瘤生长 [26]。促进胆固醇的外流也能使胰腺癌细胞的增殖和生存能力下降 [27]。肿瘤细胞吸收大量脂质后膜流动性增强，有利于肿瘤侵袭和转移 [28]。抑制胆固醇代谢可以降低癌细胞活力，抑制肿瘤迁移与上皮间质转化 [29]。

胆固醇酯化是肿瘤细胞为了应对恶劣的生存环境，将多余的游离胆固醇 (free cholesterol, FC) 酯化为胆固醇酯 (cholesterol esters, CE) 供其随时调动的生物过程。CE 的积累与肿瘤的增殖、迁移、侵袭密切相关 [30]。靶向抑制胆固醇的酯化可以抑制胰腺癌的增殖、侵袭与转移 [31]。胰腺癌耐药细胞系中 CE 的异常积累十分显著，抑制胆固醇的酯化可以逆转耐药 [32]，因此胆固醇酯化也被认为是胰腺癌耐药的潜在机制。下调胆固醇通路基因能提高胰腺癌对吉西他滨 [33]、SN38 (伊立替康的活性代谢物)[34] 的敏感性，提高化疗效果。除 CE 外，其他一些胆固醇衍生物如 27- 羟基胆固醇 (27-HC)[35]、25- 羟基胆固醇 (25-HC)[36]、24- 羟基胆固醇 (24-HC)[37] 等也能促进肿瘤进展。

脂筏是质膜表面由高浓度胆固醇和鞘磷脂组成

的生物结构域，可通过调控多种信号通路的传导影响癌细胞增殖、凋亡、转移与耐药[38]。抑制胆固醇代谢可以破坏脂筏的完整性进而抑制癌细胞的增殖[39]。改变脂筏中的胆固醇分布可以抑制癌细胞PI3K/AKT/ERK 和 NF-κB 信号转导，进而抑制肿瘤生长[40]。调节脂筏形成的天然小分子物质 10- 姜酚可以影响乳腺癌细胞中的 PI3K/AKT 信号通路，从而抑制癌细胞的增殖、迁移和侵袭，并诱导其凋亡[41]。脂筏中胆固醇的积累可以促进胰腺癌细胞ATK 生存信号传导与胰腺导管腺癌 (pancreatic ductal adenocarcinoma, PDAC) 耐药性，脂筏中的胆固醇含量降低后癌细胞的生长受到抑制，耐药作用出现逆转[42]。

胆固醇还能够影响免疫细胞对癌细胞的杀伤作用。质膜中胆固醇含量丰富的癌细胞刚性较低，这使得癌细胞对 T 细胞的细胞毒性抵抗性增强，胆固醇的耗尽则可以逆转这种现象并提高过继 T 细胞疗法的效果[43]。同样地，抑制胆固醇酯化还能增加细胞毒性因子释放，促进嵌合抗原受体 T (chimeric antigen receptor T, CAR-T) 细胞的抗肿瘤作用[44]。另外，胆固醇含量的降低与胰腺癌细胞的衰老也有着密切的关系，他汀类药物可以竞争性抑制胆固醇合成的限速酶羟甲基戊二酰辅酶 A 还原酶 (HMG-CoA reductase, HMGCR)，逆转胰腺癌中的转录因子 CP2 对胰腺癌细胞的衰老抑制作用[45]。

3 肿瘤相关成纤维细胞(cancer associated fibroblasts, CAFs)通过能量交互为胰腺癌细胞提供脂质

丰富的结缔组织增生是胰腺癌的显著特征，胰腺癌中近乎 90% 的成分由细胞外基质组成。纤维连接蛋白、胶原、透明质酸等大量的细胞外基质成分由成纤维细胞、肌成纤维细胞和胰星状细胞产生[46]。这些致密的胶原间质通过干扰局部的血液灌注引起局部耐药、缺氧和营养供给不足[47]。胰腺癌细胞为了维持旺盛的代谢需求，需要获取大量的脂质，正常的胆固醇合成与摄取途径难以满足，因此更加依赖于细胞外脂质的摄取与利用[48]。肿瘤细胞还能通过吞噬细胞外蛋白质[49]和脂质[50]获取氨基酸以及合成细胞膜必备的脂肪酸。

越来越多的证据表明 CAFs 是肿瘤细胞的额外胆固醇来源，作为肿瘤微环境中含量最丰富的间质细胞，CAFs 能合成、重塑细胞外基质以及产生多种调节因子，在肿瘤的发生、侵袭、转移、血管生成，甚至免疫逃逸以及耐药方面起到了重要的促进作用[51, 52]。星状细胞是发现于胰腺和肝脏中的储存有脂滴的独特成纤维细胞[53]，活化的胰星状细胞 (pancreatic stellate cells, PSCs) 是胰腺 CAFs 的主要类型，可以为肿瘤细胞提供丰富的胆固醇 (图 1)。PSCs 被胰腺癌细胞诱导为 CAFs 时分泌了大量包含 CE 在内的脂质，胰腺癌细胞将这些脂质摄入胞内用于新陈代谢与生长、增殖[54]。人源 CAFs 通过释放外泌体向肿瘤细胞提供其所需的脂质、三羧酸循环中间产物等一系列代谢物，这些代谢物被用于肿瘤细胞的增殖、初期代谢、以及补充三羧酸循环代谢物的水平[55]，还能增加细胞膜的流动性促进癌细胞转移[56]。

4 胰腺癌细胞胆固醇代谢重编程的调控机制

胆固醇是维持细胞膜完整性、流动性所必需的物质，也是类固醇激素、胆汁酸和特定维生素 (如维生素 D) 的前体，具有极重要的生理功能和细胞毒性，因此胆固醇的稳态受到严格调控[18](图 2)。大多数哺乳动物细胞通过内源性合成或外源性摄取来获取胆固醇[57]。胆固醇的内源性合成途径是甲羟戊酸途径，甾醇反应元件结合蛋白 (sterol regulatory element-binding proteins, SREBPs) 可通过调节脂肪酸合成酶 (fatty acid synthase, FASN)、低密度脂蛋白受体 (low-density lipoprotein receptor, LDLR)、HMGCR 的基因转录，促进胆固醇的内流和内源合成，上调脂代谢水平。外源性摄取途径则通过 LDLR 介导的内吞作用从胞外摄取富含 CE 的低密度脂蛋白；此外，甾醇 O- 酰基转移酶 (sterol O-acyltransferases，SOATs，又名 ACATs) 将 FC 转化为 CE，存储在脂滴中供细胞随时调取。细胞内胆固醇水平通过合成、摄取和向胞外流出来实现平衡。肝受体 X (liver X receptors, LXRs) 充当胆固醇稳态感受器的角色，能激活 ABCA1、ABCG1 的转录，促进胆固醇外流，并诱导 LDLR 降解蛋白 (inducible degrader of LDLR, IDOL) 表达，促进 LDLR 的降解，减少胆固醇的摄取。正常情况下细胞内过高的 FC 水平会造成内质网应激并对 SREBPs 产生负反馈，抑制胆固醇和其他脂质的生成与内流。在胰腺癌细胞中，这个负反馈调节被解除，SREBPs、LDLR、SOAT1 表达明显上调，而 LXRs 表达明显降低，肿瘤细胞的胆固醇生成与获取不再受到限制 (图 3)。

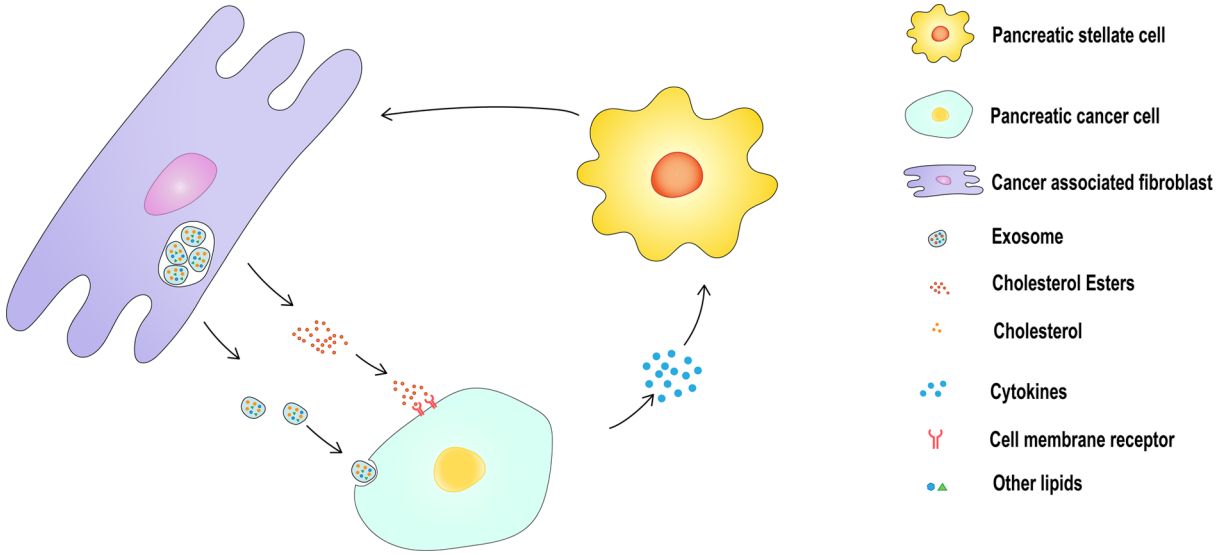

图 1. 肿瘤相关成纤维细胞为胰腺癌提供大量脂质及胆固醇

Fig. 1. Cancer associated fibroblasts provide large amounts of lipids and cholesterol to pancreatic cancer. Pancreatic stellate cells secrete a large number of lipids including cholesterol esters when induced by pancreatic cancer cells to become cancer associated fibroblasts, and pancreatic cancer cells ingest these lipids into the cells for metabolism, growth, and proliferation.

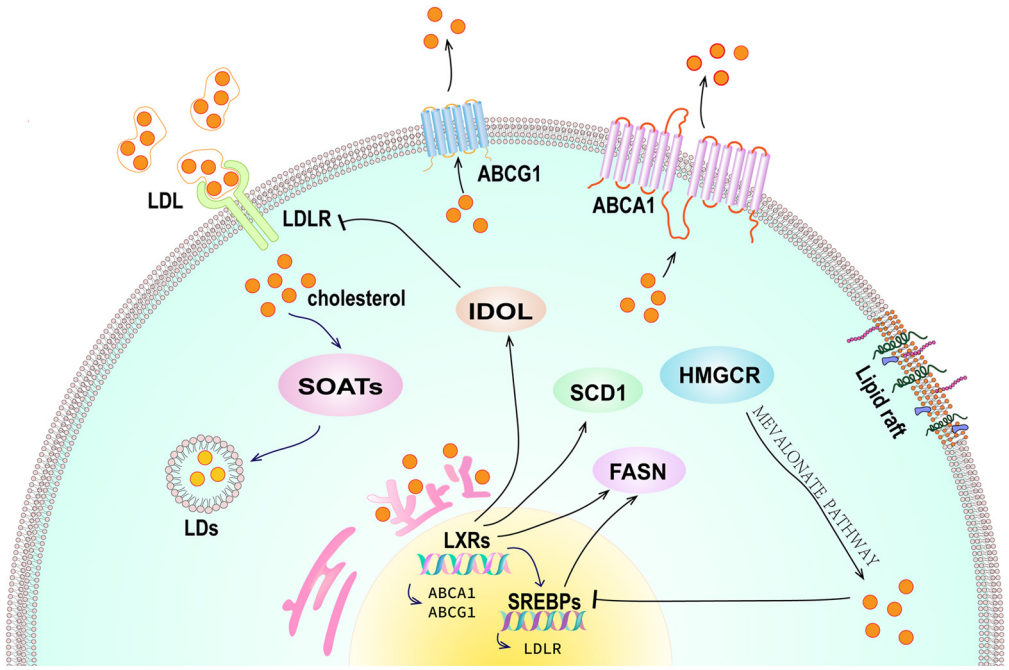

图 2. 正常细胞中胆固醇代谢

Fig. 2. Cholesterol metabolism in normal cells. Normal cellular cholesterol metabolism is strictly regulated. SREBPs can promote the influx and endogenous synthesis of cholesterol by regulating FASN, LDLR, HMGCR, and LDLR-mediated endocytosis to take CE-rich LDL from the extracellular environment. SOATs convert FC into CE, which is stored in lipid droplets for cells to retrieve at any time. LXRs can activate the transcription of ABCA1 and ABCG1 to promote cholesterol outflow. Inducing IDOL expression promotes LDLR degradation and reduces cholesterol uptake. Normally too high FC levels in cells cause endoplasmic reticulum stress and negative feedback to SREBPs, inhibiting the production and influx of cholesterol and other lipids. SREBPs: sterol regulatory element-binding proteins; SOATs: sterol O-acyltransferases; LDs: lipid droplets; LXRs: liver X receptors; LDL: low-density lipoprotein; LDLR: low-density lipoprotein receptor; IDOL: inducible degrader of LDLR; FC: free cholesterol; CE: cholesterol esters; SCD1: stearoyl-CoA desaturases 1; ABCA1: ATP binding cassette transporter A1; ABCG1: ATP binding cassette transporter G1; HMGCR: 3-hydroxy-3-methylglutaryl coenzyme-A reductase.

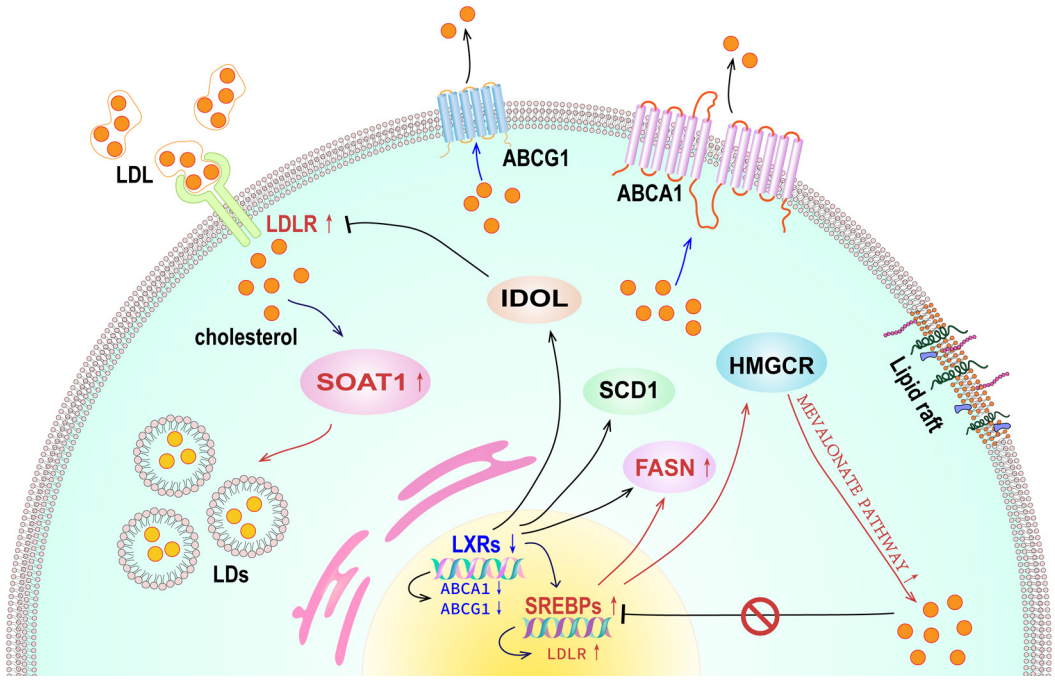

图 3. 胰腺癌细胞胆固醇代谢重编程

Fig. 3. Cholesterol metabolism reprogramming in pancreatic cancer cells. Normally too high FC levels in cells cause endoplasmic reticulum stress and negative feedback to SREBPs, inhibiting the production and influx of cholesterol and other lipids. In cancer cells, this negative feedback regulation is lifted, the increase of FC does not cause endoplasmic reticulum stress, the expression of key proteins SREBPs, LDLR and SOAT1 that regulate cholesterol production, uptake and esterification is significantly upregulated, while the expression of LXRs that inhibit cholesterol uptake and promote cholesterol outflow is significantly reduced, and the cholesterol production and acquisition of tumor cells are no longer restricted. The abbreviations are the same as those in Fig. 2. Red arrows represent protein or gene upregulation, and blue arrows indicate inhibition.

4.1 SREBPs介导胆固醇的生成

SREBPs 是调节哺乳动物体内脂质稳态的关键转录因子，可以激活胆固醇生成的所有基因 [58]。SREBPs 在哺乳动物中有 SREBP1a、SREBP1c 和 SREBP2 三种亚型，三者在功能上有一定的重合。SREBP1 主要通过调控 FASN、ACC、ACLY、硬脂酰辅酶 A 去饱和酶 1 (stearoyl-CoA desaturases 1, SCD1)、LDLR 等基因的表达，影响三羧酸循环途径，促进脂质的从头合成，进而调节胆固醇和脂肪酸的合成与摄入。SREBP2 可以诱导 LDLR 与 HMGCR 基因的表达，促进胆固醇的合成与摄取 [59]。多项临床数据显示，SREBP1 在人胰腺癌的组织和细胞系中均过表达 [60]，这往往象征着不良的生存预后 [61]。动物实验发现 SREBP1 的缺失使瘤重降低，敲除或抑制 SREBP1 基因可以抑制胰腺癌细胞的增殖并诱导凋亡 [61]。这或许与 SREBP1 能调控胰腺癌细胞中的脂质生成酶 ACC、FASN 以及 SCD1 的水平进而介导胰腺癌细胞脂质的从头合成途径有关。

在胆固醇的摄取方面，SREBP1 通过与 SRE-I 结合激活 LDLR 基因的转录，调节细胞内的胆固醇水平 [62]。细胞中的甾醇耗尽时 SREBP1 被激活，上调 LDLR 基因的转录，使细胞对低密度脂蛋白的摄取增加；若细胞内甾醇水平升高，SREBP1 活性则降低，LDLR 转录随之减少，细胞获取的低密度脂蛋白减少。这种反馈调控机制既保持了细胞的低密度脂蛋白的供应，又避免了胆固醇过度积累带来的细胞毒效应。

SREBPs 对脂代谢的调节与多种抗肿瘤药物的耐药以及机体免疫状态有密切关联。抑制 SREBPs 可以延缓肿瘤细胞耐药，提高治疗效果。研究发现顺铂耐药的癌细胞中 SREBP1 依赖的相关胆固醇代谢基因表达异常上调，阻断 SREBP1 信号则可增加癌细胞对顺铂的敏感性 [63]。SREBPs 抑制剂法图他汀有利于缓解 P53 突变的肿瘤细胞对多西他赛产生的耐药 [64]。此外，靶向抑制 SREBP1 还可以增强肿瘤细胞对安罗替尼的敏感性 [65]，逆转 EGFR 突变耐

药的非小细胞肺癌对吉非替尼的耐药[66]。Treg细胞通过上调SREBPs重编程脂代谢以获得更多脂质，维持其在肿瘤微环境中抗肿瘤免疫的功能，SREBPs的活性因子缺失不仅可以抑制肿瘤增长，还能增强PD-1的表达促进免疫治疗的功效。靶向SREBPs干扰脂质合成与代谢信号可以引起抗肿瘤免疫反应[67]。

4.2 SOAT1介导胆固醇的存储

SOAT1 (又名ACAT1)是介导胆固醇存储的关键靶点[68]。胰腺癌患者SOAT1的高表达与较差的生存期有明显关联[31]。SOAT1将FC酯化成为惰性的CE，存储在脂滴中，这样既可以保持高代谢活性，又可以避免过量的FC积累引起胆固醇调节的负反馈机制与细胞毒性。胰腺癌细胞中存在大量的脂滴，其主要成分之一就是CE[69]，而胰腺癌细胞中CE的异常积累正是由SOAT1介导的。胰腺癌对胆固醇酯化的阻断高度敏感，抑制或敲除SOAT1可干扰胆固醇的酯化，显著抑制胰腺癌的体外增殖与体内进展，使得小鼠的生存期得到大幅延长[70]。

此外，CE的积累还促使胰腺癌化疗耐药、干扰T细胞的抗肿瘤活性。胰腺癌的吉西他滨耐药细胞中存在CE异常积累的现象，SOAT1抑制剂能逆转吉西他滨耐药，抑制PDAC耐药细胞增殖[32]。SOAT1的抑制与CE的耗尽之所以能提高癌细胞对药物的敏感性或许与PI3K/AKT通路的调节[71]或小窝蛋白依赖的胆固醇外流途径受到抑制有关[72]。当胆固醇酯化受阻时免疫系统的抗肿瘤活性增强[73]。抑制CAR-T细胞胆固醇酯化酶SOAT1，能增强其对间皮素表达阳性的胰腺癌细胞的抗肿瘤作用，使小鼠肿瘤生长缓慢[44]。其中的机制或许与SOAT1受到抑制后FC上升干扰了胆固醇稳态导致SREBP1[74]和LDLR[30]表达水平降低，以及caveolin-1/MAPK通路下调，使肿瘤的侵袭性降低有关[31]。

4.3 LDLR介导胆固醇的摄取

LDLR是维持胆固醇稳态的关键受体，通过内吞作用摄取低密度脂蛋白为细胞提供胆固醇[75]，是脂蛋白携带丰富胆固醇进入癌细胞的主要途径[34]。LDLR基因的过表达已被证实是多种癌症的不良预后因素[76–78]，因此被认为是可用于肿瘤治疗的靶点[79]。在人PDAC组织中，LDLR基因在疾病的各阶段都高表达，且与疾病复发的高风险具有正相关性[34]。在正常情况下，低密度脂蛋白进入细胞之后，会抑制HMGCR的基因表达，并降低LDLR的生成，从胆固醇的生物合成与外源摄取两方面进行负反馈调节[80]。然而肿瘤细胞可通过过表达SREBPs上调LDLR解除获取外源性胆固醇的限制[23]，这种外源性获取胆固醇的途径绕过了他汀类药物的作用[64]并造成了细胞内外胆固醇含量的巨大差异，这或许是他汀类药物在癌症临床治疗中效果不稳定的原因。沉默LDLR能改变胆固醇的分布，使CE减少而FC增加，降低ERK1/2生存通路的激活，抑制PDAC的增殖与克隆能力，诱导细胞凋亡，提高胰腺癌对化疗药物的敏感性[34]，其中的机制或许与FC引起的细胞毒作用有关，但LDLR的沉默并不会引起HMGCR的表达变化，这说明胰腺癌细胞为获取胆固醇而进行的代谢重编程解除了胆固醇的摄取与合成途径之间的负反馈调节。

4.4 LXRs阻止胆固醇外流

LXRs的激活可抑制脂质供给，干扰肿瘤代谢和微环境、阻滞细胞周期并激活凋亡途径，具有显著的抗癌能力[81]。LXRs充当着胆固醇稳态传感器的角色，能促进胆固醇的逆向转运并抑制胆固醇的摄取。LXRs被其多种内源性配体激活后，上调胆固醇流出蛋白ABC转运蛋白ABCA1、ABCG1，促进细胞内胆固醇的流出，并且诱导IDOL转录从而靶向降解LDLR[82]，减少低密度脂蛋白的摄取，进而降低细胞内胆固醇水平。LXRs有LXRα (NR1H3)和LXRβ (NR1H2)两种亚型，在胰腺正常组织及癌组织中表达的主要是LXRβ，在PDAC组织的细胞核与细胞质中存在异常定位[83]。研究表明LXRs在胰腺癌患者肿瘤组织中的表达明显低于癌旁正常组织，LXRβ的降低更为明显[84]，这说明胰腺癌的异常旺盛的脂代谢与LXRβ相关性更高。激动LXRs能够阻断PDAC细胞周期，抑制PDAC细胞的增殖和克隆形成，与吉西他滨联用还可以增强抗肿瘤作用[85]。LXRβ的抗肿瘤作用是通过调节细胞内胆固醇水平实现的，LXRs激动剂可以抑制LDLR的表达[86]、上调ABCA1，通过消耗细胞内胆固醇选择性地杀死癌细胞[87]。

LXR-SREBP1信号通路通过调节下游的多核苷酸激酶/磷酸酶(polynucleotide kinase/phosphatase, PNKP)对胰腺癌细胞DNA修复与凋亡起到调控作用，使用LXRα抑制剂雷公藤内酯酮可以有效抑制胰腺癌细胞的DNA修复并促进凋亡[84]。PNKP是一种DNA单双链修复酶，靶向敲除或抑制PNKP都会使肿瘤细胞易于凋亡且对辐射和DNA损伤药物更加敏感[84]。

此外，胆固醇代谢与免疫和炎症也有着密切的联系，LXRs 是胆固醇代谢与免疫调节的中间连接点，可以直接或通过脂代谢调节的方式间接调控免疫反应。LXR 激动剂 N,N- 二甲基 -3-β 羟胆碱可以下调 LXR 依赖的基因网络，增加 $CD4^+$ 和 $CD8^+$ 效应 T 细胞并减少浸润性髓源性抑制细胞，延缓肿瘤进展和纤维化，改善免疫监测 [88]。LXR/ApoE 信号可降低抑制肿瘤免疫的髓系抑制细胞水平，驱动细胞毒性 T 淋巴细胞，增强抗肿瘤免疫作用 [89]。LXR-ABAC1 轴的抗炎作用可将胆固醇稳态与炎症调节连接起来。LXRs 通过激活 ABCA1 促进胆固醇的外排，改变质膜成分和干扰炎症信号起到抗炎的作用 [90]。吞噬凋亡细胞可以激活 LXRs，继而激活下游 Mer 和 ABCA1、ABCG1 促进凋亡细胞的清除与胆固醇外排，另一方面也抑制炎症介质的产生，维持正常免疫状态 [91]。而抑制胰腺癌相关的炎症反应又能进一步防止肿瘤的侵袭与转移 [92]。

LXRs 在调节细胞代谢方面作用广泛，不仅促进细胞内胆固醇的外排，也能促进脂质的生成。LXRs 能上调控制脂肪酸合成的 SREBP1c [93]、直接诱导脂肪从头合成的中心 ——FASN [94] 以及合成单不饱和脂肪酸所必需的限速酶 ——SCD1 的表达 [95] 促进脂质合成，因此 LXRs 的激活能降低胞内胆固醇水平，也可能触发胆固醇的合成，并非总是抗肿瘤的。研究发现抑制 LXR 活性亦能起到抗肿瘤作用。BET 溴域抑制剂对胰腺癌的生长抑制和对吉西他滨的增敏作用就是通过抑制 LXR/RXR 途径的激活以及抑制胆固醇生物合成和脂质代谢的两种蛋白 (HMGCS2 和 APOC1) 产生的 [96]。另外，LXR 的反向激动剂也能抑制脂代谢及糖代谢基因表达诱导癌细胞凋亡 [97]。虽然 LXRs 的抑制不利于胆固醇的流出，但是间接减少了其他脂质的合成，从侧面抑制了肿瘤细胞的脂代谢重编程，这表明脂代谢重编程具有高度复杂性且对肿瘤疾病有重要影响。

5 靶向胆固醇代谢药物在胰腺癌干预中的应用(图4)

5.1 他汀类药物

甲羟戊酸途径是胆固醇的从头合成途径，但受到限速酶 HMGCR 的限制，HMGCR 能促进癌细胞增殖、迁移、转移和耐药 [98]，被认为是癌症的候选代谢基因 [64]。HMGCR 能够增强腺泡细胞的可塑性，促进胰腺肿瘤的发展 [99]，抑制 HMGCR mRNA 的表达可以下调包括胆固醇在内的多种脂质水平，降低胰腺癌细胞活力与侵袭性 [100]。他汀类药物是 HMGCR 的竞争性抑制剂，可以通过抑制胆固醇的从头合成降低胆固醇水平，在胰腺癌的治疗方面颇具潜力。阿托伐他汀的使用可以调节影响脂代谢的关键通路 PI3K/AKT 通路，抑制胰腺上皮内肿瘤向胰腺癌的进展 [101]，具有降低罹患胰腺癌风险的潜在作用。氟伐他汀和洛伐他汀能抑制表皮生长因子诱导的胰腺癌侵袭与转移 [102]，他汀类药物的应用还能提高癌细胞对化疗药的敏感性 [103]。多项临床研究及大型 META 分析显示他汀类药物治疗能降低胰腺癌发病风险 [104–114]。前瞻性研究显示，被诊断为胰腺癌之前两年定期服用他汀类药物的患者，中位生存率有一定提高 [115]。他汀类药物的使用可以降低胰腺癌患者的死亡风险 [116]。

但是他汀类药物的抗胰腺癌作用仍然存在争议，一些流行病分析显示他汀类药物的使用与胰腺癌风险无关 [117, 118]，或者认为他汀类药物对胰腺癌的保护作用与胆固醇的水平无关 [116]。这是由于他汀类药物具有多种抗肿瘤机制 [119]，且胆固醇代谢调节机制十分复杂。有研究发现他汀类药物的应用会促进胰腺癌上皮间质转化的发生 [120]，但进一步研究发现，他汀类药物能通过加强间充质样细胞状态来降低细胞可塑性，这种状态虽然一定程度上增加了癌细胞的转移种植能力，但是由于癌细胞的可塑性受到抑制无法恢复到类似上皮的细胞状态，他汀类药物的应用最终能够抑制肿瘤的转移 [121]。

5.2 SREBP抑制剂

SREBPs 在脂代谢的各个环节都扮演着重要的角色，在肿瘤发生、发展中的作用越来越受到重视，被认为是胰腺癌治疗潜在的重要靶点。近年来具有抗肿瘤潜力的 SREBP 抑制剂如法图他汀、PF429242、白桦酯醇、白藜芦醇等，受到越来越多的关注。

法图他汀属于非固醇合成的二芳噻唑衍生物，可以与固醇调节元件结合蛋白裂解激活蛋白 (SREBP cleavage activating protein, SCAP) 结合，抑制 SCAP 将 SREBPs 转运到高尔基体的能力 [122]，抑制肿瘤的增殖、侵袭与转移 [123]。法图他汀可通过减少脂质生成蛋白、抑制 P53 的突变抑制胰腺癌细胞的增殖 [124]，还可抑制上皮间质转化，降低癌细胞侵袭性 [125]。

PF429242 是可逆的竞争性位点 1 蛋白酶 (site-1 protease, S1P) 抑制剂，能降低 SREBP mRNA 水平，

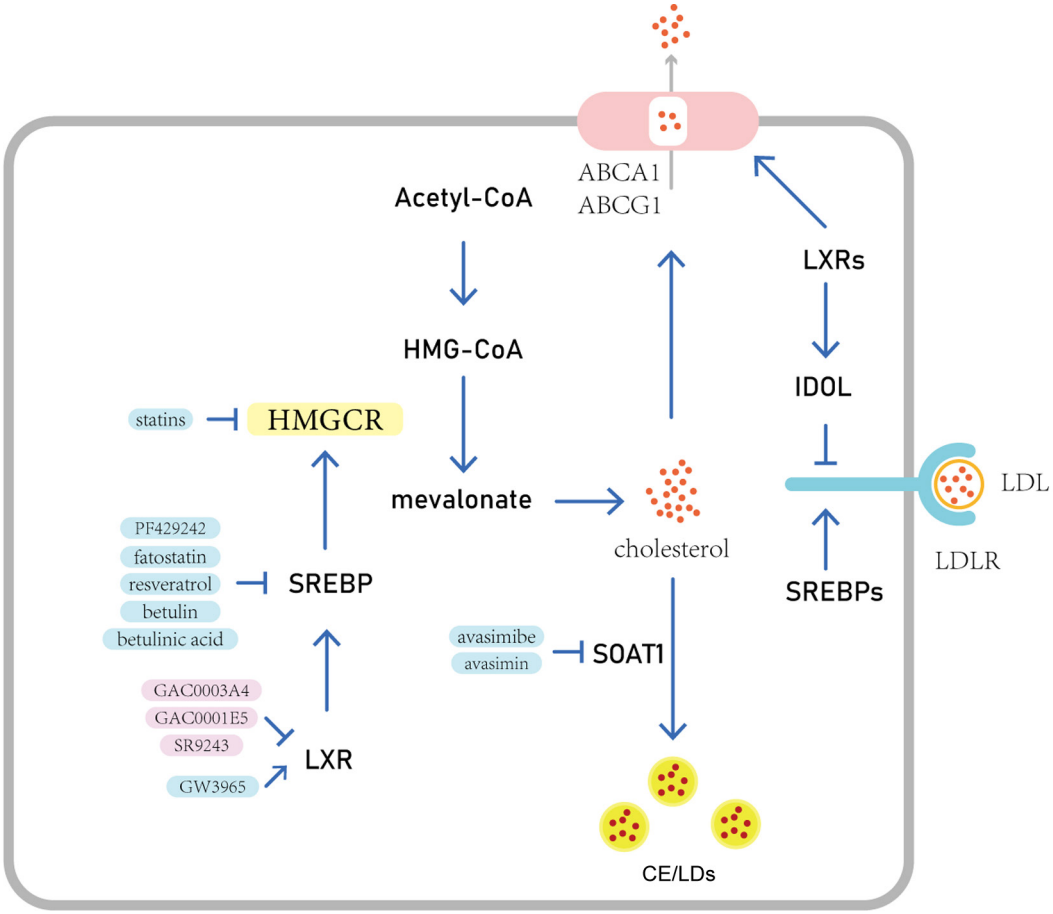

图 4. 胆固醇代谢途径的重要靶点及其抑制剂/反向激动剂

Fig. 4. Important targets of cholesterol metabolism pathways and their inhibitors/reverse agonists. SREBP: sterol regulatory element-binding protein; SOAT1: sterol O-acyltransferase 1; LXR: liver X receptor; LDLR: low-density lipoprotein receptor; IDOL: inducible degrader of LDLR; CE: cholesterol esters; LDs: lipid droplets; ABCA1: ATP binding cassette transporter A1; ABCG1: ATP binding cassette transporter G1; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme-A; HMGCR: HMG-CoA reductase.

抑制 SREBPs 的成熟[126]，减少脂质生成，对胰腺癌细胞具有选择性细胞毒性[124]。

白桦脂醇是一种天然的五环三萜类化合物，它通过促进 SCAP 和胰岛素诱导基因 1 (Insig 1) 之间的相互作用，特异性地抑制 SREBPs 的成熟，可降低胆固醇的生物合成[127]，能抑制多种癌细胞的增殖、侵袭并诱导凋亡[128]。白桦脂醇的氧化物白桦脂酸联合密曲霉素 A 经腹腔注射可抑制胰腺癌细胞增殖、侵袭，能有效阻断小鼠胰腺癌异种移植瘤的发展，且毒性低于吉西他滨[129]。白桦脂酸还能激活 AMPK 信号传导，抑制胰腺癌细胞的干性和上皮间质转化[130]。

白藜芦醇属于多酚类植物抗毒素，能通过抑制 SREBP1 增强胰腺癌细胞化疗反应，逆转吉西他滨诱导的细胞干性[131]，抑制人胰腺癌细胞增殖、转移、侵袭并促进凋亡[132]。白藜芦醇还能抑制缺氧状态下的 PSCs 激活，阻止胰腺癌细胞与 PSCs 交互作用，在一定程度上抑制上皮间质转化并促进胰腺癌细胞的凋亡[133]。

5.3 SOAT1抑制剂

阿伐麦布 (Avasimibe) 是最常用的 SOAT1 抑制剂[134]。阿伐麦布通过增加 FC 实现对 AKT 信号通路的下调，逆转胰腺癌细胞对吉西他滨的耐药[32]。Avasimin 是阿伐麦布的水溶剂型，能够降低多种癌细胞系中脂滴的 CE 储备，通过提高细胞内的 FC 水平，抑制胰腺癌、肺癌、前列腺癌[69]、肝癌[135]等多种癌细胞的增殖、迁移并促进其凋亡。

5.4 LXR配体

LXRs 是癌症相关的关键基因，LXR 对癌细胞的影响涉及胆固醇转运、脂代谢、糖代谢以及炎症

和免疫反应。LXRs 的激动剂对 PDAC 有抗增殖、促凋亡作用。GW3965 是 LXRs 的合成配体，可通过激活 LXR 信号通路，介导肿瘤的脂代谢产生抑制肿瘤细胞增殖和促进凋亡的作用。研究显示，GW3965 能抑制 PDAC 细胞的增殖与克隆形成，将 PDAC 细胞阻滞于 G1/G0 期 [85]。这或许与 Skp2 和 EGFR 的下调有关。GW3965 可以诱导 IDOL 引起 LDLR 的降解并使 ABCA1 表达上升，促进胆固醇外流，进而引起癌细胞凋亡 [23]。

令人意外的是，下调 LXRβ 的表达可以抑制参与细胞周期和生长因子传导的蛋白功能，同样能显著阻断 PDAC 细胞增殖，使 LXR 配体治疗无效 [85]。进一步研究发现新型 LXR 配体 GAC0001E5 和 GAC0003A4 通过改变受体构象和增强辅助抑制物向 LXR 复合体的募集而发挥反向激动剂的作用，也对胰腺癌细胞产生生长抑制作用 [136]。另一种 LXR 的反向激动剂 SR9243 可以诱导 LXR- 辅阻遏子相互作用，提高癌细胞对化疗药物的敏感性，通过抑制生脂基因和有氧糖酵解基因表达选择性地诱导肿瘤细胞凋亡且不引起体重减轻、肝脏毒性和炎症 [97]。鉴于 LXR 调控着下游的众多脂质代谢的关键基因，以 LXR 为靶点的药物虽然抗癌效果明显，但作用机制较为复杂，在临床上用作抗肿瘤药物仍有较长的过程。

6 小结

肿瘤细胞代谢重编程是维持肿瘤生长、增殖的必要条件，抑制胆固醇代谢能够选择性地促进癌细胞凋亡而对正常细胞无害 [69]，靶向胆固醇代谢是胰腺癌临床治疗的新思路。

高脂、高胆固醇饮食是胰腺癌的高危因素，能促进胰腺癌发生。肿瘤细胞胆固醇代谢重编程是网状的调节过程，涉及到胆固醇合成、摄取、转运、存储等多个环节，为胰腺癌细胞的增殖、侵袭、转移提供了必要原料，促进了肿瘤的耐药与免疫抑制，支持了胰腺癌的进展，增加了治疗的难度。CAFs 与胰腺癌的交互作用是癌细胞获取脂质的特殊途径，是胰腺癌细胞胆固醇代谢重编程的主要方面。

需要特别注意的是，胆固醇代谢有着复杂的反馈调控机制，对胰腺癌的影响机制也十分复杂。在动物水平和细胞层面的研究中抑制细胞胆固醇代谢的抗肿瘤作用明确，而临床实践中高血清 TC 却未必是胰腺癌的危险因素 [137–139]，提示血清胆固醇难以反映肿瘤胆固醇代谢情况，或许是由于肿瘤的胆固醇代谢重编程主要体现在细胞层面。他汀类药物的应用对胰腺癌也并非总是有利的。例如，他汀类药物对胆固醇的合成途径具有抑制作用，但是胆固醇的合成不足促使 LDLR 表达上调，增加胆固醇外源摄取 [140]，这虽然能降低血清中胆固醇的含量，却会使细胞内的胆固醇增加，这显然对肿瘤有促进作用。不同的肿瘤细胞对他汀类药物的敏感性也不同，甚至他汀类药物的应用会使某些癌细胞 HMGCR 的表达上调而产生耐药性 [141]。另一方面，在某些细胞中他汀类药物对 HMGCR 的抑制作用也有可能激活 SREBP2，使得 HMGCR 进一步上调而抵消原本的抑制作用 [142]，甚至使得癌细胞中的甲羟戊酸途径被激活 [143]。

胆固醇代谢调节的复杂性使单一靶点药物难以达到理想的效果，针对胆固醇代谢的多靶点联合治疗或许是更有前途的方向。本文梳理了胆固醇代谢重编程的关键靶点在肿瘤胆固醇代谢中的重要作用及其常见靶向药物，为胰腺癌胆固醇代谢重编程的进一步研究提供参考。

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