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文献综述 REVIEW

肾上腺素能受体信号通路与结直肠癌关系的研究进展

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Role of adrenergic receptor signaling pathway in colorectal cancer

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Abstract
Colorectal cancer is one of the most common malignancies. During the past decades, studies have continued to shed light on the role of adrenergic receptor signaling in cancer. Preclinical studies have shown that adrenergic receptor signaling is involved in colon cancer progression and metastasis and have implicated that stress hormones or behavioral changes are highly associated with tumor formation and progression. Therefore, further understanding of the role of the adrenergic receptor (AR) signaling pathway in colorectal cancer progression and metastasis will be of great value in developing therapeutic strategies for this malignancy.

Key Words: Adrenergic receptors; Colorectal cancer; Signaling pathway

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摘要
结直肠癌(colorectal cancer, CRC)是最常见的恶性肿瘤之一, 近年来研究发现肾上腺素能受体(adrenergic receptor, AR)信号通路与多种肿瘤的发生发展密切相关, 儿茶酚胺类物质具有促进肿瘤细胞增殖、侵袭、转移及诱导耐药的作用. 深入探讨AR信号通路参与肿瘤形成与进展的调控机制, 能够为结直肠癌提供更有价值的临床诊疗方案.

关键词: 肾上腺素能受体; 结直肠癌; 信号通路

核心提示: 肾上腺素能受体α亚型主要介导儿茶酚胺类物质诱导结直肠肿瘤细胞产生化疗耐药, β亚型则参与了促进肿瘤细胞增殖和转移.

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0 引言
结直肠癌最为全球最常见的恶性肿瘤之一, 其发病率及死亡率均呈上升趋势, 因此积极寻找新的治疗方向是目前结直肠癌诊治中的重要任务[1]. 研究[2-5]表明, 肾上腺素能信号途径可调节多种参与肿瘤发生发展的细胞过程, 包括炎症、血管生成、失巢凋亡、细胞侵袭、DNA损伤修复、细胞免疫应答及表皮间质细胞转化等, 因此与肿瘤的发生、发展密切相关. 本文就肾上腺素能及其受体在结直肠癌发生发展过程中的作用等方面展开综述, 分析肾上腺素能信号通路在结直肠癌预防及治疗方面的可行性.

■背景资料
近年来精神因素促进肿瘤的生长和转移已得到重视, 其中肾上腺素能受体信号通路受到越来越多的关注. 体内外实验证明, 儿茶酚胺类物质能通过β信号通路促进乳腺癌、卵巢癌、前列腺癌以及结直肠癌细胞的侵袭和转移.

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■研发前沿
研究发现β-arrestin参与β_2肾上腺素能受体(β_2-adrenergic receptor, β_2-AR)诱导的活性氧的产生, 而激活β_2-AR后G蛋白和β-arrestin介导的信号通路依赖活性氧的参与, 通过抑制活性氧能够阻断G蛋白和β-arrestin介导的Erk1/2磷酸化.

1 肾上腺素能受体及其通路

儿茶酚胺类物质的生物学效应由α_1、α_2及β肾上腺素能受体(adrenergic receptor, AR)家族介导产生[6,7]. 近年来研究发现, 其中β肾上腺素能受体(β-adrenergic receptor, β-AR)(包括β_1、β_2及β_3)与多种肿瘤的生成和转移密切相关. β-AR信号途径引起的总反应包括上调与肿瘤转移相关的涉及炎症、血管生成、组织侵袭、表皮间质细胞转化等相关基因的表达.

肾上腺素能受体属于G蛋白偶联受体家族, 当肾上腺素能受体激活后, 引起Ga蛋白介导的腺苷酸环化酶(adenylate cyclase, AC)的活化, AC将三磷酸腺苷(adenosine triphosphate, ATP)转化为环磷酸腺苷(cAMP), 使cAMP含量增高并通过下游效应系统进一步调节细胞活动. 一方面cAMP可特异性地活化蛋白激酶A(cyclin-AMP dependent protein kinase A, PKA), cAMP与PKA调节亚基结合并改变其构象, 使PKA调节亚基与催化亚基解离, 释放出催化亚基, 活化的PKA催化亚基可使细胞内cAMP反应单元结合蛋白(cAMP response element binding protein, CREB)、GATA转录因子以及β-AR激酶(β-AR kinase, BARK)等相关蛋白的丝氨酸或苏氨酸残基磷酸化, 从而完成信息传递, 改变蛋白活性及相关基因的表达. 此外由于鸟苷酸交换因子(guanine nucleotide exchange factor, GEF)含有cAMP结合位点, 受cAMP调控, 也称为cAMP直接激活的蛋白(exchange protein directly activated by cAMP, EPAC). 研究发现, 炎症、肿瘤血管生成以及细胞侵袭的作用主要是通过β-AR-cAMP-PKA通路发挥作用[8], 而β-AR-cAMP-EPAC则从不同方面对细胞形态学和移动性产生影响. EPAC可激活Ras样鸟苷三磷酸酶Rap1A, 后者进一步激活*B-Raf*基因、有丝分裂原活化蛋白(motigen-activated protein, MAP)/细胞外信号调节激酶(extracellular-signal regulated kinase, Erk1/2), 从而对细胞形态、移动等发挥重要的作用.

除G蛋白依赖的信号通路, 同时还存在非G蛋白依赖的信号途径, 即β-arrestin介导的β-AR信号途径. β-arrestin具有调控GPCR信号通路和丝裂原激活的蛋白激酶(motigen-activated protein kinase, MAPK)信号通路的作用. 研究[9]发现β_2-AR阻滞剂可阻断Ras和Scr酪氨酸激酶依赖的MAPKs和PI_3K-Akt通路, 抑制Erk及Akt磷酸化, 促使细胞色素C(cytochrome C, Cyt C)的释放并激活Caspase3和Caspase9诱导凋亡.

2 肾上腺素能受体在结直肠癌中的表达

研究[10-12]发现肾上腺素能受体在肺、乳房、卵巢、胰腺等肿瘤组织中广泛表达, 并且与肿瘤的发生发展有着密切的关系. Abel等[13]认为在人结肠癌细胞株HT-29表达β-AR可能与肿瘤血管生成有关. 当局部神经纤维释放的去甲肾上腺素或外周血液中的肾上腺素作用于肿瘤表面及基质细胞上表达的肾上腺能受体时, 从而引起一系列病理反应.

Perrone等[14]通过比较41例结直肠癌患者的癌组织与周围正常黏膜上皮的β-AR表达水平, 发现β_3-AR mRNA在癌组织中的表达水平是正常组织的两倍(P = 0.036), 而β_1-AR mRNA及β_2-AR mRNA的表达水平无明显差异, 提示β_3-AR可能参与调节人结直肠肿瘤的发生. Takezaki等[15]进一步观察131例结直肠癌患者及239名正常人群的*β_2-AR*基因(BAR2)及*β_3-AR*基因(BAR3)多态性与结直肠发生风险之间的关系, 发现*β_2-AR Gln27Glu*基因及*β_3-AR Trp64Arg*基因在两组人群之间的表达分布差异无统计学意义. 但在体质量指数(body mass index, BMI)较高的患者进一步的亚组分析中显示*Trp64Arg*基因突变将增加结肠癌发生的风险(OR = 2.63, 95%CI: 1.13-6.11).

3 基础研究

3.1 细胞增殖与耐药 吸烟、尼古丁以及尼古丁衍生物亚硝胺酮(ketone of nitrosamine, NNK)被认为是胃肠道肿瘤的危险因素. N0147III期临床研究显示, III期结肠癌中经常吸烟患者的无病生存期(disease free survival, DFS)较不吸烟者明显缩短(HR = 1.21, 95%CI: 1.01-1.42)[16]. NNK具有剂量依赖型促进吸烟相关性肿瘤的形成[17], 由于在结构上与β-AR激动剂相似, 因此NNK对β-AR具有较高的亲和性[18,19]. NNK可通过α7烟碱乙酰胆碱受体(α7nAChR)刺激去甲肾上腺素的合成, 而后者进一步通过cAMP-PKA信号通路诱导肿瘤的发生. Oliveira等[20]采用循环伏安法研究HT-29细胞株的电化学行为发现, HT-29细胞株能够以自分泌的方式分泌肾上腺素, 通过活化肾上腺素能受体促进细胞增殖, 而尼古丁能够促进HT-29细胞株分泌肾上腺素. Wong等[21]进一步研究发现尼古丁能显著升高酪氨酸羟化酶、多巴胺-β羟化酶和苯乙醇胺甲基转移酶的表达, 并且促进肾上腺素的生成, 使用儿茶酚胺

生物合成中的限速酶或α7-烟碱样乙酰胆碱受体阻滞剂均能够阻断尼古丁诱导的细胞增殖作用, 降低酪氨酸羟化酶、多巴胺-β羟化酶的表达, 减少肾上腺素的合成与分泌. 通过β_1-AR和β_2-AR阻滞剂能够阻断尼古丁对结肠癌细胞的作用, 抑制环氧合酶-2(cyclooxygenase-2, COX-2)和血管内皮生长因子(vascular endothelial growth factor, VEGF)的表达, 其中β_2-AR阻滞剂的作用效果更为明显. 提示尼古丁可能是通过α7-烟碱样乙酰胆碱受体和β-AR信号通路共同作用, 促进结肠癌细胞增殖及肿瘤血管生成. 目前关于尼古丁是通过直接的配体受体结合通路或是其他的途径来上调β-AR活性的机制仍待进一步深入研究.

相关研究证明肾上腺素具有促进肿瘤细胞生长, 并诱导其产生耐药的作用. Yao等[22]发现肾上腺素可以提高HT-29细胞株*ABCB1*基因及P-糖蛋白的表达水平, 同时诱导HT-29对5-Fu的耐药性, 应用α_2-AR阻滞剂能完全阻断肾上腺素诱导产生的耐药现象, 而α_1-AR阻滞剂和β-AR阻滞剂则对*ABCB1*基因表达没有影响. 进一步提出肾上腺素诱导结肠癌细胞产生耐药是通过磷酸化Erk1/2, 进一步激活MRPK通路. Wu等[23]研究发现安替洛尔(β_1-AR阻滞剂)和ICI 118,551(β_2-AR阻滞剂)能阻断去甲肾上腺素、异丙肾上腺素和NNK促进HT-29细胞株增殖的作用, 并且当异丙肾上腺素和NNK作用于细胞后, 激活腺苷酸环化酶, 使cAMP浓度升高. cAMP进一步升高COX-2及磷脂酶A2的表达水平, 促进前列腺素E2的生成释放增多, 而这一作用能被ICI 118,551阻断. 提示β-AR促进细胞增殖作用中β_2-AR发挥了主要作用, β-AR通路以及下游的磷脂酶A2-花生四烯酸信号途径可能参与结肠癌的发生. Faraoni等[24]研究发现miR-155在结肠癌组织中表达增高, 并促进结肠癌的侵袭转移, 抑制肿瘤细胞凋亡, 而肾上腺素可通过激活核因子kappa B(nuclear factor-κB, NF-κB)信号通路使HT-29细胞过表达miR-155, 从而促使HT-29细胞增殖, 并且抑制顺铂诱导的细胞凋亡[25,26]. 此外肾上腺素能够上调HT-29细胞株COX-2和VEGF的表达水平, 并提高MMP-9的活性, 促进PGE2的释放, 应用sc-236(COX-2抑制剂)能逆转肾上腺素诱导的细胞增殖, 降低VEGF的表达及MMP-9的活性, 应用β-AR阻滞剂亦能阻断肾上腺素诱导的细胞增殖作用[27].

3.2 肿瘤侵袭转移 肿瘤细胞的转移是由多种因素共同参与的, 其中包括体内的细胞因子、神经递质等, 近年来研究发现β-AR阻滞剂具有抗肿瘤侵袭转移的作用[28]. 结直肠癌中肝转移是最常见的死亡原因, 约50%-60%的结直肠癌患者会出现肝转移, 而20%-34%的患者在初次确诊时已有肝转移[29]. 研究[30,31]表明, 肝脏主要表达α_1-AR、α_2-AR和β_2-AR三种亚型, 其中β_2-AR-cAMP通路参与了肝脏代谢途径.

Kassahun等[32]认为在结肠癌肝转移能够使肝脏的β-AR-cAMP通路受损, 通过放射性配基结合和竞争性结合分析方法, 研究结肠癌肝转移灶组织、转移灶癌旁组织以及正常肝脏组织和结肠癌组织以及正常结肠组织, 结果发现β_2-AR在肝转移灶组织较转移灶癌旁组织以及正常肝脏组织的最大结合能力明显降低(40.09 fmol/mg±2.83 fmol/mg *vs* 23.09 fmol/mg±3.24 fmol/mg, P<0.001), 在结肠癌组织以及正常结肠组织中也得到相同的结论(37.6 fmol/mg±2.2 fmol/mg *vs* 23.8 fmol/mg±3.5 fmol/mg), 并且ICI 118,551的抑制浓度曲线与β_2-AR分布呈现相关性.

研究[33]发现去甲肾上腺素能诱导SW480细胞发生定向迁移, 而β-AR阻滞剂普萘洛尔能抑制去甲肾上腺素的促迁移作用, 但阿替洛尔(β_1-AR阻滞剂)对迁移的抑制作用却很微弱, 提示在肾上腺素能途径促进结肠癌转移中可能是通过β_2-AR发挥作用. Sorski等[34]经门静脉和脾内注射人结肠癌细胞株CT-26建立肝转移模型, 并分别给予普萘洛尔、依托度酸、普萘洛尔联合依托度酸和安慰剂, 发现通过阻断释放增多的儿茶酚胺和前列腺素通路能提高肿瘤免疫并阻断肿瘤的转移能力.

3.3 心理因素 心理与肿瘤的发生发展密切相关, 并且是直接影响到疗效和疾病的预后的关键因素[32]. 紧张的心理因素及不良情绪会导致人体肾上腺和交感神经末端释放大量儿茶酚胺类物质, 儿茶酚胺类物质可刺激肿瘤细胞增殖, 并提高肿瘤细胞的侵袭转移及促血管生成能力[35]. 此外, 长期过度的精神刺激可导致机体免疫功能失调, 使其对某些突变的上皮细胞的监视清除能力减弱或丧失. 长期慢性应激可导致DNA损伤, 并诱发肿瘤[36-38]. 慢性应激产生的儿茶酚胺类物质过与β_2-AR结合, 促进Gs蛋白依赖的PKA的活化, 并进一步募集β-arrestin至细胞膜表面, 从而削弱DNA的损伤修复功能并降低p53的表达水平[39-43]. Wu等[44]研究发现雄性小鼠

■相关报道
Cole等系统综述了β肾上腺素能信号通路促进肿瘤细胞增殖和新生血管形成, 增强肿瘤的侵袭和转移能力的分子机制.

■创新盘点
本文全面深入探讨肾上腺素能受体信号通路在结直肠癌耐药以及肿瘤细胞增殖、转移的形成与进展中的调控机制，为结直肠癌的研究提供更具价值的诊疗方案.

经社会隔离刺激后能引起免疫抑制并促进结肠癌细胞CT26-L5的肝转移能力. 经脾内注射结肠癌细胞7 d后, 应激组75%出现了肝转移, 而对照组则只有15%出现了的肝转移.

4 临床研究

临床流行病学研究发现, β-AR阻滞剂联合常规治疗方案对抑制肿瘤的进展和转移具有积极的作用[45]. Engineer等[46]通过对262例III-Ⅳ期结直肠癌患者的回顾性研究发现, 服用血管紧张素转化酶抑制剂(angiotensin-converting enzyme inhibitors, ACEIs)或血管紧张素受体阻滞剂(angiotensin receptor blockers, ARBs)联合肾上腺素能受体拮抗剂能显著降低患者肿瘤相关死亡率(HR = 0.50, 95%CI: 0.29-0.85)并减缓疾病进展(HR = 0.59, 95%CI: 0.36-0.47). Jansen等[47]通过对1975例结直肠癌患者进行Cox比例风险回归分析, 发现β-AR阻滞剂能显著延长Ⅳ期结直肠癌患者的总生存期(HR = 0.5, 95%CI: 0.33-0.78)和特异性生存期(HR = 0.47, 95%CI: 0.30-0.75), 其分别为18 mo(38 mo *vs* 20 mo)和17 mo(37 mo *vs* 20 mo). 对服用β-AR阻滞剂的结直肠癌采用巢式病例对照研究[48,49], 发现β-AR阻滞剂并未增加患者的特异性死亡率, 从而证实其临床应用的安全性. 为进一步证实结直肠癌患者服用β-AR阻滞剂是否具有生存获益, 目前采用β-AR阻滞剂用于预防结直肠癌的有效性及安全性的III期临床研究(NCT00888797)[50]中将计划接受原发瘤切除的结直肠癌患者随机分为两组, 于手术前5 d、手术当天以及术后14 d分别采用普萘洛尔40 mg/d联合依托度酸1600 mg/d及安慰剂, 用以观察两组患者的肿瘤转移及复发情况, 使β-AR阻滞剂获得更好的临床应用依据. Lindgren等[51]采用事件影响量表和CES-D抑郁自评量表对174例乳腺癌和36例结直肠癌患者进行临床观察, 结果发现应用β-AR阻滞剂能显著缓解患者的肿瘤相关性心理压力.

5 结论

肾上腺素能受体信号通路与结直肠癌的发生、发展的密切相关, 相关研究初步揭示了肾上腺素能受体的α亚型主要介导儿茶酚胺类物质诱导肿瘤细胞产生的耐药现象, 而β亚型则参与了促进肿瘤细胞增殖、转移的过程. 是否可以通过阻断相应的受体, 为化疗耐药以及转移性的结直肠癌提供治疗策略, 以及β-AR阻滞剂使患者生存获益、减轻心理压力等机制亟待进一步的研究, 从而为结直肠癌的预防及治疗提供新的思路和途径.

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■应用要点

β-AR阻滞剂被视为20世纪心血管疾病治疗学上里程碑式的进展, 如果其在防治肿瘤进展及转移方面的作用得到进一步的证实, 则可能成为防治肿瘤的有效方法之一.

■同行评价
本文全面综述了肾上腺素能受体信号通路在促进结肠癌肿瘤细胞增殖、侵袭、转移及诱导耐药的作用, 为结直肠癌的研究和治疗提供了新的方向.

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