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胆固醇在头颈部鳞状细胞癌中的研究进展

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【摘要】头颈部鳞状细胞癌(HNSCC)是源于口腔、咽部及喉部黏膜上皮的高度侵袭性恶性肿瘤,其发生发展与吸烟、饮酒、人乳头瘤病毒(HPV)感染等风险因素密切相关。尽管手术、放疗及靶向治疗等综合治疗策略不断升级,HNSCC患者仍面临局部复发、远处转移和治疗耐药等临床难题。近年来,肿瘤代谢重编程被认为是HNSCC进展的核心驱动因素之一,其中胆固醇代谢作为脂质代谢的关键分支,逐渐成为肿瘤生物学研究的前沿热点。本综述重点关注胆固醇在HNSCC的功能研究,以期为该疾病的预防及治疗策略开发提供新的理论依据。

【关键词】头颈部鳞状细胞癌; 靶向治疗; 代谢重编程; 胆固醇

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Research progress on cholesterol in head and neck squamous cell carcinoma

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【Abstract】Head and neck squamous cell carcinoma (HNSCC) is a highly aggressive malignant tumor that originates from the mucosal epithelium of the oral cavity, pharynx, and larynx, and its occurrence and development are closely associated with risk factors such as smoking, alcohol consumption, and human papillomavirus (HPV) infection. Despite the optimization of comprehensive treatment strategies such as surgery, radiotherapy, and targeted therapy, patients with HNSCC still face clinical challenges such as local recurrence, distant metastasis, and treatment resistance. In recent years, tumor metabolic reprogramming has been recognized as one of the core drivers of HNSCC progression, and cholesterol metabolism, as a key branch of lipid metabolism, has gradually emerged as a research forefront of tumor biology. This review focuses on the functional studies of cholesterol in HNSCC, and aims to offer new theoretical insights into the prevention of this disease and the development of therapeutic strategies.

【Keywords】Head and neck squamous cell carcinoma; Targeted therapy; Metabolic reprogramming; Cholesterol

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0 引言

头颈部鳞状细胞癌 (Head and Neck Squamous Cell Carcinoma, HNSCC) 是一类起源于头颈部黏膜上皮的恶性肿瘤, 主要累及口腔、咽部及喉部等区域, 病理特征为鳞状上皮细胞异常增殖, 具有高度侵袭性和异质性^[1-4]。HNSCC 占有头颈部癌症的 90% 以上, 是全球第六大常见癌症, 其发生发展与吸烟、饮酒、人乳头瘤病毒 (Human Papillomavirus, HPV) 感染等风险因素密切相关。近年来, 欧美国家 HPV 感染相关 HNSCC 占比上升, 亚洲地区则以烟酒相关类型为主^[5-6]。早期 HNSCC 患者多采取手术治疗, 局部晚期患者或术后辅助治疗采用放疗和化疗^[7-8]。HPV 阳性患者对放疗敏感性更高, 铂类和紫杉烷类可作为化疗药物的基础与放疗联用^[9-12]。靶向治疗、免疫治疗及肿瘤微环境调控作为新兴疗法, 在临床试验中显示出潜力^[9, 11, 13-16]。尽管综合治疗策略不断优化, 但患者仍面临局部复发、远处转移和治疗耐药等挑战, 总体 5 年生存率为 50%~60%, 晚期或复发患者的生存率显著降低^[14, 17-19]。因此, 寻找在调控 HNSCC 发生发展中发挥关键作用的生物标志物, 并探讨其用于诊断和精准靶向治疗的转化潜力十分重要。

胆固醇代谢在 HNSCC 的发生发展及治疗中具有重要作用。一是促进肿瘤生长和侵袭, 作为 HNSCC 的重要亚型, 口腔鳞癌中富含胆固醇的膜结

构参与肿瘤侵袭转移, 而 HNSCC 患者特征性低胆固醇可能与肿瘤微环境中胆固醇的异常消耗密切相关; 二是与临床预后相关, 高水平脂蛋白是 HNSCC 的独立预后危险因素, 载脂蛋白和低密度脂蛋白胆固醇水平则与生存期延长呈正相关关系, 基于胆固醇相关基因的风险特征模型可有效预测 HNSCC 患者的生存率; 三是影响治疗耐药性, 靶向与胆固醇代谢相关的固醇调节元件结合蛋白 1、脂肪酸合酶等分子, 可逆转 HNSCC 治疗耐药性。也有研究^[20-24]发现, 脂质代谢重编程是 HNSCC 中的一种非遗传耐药机制, 可能是克服抗表皮生长因子受体 (Epidermal Growth Factor Receptor, EGFR) 治疗获得性耐药的潜在靶点。明确胆固醇在 HNSCC 中的作用及其分子机制, 可能为诊疗提供新思路 (见图 1)。

1 胆固醇的生物学功能及其与肿瘤代谢失衡的关系

1.1 胆固醇的生物学功能

胆固醇作为类脂的重要组成成分, 对维持细胞正常的生理功能、参与物质代谢至关重要, 主要体现在三个方面。一是调节脂质运输与心血管系统稳态。胆固醇以高密度脂蛋白、低密度脂蛋白 (Low Density Lipoprotein, LDL) 和极低密度脂蛋白形式存在于循环系统, 分别承担不同的运输功能, 其水平异常会增加心血管疾病风险^[25-26]。二是维持细胞膜动态平衡。胆固醇的疏水性部分嵌入脂质双层,

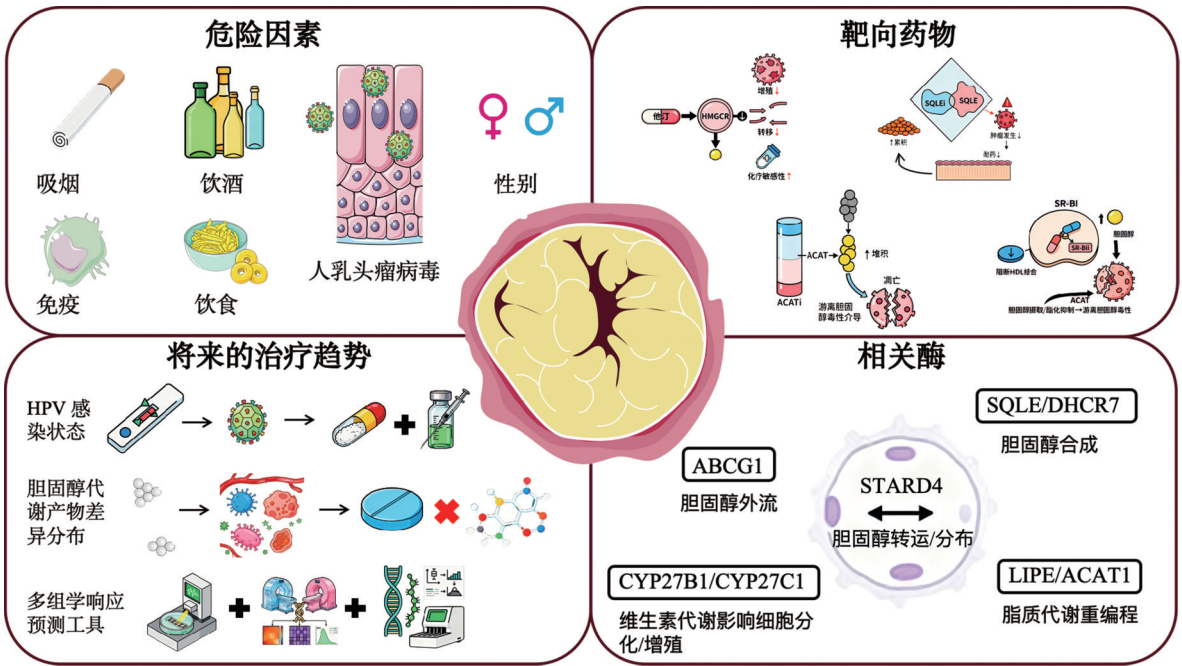


图 1 HNSCC 的易感因素、胆固醇靶向药物、胆固醇相关酶类及未来治疗方向
Figure 1 Susceptible factors, cholesterol-targeting drugs, cholesterol-related enzymes, and future therapeutic directions in HNSCC

增强细胞膜结构完整性和坚固性,还可与特定脂质和蛋白质形成脂筏,保障受体和信号传导分子的有效互动^[27-29]。三是作为类固醇激素的前体分子。胆固醇在线粒体内细胞色素P450酶系催化生成孕烯醇酮,进而通过组织特异性代谢途径转化为各类激素,其代谢紊乱可导致内分泌失调、免疫异常等多系统功能紊乱^[30-32]。

1.2 胆固醇代谢异常与肿瘤代谢重编程

胆固醇与肿瘤的关系逐渐成为肿瘤生物学研究热点。胆固醇稳态失衡可通过多种机制参与肿瘤恶性表型塑造,这与异常的脂质代谢联系密切。二者共享部分酶和代谢中间体,胆固醇代谢水平直接影响脂蛋白组成和功能,胆固醇过量积累或代谢紊乱可能诱导氧化应激,并通过调节核受体影响脂质代谢^[33-34]。这些异常的脂质代谢与致癌信号整合调节,促进癌细胞的增殖、生存和迁移,成为癌症潜在的治疗靶点^[35]。

在机体层面,脂质代谢紊乱可引发一系列级联反应:在肝脏,脂质代谢紊乱导致甘油三酯输出受阻,引发非酒精性脂肪性肝病,可能向肝细胞癌进展;在心血管系统,升高的LDL和氧化修饰低密度脂蛋白(oxidized Low Density Lipoprotein, ox-LDL)通过脂质毒性和氧化应激驱动动脉粥样硬化;在胰腺,胰岛 β 细胞的脂毒性会损害胰岛素分泌,促发2型糖尿病,其伴随的高胰岛素-IGF轴又能进一步强化促癌信号^[36-38]。这些系统性改变创造的慢性炎症状态、免疫抑制环境及激素水平波动,为肿瘤的发生与发展提供条件^[39-41]。在HNSCC中,高胆固醇、高LDL/ox-LDL和高“重新脂合成”活性共同驱动肿瘤增殖、侵袭、免疫逃逸和耐药^[42-43]。分子机制上,脂质代谢相关基因的异常表达提供能量与膜合成原料,脂质代谢重组通过增强上皮-间质转化(Epithelial-Mesenchymal Transition, EMT)途径促进转移。例如,长链酰基辅酶A合成酶4介导脂肪酸激活、miR-181a-5p/PPAR信号轴失调等,还可通过改变肿瘤微环境促进免疫抑制,诱导治疗抵抗^[42,44-47]。例如氧化脂质代谢相关长链非编码RNA的异常表达影响免疫细胞浸润状态,氨基酸代谢物犬尿氨酸的上调可增加免疫检查点分子表达促进HNSCC的免疫逃逸;脂质代谢驱动的铁死亡抑制蛋白1高表达与顺铂耐药相关,通过抵抗铁死亡致治疗受阻;过氧化物酶体增殖物激活受体 α 相关基因特征与抗EGFR治疗抵抗相关^[21,48-49]。综上,靶向脂质代谢关键环节有望成为改善HNSCC治疗策略的潜在突破口。

2 胆固醇在HNSCC中的功能研究

2.1 HNSCC膜结构与胆固醇动态

HNSCC细胞需要大量胆固醇进行细胞膜生物合成,这一过程可能通过LDL受体介导的内吞途径实现^[50-51]。胆固醇作为细胞膜脂筏的核心组分,可通过动态调节膜区室化影响肿瘤生物学行为,促进小窝蛋白1亚细胞定位变化,激活Rac1/CK2 α 信号级联反应,驱动侵袭性伪足形成并增强细胞迁移能力^[52-53]。HNSCC还可能依赖脂筏结构激活如EGFR等的跨膜受体信号,促进肿瘤细胞获得耐药表型^[54]。此外,胆固醇介导的膜的物理特性改变可形成药物渗透屏障,抑制脂质过氧化底物的跨膜扩散,影响治疗效果^[55]。

靶向膜胆固醇可能增强HNSCC的免疫治疗效果。前蛋白转化酶枯草溶菌素9在HNSCC组织中高表达且与不良预后相关。抑制或敲低该蛋白可增加肿瘤内CD8⁺T细胞浸润,减少髓系抑制细胞(Myeloid-Derived Suppressor Cells, MDSCs)积累,增强抗程序性死亡受体-1(Programmed Cell Death Protein 1, PD-1)免疫治疗的效果^[56-57]。激活肝X受体可增强ATP结合盒转运蛋白A1介导的胆固醇外流,抑制肿瘤进展^[58]。但胆固醇缺乏也可能改变HNSCC细胞系形态诱导并增加EMT标记的基因表达,形成促癌微环境^[22-23]。因此,胆固醇在HNSCC发生中起双重作用,可能取决于细胞类型和肿瘤分期。在原发口腔鳞癌细胞SCC-25中,胆固醇耗竭显著降低细胞活力、增加膜流动性,并减少EMT标志物表达;在转移性细胞HSC-3中,对细胞活力和膜流动性影响较小,但会降低迁移能力。胆固醇耗竭后,SCC-25侵袭能力增强,HSC-3侵袭能力降低,表明胆固醇代谢对不同细胞系的侵袭行为有相反作用^[22]。肿瘤发生早期或原位癌阶段,癌细胞增殖高度依赖胆固醇构建细胞膜并维持促增殖信号,胆固醇耗竭能有效抑制肿瘤生长^[20]。在晚期或已发生EMT的侵袭性肿瘤中,胆固醇缺乏可能作为一种应激信号增强癌细胞的塑性,而在晚期可切除HNSCC患者中,高总胆固醇水平与更长生存期相关^[59-62]。靶向膜胆固醇稳态已成为HNSCC治疗的重要策略^[63]。

2.2 癌基因活化与信号转导

胆固醇代谢紊乱与癌基因转录调控网络的交互作用在HNSCC中有显著组织特异性。角鲨烯环氧化物(Squalene Epoxidase, SQLE)作为胆固醇生物合成通路的关键限速酶,可通过促进胆固醇前体

累和激活 Src/PI3K/Akt 信号轴, 驱动 HNSCC 恶性进展和顺铂耐药^[64-65]。同时, SQLE 介导的胆固醇生物合成增强会导致脂筏结构重构, 形成 EGFR/HER2 受体二聚化依赖的致癌信号微环境, 持续激

活下游 MAPK/ERK 和 PI3K/Akt/mTOR 信号通路^[66]。低胆固醇微环境可通过抑制 β 2-肾上腺素受体-cAMP-PKA 信号级联, 增强细胞侵袭能力^[67]。因此, 维持胆固醇稳态至关重要 (见图2)。

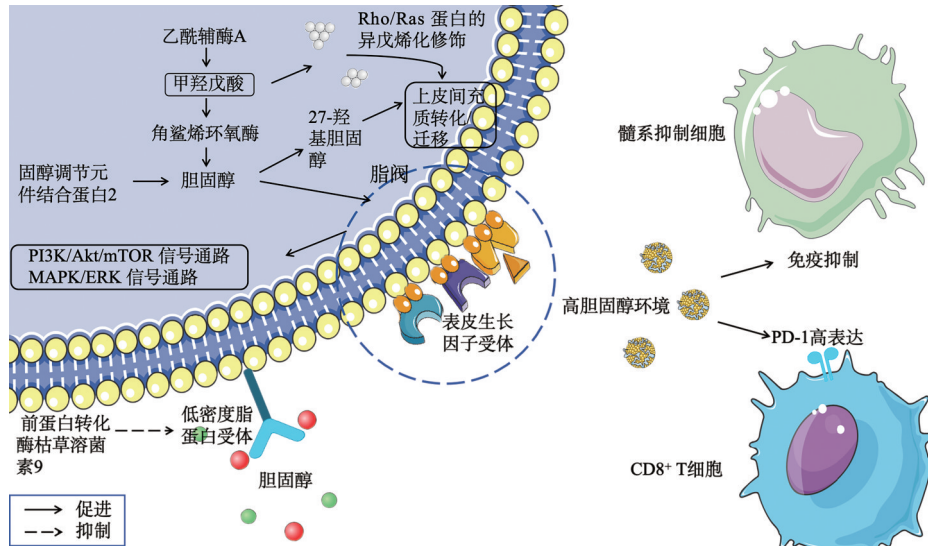


图2 胆固醇对 HNSCC 肿瘤微环境的影响

Figure 2 Effect of cholesterol on tumor microenvironment in HNSCC

在肿瘤免疫微环境中, 胆固醇积累可以抑制 T 细胞受体信号转导, 削弱抗肿瘤免疫应答。胆固醇代谢物 25-羟基胆固醇可通过激活信号转导及转录激活蛋白 6 通路促进 MDSCs 的免疫抑制功能^[68-69]。胆固醇代谢物 27-羟基胆固醇 (27-Hydroxycholesterol, 27-HC) 可诱导间质标志物表达、诱导活性氧生成、激活 MAPK 信号和 EMT 相关基因, 还能上调转化生长因子- β 1 表达, 驱动 EMT^[70-72]。在食管鳞癌模型中, 活性氧聚集与肿瘤侵袭性相关, 抗氧化剂可用于抑制 EMT 达到抗肿瘤效果^[73]。在非小细胞肺癌的鳞癌亚型中, 27-HC 表达明显增加, 可能通过雌激素受体参与肿瘤进展^[74-75]。胆固醇代谢中间体甲羟戊酸通过异戊烯化修饰 Rho 家族蛋白, 促进细胞迁移和侵袭, 与鳞癌的转移表型密切相关^[76]。

2.3 胆固醇代谢通路的关键酶

胆固醇复杂的代谢网络在 HNSCC 发生发展中具有层级化调控特征。HMG-CoA 还原酶 (3-Hydroxy-3-Methyl Glutaryl Coenzyme A Reductase, HMGCR) 作为甲羟戊酸途径的限速酶, 活性异常升高时不仅导致胆固醇超量合成, 还能通过修饰 Ras/Rho GTP 酶, 驱动细胞周期蛋白表达上调并抑制 Bax 依赖性凋亡通路, 建立促癌代谢表型^[77]。HMGCR 与 TGF- β 之间可形成正向调控环路, HMGCR 抑制剂洛伐他汀联合 TGF- β 受体激酶抑制

剂可使 HNSCC 细胞增殖明显抑制^[78]。香叶基香叶基焦磷酸合成酶 1 作为甲羟戊酸途径的关键分支酶, 在口腔鳞癌中显著表达异常, 其过表达与总生存期缩短独立相关, 可作为生物标志物^[79]。其催化生成的香叶基香叶基焦磷酸能支持细胞膜动态重构, 通过激活 mTORC1 信号轴促进肿瘤细胞增殖^[80-81]。

在胆固醇稳态调控层面, 胆固醇酯化酶如乙酰辅酶 A 乙酰转移酶 1 (Acetyl-Coenzyme A Acetyltransferase 1, ACAT1) 介导的酯化反应可在肿瘤细胞中促进胆固醇酯储存, 在 CD8⁺ T 细胞中诱导脂滴异常积累, 抑制其效应功能。ACAT1 抑制剂可能通过减少酯化胆固醇恢复 T 细胞活性, 增强免疫治疗效果^[82]。7-脱氢胆固醇还原酶 (7-Dehydrocholesterol Reductase, DHCR7) 作为胆固醇合成通路的终末酶, 在 HNSCC 中被列为关键脂质代谢基因, 其过表达与临床分期呈显著正相关关系^[83-84]。研究^[85]发现, DHCR7 通过抑制铁死亡和激活 PI3K/Akt/mTOR 通路, 增强肿瘤细胞的存活和侵袭性, 使 HNSCC 细胞更具耐药性。

基于上述代谢脆弱性, 相关的药物可作为潜在治疗策略, SQLE 抑制剂可诱导内质网应激, 他汀类药物可阻断甲羟戊酸途径。联合治疗策略可产生显著协同效应, 显著提高抗 PD-1 抗体对 HNSCC 移植瘤的抑制率^[86-87]。

2.4 胆固醇受体介导的免疫调控

胆固醇代谢可通过多种受体调节免疫细胞的活性、信号转导及肿瘤免疫应答。其中, LDL受体不仅负责胆固醇细胞摄取, 还能与T细胞受体复合物相互作用, 调节其再循环和信号转导, 促进细胞毒性T淋巴细胞效应功能^[88-89]。肿瘤微环境中高浓度胆固醇代谢物可激活LXR信号, 抑制树突状细胞的迁移, 诱导CD8⁺T细胞表达免疫检查点分子, 还可与细胞膜受体结合, 调节免疫细胞功能^[90-93]。作为胆固醇合成调控因子, 固醇调节元件结合蛋白2 (Sterol Regulatory Element-Binding Protein 2, SREBP-2) 在肿瘤微环境中被失调胆固醇水平抑制, 导致T细胞胆固醇合成受阻, 增强免疫抑制, 其与LXR的相互调控是胆固醇依赖性T细胞衰竭的核心机制^[94-95]。胆固醇代谢在肿瘤免疫中具有“双刃剑”作用: 一方面导致CD8⁺T细胞衰竭、树突细胞功能障碍和免疫抑制细胞活化, 促进肿瘤逃逸; 另一方面, 靶向这些受体可恢复抗肿瘤免疫应答, 提高免疫治疗疗效。这一机制涉及多个信号通路, 包括T细胞受体再循环、内质网应激和mTORC1信号^[96-97]。

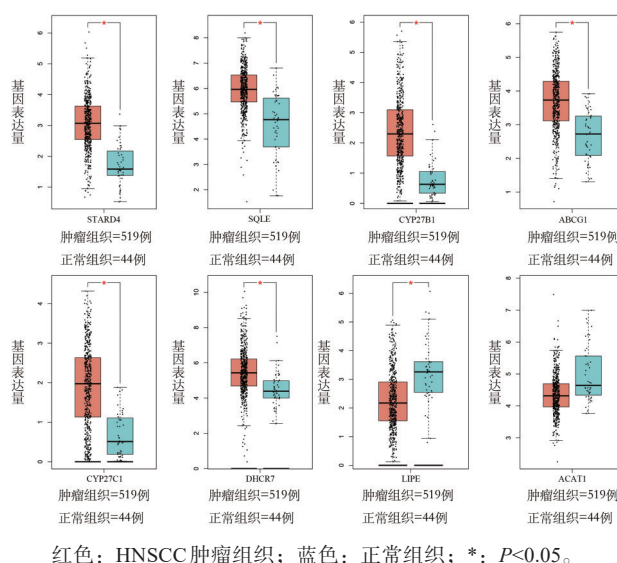
3 靶向胆固醇代谢的治疗策略

胆固醇在肿瘤微环境中主要通过调控程序性死亡配体1 (Programmed Cell Death Ligand 1, PD-L1) 表达和T细胞功能, 形成免疫抑制环境, 降低PD-1/PD-L1抑制剂的疗效。高胆固醇水平可通过激活胆固醇/p38-MAPK轴, 阻断E3泛素连接酶介导的PD-L1泛素化和降解, 增强肿瘤细胞免疫逃逸能力^[98]。肿瘤相关巨噬细胞和MDSCs在高胆固醇环境下表达高水平胆固醇相关代谢物, 间接上调PD-L1表达并抑制CD8⁺T细胞功能^[99]。降低胆固醇水平或靶向胆固醇代谢通路, 可逆转上述免疫抑制效应, 提高免疫治疗疗效。

基于现有研究, 靶向胆固醇代谢治疗HNSCC的药物包括他汀类药物、SQLE抑制剂、SREBP-2抑制剂等^[65, 100-101]。他汀类药物通过阻断甲羟戊酸途径, 抑制胆固醇合成, 增强化疗敏感性; SQLE抑制剂阻断胆固醇合成通路, 降低化疗耐药性; SREBP-2抑制剂可下调HMGCR、SQLE等基因表达, 抑制胆固醇合成; ACAT抑制剂使游离胆固醇堆积, 诱导肿瘤细胞凋亡; SR-BI抑制剂通过阻断HDL摄取和抑制胆固醇酯化, 诱导肿瘤细胞凋亡; 胆固醇外流调节剂可通过直接去除细胞膜胆固醇或调节胆固醇代谢, 增强免疫治疗效果^[65, 102-107]。联合

用药策略也显示出潜力, 如他汀类药物联合化疗/免疫治疗、METTL3抑制剂联合抗PD-1等^[108-109]。然而, 以上药物多数处于临床前或早期临床试验阶段, 需进一步验证疗效及安全性, 肿瘤微环境中胆固醇分布不均也可能影响疗效。开发基于胆固醇稳态基因的预测标志物, 探索协同作用, 可为靶向胆固醇治疗HNSCC提供思路。

在人类蛋白图谱 (Human Protein Atlas, HPA) (<https://www.proteinatlas.org/>)、癌症基因组图谱 (The Cancer Genome Atlas, TCGA) (<https://portal.gdc.cancer.gov/>)、基因型-组织表达 (Genotype-Tissue Expression, GTEx) (<https://gtexportal.org/home/>) 数据库中下载HNSCC相关临床及RNA测序数据。将TCGA数据库中的癌旁正常组织与GTEx数据库中的健康正常组织进行匹配整合, 共纳入563例临床样本, 其中包含肿瘤组织519例, 正常组织44例, 基因表达量均经过 $\log_2(\text{TPM} + 1)$ 转换。表达差异阈值设定为 $|\log_2\text{FC}| > 1$ 且 $P < 0.01$, 采用单因素方差分析对数据进行分析, 系统解析胆固醇代谢酶类基因的临床预测价值。发现STARD4、SQLE、CYP27B1、ABCG1、CYP27C1、DHCR7、LIPE (均 $P < 0.05$) 在HNSCC肿瘤组织中的mRNA水平高于正常对照组织, LIPE ($P < 0.05$) 呈现低表达, ACAT1呈现低表达趋势 (见图3)。这些基因在胆固醇的代谢、合成、转运和储存中发挥着重要作用。STARD4是固醇转运蛋白相关基因, 负责细胞内胆固醇的转运与分布, 其高表达支持快速增殖所需的生物膜合成与信号转导^[110]。ABCG1主要介



红色: HNSCC 肿瘤组织; 蓝色: 正常组织; *: $P < 0.05$ 。

图3 不同酶类的基因表达差异

Figure 3 Differential expression of genes encoding different enzymes

导细胞内胆固醇向细胞外的流出,或在细胞内重新分布,其高表达提示可能参与HNSCC的胆固醇稳态调控^[111-112]。*SQLE*、*DHCR7*是胆固醇生物合成通路的关键酶基因,提示HNSCC中存在胆固醇合成通路的全面活化,为肿瘤细胞快速增殖提供必需的胆固醇前体与结构成分^[113-114]。*CYP27B1*是维生素D活化的关键酶基因,*CYP27C1*参与维生素A代谢的羟化反应,对细胞分化、增殖至关重要^[115-117]。*LIPE*、*ACAT1*的下调提示HNSCC微环境中脂质的代谢重编程^[118-122]。进一步进行卡普兰-梅勒(Kaplan-Meier, KM)生存分析,将患者按照基因表达中位数分为高表达组和低表达组,分析基因表达水平与患者总生存期(Overall Survival, OS)和无瘤生存率(Disease-Free Survival, DFS)的相关性(见图4)。结果显示KM生存分析的危险比(Hazard Ratio, HR)并设定 $P<0.05$ 有统计学意义,Log-rank检验用于比较生存曲线的差异。结果表明,*SQLE*的表达水平对OS($HR>1$, $P<0.001$)和DFS($HR>1$, $P<0.05$)有显著统计学差异,可能作为检测和预后的生物标志物;*ACAT1*、*STARD4*的表达水平对DFS差异有统计学意义(*ACAT1*: $HR>1$, $P<0.01$; *STARD4*: $HR>1$, $P<0.05$),这反映其可能用于评估患者疾病复发风险。但其在HNSCC中发挥的具体作用,仍需进一步展开研究。

4 总结与展望

本综述聚焦于胆固醇在HNSCC中的功能与作

用。HNSCC具有局部复发、远处转移和发生治疗耐药等特征,胆固醇在其发生发展中发挥重要作用:通过改变膜结构、激活致癌基因及调节免疫微环境等促进HNSCC发展;过量积累或代谢紊乱与癌细胞增殖、迁移及抗药性密切相关;代谢产物会促进肿瘤侵袭和免疫逃逸。胆固醇相关酶类基因的表达差异及生存分析表明,其可能成为HNSCC的潜在生物标志物和预后指标。针对胆固醇代谢的治疗策略已成为提升HNSCC治疗效果的重要方向。

以下几个关键科学问题可能为HNSCC的精准治疗提供理论依据:(1) HPV感染状态是否通过胆固醇代谢驱动HNSCC异质性发生及影响免疫治疗差异响应?若证实HPV阳性HNSCC通过上调胆固醇合成驱动肿瘤异质性,并降低免疫治疗敏感性,则可将“HPV状态+胆固醇代谢标志物”作为双重分层指标,实现治疗方案的精准匹配。(2) 胆固醇代谢产物在HNSCC不同区域的分布差异是否调控T细胞浸润?若明确27-HC在肿瘤核心区高表达并抑制T细胞浸润,可将27-HC水平作为免疫治疗响应的预测标志物并开发27-HC中和抗体或27-HC合成酶抑制剂,通过降低肿瘤局部27-HC含量,解除对T细胞的抑制,为低T细胞浸润HNSCC患者提供免疫增敏策略。(3) 能否联合脂质组学、转录组学和影像组学特征,构建HNSCC免疫治疗响应预测工具?基于多组学构建的预测模型,可自动输出患者免疫治疗响应概率,帮助医生规避无效治疗,减少患者经济负担与不良反应风险。然而,药

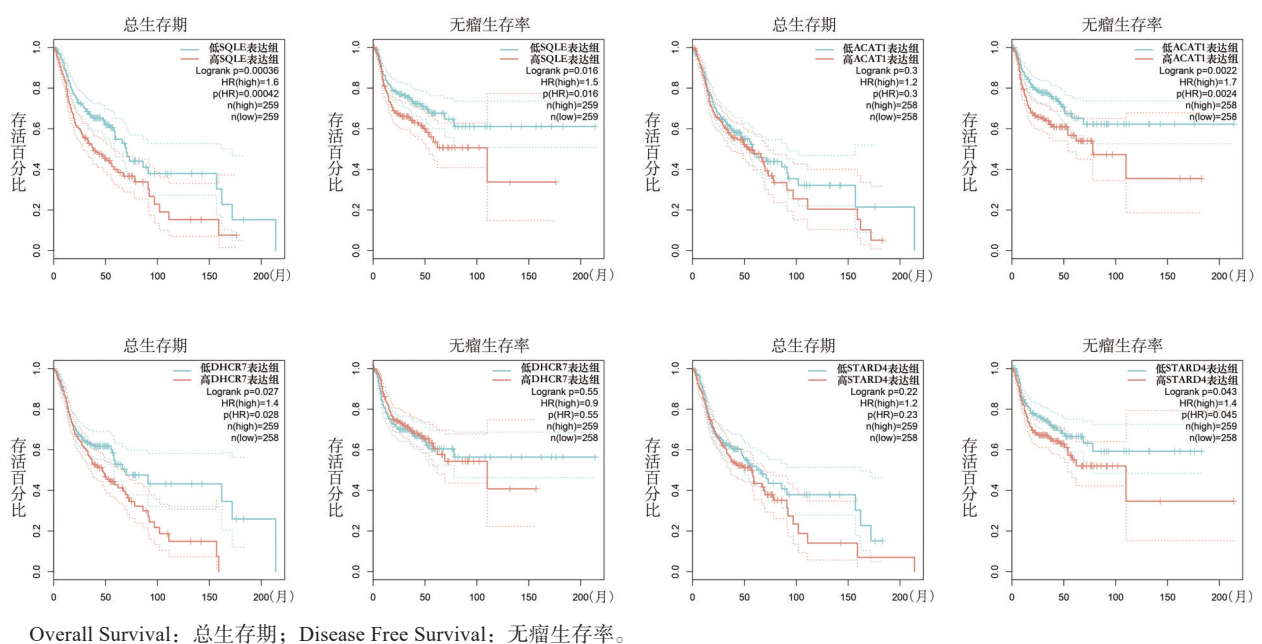


图4 不同酶类的基因在HNSCC的生存分析

Figure 4 Survival analysis of genes encoding different enzymes in HNSCC

物可能引发不良反应、检测结果差异导致标志物临界值难以统一, 以及部分医生对新治疗策略信任度较低, 这些问题给研发精准治疗策略带来挑战。系统解析关键科学问题, 能深化分子机制认知, 推动 HNSCC 精准治疗从理论迈向临床应用, 为改善患者预后奠定基础。

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