Molecular Cancer

BioMed Central

Review

Open Access

Lipoxygenase and cyclooxygenase metabolism: new insights in treatment and chemoprevention of pancreatic cancer

Xian-Zhong Ding, Rene Hennig and Thomas E Adrian*

Address: Department of Surgery and Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, 303 East Chicago Avenue, Tarry 4-711, Chicago, IL 60611, U.S.A

Email: Xian-Zhong Ding - xzding@northwestern.edu; Rene Hennig - rh73@lycos.com; Thomas E Adrian* - tadrian@northwestern.edu

* Corresponding author

Published: 7 January 2003

Molecular Cancer 2003, **2**:10

Received: 21 December 2002

Accepted: 7 January 2003

This article is available from: http://www.molecular-cancer.com/content/2/1/10

Abstract

The essential fatty acids, linoleic acid and arachidonic acid play an important role in pancreatic cancer development and progression. These fatty acids are metabolized to eicosanoids by cyclooxygenases and lipoxygenases. Abnormal expression and activities of both cyclooxygenases and lipoxygenases have been reported in pancreatic cancer. In this article, we aim to provide a brief summary of (1) our understanding of the roles of these enzymes in pancreatic cancer tumorigenesis and progression; and (2) the potential of using cyclooxygenase and lipoxygenase inhibitors for pancreatic cancer treatment and prevention.

Review

Molecular studies of the well-known relationship between polyunsaturated fatty acid metabolism and carcinogenesis have revealed novel molecular targets for cancer chemoprevention and treatment [1–4]. Polyunsaturated fatty acids are esterified in membrane phospholipids and triglycerides in all mammalian tissues [5]. In this form, they are usually not substrates for metabolizing enzymes, but serve the function of sustaining membrane fluidity as well as that of substrate storage [5]. Oxidative metabolism of these fatty acids to prostaglandins, hydroxy-fatty acids and leukotrienes, collectively referred to as eicosanoids, depends on the availability of free, non-esterified fatty acids [5]. These fatty acids are substrates for three distinctively different enzymatic pathways, cyclooxygenase (COX), lipoxygenase (LOX) and epoxygenase [5]. This article presents a new perspective about the role of cyclooxygenase and lipoxygenase on pancreatic cancer development and growth, the underlying mechanisms by which they mediate these effects and their potential as targets for pancreatic cancer prevention and treatment.

Cyclooxygenases and lipoxygenases: the key metabolic enzymes for arachidonic acid and linoleic acid

Cyclooxygenases

Cyclooxygenase (COX) which has two isoforms, COX-1 and COX-2 is the enzyme that catalyzes the rate-limiting step in prostaglandin synthesis, converting arachidonic acid into prostaglandin H_2, which is then further metabolized to prostaglandin E2 (PGE_2), $PGF_{2\alpha}$, PGD_2 and other eicosanoids [5,6]. COX-1 is constitutively expressed in many tissues and plays a role in tissue homeostasis. COX-2, which can be expressed in a variety of cells and tissues, is an inducible isoform the expression of which is stimulated by growth factors, cytokines, and tumor promoters. Despite the structural similarity between the two isoforms, COX-1 and COX-2 differ substantially in the regulation of their expression and their roles in tissue biology and disease [5,6]. In the past decade, tremendous progress has been made in understanding the functional roles of COX in cancer development and growth. COX-2 is up-reg-

ulated in many cancer types, including the colon, breast, lung, pancreas, and esophagus as well as squamous cell carcinoma of the head and neck [7–11]. COX-2 specific inhibitors inhibit cell growth in a number of tumors including skin, colonic, gallbladder, esophageal and pancreatic cancer cells [7–11]. Studies from both COX-2 transgenic and COX-2 knockout mice confirm that COX-2 plays a key role in colonic cancer development [12]. However, a recent study in COX-1 deficient mice, showed that lack of COX-1 also significantly reduced intestinal tumorigenesis in *min* mice, a phenotype similar to that of COX-2$^{-/-}$ mice [12]. Furthermore, there may be other forms of COX enzymes, making things even more complicated. Simmons and colleagues, recently identified an enzyme that they have called cyclooxygenase-3, or COX-3. COX-3 is an isoform of COX-1, but is expressed in cells in an inducible manner [13]. COX-3 is selectively inhibited by different NSAIDs and has a high sensitivity to acetaminophen. However, whether COX-3 is involved in tumorigenesis is unknown [13].

Lipoxygenases

Lipoxygenases possess regiospecificity during interaction with substrates and on this basis have been designated as arachidonate 5-, 8, 12-, 15-lipoxygenase (5-LOX, 8-LOX, 12-LOX, and 15-LOX) [5,13–17]. The four distinct enzymes insert oxygen at carbon 5, 8, 12 or 15 of arachidonate acid. The primary products are 5S-, 12S-, or 15S-hydroperoxyeicosatetraenoic acid (5-, 8-, 12-, or 15-HPETE), which can be further reduced by glutathione peroxidase to the hydroxy forms (5-, 8-, 12-, 15-HETE) respectively [5,13–17]. 5-LOX represents a dioxygenase that possesses two distinct enzymatic activities leading to the formation of LTA_4. First it catalyzes the incorporation of molecular oxygen into arachidonic acid (oxygenase activity), producing HPETE and subsequently forms the unstable epoxide LTA_4 (LTA_4 synthase activity) [5,6]. This is followed by the insertion of molecular oxygen at position C-5, converting LTA_4 to either 5(S)-hydroxy-6-trans-8,11,14-cis-eicosatetranoic acid (5-HETE) or leukotrienes. Five Lipoxygenase Activating Protein (FLAP), which is a 18 kDa membrane-bound protein, plays an important role in mediating the arachidonic catalytic activity of 5-LOX [5,6]. FLAP activity can be blocked by the FLAP inhibitor, MK886 [5,6]. Hydrolytic attack of LTA_4 by leukotriene A_4 hydrolase yields LTB_4, a potent neutrophil chemoattractant and stimulator of leukocyte adhesion to endothelial cells. LTC_4 synthase catalyzes the conjugation of LTA_4 with glutathione to form LTC_4 at the nuclear envelope. The peptide moiety of LTC_4 is subject to extracellular metabolism, forming LTD_4 and LTE_4 [5,6]. These three leukotrienes comprising the cysteinyl leukotrienes, before their structures were identified were known as the "slow-reacting substance of anaphylaxis" named for their slow and sustained smooth muscle contracting abilities [5,6]. Accumulating evidence suggests that the 5-LOX pathway has profound influence on the development and progression of human cancers [18]. 5-LOX inhibitors have chemopreventive effects in animal lung carcinogenesis [19]. Furthermore, the 5-LOX pathway interacts with multiple intracellular signaling pathways that control cancer cell proliferation [9]. Blockade of 5-LOX inhibits prostate cancer cell proliferation while the 5-LOX metabolite, 5-HETE stimulates prostate cancer cell growth [20]. Furthermore, the FLAP inhibitor, MK886 exerts a similar growth inhibitory effect on cancer cell proliferation to 5-LOX inhibitors, further supporting a role for 5-LOX as a mediator of cancer cell proliferation [21].

Three forms of 12-lipoxygenase have been identified, including the leukocyte-type and platelet-type (both 12(S) LOXs) as well as an epidermal form (also called 12(R) LOX), with differences in tissue localization, substrate specificities, immunogenicities and sequence homology [14,15]. The "platelet-type" 12-LOX converts arachidonic acid to 12-(S)-HETE while the "leukocyte type" 12-LOX metabolizes arachidonic acid or linoleic acid to either 12(S)-HETE or 15(S)-HETE [14,15]. Both the leukocyte-type and platelet-type12-LOX have been found in different cancer tissues, including melanoma, prostate and epidermal cancers [18]. Evidence indicates that 12-LOX is involved in both cancer cell proliferation and survival [15]. Inhibition of 12-LOX with either 12-LOX inhibitors or a 12-LOX antisense oligonucleotide inhibits proliferation and induces apoptosis in carcinosarcoma cells, while adding back the 12-LOX metabolite, 12(S)-HETE prevents 12-LOX inhibitor-induced apoptosis [22]. Expression of 12-LOX is also correlated with tumor cell metastasis. 12(S)-HETE directly stimulates prostate cancer cell migration. Clinically, the degree of 12-LOX expression in human prostate cancer correlates with the tumor grade and stage and 12-LOX expression level is higher in metastatic prostate cancers than in nonmetastatic ones [23].

Another arachidonic acid-metabolizing enzyme is 8-lipoxygenase, which was cloned recently. This enzyme is expressed in the skin after irritation or treatment with tumor promoters [25]. To understand the function of the product of 8-lipoxygenase, 8-hydroxyeicosatetraenoic acid transgenic mice have been generated [26]. These animals show enhanced differentiation of epidermal keratinocytes along with enhanced proliferation of the basal cell population. While the function of 8-HPETE and 8-HETE are unknown, their importance in tumor promoter-elicited events is suggested by the finding that application of the lipoxygenase inhibitor, eicosatetraenoic acid maximally inhibits tumor promotion when applied at the time of maximum induction of 8-lipoxygenase [26,27]. Compared with other LOX enzymes, 8-LOX has received little attention for its role in carcinogenesis and cancer growth.

Expression and function of 8-LOX in pancreatic cancer have not been investigated to date even though 8-LOX cDNA and antibody are available [27].

15-lipoxygenase, which is distributed widely in tissues, converts arachidonic acid to 15-HPETE which is then reduced by glutathione peroxidase to 15-HETE [16,17,24,28]. There are two 15-LOX isoenzymes, 15-LOX-1 and 15-LOX-2 [28]. The preferred substrate for 15-LOX-1 is linoleic acid and for 15-LOX-2 is arachidonic acid. 15-LOX-1 metabolizes linoleic acid to 13-S-HODE, which differs from 15-LOX-2 which, as expected, converts arachidonic acid to 15-HETE [28]. The role of 15-LOX in cancer development is unclear and somewhat controversial [28]. A series of studies from one group suggest that the 15-LOX-1 product, 13-S-HODE enhances colonic tumorigenesis. 13-S-HODE enhances cell proliferation and potentiates the mitogenic response to EGF in different cell types [29,30]. These proposed effects, however, are not consistent with other reports that 13-S-HODE did not enhance EGF-dependent DNA synthesis [28]. Indeed, Lippman *et al* reported that 13-S-HODE induces apoptosis and cell cycle arrest in colorectal cancer cells [31]. Evidence also indicates that 15-S-HETE may have anti-tumorigenic effects by antagonizing other LOX products, such as LTB_4 and 12-S-HETE [28]. 15-HETE inhibits LTB_4 production and reduces LTB_4 binding to its receptors and thereby blocks cellular responses to LTB_4. 15-HETE also blocks platelet-type 12-LOX activity and reduces 5-LOX activity in rat basophilic leukemia cells [28,32]. Different studies have suggested that 15-S-HETE may suppress apoptosis, or have no effect on apoptosis in cancer cells [28]. A recent study has shown that 15-S-HETE inhibits proliferation in PC3 prostate carcinoma cells, possibly through activation of PPARγ [33]. Therefore, further studies are required to clarify the role of 15-LOX in tumorigenesis and cancer growth.

Cyclooxygenases and lipoxygenases in pancreatic cancer

COX inhibition and pancreatic cancer incidence, the epidemiological observations

Tumorigenesis is a complex process and understanding its mechanisms is the key to designing effective targeted therapies. Several epidemiologic studies have shown an inverse correlation between the incidence of colon cancer and the use of nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin synthesis [8]. Because COX-2 is frequently over-expressed in premalignant lesions and neoplasms, specific COX-2 inhibitors have been investigated as chemo-preventive and potential chemotherapeutic agents [6–8]. New preclinical and early clinical data suggest, that inhibitors of COX-2 may protect against colon, breast, lung, esophageal, and oral tumors [8]. Even though epidemiological studies on the role of NSAIDs in pancreatic cancer incidence are not as detailed as in colonic cancer, evidence does suggest that NSAIDs might decrease the incidence of pancreatic cancer [34]. Recently, Anderson and colleagues [34] from University of Minnesota investigated the association between pancreatic cancer and aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) in 28283 participants. Multivariate analysis suggested that women who used aspirin had a 43% lower risk of pancreatic cancer compared with those who did not use aspirin. Furthermore, the association appeared to be related to the dose; women who took aspirin 2–5 times a week had a 53% lower risk, and those who took aspirin six or more times a week had a 60% lower risk than women who never took aspirin. In contrast to COX inhibitors, epidemiological evidence regarding the effect of LOX inhibitors on pancreatic cancer incidence is lacking, since specific LOX inhibitors have only recently become available in the clinic.

Expression of COX and LOX in pancreatic cancer

COX-2 is only expressed in pancreatic islets and has no expression in normal exocrine pancreatic tissues [35]. A considerable amount of evidence from several clinical studies in the United States and Japan supports that COX-2 is up-regulated in pancreatic adenocarcinoma. Studies that demonstrate this have employed RT-PCR, quantitative RT-PCR, *in situ* hybridization, western blotting and immunohistochemistry [36–42]. One report showed that levels of COX-2 mRNA were more than 60-fold increased in pancreatic cancer compared to adjacent non-tumor tissue [36]. The COX-2 protein was detected in 90% of pancreatic adenocarcinomas [36]. In general, studies suggest that COX-2 is weakly expressed in benign pancreatic adenoma, but dramatically up-regulated in pancreatic adenocarcinoma, even though extent of COX-2 expression differs from one study to another [36–42]. Expression of COX-2 has been demonstrated in several pancreatic cancer cell lines, although once again there is a lack of consistency between different studies [38,43]. Nzeako and Gores, analyzed possible reasons for the inconsistent reporting of COX-2 expression by different groups [44]. Firstly, the lack of correlation in immunohistochemical staining intensity for COX-2 may result from working with previously fixed and embedded tissue, the fixation methods used and the duration of fixation. The process of fixing and embedding can destroy or denature cellular proteins, thereby altering antigenic recognition by immunohistochemistry [44]. Under such circumstances, attempts at correlating staining intensity with other variables are very likely to yield spurious results. In this situation, more reliable results may be obtained using frozen tissues with a standardized fixation procedure. Secondly, the use of polyclonal antibodies for immunohistochemistry may diminish reliability, since other tissue proteins may be inadvertently stained [44].

Despite these inconsistencies, all of these studies indicate that COX-2 is over-expressed in pancreatic cancer. A recent study showed, that perineural invasion was associated with COX-2 expression in pancreatic cancer and increased COX-2 expression was more common in the glandular component than the solid component of the tumors [41]. Regarding expression of COX-2 in early neoplastic lesions of the pancreas, researchers from John Hopkins immunohistochemically examined expression of COX-2 in adenocarcinomas, pancreatic intraepithelial neoplasia [PanIN] and normal pancreatic ducts with an automated platform [42]. The overall percentage of positive cells was 47.3% in adenocarcinomas, 36.3% in PanINs and 19.2% in normal ducts. COX-2 was expressed in more than 20% of cells in 23 adenocarcinomas (77%), 42 PanINs (65%), and 12 normal ducts (40%). Significant differences in COX-2 expression were demonstrable in both adenocarcinomas vs normal ducts and PanINs vs normal ducts [42]. The up-regulation of COX-2 in a subset of noninvasive precursor lesions makes it a potential target for chemoprevention using selective COX-2 inhibitors.

Expression of LOX is also up-regulated in both adenocarcinomas and early neoplastic lesions of the pancreas. Reverse transcriptase-polymerase chain reaction revealed expression of 5-LOX mRNA in all of the commonly used pancreatic cancer cell lines, including PANC-1, AsPC-1, and MiaPaCa2 cells, but not in normal pancreatic ductal cells [45]. The expression of the 5-LOX protein in pancreatic cancer cell lines was confirmed by western blotting [46]. 5-LOX up-regulation in human pancreatic cancer tissues was verified by immunohistochemistry, which revealed intense positive staining in cancer cells [46]. Staining of the 5-LOX protein was particularly evident in the ductal components of the more differentiated tumors but, in contrast, ductal cells in normal pancreatic tissues from organ donors did not stain. Immunohistochemistry also revealed strong staining of cancer tissues with an antibody to the receptor of the downstream 5-LOX metabolite, leukotriene B4 [46]. It also appears that levels of 5-LOX in hepatic metastases of pancreatic cancer express more 5-LOX than the primary tumors [46]. These findings provide further evidence of up-regulation of this pathway in pancreatic cancer and suggest that LOX inhibitors are likely to be valuable for the treatment or prevention of this dreadful disease.

There is also RT-PCR evidence of 12-LOX expression in pancreatic cancer cell lines [45]. Expression of 12-LOX in pancreatic islets has been reported and it is not yet clear, whether 12-LOX is expressed or up-regulated in pancreatic cancer [47]. Whether 15-LOX and 8-LOX are expressed in pancreatic cancer or in normal pancreatic tissues has not been investigated.

Effects of COX and LOX inhibition on pancreatic cancer growth and apoptosis: In vitro and in vivo studies

The effects of COX inhibition on pancreatic cancer growth has been examined both *in vitro* and *in vivo*, using both non-specific NSAIDs and specific COX-2 inhibitors. The effect of these inhibitors depends, at least in part, on the COX-2 pathway in cultured pancreatic cancer cell lines [48]. One study showed that COX inhibitors significantly suppressed proliferation of cells that have high levels of COX-2 expression, but exerted minimal effects on proliferation in cells with a significantly lower level of COX-2 [48]. We have reported that the non-specific COX inhibitor, indomethacin is equally potent in inhibiting pancreatic cancer cell proliferation compared with the specific COX-2 inhibitor, NS398 [43].

Another important action of the COX-2 enzyme is inhibition of apoptosis, which in many cases constitutes another mechanism to promote tumor cell growth. Several studies have revealed that COX-2-specific and non-specific NSAIDs induce apoptosis in a variety of cancer cells, including colon, gastric, glioma, and lung cancer cells [6–8]. Recently, we and others have demonstrated that COX inhibitors significantly induce apoptosis in pancreatic cancer cells [43]. Non-specific NSAIDs and COX-2 specific inhibitors were also equipotent for inducing apoptosis, suggesting that the COX-2 pathway plays a key role in preventing apoptosis and that NSAIDs reverse this effect by inhibiting the pathway [43]. Pancreatic cancer growth is inhibited by COX-2 in animal models as well as *in vitro*. Our data show that the COX-2 inhibitor, celecoxib significantly decreases both volume and weight of pancreatic tumors xenografted subcutaneously into nude mice.

Compared with the investigations on the role of COX in the development and growth of cancers, information regarding the role of lipoxygenases in the regulation of pancreatic cancer growth is limited. Studies conducted by Anderson *et al* showed inhibition of pancreatic cancer cell proliferation following treatment with the 5-lipoxygenase activating protein (FLAP) inhibitor, MK886 [49–51]. Coincident with growth inhibition, changes in expression of several genes, including tumor suppressor genes and growth factor receptors were induced by MK886 [50]. Anderson *et al* reported that MK886 induces an "atypical" apoptosis in PANC-1 pancreatic cancer cells which is enhanced by gamma linolenic acid [51]. We recently explored the effect of LOX inhibition on pancreatic cancer cell proliferation and survival using pharmacological LOX inhibitors and a FLAP inhibitor, as well as antisense oligonucleotides targeting 5-LOX, 12-LOX or 15-LOX expression [45,52]. Blockade of either 5-LOX or 12-LOX markedly inhibited cell proliferation and induced apoptosis in all of the pancreatic cancer cell lines studied. Apoptosis induced by blockade of either the 5-LOX or 12-LOX

enzyme was documented by propidium iodide DNA staining, demonstration of DNA fragmentation by electrophoresis as well as by the TUNEL assay [45,52]. Antisense oligonucleotides directed against both 5-LOX and 12-LOX had similar inhibitory effects on pancreatic cancer cell proliferation to the small drug LOX inhibitors. In contrast, 15-LOX does not appear to play any important role in pancreatic cancer cell growth, since transfection of 15-LOX antisense oligonucleotide did not affect DNA synthesis of pancreatic cancer cells in our studies [45]. These studies support the potential use of LOX inhibitors in pancreatic cancer treatment or prevention. Animal experiments conducted in our laboratory indicate that blockade of LOX pathways also inhibits growth of pancreatic cancers xenografted into athymic nude mice [53,54]. While the study conducted by Anderson *et al* showed that blockade of 5-LOX induced only an "atypical" apoptosis, our data clearly show that apoptosis is induced by LOX enzyme inhibition [52]. The reasons for these different results are not clear. To confirm that apoptosis occurs in pancreatic cancer cells following LOX inhibitor treatment, we conducted further studies that showed that LOX inhibitors reduce expression of Bcl-2 and Mcl-1 and induce activation of caspase-3 and -9 as well as cleavage of the caspase-3 target, PARP [53,54].

Prevention of pancreatic cancer with COX and LOX inhibitors

Pancreatic carcinoma can be induced in hamster models by administering N-nitrosobis(2-oxopropyl)amine (BOP). This animal model mimics human pancreatic cancer biologically and genetically, including mutated *k*-Ras, desmoplasia and insulin resistance [55–57]. Takahashi *et al* treated hamsters with BOP and then subsequently treated them with the non-selective COX inhibitors, indomethacin or aspirin [58]. Animals in the indomethacin group developed significantly fewer tumors than the control group. Aspirin also had a tendency to decrease the incidence of pancreatic cancers [58]. Using the same pancreatic cancer model, Wenger *et al* reported that the specific COX-2 inhibitor, celebrex also prevented pancreatic cancer [59].

Several excellent studies support the use of COX inhibitors for preventing cancer of different organs including colon, lung, breast and pancreas, while exploration of the potential for LOX inhibitors as chemopreventive agents is just beginning. It was recently reported that 5-LOX pathway inhibitors, accolate, MK-886, zileuton, and combinations of zileuton with either accolate or MK-886 reduced lung tumor multiplicity by 37.8, 29.5, and 28.1%, respectively following injection of lung cancer carcinogen vinyl carbamate into mice [60]. These inhibitors also decreased the size of the tumors and the yield of carcinomas [60]. An extract from the sea cucumber, *Cucumaria frondosa* which is a potent LOX inhibitor, attenuates pancreatic cancer development. In our recent study, hamsters were fed with an extract of sea cucumber for one week before pancreatic cancer cells were transplanted orthotopically into the pancreas. The extract decreased pancreatic cancer incidence as well as tumor size.

Molecular mechanisms of COX and LOX-mediated pancreatic cancer development

Mitogenic effects of COX and LOX metabolites

Evidence suggests that the prostaglandin products of the COX pathway, especially PGE2 enhance cell proliferation in either normal and cancer cells through specific receptors [61–67]. Prostaglandins exert their effects locally in both an autocrine and paracrine manner. PGE_2 receptors are a family of G-protein-coupled receptors, namely, EP_1, EP_2, EP_3, and EP_4 [68]. Functional studies on the EP receptors have relied on use of EP knockout mice. The deficiency of the prostaglandin receptor EP_2 gene reduced the size and number of intestinal tumors in APC^{716} mice, similar to deficiency of the COX-2 gene [69]. Besides prostaglandin E2 and its receptor, thromboxane A2 is also involved in cancer development [70–75]. Thromboxane A2 enhances cancer cell proliferation, while its antagonist blocks cancer cell growth. We have shown that both 5-LOX and 12-LOX are also involved in pancreatic cancer cell proliferation. Both 5-HETE and 12-HETE enhance DNA synthesis in pancreatic cancer cells by activating multiple intracellular signal pathways [76–78]. Our most recent study suggests that LTB4 receptors are up-regulated in human pancreatic cancer tissues and coincidentally, pancreatic cancer cells produce LTB4 [46]. This autocrine loop might be important for pancreatic cancer cell growth, as LTB4 itself stimulates pancreatic cancer cell growth while the LTB4 receptor antagonist, LY293111 blocks growth of pancreatic cancer both *in vitro* and *in vivo* [79]. The signaling pathways that respond to COX and LOX-derived metabolites in cancer cells include ERK1/2, PI3 kinase/AKT cascade, tyrosine kinases, STAT, c-Myc and others which are summarized in Table 1.

Regulation of cell survival by COX and LOX

Inhibition of either COX or LOX induces apoptosis of pancreatic cancer cells while forced expression of COX-2 prevents apoptosis. Multiple cellular proteins are involved in this process and mitochondria are the key organelles for COX or LOX inhibition-induced apoptosis [83–86]. Treatment of cancer cells with COX inhibitors induces cytochrome C release from mitochondria, which in turn activates caspase-9 and then caspase-3 [83–86]. Cytochrome C release seems to be directly related to COX inhibition since addition of prostaglandin E2 can prevent NS398-induced cytochrome C release, caspase activation and PARP cleavage [83–86]. Other studies have shown

Table 1: Signal molecules activated or upregulated by COX and LOX metabolites

Metaboltes	Activated Molecules	References
13-HODE	PKCα	Liu et al, 1995
12-HETE	PKCα	Liu et al, 1997
12-HETE	c-Src	Szekeres et al, 2000
12-HETE	PI3 kinase	Szekeres et al, 2000
5-HETE	PI3 kinase	Ding et al, 2001
5-HETE	tyrosine kinase	Ding et al, 2001
5-HETE/12-HETE	P38 kinase	Ding et al, 2001
PGE2	VEGF	Pai et al, 2001
12-HETE	ERK1/2	Ding et al, 2001
PGE2/EP3 receptor	Ras/MEK/ERK	Yano et al, 2002
PGE2	EGF receptor	Pai et al, 2002
PGE2/EP4	IL-6 release	Fiebich et al, 2001
PGE2/EP2/EP4	PI3 kinase/GSK	Fujino et al, 2002
PGE2	STAT	Liu et al, 2002
LTB4	ERK1/2	Tong et al, 2002

that over-expression of COX-2 increases Bcl-2 expression, which might be responsible for preventing cytochrome C release from mitochondria [87]. A recent study showed that death receptors are also involved in COX-regulated cancer cell survival [88–90]. Forced COX-2 expression significantly attenuated TRAIL-induced apoptosis and was associated with transcriptional repression of death receptor-5 and up-regulation of Bcl-2 [89]. Over-expression of COX-2 also reduced caspase-8, caspase-3, and caspase-9 activation relative to corresponding parental cells [89]. In contrast, COX inhibitors were able to restore death receptor-5 expression. Several lines of evidence suggests that NFκB and PI3 kinase are involved in NSAID-induced cancer cell apoptosis [89]. NSAIDs inhibit NFκB and PI3 kinase activity, while restoration of NFκB or PI3 kinase activity blocks NSAID-induced apoptosis [91–93]. Inhibition of COX-2 causes an increase in tissue concentrations of ceramide. Since ceramide is an effective inducer of apoptosis, metabolism of arachidonic acid by COX-2 might prevent apoptosis by reducing intracellular ceramide concentrations. Therefore, an imbalance between PGE2 and ceramide may contribute to the apoptosis-preventing effects of COX-2 in cancer cells [94,95]. The mechanisms involved in COX-mediated cancer cell survival are complex and it is likely that even more pathways involved in these effects will be identified in the future.

To date, three signal cascades have been shown to be linked to LOX-regulated pancreatic cancer cell survival. The first pathway is the Bcl protein family-release of cytochrome C from mitochondria-caspase cascade [53,54,96–98]. Treatment of pancreatic cancer cells with either 5-LOX or 12-LOX inhibitors, dramatically upsets the balance between the anti-apoptotic proteins (such as Bcl-2, Mcl-1) and the pro-apoptotic protein (Bax). This increased pro/anti-apoptotic protein ratio triggers cytochrome C release from mitochondria, which in turn activates caspase cascade and results in apoptosis. The second cascade is the extracellular regulated kinase cascade (MEK/ERK). It is known that activation of the MEK/ERK signal transduction pathway prevents apoptosis. Our studies show that the LOX metabolites, 5-HETE, 12-HETE and LTB4 stimulate MEK/ERK phosphorylation [76–78,80]. PI3 kinase/AKT protects cells from apoptosis by phosphorylation of Bad. Bad is a pro-apoptotic member of the Bcl-2 family that can displace Bax from binding to Bcl-2 and Bcl-xL, resulting in cell death. Phosphorylation of Bad results in its binding to 14-3-3 proteins and prevents it binding to Bcl-2 and Bcl-xL. We have shown that both 5-HETE and LTB4 activate the PI3 kinase/AKT cascade, which constitutes the third pathway which links LOX activation to the prevention of apoptosis in pancreatic cancer cells [78–80].

Modulation of cell migration, invasion and angiogenesis

It is well documented that COX inhibitors reduce cancer cell migration, cell adhesion and tumor invasiveness [6,7,99]. In contrast, constitutive COX-2 expression leads to enhanced cell invasiveness [100,101]. The biochemical changes associated with over-expression of COX-2 include increased expression and activation of metalloproteinase-2 (MMP-2) and reduced expression of E-cadherin [102–104]. We speculate that there are likely to be several pathways that mediate COX-2-promoted cell invasion, which may be cell-type dependent. The multiple effects of COX-2 on cell motility and cell adhesion suggest a key role for COX-2 in tumor invasiveness and angiogenesis.

Both non-specific and specific COX-2 inhibitors significantly inhibit angiogenesis, a process that involves inacti-

vation of the MAPK pathway. COX-2 induces the production of vascular endothelial growth factor (VEGF), a proangiogenic growth factor. This induction is blocked by a COX-2 specific inhibitor, NS-398 [105–107]. Recently, the molecular mechanism for COX-2-mediated VEGF expression has been elucidated. A large amount of PGE_2 is generated when COX-2 expression is induced or over-expressed in pancreatic cancer. Activation of the PGE_2 surface membrane receptors increases intracellular cAMP, in turn stimulating VEGF production and thereby promoting neovascularization and tumor angiogenesis [108]. Separate studies suggest that other products of the COX pathway, thromboxane A_2 and PGI_2 also promote angiogenesis [72,75,109,110]. The thromboxane A2 analogue, U46619, stimulates endothelial cell migration [72]. On the other hand, basic fibroblast growth factor (bFGF) or vascular endothelial growth factor (VEGF), which are angiogenic, increase thromboxane A2 synthesis [111–113]. In contrast, inhibition of thromboxane A2 synthesis reduces HUVEC migration stimulated by VEGF or bFGF [75,114]. Furthermore, the thromboxane A2 receptor antagonist inhibits VEGF- or bFGF-stimulated endothelial cell migration and bFGF-induced angiogenesis *in vivo* [75,114].

LOX activity is required for serum- and bFGF-stimulated endothelial cell proliferation and for modified low-density lipoprotein-induced monocyte binding to endothelial cells [115]. 12(S)-HETE can directly stimulate endothelial cell mitogenesis, migration and surface expression of integrin [115–118]. In addition to its role in endothelial cell migration, 12-LOX is also involved in endothelial cell differentiation, seen as tube formation [115]. Pretreatment of endothelial cells with the 12-LOX inhibitor, BHPP inhibits the formation of these vessel-like structures in Matrigel. Exogenous 12(S)-HETE can induce a reversible retraction of endothelial cell monolayers cultured on collagen by regulating PKC [115–118]. The involvement of 12-LOX in endothelial cell angiogenic responses seen *in vitro* has been confirmed *in vivo*, by the observation that the 12-LOX inhibitor, BHPP significantly reduces bFGF-stimulated angiogenesis [115]. The role of 12-LOX in endothelial cell proliferation, together with the finding that 12-LOX is involved in endothelial cell migration and differentiation, implicate the mobilization of arachidonic acid and the generation of 12(S)-HETE in endothelial cells as an early event in the intracellular cascade of angiogenic responses. We have reported that levels of 5-LOX in metastatic pancreatic cancer are higher than in non-metastatic tumor. However, there is little information on the role of 5-LOX on the regulation of angiogenesis and cancer metastasis.

Immune suppression

Individuals at high risk for pancreatic cancer include smokers, and persons with all forms of chronic alcoholic, metabolic, tropical or hereditary pancreatitis. The duration of exposure to inflammation seems to be the major factor involved in the transition from benign to malignant condition [119–122]. Cytokine-mediated up-regulation of COX-2 contributes to increased synthesis of PGs in inflamed tissues [119–122]. The occurrence and growth of various tumors are associated with immune suppression and prostaglandin E2 itself is a potent immunsuppressor [119–121]. Not only do cancer cells themselves produce prostaglandins, but factors released from tumor cells activate monocytes and macrophages to synthesize PGE_2. In turn, PGE_2 inhibits the production of immune regulatory lymphokines, T-cell and B-cell proliferation, and the cytotoxic activity of natural killer cells, thus favoring tumor growth [119–121]. PGE_2 also inhibits the production of tumor necrosis factor-α and induces the production of IL-10, an immunosuppressive cytokine [119–123]. Recently, more molecular mechanisms for PGE_2-mediated immunosuppression have been revealed. For example, PGE2 suppressed IL-15-mediated human natural killer cell function [123].

Free radicals and peroxidation

Nitric oxide (NO) is a short-lived molecule required for many physiological functions which is produced from L-arginine by NO synthases (NOS) [124]. It is a free radical, producing many reactive intermediates that account for its bioactivity [124]. Sustained induction of the inducible form of NOS (iNOS) in chronic inflammation may be mutagenic, either through NO-mediated DNA damage or by hindering DNA repair. Thus sustained NO production is potentially carcinogenic [124]. Progression of the majority of human and experimental tumors appears to be stimulated by NO resulting from activation of iNOS or constitutive NOS [124]. NO can stimulate tumor growth and metastasis by promoting migration and invasion, which may also be triggered by activation of cyclooxygenase [125,126]. Furthermore, iNOS is induced by COX-2 and there is a significant correlation between positive COX-2 and iNOS expression in cancer tissues [125,126].

Both COX and LOX enzymes are peroxidases. It has been proposed that the peroxidase activity of these enzymes may catalyze the conversion of procarcinogens into carcinogens [127–134]. In the liver, such oxidative reactions are catalyzed principally by cytochrome P-450s. However, pancreatic tissues and other organs frequently have low concentrations of P-450s and, therefore, significant amounts of xenobiotics may be co-oxidized to mutagens by the peroxidase activities of COX and LOX [126]. In addition to catalyzing the synthesis of mutagens, both COX-2 and LOX can be induced by carcinogens, such as NNK

and BOP [131–134]. Our unpublished data show that both 5-LOX and 12-LOX are induced in pancreatic ductal cells following treatment with BOP or NNK. Other studies showed that carcinogens induce COX-2 expression and COX-2 in turn catalyzes the oxidation of procarcinogens to produce a highly reactive and strongly mutagenic compounds [132,127,133]. Taken together, these findings suggest a role for COX-2 or LOX inhibitors in preventing carcinogen-induced DNA damage, thereby preventing cancer development.

Feasibility of targeting cyclooxygenase and lipoxygenase for treatment and prevention of pancreatic cancer

The requirements for a chemopreventive drug are that it must have specific targets that are highly expressed in precancer or cancer cells. Such an agent should not be toxic and not disrupt normal cellular functions. Both COX-2 and LOX are up-regulated in cancer and genetic knockouts of these targets do not appear to disrupt normal functions of mice, although there is loss of inflammatory function. These enzymes should, therefore, be ideal targets for pancreatic cancer treatment and chemoprevention. Indeed, COX-2 inhibitors are already being used clinically for colon cancer prevention. Molecular studies indicate that carcinogenesis is a multistep (accumulated genetic and epigenetic alterations), multipath (multiple functional pathways) and multifocal process, frequently driven by genetic instability. Therefore, a combination of drugs with different targets is likely to enhance the efficiency of cancer treatment and chemoprevention. We believe that a combination of COX and LOX inhibitors will yield better results in pancreatic cancer treatment and prevention. Although this approach needs to be confirmed in future studies. Development of drugs targeting both enzymes would be another useful future direction for cancer treatment and prevention.

Several compounds that have either anti-COX or anti-LOX activities have been identified from natural products or food supplements. For example, a polyphenol isolated from the skins of grapes, resveratrol has been shown to be a potent anti-pancreatic cancer agent and is also a COX inhibitor [135]. Ajoene, a garlic-derived natural product that interfaces with the COX-2 enzyme, has anti-cancer activities [136,137]. Other anti-COX-2 agents extracted from green tea and certain herbal medicines also have effects on cancer development [138,139]. Recently, we found that a polar lipid isolate from sea cucumbers markedly blocks pancreatic cancer cell proliferation and induces apoptosis. The anti-pancreatic cancer activity of this extract is probably mediated through inhibition of LOX activity, since it inhibits LTB4 secretion. Furthermore, adding LOX metabolites blocks the inhibitory effect of this extract on pancreatic cancer cell proliferation. These natural products are likely to be valuable in preventing pancreatic cancer development if we could identify high risk pancreatic cancer populations, since these natural products are available in the food chain.

There are, of course, certain problems which need to be solved before the use of COX and LOX enzyme inhibitors can be translated into the clinic for pancreatic cancer treatment and prevention. The specificity of drugs is an important issue facing clinicians [140]. Even though it is claimed that celecoxib and other compounds are specific COX-2 inhibitors, the interpretation of COX-2 studies is complicated by possible COX-2-independent mechanisms [140]. In some cases, NSAIDs only induce apoptosis at concentrations that are much higher than their IC_{50}s [140]. In addition, NSAIDs have been shown to trigger apoptosis in COX-2 deficient cells and NSAID metabolites that do not inhibit COX, such as sulindac sulfone, can also cause apoptosis by inhibiting cGMP-dependent phosphodiesterase [140]. Therefore, the cancer inhibitory effects of COX-2 inhibitors seem to involve COX-2 independent mechanisms [140]. With regard to LOX inhibitors, none of these have yet reached the clinic for testing of anti-cancer activity.

There still is debate about the specific role of COX-2 in cancer development. It is indeed that COX-2 over-expression increases tumor growth and that the COX-2 protein is strongly induced in cancer cells. However, COX-1 may have an important role in cancer prevention as suggested by the COX-1-deficient *Min* mice. When *Min* mice were treated with celecoxib or the conventional NSAID piroxicam, the number of tumors per animal was significantly reduced. Knocking out the COX-2 gene resulted in an 8-fold reduction in the intestinal tumor burden. However, COX-1-deficient *Min* mice exhibit similar decreases in intestinal tumorigenesis as COX-2-null *Min* mice [12]. The recent finding of an inducible splicing variant of COX-1 (COX-3) can only further complicate the current controversy.

Further work is needed to target LOX enzymes chemoprevention, including the validation of these targets and the establishment of useful LOX modulators. It is important to clarify the mechanism by which LOX inhibition affects cell proliferation and apoptosis. The roles of 15-LOX and 8-LOX in pancreatic cancer development and growth still need to be clarified. Further studies may reveal new LOXs and new roles for known LOXs in the development and reversal of cancer and this will also help us to define a specific and effective LOX inhibitor for preventing pancreatic cancer.

Conclusion

COX and LOX metabolism of linoleic and arachidonic acids leads to the formation of a variety of metabolically active products with different roles in carcinogenesis. Our understanding of these roles is steadily increasing. This new information is providing a theoretical basis for development of new cancer chemoprevention approaches targeted to COX and LOX activity. Since no effective treatment is currently available for pancreatic cancer, blockade of the COX and LOX pathways might be valuable in the future for treating and preventing this dreadful disease.

Authors' contributions

Xian-Zhong Ding conducted the literature reviews and drafted this article. Rene Hennig and Thomas E. Adrian provided suggestions and edited the manuscript. All authors read and approved the content of the final manuscript.

Acknowledgments

Supported by grants from the NCI SPORE program (P50 CA72712), the Lustgarten Foundation for Pancreatic Cancer Research (LF49), and the American Institute for Cancer Research (00B065).

References

1. Lipkin M, Reddy B, Newmark H and Lamprecht SA **Dietary factors in human colorectal cancer.** *Annu Rev Nutr* 1999, **19:**545-586
2. Willett WC **Specific fatty acids and risks of breast and prostate cancer: dietary intake.** *Am J Clin Nutr* 1997, **66(6 Suppl):**1557S-1563S
3. Klurfeld DM and Bull AW **Fatty acids and colon cancer in experimental models.** *Am J Clin Nutr* 1997, **66(6 Suppl):**1530S-1538S
4. Guthrie N and Carroll KK **Specific versus non-specific effects of dietary fat on carcinogenesis.** *Prog Lipid Res* 1999, **38:**261-271
5. Funk CD **Prostaglandins and leukotrienes: advances in eicosanoid biology.** *Science* 2001, **294(5548):**1871-1875
6. Cao Y and Prescott SM **Many actions of cyclooxygenase-2 in cellular dynamics and in cancer.** *J Cell Physiol* 2002, **190:**279-286
7. Lin DT, Subbaramaiah K, Shah JP, Dannenberg AJ and Boyle JO **Cyclooxygenase-2: A novel molecular target for the prevention and treatment of head and neck cancer.** *Head Neck* 2002, **24:**792-799
8. Howe LR and Dannenberg AJ **A role for cyclooxygenase-2 inhibitors in the prevention and treatment of cancer.** *Semin Oncol* 2002, **29(3 Suppl 11):**111-119
9. Ding XZ, Tong WG and Adrian TE **Cyclooxygenases and lipoxygenases as potential targets for treatment of pancreatic cancer.** *Pancreatology* 2001, **1(4):**91-99
10. Dannenberg AJ, Altorki NK, Boyle JO, Dang C, Howe LR, Weksler BB and Subbaramaiah K **Cyclo-oxygenase 2: a pharmacological target for the prevention of cancer.** *Lancet Oncol* 2001, **2:**544-551
11. Gupta RA and Dubois RN **Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2.** *Nat Rev Cancer* 2001, **1:**11-21
12. Williams CS, Mann M and DuBois RN **The role of cyclooxygenases in inflammation, cancer, and development.** *Oncogene* 1999, **18:**7908-7916
13. Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS and Simmons DL **From the Cover: COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression.** *PNAS* 2002, **99:**13926-13931
14. Iversen L and Kragballe K **Arachidonic acid metabolism in skin health and disease.** *Prostaglandins Other Lipid Mediat* 2000, **63:**25-42
15. Yamamoto S, Suzuki H, Nakamura M and Ishimura K **Arachidonate 12-lipoxygenase isozymes.** *Adv Exp Med Biol* 1999, **447:**37-44
16. Brash AR, Jisaka M, Boeglin WE and Chang MS **Molecular cloning of a second human 15S-lipoxygenase and its murine homologue, an 8S-lipoxygenase. Their relationship to other mammalian lipoxygenases.** *Adv Exp Med Biol* 1999, **447:**29-36
17. Kuhn H and Borngraber S **Mammalian 15-lipoxygenases. Enzymatic properties and biological implications.** *Adv Exp Med Biol* 1999, **447:**5-28
18. Steele VE, Holmes CA, Hawk ET, Kopelovich L, Lubet RA, Crowell JA, Sigman CC and Kelloff GJ **Lipoxygenase inhibitors as potential cancer chemopreventives.** *Cancer Epidemiol Biomarkers Prev* 1999, **8:**467-83
19. Gunning WT, Kramer PM, Steele VE and Pereira MA **Chemoprevention by lipoxygenase and leukotriene pathway inhibitors of vinyl carbamate-induced lung tumors in mice.** *Cancer Res* 2002, **62:**4199-4201
20. Ghosh J and Myers CE **Central role of arachidonate 5-lipoxygenase in the regulation of cell growth and apoptosis in human prostate cancer cells.** *Adv Exp Med Biol* 1999, **469:**577-82
21. Anderson KM, Seed T, Jajeh A, Dudeja P, Byun T, Meng J, Ou D, Bonomi P and Harris JE **An in vivo inhibitor of 5-lipoxygenase, MK886, at micromolar concentration induces apoptosis in U937 and CML cells.** *Anticancer Res* 1996, **16(5A):**2589-99
22. Tang DG and Honn KV **Apoptosis of W256 carcinosarcoma cells of the monocytoid origin induced by NDGA involves lipid peroxidation and depletion of GSH: role of 12-lipoxygenase in regulating tumor cell survival.** *J Cell Physiol* 1997, **172(2):**155-70
23. Nie D, Che M, Grignon D, Tang K and Honn KV **Role of eicosanoids in prostate cancer progression.** *Cancer Metastasis Rev* 2001, **20:**195-206
24. Brash AR, Jisaka M, Boeglin WE and Chang MS **Molecular cloning of a second human 15S-lipoxygenase and its murine homologue, an 8S-lipoxygenase. Their relationship to other mammalian lipoxygenases.** *Adv Exp Med Biol* 1999, **447:**29-36
25. Iversen L and Kragballe K **Arachidonic acid metabolism in skin health and disease.** *Prostaglandins Other Lipid Mediat* 2000, **63:**25-42
26. Muga SJ, Thuillier P, Pavone A, Rundhaug JE, Boeglin WE, Jisaka M, Brash AR and Fischer SM **8S-lipoxygenase products activate peroxisome proliferator-activated receptor alpha and induce differentiation in murine keratinocytes.** *Cell Growth Differ* 2000, **11(8):**447-54
27. Burger F, Krieg P, Kinzig A, Schurich B, Marks F and Furstenberger G **Constitutive expression of 8-lipoxygenase in papillomas and clastogenic effects of lipoxygenase-derived arachidonic acid metabolites in keratinocytes.** *Mol Carcinog* 1999, **24:**108-17
28. Shureiqi I and Lippman SM **Lipoxygenase modulation to reverse carcinogenesis.** *Cancer Res* 2001, **61:**6307-12
29. Eling TE and Glasgow WC **Cellular proliferation and lipid metabolism: importance of lipoxygenases in modulating epidermal growth factor-dependent mitogenesis.** *Cancer Metastasis Rev* 1994, **13:**397-410
30. Eling TE, Everhart AL, Angerman-Stewart J, Hui R and Glasgow WC **Modulation of epidermal growth factor signal transduction by linoleic acid metabolites.** *Adv Exp Med Biol* 1997, **407:**319-22
31. Shureiqi I, Chen D, Lotan R, Yang P, Newman RA, Fischer SM and Lippman SM **15-Lipoxygenase-1 mediates nonsteroidal anti-inflammatory drug-induced apoptosis independently of cyclooxygenase-2 in colon cancer cells.** *Cancer Res* 2000, **60:**6846-50
32. Profita M, Sala A, Siena L, Henson PM, Murphy RC, Paterno A, Bonanno A, Riccobono L, Mirabella A, Bonsignore G and Vignola AM **Leukotriene B4 production in human mononuclear phagocytes is modulated by interleukin-4-induced 15-lipoxygenase.** *J Pharmacol Exp Ther* 2002, **300:**868-75
33. Shappell SB, Gupta RA, Manning S, Whitehead R, Boeglin WE, Schneider C, Case T, Price J, Jack GS, Wheeler TM, Matusik RJ, Brash AR and Dubois RN **15S-Hydroxyeicosatetraenoic acid activates peroxisome proliferator-activated receptor gamma and inhibits proliferation in PC3 prostate carcinoma cells.** *Cancer Res* 2001, **61:**497-503
34. Anderson KE, Johnson TW, Lazovich D and Folsom AR **Association between nonsteroidal anti-inflammatory drug use and the incidence of pancreatic cancer.** *J Natl Cancer Inst* 2002, **94:**1168-71

35. O'Neill GP and Ford-Hutchinson AW **Expression of mRNA for cyclooxygenase-1 and cyclooxygenase-2 in human tissues.** *FEBS Lett* 1993, **330:**156-60
36. Tucker ON, Dannenberg AJ, Yang EK, Zhang F, Teng L, Daly JM, Soslow RA, Masferrer JL, Woerner BM, Koki AT and Fahey TJ 3rd **Cyclooxygenase-2 expression is up-regulated in human pancreatic cancer.** *Cancer Res* 1999, **59:**987-90
37. Okami J, Yamamoto H, Fujiwara Y, Tsujie M, Kondo M, Noura S, Oshima S, Nagano H, Dono K, Umeshita K, Ishikawa O, Sakon M, Matsuura N, Nakamori S and Monden M **Overexpression of cyclooxygenase-2 in carcinoma of the pancreas.** *Clin Cancer Res* 1999, **5:**2018-24
38. Molina MA, Sitja-Arnau M, Lemoine MG, Frazier ML and Sinicrope FA **Increased cyclooxygenase-2 expression in human pancreatic carcinomas and cell lines: growth inhibition by nonsteroidal anti-inflammatory drugs.** *Cancer Res* 1999, **59(17):**4356-4362
39. Yip-Schneider MT, Barnard DS, Billings SD, Cheng L, Heilman DK, Lin A, Marshall SJ, Crowell PL, Marshall MS and Sweeney CJ **Cyclooxygenase-2 expression in human pancreatic adenocarcinomas.** *Carcinogenesis* 2000, **21:**139-46
40. Kokawa A, Kondo H, Gotoda T, Ono H, Saito D, Nakadaira S, Kosuge T and Yoshida S **Increased expression of cyclooxygenase-2 in human pancreatic neoplasms and potential for chemoprevention by cyclooxygenase inhibitors.** *Cancer* 2001, **91:**333-8
41. Merati K, said Siadaty M, Andea A, Sarkar F, Ben-Josef E, Mohammad R, Philip P, Shields AF, Vaitkevicius V, Grignon DJ and Adsay NV **Expression of inflammatory modulator COX-2 in pancreatic ductal adenocarcinoma and its relationship to pathologic and clinical parameters.** *Am J Clin Oncol* 2001, **24:**447-52
42. Maitra A, Ashfaq R, Gunn CR, Rahman A, Yeo CJ, Sohn TA, Cameron JL, Hruban RH and Wilentz RE **Cyclooxygenase 2 expression in pancreatic adenocarcinoma and pancreatic intraepithelial neoplasia: an immunohistochemical analysis with automated cellular imaging.** *Am J Clin Pathol* 2002, **118:**194-201
43. Ding XZ, Tong WG and Adrian TE **Blockade of cyclooxygenase-2 inhibits proliferation and induces apoptosis in human pancreatic cancer cells.** *Anticancer Res* 2000, **20:**2625-31
44. Nzeako UC and Gores GJ **Increased expression of cyclooxygenase-2 in human pancreatic neoplasms and potential for chemoprevention by cyclooxygenase inhibitors.** *Cancer* 2002, **94:**1903-4
45. Ding XZ, Iversen P, Cluck MW, Knezetic JA and Adrian TE **Lipoxygenase inhibitors abolish proliferation of human pancreatic cancer cells.** *Biochem Biophys Res Commun* 1999, **261:**218-23
46. Hennig R, Ding XZ, Tong WG, Schneider MB, Standop J, Friess H, Buchler MW, Pour PM and Adrian TE **5-Lipoxygenase and leukotriene B(4) receptor are expressed in human pancreatic cancers but not in pancreatic ducts in normal tissue.** *Am J Pathol* 2002, **161:**421-8
47. Bleich D, Chen S, Gu JL and Nadler JL **The role of 12-lipoxygenase in pancreatic-cells (Review).** *Int J Mol Med* 1998, **1:**265-72
48. Yip-Schneider MT, Barnard DS, Billings SD, Cheng L, Heilman DK, Lin A, Marshall SJ, Crowell PL, Marshall MS and Sweeney CJ **Cyclooxygenase-2 expression in human pancreatic adenocarcinomas.** *Carcinogenesis* 2000, **21:**139-46
49. Anderson KM, Seed T, Meng J, Ou D, Alrefai WA and Harris JE **Five-lipoxygenase inhibitors reduce Panc-1 survival: the mode of cell death and synergism of MK886 with gamma linolenic acid.** *Anticancer Res* 1998, **18(2A):**791-800
50. Anderson KM, Alrefai WA, Bonomi P, Dudeja P, Ou D, Anderson C and Harris JE **Altered oncogene, tumor suppressor and cell-cycle gene expression in PANC-1 cells cultured with the pleiotrophic 5-lipoxygenase inhibitor, MK886, assessed with a gene chip.** *Anticancer Res* 1999, **19(5B):**3873-87
51. Harris JE, Alrefai WA, Meng J and Anderson KM **Five-lipoxygenase inhibitors reduce Panc-1 survival: synergism of MK886 with gamma linolenic acid.** *Adv Exp Med Biol* 1999, **469:**505-10
52. Ding XZ, Kuszynski CA, El-Metwally TH and Adrian TE **Lipoxygenase inhibition induced apoptosis, morphological changes, and carbonic anhydrase expression in human pancreatic cancer cells.** *Biochem Biophys Res Commun* 1999, **266:**392-9
53. Tong WG, Ding XZ, Witt RC and Adrian TE **Lipoxygenase Inhibitors Attenuate Growth of Human Pancreatic Cancer Xenografts and Induce Apoptosis through the Mitochondrial Pathway.** *Mol Cancer Ther* 2002, **1:**929-935
54. Tong WG, Ding XZ and Adrian TE **The mechanisms of lipoxygenase inhibitor-induced apoptosis in human breast cancer cells.** *Biochem Biophys Res Commun* 2002, **296:**942-8
55. Pour P, Althoff J, Kruger FW and Mohr U **A potent pancreatic carcinogen in Syrian hamsters: N-nitrosobis(2-oxopropyl)amine.** *J Natl Cancer Inst* 1977, **58(5):**1449-53
56. Egami H, Takiyama Y, Chaney WG, Cano M, Fujii H, Tomioka T, Metzgar R and Pour PM **Comparative studies on expression of tumor-associated antigens in human and induced pancreatic cancer in Syrian hamsters.** *Int J Pancreatol* 1990, **7(1–3):**91-100
57. Ishikawa O, Ohigashi H, Imaoka S, Nakai I, Mitsuo M, Weide L and Pour PM **The role of pancreatic islets in experimental pancreatic carcinogenicity.** *Am J Pathol* 1995, **147:**1456-64
58. Takahashi M, Furukawa F, Toyoda K, Sato H, Hasegawa R, Imaida K and Hayashi Y **Effects of various prostaglandin synthesis inhibitors on pancreatic carcinogenesis in hamsters after initiation with N-nitrosobis(2-oxopropyl)amine.** *Carcinogenesis* 1990, **11(3):**393-5
59. Wenger FA, Kilian M, Achucarro P, Heinicken D, Schimke I, Guski H, Jacobi CA and Muller JM **Effects of Celebrex and Zyflo on BOP-induced pancreatic cancer in Syrian hamsters.** *Pancreatology* 2002, **2:**54-60
60. Gunning WT, Kramer PM, Steele VE and Pereira MA **Chemoprevention by lipoxygenase and leukotriene pathway inhibitors of vinyl carbamate-induced lung tumors in mice.** *Cancer Res* 2002, **62:**4199-4201
61. Yano T, Zissel G, Muller-Qernheim J, Jae Shin S, Satoh H and Ichikawa T **Prostaglandin E2 reinforces the activation of Ras signal pathway in lung adenocarcinoma cells via EP3.** *FEBS Lett* 2002, **518:**154-158
62. Pai R, Soreghan B, Szabo IL, Pavelka M, Baatar D and Tarnawski AS **Prostaglandin E2 transactivates EGF receptor: a novel mechanism for promoting colon cancer growth and gastrointestinal hypertrophy.** *Nat Med* 2002, **8:**289-293
63. Fiebich BL, Schleicher S, Spleiss O, Czygan M and Hull M **Mechanisms of prostaglandin E2-induced interleukin-6 release in astrocytes: possible involvement of EP4-like receptors, p38 mitogen-activated protein kinase and protein kinase C:** *J Neurochem* 2001, **79:**950-958
64. Pai R, Szabo IL, Soreghan BA, Atay S, Kawanaka H and Tarnawski AS **PGE(2) stimulates VEGF expression in endothelial cells via ERK2/JNK1 signaling pathways.** *Biochem Biophys Res Commun* 2001, **286:**923-928
65. Fujino H, West KA and Regan JW **Phosphorylation of glycogen synthase kinase-3 and stimulation of T-cell factor signaling following activation of EP2 and EP4 prostanoid receptors by prostaglandin E2.** *J Biol Chem* 2002, **277:**2614-2619
66. Liu XH, Kirschenbaum A, Lu M, Yao S, Klausner A, Preston C, Holland JF and Levine AC **Prostaglandin E(2) stimulates prostatic intraepithelial neoplasia cell growth through activation of the interleukin-6/GP130/STAT-3 signaling pathway.** *Biochem Biophys Res Commun* 2002, **290:**249-255
67. Bishop-Bailey D, Calatayud S, Warner TD, Hla T and Mitchell JA **Prostaglandins and the regulation of tumor growth.** *J Environ Pathol Toxicol Oncol* 2002, **21:**93-101
68. Breyer RM **Prostaglandin EP(1) receptor subtype selectivity takes shape.** *Mol Pharmacol* 2001, **59:**1357-9
69. Sonoshita M, Takaku K, Sasaki N, Sugimoto Y, Ushikubi F, Narumiya S, Oshima M and Taketo MM **Acceleration of intestinal polyposis through prostaglandin receptor EP2 in Apc(Delta 716) knockout mice.** *Nat Med* 2001, **7:**1048-51
70. Rodrigues S, Nguyen QD, Faivre S, Bruyneel E, Thim L, Westley B, May F, Flatau G, Mareel M, Gespach C and Emami S **Activation of cellular invasion by trefoil peptides and src is mediated by cyclooxygenase- and thromboxane A2 receptor-dependent signaling pathways.** *FASEB J* 2001, **15:**1517-28
71. Nie D, Lamberti M, Zacharek A, Li L, Szekeres K, Tang K, Chen Y and Honn KV **Thromboxane A(2) regulation of endothelial cell migration, angiogenesis, and tumor metastasis.** *Biochem Biophys Res Commun* 2000, **267:**245-51
72. Kasahara K, Fujimura M, Bando T, Shibata K, Shirasaki H and Matsuda T **Modulation of sensitivity to cis-diamminedichloroplatinum (II) by thromboxane A2 receptor antagonists in non-small lung cell lines.** *Br J Cancer* 1996, **74:**1553-8
73. Rodrigues S, Nguyen QD, Faivre S, Bruyneel E, Thim L, Westley B, May F, Flatau G, Mareel M, Gespach C and Emami S **Activation of**

cellular invasion by trefoil peptides and src is mediated by cyclooxygenase- and thromboxane A2 receptor-dependent signaling pathways. *FASEB J* 2001, **15:**1517-28
74. Fujimura M, Kasahara K, Shirasaki H, Heki U, Iwasa K, Ueda A and Matsuda T **Up-regulation of ICH-1L protein by thromboxane A2 antagonists enhances cisplatin-induced apoptosis in non-small-cell lung-cancer cell lines.** *J Cancer Res Clin Oncol* 1999, **125:**389-94
75. Pakala R and Benedict CR **Effect of serotonin and thromboxane A2 on endothelial cell proliferation: effect of specific receptor antagonists.** *J Lab Clin Med* 1998, **131:**527-37
76. Ding XZ, Tong WG and Adrian TE **12-lipoxygenase metabolite, 12(S)-HETE stimulates pancreatic cancer cell proliferation. Involvement of tyrosine phosphorylation and MEK/ERK activation.** *Int J Cancer* 2001, **94:**630-636
77. Ding XZ, Tong WG and Adrian TE **Interaction between the 5-lipoxygenase and EGF-mediated signaling pathways is important in the control of pancreatic cancer cell proliferation.** *Pancreas* 2001, **23:**434
78. Adrian TE, Ding XZ and Tong WG **The mitogenic effect of 5-lipoxygenase metabolite, 5-HETE on pancreatic cancer cell proliferation through activation of multiple signaling pathways.** *FASEB J* 2001, **15:**A1163
79. Tong WG, Ding XZ, Hennig R, Witt RC, Standop J, Pour PM and Adrian TE **Leukotriene B4 Receptor Antagonist LY293111 Inhibits Proliferation and Induces Apoptosis in Human Pancreatic Cancer Cells.** *Clin Cancer Res* 2002, **8:**3232-3242
80. Szekeres CK, Tang K, Trikha M and Honn KV **Eicosanoid activation of extracellular signal-regulated kinase1/2 in human epidermoid carcinoma cells.** *J Biol Chem* 2000, **275:**38831-3841
81. Liu B, Maher RJ, De Jonckheere JP, Popat RU, Stojakovic S, Hannun YA, Porter AT and Honn KV **12(S)-HETE increases the motility of prostate tumor cells through selective activation of PKC alpha.** *Adv Exp Med Biol* 1997, **400B:**707-718
82. Liu B, Khan WA, Hannun YA, Timar J, Taylor JD, Lundy S, Butovich I and Honn KV **12(S)-hydroxyeicosatetraenoic acid and 13(S)-hydroxyoctadecadienoic acid regulation of protein kinase C-alpha in melanoma cells: role of receptor-mediated hydrolysis of inositol phospholipids.** *Proc Natl Acad Sci U S A* 1995, **92:**9323-9327
83. Li M, Wu X and Xu XC **Induction of apoptosis by cyclo-oxygenase-2 inhibitor NS398 through a cytochrome C-dependent pathway in esophageal cancer cells.** *Int J Cancer* 2001, **93:**218-23
84. Li M, Wu X and Xu XC **Induction of apoptosis in colon cancer cells by cyclooxygenase-2 inhibitor NS398 through a cytochrome c-dependent pathway.** *Clin Cancer Res* 2001, **7:**1010-6
85. Aggarwal S, Taneja N, Lin L, Orringer MB, Rehemtulla A and Beer DG **Indomethacin-induced apoptosis in esophageal adenocarcinoma cells involves upregulation of Bax and translocation of mitochondrial cytochrome C independent of COX-2 expression.** *Neoplasia* 2000, **2(4):**346-56
86. Munkarah AR, Morris R, Baumann P, Deppe G, Malone J, Diamond MP and Saed GM **Effects of prostaglandin E(2) on proliferation and apoptosis of epithelial ovarian cancer cells.** *J Soc Gynecol Investig* 2002, **9:**168-73
87. Lin MT, Lee RC, Yang PC, Ho FM and Kuo ML **Cyclooxygenase-2 inducing Mcl-1-dependent survival mechanism in human lung adenocarcinoma CL1.0 cells. Involvement of phosphatidylinositol 3-kinase/Akt pathway.** *J Biol Chem* 2001, **276:**48997-9002
88. Nzeako UC, Guicciardi ME, Yoon JH, Bronk SF and Gores GJ **COX-2 inhibits Fas-mediated apoptosis in cholangiocarcinoma cells.** *Hepatology* 2002, **35:**552-9
89. Tang X, Sun YJ, Half E, Kuo MT and Sinicrope F **Cyclooxygenase-2 overexpression inhibits death receptor 5 expression and confers resistance to tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis in human colon cancer cells.** *Cancer Res* 2002, **62:**4903-8
90. He Q, Luo X, Huang Y and Sheikh MS **Apo2L/TRAIL differentially modulates the apoptotic effects of sulindac and a COX-2 selective non-steroidal anti-inflammatory agent in Bax-deficient cells.** *Oncogene* 2002, **21:**6032-40
91. Chan TA **Nonsteroidal anti-inflammatory drugs, apoptosis, and colon-cancer chemoprevention.** *Lancet Oncol* 2002, **3:**166-74
92. Thun MJ, Henley SJ and Patrono C **Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues.** *J Natl Cancer Inst* 2002, **94:**252-66
93. Hsu AL, Ching TT, Wang DS, Song X, Rangnekar VM and Chen CS **The cyclooxygenase-2 inhibitor celecoxib induces apoptosis by blocking Akt activation in human prostate cancer cells independently of Bcl-2.** *J Biol Chem* 2000, **275:**11397-403
94. Shimada T, Hiraishi H and Terano A **Hepatocyte growth factor protects gastric epithelial cells against ceramide-induced apoptosis through induction of cyclooxygenase-2.** *Life Sci* 2000, **68:**539-46
95. Chan TA, Morin PJ, Vogelstein B and Kinzler KW **Mechanisms underlying nonsteroidal antiinflammatory drug-mediated apoptosis.** *Proc Natl Acad Sci U S A* 1998, **95:**681-6
96. Pidgeon GP, Kandouz M, Meram A and Honn KV **Mechanisms controlling cell cycle arrest and induction of apoptosis after 12-lipoxygenase inhibition in prostate cancer cells.** *Cancer Res* 2002, **62:**2721-7
97. Wong BC, Wang WP, Cho CH, Fan XM, Lin MC, Kung HF and Lam SK **12-Lipoxygenase inhibition induced apoptosis in human gastric cancer cells.** *Carcinogenesis* 2001, **22:**1349-54
98. Tang DG, Chen YQ and Honn KV **Arachidonate lipoxygenases as essential regulators of cell survival and apoptosis.** *Proc Natl Acad Sci U S A* 1996, **93:**5241-6
99. Rozic JG, Chakraborty C and Lala PK **Cyclooxygenase inhibitors retard murine mammary tumor progression by reducing tumor cell migration, invasiveness and angiogenesis.** *Int J Cancer* 2001, **93:**497-506
100. Sheng H, Shao J, Washington MK and DuBois RN **Prostaglandin E2 increases growth and motility of colorectal carcinoma cells.** *J Biol Chem* 2001, **276:**18075-81
101. Gately S **The contributions of cyclooxygenase-2 to tumor angiogenesis.** *Cancer Metastasis Rev* 2000, **19:**19-27
102. Pan MR, Chuang LY and Hung WC **Non-steroidal anti-inflammatory drugs inhibit matrix metalloproteinase-2 expression via repression of transcription in lung cancer cells.** *FEBS Lett* 2001, **508:**365-8
103. Jiang MC, Liao CF and Lee PH **Aspirin inhibits matrix metalloproteinase-2 activity, increases E-cadherin production, and inhibits in vitro invasion of tumor cells.** *Biochem Biophys Res Commun* 2001, **282:**671-7
104. Attiga FA, Fernandez PM, Weeraratna AT, Manyak MJ and Patierno SR **Inhibitors of prostaglandin synthesis inhibit human prostate tumor cell invasiveness and reduce the release of matrix metalloproteinases.** *Cancer Res* 2000, **60:**4629-37
105. Fosslien E **Review: molecular pathology of cyclooxygenase-2 in cancer-induced angiogenesis.** *Ann Clin Lab Sci* 2001, **31:**325-48
106. Gately S **The contributions of cyclooxygenase-2 to tumor angiogenesis.** *Cancer Metastasis Rev* 2000, **19(1–2):**19-27
107. Masferrer JL, Koki A and Seibert K **COX-2 inhibitors. A new class of antiangiogenic agents.** *Ann N Y Acad Sci* 1999, **889:**84-6
108. Sonoshita M, Takaku K, Sasaki N, Sugimoto Y, Ushikubi F, Narumiya S, Oshima M and Taketo MM **Acceleration of intestinal polyposis through prostaglandin receptor EP2 in Apc(Delta 716) knockout mice.** *Nat Med* 2001, **7:**1048-51
109. Daniel TO, Liu H, Morrow JD, Crews BC and Marnett LJ **Thromboxane A2 is a mediator of cyclooxygenase-2-dependent endothelial migration and angiogenesis.** *Cancer Res* 1999, **59:**4574-7
110. Spisni E, Griffoni C, Santi S, Riccio M, Marulli R, Bartolini G, Toni M, Ullrich V and Tomasi V **Colocalization prostacyclin (PGI2) synthase – caveolin-1 in endothelial cells and new roles for PGI2 in angiogenesis.** *Exp Cell Res* 2001, **266:**31-43
111. Ali S, Davis MG, Becker MW and Dorn GW 2nd **Thromboxane A2 stimulates vascular smooth muscle hypertrophy by up-regulating the synthesis and release of endogenous basic fibroblast growth factor.** *J Biol Chem* 1993, **268:**17397-403
112. Chen G, Wilson R, McKillop JH and Walker JJ **The role of cytokines in the production of prostacyclin and thromboxane in human mononuclear cells.** *Immunol Invest* 1994, **23:**269-79
113. Bartolini G, Orlandi M, Chiricolo M, Minghetti L, Guerrini F, Fidan M, Franceschi C and Tomasi V **Regulation of thromboxane A2 biosynthesis in platelet-free human monocytes and the possible role of polypeptide growth factor(s) in the induction of cyclooxygenase system.** *Biochim Biophys Acta* 1986, **876:**486-93

114. Dethlefsen SM, Shepro D and D'Amore PA **Arachidonic acid metabolites in bFGF-, PDGF-, and serum-stimulated vascular cell growth.** *Exp Cell Res* 1994, **12:**262-73
115. Nie D, Tang K, Diglio C and Honn KV **Eicosanoid regulation of angiogenesis: role of endothelial arachidonate 12-lipoxygenase.** *Blood* 2000, **95:**2304-11
116. Nie D, Tang K, Szekeres K, Li L and Honn KV **Eicosanoid regulation of angiogenesis in human prostate carcinoma and its therapeutic implications.** *Ann N Y Acad Sci* 2000, **905:**165-76
117. Nie D, Hillman GG, Geddes T, Tang K, Pierson C, Grignon DJ and Honn KV **Platelet-type 12-lipoxygenase regulates angiogenesis in human prostate carcinoma.** *Adv Exp Med Biol* 1999, **469:**623-30
118. Nie D, Hillman GG, Geddes T, Tang K, Pierson C, Grignon DJ and Honn KV **Platelet-type 12-lipoxygenase in a human prostate carcinoma stimulates angiogenesis and tumor growth.** *Cancer Res* 1998, **58:**4047-51
119. O'Byrne KJ and Dalgleish AG **Chronic immune activation and inflammation as the cause of malignancy.** *Br J Cancer* 2001, **85:**473-83
120. Goodwin JS and Ceuppens J **Regulation of the immune response by prostaglandins.** *J Clin Immunol* 1983, **3:**295-315
121. Ceuppens J and Goodwin J **Prostaglandins and the immune response to cancer.** *Anticancer Res* 1981, **1:**71-8
122. Farrow B and Evers BM **Inflammation and the development of pancreatic cancer.** *Surg Oncol* 2002, **10:**153-69
123. Joshi PC, Zhou X, Cuchens M and Jones Q **Prostaglandin E2 suppressed IL-15-mediated human NK cell function through down-regulation of common gamma-chain.** *J Immunol* 2001, **166:**885-91
124. Lala PK and Chakraborty C **Role of nitric oxide in carcinogenesis and tumour progression.** *Lancet Oncol* 2001, **2:**149-56
125. Jadeski LC, Hum KO, Chakraborty C and Lala PK **Nitric oxide promotes murine mammary tumour growth and metastasis by stimulating tumour cell migration, invasiveness and angiogenesis.** *Int J Cancer* 2000, **86:**30-9
126. Kong G, Kim EK, Kim WS, Lee KT, Lee YW, Lee JK, Paik SW and Rhee JC **Role of cyclooxygenase-2 and inducible nitric oxide synthase in pancreatic cancer.** *J Gastroenterol Hepatol* 2002, **17:**914-21
127. de Ledinghen V, Liu H, Zhang F, Lo CR, Subbaramaiah K, Dannenberg AJ and Czaja MJ **Induction of cyclooxygenase-2 by tumor promoters in transformed and cytochrome P450 2E1-expressing hepatocytes.** *Carcinogenesis* 2002, **23:**73-9
128. Keith RL, Miller YE, Hoshikawa Y, Moore MD, Gesell TL, Gao B, Malkinson AM, Golpon HA, Nemenoff RA and Geraci MW **Manipulation of pulmonary prostacyclin synthase expression prevents murine lung cancer.** *Cancer Res* 2002, **62:**734-40
129. Degen GH **SEMV cell cultures: a model for studies of prostaglandin-H synthase-mediated metabolism and genotoxicity of xenobiotics.** *Toxicol Lett* 1993, **67:**187-200
130. Marnett LJ **Prostaglandin synthase-mediated metabolism of carcinogens and a potential role for peroxyl radicals as reactive intermediates.** *Environ Health Perspect* 1990, **88:**5-12
131. Schuller HM, Zhang L, Weddle DL, Castonguay A, Walker K and Miller MS **The cyclooxygenase inhibitor ibuprofen and the FLAP inhibitor MK886 inhibit pancreatic carcinogenesis induced in hamsters by transplacental exposure to ethanol and the tobacco carcinogen NNK.** *J Cancer Res Clin Oncol* 2002, **128:**525-32
132. Castonguay A, Rioux N, Duperron C and Jalbert G **Inhibition of lung tumorigenesis by NSAIDS: a working hypothesis.** *Exp Lung Res* 1998, **24:**605-15
133. Schuller HM, Tithof PK, Williams M and Plummer H 3rd **The tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone is a beta-adrenergic agonist and stimulates DNA synthesis in lung adenocarcinoma via beta-adrenergic receptor-mediated release of arachidonic acid.** *Cancer Res* 1999, **59:**4510-5
134. Smith TJ, Stoner GD and Yang CS **Activation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in human lung microsomes by cytochromes P450, lipoxygenase, and hydroperoxides.** *Cancer Res* 1995, **55:**5566-73
135. Bhat KP and Pezzuto JM **Cancer chemopreventive activity of resveratrol.** *Ann N Y Acad Sci* 2002, **957:**210-29
136. Dirsch VM and Vollmar AM **Ajoene, a natural product with non-steroidal anti-inflammatory drug (NSAID)-like properties.** *Biochem Pharmacol* 2001, **61:**587-93
137. Pinto JT, Lapsia S, Shah A, Santiago H and Kim G **Antiproliferative effects of garlic-derived and other allium related compounds.** *Adv Exp Med Biol* 2001, **492:**83-106
138. Yang CS, Maliakal P and Meng X **Inhibition of carcinogenesis by tea.** *Annu Rev Pharmacol Toxicol* 2002, **42:**25-54
139. Wargovich MJ, Woods C, Hollis DM and Zander ME **Herbals, cancer prevention and health.** *J Nutr* 2001, **131(11 Suppl):**3034S-6S
140. Hwang DH, Fung V and Dannenberg AJ **National Cancer Institute workshop on chemopreventive properties of nonsteroidal anti-inflammatory drugs: role of COX-dependent and -independent mechanisms.** *Neoplasia* 2002, **4:**91-97