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A DISCUSSION ON CHEMOPREVENTION OF ORAL CANCER BY SELECTIVE CYCLOOXYGENASE-2 (COX-2) INHIBITORS

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Oral cancers are potentially fatal diseases, have a high mortality rate and because of this it is highly challenging for the clinicians. Cyclooxygenase (COX), the key enzyme in prostaglandin cascade, is expressed in two isoform: the constitutive COX-1 and inducible COX-2. COX-2 expression extensively up regulated in oral cancer, oral premalignant lesion and seemed to be enhanced specifically in high-risk oral lesions. In recent studies it has been found that Zinc regulates COX-2 expression in vivo, in animal model may lead to prevention or therapeutic possibilities for upper aerodigestive tract cancer. The data in recent literatures strongly indicate that COX-2 expression is extensively up-regulated in oral cancer and it is believed that COX-2 inhibition strongly suppressed the oral lesion therefore; selective COX-2 inhibitor should be investigated as new chemopreventive agents for patient who are at high risk for developing oral cancer.

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1. Introduction

Oral malignancy, (OSCC), is a major health problem worldwide (400,000 cases per year) [1]. Sixteen million new cases of cancer are estimated every year by 2020 [2]. Its incidence and mortality in the United States is increasing in recent years especially among young males [3] and approximately 28260 new cases and 7230 deaths were expected in 2004 [4]. The five year survival rate remains about 50% inspite of advances in chemotherapy and Radiotherapy. The surviving patients are also left with severe functional compromise and may develop a second cancer within a few years [4, 5]. It is important to recognize preventive strategies for this disease. The advent of genomics has provided insight into the mechanisms by which normal cells become cancerous [6].

The arachidonic acid metabolism has been suggested to play an important role in oral carcinogenesis [7]. Cyclooxygenase (COX), the key enzyme required for the conversion of arachidonic acid to prostaglandins was first identified over 20 years ago. Drugs like aspirin that inhibit cyclooxygenase activity have been available to the public for about 100 years. Two-cyclooxygenase isoform have been identified and are referred to as COX-1 and COX-2. Under many circumstances the COX-1 enzyme is produced constitutively (i.e. gastric mucosa) where as COX-2 are inducible (i.e. site of inflammation) [8]. Cyclooxygenase-2 (COX-2) was barely detectable in the normal epithelium but u-pregulated in hyperplasia and squamous cell carcinoma [9]. The development of resistance to variety of chemotherapeutic agents is one of the major challenges in effective cancer treatment [10]. COX-2 inhibitor prevent the growth of human oral

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cancer in both prostaglandin E2 (PGE2) dependent and independent manners [11] and suppressed 4 nitroquinoline-1-oxide induced tongue cancer in rats as well [12]. COX-2 selective inhibitor includes, SC-58125 [13], Celecoxib [14] and NS398 [15]. These inhibitor do not induce the gastric ulceration associated with the use of traditional NSAIDs, and in clinical trial, celecoxib reduced duodenal polyposis [16].

In the 1980s, work using a number of animal models of oral cancer chemoprevention suggested that nonselective NSAIDs could inhibit tumor development [17, 18]. Furthermore, indomethacin, a nonselective COX inhibitor inhibited the growth of squamous carcinoma of head and neck in clinical study [19]. Recently this idea has been revisited exploring the potential of COX-2 selective inhibitors for oral cancer prevention [20, 12]. Shiotani et al [12] showed inhibition of post initiation tumor development by the NS398 analogue nimesulide in rat oral carcinogenesis model in which COX-2 was overexpressed during carcinogenesis [12]. These observations underscore the importance of the action of COX-2 selective inhibition in oral carcinoma cells. NSAIDs are known to exert their effect by mechanism dependent and independent of the inhibition of prostaglandin synthesis [21].

NS398 might induce growth inhibition in oral cancer cells by either of these mechanisms. High concentration of NS398 (greater those required to inhibit prostaglandin synthesis) has been shown to induce COX-2 independent apoptosis in colon carcinoma cell lines [22]. Because topical treatment is a viable option for oral cancer chemoprevention, effects of relatively high concentration of COX-2 selective inhibitor would be clinically relevant. However COX-2 dependent effects of NS398 occur at low concentration and would on the expression of COX-2 in oral tumors. COX-2 is over expressed in oral squamous cell carcinoma (OSCC), particularly in early stage tumors. The COX-2 inhibitor NS398 was found to inhibit cell proliferation by mechanism that at low and high concentration, are dependent on or independent of reduced PGE2 synthesis respectively. Furthermore, suppression of the production of secreted PGE2 is a major mechanism of COX-2 dependent growth inhibition [1].

2. Oral cancer

Tobacco has been identified as a key cause of oral cancer. Worldwide there are 1 billion people smoke and 600 million-chew tobaccos [23]. Seemingly oral cancer only accounts for a small portion of all cancer occurring in humans. However real situation is much more serious because this disease develop slowly (typically requiring about 20 years or even longer to develop on invasive lesions) so that there are large no of individuals at risk at any point of time. According to a formula developed for estimating the size of a risk group (yearly incidence rate x latent year), a time interval on the order of 20 years can serve as a rough estimates [24]. Despite the ready accessibility of oral cavity to direct examination, oral malignancy is still, often not detected until a late stage. Over the past three decades, inspite of advancement of many treatments these cancers have been developed with the most recent protocols for surgery, radiation or chemotherapy, post treatments survival has been improved only marginally [25]. Ever after successful primarily therapies, 30%-50% of patients have local, or regional recurrence and 10%-40% have a second primary tumor [26, 27].

3. Cyclooxygenase

In 19th century, the Bayer Company produced a molecule having analgesic activity called acetylsalicylic acid or aspirin, called nonsteroidal anti-inflammatory drugs (NSAIDs), which are still 100 years later among the most widely, used therapeutic agents known to human kind. In one year in the US alone approximately 50 million people, spending some 5-10 billion dollars, consume NSAIDs for the treatment of a wide spectrum of pathophysiological conditions. These include prophylaxis against cardiovascular disease, relief of the discomfort associated with minor injuries and headaches, and allevation of severe pain caused by variety of inflammatory and degenerative joint diseases [9].

Despite the wide use of NSAIDs over the last century the mechanism of action was not fully appreciated until 1971, when Vane published his seminal observation proposing that the ability of NSAIDs to suppress inflammation rests primarily on their ability to inhibit the cyclooxygenase (COX) enzyme [28]. This would limit the production of proinflammatory prostaglandins (PGs) at a site of injury. Given this, NSAIDs have been used by scientists for last 25 years to dissect the critical role that both the COX enzyme and the eicosinoids (PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2, and TXA_2.) derived from this pathway have a normal and abnormal physiological status. The chemistry of the eicosanoid biosynthetic pathway is well known. Prostaglandins are formed by the oxidative cyclization of the central 5 carbons within 20 carbon polyunsaturated fatty acids [29]. The key regulatory enzyme of this pathway is COX (COX) (PGH synthase), which catalyzes the conversion of arachidonic acid (or other 20 carbon fatty acids) to prostaglandin (PG) G_2 and PGH_2. PGH_2 is subsequently converted to a variety of eicosanoids that include PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2, and thromboxane (TX) A_2. (Fig.1).

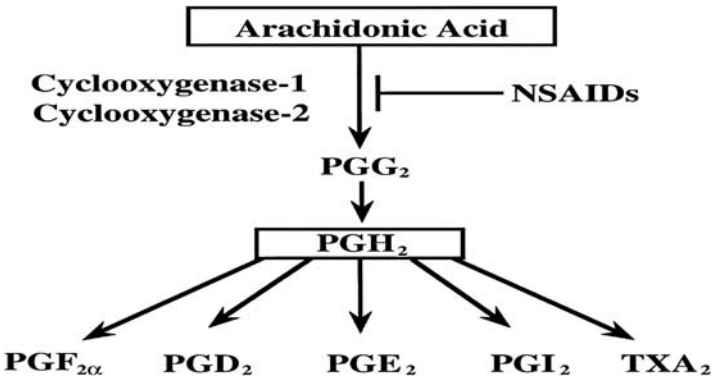

Fig. 1. Schematic diagram for the conversion of arachidonic acid to prostaglandins and other eicosanoids by the cyclooxygenase enzymes.

The array of PGs produced varies depending on the downstream enzymatic machinery present in a particular cell type. For example, endothelial cells primarily produce PGI_2, whereas platelets mainly produce TXA_2 [30, 31]. All NSAIDs in clinical use have been shown to inhibit COX, leading to a marked decrease in PG synthesis [32]. Prostaglandins are present in a wide variety of human tissues [29]. PGs not only play a central role in inflammation, but also regulate other critical physiological responses. In humans, prostaglandins are involved in diverse functions, including blood clotting, ovulation, initiation of labor, bone metabolism, nerve growth and development, wound healing, kidney function, blood vessel tone, and immune responses. In contrast to hormones such as cortisone or thyroxin, which have broad systemic effects despite being released from a single site in the body, PGs are synthesized in a broad range of tissue types and serve as autocrine or paracrine mediators to signal changes within the immediate environment. (Fig.2).

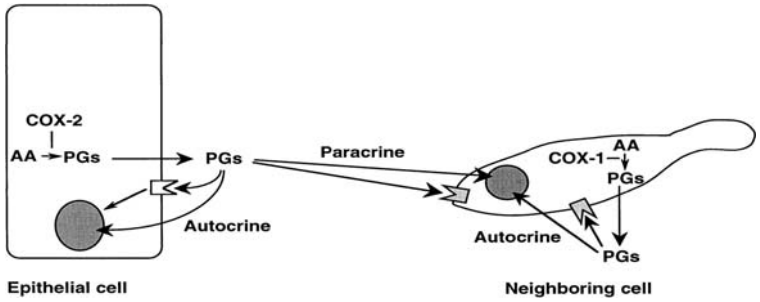

Fig. 2. Schematic diagram of potential mechanisms involved in the cyclooxygenase-mediated regulation via paracrine and autocrine pathways. Arachidonic acid, AA; prostaglandins, PGs; receptor-mediated pathways are indicated. Prostaglandins can act via G-coupled cytoplasmic membrane receptors or nuclear peroxisome proliferator activated receptors (PPARs). Obviously, to activate PPARs, prostaglandins would not necessarily have to exit the cell and then reenter; they could transit directly from the cytoplasm to the nucleus.

Two classes of prostaglandin receptors exist to transduce signals upon binding of ligand, the G-coupled cytoplasmic receptor class (i.e., EP1-4 for PGE_2) and the nuclear PPAR receptor class (i.e., PPARα, PPARγ, PPARδ), which acts directly as a transcription factor upon ligand binding [33]. It is not surprising that systemic suppression of PG synthesis through inhibition of COX can lead to unwanted side effects. In particular, individuals taking NSAIDs for even short periods of time can experience gastrointestinal and renal side effects [34, 35] in addition to effects on other physiological systems. As many as 25% of individuals using NSAIDs experience some type of side effect, and as many as 5% develop serious health consequences. Concurrently, investigators looking at PG production in response to cytokines and other inflammatory factors noted increases in COX activity that could only be accounted for by increased expression of another cyclooxygenase [36]. Both immunoprecipitation of this COX variant with an anti-COX antibody, as well as the production of an antibody that precipitated only the COX-2 isoform, allowed for the identification of two different COX isoforms. It was subsequently determined that the COX-1 and COX-2 proteins are derived from distinct genes that diverged well before birds and mammals [37]. These early studies revealed that while both enzymes carry out essentially the same catalytic reaction and have similar primary protein structures [38], many of the inflammatory, inducible effects of COX appeared to be mediated by the newly discovered COX-2, while many of the 'housekeeping' effects of COX appear to be mediated by COX-1. This functional role for each isoform is consistent with their tissue expression patterns: nearly all normal tissues were found to express COX-1 with low to undetectable levels of COX-2. However, COX-2 is constitutively expressed in the brain and kidney of rodents. Other differences between COX-1 and COX-2 include differences in utilization of arachidonic acid substrate pools as well as in mRNA stability [39, 40]. COX-1 and COX-2 also show major differences in mRNA splicing, stability, and translational efficiency. Regulation of COX-2 at the mRNA level appears to be an important mechanism by which some physiological mediators, notably the corticosteroids (consistent with their immunosuppresive properties, down-regulate COX-2 expression), act to regulate PG production. Another major difference between COX-1 and COX-2 appears to be in their ability to use different substrate pools. For example, in both fibroblasts and immune cells, COX-2 was able to utilize endogenous arachidonic acid whereas COX-1 was not. In these systems, COX-1 requires exogenous substrate. Soluble PLA_2 can produce an alternative source of substrate for COX-1, and Herschman [30] has suggested that in some tissues the release of $sPLA_2$ from neighboring cells might provide the primary regulation of COX-1 activity. If this is the case, then the regulatory elements responsible for increasing PG production would not involve the COX-1 gene, but rather the $sPLA_2$ gene. In summary, the COX-1 and COX-2 genes are regulated by two independent and quite different systems even though the enzymatic reaction they catalyze is identical.

4. COX-2 in oral cancer and premalignancy

Analysis by the use immunohistochemical shows expression of COX-2 in multiple cancers occurring in humans, including those involving the esophagus stomach, breast, pancreas, lung, colon, skin, urinary bladder and prostate [23]. The selective COX-2 inhibitors have been shown to affect induction of cancer in colon, lung, and other epithelial cells [41, 42].

Immunostaining of human tissue shows that COX-2 enzyme is extensively expressed in oral cancer and other head and neck cancer compared with normal oral mucosa, COX-2 enzyme is

increased by nearly 150 fold in cancerous lesion. An increased expression of COX-2 is also found in human salivary gland adenomas and carcinomas [43-45]. Western blot analysis shows that COX-2 level is increased markedly in cell lines obtained from laryngeal and oral SCC [46]. In a clinical study, levels of COX-2 mRNA were measured in 15 patients who underwent resection of head neck squamous cell carcinoma (HNSCC). Normal oral mucosa was obtained from 10 nonsmoking, non drinking healthy volunteer subjects. A nearly 100 fold increase in COX-2 mRNA amount was detected in HNSCC. By immunoblat analysis; COX-2 protein was detected in HNSCC cases but was undetectable in normal mucosa. New studies also show that the COX-2 enzyme is overexpressed in variety of human oral leukoplakia and premalignancies [47-50]. In a recent clinical study, for example, COX-2 gene product was examined in healthy person, oral dysplastic cases and carcinoma. The examinations were conducted, in 30 healthy people, in 22 patients with dysplastic lesion without previous and concomitant carcinomas and in 29 patients with oral carcinomas. The immunohistochemical findings were verified by western blotting, COX-2 expression was correlated to DNA content as genetic risk marker of oral cancer. COX-2 is upregulated from healthy to premalignant to cancerous oral mucosa. Weak COX-2 staining was found only in 1 case of healthy oral mucosa (3%) as compared with strong staining in 9 of 22 dysplastic lesions (41%) and in 26 of 29 carcinoma (88%) [51].

There are several theories to explain, the role of COX-2 plays in oral cancer or premalignancy but the main mechanism remain unclear. A large body of data particularly research studies in colon or other tissue/organ suggest that the effect of COX-2 on tumor development and progression are most likely to be multifactorial and should include the following ways [23].

a) Inhibition of apoptosis: Increase expression of antiapoptotic proteins and decrease expression of proapoptotic proteins.

b) Stimulation of angiogenesis: Stimulate angiogenesis and increase expression of VEGF, a proangiogenic protein.

c) Immunosupression: Decrease immune surveillance by increasing IL-10 and decreasing IL-12, which in turn can suppress immune cells.

d) Enhanced invasiveness: increase expression of various matrix metalloproteinases, which are a family of degradative enzyme and would play a key role in the cancer invasiveness and metastasis.

e) Increased Mutagenesis: Result in the formation of highly reactive byproducts that act as mutagens by forming DNA adducts.

5. COX-2 with biomarkers

Studies have demonstrated the value of DNA (diploid) contents as prognostic marker. It serves as a harbinger of a multitude of early and significant events in cancer development [52]. Recently a clinical study, conducted in a total of 81 clinical subjects: collected normal samples, dysplastic lesions and carcinomas from the oral cavity. In addition to examination of COX-2 expression in the tissue samples, COX-2 level was compared with occurrence of DNA ploidy status that serves as genetic risk marker of oral cancer. The findings showed significant difference in the distribution of DNA content between the COX-2 expressing and non-expressing lesions. All healthy mucosa had a normal DNA content. In 22 cases with dysplasia, 9 patients had an aberration (aneuploid). COX-2 over-expression was observed in these 9 patients with premalignant lesion and exclusively in a subgroup of lesions with aberrant DNA content. By contrast, none of the other 13 cases with diploid or tetraploid dysplasia showed COX-2 expression. This study provides a novel link between COX-2 overexpression and DNA aneuploidy in dysplastic oral lesion. In oral premalignant lesion COX-2 is exclusively expressed in those lesion identified to be at considerable increased risk of carcinoma by the aberrant DNA content. This premalignant lesion at high risk of developing oral cancer indicates a prognostic role for COX-2 over-expression [41, 53]. This clinical study also examined the correlation of COX-2 expression with eIF4E, which is believed to be a biomarker in individuals at high risk for relapse after treatment of HNSCC. Immuno-histochemical analysis showed expression of COX-2 and eIF4E in all cancers but no expression in normal tissue. Particularly, in dysplastic epithelium, there was a significant

correlation between the expression of eIF4E and COX-2. There was a significant increase in the proportion of cases that expressed both molecular marker and COX-2 with increased grades of dysplasia [46].

6. Dietary zinc modultion of COX-2 expression

Esophageal and tongue cancers have both been associated with dietary zinc deficiency (ZD), and cyclooxygenase *(*COX-2) is often overexpressed in these cancers [54]. By using rat models, they examined whether zinc regulates COX-2 expression in these cancers. Expression of COX-2 protein and mRNA in rat lingual and esophageal epithelia in control (zinc sufficient [ZS]) rats, during ZD, and after intragastric zinc replenishment (ZR) were determined by immuno-blotting, immuno-histochemistry, and real-time quantitative polymerase chain reaction. COX-2 gene expression, cell proliferation, and apoptosis were analyzed in ZD, ZR, and ZD rats treated with the COX-2 inhibitors celecoxib and indomethacin. Tumor development in ZD rats treated by continuous exposure to the carcinogen 4-nitroquinoline 1 oxide (NQO), which causes tongue tumors in rats, was compared with those in NQO-treated ZS rats. Statistical tests were two-sided. The esophagus and tongue of ZD rats were hyperplastic and expressed COX-2 protein and mRNA at 8- to 14.7-fold higher levels than control rats. Within hours ZR reduced COX-2 overexpression to threefold than in control rats and reversed the hyperplastic phenotypes. The esophagus of ZD rats treated with celecoxib or indomethacin showed a reduction in cell proliferation and stimulation of apoptosis. NQO treatment resulted in greater incidence of lingual squamous cell carcinomas and greater tumor multiplicity COX-2 overexpression accompanies hyperplasia in ZD rats. Increased cell proliferation in NQO-treated ZD rats facilitates the development of tumors at multiple sites. The finding that zinc regulates COX-2 expression in vivo in an animal model may lead to prevention or therapeutic possibilities for upper aerodigestive tract cancer.

7. COX-2 inhibitor and oral cancer chemoprevention

In most preclinical study, cox-2 inhibitor reduces the growth rate of established tumors rather than causing tumor regression. Therefore to date, major emphasis on selective cox-2 inhibitor has focused on evaluating their role in cancer prevention [55]. Cancer chemoprevention is the use of pharmacological or natural agent to prevent, suppress, or reverse the process of carcinogenesis. For this purpose, selective cox-2 inhibitors are tested in numerous studies and have shown a potential role for prevention of colon, breast, skin, bladder, and other cancers [57-59]. Moreover, recent studies also indicate such efficacy of selective COX-2 inhibitor for oral cancer chemoprevention.

Researchers studied the inhibitory effects of selective COX-2 inhibitors on the development of dysplasia in the tongues of rats initiated with a carcinogen, 4-nitroquinoline 1-oxide. The study rats were given 15 ppm of the carcinogen in their drinking water for 8 weeks, followed by a diet containing one of two selective COX-2 inhibitors (150 and 300 ppm of either nimesulide or etodolac for 16 weeks). Study findings indicated that both inhibitors reduce the incidence and multiplicity of oral squamous dysplasia and carcinomas [60]. In another study, using the same rat model and the same procedures to produce the oral premalignancy, nimesulide inhibited chemically induced oral carcinogenesis through suppression of COX-2 expression. This treatment exerted chemopreventive ability by inhibiting cell proliferation activity and inducible nitric oxide synthesis expression [61].

In an *in vitro* study using cultured oral SCC cells, an inhibitory effect from NS398 (a COX-2 inhibitor) on PGE2 production and growth of the carcinoma cell lines was found. These findings suggest that molecular targeting of COX-2 and PGE2 may be useful as a chemopreventive strategy for oral cancer [62].

In an *in vitro* study, JTE-522 (a COX-2 inhibitor) was used to treat cultured oral SCC, KB cell line. The treatment induced an increase of G1 phase-arrested cells, suppression of platelet-derived growth factor (PDGF) production, and inhibition of derived telomerase activity. In this *in*

vivo study, the growth of the oral SCC tumor xenografted into nude mice was observed. Selective COX-2 inhibitor significantly suppressed tumor growth and angiogenesis at the periphery of the tumor. The treatment produced suppression of telomerase activity and an increase of apoptotic cell death in the tumor [60]. Researchers also investigated the effect of selective COX-2 inhibitor, NS398, on the growth of HNSCC cell lines by using cell proliferation way, cell cycle analysis, and quantification of apoptosis. This agent resulted in a significant dose-dependent inhibition of cell growth and a significant increase in the number of cells in the G0/G1- phases of the cell cycle [64]. Recently, new studies, using the same animal model and cell line, have started treatment immediately after inoculation of the malignant cells. The selective COX-2 inhibitor treatment, with the use of 1, 500 ppm and 3, 000 ppm Celecoxib, resulted in an inhibitory effect on SCC.

8. Combind treatment strategy with COX-2 inhibitors

Selective COX-2 inhibitors show a reduced growth rate, not a regression, of established tumors in most preclinical studies. Therefore, selective COX-2 inhibitors are believed to be most beneficial when administered in combination with radiation or other standard therapies to improve the efficacy of these treatments [65]. Several experimental studies have been conducted, with encouraging results, to investigate such enhancement of treatment efficacy when chemotherapy or radiations are combined with selective COX-2 inhibitors [67-69]. Researchers also expect that a combined strategy using selective COX-2 inhibitor and a retinoid could be more effective than either agent alone. This treatment strategy would permit a lower dose of retinoid to avoid the associated toxicity of oral cancer chemoprevention [55]. Additionally, recent animal studies have tested a new and localized treatment strategy of topically applied, polymer-delivered Celecoxib to targeted lesions for COX-2 inhibition of oral SCC. This topical approach could further reduce the risk of systemic side effects with administration of selective COX-2 inhibitors without sacrificing treatment efficacy [69]. Torrance et al [70] made a major contribution to the field of cancer chemoprevention when they presented strong evidence supporting molecular-targeted approaches with combined agents. EKB-569 (an irreversible inhibitor of the intracellular tyrosine kinase domain of EGFR) and the non-selective COX inhibitor, sulindac, demonstrated major activity in a 2 x 2 factorial design involving an animal model of intestinal neoplasia. This led to recent follow-up studies of the COX-2-selective inhibitor celecoxib combined with EKB-569, which showed similar results to the sulindac-EKB-569 data in the same *in vivo* model. Celecoxib combined with EKB-569 produced highly significant reductions in polyp number and in survival when compared with the diet only control group or with the two groups receiving EKB-569 or celecoxib alone. The molecular basis of cross talk between EGFR signaling and COX-2 metabolic pathways is becoming more clear (Fig. 3).

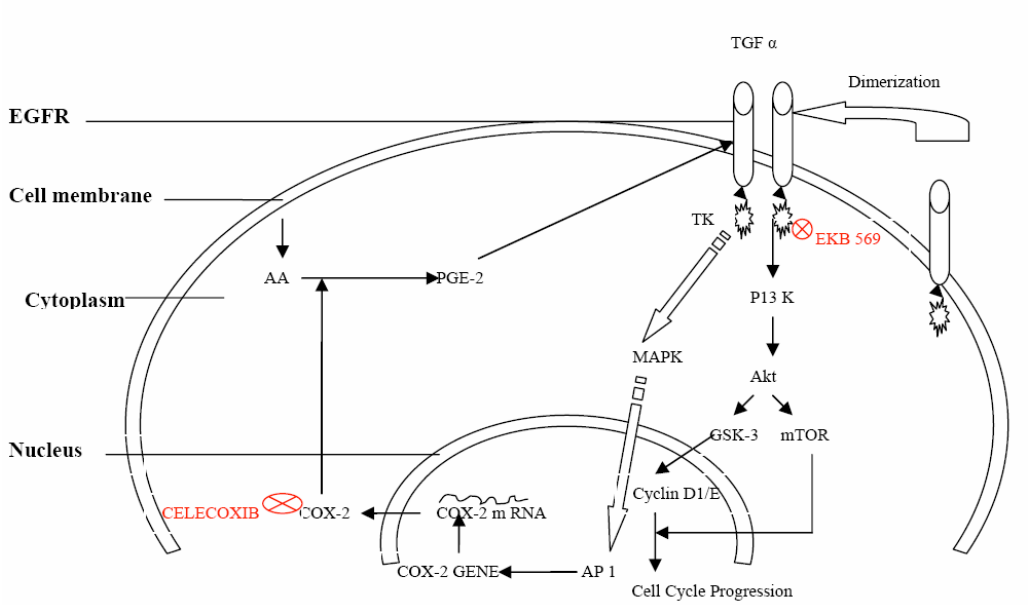

Fig. 3. Activation of the EGFR and downstream mechanisms activates cyclin D1 through MAP kinases (MAPK), but may in addition activate COX-2, which synthesizes PGE2. PGE2 may in turn stimulate EGFR through mechanisms that are cell type specific. In some cells, PGE2 can stimulate protease activity resulting in the release of ligands of EGFR from the plasma membrane, which then leads to EGFR activation. In other cell types, PGE2 can induce the transcription of amphiregulin, resulting in increased EGFR signaling. The mechanisms that are important in aneuploid oral leukoplakia are yet to be determined. In clinically relevant doses, EKB 569, an inhibitor of EGFR, inhibits cell proliferation, an effect that is reversed by PGE2. Likewise, in clinically relevant doses, celecoxib, a selective inhibitor of COX-2, blocks EGFR stimulated cell proliferation. Activator protein-1 (AP-1) is a family of proteins, responsible for the regulation of expression of a number of genes, including the COX-2 gene.

Other data showing the clinical promise of the combination of EKB-569 plus celecoxib include the following: the combination of a HER2 antibody plus a COX-2 inhibitor, tested *in vivo*, was more active than either one alone [71]. COX-2/prostaglandin E2 (PGE2) can increase EGFR activity *in vitro* and *in vivo* [72, 73] EGFR and HER2 can regulate COX-2 transcription (via MAPK/AP1) [74, 75] and EGFR TKIs can downregulate COX-2 [76, 77]. Recently, Chen et al [78] reported *in vitro* studies of the interactions of celecoxib with two reversible EGFR TKIs in several head-and-neck cell lines (including the 686 cell line from the oral cavity). They reported significant combined activity in all cell lines, including synergistic growth inhibition in cell line 686. The combined agents acted mainly on the G1 phase of the cell cycle and on the induction of apoptosis, and had strong antiangiogenic activity. Furthermore, the combination (versus the single agents) enhanced down-regulation of phospho-EGFR and effectively blocked downstream signaling molecules (phospho-MAPK, -STAT3 and –AKT).

Since inhibitors of EGFR and COX-2 are cytostatic and oral cancer involves alterations in more than one signaling pathway, neither agent, targeted specifically and solely, can be expected to completely block tumor formation or progression. Taken together, these findings suggest that inhibiting EGFR or COX-2 would be promising strategies for preventing and treating head and neck cancer.

Abbreviation

NSAIDs = Non-steroidal anti-inflammatory drugs
COX = Cyclooxygenase
SCC = Squamous cell carcinoma
VEGF = Vascular Endothelial Growth Factor
HNSCC = Head neck Squamous cell carcinoma
PG = Prostaglandin
IL = Interleukin

9. Conclusion

Oral cancer has a high mortality rate hence it is challenging disease for clinicians. It is difficult to identify a new and effective agent for chemoprevention or early treatment of oral cancer that mitigates or eliminates serious side effects. COX-2 is extensively upregulated in oral SCCs and premalignant lesions. It is finding that zinc regulates COX-2 expression and may lead to prevention or therapeutic possibilities for upper aerodigestive tract cancer. Selective COX-2 inhibitors have potential role for clinical application against this disease. Selective COX-2 inhibitors are believed to be most beneficial when administered in combination with radiation or other standard therapies to improve the efficacy of these treatments Therefore, further studies and clinical trials appear to be warranted.

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