The Pharma Innovation Journal 2017; 6(1): 22-30

www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2017; 6(2): 22-30

www.thepharmajournal.com
Received: 06-12-2016
Accepted: 07-01-2017

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A paradigm of lipoxygenase and cyclooxygenase metabolism: Focusing new insights and positive biofeedback in the treatment and chemoprevention of pancreatic cancer

Partha Majumder

Abstract
In human body, we have two essential fatty acids such as linoleic acid and arachidonic acid which are playing an important role in the development and progression of pancreatic cancer. Both of these fatty acids are metabolized to eicosanoids by cyclooxygenases and lipoxygenases. Extensive scientific studies show that abnormal expression and activities of both cyclooxygenases and lipoxygenases are correlated with pancreatic cancer. In this review, my aim is to focus a brief summary regarding (1) our understanding of the roles of these enzymes as causal factors of pancreatic cancer tumorigenesis and progression; and (2) positive biofeedback of using cyclooxygenase and lipoxygenase inhibitors for the treatment and prevention of pancreatic cancer.

Keywords: Lipoxygenase, cyclooxygenase, pancreatic cancer, eicosanoids, epoxygenase

Introduction
Extensive study in the molecular level unwinded the relationship between polyunsaturated fatty acid metabolism and carcinogenesis have revealed novel molecular targets for cancer chemoprevention and treatment [1-4]. From the detailed study of fatty acid metabolism in human body and mammals it is clear that, 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 [Fig: 1A], depends on the availability of free, non-esterified fatty acids [5]. These fatty acids are substrates for three distinctively different enzymatic pathways, cyclooxygenase (COX) [5], lipoxygenase (LOX) [5] and epoxygenase [5]. This review 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 the prevention and treatment of pancreatic cancer.

Cyclooxygenases and lipoxygenases: Major metabolic enzymes for arachidonic acid and linoleic acid
Cyclooxygenases
Cyclooxygenase (COX), officially known as prostaglandin-endoperoxide synthase (PTGS), is an enzyme that is responsible for formation of prostanoids, including thromboxane and prostaglandins such as prostacyclin. [Fig-1, Fig-2, Fig-3, Fig-4].
In terms of their molecular biology, COX-1 and COX-2 are of similar molecular weight, approximately 70 and 72 kDa, respectively, and having 65% amino acid sequence homology and near-identical catalytic sites. The most significant difference between the isoenzymes, which allows for selective inhibition, is the substitution of isoleucine at position 523 in COX-1 with valine in COX-2. The smaller Val_{523} residue in COX-2 allows access to a hydrophobic side-pocket in the enzyme (which Ile_{523} sterically hinders). Drug molecules, such as DuP-697 and the coxibs derived from it, bind to this alternative site and are considered to be selective inhibitors of COX-2.

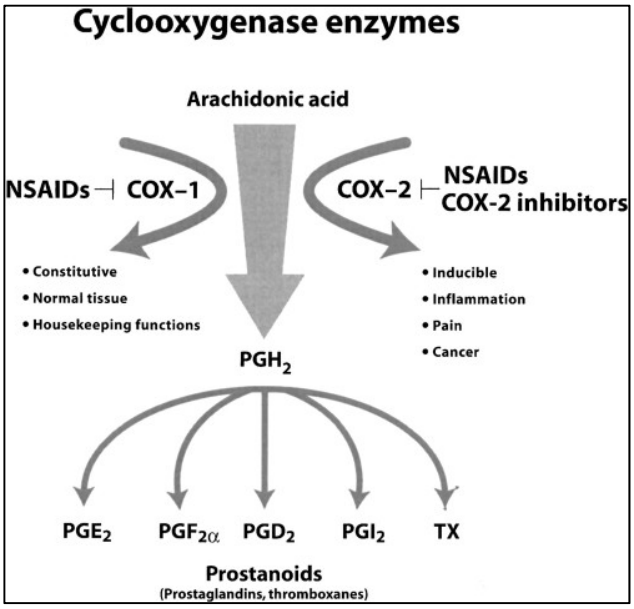

Fig 1: demonstrates Cyclooxygenase enzymes.

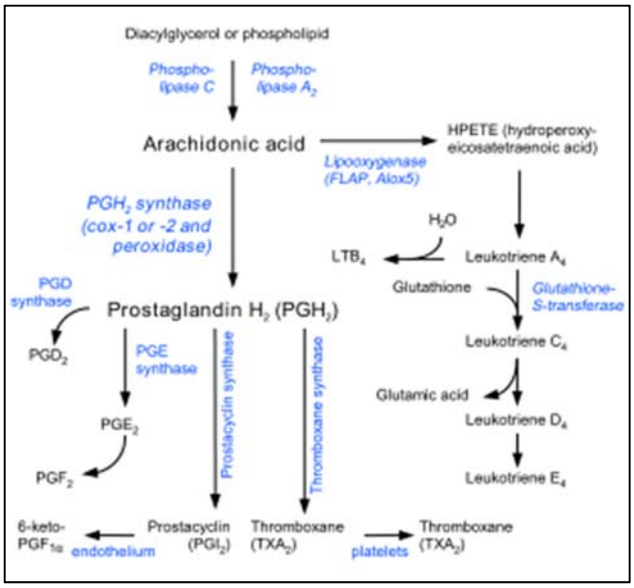

Fig 1A: demonstrates eicosanoid synthesis

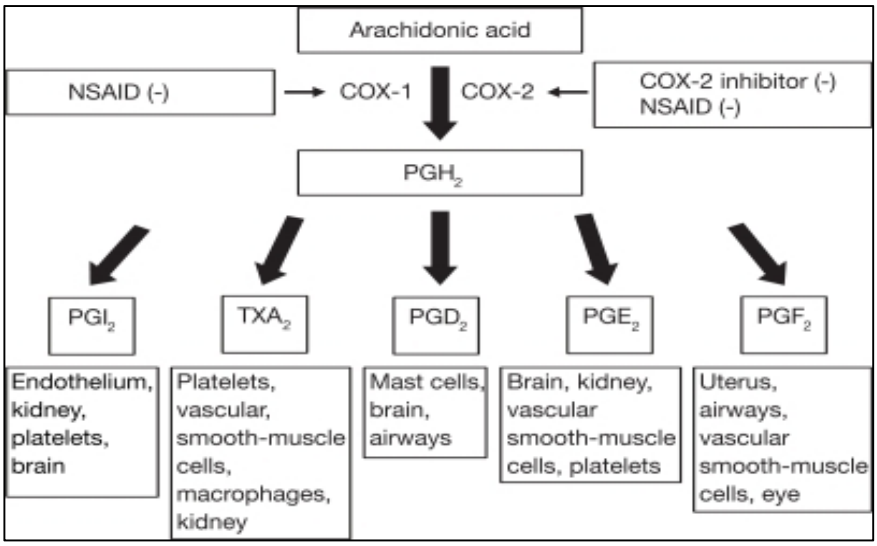

Fig 2: demonstrates Arachidonic acid metabolism

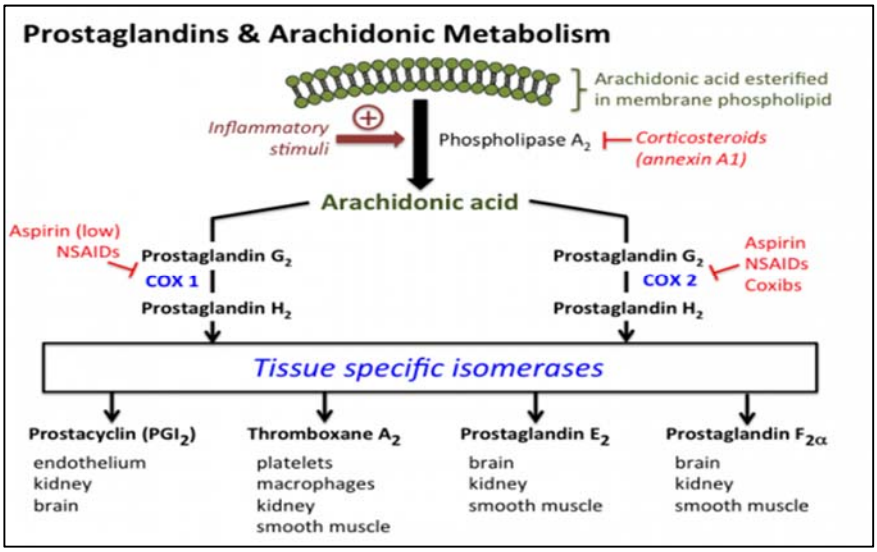

Fig 3: demonstrates Prostaglandin and arachidonic metabolism

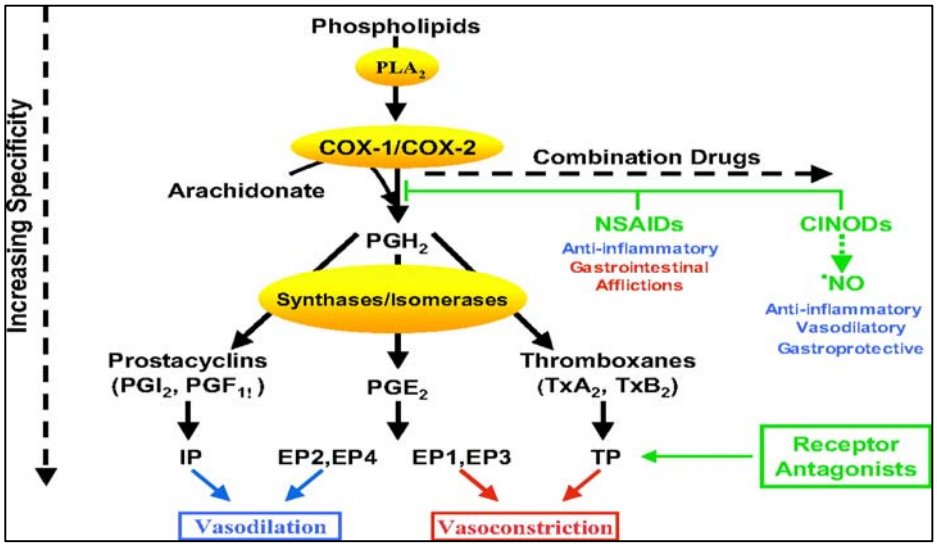

Fig 4: demonstrates the fate of phospholipids in both COX- 1 and COX-2

As mentioned above, these two isoforms, COX-1 and COX-2 are the enzymes that catalyze 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 is found to express in a variety of cells and tissues, is an inducible isoform paying regards to 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]. It is already an established fact that there are so many functional roles of COX in cancer development and growth. COX-2 is up-regulated 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]. In depth 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 [12].

Lipoxygenases

Lipoxygenases are a family of (non-heme), iron containing enzymes most of which catalyze the dioxygenation of polyunsaturated fatty acids in lipids containing a cis,cis-1,4-pentadiene into cell signaling agents that serve diverse roles as autocrine signals that regulate the function of their parent cells, paracrine signals that regulate the function of nearby cells, and endocrine signals that regulate the function of distant cells. The typical lipoxygenase catalyzes the following reaction:

The lipoxygenases are related to each other based upon their similar genetic structure and dioxygenation activity. However, one lipoxygenase, ALOXE3, while having a lipoxygenase genetic structure, possesses relatively little dioxygenation activity; rather its primary activity appears to be as an isomerase that catalyzes the conversion of hydroperoxy unsaturated fatty acids to their 1,5-epoxide, hydroxyl derivatives.

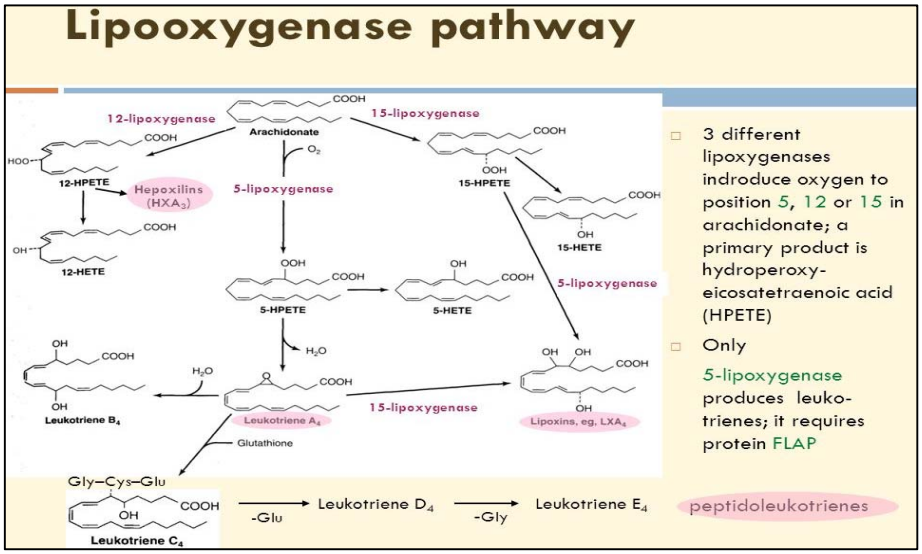

Fig 5: demonstrates Lipoxygenase pathway

Lipoxygenases possess region-specificity 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]. 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 (Leukotriene C4 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.

Leukotriene C4 synthase [Fig: 6] is an enzyme that in humans is encoded by the LTC4S gene. The protein encoded by this gene, LTC4S (or glutathione S-transferase II) is an enzyme that converts leukotriene A4 and glutathione to create leukotriene C4. This is a member of MAPEG family of transmembrane proteins. A trimer of Leukotriene C4 synthase is localized on the outer nuclear membrane and endoplasmic reticulum, where it forms a complex with 5-Lipoxygenase-activating protein. This protein is remotely related to microsomal glutathione S-transferase.

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]. Accumulating evidence suggests that the 5-LOX pathway has profound influence on the development and progression of human cancers [18]. 5-LOX inhibitors have chemo-preventive 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, immune-genicities 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 [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]. Extensive studies 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].

Role of Cyclooxygenases and lipoxygenases in pancreatic cancer

From the extensive review it has been found that, 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 says 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]. 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 immune-histochemical examination related to the expression of COX-2 in adenocarcinomas, pancreatic intraepithelial neoplasia [PanIN] and normal pancreatic ducts with an automated platform [42]. From the study it was found that, 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.

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.

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 appears as the key organelles for COX or LOX inhibition-induced apoptosis [61, 62]. Treatment of cancer cells with COX inhibitors induces cytochrome C release from mitochondria, which in turn activates caspase-9 and then caspase-3 [61, 62]. 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 [61, 62]. Other studies have shown that over-expression of COX-2 increases Bcl-2 expression, which might be responsible for preventing cytochrome C release from mitochondria. A recent study showed that death receptors are also involved in COX-regulated cancer cell survival. 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. Over-expression of COX-2 also reduced caspase-8, caspase-3, and caspase-9 activation relative to corresponding parental cells. 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. NSAIDs inhibit NFκB and PI3 kinase activity, while restoration of NFκB or PI3 kinase activity blocks NSAID-induced apoptosis [63]. 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.

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. 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. In this review, it is shown that the LOX metabolites, 5-HETE, 12-HETE and LTB4 stimulate MEK/ERK phosphorylation. 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. It has also been demonstrated 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 [63, 64].

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. Cytokine-mediated up-regulation of COX-2 contributes to increased synthesis of PGs in inflamed tissues. The occurrence and growth of various tumors are associated with immune suppression and prostaglandin E2 itself is a potent immune-suppressor. 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. PGE_2 also inhibits the production of tumor necrosis factor-α and induces the production of IL-10, an immunosuppressive cytokine. Recently, more molecular mechanisms for PGE_2-mediated immunosuppression have been revealed. For example, PGE2 suppressed IL-15-mediated human natural killer cell function.

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 [65]. 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. In addition to catalyzing the synthesis of mutagens, both COX-2 and LOX can be induced by carcinogens, such as NNK and BOP. 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. Considering all the matters together, these findings suggest a role for COX-2 or LOX inhibitors in preventing carcinogen-induced DNA damage, thereby preventing cancer development.

Capability of cyclooxygenase and lipoxygenase for treatment and prevention of pancreatic cancer

The requirements for a chemo-preventive drug are that it must have specific targets that are highly expressed in pre-cancer 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.

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. 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. In some cases, NSAIDs only induce apoptosis at concentrations that are much higher than their IC_{50}s. 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. Therefore, the cancer inhibitory effects of COX-2 inhibitors seem to involve COX-2 independent mechanisms. 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. The recent finding of an inducible splicing variant of COX-1 (COX-3) can only further complicate the current controversy.

Relevant progressive works are 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. Further studies may unwind new LOXs and new roles for known LOXs in the development and reversal of cancer and this will also help our knowledge 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. Extensive review help us to unwind the spectrum of understanding of these roles which are 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 concrete 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's contribution

Author has extended in depth research and exclusive study regarding the present spectrum that has been manifested to write him this review in favour of mankind and well-being of health science and cultivation.

In this paper, the author achieved extreme guidance favoring the in depth cultivation with a positive output from Dr. D. N. Tibarewala, Former Professor, School of Biosciences and Engineering, Jadavpur University, Kolkata, India. Partha Majumder contributed a pioneer role to the design of the study, data analysis, and revision of the manuscript.

Acknowledgement

The author, Partha Majumder dedicated this paper to Divine Mother—DEVI DURGA and LORD SHIVA, keeping the memory of his parents late Anil Chandra Majumder and Late Gita Majumder for their evergreen inspiration and blessings that enriched me favoring the ability to write this paper in favor of Mankind.

It is an established fact that every mission needs a spirit of dedication and hard work but more than anything else it needs proper guidance. We feel proud in taking this opportunity to express our heartiest regards and deep sense of gratitude to our beloved Swami Mukteswarananji Maharaj, President of Acharya Pranavananda Sevashram**,** located at Po: Purba Nischintapur, Budge Budge, Kolkata- 700138, India.

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