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Arachidonic Acid Metabolism and Its Implication on Head and Neck Cancer

Sittichai Koontongkaew[1,2] and Kantima Leelahavanichkul[1]
[1]*Faculty of Dentistry, Thammasat University, Pathumthani*
[2]*Medicinal Herb Research Unit, Thammasat University, Pathumthani*
Thailand

1. Introduction

Most of head and neck cancer (HNC) are squamous cell carcinoma. Recent advances in molecular biology have documented significant genetic differences between head and neck squamous cell carcinoma (HNSCC) cells and normal cells, leading to the development of potential new therapeutics and chemoprevention (Choi & Myers, 2008). Historically, the association between inflammation and cancer has been recognized. More recently, a number of chronic inflammatory diseases have been shown to be associated with a variety of human cancers, including HNC (Conroy *et al.*, 2010; Fitzpatrick & Katz, 2010). The relationship between oral health and cancer has been examined for a number of specific cancer sites. Several studies have reported associations between periodontal disease or tooth loss and risk of oral, upper gastrointestinal, lung, and pancreatic cancer in different populations (Meyer *et al.*, 2008). Cumulating evidences support the view that inflammatory mediators, some of that may downregulate DNA repair pathways directly or indirectly. Certain inflammatory mediators may affect on cell cycle checkpoints that result in the accumulation of random genetic alterations. These in turn lead to a genomically heterogenous population of expanding cells naturally selected for their ability to proliferate, invade and evade hose defenses (Colotta *et al.*, 2009).

Molecular studies of the well-known relationship between polyunsaturated fatty acid metabolism and carcinogenesis provide novel molecular targets for cancer chemoprevention and treatments. Several classes of agents have shown promise as chemopreventive agents, including the nonsteroidal anti-inflammatory drugs (NSAIDs), which posses a valid scientific basis for the prevention of multiple cancers, including HNC. Because NSAIDs are well-accepted inhibitors of cyclooxygenase (COX) and prostaglandin (PG) production, research work initially focused on COX-and PG-dependent mechanism of NSAIDs actions. Polyunsaturated fatty acid, including arachidonic and linoleic acids, can enhance tumorigenesis (Shureiqi & Lippman, 2001). Aberrant arachidonic acid (AA) metabolism, especially COX-2 and 5-lipoxygenase (5-LOX) pathways, are activated during oral carcinogenesis, and can be targeted for cancer prevention (el-Hakim & Langdon, 1991). Recently, we found that inhibition of AA metabolism caused a decrease in HNSCC cell invasion and matrix metalloproteinase (MMP) activities. Our findings suggest the contributory roles of COX and LOX in HNC development and progression (Koontongkaew *et al.*, 2010).

This review will briefly summarize the implication of AA metabolism in HNC. We will discuss what are known of COX and LOX in tumorigenesis of HNC. Possible mechanisms of action of COX and LOX and potential roles for AA inhibitors in the prevention and therapy of this cancer will be documented in this review.

2. Arachidonic acid cascade

AA is a long chain polyunsaturated fatty acid containing 20 carbons. It can be stored in membrane phospholipids and released from nuclear envelop or plasma membrane by cytosolic phospholipase A2 (cPLA2), either constitutively or in respond to a variety of cell specific stimuli, including growth factors, hormones, cytokines, signaling molecules, or cell trauma. Free AA can be subsequently metabolized by three key enzymes, COX, LOX, or cytochrome P450 (CYP450) to generate lipid mediators, eicosanoids, which involved in various biological function, inflammation regulation, and more recently, tumor progression (Funk, 2001; Wang *et al.*, 2007; Hyde & Missailidis, 2009). COX metabolism generates prostanoids, including prostaglandins (PGs) and thromboxanes (TXs). LOX generates leukotrienes (LTs), lipoxin (LXs) and hepoxillins (HOs). CYP450 metabolic pathway gives a family of lipoxygenase-like hydroeicosatetraenoic acids (HETEs), epoxyeicosatrienoic acids (EETs) and ω-HETEs (Capdevila *et al.*, 2000).

2.1 The COX pathway

In the COX pathway, COX first oxidized AA to form prostaglandin G2 (PGG_2), and is then metabolized into an intermediate prostaglandin H_2 (PGH_2) by peroxidase activity (Figure 1). PGH_2 is an unstable endoperoxide, which is catalyzed to five primary prostanoids, including PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and thromboxane A_2 by specific synthases.

Three isoforms of COX have been identified, COX-1, COX-2 and COX-3 (Williams *et al.*, 1999; Wang *et al.*, 2007). COX-1 and COX-2 are similar in structure and catalytic activity. Both enzymes have the same molecular weight and share a 61% amino acid sequence homology. COX-3 is the splice variants of COX-1, which retains intron 1 and has a frameshift mutation (Wang *et al.*, 2007). COX-3 was constitutively highest expressed in the cerebral cortex and heart tissue (Chandrasekharan *et al.*, 2002). COX-1 is constitutively expressed in almost all tissues and resident inflammatory cells. It generates PGs that control homeostasis. COX-2 is normally undetectable. Constitutive COX-2 expression is well recognized in brain, kidney and the female reproductive tract. However, COX-2 is the most important regulator in the respond to inflammation and many types of cancers. COX-2 can be induced by multiple cytokines and growth factors, via activation of transcription factors that act on the promoter region, including TATA box, and NF-IL6 motif, two AP-2 sites, three Sp1 sites, two NF-κB sites, a CRE motif and an E-box (Park *et al.*, 2006).

The PGEs subclass, including cytosolic PGE synthase (cPGEs) and membrane-bound PGE synthases (mPGEs), is also involved in inflammation and carcinogenesis. Once the various PGs are synthesized, they are exported into the extracellular microenvironment and bind to the specific G-protein coupled receptors (GPCRs) that can be activated by autocrine and paracrine fashions in the tumor microenvironment (Sugimoto & Narumiya, 2007).

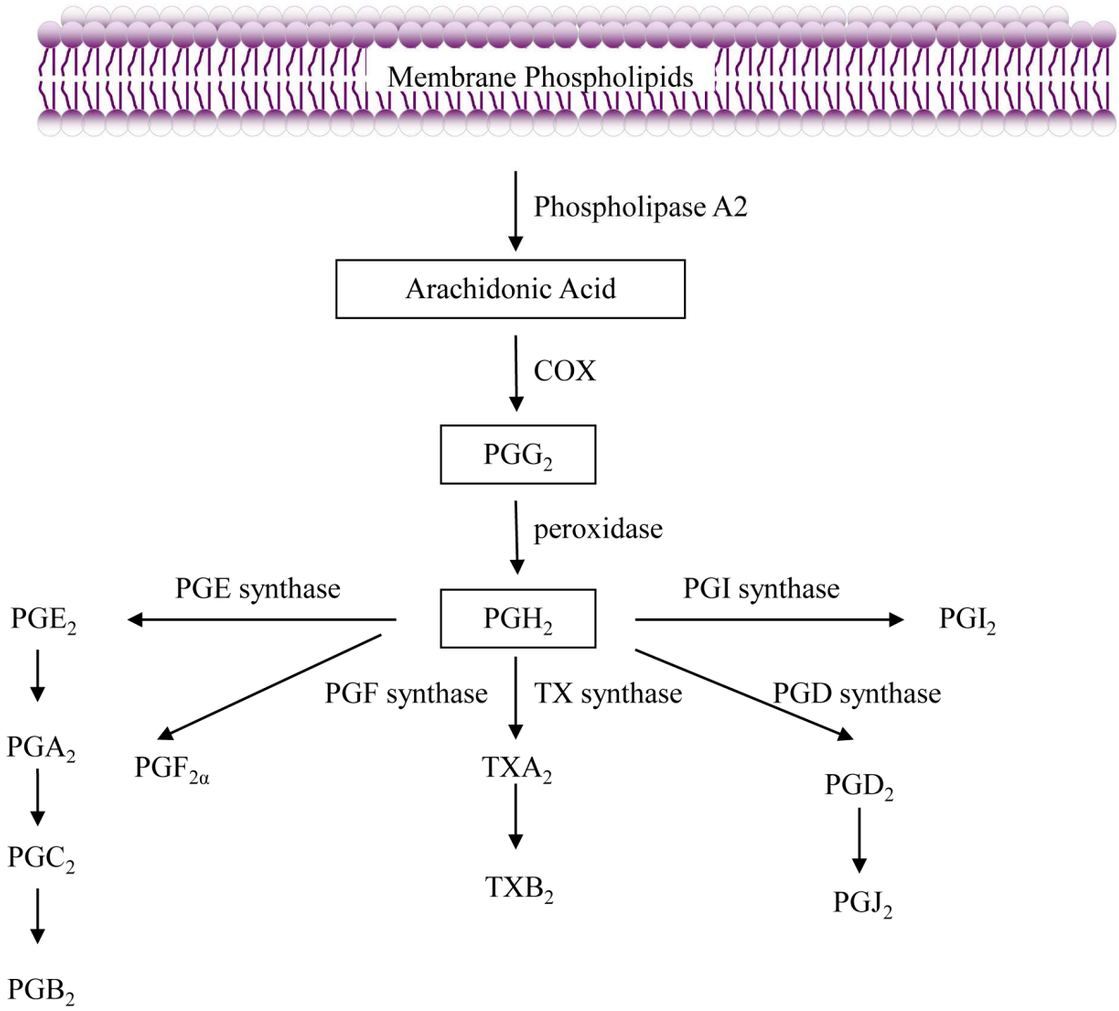

Fig. 1. Main products and enzymes of the COX pathway. COX: cyclooxygenase; PG: prostaglandin; TX: thromboxane.

3. COX and HNC

In the last decade inflammation and cancer had been linked together as biomarkers and novel targets of cancer therapy in a large number of cancers, including HNC. Overexpressions of COX-2 and prostanoids have been shown in various forms of human cancers, including HNC, and they can be linked with cancer progression and metastasis (Lee *et al.*, 2001; Krysan *et al.*, 2004; Huh *et al.*, 2009). COX-2 expression was correlated with shorter survival in non-small cell lung cancer and poor survival in prostate cancer and gliomas patients (Khuri *et al.*, 2001; Shono *et al.*, 2001; Khor *et al.*, 2007). Upregulation of COX-2 has been reported in human tissues and cell lines as well as in serum of patients with HNC. The increased levels of COX-2 were associated with the risk of tobacco- and betel nut-related cancers, advance clinical stage, survival and lymph node metastasis (Tang *et al.*, 2003; Molinolo *et al.*, 2007; Chiang *et al.*, 2008; Husvik *et al.*, 2009; Saba *et al.*, 2009; Kapoor *et al.*, 2010; Mittal *et al.*, 2010). In addition, PGE_2 receptors are widely expressed in a variety of HNSCC cell lines as well as in tumor tissues (Abrahao *et al.*, 2010).

Several studies showed the effects of COX inhibitors on cancer cell proliferation, invasion and proliferation, invasion and metastasis. Selective COX-2 inhibitors decreased viability, invasion and adhesion of HNSCC cells by down-regulated MMP-2, MMP-9 and vascular endothelial growth factor (VEGF) secretion (Kim *et al.*, 2010; Koontongkaew *et al.*, 2010; Li *et al.*, 2010). Moreover, suppression of COX-2 expression by small RNAs reduced cancer cell proliferation and invasion by decreased VEGF production (Park *et al.*, 2010; Wang *et al.*, 2010). Selective COX-1 inhibitor also decreased cancer cell proliferation (Koontongkaew *et al.*, 2010). However, little is known about the molecular mechanism of the COX-2 pathway in the regulation of HNSCC cell growth. Molecular mechanism of cell apoptosis by COX-2/PGE_2 through phosphatidylinositol 3-kinase (PI3K)/AKT pathway has been suggested in human epidermoid carcinoma cells (Agarwal *et al.*, 2009).

COX-2 is expressed in tumor neovasculature as well as in tumor tissues. The proangiogenic factors of COX-2 are TXA_2, PGI_2 and PGE_2. Selective inhibitor of COX-2 has been shown to suppress angiogenesis *in vitro* and *in vivo* by reduced VEGF production (Williams *et al.*, 2000). This suggests a role of COX in the process of angiogenesis, which might have an effect in HNSCC cell proliferation.

3.1 COX and ERK pathway

Upregulation of epidermal growth factor receptor (EGFR) has been suggested as a major pathway involved in HNSCC progression (Le Tourneau *et al.*, 2007; Molinolo *et al.*, 2009). Activation of EGFR has been shown to induce increased COX-2 expression in various normal and cancer cell lines, including HNSCC cells. However, the signaling pathway involved in COX-2 via EGFR varies depending on the type of cells and inducers, but the ras/ raf/ mitogen-activated protein kinases (MAPKs) signaling pathways mainly contribute to both increased transcriptional and posttranscriptional controls. On the other hand, COX-2 could induce transactivation or upregulate EGFR expression (Choe *et al.*, 2005; Husvik *et al.*, 2009).

Selective COX-2 inhibitors have been shown to decrease PGE_2 production *in vitro* and *in vivo* (Hoshikawa *et al.*, 2009; Abrahao *et al.*, 2010). This implies that upregulated PGE_2 in tumor microenvironment by COX-2 overexpression may promote the growth of HNSCC cells in an autocrine and/or paracrine effects by acting on widely expressed PGE_2 receptors in HNSCC cells. Additionally, p53, a tumor suppressor, play an inhibitory role in AA metabolism. It downregulates COX-2 expression and leads to tumor cell apoptosis (Subbaramaiah *et al.*, 1999).

3.2 COX and PI3K/AKT pathway

The PI3K/AKT pathway plays critical roles in the control of cancer cell survival and apoptosis in many cancers, including HNC (Jiang & Liu, 2008; Cohen *et al.*, 2011). It has been recognized that protein kinase B (Akt/PKB) activity is implicated in K-Ras-induced expression of COX-2, and the mRNA stability of COX-2 partially depends on the activation of AKT (Sheng *et al.*, 2001). Indomethacin, a NSAID, has been found to induce apoptosis in renal cell carcinoma cells by activating AKT and MAPK signaling (Ou *et al.*, 2007). Celecoxib, a selective COX-2 inhibitor, had been shown to induce apoptosis through (PI3K)/AKT and the COX-2 signaling pathway in various cancers, including non-small cell

lung carcinoma, prostate and gastric cancers (Kulp *et al.*, 2004; Zhu *et al.*, 2004; Fan *et al.*, 2006). In HNC, however, the mechanism of COX-2 upregulation is not fully understood. There was reported that COX alone did not effect on pEGFR, pERK1/2 and pAKT. However, inhibition of combination of COX and EGFR reduced the AKT activities of HNSCC cells (Chen *et al.*, 2004b).

3.3 COX and tumor invasion

It is well documented that COX inhibitors reduce cancer cell migration, cell adhesion and tumor invasiveness (Lin *et al.*, 2002). Increased invasiveness has been associated with activation of MMPs. MMPs are a family of proteolytic enzymes linked to several malignant properties of a variety of tumor cells, including HNSCC cells (Rosenthal & Matrisian, 2006). Therefore, it is possible that COX-2 enhances tumor cell invasion through the upregulated MMP activities. To date, however, a few studies have investigated the importance of COX-2 in modulating the invasive properties of HNSCC cells. Recently, we found that COX-1 and COX-2 inhibitors reduced cell viability, MMP-2 and MMP-9 activities, and *in vitro* invasion of primary and metastatic HNSCC cells (Koontongkaew *et al.*, 2010). Our findings are consistent with other studies that demonstrated the inhibitory effects of COX inhibitors on MMP activities in breast (Larkins *et al.*, 2006), prostate (Attiga *et al.*, 2000), colon (Ishizaki *et al.*, 2006) and lung cancer cells (Karna & Palka, 2002). Regarding the role of COX-2 in the metastasis and invasion of HNSCC cells, the precise mechanism remains obscure, but a decrease of COX-2 dependent PGE_2 may downregulate MMP production through PGE_2 receptors (Dohadwala *et al.*, 2002).

4. Inhibition of COX

NSAIDs, non-selective inhibitors for COX, are over-the-counter drugs and widely use as analgesics, anti-inflammations, antipyretic and chemoprevention in cardiovascular diseases and other disorders. Experimental tumor model studies show that NSAIDs impair the growth and development of HNSCC, indicating potential as a chemopreventive agent (Cornwall *et al.*, 1983; Lin *et al.*, 2002; Mohan & Epstein, 2003). Moreover, both non-selective and selective of COX prevented 4-nitroquinoline- oxide (NQO)-induced tumorigenesis in rats (McCormick *et al.*, 2010). Regular use of aspirin has been shown to reduce the risk of colon cancer (Dube *et al.*, 2007). Celecoxib is approved for the chemoprevention of colon cancer in patients with familial adenomatous polyposis. This COX-2 inhibitor has also been shown to reduce the incidence of various cancers *in vivo* (Grosch *et al.*, 2006). To date, however, no definitive conclusion on the effect of NSAIDs/aspirin use on the risk of HNSCC is well documented (Wilson *et al.*, 2011). Although NSAIDs or aspirin may have protective effect on HNSCC, further large-scale studies are required.

Selective COX-2 inhibitors were reported to enhance treatment responds to radiotherapy or combination of radiotherapy and chemotherapy, suggesting that the inhibitors can improve the response of various cancers to conventional cancer therapies (Liao *et al.*, 2003; Komaki *et al.*, 2004). To date, several concurrent clinical trial studies of HNC are using a combination of standard treatment with a selective COX-2 inhibitor and the others, such as EGFR inhibitor, which has been shown to improve survival in patients with non-small cell lung cancer (Fidler *et al.*, 2008). A combination of EGFR-selective tyrosine kinase inhibitor with a COX-

2 inhibitor (celecoxib) induced cell cycle arrest and apopotosis in HNSCC cells. The combination showed strong reduction of EGFR, ERK1/2 and AKT activations (Chen *et al.*, 2004b). The phase 1 clinical trial, using a combination of an EGFR inhibitor (erlotinib), a selective COX-2 inhibitor (celecoxib) and reirradiation showed a feasible and clinically active regimen for recurrent HNC patients (Kao *et al.*, 2011). During and after radiotherapy in combination with celecoxib, significant decrease of the plasma levels of VEGF were observed in patients with advanced HNC who had high COX-2 expression in their tumor tissues (Halamka *et al.*, 2011).

5. The LOX pathway

In human cells, generally, four types of LOXs have been identified, namely 5-, 12- and 15-LOX-1 and LOX-2. Collectively, they catalyze the oxygenation of AA into hydroperoxyeicosatetraenoic acids (HPETEs) (Figure 2). Ultimately, this is followed by their conversion to their corresponding hydroeicosatetraenoic acids (HETEs), leading to the formation of LTs, LXs and HOs. The metabolism of linoleic acid preferentially results in the formation of hydroxyloctadecadienoic acids (HODEs). 5-LOX catalyzes the first step in the oxygenation of AA to produce 5-HPETE, and the subsequent metabolism of 5-HPETE to 5-HETE and LTs. LTs belong to a key group of pro-inflammatory mediators that are synthesized from AA via the 5-LOX pathway. The activity of 5-LOX leads to the formation of unstable LTA4, which can be converted into LTB4 or cysteinyl LTs (LTC4, LTD4 and LTE4) Platelet-type 12-LOX (*p*12-LOX) exclusively uses AA released from glycerol-phospholipid pools to synthesize 12S-HPETE and 12S-HETE, whereas leukocyte-type 12-LOX can also synthesize 15S-HETE and 12S-HETE. In addition to leukocytes and platelets, the expression of 12-LOX isozymes has been observed in various types of cells, including smooth muscle cells, endothelial cells and keratinocytes. 15-lipoxygeases (15-LOX) can be subdivided into two isoforms, namely 15-LOX-1 and 15-LOX-2. 15-LOX-1 is mainly expressed in reticulocytes, eosinophils and airway epithelial cells, as well as in macrophages. In terms of enzymatic characteristics, 15-LOX-1 preferentially metabolizes linoleic acid primarily to 13S-HODE, but also metabolizes AA to 15S-HETE. 15-LOX-2, on the other hand, converts AA to 15S-HETE and poorly metabolizes linoleic acid (Romano & Claria, 2003).

The products of LOX metabolism represent either intermediary products such as HPETE, which are transformed enzymatically into secondary products, including LTs, LXs, HOs and HETEs, which can act as signaling molecules in their own right or give rise to the production of reactive oxygen species (ROS). Signaling of LOX-derived products can occur through either G protein coupled cell-surface receptors, in the case of LOs and LTs, or through activation of nuclear receptors such as peroxisome proliferator activated receptors (PPARs) in the case of HETEs and HODEs (Pidgeon *et al.*, 2007).

6. LOX and HNC

Early tumorigenesis studies in animals demonstrated the contributory roles of AA and linoleic acid in tumorigenesis. Various LOX products have been linked to tumorigenesis *in vitro* and also *in vivo* in animal models. In addition, the modulation of LOX metabolism has anticarcinogenic effects on tumor development. Therefore, it suggests that LOX modulation has been targeted for developing anticarcinogenic agents (Shureiqi & Lippman, 2001).

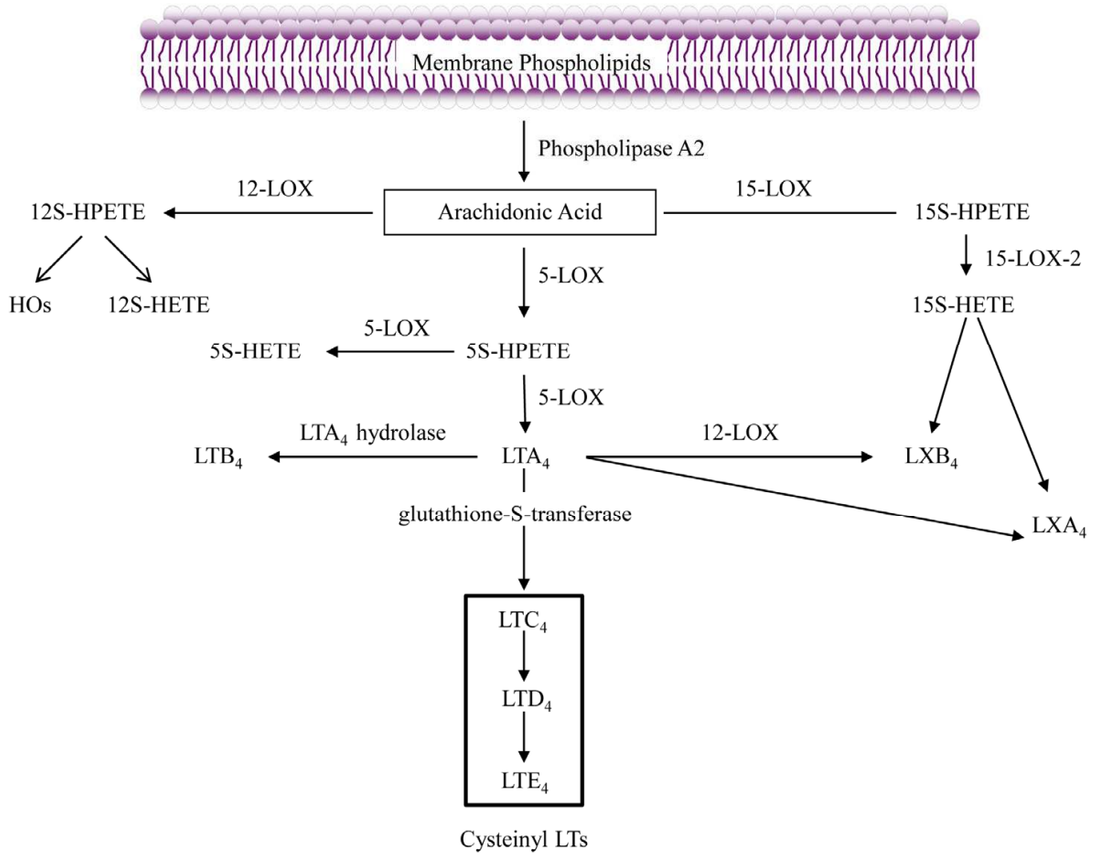

Fig. 2. Main products and enzymes of the LOX pathway. LOX: lipoxygenase; HPETE: hydroperoxyeicosatetraenoic acid; HETE: hydroxyeisatetraenoic acid; HOs: Hepoxillins; LXs: lipoxins; LT: leukotriene.

5-LOX, 12-LOX, 15-LOX-1 and 15-LOX-2 were detected in HNSCC cell lines derived from primary and metastatic tumors. Therefore, it is not surprised that LOX metabolites, including 5-HETE, 12-HETE, 15-HETE and 13-HODE were found in primary and metastatic HNSCC cells. However, there was no correlation between LOX isoforms and their metabolites in HNSCC cells (Schroeder *et al.*, 2004). The level of LTB4, a metabolite of the 5-LOX pathway, was found to be higher in oral cancer lesions in human and hamsters (el-Hakim *et al.*, 1990; Li *et al.*, 2005). This enzyme was also upregulated in other cancers, including prostate (Gupta *et al.*, 2001), pancreatic (Hennig *et al.*, 2002), colon (Ohd *et al.*, 2003) and esophageal cancers (Chen *et al.*, 2004a). Previous studies in 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced hamster oral cancer demonstrated overexpression of 5-LOX in the stromal inflammatory cells and epithelial cells at the early stages of oral squamous cell carcinogenesis. Moreover, zileuton, a specific 5-LOX inhibitor and celecoxib (a specific COX-2 inhibitor), either alone or in combination, had an inhibitory effect on the incidence of oral tumor in DMBA-treated animals. Zileuton seems even more effective than celecoxib. These findings suggest that the 5-LOX pathway of AA metabolism plays an important role in inflammation-associated oral cancer (Li *et al.*, 2005).

Recently, studies in the mouse model showed that the expression of 5-LOX and COX-2 was increased in dysplasia and squamous cell carcinoma of 4-nitroquinoline-1-oxide (4NQO)-

treated tongues, and further enhanced by ethanol. Fewer tumors were induced in Alox5-/- mice, as were cell proliferation, inflammation, and angiogenesis in the tongue, as compared with Alox5+/+ mice. COX-2 expression was induced by ethanol in knockout mice, while 5-LOX and LTA4H expression and LTB4 biosynthesis were dramatically reduced. Moreover, ethanol enhanced expression and nuclear localization of 5-LOX and stimulated LTB4 biosynthesis in human tongue squamous cell lines. These findings suggest that the activation of the 5-LOX pathway of AA metabolism involves in oral carcinogenesis (Guo *et al.*, 2011).

Inhibition of AA metabolism (COX-2 and 5-LOX) by curcumin has also been suggested as a key mechanism of its anticarcinogenic action in DMBA-induced hamster oral carcinoma (Li *et al.*, 2002; Bengmark, 2006). Zyflamed, a product containing 10- concentrate herbal extracts significantly reduced infiltration of inflammatory cells, incidence of hyperplasia and dysplastic lesions, cell proliferation as well as number of tumors in the DMBA-induced hamster cheek pouch model. Furthermore, it was shown that zyflamed reduced LTB4 formation compared with that of the control (Yang *et al.*, 2008).

In a long-term carcinogenesis study, topical application of LTB4 enhanced oral carcinogenesis by increasing the incidence and sizes of tumors. LTB4 inhibitors significantly inhibited oral carcinogenesis, and the anticarcinogenesis as such correlated with reduced levels of LTB4 (Sun *et al.*, 2006). An *in-vitro* study demonstrated that addition of LTB4 to RBL-1 cells, a rat leukemia cell line expressing high levels of 5-LOX, could counteract the inhibition of cell proliferation produced by a LOX inhibitor (zyflamed) (Yang *et al.*, 2008).

LOX products were indentified in human mixed saliva and in saliva fractions obtained from a parotid or submandibular gland. In glandular saliva, only linoleic acid was detected at levels of 20-30 ng/ml. In contrast, mixed saliva showed a linoleic acid concentration of around 300 ng/ml, AA levels of around 30 ng/ml, HODE levels between 5 and 10 ng/ml, and HETE levels up to 25 ng/ml. By far the most abundant HETE was 12-HETE, and incubation experiments with AA showed the presence of a substantial 12-LOX activity in human mixed saliva, but not in saliva fractions. Investigating mixed saliva and glandular saliva of patients with squamous cell carcinoma in the upper aerodigestive tract and of controls; most patients showed elevated levels of free AA and elevated HETE levels. Besides a moderate increase in 12-HETE levels, markedly elevated concentrations of 5-HETE and 15-HETE were observed for the carcinoma patients. Therefore, it is proposed that the level of free AA, and the quantitative HETE profile appear to be good markers for the inflammatory processes occurring in the oral mucosa and in saliva in response to the development of squamous cell carcinoma (Metzger *et al.*, 1995).

6.1 Molecular mechanisms of LOX-mediated HNC development

As mentioned above, substantial evidence supports a functional role for LOX-catalyzed AA metabolism in HNC development. Pharmacologic and natural inhibitors of LOX have been shown to suppress carcinogenesis and tumor growth in a number of experimental models. In recent years participation of LOX in the regulation of cell proliferation, apoptosis and angiogenesis has emerged. Many cell pathways are involved in the process by which cells choose between growth arrest, apoptosis or survival. The crosstalk of LOX derived products

with different growth factor receptor-induced signaling cascades is involved in the stimulation of tumor cell growth.

The aberrant activation of multiple signaling pathways, including EGFR, *ras*, NFκB, STAT, Wnt/β-catenin, TGF-β and PI3K/AKT were observed in HNSCC (Molinolo *et al.*, 2009). Oncogenic events in HNC associated with abnormal activation of the PI3K/AKT pathway include mutations, allelic loss, or the promoter methylation of the negative regulator phosphatase and tensin homolog (PTEN) (Cohen *et al.*, 2011). LOX metabolites may exert their biological effects in an intracrine manner, through the activation of transcription factors of the PPAR family, or they may interact with specific trans-membrane G protein-couple cell surface receptors in an autocrine or paracrine manner (Pidgeon *et al.*, 2007). LOX metabolites may involve in ERK1/2, PI3K/AKT cascade, and STAT signaling pathways in HNSCC cells (Pidgeon *et al.*, 2007). PTEN may be oxidized and inactivated during AA metabolism in cancer cells. Oxidation of PTEN resulted in a decrease of its phosphatase activity, favoring increased PI-3, 4, 5-trisphosphate (PIP_3) production, activation of AKT and phosphorylation of downstream AKT targets. Such activation leads to cell cycle induction during HNC development (Covey *et al.*, 2007; Jiang & Liu, 2008).

Tumor growth does not only depend on increased cell proliferation but also on prolonged cell survival through the inhibition of cell death or apoptosis. LOX inhibition has been shown to induce apoptosis in cancer cells (Lepage *et al.,* 2010). LOX metabolites may enhance cancer cell survival through an increase in Bcl-2. In addition, they can upregulate the p-ERK and p-AKT levels, suggesting the involvement of ERK and AKT pathways in the LOX-mediated regulation of growth in cancer cells (Agarwal *et al.*, 2009). However, it was found that metabolism of AA by 5-LOX activity promotes survival of cancer cells via signaling through PKCε, a pro-survival serine/threonine kinase which is not dependent on the AKT and ERK-pathway (Sarveswaran *et al.*, 2011).

In addition to its role in neoplastic transformation, 5-LOX and its AA metabolite had shown to be involved in angiogenesis. 12S-HETE has been shown to be a mitogenic factor for microvascular endothelial cells and stimulates endothelial cell migration. Moreover, 12S-HETE has an ability to induce the expression of VEGF, an important proangiogenic factor, at both protein and promoter levels (Pidgeon *et al.*, 2007).

However, little is known about the role of LOX in HNC cell metastasis. The process of tumor invasion by cancer cells involves degradation of the underlying basement membrane, which largely made up of collagen IV. MMP-2 and MMP-9 showed substrate specificity toward type IV and V collagen and a number of studies have demonstrated a strong correlation between MMP expression and metastatic potential (Rosenthal & Matrisian, 2006). Recently, our findings demonstrated the inhibitory effects of NDGA (nordihydroguaiaretic acid, the selective LOX inhibitor) and ETYA (5, 8, 11, 14-eicosatetraynoic acid, the COX and LOX inhibitor) on cell proliferation, MMP activity and invasion in primary and metastatic HNSCC cells (Koontongkaew *et al.*, 2010). It is possible that LOX inhibitors activate PPARγ activity and subsequent reduction in MMP-9 signaling (Hyde & Missailidis, 2009).

The ability of tumor cells to generate 12S-HETE is positively correlated to their metastatic potential and the increased expression of *p*12-LOX enhanced the metastatic potential of cancer cells. Moreover, 12S-HETE has been found to modulate multi steps of the metastatic

process encompassing tumor cell and endothelial cell interactions, tumor cell motility, proteolysis and invasion (Furstenberger *et al.*, 2006). Moreover, LOX may promote tumor cell migration through FAK (focal adhesion kinase) activation (Navarro-Tito *et al.*, 2008).

It should be noted that the role of LOX in HNC development is thought to be more complex, compared with that of COX because 6 LOX genes have been identified in human and different profiles of LOX were found in studies on human tumor biopsies and experimentally induced animal tumor models. The inverse expression pattern of individual LOX isoenzymes in normal versus malignant tissues and the biological effects of the corresponding LOX products propose the important role of dynamic balance among LOX isoenzymes in tumorigenesis. It has been shown a dynamic balance among LOX shifting toward the procarcinogenic 5- and *p*12-LOX and away from anticarcinogenic LOXs such as 15-LOX-1, 15-LOX-2, 8-LOX and epidermal-type 12-LOX (*e*12-LOX) during prostate and colon cancer development (Menna *et al.*, 2010). However, at present little is known about modulation of carcinogenesis through pro-and anticarcinogenic LOX isoforms in HNC development and progression.

7. Converging pathways of COX and LOX in HNC

The AA-metabolizing enzymes are overexpressed during animal and human carcinogenesis and AA metabolites such as PGE_2, 5-HETE and LTB4 had been implicated in HNC development. COX-2 and 5-LOX play important roles in inflammation and inflammation-associated tumorigenesis. It is evident that COX and LOX display similarities in expression and functions in HNC. In particular, the COX-2 and 5-LOX pathways are activated together during inflammation, and blocking one pathway may activate the other. It was shown that inhibition of COX-2 might lead to a shunt of AA metabolism towards the LT pathway in HNC. Suppressing PGE_2 levels by a COX-2 inhibitors, celecoxib, leads to an increase in the activity of 5-LOX, 12-LOX and 15-LOX-2 and results in the increase of their products, including, 5-HETE, 12-HETE and 15-HETE (Schroeder *et al.*, 2004). A study in the mouse model of HNC, demonstrated an increase of LTB4 in tumor tissues in mice treated with PGE_2. In contrast, LTB4 could not decrease tumor tissue levels of PGE_2 (Scioscia *et al.*, 2000). Therefore, simultaneous blocking of each enzyme may be required to achieve substantial elevation in free AA levels and prevent the shunting of metabolism to another active pathway.

Taken together, COX-2 and 5-LOX may have redundant function in HNC pathobiology. First, COX-2 and 5-LOX enhance tumor cell proliferation. Second, both COX-2 and 5-LOX are proangiogenic with a convergent targeting on VEGF, FGF and MMPs. Third, COX-2 as well as 5-LOX inhibitors, arrest cell cycle progression and induce apoptotic cell death in HNSCC cells. Fourth, both COX-2 and 5-LOX enhance HNSCC cell invasion and tumor metastasis. In addition, active COX2 and 5-LOX are localized in the nucleus, and they may function as endogenous ligands for nuclear receptors such as the PPARs (Menna *et al.*; Romano & Claria, 2003) (Figure 3).

8. Future prospects and conclusions

The summarized findings contained in this review support the contributory role of chronic inflammation in the pathogenesis of HNC. A hallmark of the inflammatory process is the

synthesis of inflammatory cytokines and AA metabolites. Two major AA metabolic routes, *i.e.*, the COX and LOX pathways control the biosynthesis of eicosanoid. COX-derived eicosanoids comprise PG and TXA_2, whereas HPETE and LTs are products of LOX-catalyzed arachidonic acid metabolism. In HNC, COX-2 and LOX are coexpressed and upregulated in tumor cell lines, experimentally induced animal tumor models and human tumor biopsies. Currently, the underlying mechanisms for the tumorigenic effects of COX and LOX remain somewhat undefined. A number of studies of HNC have suggested the involvement of COX-2 and/ or 5-LOX in tumor cell proliferation, apoptosis, angiogenesis and metastasis.

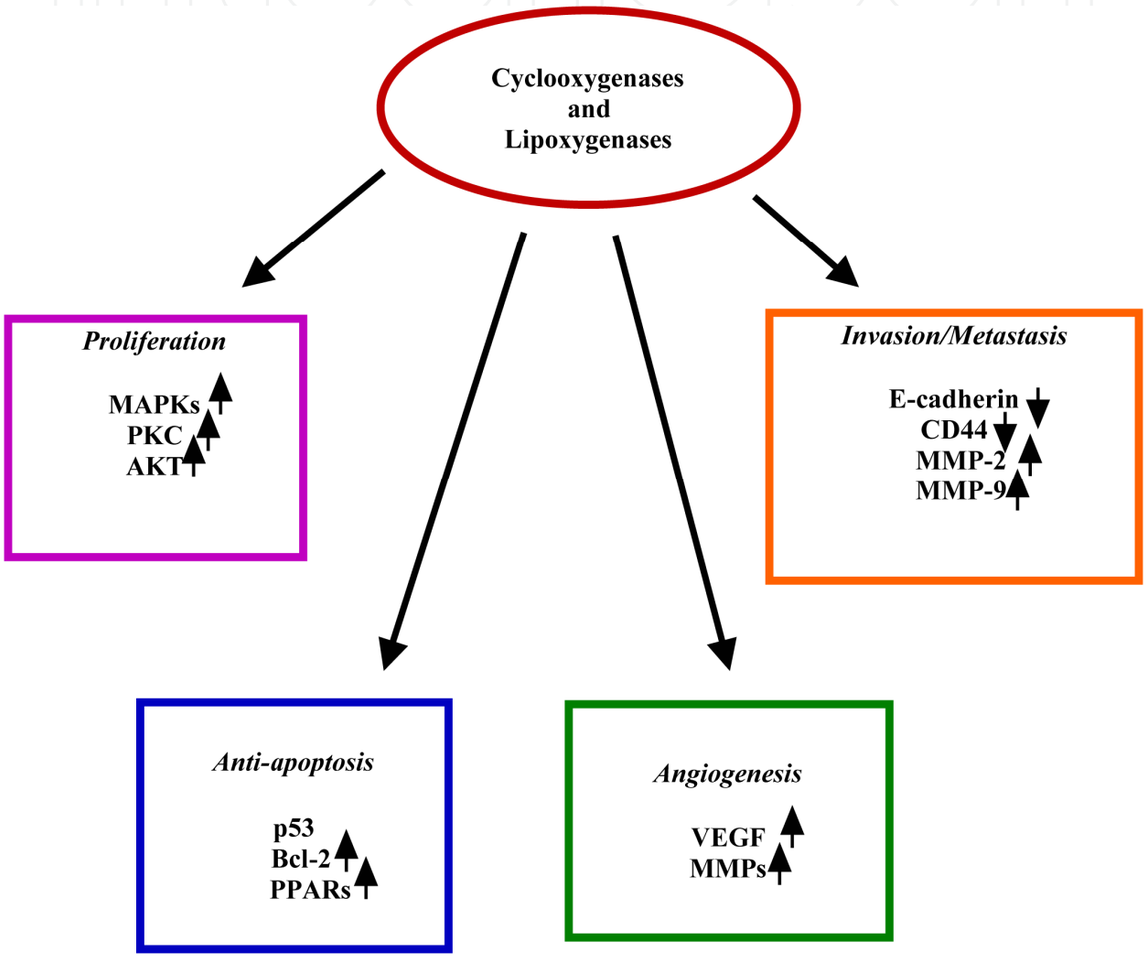

Fig. 3. Effects of COXs and LOXs on tumerigenesis. Both COXs and LOXs stimulate proliferation, inhibit apoptosis, induce angiogenesis, and enhance invasion and metastasis in cancer cells. MAPKs: mitogen activated protein kinases; PKC: protein kinase C; Bcl-2: B-cell lymphoma2; PPARs: peroxisome proliferator-activated receptor; VEGF: vascular endothelial growth factor; MMP: matrix metalloproteinase.

COX and/ or LOX inhibitors in many instances demonstrate potent anticancer effects. Manipulation of AA metabolism, therefore, represents a promising approach to develop HNC therapy. However, in spite of extensive research in COX and LOX inhibitors, their

combined use for chemoprevention is still in its development stage. Further investigations are indeed necessary to develop appreciate chemopreventive strategies in HNC. First, the mechanism by which COX and LOX pathways are deregulated, interacted with each other, or contribute to head and neck tumorigenesis must be more clarified. Second, more clinical studies are critical to evaluate the effectiveness of COX and LOX inhibitors and to understand their mechanisms of action a single agent and in combination in HNC, specifically. Eventually, possible drug toxicity from a combined use must be evaluated over the long term.

9. References

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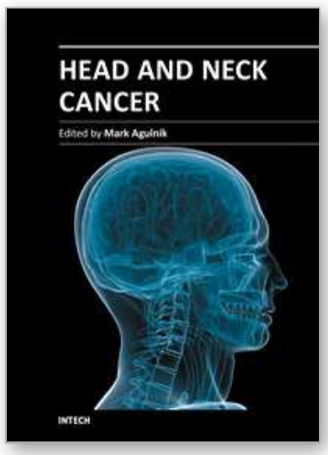

Head and Neck Cancer
Edited by Dr. Mark Agulnik

ISBN 978-953-51-0236-6
Hard cover, 440 pages
Publisher InTech
Published online 14, March, 2012
Published in print edition March, 2012

Head and Neck Cancer provides an interesting and comprehensive overview of all aspects of head and neck cancer including overviews of the disease, basic science aspects pertaining to the disease, diagnosis, treatment and outcomes for patients with this disease. The chapters written by world renowned experts cover the entire discipline of head and neck oncology and include discussions of regional disparity is, advances in basic science understanding, advances in her radiotherapy, chemotherapy and targeted agents as well as a focus on reconstruction, prostheses, and aspects of quality of life and health outcomes. The book is designed to be both practical and comprehensive for every physician treating his complex disease.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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