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CAV1 在消化道肿瘤中的研究进展

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【摘要】 消化道肿瘤是目前全球最常见的癌症之一,包括食管癌、胃癌、肝癌、胰腺癌和结直肠癌等,其预后不佳,治疗方法仍需进一步改进。小窝蛋白-1(caveolin-1,CAV1)在消化道肿瘤中具有双重调节作用,既是肿瘤抑制因子又是致癌因子。CAV1 对消化道肿瘤的细胞增殖、侵袭、转移、血管生成和药物耐受性等方面具有重要作用,调节 CAV1 蛋白及其相关信号通路可能成为治疗消化道肿瘤的策略之一。因此,本综述就 CAV1 的结构、功能、表达调控以及调节消化道肿瘤上皮-间充质转换(epithelial-mesenchymal transition,EMT)及其耐药性等方面分析 CAV1 与消化道肿瘤的关系,以期为临床消化道肿瘤的诊疗提供新的思路。

【关键词】 CAV1;消化道肿瘤;EMT;耐药
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Advances in the study of CAV1 in digestive tract tumors

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【Abstract】 Digestive tract tumors are currently one of the most common types of cancer, including esophageal cancer, gastric cancer, hepatocellular carcinoma, pancreatic cancer, and colorectal cancer. Their prognoses are poor and the treatments require further improvement. Caveolin-1 (CAV1) has a dual regulatory effect on digestive tract tumors as a tumor suppressor and cancer promoter. CAV1 plays a major role in cell proliferation, invasion, metastasis, angiogenesis, and drug tolerance of digestive tract tumors. The regulation of CAV1 protein and its related signaling pathways may be a strategy for the treatment of digestive tract tumors. This review analyzes the relationship between CAV1 and digestive tract tumors in terms of structure, function, expression regulation, regulation of epithelial-mesenchymal transition, and drug resistance in digestive tract tumors to provide new ideas for the diagnosis and treatment of digestive tract tumors.

【Keywords】 CAV1; digestive tract tumor; EMT; drug resistance
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消化道恶性肿瘤的发病率在世界范围内位居各种恶性肿瘤前列,并且相对病死率近年来有所增加[1-2]。尽管目前的治疗方法(包括手术、放疗和免疫治疗)正在不断改善,但由于消化道肿瘤症状隐

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秘、侵袭性强、发展迅速,因此消化道恶性肿瘤患者的平均生存率仍然较低[3]。

小窝蛋白-1(caveolin-1,CAV1)长期以来一直与肿瘤进展相关,被广泛认为是肿瘤相关蛋白,可以参与肿瘤细胞黏附、侵袭、迁移、上皮-间充质转换等多种肿瘤形成过程[4-5]。研究发现 CAV1 作用肿瘤细胞具有分期依赖性,CAV1 在早期下调并执行肿瘤抑制功能,然而在发展晚期 CAV1 促进肿瘤细胞生长和迁移导致肿瘤恶化[6]。目前为止,CAV1 在消化道肿瘤中的作用尚未得到清晰的认识,为了明确 CAV1 与消化道肿瘤之间的相互作用,本文涵盖了 CAV1 和消化道肿瘤的最新研究成果,描述 CAV1 干预肿瘤细胞增殖、侵袭、迁移等作用,从而影响消化道肿瘤进展;此外,通过探讨 CAV1 在临床治疗中与耐药性的关系,为 CAV1 和消化道肿瘤的进一步研究提供方向和思路,促进 CAV1 的临床应用。

1　CAV1 的介绍

1.1　CAV1 的结构

小窝蛋白最初被发现为内皮细胞和上皮细胞中质膜的烧瓶状内陷结构,呈 50~100 nm Ω 形(见图 1),具有膜运输、脂质代谢和细胞信号转导等作用,与各种疾病的发生发展相关[4,7]。研究表明,小窝蛋白主要成分小窝蛋白家族(CAVs)含有 3 种亚型 CAV1、CAV2 和 CAV3[8]。CAV1 和 CAV2 在除骨骼肌以外的所有组织中均表达,而 CAV3 主要在横纹肌中表达;有趣的是,在一些特定的细胞或组织中(如心肌和平滑肌)可以同时表达 CAV1、CAV2 和 CAV3 这 3 种 CAVs[6]。小窝蛋白的主要成员——CAV1,是一种微小的寡聚支架蛋白,其基因位于人类染色体 7q31.1 上,含有 15 个外显子[4]。CAV1 以两种亚型 α 和 β 存在,每种亚型都具有能够二聚化的发夹构象,CAV1 α 含有 24 kDa 残基,而 CAV1 β 含有 21 kDa 残基。研究表明,这两种单体由不同的 mRNA 编码[9]。CAV1 蛋白序列由 4 个不同结构域组成:N 末端结构域、支架蛋白结构域 、膜内结构域和 C 末端结构域[10-12]。CAV1 的 C 末端和 N 末端都暴露于细胞质中,C 末端结构域包含 3 个棕榈酰化位点,棕榈酰化位点和膜内结构域以 U 形构象的形式嵌入到细胞脂质双分子层中[11,13-14]。而其 N 末端结构域包含两个磷酸化位点:酪氨酸位点和丝氨酸位点。酪氨酸位点 Y14 可以被酪氨酸蛋白激酶磷酸化调节信号蛋白,丝氨酸位点 S80 磷酸化的 CAV1 可以靶向内质网参与 CAV1 的合成分泌[12,15](见图 1)。

1.2　CAV1 的功能

CAV1 能够与多种蛋白质结合,控制胆固醇稳态,调节多种细胞功能,如内吞作用、胆固醇积累以及细胞的信号传导、增殖和死亡。CAV1 不仅是肿瘤抑制因子,也是致癌因子[4]。这种双重调节作用具有分期依赖性,一方面,CAV1 能够延缓癌前病变

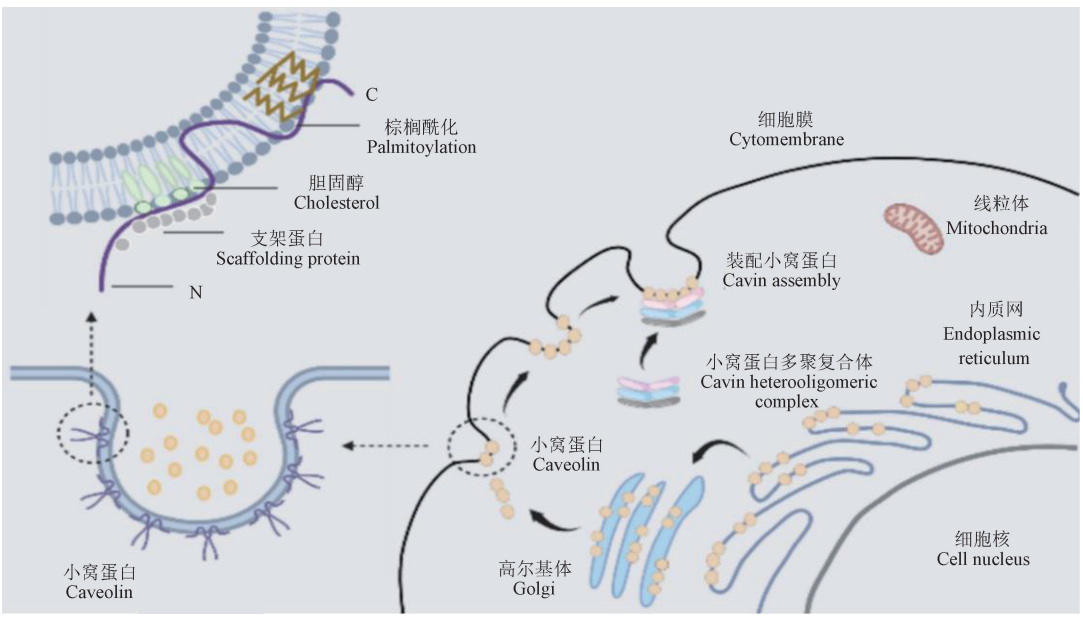


图 1　小窝蛋白合成机制图

Figure 1　Diagram of the mechanism of caveolin synthesis

向癌症转化[16]。另一方面,在癌症晚期观察到 CAV1 过表达与癌症进展、多重耐药性和转移有关[17]。CAV1 的双重调节性在一定程度上与 CAV1 在细胞内定位及信号传导相关[18]。CAV1 已经被证实在多种消化道肿瘤中存在差异性表达,在食管癌、胃癌、肝癌、胰腺癌中 CAV1 呈现出高表达。然而,在结直肠癌中 CAV1 呈现表达下调[19-23](见表 1,图 2)。

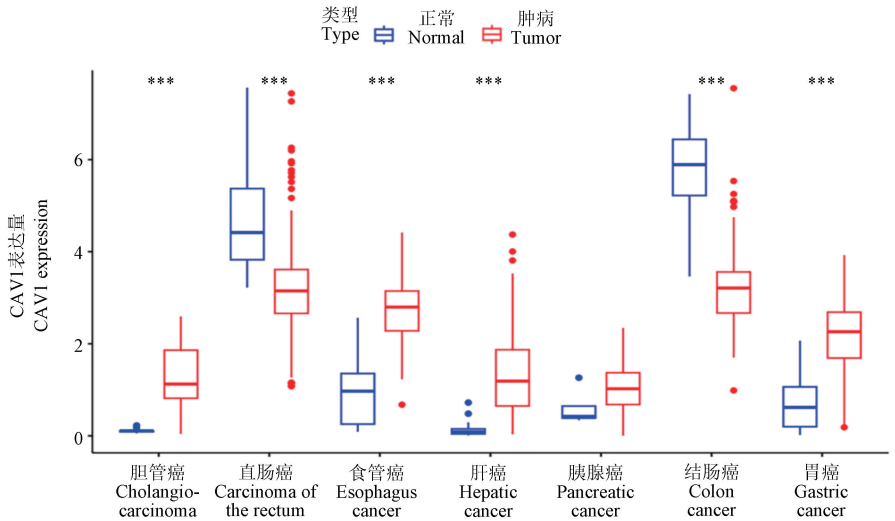
1.3 CAV1 的表达调控

CAV1 的表达受 3 种方式调控:基因组表观遗传修饰、转录和转录后调控机制。CAV1 的基因组表观遗传修饰可分为 DNA 甲基化修饰和组蛋白修饰(如磷酸化、乙酰化和泛素化等)[54]。雌激素受体的异位表达能够引起神经细胞中 CAV1 的 DNA 甲基化或组蛋白去乙酰化,从而调节其 mRNA 表达[55]。Sanders 等[56]发现应用转化生长因子 β1(transforming growth factor-β1,TGF-β1)处理正常成纤维细胞后,CAV1 mRNA 表达受到组蛋白修饰作用而下调,这可能与特发性肺纤维化有关。此外,Yan 等[54]研究 CAV1 DNA 甲基化在慢性肺病中的

表 1 CAV1 在恶性肿瘤中的表达情况

Table 1 Expression of CAV1 in malignant tumors

肿瘤 Tumour	意义 Significance	调控通路 Regulatory pathway
食管癌[19] Esophagus cancer	促肿瘤 Promote tumor	线粒体凋亡途径 Mitochondria apoptosis pathway
胃癌[21, 24-25] Gastric cancer	促肿瘤 Promote tumor	EGFR/ITGB1;c-Src/CAV1; Wnt/β-catenin
肝癌[26-32] Hepatic cancer	促肿瘤 Promote tumor	Wnt/β-catenin;Notch; PI3K/AKT/mTOR; CAV1/SREBP1/ACADM; 整合素 α/CAV1; Integrin α/CAV1; Erk/Jnk/p38
胰腺癌[22, 33] Pancreatic cancer	抗肿瘤 Anti tumor	CAV1-ROS; shh/MMP2/bFGF/IL-6
结直肠癌[34-35] Colorectal cancer	抗肿瘤 Anti tumor	CAV1/STAT;CAV1/MMP1
膀胱癌[36] Bladder cancer	促肿瘤 Promote tumor	不详 Unknown
肺癌[37] Lung cancer	促肿瘤 Promote tumor	CAV1/AKT/Bad
宫颈癌[38] Cervical cancer	促肿瘤 Promote tumor	AKT/mTOR
骨癌[39] Osteocarcinoma	抗肿瘤 Anti tumor	不详 Unknown
胶质瘤[5, 40-41] Glioma	促肿瘤 Promote tumor	Wnt/β-catenin; PTEN/PI3K/PKB/Src/CAV1; TRAF4/CAV1
卵巢癌[42-43] Ovarian cancer	抗肿瘤 Anti tumor	CAV1/p-gp/M2 型巨噬细胞; CAV1/p-gp/M2 Macrophage; CAV1/ACE2
皮肤癌[44-45] Skin cancer	促肿瘤 Promote tumor	不详 Unknown
前列腺癌[46-48] Prostate cancer	促肿瘤 Promote tumor	Wnt/β-catenin
乳腺癌[49-50] Breast cancer	抗肿瘤 Anti tumor	CAV1/NF-κB/c-Myc; TGF-β1/Smad
肾癌[51] Renal cell carcinoma	促肿瘤 Promote tumor	PI3K/AKT
头颈癌[52-53] Head and neck cancer	促肿瘤 Promote tumor	CAV1/EREG/YAP;TGF-β/SMAD



注：与正常组比较，*** $P<0.001$；在胆管癌、食管癌、肝癌、胃癌组织中 CAV1 高表达，在直肠癌、结肠癌组织中 CAV1 低表达，其差异具有统计学意义。

图 2　CAV1 在消化道肿瘤中的表达情况

Note. Compared with normal group, *** $P<0.001$. In the cholangiocarcinoma, esophagus cancer, hepatic cancer, gastric cancer tissues CAV1 high expression, CAV1 low expression in carcinoma of the rectum, colon cancer tissue, and the difference was statistically significant.

Figure 2　Expression of CAV1 in GI tumors

可能机制，并将其视为慢性肺病早期诊断和治疗的可能靶点。然而，它是否能够作为生物标志物应用还有待进一步研究。

CAV1 的启动子序列包括 3 个富含 G+C 的固醇调节元件，包括 CAAT 序列、Sp1 共识序列和过氧化物酶增殖反应元件[57-59]。细胞内游离胆固醇的增加可以刺激 SRE 结合蛋白 1（sterol regulatory element binding protein 1，SREBP 1）与 CAV1 启动子中的胆固醇调节元件结合，调节 CAV1 mRNA 表达。此外，其他转录因子 GAT 结合因子 6、NF-κB 也可以与 CAV1 启动子相结合，调节其转录水平[60-61]。

许多因素能够影响 CAV1 的转录后调节，例如微小 RNA（microRNA，miRNA）、长链非编码 RNA（long non-coding RNA，lncRNA）、环状 RNA（circular RNA，circRNA）以及其他蛋白质可以对 CAV1 的转录后水平进行调节。其中 miRNA 包括 miR-199a-5p[62]、miR-96[38]、miR-124[23]、miR-103/107[63]、miR-204[37]、miR-130a[64] 和 miR-103-3p[65] 已被证明可以识别同源 CAV1 mRNA 导致 CAV1 mRNA 降解、抑制其翻译。lncRNA 包括 lncRNA ANRIL[62]、lnc-BMP1-1[66] 和 lncRNA IMFLNC1[67]，可以调节 CAV1 蛋白表达及其功能。最近的研究表明，circRNA 在 CAV1 的转录后调控中起关键作用[68-69]。Li 等[70] 研究发现 circRNA TADA2A 含有丰富的 miR-526b 结合位点，具有 miR-526b 和 miR-203 的海绵功能，能够促进 CAV1 表达。一些蛋白质如聚合酶 I 和转录本释放因子（polymerase-1 and transcript release factor，PTRF/Cavin-1）、浮舰蛋白 1 和 RNA 结合蛋白 HuR 也可以影响 CAV1 的蛋白表达和稳定性[71-74]；E3 泛素连接酶 ZNRF1 和过氧化氢酶诱导 CAV1 泛素化[75-77]；酪氨酸蛋白激酶（tyrosine protein kinase，TPK）可以与 CAV1 的酪氨酸 14 位点结合，诱导其磷酸化，导致 CAV1 不稳定、降解[78]。此外，CAV1 是星形胶质细胞存活的必需蛋白质，可以通过自噬降解。研究发现 CAV1 的自噬降解可以促进棕榈酸（palmitic acid，PA）诱导的星形胶质细胞凋亡和炎症反应，CAV1 可能是 PA 积累引起中枢神经系统损伤的潜在治疗靶点[79]。综上所述，CAV1 的表达不仅受非编码 RNA 的调控，而且还受到蛋白酶的干预。

2　CAV1 对肿瘤 EMT 的影响

CAV1 与多种肿瘤上皮-间充质转换（EMT）相关[80]。在肝癌中，CAV1 的上调会导致 ST6GAL1 表达增加，从而促进 EMT、癌细胞迁移、侵袭，并与不良预后相关[29]。铁死亡标志物 CAV1 与 EMT 之间存在很强的相关性，可以促进 EMT 过程[81]。miRNA-203 通过抑制 CAV1 使 PI3K/AKT 信号通路

失活,增加 E-钙粘蛋白的表达和诱导细胞凋亡,从而抑制肾癌细胞 EMT、迁移和侵袭[51]。与 EMT 和甲状腺癌干细胞样特性相关的基因 CAV1 在甲状腺微小癌的早期广泛淋巴结扩散中表达上调[82]。CAV1 作为前列腺癌进展的关键驱动因素,能够诱导肿瘤 EMT[46]。对于恶性周围神经鞘肿瘤,低表达武藏蛋白 2(musashi 2,MSI2)能增加 CAV1 蛋白表达,然而敲低 MSI1 可以抑制 CAV1 介导的细胞 EMT 和转移[83]。在乳腺癌中,CAV1 与 EMT 相关,缺乏 CAV1 的成纤维细胞可通过介导 TGF-β1/Smad 信号通路促进乳腺癌 EMT 进程[84-85]。此外,中草药地榆能抑制小鼠乳腺癌的生长、EMT、晚期自噬和缺氧诱导因子-1α/CAV1 信号传导[86]。CAV1 沉默可能会增强自我更新调节因子 BMI1 表达并促进 EMT[87]。CAV1 在多种肿瘤中与迁移和侵袭密切相关,其上调或沉默对肿瘤细胞的 EMT 具有重要影响。

3 CAV1 与肿瘤耐药的关系

3.1 CAV1 与消化道肿瘤耐药的关系

针对不同水平 CAV1 的异种胃癌移植物模型,Pereira 等[88]发现帕妥珠单抗与洛伐他汀联合应用优于单独使用,可显著提高抗体-肿瘤结合率和反应率。最近的研究表明 CAV1 通过激活 Wnt/β-catenin 通路来参与胃癌细胞对顺铂耐药性的形成[25]。在缺乏 CAV1 的条件下,使用 8 μg/mL 顺铂处理胃癌细胞 24 h 后,胃癌细胞凋亡率显著升高。CAV1 可能是间质-上皮细胞转化因子(mesenchymal epithelial transition factor,MET)和人类表皮生长因子受体 2(human epidermal growth factor receptor 2,HER2)信号通路之间正串扰的关键连接体,通过酪氨酸 1221 和 1222 位点的 HER2 磷酸化来抑制顺铂诱导的胃癌细胞凋亡。CXCR4 过表达可以激活 CAV1 信号通路,促进肝癌细胞对吉非替尼的耐药性[89]。CAV1 表达水平较高与显著较差的总生存期(overall survival,OS)相关。然而,在癌细胞中 CAV1 下调可能也会导致细胞增殖,Kamposioras 等[90]研究表明当 CAV1 在成纤维细胞中共同注射到免疫缺陷小鼠体内以产生混合成纤维细胞/癌细胞异种移植物时,CAV1 的表达降低导致癌细胞的生长和化学耐药性。在接受吉西他滨+nab-紫杉醇治疗的患者中,用吉西他滨预处理可增加 CAV1 和白蛋白的摄取,显著降低胰腺癌细胞的增殖和克隆原性,并增强胰腺癌细胞对 nab-紫杉醇的敏感性,使癌细胞凋亡水平升高[91]。

3.2 CAV1 与非消化道肿瘤耐药的关系

研究发现外泌体 miR-1246 通过靶向卵巢透明细胞癌中的 CAV1/p-gp/M2 型巨噬细胞轴赋予紫杉醇耐药性[42]。使用金托联苄基治疗可通过抑制 CAV1 以及 EMT,抑制肺癌细胞迁移并使得肺癌细胞对顺铂介导的细胞凋亡变得敏感[92]。另一项研究表明 miR-204 过表达可通过抑制 CAV1/AKT/Bad 途径使得肺癌细胞对顺铂诱导的线粒体细胞凋亡敏感。CAV1 和 CRAF/BRAF 蛋白异二聚化相结合与达沙替尼靶向 EphA2 的耐药性相关;达沙替尼、紫杉醇和卡铂三联组合使用在子宫内膜癌中显示出临床活性,具有一定的细胞毒性[93]。然而,高表达的 CAV1 与卵巢癌患者的良好预后呈正相关,过表达 CAV1 可增强顺铂治疗的敏感性,CAV1 缺乏能够促进卵巢癌细胞的化学耐药性[43]。在乳腺癌研究中,CAV1 水平高与 nab-紫杉醇和吉西他滨治疗的无进展生存期较长有显著关联;低剪切应力通过抑制 CAV1 依赖性外在和内在凋亡途径诱导乳腺癌细胞耐药性的形成[94-95]。

4 CAV1 对消化道恶性肿瘤的影响

4.1 食管癌

CAV1 在食管癌(esophageal cancer,ECC)中扮演着诊断和预后标志物的角色。Wang 等[19]研究表明 CAV1 高表达会抑制细胞信号传递并降低活性氧 ROS 水平,而 CAV1 敲低则能够加速 G_0/G_1 期 ECC 细胞凋亡、细胞活性氧 ROS 形成并停滞细胞周期。此外,CAV1 的表达与肿瘤浸润免疫细胞、肿瘤发炎指数等免疫系统相关的因素呈正相关,CAV1 可能成为 ECC 免疫治疗的新靶点[96]。CAV1 基因的高甲基化及其基因沉默通常出现在食管腺癌中,与 Barrett 食管早期肿瘤进展有关;CAV1 基因的多态性与个体发展为食管癌的易感性相关[97-98]。Jia 等[99]多变量分析研究表明,无论何时对 CAV1 的表达进行分析,其在 ECC 组织中的表达水平始终高于邻近或远处的正常组织。另外,抑制 Rho/ROCK 通路可以明显抑制 CAV1 和磷酸化小窝蛋白-1(pY14 caveolin-1,pY14CAV1)的表达,并显著减少 ECC 细胞的迁移和侵袭;CAV1、pY14CAV1 与 ECC 癌变及淋巴转移呈正相关[100]。

4.2 胃癌

CAV1 是胃癌(gastric cancer,GC)的一种新型

预后标志物,Bertero 等[101]通过临床、组织病理学和分子特征的相关性分析发现了这一结论,同时与血小板衍生生长因子受体 α(platelet derived growth factor receptor alpha, PDGFRA)突变相关。敲低 CAV1 阻断表皮生长因子受体(epidermal growth factor receptor, EGFR)的激活并降低 GC 细胞迁移[102];选择性剪接调控蛋白 PTBP3 能够选择性剪接 CAV1,调节 GC 转移[20];脂肪质量与肥胖相关蛋白(fat mass and obesity associated protein,FTO)抑制 CAV1 表达从而抑制 GC 细胞增殖、迁移和侵袭[103]。Circ CCDC9 作为肿瘤抑制因子,抑制 miR-6792-3p/CAV1 信号轴,减少 CAV1 表达,进而抑制 GC 肿瘤发生[104]。研究发现,增加胃癌细胞中 miR-451a 的表达会抑制细胞生长、迁移和侵袭性,并促进细胞凋亡;高表达 CAV1 后,这些生物过程恢复[105]。Wang 等[21]发现 CAV1 的肿瘤表达增加与明显恶化的总生存期 OS 相关。Sun 等[106]指出 CAV1 在非原发肿瘤淋巴结中的表达可以预测较差的生存结果,具有新的肿瘤预后标志物的潜力。此外,CAV1 基因甲基化可能在胃贲门腺癌(gastric cardia adenocarcinoma,GCA)的进展中起重要作用,可以作为 GCA 患者的预后甲基化生物标志物[107]。许多研究结果表明 CAV1 与 GC 癌症病情和生存预后之间相关联。然而,CAV1 在 GC 中受到种属差异性、个体差异性的影响,其调控作用尚不明确。

4.3 肝癌

CAV1 在肝细胞癌(hepatocellular carcinoma, HCC)的发展中扮演着重要的角色,CAV1 表达可预测肝细胞癌发展,是潜在的生物标志物和预防性治疗靶标[108]。高表达的 CAV1 促进 O-GlcNAc 转移酶(O-GlcNAc transferase, OGT)的表达,催化 O-GlcNAc 残基添加到多种核蛋白和细胞质蛋白中,促进 HCC 细胞的迁移、侵袭[109]。过表达的 CAV1 可以通过 Wnt/β-catenin 信号途径促进乙型肝炎病毒(hepatitis B virus, HBV)相关的 HCC 细胞转移。CAV1 诱导的岩藻糖基转移酶 8 表达上调增强了小鼠 HCC 细胞在体外的增殖、侵袭,CAV1 也在 Wnt/β-catenin 信号途径、调节糖基转移酶表达和参与异常糖基化等方面介导 HCC 的增殖、侵袭[26]。另一项研究发现,肝硬化 HCC 的 CAV1 蛋白过表达率显著高于无肝硬化的 HCC,这表明 CAV1 蛋白过表达可能引发肝硬化肝癌变,促进肝细胞癌的发生[110-111]。CAV1 可以上调蛋白 O-岩藻糖基转移酶 1 表达来激活 Notch 通路,增强小鼠 HCC 细胞在体内、体外的侵袭和转移[28]。CAV1 的表达能够激活 PI3K/AKT/mTOR 信号通路,促进转录因子 NR4A2 和磷酸化 RXRα 形成,并与 ST6GAL1 启动子结合诱导转录[29]。Chai 等[112]发现 HCC 的进展与异常的细胞代谢有关,HCC 细胞中 CAV1 或己糖激酶 2(hexokinase 2,HK2)的过表达能够增强葡萄糖和乳酸代谢,导致 HCC 细胞迁移、侵袭。此外,由 CAV1/SREBP1/ACADM 轴介导的脂肪酸氧化失调可以促进 HCC 发展[30]。多因素分析显示,内质网整合膜蛋白 Sec62 是肝癌术后早期复发的独立预后因素。Sec62 通过整合素 α/CAV1 信号传导促进 HCC 转移[31]。Takeda 等[113]发现 CAV1 在 HCC 患者的临床标本中过表达;细胞实验表明 CAV1 通过降低含油酸(oleic acid,OA)的促凋亡因子神经酰胺水平来抑制 HCC 细胞凋亡。Zhang 等[32]研究表明 CAV1 可以通过 MAPK 信号通路促进转录因子 HNF4A 和 Sp1 的磷酸化,这些转录因子与 O-岩藻糖肽 3-β-N-乙酰氨基葡萄糖转移酶(recombinant O-fucosylpeptide-3-β-N-acetylglucosaminyltran sferase, RFNG)启动子区域结合,诱导 RFNG 转录;CAV1 在调节糖基转移酶表达中起重要作用,参与 HCC 异常蛋白质糖基化,促进细胞侵袭转移。

4.4 胰腺癌

CAV1 是胰腺癌(pancreatic cancer,PC)发展过程中一个重要调节因子,在 PC 基质中低表达,基质 CAV1 的缺失与生存率低有关。在胰腺星状细胞(pancreatic stellate cells,PSCs)中,敲低 CAV1 促进活性氧 ROS 的产生,ROS 的产生进一步降低 CAV1 表达。PSCs 中的 CAV1-ROS 信号传导发生正反馈,促进 PC 生长并诱导 PC 基质-肿瘤代谢耦合[22]。CAV1 沉默的 PSCs 表现出 shh 表达增加,激活胰腺癌细胞中 shh 信号通路。同时,PSCs 积累的 ROS 促进胰腺癌细胞血管生成[33]。CAV1 在 PC 癌症相关成纤维细胞(cancer-associated fibroblasts, CAFs)中的表达与患者预后不良相关,CAFs 中 CAV1 的下调降低了 PC 细胞的侵袭性[114]。另外,通过洛伐他汀或消耗 CAV1 可以抑制甲羟戊酸途径,降低 $CD133^+$ PC 细胞的转移潜力和化学耐药性[115]。

4.5 结直肠癌

CAV1 是 STAT 信号传导的枢纽,与肿瘤免疫微环境相关。CAV1 抑制结直肠癌(colorectal cancer, CRC)细胞增殖并诱导细胞凋亡和衰老;过表达

CAV1 可抑制 CRC 的肿瘤血管生成[34]。在对 76 名表达 EGFR 的结直肠肿瘤患者进行研究,Yang 等[116]发现 CAV1 的表达与淋巴结及远处转移呈负相关。CAV1 过表达可能抑制肿瘤进展,高水平的 CAV1 可能是一个良好的预后因素。Lin 等[117]发现通过补体与凝血级联反应以及局灶性粘附途径可以干预结直肠癌肝转移,CAV1 可能是 CRC 肝转移早期标志物。CD26 是结直肠癌干细胞的肿瘤标志物,$CD26^+$结直肠癌干细胞具有肿瘤增殖特性并能够进行 CRC 转移。CD26 通过抑制 CAV1,诱导基质金属蛋白酶 1(matrix metalloproteinase 1,MMP1)表达,引起 CRC 的迁移、侵袭和血管生成[35]。

5 结语

综上所述,CAV1 既能够作为肿瘤抑制因子又可以作为致癌因子参与肿瘤形成过程,各方面都已经证实 CAV1 与 ECC、GC、HCC、PC 等消化道肿瘤密切相关。CAV1 可能成为消化道肿瘤的一种重要早期预测和预后生物标志物,这有助于肿瘤的治疗。然而,目前仍存在一些问题:(1)消化道肿瘤的发生机制具有多样性与复杂性,生理、生化等诸多不清楚问题有待进一步研究;(2)CAV1 与肿瘤相关的关键信号分子改变目前还是未知的,在肿瘤的发生发展及治疗反应中的病理意义研究较少;(3)CAV1 阳性或阴性预后标志物的参考临界值目前没有明确指标;(4)目前还没有临床药物试验前瞻性地探讨 CAV1 在消化道恶性肿瘤中的作用。上述这些存在的问题需要更多关于 CAV1 的试验研究来阐明。在回顾关于消化道肿瘤中 CAV1 的文献时,我们更加相信 CAV1 在肿瘤形成和发展中的作用具有重要研究前景,应用更多新药干预肿瘤细胞 CAV1 的蛋白表达可以作为未来肿瘤治疗的新方向。

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