程序性细胞死亡4在结直肠癌中的作用

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提 要：程序性细胞死亡4(programmed cell death 4，PDCD4)基因定位于染色体10q24，通过阻碍真核生物翻译起始因子复合物eIF4F合成，在转录和翻译水平抑制肿瘤发展。PDCD4基因在结直肠癌中的表达调节机制非常复杂，涉及多条信号转导通路，并影响肿瘤细胞增殖、侵袭、转移及耐药。该文综述了PDCD4在结直肠癌发展中分子机制、表达及预后判断等相关研究进展。

关键词：PDCD4；结直肠癌；综述文献

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Role of programmed cell death 4 in colorectal cancer

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Abstract: The programmed cell death 4 (PDCD4) gene is located on chromosome 10q24 and inhibits tumor progression at transcriptional and translational levels by blocking the eukaryotic biological translation initiation factor complex eIF4F synthesis. The regulatory mechanism of PDCD4 gene expression in colorectal cancer (CRC) is sophisticated, by which involves multiple signal transduction pathways and affects the proliferation, invasion, metastasis and drug resistance of CRC cells. That review summarizes the molecular mechanisms, expression and prognosis of PDCD4 in the development of CRC.

Key words: PDCD4; colorectal cancer; review

结直肠癌(CRC)是世界第三大常见恶性肿瘤，每年约有140万新病例和60万例患者死亡。由于CRC早期诊断困难、术后复发率高，且目前缺乏有效的治疗手段，故病死率高。因此，研究CRC进展的分子机制有助于提高临床诊治水平，改善患者预后。PDCD4基因最早发现于小鼠实验中[1]，此后研究证实，人类PDCD4基因位于染色体10q24，调节细胞凋亡，被认为是一种新型的抑癌基因。PDCD4基因通过其蛋白中保守的α螺旋MA-3结构与真核细胞翻译起始因子4A(eukaryotic initiation factor-4A，eIF4A)N端功能域结合，抑制eIF4A解螺旋酶活性从而抑制核糖体复合物和蛋白质的合成[2]。也有研究表明，PDCD4基因能够不依赖eIF4A途径而直接与肿瘤细胞核糖体结合并影响其翻译过程，从而导致肿瘤细胞凋亡[3]。正常生理状态下，PDCD4基因主要存在于细胞核内，当细胞周围环境发生改变时，如细胞发生恶性增殖，它可以通过羧基末端的核输出信号(nuclear export signals，NES)转移到细胞浆中[4]。本文就近年PDCD4在CRC发展中的分子机制、表达及预后判断等相关研究进展进行综述。

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1 PDCD4在CRC发展中的分子机制

1.1 PDCD4与CRC增殖、凋亡的相关分子机制

Goke等[5]研究发现，有丝分裂促进因子中的细胞周期依赖性蛋白激酶1(cyclin dependent kinase 1，CDK1)表达水平伴随CRC恶性变化程度而升高。PDCD4通过上调p21Waf1/Cip1转录而抑制CDK1的表达，抑制肿瘤的恶性转化。硫利达嗪上调PDCD4基因表达和抑制PI3K/Akt通路从而抑制原位直肠腺癌细胞SW480增殖并诱导细胞凋亡[6]。Tili等[7]发现，白藜芦醇调节SW480细胞中PDCD4基因和转化生长因子-β(Transforming growth factor-β，TGF-β)信号通路的效应子水平可抑制CRC的发展。抑制多元醇途径酶醛糖还原酶(Aldosereductase，AR)可下调miR-21表达并通过ROS/AMPK/mTOR/AP1/4E-BP1途径增加PDCD4水平而阻止生长因子诱导结肠癌细胞生长[8]。

1.2 PDCD4在CRC细胞侵袭、转移中相关分子机制

Yang等[9]研究表明PDCD4基因可阻碍丝裂原活化蛋白激酶激酶激酶激酶1(Mitogen-activated protein kinase kinase kinase kinase 1，MAP4K1)蛋白转录而抑制c-Jun蛋白激活和转录激活因子AP-1转录进而抑制人结直肠癌细胞的侵袭、转移及细胞外基质蛋白酶活性。Wang等[10]发现，PDCD4基因敲除可致结直肠癌HT29细胞呈成纤维细胞样转变，PDCD4基因敲除可使活性β-链蛋白(β-catenin)和AP-1表达增加，E-钙粘蛋白(E-cadherin)表达减少，而活性的β-catenin可激活β–catenin/Tcf(T-cell factor 4)依赖性转录，进而增强结直肠癌细胞侵袭能力。Mudduluru等[11]研究揭示姜黄素通过AP-1抑制miR-21转录调节，稳定PDCD4蛋白在结直肠癌中的表达，抑制肿瘤细胞增殖、侵袭和体内转移。 Leupold等[12]报道了PDCD4基因通过抑制Sp1/Sp3转录因子介导的尿激酶型纤溶酶原激活物受体(Urokinase-type plasminogen activator receptor，u-PAR)进而抑制结直肠肿瘤细胞的入侵/血管浸润。

1.3　PDCD4在炎症性CRC中的相关分子机制

炎症性肠病(Inflammatory bowel disease，IBD)包括溃疡性结肠炎(Ulcerative colitis， UC)和克罗恩病性结肠炎(Crohn's disease，CD)，是结直肠癌发生、发展的危险因素，越来越多的实验证明PDCD4 基因在介导炎症性CRC进展中作用明显。Ludwig等[13]分析发现，活动性IBD组织标本及IBD相关发育不良病变标本的PDCD4核表达显著低于无活性IBD组织标本及肠易激综合征患者肠组织标本的PDCD4核表达。Schmid 等[14]发现炎症相关的巨噬细胞诱导PDCD4蛋白降解，其机制可能与PI3K-mTOR信号通路有关。在结直肠癌细胞中，PDCD4基因抑制PI3K/AKt/m TOR信号通路下游效应分子S6K1(Ribosomal protein S6 kinase beta-1)的激活克服胰岛素样生长因子1受体(IGF-1R)抑制剂治疗结直肠癌的抗性[15]。PDCD4基因的缺乏加速结直肠肿瘤上皮细胞增殖，显著上调促炎细胞因子如白细胞介素IL-6(Interleukin 6)的表达，并增强信号转导和转录因子(Signal transducer and activator of transcription 3，STAT3)的激活[16]。此外，通过抑制剂sgp130Fc(soluble gp130-Fc) 阻断IL-6/STAT3通路可逆转PDCD4基因缺乏对体内结肠上皮细胞增殖的促进作用，表明PDCD4基因缺乏可能通过上调IL-6/STAT3通路促进结肠炎和结肠炎相关CRC的发展。Peacock等[17]在结肠腺癌细胞体外研究发现，前列腺素E2(Prostaglandin E2，PGE2)可上调miR-21表达水平及下调PDCD4蛋白表达水平，而使用选择性环氧合酶–2(Cyclooxygenase 2，COX-2)抑制剂NS398治疗可显著降低miR-21水平和增加PDCD4蛋白水平，表明miR-21是COX-2炎症通路的组分，该通路通过诱导PGE2积累增加miR-21表达水平，伴随PDCD4蛋白下调而促进结直肠癌疾病的恶化。

1.4　miRNA在转录后水平调控PDCD4基因的表达从而影响CRC进展

microNRA是一类内源性表达的小分子非编码单链RNA，通过与靶基因3'-UTR结合，抑制mRNA翻译或直接降解mRNA来负性调节靶基因的功能。大量研究表明，PDCD4基因是某些microRNA的靶基因，这些microRNA通过调节PDCD4的表达水平进而影响CRC细胞的侵袭和转移、介导炎症性CRC等发展过程。

Asangani等[18]第一次报道了miR-21通过靶向作用于PDCD4基因3'-UTR而下调PDCD4，进而促进CRC的侵入、血管浸润和转移。miR-21可调控PDCD4 表达进而介导结直肠癌细胞对治疗药物的敏感性。Wu等[19]发现miR-21可通过抑制PDCD4表达介导RKO细胞对5-氟尿嘧啶药物耐药。另外，PDCD4与miR-21在介导炎症性CRC发展中起了重要作用。Ando等[20]研究发现，UC缓解期较活动期患者CD3 T细胞的miR-21表达水平下降，而PDCD4表达升高，提示miR-21和结肠T细胞相关通路可能在限制致病性T细胞反应中发挥作用。Shi等[21]检测CRC患者癌组织、结肠炎相关性结直肠癌(CAC)组织与CAC小鼠模型肿瘤组织发现，miR-21表达水平显著增高。miR-21的敲除增加其目标基因PDCD4的表达水平而促进调节核因子NF-κB(Nuclear factor kappa-light-chain-enhancer of activated B cells)激活。且miR-21敲除小鼠的促炎及致癌细胞因子(白细胞介素IL-6，IL-23，IL-17A和IL-21)表达降低，E-cadherin增加及β-catenin、转录因子SOX9 和抗原 KI-67减少，肿瘤细胞的增殖减弱。

研究发现其他一些microRNA也可调控PDCD4并影响结直肠癌的发展。Muppala等[22]检测发现，肿瘤组织中PDCD4基因和miR-34a的表达显著低于相应正常组织，而细胞粘附分子CD24(Cluster of differentiation 24)、肉瘤基因(Sarcoma gene，Src)较相应正常组织高，且miR-34a和Src蛋白水平呈负相关。CD24激活Src，诱导c-Jun基因与c-Fos基因的表达，

而miR-34a在转录后下调CD24和Src。Liu等[23]研究发现，原位直肠腺癌细胞SW480中miR-499-5pa表达水平显著低于同患者来源的淋巴转移灶细胞SW620，miR-499-5p可抑制PDCD4的表达，且高表达的miR-499-5p促进体外CRC细胞侵袭和转移，并在促进体内肺和肝转移。IL-6/STAT3信号通路的激活增加表达水平，高表达的miR-181b可下调CRC细胞PDCD4的表达，表明miR-181b可促进细胞增殖和转移，抑制CRC细胞的凋亡，并可能通过靶向作用于PDCD4基因而加速异种移植小鼠中肿瘤的生长[24]。

2 PDCD4基因在结直肠癌中的表达预后判断

PDCD4的表达与结直肠癌的预后判断密切相关。Mudduluru等[25]通过免疫组织化学结果发现，正常粘膜表现出强的核PDCD4，在腺瘤中核PDCD4显著减少，而在CRC中核PDCD4几乎完全缺失，且CRC中总PDCD4和核PDCD4的缺失程度与患者总生存率及疾病特异生存率显著相关。中度或低度分化的消化道恶性肿瘤组织中PDCD4表达水平显著低于良好分化的肿瘤组织[26]。Dukes'B期和C期中低PDCD4水平患者的总生存率(Overall survival，OS)及无病生存率(Disease free survival,DFS)比高PDCD4水平患者的OS及DFS低；而在Dukes'D期中，低PDCD4表达的患者比高PDCD4表达的患者OS更低。PDCD4表达水平也作为Dukes' B，C和D期的独立预后因子[27]。PDCD4基因表达水平是结直肠癌的一个新型和独立的预后因素，其可用于区分正常结直肠组织、良性腺瘤和结直肠癌，临床中如果将PDCD4作为检测指标，有助于提高早期CRC检出率[28]。Ferraro等[29]研究也表明检测miR-21-ITGB4-PDCD4可作为CRC转移的预测因子。

3 小结

PDCD4基因可在转录、翻译过程中抑制细胞生长，其异常表达在CRC的发生、发展中起重要作用。近年来虽然对于PDCD4基因在CRC中的作用已有较多研究，但仍存在很多需要解决的问题，进一步深入研究PDCD4基因在CRC中的作用机制，对CRC的临床诊疗具有广阔的应用前景。

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