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Review Article

Biochemistry of Prostaglandins and Cyclooxygenase in Cancer

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ABSTRACT

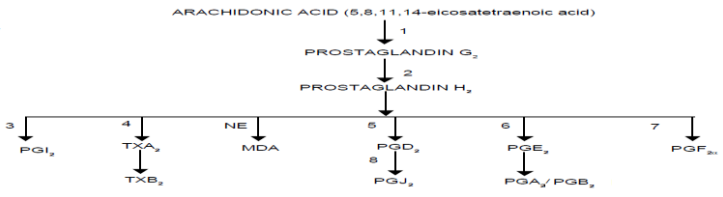
Colorectal is the third most prevalent form of cancer in the world. Several studies report that prostaglandins are mediators of carcinogenesis cyclooxygenase known as prostaglandin endoperoxidase H synthase. Levels of COX-2 isoenzyme and prostaglandins like PGE_2, PGF_2 alpha and PGE_1 are found to be higher in certain cancers like colorectal carcinoma, squamous cell carcinoma of head and neck, also in certain types of breast cancer. Prostaglandins may contribute to the cancer processes through one or more of several mechanism including increased proliferation, apoptosis, enhanced carcinogen metabolism of immune system. Decreasing the high level of COX-2 and prostaglandins already mentioned has shown to decrease carcinogenesis. The understanding of the regulation of substrate availability and of a regulation (Dysregulation in many neoplasis) of the synthesis enzymes has opened avenues leading to design of isoenzyme specific inhibitors and better cancer strategies.

Keywords: COX-enzymes, prostaglandin, Cancer, NSAID

INTRODUCTION

Prostaglandin are formed from their respective unsaturated fatty acid precursors by the action of cyclooxygenase(COX) isoenzyme viz. COX1 and COX2 is believed to be involved in house keeping functions of body while COX2 is expressed only under special conditions like inflammation. The COX isoenzyme catalyse to important steps in the prostaglandin biosynthesis. First step is the synthesis of cyclic endoperoxide prostaglandin (PGG) from respective precursors by oxygenation and cyclisation catalysed by sythase component of COX-isoenzyme. The second step is catalysed by the peroxidise component of COX isoenzyme in which prostaglandin of G Class are reduced to form prostaglandin of H class that are later acted upon by respective enzyme to form prostaglandin of different class. The active sites responsible for catalysis of two steps are different within an isoenzyme and the active sites catalysing the same action are different for the different isoenzyme. Most of the tissues synthesized PGG and PGH from respective fatty acid precursors but their fate in these tissues and depends on the presence of other enzymes that convert PGH to other prostaglandins [1, 2].

Biosynthesis



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1. Endoperoxide synthase component of cyclooxygenase isoenzymes.
2. Peroxidase component of cyclooxygenase isoenzymes.
3. Prostacyclin synthase enzyme.
4. Thrombaxane synthase enzyme.
5. Endoperoxidase isomerase enzyme (soluble form).
6. Endoperoxidase isomerase enzyme (insoluble form).
7. Endoperoxidase reductase enzyme.
8. Conversion of PGD2 to PGJ2. Occurs in plasma and by albumin. No enzymes characterised.

NE means non-enzymatic conversion.
MDA is malondialdehyde

The role of prostaglandins and COX in cancer:
Recent studies have shown that the levels of COX-2isoenzyme are elevated in certain cancers like colorectal carcinoma (CRC), squamous cell carcinoma of head and neck (SCCHN), and certain cancers of the lung and breast[3]. In human and animal models, COX-
2 levels were higher in the intestinal-type gastric adenocarcinoma and in pre-carcinogenic lesions like familial adenomatous polyposis that lead to CRC as compared with the normal intestinal cells. Similarly in SCCHN, levels of COX-2, prostaglandins like$PGF_2\alpha$, $PGE_2$and their metabolites were found to be higher than the normal tissue. Mice, in whom the tumor suppressor gene APC had been knocked out, developed adenomatous polyps. The same mice,
when bred with COX-2 knock out mice (producingCOX-2 and APC double mutants) showed substantial decrease in polyp production[4-5]. These and other similar observations led to the hypothesis that COX-2 and certain prostaglandins might play a crucial role in carcinogenesis. In certain experiments, prostaglandins like $PGF_2\alpha$, PGE_2, PGD_2, PGE_1, were found to stimulate DNA synthesis in a dose dependent manner in quiescent NIH-3T3 cells[6]. Prostaglandins and their metabolites have been shown to regulate cellular processes like mitosis, cell proliferation, cell adhesion. Epidemiological studies have suggested a decreased incidence of cancer of the oesophagus, stomach, colon, and rectum in people who use nonsteroidal antiinflammatory drugs (NSAIDs) regularly, although a delay of about a decade is seen to realize the outcome. The cancers do recur and re-grow when treatment is curtailed[7].

Epidemiological studies indicate that use of aspirin decreases incidence of mortality from GI cancers. Data also indicate that COX-2 is expressed in majority squamous cell and adenocarcinomas. It also demonstrates that COX-2 derived prostaglandins play an important role in regulation of proliferation and apoptosis of esophageal tumor cells. Thus COX-2inhibition may be useful in therapy of various esophageal cancers[8].
Other epidemiological studies in humans suggest that aspirin and other NSAIDs may be protective against colon cancers. It was observed that the death rates from colon cancers decreased with more frequent aspirin use in both men and women in a study conducted on 662,424 adults[9].
Several epidemiological studies have also identified an association between use of NSAIDs and reduced colorectal cancer risk in women. In a study exclusively done on female subjects, those who used nonaspirin compounds had a significant lower risk of colorectal carcinoma compared to non-users, whereas aspirin users had only a small insignificant reduction in cancer and significant benefit from this therapy may only be evident only after a decade of regular aspirin consumption[10].
Certain types of prostaglandins like $PGA_1$and PGJ_2(mainly D^7PGA_1methyl ester) have been shown to oppose tumorigenesis in some *in vitro* studies on cancer cell lines[11].

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Table 1.Various therapeutic applications of prostaglandins.

Body system	PGS involved	Action
CVS	PGE_2	Vasodilation vasoconstriction in selected sites
	PGI_2	Generally decrease in BP
	PGD_2	Vasodilation or vasoconstriction in different sites
	TXA_2	Potent vasoconstrictor
Blood	PGD_2, PGI_2	Inhibits platelet aggregation
	TXA_2	Induces platelet aggregation
Smooth muscles		
1. Bronchial	$PGF_2\alpha$, PGD_2,TXA_2	Generally constriction
	PGE_2	Effect variable depending on the series
2. Uterus	PGI_2	Relaxation
	PGE_2,$PGF_2\alpha$	Contraction
3. GI muscles	$PGF_2\alpha$, TXA_2	Contraction
	PGE_2	Relaxation
	$PGF_2\alpha$	Contraction of longitudinal and circular muscles.
	PGE_2	Contraction of longitudinal muscles, relaxation of circular muscles and also cause diarrhoea
Kidney	PGE_2, PGI_2	Increase renal blood flow
	TXA_2	Decrease renal bold flow.
Endocrine system	PGE_2	Increases circulating concentration of ACTH , GH and prolactin stimulates insulin release.
Metabolism	PGE_2	Inhibits basal rate of lipolysis of adipose tissue.

Table 2: Therapeutic applications of prostaglandins

Therapeutic settings	Prostaglandin involved
Therapeutic abortion	$PGF_{2\alpha}$, PGE_2
Gastric cytoprotection	PGE_1, PGE_2 and their analogues
Platelets storage and transfusion impotence	PGI_2, PGE_2 and PGE_1
To increase pulmonary blood flow	PGE_1 , PGI_2 and their analogues

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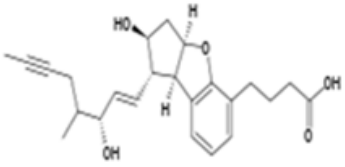
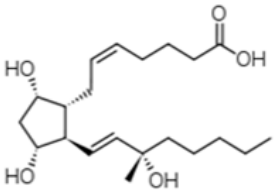
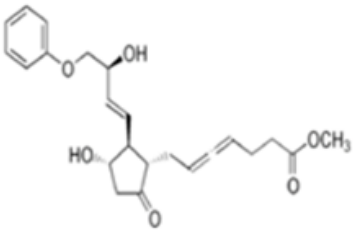
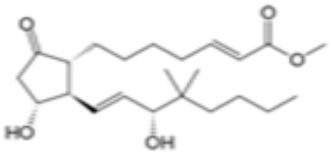
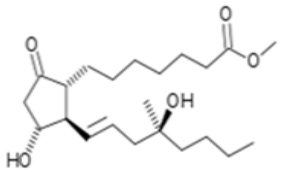
VARIOUS PROSTAGLANDIN DRUGS USED WORLDWIDE

Drugs	Uses	References
Beraprost  2,3,3a,8b-Tetrahydro-2-hydroxy-1-(3-hydroxy-4-methyl-1-octen-6-ynyl)-1H-cyclopenta(b)benzofuran-5-butanoic acid	Beraprost is synthetic analogue of prostacyclin under clinical trial for the treatment of pulmonary hypertension.	Park.J.et.al[12]
Carboprost  (5Z,9α,11α,13E,15S)-9,11,15-Trihydroxy-15-methylprosta-5,13-diene-1-oic acid.	Carboprost induces contraction and can trigger abortion in early pregnancy. It also reduces post partum bleeding.	Ppolitic.et.al[13]
Enprostil  Methyl-7-[(1S,2S,3S)-3-hydroxy-2-[(S,E)-3-hydroxy-4-phenoxybut-1-enyl]-5-oxocyclopentyl]hepta-4,5-dienoate	Enprostil was found to be a highly potent inhibitor of gastric HCl secretion.	Tari.et.al[14]
Gemeprost  Methyl(2E,11α,13E,15R)-11,15-dihydroxy-16,16-dimethyl-9-oxoprosta-2,13-diene-1-oate.	It is used as treatment for bleeding. It is used with mifepristone to terminate pregnancy upto 24 weeks gestation.	Bartley.et.al[15]
Misoprostol 	It is a drug that is used for the prevention of non steroidalanti inflammatorydrug(NSAID) induced gastric ulcers to treat missed miscarriage to	Wood.et.al[16]

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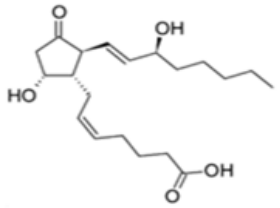
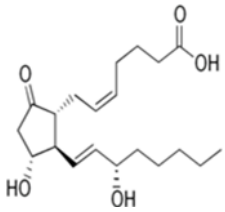
Methyl-7-[(1R,2R,3R)-3-hydroxy-2-[(S,E)-4-hydroxy-4-methyl oct-1-enyl)-5-oxocyclopentyl)heptaneoate	induce labour and as an abortifacient.	
Prostaglandin D_2  9α,15S-Dihydroxy-11-oxo-prosta-5Z,13E-dien-1-oic acid	It causes vasodilation and regulation of reducing body temperature in sleep	Onoe.H.et.al[17]
Prostaglandin E_2(dinoprostone)  (5Z,11α,13E,15S)-7-[3-hydroxy-2-(3-hydroxyoct-1-enyl)-5-oxo-cyclopentyl]hept-5-enoic acid.	It has important effects in labour(softens cervix and causes uterine contraction) and also stimulates osteoblasts to release factors that stimulates born resorptions by osteoclasts.	Rang.et.al[18]

Certain prostaglandins and COX-2 isoenzyme may aid in carcinogenesis by altering the normal cellular processes like:

1. Cell proliferation
2. Angiogenesis
3. Apoptosis
4. Immunomodulation
5. Carcinogen metabolism

Cell proliferation: Prostaglandins appear to increase cell proliferation with the help of biological modifiers like polyamines; increased polyamine levels are associated with increased DNA synthesis, which results from ornithine decarboxylase activity (ODC). In colonic epithelial and murine epidermal cell lines, it is shown that exogenous and endogenous tumor promoters induce ODC activity *via* a PGE_2dependant process. PGE_2appears to be an important human keratinocyte cell culture proliferator. Similarly, in murine models, prostaglandins appear to be important for epidermal cell growth[19].In skin carcinoma models, ODC induction is seen in tumorigenesis. PGE_2can mimic the effects of COX-2 expression *in vitro* and is thought to be one of the main factors in promoting tumor cell growth and survival.

In a study on quiescent cell culture of NIH-3T3 cells,$PGF_{2\alpha}$ enhanced DNA synthesis *via* a calcium (Ca^{2+})dependant intracellular pathway (independent of protein kinase C and calcium/calmodulin pathways) by increasing inositol phosphate formation, thymidine incorporation in the cells and thymidine phosphorylation; all these processes are important for the DNA synthesis. PGE_2, PGD_2, PGE_1, PGI_2 agonist ibuprost showed similar actions[6,20].

Elevated serum and mucosal levels of PGs have been shown to be associated with colorectal tumors. Exogenous PGs have been shown to stimulate the proliferation of normal and tumor cells in the intestinal epithelium both *in vitro*

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and *in vivo*. In CRC cell lineHCA-7 colony 29, EGFR activation by a-Tumor growth factor (a-TGF) resulted in increased COX-2 gene expression, increased COX-2 production, its translocation to nucleus, vectorial release of prostaglandins and mitogenesis in a dose dependant manner[19]. CRC cell lines HT-29 and SW-1116 showed increased proliferation to PGE_2 and PGI_2respectively[19,22].$PGF_{2\alpha}$ has been found to enhance mitogenic effect of growth factors (GF) like insulin by increasing high affinity binding sites for GF, thereby stimulating cell proliferation mainly of Balb/c 3T3 cells, MC3T3-E1cells and oesteoblasts. TXA_2acts in the same way on mammary epithelial cells[19].

Biosynthesis of certain lipids precedes S-phase of cell cycle, DNA synthesis and mitosis. Prostaglandins were shown to modulate this lipogenesis in cultured cells depending upon cell-cycle phase and intrinsic lipid metabolism diversity[23]When intra-tumoral TXA_2 / PGI_2ratio rises, platelets aggregate giving rise to disseminated intravascular coagulation often a character of metastasizing tumors When the ratio is low, metastasis is low[22-24]. Over expression of COX-2 rat intestinal endothelial (RIE) cells results in increased Bcl-2 expression increased adhesion of cell with the basement membrane, reduced Ecadher in expression (hallmarks of cell proliferation and invasiveness) and elevated levels of PGE_2[19,22]. Over expression of COX-2 in colorectal tumor cell lines like caco-2 results in increased metastatic potential[25].These evidences suggest a link between prostaglandins, COX-2expression, cell proliferation and metastasis.

Angiogenesis: Angiogenesis is an essential feature for tumor growth and proliferation. This process is essential for the proper nourishment and oxygen supply to highly dividing and proliferating cells. Tumor hypoxia is supposed to be the main stimulus for initiating tumor angiogenesis. Normal blood vessel endothelium expresses COX-1 isoenzyme whereas angiogenic blood vessel endothelium expresses COX-2 isoenzyme[26].COX-2 is expressed in different types of neoplastic cells including human colon, breast, prostate and lung cancer cells. PGE_1, PGE_2, $PGI_2$and $TXA_2$are believed to be involved in different steps of tumor angiogenesis[24]. Interstitial fluid of some tumors was found to be rich in prostaglandins of the E class, which are believed to be more potent angiogenesis inducers[27,28].

COX-2 was also observed in human tumor vasculature, suggesting that COX-2 derived prostaglandins contribute to tumor growth by inducing angiogenesis. Studies in nude mice with gastro-intestinal cancer xenografts showed that non-specific COX inhibitors inhibited tumor angiogenesis. Levels of potent angiogenic factors like vascular endothelial growth factor(VEGF), basic fibroblastic growth factor (bFGF)were also reduced[29]. This fact has also been endorsed by a study where in human colon tumors (HT-29), when implanted in nude mice, were dose dependently inhibited by celecoxib: a specific COX-2 inhibitor by68%. 5-Flurouracil (5-FU), when added to celecoxib showed synergistic activity by inhibiting the same tumor growth by 83%. This is suggestive of anti-angiogenic activity of celecoxib inhibiting tumor growth, which is synergistically supported by 5-FU suppressing the DNA synthesis.

Another study also indicated that celecoxib dose dependently inhibited tumor growth in mice bearing Lewis lung carcinoma. Maximum inhibition by celecoxib alone was 86% whereas along with cyclophosphamide, the inhibition was 97% (near complete inhibition of the tumor)[30].

COX-2 over expression is found to be associated with increased PGE**2**biosynthesis, which along with its metabolites may aid angiogenesis by helping the secretion of angiogenic factors. Certain cytokines likeinterleukin-1 (IL-1) which are associated with tumors have been shown to increase COX-2 gene expression and half-life of

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COX-2 mRNA[24,27]. COX-2 and thromboxaneA_2receptor dependant signaling pathways have been shown to activate cellular invasion and angiogenesis[31].COX-2 expression is induced in a variety of cells leading to high levels of prostaglandins production. Such aberrant expression of COX-2 has been reported in murine and human breast cancer, human colon cancer, lung cancer, head and neck cancer and pancreatic cancer[25,32-36]. Prostaglandins suppress the natural killer cells (NK) activity in tumor bearing mice. This suppression also includes inhibition of IL-2 and IFN-a and down regulation of their receptors on effector cells. It has been shown that prostaglandins have immune suppressive roles in cancer, indicating host related mechanisms responsible for tumor progression[9,37-38] and at the same time the direct role of prostaglandins in tumor cell functions that are required for tumor progression have been limited[39,40].

One of the studies in murine mammary tumor model revealed that tumor derived prostaglandins owing toCOX-2 expression by the tumor cells, stimulated their migration, invasiveness as well as tumor induced angiogenesis. Cellular migration is an essential step for invasion and metastasis[30]. This was attributed to high levels of endogenous prostaglandins released by C3L5 cells in medium and was confirmed by the fact that the non-selective COX inhibitor indomethacin(56-112 mM) lead to significant reduction in migration, which was partially abrogated by addition of exogenousPGE_2.

Migration stimulating effects of endogenous PGE_2were primarily due to COX-2 activity. The migration inhibition was shown by addition of selective COX-2inhibitor NS-398 and this inhibition of migration was abrogated by addition of exogenous PGE_2at lower inhibitor concentration. This study shows the role of endogenous prostaglandins and particularly COX-2expression in cellular migration and in turn cell invasion and metastasis[41].

The above study using C3L5 cells also established that endogenous prostaglandin production promoted tumor induced angiogenesis. Also, mostly COX-2 and to a minor extent COX-1 have been implicated in angiogenesis; *e.g.* COX-2 selective inhibitor NS-398 inhibited colon cancer cell-induced migration of endothelial cells responsible for development of new blood vessels. In contrast to this above study, angiogenesis in a corneal angiogenesis model was inhibited with selective COX-2 inhibitors like celecoxib and NS-398,but not with selective COX-1 inhibitor [41-42].

Growth factors like hepatocyte growth factor (HGF), which is produced by fibroblasts, has been shown to aid carcinogenesis and the progression of various human cancers by promoting angiogenesis. It stimulates the endothelial cell growth and acts as a factor against endothelial cell death, thus aiding angiogenesis[43-44]. In a study on cultured human colonic fibroblasts, it was shown that IL-1b induced COX-2 isoenzyme, which in turn increased prostaglandinE_2production and stimulated HGF production. Prostaglandins and COX-2 isoenzyme are thus shown to be the factors necessary for production of HGF by human colonic fibroblasts. Indomethacin was shown to reduce endogenous prostaglandin production, which suppressed HGF production. NSAIDs may thus suppress colon carcinogenesis by suppression of HGF expression by inhibiting prostaglandin production[45].

Above examples clearly indicate that COX-2 derived prostaglandins play a major role in the development of cancer through distinct bio-chemical mechanisms including stimulation of tumor growth and neovascularisation.

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Apoptosis: Apoptosis (programmed cell death) is the biochemical form of cell death. Some cancerous cells have been shown to increase levels of COX-2[19]. Overproduction of certain prostaglandins like $PGE_2$by thisCOX-2 may also send improper signals in the cells, thereby stimulating cell growth inappropriately or reducing apoptosis[46]. Studies with NSAIDs acting by inhibition of COX isoenzymes revealed that they induced apoptosis in cancerous cells and it was thought that this was due to inhibition of COX-2 isoenzyme, thus reducing the levels of prostaglandins in cancerous cells. Some specific inhibitors of COX-2 isoenzyme also showed this result. Bcl-2 gene is an important gene in regulating apoptosis. Murine intestinal cell line like RIE-S showed that over expression of the COX-2 isoenzyme in cancerous cells was associated with the over expression of Bcl-2 gene, which prolongs cell's life by inhibiting apoptosis. Bcl-2 gen was also found to be over expressed in colon cancer cell lines that over expressed COX-2 isoenzyme[22].The exact relation between COX-2 over-expression, production of prostaglandins and expression of Bcl-2gene in cancer is yet to be investigated.

Inhibition of the COX isoenzymes results in decreased production of prostaglandins form their substrates like arachidonic acid, leading to the accumulation of the substrate. Substrates like arachidonic acid, when present in increased concentration in the cells, is supposed to stimulate the fragmentation of the DNA and conversion of sphingomyelin to ceramide in the cells, which is a known inducer of apoptosis[47]. Metabolite of sulindac (a NSAID) *viz.* sulindac sulphone, which does not have any activity against either of the COX isoenzymes, also has been shown to induce apoptosis[19,24].This indicates that COX isoenzymes and prostaglandins may not be directly involved in inhibiting apoptosis in cancerous cells that over express COX-2 isoenzyme and they may be the products in the later stage of cascade of reactions happening in the cells during apoptosis, thereby preventing apoptosis. The exact relation between COX isoenzymes, prostaglandins and apoptosis is yet to be fully elucidated.

Immunomodulation: High concentration of certain prostaglandins like PGE_2attenuate hosts immune response preventing the killing of malignant cells[19,48]. PGE_2shows a potent immunosuppressive effect by acting as a negative feedback inhibitor, thereby inhibiting T-cell activity, lymphocytic mitogenesis, macrophage activity, antibody production, production of cytokines by immune cells, natural killer cell activity etc.[19,24,48]. Tumor-bearing animals and cancer patients have been shown to have dendritic cells with suboptimal antigen-presenting function due to VEGF produced by tumors, IL-10and prostaglandins like PGE_2[49]. It is believed that macrophages also produce PGE_2under the influence of tumor, but is high only in the initial phase of cancer. COX inhibitors, when given immediately after tumor transplant in animal models, decrease PGE2levels and tumor growth[19,48].

Carcinogen metabolism: The peroxidase component of COX isoenzymes has broad specificity and can oxidise a variety of xenobiotics including certain pro-carcinogens and carcinogens. Classes of compounds like aflatoxins, halogens, halogenated pesticides, polycyclic hydrocarbons, hetrocyclic amines, *etc.* whose hydro-peroxides are generated in the body are acted upon by the peroxide component of the COX to form mutagenic carcinogens. COX isoenzymes may also promote formation of peroxide radicals during lipid peroxidation and reaction of PUFA hydroperoxides with metals ormetallo proteins. These radicals react with the DNA forming harmful adducts with DNA and damaging it[19,22,50]. This may be important in the colon

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carcinogenesis, where cells are exposed to many strange molecules from the diet.
Prostaglandins of H series, formed by peroxidation of prostaglandin G series, can form malon-dialdehyde(MDA) non-enzymatically. MDA has been found to be carcinogenic and forms multiple DNA adducts with deoxy nucleotides leading to many base-pair substitutions and frame-shift mutagenesis that may initiate cancer[19,22]. COX inhibitors along with anti-oxidants may play a role to protect the cells and DNA from the damage from above-mentioned mechanisms[51].

Prostaglandin and COX as anti cancer agents: Inflammatory mediators such as cytokines, eicosanoids, and growth factors are thought to play a critical role in the initiation and maintenance of cancer cell survival and growth[52]. One of these mediators, PGE2[53], is produced in large amounts by tumors. PGE2 is produced from arachidonic acid by either of two enzymes: COX-1 or COX-2. Both COX isozymes can be inhibited by traditional NSAIDs, such as aspirin and indomethacin. Several studies show that regularly taking aspirin or other conventional NSAIDs provides a 40–50% reduction in relative risk of death by colon cancer, indicating that inhibition of COX in humans has a chemopreventive effect1. In rodent models of FAP, a genetic disease leading to colon carcinoma, blockade of COX-2, either by gene deletion or by pharmacological inhibition of enzyme activity, suppresses intestinal polyp formation. COX-2 inhibition also demonstrates chemopreventive activity against colon carcinogenesis. Taken together, these data provide strong evidence for the importance of COX-2 enzyme activity in oncogenesis.

Several recent reviews[54-56] have summarized the intriguing and accumulating evidence that non steroidal anti-inflammatory drugs (NSAIDs) have a promise as anticancer drugs. NSAIDs have been shown experimentally to stimulate apoptosis and to inhibit angiogenesis, two mechanisms that help to suppress malignant transformation and tumor growth. Randomized clinical trials have confirmed that two NSAIDs, the prodrug sulindac[57] and the selective cyclooxygenase (COX-2) inhibitor celecoxib[58], effectively inhibit the growth of adenomatous polyps and cause regression of existing polyps in patients with the unusual hereditary condition familial adenomatous polyposis (FAP).

Evidence for cancer prevention properties of NSAIDs : The hypothesis that NSAIDs might inhibit the occurrence or growth of colorectal cancer arose in the mid-70s, when Bennett and Del Tacca[59] and Jaffe[60] reported that the concentration of prostaglandin E2 was higher in human colorectal tumor tissue than in the surrounding normal mucosa. Conventional NSAIDs (such as piroxicam, indomethacin, sulindac, ibuprofen, and ketoprofen), and selective COX-2 inhibitors [e.g., celecoxib] inhibit chemically induced carcinogenesis in rats and mice. Nonselective NSAIDs suppress tumor growth to a greater extent and at lower doses when treatment is begun before or coincident with exposure to the carcinogen than when it is delayed until the tumor promotion/progression phase. For example, low-dose piroxicam (25 ppm in food) caused a 30% reduction in tumors when treatment was begun soon after exposure to the carcinogen but only a 12% reduction when treatment was begun 23 weeks after exposure[61]. Early initiation of treatment also improves tumor suppression by sulindac sulfone and celecoxib. Both nonselective and selective NSAIDs effectively inhibit the early stages of tumor development, whereas only selective COX-2 inhibitors are effective when treatment is delayed. For example, celecoxib (1500 ppm in food) reduced tumor incidence and multiplicity by approximately half, even when treatment was delayed until the tumor Promotion / progression stage.

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FUTURE PERSPECTIVES

Familial adenomatous polyposis (FAP) is an inherited disorder of the colon and the rectum almost always leading to cancer. In individuals with FAP, one of the genes, APC gene is mutated. Surgery is presently the only answer to FAP. The discovery of COX-2 in cancers like CRC and certain experiments in mice inferring that COX-2 causes polyp formation have raised the possibility of treating such tumors by targetingCOX-2. Traditional NSAIDs and COX-2 inhibitors like celecoxib have been shown to reduce the number of polyps and their size in colon and rectumin FAP patients. Presently, FAP patients are advised to undergo regular colonoscopy and colectomy is indicated in many cases. COX-2 inhibitors could be used preferably than traditional NSAIDs to treat FAP as the side effects of the later are believed to be more than the former, thus surgery in FAP could be postponed or prevented. Highly selective COX-2 inhibitors like celecoxib may also play a role as treatment adjuvants in cancers of the head/neck, breast, lung, pancreas, stomach and prostate[62].

CONCLUSION

Thus, we see that prostaglandin and cyclooxygenase are amongst the most critical mediators which lead to the progression of various types of tumor formations, which ultimately result in the development of malignancies. The elevated levels of cyclooxygenase-2 in the cancer patients, which is a prime precursor enzyme for the formation of prostaglandins, clearly suggest that there is a certain link between this enzyme and the tumor formation. Also, the various studies and researches carried later in this aspect gave a clear proof of its involvement. Hence, more such studies are required to establish all possible links between the pathway leading to the formation and growth of tumor due to the action of cyclooxygenase enzyme so that better understanding of the matter could possibly lead to more suitable and appropriate development of techniques which could help in the management of such pathways which lead to the development of cancer and thus assist in providing better medical care and services accordingly.

↓ REFERENCES

1. Borne RF: Principles of Medicinal Chemistry, 4th ed. New Delhi: B.I.Waverly Pvt. Ltd., 1999, 535-580.
2. Campbell WB, Halushka PV: Goodman and Gilman's The pharmacological basis of therapeutics, 9th ed. New York: McGraw-Hill, 1996, 601-16.
3. Dubois RN, Abramson SB, Crofford L, Gupta RA, SimonLS, Van De Putte Leo BA,Lipsky PE:Cyclooxigenase in biology and disease.FASEB J1998, 12:1063-73.
4. Marjerus PW: Prostaglandins: Critical roles in pregnancy and colon cancer. CurrBiol1998, 8:87-9.
5. Williams CS, Shattuk-Brandts RL, Dubois RN: The role ofCOX-2 in intestinal cancer. Expert Opin Invest Drugs1999, 8:1-12.
6. Wantanabe T, Satoh H, Togoh M, Taniguchi S, HashimotoY, Kurokawa K:Positive and negative regulation of cell proliferation through prostaglandin receptor in NIH-3T3 cells. J Cell Physiol1998, 169:401-9.
7. Sharma RA, Gescher AJ, O'Byrne KJ, Steward WP: Familiardrugs may prevent cancer. Postgrad Med J 2001, 77:492-7.
8. Zimmermann KC, Sarbia M, Weber AA, BorchardF, Gabbert HE, Schror K:Cyclooxygenase-2 expressionin human esophageal carcinoma. Cancer Res, 1999, 59:198-204.
9. Giovannucci E, Egan KM, Hunter DJ, Stampfer MJ, ColditzGA, Willett WC, Speizer FE: Aspirin and the Risk of ColorectalCancer in Women. N Eng J Med1995, 333:609-14.

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

10. Reeves MJ, Newcomb PA, Trentham-Dietz A, Storer BE, Remington PL:Nonsteroidal anti-inflammatory drug useand protection against colorectal cancer in women. Cancer Epidemiol Biomarkers Prev1996, 5:955-60.
11. Suzuki M, Mori M, Niwa T, Hirata R, Furuta K, Ishikowa T,Noyori R: Chemical implications for anti-tumor and anti-viralprostaglandins: Reaction of D7 -prostaglandin A1andprostaglandin A1methyl esters with thiols. J Am ChemSoc1997, 119:2376-85.
12. Park J, Cho HK, MoonJ: Changes to upper eyelid orbital fat from use of topical bimatoprost. Jpn J Ophthalmol, 2011, 55(1): 22-7.
13. IppolitiC,Pprzepiorka D, Mehra R, Newmann J, Wood J, Claxton D, Gajewskij, Khowi I, van Besien k, Anderson B: Intravesular carboprost for the treatment of hemorrhagic cystitis after marrow transplantation. Urology 1995, 46(6):811-5.
14. Tari A, Hamada M,Kamiyasu T, SumiiK, Haruma K,Inoue M, Kishimatu S, KajiyamaG, Walsh JH: Effect of enprospil on omeprazole induced hyper gastricnemia and inhibition of gastric acid secretion in peptic ulcer patients.Digestive diseases and sciences 1997, 42(8):1741-6.
15. Bartley J, Brown A, Elton R, Baird DT: Double blind randomised trial of mifepristone in combination with vaginal gemeprost or misoprostol for induction of abortion upto 63 days gestation. Human reproduction(Oxford England) 2011, 16(10):2098-102.
16. Goldberg AB, Greenberg MB, Darney PD: Misoprostol and pregnancy. New England Journal of medicine 2011, 344(1): 38-47.
17. Onoe HI, Ueno R, Fujita I, Nishino H, Oomura Y, HayaishiO: Prostaglandin D2Acerebral sleep inducing substance in monkeys.Preceedings of national academy of sciences of United States of America 2012, 85(11):4082-4086.
18. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G:Rang & Dale's Pharmacology. Churchill Livingstone Elsevier, 2007.
19. Fischer SM: Prostaglandins and cancer [Reviews:Basic Science]. Front Biosci1997, 2:482-500.
20. Wantanabe T, Nakao A, Emerling D, Hashimoto Y,Tsukamoto K, Kinoshita M, Kurokawa K:Prosataglandin F2a enhancestyrosine phosphorylation and DNA synthesisthrough phospholipase C-coupled receptor via Ca2+-dependantintracellular pathway in NIH-3T3 cells. J BiolChem1994, 269:17619-25.
21. Coffey RJ, Hawkey CJ, Damstrup L, Graves-Deal R,Daneil VC, Dempsey PJ,Chinery R, Kirkland SC, DuBois RN, Jetton TL, Morrow JD: Epidermal growth factorreceptor activation induces nuclear targeting of cyclooxygenase-2, baso lateral release of prostaglandins and mitogenesis in polarizing colon cancer cells. ProcNatlAcadSci USA1997, 94:657-62.
22. Levy Gerald N: Prostaglandin-H synthase, non steroidalanti-inflammatory drugs and colon cancer. FASEB J1997, 11:234-47.
23. de Bitten court HPI Jr.,Yane MM, Hirata MH, Williams JF: Evidence that prostaglandins modulate lipogenesis in cultured lymphocytes-comparison with its effect on macrophages and tumor cells. BiochemMolBiolInt1994, 33:463-75.
24.Spisni E, Tomasi V: Tumor Angiogenesis 1st ed. New York: Oxford University Press, 1997, 291-300.
25. Tsujii M, Kwano S, Dubois RN: Cyclooxygenase-2 expression in human colon cancer cells increases the metastatic potential. ProcNatl AcadSci USA1997, 94:3336-40.
26. Masferrer JL, Koki A, Seibert K: COX-2 inhibitors as new class of anti-angiogenic drugs. Annal N.Y. Acad Sci1999, 889:84-5.
27. Uefuji K, Ichikura T, Mochizuki H: Cyclooxygenase-2 expression is related to prostaglandin biosynthesis and angiogenesis in human gastric cancer. Clinical Cancer Research 2000,6:135-8.

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

28. Chiarugi V, Magnelli L, Gallo O: COX-2, iNOS and p53 as playmakers of tumor angiogenesis. Int J Mol Med1998, 2:715-9.
29. Sawaoka H, Tsuji S, Tsuji M, Gunawan ES, Saski Y,Kawano S, Hori M: COX inhibitors suppress angiogenesisand reduce tumor growth in vivo. Lab Invest 1999, 79:1469-77.
30. Masferrer JL, Leahy K, Zweifl BS, Moore R, Heuvelman D, Seibert K:Celecoxib: A specific cyclooxygenase(COX-2) inhibitor with antiangiogenic and anticancer activities. Proceedings of the 11th NCI.EORTC. AACR Symposium on New Drugs in Cancer Therapy; 2000 Nov7-10; Vrije Universiteit, Amsterdam, The Netherlands. Clinical Cancer Research 2000, 6:4486S.
31. Rodrigues S, Nguyen Quang-dé, Faivre S, BruyneelE,Thim L, Westley B, May F, Flatau G, Mareel M, Gespach C, 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.
32. Rozic JG, Chakraborty C, Lala PK: Cyclooxygenase inhibitors retard murine mammary tumor progression by reducing tumor cell migration, invasiveness and angiogenesis. Int J Cancer 2001, 93:497-506.
33. Lala PK, Al-Mutter N, Orucevic A: Effects of chronic indomethacin therapy on the development and progression of spontaneous mammary tumors in C3H/HeJ mice.
Int J Cancer 1997, 73:371-80.
34. Parrett ML, Harris RE, Joarder FS, Ross MS, Clausen KP, Robertson FM: Cyclooxygenase-2 gene expressionin human breast cancer. Int J Oncol1997, 10:503-7.
35. Hida T, Yatabe Y, Achiwa H, Muramatsu H, KozakiK, Nakamura S: Increased expression of cyclo-oxygenase m2 occurs frequently in human lung cancers, specifically in adenocarcinomas. Cancer Res 1998, 58: 3761-4.
36. Tucker ON, Dannenberg AJ, Yang EK, Zhang F, Teng L,Daly JM,Soslow RA, Masferrar JL, Woerner BM, Koki AT, Fahey TJ 3rd: Cyclooxygenase-2 expression is up-regulated in human pancreatic cancer. Cancer Res 1999, 59:987-90.
37. Sano H, Kawahito Y, Wilder RL, Hashiramoto A, MukaiS,Asai K, Kimura S, Kato H, Kondo M, Hla T: Expression of cyclooxygenase-1 and -2 inhuman colorectal cancer. Cancer Res 1995, 55:2556-9.
38. Baxevanis CN, Reclos GJ, Gritzapis AD, DedousisGVZ, Missitzis I, Papami chail M: Elevated prostaglandin E2production by monocytes is responsible for the depressed levels of natural killer and Lymphokine-activated killer cell function in patients with breast cancer. Cancer1993, 72:491-501.
39. Young MR, Young ME, Wepsic HT: Effect of prostaglandinE2 producing nonmetastatic Lewis Lung Carcinoma cellson the migration of prostaglandin E2-responsive metastatic Lewis Lung Carcinoma cells. Cancer Res 1987, 47:3679-83.
40. Tsuji M, Kawano S, Tsuji S, Sawaoka H, Hori M, Sawaoka H, Hori M, DuBois RN: Cyclooxygenase regulates angiogenesis inducedby colon cancer cells. Cell 1998, 93:705-16.
41. Yamada M, Kawai M, Kawai K, Mashima Y: The effect of selective cyclooxygenase-2 inhibitor on corneal angiogenesis in the rat. Curr Eye Res 1999, 19:300-4.
42. Masferrer JL, Leahy KM, Koki AT, Zweifel BS, Settle SL,Woerner B, Edwards DA, Flinckinger AG, Moore RJ, Seibert K:Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. Cancer Res 2000, 60:1306-11.
43. Morishita R, Nakamura S, Hayashi Shin-ichiro, TaniyamaY, Moriguchi A, Nagano T, Taiji M, Noguchi H, Takeshita S, Matsumoto K, Nakamura T, Higaki J, Ogihara T: Therapeutic angiogenesis induced by hepatic growth factor in rabbit hind limbischemia model as cytokine supplement therapy. Hypertension1999, 33:1379-84.
44. Van BE, Witzenbichler B, Chen D, Silver M, Chang L,Schwall R,Isner JM. Potentiated angiogenic effect

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

of scatter factor/hepatocyte growth factor via induction of vascular endothelial growth factor. The case for paracrine amplification of angiogenesis. Circulation 1998, 97:381-90.
45. Ota S, Tanaka Y, Bamba H, Kato A, Matsuzaki F:Nonsteroidalanti-inflammatory drugs may prevent colon cancer through suppression of hepatocyte growth factor expression. Eur J Pharmacol1999, 367:131-8.
46. Sheng H, Shao J, Morrow JD, Beauchamp RD, DuBoisRN: Modulation of apoptosis and Bcl-2 expression by prostaglandin E2 in human colon cancer cells. CancerRes1998, 58:362-6.
47. Chan TA, Morin PJ, Vogelstein B, Kinzler W: Mechanisms under lyingn on steroidal anti-inflammatory drugs mediated apoptosis. Proc Natl Acad Sci USA 1998, 95:681-6.
48. Cross DS, Platt JL, John SK, Bach FH, Adams GL: Tumor infiltrating lymphocytes in squamous cell carcinoma of head and neck: Mechanism of enhancement using PG synthetase inhibitors. Adv Exp Med Biol1997, 400:1013-24.
49. Ribas A, Butterfield LH, Economou JS: Genetic immuno therapy for cancer. The Oncologist 2000, 5:87-98.
50. David SG: The Molecular Perspective: Cyclooxy-genase-2. The Oncologist 2000, 5:169-71.
51. Chinery R, Beauchamp RD, Shyr Yu, Kirkland SC, Coffey RJ, Morrow JD: Antioxidants reduce COX-2 expression, PG production and proliferation of colorectal cells. Cancer Res 1998, 58:2323-7.
52. Seed MP: Angiogenesis inhibition as a drug target for disease: an update. In. Exp. Opin. Invest. Drugs1996,5: 1617-1637.
53. Needleman P, Turk J, Jakschik BA, Morrison AR Lefkowith JB: Arachidonic acid metabolism. Annu Rev Biochem 1986, 55: 69-102.
54. Taketo M: Cyclooxygenase-2 inhibitors in tumorigenesis (part I). J Natl Cancer Inst 1998, 90:1529-1536.
55. Taketo M: Cyclooxygenase-2 inhibitors in tumorigenesis (part II). J Natl Cancer Inst 1998, 90:1609-1620.
56. Janne PA, Mayer RJ: Chemoprevention of colorectal cancer. N Engl J 2000, 342:1960-1968.
57. Labayle D, Fischer D, Vielh P, Drouhin F, Pariente A, Bories C:Sulindac causes regression of rectal polyps in familial adenomatous polyposis. Gastroenterology 1991, 101:635-639.
58. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB: The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000, 342:1946-1952.
59. Bennett A, Del Tacca M: Proceedings: Prostaglandins in human colonic carcinoma. Gut 1975, 16:409.
60. Jaffe BM: Prostaglandins and cancer: an update. Prostaglandins 1974, 6: 453-461.
61. Reddy BS, Maruyama H,Kelloff G: Dose-related inhibition of colon carcinogenesis by dietary piroxicam, a nonsteroidal antiinflammatory drug, during different stages of rat colon tumor development. Cancer Res 1987, 47:5340-5346.
62. Steinbach G, Lynch PM, Phillips Robin KS, Wallace MH, Hawk E, Gordon GB, Wakabayashi N, Saunders B, Shen Y, Fujimura T, Su LK, Levin B, Godio L, Patterson S, Rodriguez-Bigas MA, Jester SL, King KL, Schumacher M, Abbruzzese J, DuBois RN, Hittelman WN, Zimmerman S, Sherman JW, Kelloff G: The Effect of Celecoxib, a Cyclooxygenase-2 Inhibitor, in Familial Adenomatous Polyposis. N Eng J Med 2000, 342:1946-52.