

## *The Biology Behind*

# NSAIDs for the Chemoprevention of Oral Cancer: Promise or Pessimism?

Commentary re J. L. Mulshine *et al.*, Randomized, Double-Blind, Placebo-Controlled, Phase IIB Trial of the Cyclooxygenase Inhibitor Ketorolac as an Oral Rinse in Oropharyngeal Leukoplakia. *Clin. Cancer Res.*, 10: 1565–1573, 2004.

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### Introduction

Oral cancer causes considerable morbidity and is associated with a 5-year survival rate of less than 50%. It is a major problem in populations in which alcohol and tobacco use are prevalent such as in lower socioeconomic communities. Oral cancer, like cancers in many other sites, is often preceded by the development of premalignant lesions of the oral mucosa, also termed intraepithelial neoplasia. Among these premalignant lesions are leukoplakia, erythroplakia, hyperplasia, and dysplasia with leukoplakia being the most common (1). To date, there are no effective treatments documented in randomized controlled clinical trials to prevent malignant transformation of leukoplakia (2). Isotretinoin has been shown to be effective in the resolution of these lesions; however, relapses and significant adverse effects are common (3). The present treatment of choice for premalignant localized oral leukoplakia is surgical removal, but wide distribution of mucosal lesions precludes excision in many patients. Despite even aggressive mucosal resections, these lesions tend to relapse or new lesions appear. In addition, a substantial portion of oral cancers develop away from the site of the visible lesions, perhaps because of widespread abnormalities, the so-called field defect, or through lateral spread from the sentinel lesion further bolsters the appeal of chemoprevention in this clinical setting (4). Therefore, chemoprevention is an attractive approach to the treatment of leukoplakia and oral cancer prevention. Lack of effective therapy is the main rationale for studies examining the ability of a variety of agents, both natural or synthetic, to inhibit carcinogenetic events in the oral mucosa.

Premalignant lesions and malignant lesions of the upper aerodigestive tract have been shown to express genotypic and phenotypic abnormalities including increased DNA index, specific chromosomal abnormalities, and an inactivating mutation of the *p53* tumor suppressor gene (5–8). The dysregulation of *p53* in the mucosal epithelium correlates with increased proliferative activity (9). Moreover, *p53* status has been shown to be a predictor of progression of premalignant oral dysplasias to invasive cancers (10). These molecular alterations have stimulated rational chemopreventive agent selection that targets specific abnormalities detected in the cells of the oral mucosa.

Several classes of agents have shown promise as chemopreventive agents including the nonsteroidal anti-inflammatory drugs (NSAIDs), which possess a valid scientific basis for the chemoprevention of multiple cancers. For those cancers in which they have demonstrated chemopreventive potential, evidence of efficacy is derived from epidemiological, animal studies in relevant model systems, and from tissue cell culture studies. In addition, recent prospective randomized controlled trials have demonstrated convincingly that aspirin prevents the development of intraepithelial neoplasia in the colon and rectum (11, 12).

Because NSAIDs are well-known, well-accepted inhibitors of cyclooxygenase (COX) and prostaglandin (PG) production (Fig. 1), work initially focused on COX- and PG-dependent mechanisms of action of NSAIDs. There are a number of potential COX activities, including multiple mechanisms acting at different stages of carcinogenesis, that could be targets for chemoprevention (Fig. 2). PGs, especially PGE<sub>2</sub>, appear to be important in the pathogenesis of cancer secondary to effects on mitogenesis, cellular adhesion, immune surveillance and inflammation, and apoptosis.

### Evidence for the Chemopreventive Properties of NSAIDs

Correlative studies have shown that PGE<sub>2</sub> and COX-2 are overproduced in colon neoplastic lesions. Additionally, COX-2 has been implicated in tumorigenesis in a variety of tissues including tumors of the head and neck (13). COX-2 is a member of a family of dual function enzymes, PGH synthases, that catalyze the formation of PGs from the fatty acid arachidonic acid. COX-2 mRNA and protein expression is inducible in most tissues by external stimuli such as tumor promoters, growth factors, and cytokines. Overexpression of COX-2 is thought to contribute to carcinogenesis by stimulating cell proliferation (14), inhibiting apoptosis (15), and enhancing angiogenesis (16). These effects are thought to be PG-dependent effects. COX-2 is also thought to hasten carcinogenesis by producing reactive oxygen products as a by-product of its catalytic function (14). In addition, data suggest that PGs contribute to the inhibition of antitumor immune defense mechanisms. As a result, cancer preventive and treatment strategies using NSAIDs, both nonselective and highly selective COX-2 inhibitors, have been focused on tissues that overexpress COX-2. Studies reveal increased levels of COX-2 in premalignant and malignant lesions of the oral cavity (13), which is one rationale for testing these

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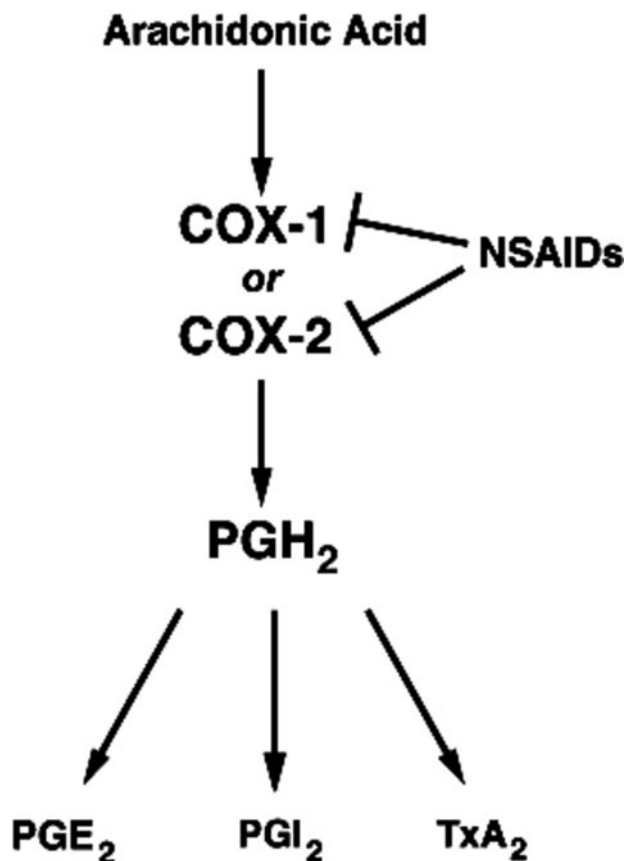


Fig. 1 The catalytic activity of COX-1 and COX-2. Arachidonic acid hydrolyzed from cell membrane phospholipids is transformed into  $\text{PGH}_2$ . Tissue cell specific prostaglandin or thromboxane synthases rapidly convert  $\text{PGH}_2$  into  $\text{PGE}_2$  or  $\text{PGI}_2$  type PGs or thromboxanes.  $\text{PGE}_2$ , prostaglandin  $\text{E}_2$ ;  $\text{PGI}_2$ , prostaglandin  $\text{I}_2$ ;  $\text{TXA}_2$ , thromboxane  $\text{A}_2$ .

compounds in the treatment of lesions such as oral leukoplakia. Additionally, immunohistochemical evidence of expression of COX-2 protein in oral mucosal lesions with a gradient of increasing COX-2 stain was found increasing from hyperplasia to dysplasia and was highest in squamous cell carcinoma (17). Finally, preclinical models have also demonstrated that NSAIDs can inhibit oral cancer development in various models. Interestingly, there are no population-based epidemiological studies examining whether aspirin or NSAID use specifically reduces the incidence or mortality from oral cancer. A large study performed by the American Cancer Society looking at many cancer sites showed a trend toward a reduced risk for occasional aspirin use in males [relative risk, 0.7 (confidence interval, 0.31–1.59)] and an occasional or 1–15 years of use in females [relative risk, 0.68 (confidence interval, 0.2–2.29) or relative risk, 0.55 (confidence interval, 0.09–3.44), respectively; Ref. 18].

Direct evidence of COX in tongue carcinogenesis has been shown in a rat model with inhibition of dysplasia occurring with the administration of NSAIDs in animal models (19–22). Another study with COX-2 overexpression in precancerous lesions and squamous cell carcinomas in rat tongue revealed that the administration of an NSAID reduced the incidence of squamous

cell carcinoma in animals to 23–31% compared with 71% in untreated controls (19). These studies reveal that COX inhibition, particularly COX-2 inhibition, has a potential role in the chemoprevention of head and neck squamous cell carcinomas.

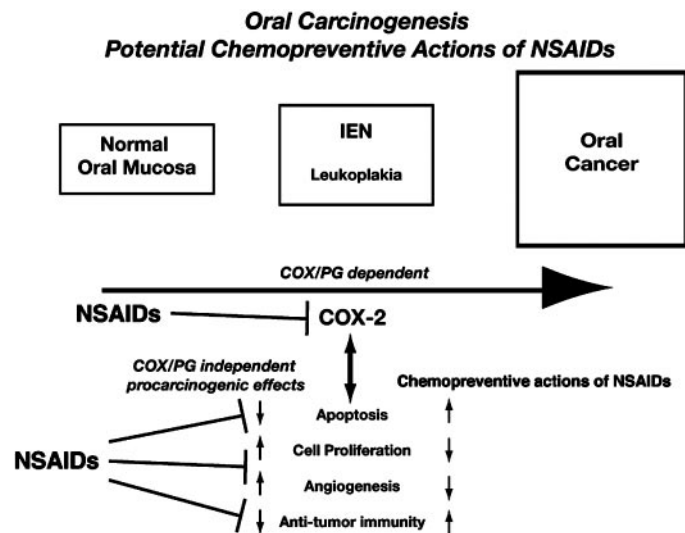
Overexpression of COX-2 increases the level of the anti-apoptotic protein bcl-2 and may cause resistant to apoptosis in premalignant cells, resulting in the survival of damaged cells leading to tumorigenesis (23). An inverse relationship between bcl-2 and apoptosis has been reported in oral epithelial dysplasia (24). These data reveal a clear linkage between expression of COX-2 and inhibition of apoptosis. Additionally, a correlation between p53 and COX-2 expression has been reported with cells that carry mutant p53 expressing high levels of COX-2 (25, 26). Of note, NSAIDs induce apoptosis in colon cancer cells and other tissues, regardless of p53 status (27).

Cell proliferation and angiogenesis is essential for tumor growth and metastasis and is important even in premalignant lesions (28). An additional cellular process by which NSAIDs may inhibit tumor growth is through the inhibition of angiogenesis. A correlation between COX-2 levels and angiogenesis has been shown in several studies with increased production of vascular-endothelial growth factor by epithelial cells (29, 30). Additionally, increased levels of PG synthesis has also been shown to promote cell proliferation and angiogenesis (30). Vascular-endothelial growth factor has been shown to be elevated early in the progression from dysplasia to carcinoma in oral squamous cell carcinoma (31). These findings are consistent with prior reports that revealed overexpression of COX-2 in epithelial cells led to enhanced production of vascular growth factors and the formation of capillary-like networks (32). The inhibition of COX has been shown to cause reductions in angiogenic activity (30, 32) and to reduce tumor invasiveness and metastasis (33, 34). Recently, a selective COX-2 inhibitor was shown in a nude mouse model of oral cancer to delay cell growth and tumor volume by reducing the quantity of new vasculature, providing the additional evidence of the chemopreventive efficacy of COX inhibition in oral cancer (21).

The epidermal growth factor receptor (EGFR), a product of the *erb* oncogene, is also overexpressed in the development of certain epithelial neoplasms early in the development of cancers of the upper aerodigestive tract (35), including oral cancer. It is also overexpressed in premalignant oral leukoplakia as well. Furthermore, EGFR expression has been correlated with lesion severity and proliferative capacity (35). EGF and the ligand of the EGFR induce COX-2, contributing to the increased levels of PG in premalignant and malignant cells in head and neck tumors (36). Retinoids have been shown to inhibit the increased production of COX-2 induced by EGF with no effects on COX-1 and EGFR (36). On the basis of the results of this study, NSAIDs may be useful as chemoprevention agents in head and neck squamous cell carcinoma.

NSAIDs and selective COX-2 inhibitors may prevent carcinogenesis by affecting other non-COX-, non-PG-related molecular mechanisms. The effects of these compounds on cell proliferation, cell survival, or transformation do not appear to be related to the expression of COX isoforms or PGs. Many molecular pathways have been shown to be affected by these agents associated with their effects on cell growth inhibition, including

Fig. 2 Oral carcinogenesis: potential chemopreventive actions of nonsteroidal anti-inflammatory drugs (NSAIDs). IEN, intraepithelial neoplasia; COX, cyclooxygenase; PG, prostaglandin.



peroxisome proliferator-activated receptors, nuclear factor- $\kappa$ B, and apoptosis effector molecules such as BAX, among others (37).

### Limitations of NSAIDs for Chemoprevention in the Oral Mucosa

Transforming growth factor- $\alpha$  (TGF- $\alpha$ ), the ligand of EGFR, is also overexpressed in dysplastic oral leukoplakia. Significant overexpression of TGF- $\alpha$  mRNA was predictive of a response to chemopreventive intervention with 13-*cis*-retinoic acid and its levels were also modulated by this treatment (38). Thus, agents that affect upstream factors in the EGF signaling pathway may be useful chemoprevention agents in oral cancer. Although NSAIDs may be beneficial in inhibiting EGF-induced increases in COX-2, they have not been shown to affect the expression of TGF- $\alpha$  mRNA.

Whereas the NSAIDs are promising chemopreventive agents, prolonged use of these agents is limited by gastric and renal toxicity. As preventive agents, they must possess minimal toxicity for long-term therapy. Novel methods of administration have been evaluated to maximize exposure while minimizing toxicity, with topical therapy being an effective method of administration in animal models (39). These considerations prompted Mulshine *et al.* (40) to conduct a randomized, double-blind, placebo-controlled, trial of the NSAID ketorolac as an oral rinse in oropharyngeal leukoplakia patients. Fifty-seven patients were randomized in a 2:1 ratio to receive ketorolac rinse or placebo twice daily for 30 s over a period of 90 days. Although a valid scientific rationale exists for the use of NSAIDs in oral leukoplakia, similar response rates were observed for the ketorolac and placebo arm, 30 and 32%, respectively, highlighting the need to conduct placebo-controlled trials in this setting. However, is the lack of a differing effect between the ketorolac and the placebo arm because the COX hypothesis is wrong and that inhibiting the pathway does not translate into effectiveness? Does the lack of significant toxicity reported by the authors indicate a lack of systemic exposure in both target tissue and normal tissue? Surrogate measures of activity, including measurements of exposure in the oral cavity (*e.g.*, PGE2

inhibition), would have been beneficial in determining the utility of ketorolac rinse in this trial and for the development of future studies (40). Without biological end points in the target tissue, including assessment of the delivery to the level of the epithelial cells in the basement membrane, we should not abandon the possible role of NSAIDs or COX-2 inhibitors in the prevention of oropharyngeal carcinogenesis.

### Conclusions

Multiple mechanisms by which COX and PG contribute to carcinogenesis have been identified, including the inhibition of apoptosis, increased angiogenesis and invasiveness, modulation of inflammation and immunosuppression, and conversion of procarcinogens to carcinogens (15, 23, 41–43). The NSAIDs, including selective COX-2 inhibitors, induce apoptosis, reduce cell proliferation, and inhibit angiogenesis by both COX-dependent and likely COX-independent mechanisms. Additional mechanistic studies of NSAIDs are needed to determine the relative importance of each of the currently known mechanisms in oral carcinogenesis. COX inhibitors have been shown to be effective chemopreventive agents in the colon and may possess activity in other tissues against other cancers. Although major progress has been made in understanding the link between COX and carcinogenesis, questions remain as to whether NSAIDs would be useful in the treatment of premalignant lesions of the oral cavity.

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