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文献综述 REVIEW

前列腺素类物质在胃肠道肿瘤发病机制中的作用

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Role of prostaglandins in pathogenesis of gastrointestinal cancer

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Abstract

There are 2 cyclooxygenase (COX) isoforms commonly referred to COX-1 and COX-2 for the temporal order of their discovery. Although both COX-1 and COX-2 are up-regulated in a variety of circumstances, normally, COX-1 is constitutively expressed in a broad range of cells and tissues. COX-1 expression remains constant under most physiologic or pathologic conditions, and COX-1-derived prostaglandins are considered to play a role in many normal physiologic processes. COX-2, by contrast, is an immediate-early response gene normally absent from most cells but highly inducible in response to inflammatory stimuli, including endotoxin, cytokines, hormones, and tumor promoters. Prostaglandins derived from COX-1 and COX-2 are involved in a variety of physiologic and pathologic processes in the gastrointestinal tract. Recent efforts to identify the molecular mechanisms by which COX-2-derived prostanoids exert their proneoplastic effects have provided a rationale for the possible use of non-steroidal anti-inflammatory drugs alone or in combination with conventional or experimental anticancer agents for the treatment or prevention of gastrointestinal cancers.

Key Words: Prostaglandins; Cyclooxygenase; Gastrointestinal cancers; Molecular mechanisms

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摘要

环氧合酶(cyclooxygenase, COX)是催化花生四烯酸转化为前列腺素过程中的一个关键限速酶. 哺乳动物的COX有两种形式, 即COX-1和COX-2. COX-1在大多数组织中都有表达, 其催化产生的前列腺素参与维持机体正常的生理机能. 而COX-2是一种诱导酶, 在细胞受到各种刺激时, 如组织损伤、炎症或细胞恶性转化时表达增强. 近年来大量研究表明, COX-2通过前列腺素途径除参与炎症反应外, 还与胃肠道肿瘤发生、发展关系密切, COX-2在结直肠癌、胃癌和食管癌中的作用主要是通过PGE_2等前列腺素来调节的, 目前的研究认为前列腺素对肿瘤的促进作用主要牵涉下列分子机制: 促进细胞增殖、抑制凋亡、促进侵袭和转移、刺激血管生成和诱导免疫抑制. 本文就前列腺素类物质在胃肠道肿瘤发病机制中的研究进展作一综述.

关键词: 前列腺素类物质; 环氧化酶; 胃肠道肿瘤; 分子机制

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■**背景资料**
胃肠道恶性肿瘤是发病率和死亡率均较高的疾病, 严重威胁着人民健康. 探讨胃肠道恶性肿瘤发病的分子机制, 以找寻新的预防和治疗方案已迫在眉睫. 目前, 环氧合酶及其催化产生的前列腺素类物质在胃肠道肿瘤发病机制中的作用受到关注.

0 引言

胃肠道恶性肿瘤是发病率和死亡率均较高的疾病, 严重威胁着人民健康. 探讨胃肠道恶性肿瘤发病的分子机制, 以找寻新的预防和治疗方案已迫在眉睫. 目前, 环氧合酶(COX)及其催化产生的前列腺素类物质在胃肠道肿瘤发病机制中的作用受到关注. 研究认为, 前列腺素(PG)对肿

■研发前沿
COX-2通过前列腺素途径除参与炎症反应外, 还与胃肠道肿瘤发生、发展关系密切, COX-2在结直肠癌、胃癌和食管癌中的作用主要是通过PGE_2等前列腺素来调节的, 目前的研究认为, 前列腺素对肿瘤的促进作用主要牵涉下列分子机制: 促进细胞增殖、抑制凋亡、促进侵袭和转移、刺激血管生成和诱导免疫抑制.

瘤的促进作用主要牵涉下列分子机制: 促进细胞增殖、抑制凋亡、促进侵袭和转移、刺激血管生成和诱导免疫抑制. 对这些机制的研究, 可为COX-2抑制剂在胃肠道肿瘤防治方面的应用提供分子学依据.

1 概述

当组织受到各种生理和病理因子刺激时, 多不饱和脂肪酸(如花生四烯酸)在磷酸酶A_2的作用下, 从细胞膜磷脂上游离出来, 花生四烯酸可通过3种途径代谢: 环氧合酶途径、脂氧合酶途径和细胞P450单氧合酶途径. 通过COX作用, 游离的花生四烯酸可合成多种前列腺素和血栓烷素(TXs)[1-4]. 在此过程中, 花生四烯酸由环氧合酶作用转化成PGH_2为关键的调节步骤, PGH_2再由多个特异性PG合成酶作用而生成至少5种结构相似的有生物活性的脂类分子, 包括PGE_2、PGD_2、$PGF_{2\alpha}$. PGI_2和血栓烷素A_2(TXA_2). NSAIDs就是通过抑制环氧合酶而抑制了前列腺素的生物合成, 从而发挥抗炎、镇痛、退热的作用. COX-2催化所产生的PGE_2等前列腺素和消化道肿瘤有密切关系[5-6]. 前列腺素通过结合位于细胞表面的受体而发挥他的细胞生理功能, 这些受体属于G蛋白耦联受体(GPCR), PGD_2受体被命名为DP, PGE_2受体为EP (EP_1、EP_2、EP_3和EP_4), $PGF_{2\alpha}$受体为FP, PGI_2受体为IP, TXA_2受体为TP. 最近研究表明, PGE_2显著增加了氧化偶氮甲烷(AOM)所诱导的结肠肿瘤的发生率和多样性[7], 进一步的实验发现, PGE_2明显增加了AOM诱导的结肠癌细胞增殖并减少凋亡, 在这些肿瘤组织中能检测到所有4种EP受体, 提示PGE_2通过与其受体相结合而发挥了上述作用. PGE_2在结直肠癌发生中的重要作用通过PGE_2受体纯合子缺失实验被进一步证实, 实验发现, EP_1和EP_4受体在其中发挥重要作用[8-10]. 另外, 研究还发现, EP_2受体破坏可减少$APC^{\triangle 716}$敲除鼠的肠息肉的数量和大小[11]. 同时, 在致癌原处理的野生型鼠中, EP_1受体拮抗剂也能减少结肠癌的发生率, 相似的实验还有: 在APC^{min}鼠中用EP_1受体拮抗剂和EP_4受体拮抗剂处理后, 其肠道息肉分别减少57%和69%[8-9], 除结直肠癌之外, 在COX-2 MMTV乳腺癌鼠中也发现EP_1, EP_2和EP_4受体高表达[12]. 这些实验充分说明PGE_2与肿瘤发生、发展的密切相关性.

已有研究显示, 在结肠癌、胃癌和乳腺癌中, COX-2表达与肿瘤血管形成, 淋巴结转移和凋亡减少呈正相关[13-16], 为探索COX-2的生物学作用, 对COX-2来源的PGE_2作用机制成为目前研究的热点之一. 众多的研究提示, COX-2来源的PGE_2通过活化EP受体而激活下游的信号通路, 随后增加细胞增殖、抑制凋亡、促进血管形成、刺激侵袭和转移, 抑制免疫反应, 从而促进肿瘤的发生、发展.

2 前列腺素类物质在胃肠道肿瘤发生中的分子机制

2.1 刺激细胞增殖 COX-2来源的PGE_2可明显刺激结直肠癌(CRC)细胞增殖[17], 但PGE_2诱导的细胞增殖的相关下游信号通路尚不清楚, 在CRC细胞中, 增加COX-2的表达能反向激活(transactive)EGFR而刺激细胞增殖[18], 在乳腺癌和肺癌中也发现PGE_2在的作用涉及EGFR信号通路[19]. 联合应用非选择性NSAIDs抑制剂与EGFR抑制剂可显著减少APC^{min}鼠结肠息肉的形成[20], 提示联合应用EGFR抑制剂用于癌症防治的有效性. 同时, 在移植瘤研究中联合COX-2选择性抑制剂、EGFR抑制剂和蛋白激酶A反义核苷酸, 可明显减少结肠癌和乳腺癌细胞的增殖和血管形成[21], 还有报道, 阻滞EGFR信号通路可抑制COX-2诱导的HCA-7移植瘤的生长[22-23]. 上述研究都提示EGFR信号通路的激活可能参与了PGE_2对胃肠道恶性肿瘤的促进作用.

2.2 促进血管形成 由于>2-3 mm的实体瘤均需血管形成而得以继续增生[24-25], 因而血管生成在人类肿瘤生长中发挥了关键作用, 故抑制肿瘤相关的血管生成成为肿瘤治疗的策略之一. 最近, VEGF抗体bevacizumab被发现能够延长转移性直结肠癌(CRC)无浸润生存期约10 mo[26], 故VEGF成为CRC的有效治疗靶点, 同时与VEGF相关的基因研究也成为研究热点. 在COX-2基因敲除鼠中结直肠癌生长和血管密度明显减弱, 说明COX-2在肿瘤血管形成过程中发挥重要作用, 另一方面非选择性和选择性NSAIDs都能有效抑制血管生成相关因子分泌, 从而抑制血管内皮细胞增殖、迁移和血管形成[27-30]. 这些研究结果充分说明, COX-2可通过诱导血管生成因子的分泌而刺激内皮细胞增殖、迁移和血管形成. 更深入的研究发现非选择性和选择性NSAIDs可通过抑制COX-2而抑制MAPK信号转导途径, 从而减少内皮细胞的增殖、迁移和血管形成[27,31], COX-2抑制剂还能抑制$\alpha V\beta 3$调节的Cdc42/Rac依赖的内皮细胞的迁移[32], 这些结果又进一步

证实, COX-2在肿瘤的血管形成中发挥重要作用, 提示NSAIDs可作为抗肿瘤血管生成药物而应用于临床. 在CRC细胞中, COX-2过表达可刺激血管生成因子如VEGF和bFGF分泌[26], 这些作用主要可能由PGE_2来调节. 研究已发现, PGE_2能够逆转NSAIDs的抗血管生成作用[33], 而EP_2纯合子缺失能明显也减少$APC^{\triangle 716}$鼠息肉中VEGF的产生[34], 说明PGE_2通过EP受体而上调了血管生成因子. 这方面的研究方兴未艾, Trompezinski *et al*[35]报道, PGE_2可上调人成纤维细胞的VEGF的表达、Pai *et al*[36]报道, PGE_2通过激活ERK_2/JNK_1信号通路增加血管内皮细胞VEGF和bFGF的表达、Dormond *et al*[37]又报道PGE_2还能促进αVβ3-Cdc42/Rac依赖的内皮细胞的迁移和侵袭, 还有研究报道[38-39]PGE_2亦可促进胃癌细胞VEGF的表达,可能经由EGFR介导的通路. 这些研究几乎同时证明PGE_2对肿瘤血管形成的促进作用. 有趣的是, VEGF和bFGF也能够反过来诱导内皮细胞COX-2表达和相应前列腺素物质的增加[40], 上调的PGE_2又进一步上调VEGF和bFGF诱导的CXCR4依赖的肿瘤血管形成[41], 因此, COX-2来源的PGE_2在肿瘤血管形成中的作用可能通过其正反馈环效应而进一步放大.

2.3 *抑制凋亡* 细胞增殖和凋亡的失衡导致肿瘤生长, 抑制凋亡而延长细胞生存, 使得基因突变进一步积累, 导致肿瘤的进展. 在散发性结肠腺瘤和癌中, 细胞凋亡减少, 在FAP患者的结直肠黏膜中也有类似情况[42-43]. 在结肠腺瘤和结肠癌中分别有50%和90%患者COX-2表达增加, 而在正常结肠黏膜中无表达, 进一步的研究发现, COX-2过表达能够抑制丁酸钠所诱导的鼠肠上皮细胞凋亡、增加Bcl-2蛋白表达[44]. 选择性COX-2抑制剂NS398能诱导15种结直肠癌细胞系凋亡, 而在表达COX-2细胞系中效果更显著, 在小鼠的胃癌细胞中提示NSAIDs能通过抑制COX-2而抑制细胞的增殖并诱导肿瘤细胞凋亡[45-47]. 上述研究证据说明, COX-2在CRC的细胞凋亡抑制中发挥了重要作用. COX-2抑制凋亡的机制和其产物前列腺素有密切关系. 研究已显示, PGE_2在大部分人结肠癌中高表达, 同时PGE_2能够抑制非选择性NSAIDs和选择性COX-2抑制剂SC-58125所诱导的人结肠癌细胞凋亡[45], 提示PGE_2可增强细胞对凋亡的抵制能力, 然而PGE_2影响细胞凋亡的详细机制仍不清楚. PGE_2可能通过增加抗凋亡蛋白如Bcl-2或其他Bcl基因家族成员如Mcl-1的水平来减少细胞凋亡[48], 另一种可能是PGE_2诱导了抗凋亡信号通路NF-κB的转录活性[49]. 在研究PGE_2对细胞凋亡影响的同时, 关于NSAID诱导凋亡的非COX依赖机制又被报道[50], 研究表明, NSAIDs的抗肿瘤效应并不完全依赖于COX途径, 高剂量的NSAIDs能够调节非COX基因[51-52], 包括15-LOX-1[53]、促凋亡基因Par-4[54]、抗凋亡基因Bcl-X2[55]和抗凋亡基因NF-κB[56-57], 从而抑制肿瘤生长, 促进凋亡. 这两方面的作用机制都有待人们去进一步研究. 高表达的COX-2和高水平的PGE_2抑制凋亡、延长细胞生存, 从而导致治疗抵抗, 引起学者对于联合NSAIDs和传统抗癌药物(如顺铂)应用于肿瘤治疗产生了巨大兴趣, 是否联合化疗药(和/或放疗)与长期服用NSAIDs有更好的反应, 尚须进一步研究. 初步研究显示, COX-2选择性抑制剂可增强放疗效果[58].

2.4 *增强侵袭性* 大部分实体恶性肿瘤, 如结直肠癌, 主要死因是远处转移. 一项临床研究显示, 非选择性NSAIDs吲哚美辛能增加晚期转移性胃和结肠癌患者的生存期, 并能减轻其疼痛[59]. 然而另一项临床实验显示, 选择性COX-2抑制剂罗非昔布治疗转移性CRC收益较小[60], 但在鼠肝转移模型的研究中, 罗非昔布却能够明显抑制结直肠癌细胞的生长和转移能力[61-62]. 此外, 体外研究证实, COX-2的过表达增加了结直肠癌细胞的侵袭性[63], 这些研究都提示, COX-2/PGE_2在消化道肿瘤侵袭和转移过程中扮演了重要角色. 最近的研究正在探索PGE_2作用所可能涉及的下游信号转导通路, Pai *et al*[64]的研究发现, PGE_2通过反向激活(transactivate)EGFR而促进CaCo-2结肠癌细胞生长、最近Buchanan *et al*[65]又报道, PGE_2可通过EP4-EGFR-PI3K-AKT途径促进LS-174T结肠癌细胞株的侵袭性, 这两项研究都提示, EGFR信号通路在PGE_2促进肿瘤侵袭和转移过程中可能发挥重要作用. 之前的研究已发现, EGFR的表达与CRC肝转移能力相关[66], 现在又进一步在分子水平上证实EGFR和肿瘤发生、发展的高度相关性, 显示了EGFR抑制剂在临床肿瘤治疗中的价值和地位. 研究已证明, 联合应用NSAIDs和EGFR抑制剂可显著抑制APC^{min}鼠结肠息肉的形成[19], 可见EGFR抑制剂用于消化道肿瘤的防治已初见端倪.

2.5 *免疫抑制* 恶性肿瘤的免疫反应可分为两大类: 细胞免疫和体液免疫. 树突细胞(DCS)作为专职抗原递呈细胞, 在激活人体对肿瘤的免疫反应中起关键作用. 研究已发现, DCS内COX-2表达能抑制DCS功能[67], 而且PGE_2通过EP_2受

■相关报道
目前, 已有一些研究在探索4种EP受体在不同肿瘤中表达情况和PGE_2等前列腺素作用于不同EP受体后各自介导的生物学行为之间的区别, 这些问题的阐明能为肿瘤防治提供新的药物作用靶点.

■创新盘点
本文从刺激细胞增殖、促进血管形成、抑制凋亡、增强侵袭性、免疫抑制、增加基因突变等多个方面综述了前列腺素类物质在胃肠道肿瘤发病分子机制中的作用.

体也可抑制DCS的分化和功能, 从而减弱细胞免疫所调节的抗肿瘤反应[68]. 进一步研究发现, PGE_2能抑制NK细胞和巨噬细胞的抗肿瘤活性, 还能抑制T淋巴细胞产生抗肿瘤Th1相关细胞因子(如TNF-α, IFN-γ和IL-2)的能力[69], 同时PGE_2却上调Th_2相关细胞因子的产生, 如角化细胞产生的IL-4, 外周血淋巴细胞和巨噬细胞产生的IL-10[70-71]和T淋巴细胞产生的IL-6[72]. 在恶性肿瘤中, 从Th_1免疫反应转换成Th_2占优势的免疫反应, 可导致机体抗肿瘤的细胞免疫反应被抑制, 可见, PGE_2可给予肿瘤细胞逃避免疫攻击的机会.

2.6 增加基因突变 环氧合酶有过氧化物酶的活性作用[73-74], COX-1和COX-2能活化多种环境和食物致癌原, 导致基因突变[75-76]. 但COX-2和PGE_2在消化道肿瘤中的这部分作用尚待进一步研究.

3 展望

胃肠道肿瘤发生、发展是多基因、多因素、多步骤的协同作用过程, COX-2及其前列腺素类物质的过表达只是其中的一种机制, 对COX-2及其选择性抑制剂作用的分子机制的研究有可能进一步揭示肿瘤发生、发展的过程, 并为肿瘤化学预防提供新途径. 有证据已提示非选择性NSAIDs和COX-2选择性抑制剂能通过抑制PGE_2的合成, 从而降低结直肠癌、胃癌和食管癌的风险, 这些抑制剂也能使癌前病变的腺瘤消退. 同时许多研究也直接证实了COX-2在结直肠癌、胃癌和食管癌中的作用主要是通过PGE_2来实现的, COX-2来源的PGE_2的作用是复杂的, 其能够促进细胞增殖, 抑制凋亡, 促进侵袭和转移, 刺激血管生成, 诱导免疫抑制. 因此, PGE_2受体和/或PGE合成酶可能是结直肠癌、胃癌和食管癌化学预防和治疗的新靶点之一.

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■应用要点

COX-2来源的PGE_2等前列腺素类物质与胃肠道肿瘤发生、发展关系密切, 因此, PGE_2受体和/或PGE合成酶可能是结直肠癌、胃癌和食管癌化学预防和治疗的新靶点之一, 同时为COX-2选择性抑制剂在临床的应用提供了更多的分子学依据.

■同行评价
本文科学性强、文字比较精练，比较客观的综述了前列腺素物质在胃肠道肿瘤发病机制中的作用，具有一定的可读性和参考性.

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