·综述·

环氧合酶2/前列腺素E_2通路调控口腔肿瘤机制的研究进展

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[摘要] 口咽癌是全球第6大最常见的恶性肿瘤，5年生存率低于60%，严重影响着人类的健康和生活质量。口腔肿瘤中环氧合酶2（COX-2）/前列腺素E_2（PGE_2）显著高表达，表明该通路与口腔肿瘤密切相关，是口腔肿瘤重要的调控通路。研究表明COX-2/PGE_2通路可通过上调表皮生长因子受体促进肿瘤生长、上调内皮生长因子调节血管生成、上调Bcl-2调节凋亡等不同方式调节口腔肿瘤的发生、发展。本文对该通路在口腔肿瘤中的研究进展进行综述。

[关键词] 环氧合酶2； 口腔肿瘤； 口腔恶性肿瘤； 炎性通路； 癌前病变； 抗肿瘤

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Research progress on regulation of cyclooxygenase-2/prostaglandin E_2 pathway on oral cancer *Kong Lixin, Ren Biao, Cheng Lei. (State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases & Dept. of Cariology and Endodontics, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China)*

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[Abstract] Oral cancer is the sixth most common tumour worldwide. The 5-year survival rate of oral cancer is lower than 60%, and this disease seriously affects human health and quality of life. The cyclooxygenase (COX)-2/prostaglandin (PG) E_2 pathway is significantly elevated in oral tumour tissues. This pathway is thus closely related to oral cancer. The COX-2/PGE_2 pathway can upregulate epidermal growth factor receptor to enhance cancer growth, upregulate vascular endothelial growth factor to promote angiogenesis and upregulate Bcl-2 to induce cancer apoptosis. The COX-2/PGE_2 pathway is one of the most important regulatory pathways in oral cancer. This article will summarise the latest research progress on this pathway in oral cancer.

[Key words] cyclooxygenase-2; oral cancer; oral malignant cancer; inflammatory pathway; precancerous lesions; anti-cancer

肿瘤是在全球范围内导致死亡的一个主要原因。其中口咽癌是全球第6大最常见的恶性肿瘤[1]，包括口腔癌及下咽癌，据估计口腔癌每年新增病例超过500 000例[2]，2/3发生在发展中国家。中国是口腔肿瘤的高发国家[3]，每年新增病例超过11 900例[4]。口腔肿瘤具有高侵袭性，易发生淋巴结转移[5]，也有肺部、心脏等远处器官转移的报道[6-7]，导致治疗困难，易复发，5年生存率低于60%[5-9]，已经对公共健康构成了严重的威胁[10]。

研究[11]证实，肿瘤的发生、发展及转移与环氧合酶（cyclooxygenase，COX）-2/前列腺素（prostaglandin，PG）E_2通路关系密切。该通路已成为肺癌和结直肠癌等的候选治疗靶点，针对该通路的非甾体类抗炎药（nonsteroidal anti-inflammatory drug）具有显著的抗肿瘤活性，有望成为预防肿瘤的候选药物[12-14]。在口腔肿瘤的发生、发展及转移过程中，COX-2/PGE_2通路显著高表

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达，而且研究[15-18]证明该通路可促进口腔肿瘤的生长，抑制细胞凋亡，促进血管生成，增加对化疗药物的耐药等，因此该通路同样是口腔肿瘤中重要的调节通路，也有望成为口腔肿瘤治疗靶点之一。

1 COX-2/PGE_2通路

COX-2/PGE_2通路是一条经典的促炎通路，非甾体类抗炎药的抗炎作用机制即与抑制COX-2有关。COX-2是合成PG的一种主要的酶，PGE_2是一种G蛋白偶联受体配体。COX-2/PGE_2可介导不同的上下游通路，组成复杂的信号通路网。

1.1 COX-2与PGE_2

COX可催化花生四烯酸环化、氧化，生成PG[19]。现有研究[20]将COX分为3类：COX-1、COX-2以及COX-3。COX-1在大多数组织中持续稳定表达，且呈中低表达水平，主要参与调节生理功能，如维持胃肠黏膜完整性、调节血小板功能和肾血流等，维持不同生理功能稳态[19-21]。COX-2的主要功能是调节生理、病理反应，比如炎症[21]。在炎症状态下，PG的合成主要依赖COX-2[19]。在肿瘤的发生、发展及转移过程中，COX-2呈现高表达，与肿瘤密切相关[11]。COX-3是COX-1的另一种剪接异构体，一些止痛药和退烧药（如对乙酰氨基酚、非那西汀、安替比林、安乃近等）能抑制COX-3，从而在疼痛和发烧时发挥作用，但是这种酶确切的功能仍待研究[20,22]。

PG是一种普遍存在的脂肪酸衍生物，在肿瘤、炎症反应、心脏保护、疼痛、发烧等方面发挥重要作用[23]。按结构，PG可分为A、B、C、D、E、F、G、H、I等类型，其中PGE_2是PG家族中主要的一员，在人体内广泛存在。PGE_2是维持内环境稳态的因子，也是长期感染和肿瘤中的重要的介质。PGE_2可选择性地抑制巨噬细胞和中性粒细胞的功能，以及辅助性T（T helper，Th）1细胞、细胞毒性T淋巴细胞和自然杀伤细胞介导的Ⅰ型免疫，促进Th2细胞、Th17细胞和调节性T细胞的应答[24]。PGE_2在人体所有细胞中均可产生，需在磷酸脂酶A的家族成员作用下，先将细胞膜中的磷脂分解成花生四烯酸，再在COX作用下将花生四烯酸转换成PGH_2，最终经PGE异构酶的转换形成PGE_2（图1），其合成的速度主要受COX-2的活性影响[24]。

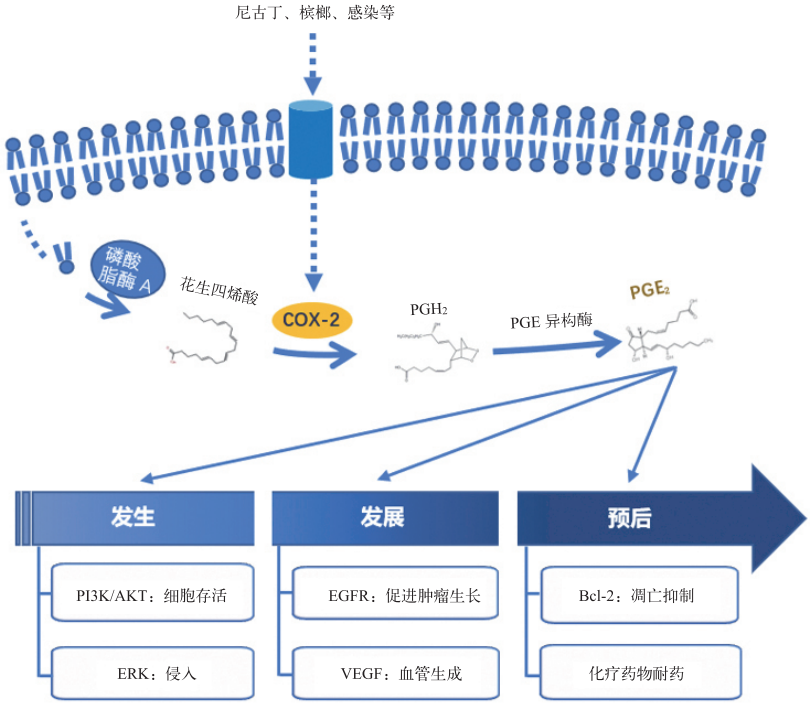

图 1 COX-2/PGE_2通路

Fig 1 COX-2/PGE_2 pathway

1.2 COX-2/PGE_2调节通路

COX-2/PGE_2通路是一条经典的促炎通路，可参与肿瘤发生、发展、转移等多种功能。研究表明，COX-2/PGE_2通路可通过上调B细胞瘤-2基因

（Bcl-2）调节凋亡抑制；通过上调血管内皮生长因子（vascular endothelial growth factor，VEGF）调节血管生成；通过上调基质金属蛋白酶（matrix metalloproteinase，MMP）-2、MMP-9、IL-11以及致癌miR526b调节癌症转移；通过上调表皮生长因子受体（epidermal growth factor receptor，EGFR）促进肿瘤生长；通过激活Wnt/β-连环蛋白/T细胞因子和miR526b抑制双特异性磷酸酶2，进而维持癌干细胞样活性；通过与磷酸肌醇-3激酶（phospho-inositide-3 kinase，PI3K）/蛋白激酶B（protein kinase B，PKB/AKT）的相互作用，维持癌症细胞的存活和炎症状态；通过上调细胞外信号调节激酶（extracellular signal regulated kinase，ERK）和膜蛋白酶促进癌细胞侵入；通过增加调节性T细胞的活性和原肿瘤M2细胞的活性调节免疫系统等[25-26]（图1）。使用非甾体类抗炎药，通过抑制COX-2，抑制PG的合成，并可能通过增强细胞凋亡来抑制增殖，有助于降低癌症风险[14,27]。

2 口腔中COX-2/PGE_2通路的激活

在口腔致癌过程中，常见的口腔致癌物（如香烟和槟榔中的有害成分）被认为是COX-2的强诱导物[18]。例如，尼古丁能通过激活COX-2的表达，促进口腔肿瘤血管生成，进一步促进口腔肿瘤发展[15]。此外，香烟烟雾提取物和镉也可导致大鼠细胞中COX-2的表达增加[28]。咀嚼槟榔是口腔癌的主要危险因素之一，可诱导组织损伤和炎症、COX-2表达和PGE_2生成。槟榔的组分可激活PI3K/AKT、有丝分裂原活性蛋白激酶/细胞外信号调节激酶激酶[mitogen activated protein kinase（MAPK）/extracellular signal regulated kinase（ERK）kinase，MEK]、c-Jun氨基末端激酶（c-Jun N-terminal kinase，JNK）、p38和核因子（nuclear factor，NF）-κB信号传导，介导COX-2表达、PGE_2产生和细胞分化[29]。槟榔提取物还能显著增加人免疫细胞和HacaT细胞中COX-2、PGE_2的表达。将槟榔碱含量降低到50%可显著下调HacaT细胞中c-Jun、c-fos、COX-2和PGE_2的表达，即去除槟榔中50%的槟榔碱可以显著降低槟榔致癌的风险[30]。

口腔微生物也是COX-2/PGE_2通路的诱导因素。例如，用紫外线灭活的口腔共生缓症链球菌（*Streptococcus mitis*）与单核细胞进行共培养，发现PGE_2水平显著升高[31]。而感染缓症链球菌6 h的口腔角质细胞培养液的上清液中PGE_2的水平也显著上升[32]。此外，发现金黄色葡萄球菌也可以诱导COX-2的表达，并增加口腔上皮细胞HOK中PGE_2的产生。而且PGE_2会促进金黄色葡萄球菌的生长以及与纤维连接蛋白的结合，促进金黄色葡萄球菌与口腔上皮细胞的黏附[33]。

3 COX-2/PGE_2与口腔癌前病变及癌前状态

炎症在组织细胞癌变过程中起着重要作用。在炎症过程中通常会表达COX-2，参与组织修复，促进血管生成以及细胞增殖和分化，COX-2水平的变化可能增加细胞癌变风险[34]。在口腔内，各种类型的病变（包括口腔扁平苔藓、口腔白斑和黏膜下纤维化）都有潜在的恶变可能。

口腔扁平苔藓是一种常见口腔黏膜慢性非感染性炎性疾病，有恶变现象，被世界卫生组织列入癌前状态[35]。研究[36-38]发现，70%口腔扁平苔藓病例出现COX-2的过度表达。在侵蚀型口腔扁平苔藓中，COX-2的表达量更高，导致基底膜完整性的破坏，肥大细胞增加[38]。进一步研究[39]发现，COX-2表达增加与口腔扁平苔藓的严重程度呈正相关。而且口腔扁平苔藓炎性渗出液中高表达的COX-2直接调节着萎缩或溃疡/侵蚀型患者的灼热感或疼痛[39]。因此，基于*COX*-2在口腔扁平苔藓发病机制中的特殊作用，研发*COX*-2抑制剂可降低口腔扁平苔藓免疫失调前的炎症过程，对促进口腔扁平苔藓的治疗具有重要意义[38]。

口腔白斑病是指发生于口腔黏膜上以白色角化性病变为主的斑块状损害，是口腔黏膜恶性潜能最高的疾病，属于癌前病变或为潜在恶性病变[40]。研究[41]表明，COX-2在口腔白斑的恶性转化过程中显著高表达，可作为评估口腔白斑恶性转化的标志物。同时，Lin等[42]发现*COX*-2基因的765位点是高发突变位点，该位点为C的等位基因是口腔白斑发展为恶性肿瘤的危险因素，说明*COX*-2基因的突变以及表达水平均可作为监测口腔白斑恶性病变的生物标志物。上皮不典型增生的白斑具有更大的恶变倾向，研究[43]表明可通过拮抗COX-2上调治疗此类白斑。

口腔黏膜下纤维化是一种局限性硬皮病，以口腔黏膜硬化、张口受限为主要特征，与咀嚼槟榔有密切关系，因其发生恶性转化的概率较高，

被列为典型的癌前状态[44]。研究[45]发现，COX-2、P53和MDM2的表达与口腔黏膜下纤维化的进展呈显著正相关。而且当成纤维细胞受到致口腔黏膜下纤维化药物的诱导时，30 min内COX-2即显著上调[46]。因此，COX-2也可作为口腔黏膜下纤维化进展的重要标志物[45]。

由此可见，COX-2/PGE_2对口腔癌前病变、癌前状态以及其恶变过程具有重要的调控作用，也是预测恶变转化的重要标志物。

4 COX-2/PGE_2与口腔癌

大量研究[47-49]表明，COX-2/PGE_2通路可调控肿瘤发生、发展、预后等过程。COX-2的表达与口腔肿瘤细胞的恶性程度呈显著正相关。而PGE_2能促进细胞的增殖，增加细胞的侵袭性，抑制细胞凋亡，还能促进肿瘤相关的血管生成，从而促进肿瘤的生长[15]。

首先，COX-2在口腔鳞状细胞癌的早期即发挥重要作用。有1篇汇集了7项研究的meta分析共纳入2 296名口腔癌患者和3 647名健康对照者，结果表明*COX*-2基因多态性与口腔癌易感性呈显著相关[47]。COX-2能通过与PI3K/AKT相互作用，维持癌症细胞存活和炎症。COX-2抑制剂非甾体类抗炎药可以抑制口腔鳞状细胞癌细胞PI3K/AKT通路活化，达到预防口腔鳞状细胞癌的作用[50]。COX-2/PGE_2也与癌症细胞的侵入有关，COX-2/PGE_2通路可通过上调ERK和膜蛋白酶促进癌细胞侵入。COX-2抑制剂非甾体类抗炎药可抑制口腔鳞状细胞癌细胞ERK表达[50]。

其次，COX-2/PGE_2通路也与口腔鳞状细胞癌发展有关。大量研究[10,51]表明，口腔鳞状细胞癌中COX-2/PGE_2通路显著上调。PGE_2能够上调EGFR信号，促进细胞的增殖[52]。因此，减少PGE_2和EGFR信号间的相互作用，能够减少患口腔癌的风险[52]。比如一种提取自台湾杉的赛菊芋黄素能通过抑制PGE_2与EGFR之间的相互作用，抑制转移瘤裸鼠体内移植口腔鳞状细胞癌的增长[52]。在动物模型研究[53-54]中也发现，抑制COX-2，阻止了口腔鳞状细胞癌的发展。头颈癌的淋巴结转移被证明与COX-2调控VEGF表达相关，这表明COX-2通路在血管生成中起着重要的作用[17]。

再次，COX-2还会影响口腔鳞状细胞癌预后。COX-2过度表达与淋巴结转移相关，即90%淋巴结转移患者被发现有COX-2过度表达，还在93.33%的局部复发病例中发现COX-2过度表达，患者总生存率与COX-2的过度表达密切相关[51]，证明COX-2在评估口腔鳞状细胞癌预后方面具有临床价值[55]。此外，在癌变过程中，凋亡会减少，*Bcl*-2是一种与延长细胞寿命和肿瘤进展相关并抑制细胞凋亡的致癌基因[16]。COX-2的上调可通过介导*Bcl*-2的过度表达，抑制凋亡[16]。

最后，COX-2还会影响化学治疗药物的疗效。顺铂耐药性是一个严重的问题，影响全身化学治疗的长期有效性，晚期头颈部肿瘤的治疗至关重要。研究[18]表明，COX-2表达通过介导晚期头颈部肿瘤的顺铂耐药性，显著增加患者肿瘤复发率。

由此可见，COX-2/PGE_2通路可影响口腔癌细胞的存活、侵入，促进细胞生长、血管生成，抑制凋亡等，与口腔癌密切相关。在很多肿瘤的研究中，都尝试使用选择性抑制COX-2的抑制剂作为一种治疗肿瘤的方法。COX-2的抑制剂能通过抑制COX-2的表达，发挥治疗口腔癌的作用[15]。目前，COX-2抑制剂已经进入预防口腔癌的临床试验阶段[56]。

5 COX-2/PGE_2与口腔颌面部良性肿瘤及囊肿

除了口腔癌，COX-2/PGE_2也与口腔颌面部良性肿瘤及囊肿密切相关。成釉细胞瘤是一种良性的牙源性上皮性肿瘤，约占所有颌骨肿瘤和囊肿的14%，约占口腔肿瘤的1%，是发展中国家最常见的牙源性肿瘤[57-58]。成釉细胞瘤具有局部侵袭性，生长能力不受限制，有很高的恶性转化和转移潜力，约70%的病例发生恶性转化[59]。

促进牙源性上皮向成釉细胞瘤转化的分子和遗传因素与多个基因的失调密切相关[60]。COX-2在成釉细胞瘤中高表达，可通过增加牙本质上皮细胞的增殖，促进成釉细胞瘤的局部扩展，因此COX-2可作为治疗成釉细胞瘤的潜在靶点[60]。COX-2还影响成釉细胞瘤血管生成及其预后。研究[61]发现，当COX-2高表达时，患者5年无病生存率较低，复发率较高。由此可见，COX-2在成釉细胞瘤中表达量上调，且与局部扩展及复发率较高相关，可能影响其预后。2005年世界卫生组织将牙源性角化囊性瘤归类为良性牙源性肿瘤，其可发生在任何年龄，可引起病理性骨折或神经麻

木等。虽然牙源性角化囊性瘤为良性，但也有局部侵袭性[62]，已有恶性转化为鳞状细胞癌的报道[63-66]。Mendes等[67]分析了116例牙源性角化囊性瘤，发现83例（71.6%）患者COX-2表达增加。因此，COX-2通路可能为颌骨侵袭性肿瘤的生物学机制探究提供一些启示[68]。

根尖周囊肿是颌骨内最常见的牙源性囊肿，占所有影响人类颌骨的囊肿的52%~68%[69]。有研究[69]采用免疫组织化学方法检测30例根尖周囊肿活组织检查标本中COX-2的表达，发现COX-2在所有根尖周囊肿标本的内层上皮和上皮下成纤维细胞、巨噬细胞和内皮细胞中均有表达，认为COX-2可能参与了根尖周囊肿发生、发展。含牙囊肿是一种牙源性病变，是继根尖周囊肿之后第2常见的牙源性囊肿，占颌骨所有真性囊肿的约24%[70]，Alsaegh等[60]还发现，COX-2在含牙囊肿上皮中表达，认为COX-2可以通过增加牙源性上皮细胞的增殖，促进其局部扩展。

综上，COX-2在多种口腔颌面部良性肿瘤（尤其是成釉细胞瘤）与囊肿中表达量上调，可能促进病变进展，影响预后。

6 总结

COX-2/PGE_2通路与肿瘤密切相关，其在多数肿瘤细胞中显著高表达。COX-2/PGE_2通路在口腔癌前病变和癌前状态恶变过程中，以及在预测口腔癌前状态恶变转化过程中发挥着重要的调控作用。

COX-2/PGE_2通路还能影响口腔癌细胞存活、侵入，促进细胞生长、血管生成，抑制凋亡等，进而促进肿瘤的增殖和转移。此外，COX-2/PGE_2通路与化学治疗药物耐药性也密切相关。

COX-2/PGE_2可介导不同的上下游通路，组成复杂的信号通路网，起到相互调节的作用，目前研究较为广泛的包括EGFR、VEGF等，但其参与恶性肿瘤具体的机制还不明确，在调控侵入、细胞生长和凋亡等过程中下游信号分子间的相互作用也不清楚，且其与MAPK通路、Wnt通路等其他肿瘤相关调控通路间的交叉作用还有待进一步研究。

此外，COX-2在多种口腔颌面部良性肿瘤及囊肿中也出现类似恶性肿瘤的变化，能促进其进展，在恶化过程中起到调控的作用，但与良性肿瘤的关系及具体调控机制还有待进一步研究。随着对COX-2/PGE_2通路更深入的研究，其有望成为抗炎、肿瘤预防及治疗的靶点。

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