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Review Article

COX2- Inhibitors and Their Role in Cancer Prevention and Treatment

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Abstract

The various steps, in the process of carcinogenesis take many years, which contributes to several opportunities for intervention to inhibit growth of the disease. The reduction in the risk associated with cancer may be done by few effective chemopreventive agents through inhibition of the initiation of carcinoma or induction of apoptosis or DNA repair in cells harboring mutations. Over expression of **cyclooxygenase-2(**COX-2) has been identified in precancerous, cancerous and metastatic human cancers and its level was found to be significantly correlating with cancer. *In vitro*, preclinical and clinical data have supported the hypothesis that COX-2 plays a central role in oncogenesis and treatment with COX-2 inhibitors provides an effective chemopreventive approach like activity of celecoxib in familial adenomatous polyposis. Understanding the role of COX-2 in initiation of carcinomas can lead to many clinical trials testing COX-2 inhibitors for the chemoprevention of a wide variety of cancers that over-express COX-2.

Keywords: COX-2; Prostaglandins; Tumorigenesis; COX-2 inhibitors; Chemoprevention

Abbreviations

COX: Cyclooxygenase;

NSAIDs: Non Steroidal Anti-inflammatory Drugs;

DNA: Deoxyribonucleic Acid;

IL: Interleukin;

PG: Prostaglandin;

VEGF: Vascular endothelial growth factor ;

Bcl: B-cell lymphoma;

FAP: Familial Adenomatous Polyposis;

APC: Adenomatous Polyposis Coli ;

DCIS: Ductal carcinoma *in situ;*

Introduction

Cyclooxygenases are group of key enzymes involved in the synthesis of prostaglandin. Cyclooxygenase-2 (COX-2) is an inducible isoenzyme that plays a pivotal role as a mediator of inflammation. Cyclooxygenases catalyze the process of the conversion of arachidonic acid into prostaglandins [1-3]. Prostaglandins along with other arachidonic acid products such as thromboxane and 15-hydroxy-eicosatetraenoic acids belongs to the eicosanoid family of fatty acid molecules, which are known to regulate many physiological processes including the inflammatory response, immune responses like immunosuppressive effect [4-6], ovulation [7,8], and induction of mitosis in a cell [9,10]. Epidemiological studies showed that use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs), which are prototypic inhibitors of COX, are associated with a reduced risk of various types of cancers [11].

Appropriately, growth and formation of tumor are also reduced on treatment with COX-2 inhibitors [12-18], COX-2 inhibitors causes fewer adverse effects as compared to traditional NSAIDs [19]. The improved safety profile of selective COX2 inhibitors makes it realistic to consider their long-term use in individuals from low to moderate risk of cancer. This review focuses on the rationale for using selective COX 2 inhibitors to prevent cancer.

Isoforms of cyclooxygensases (COX's)

There are two isoforms of COX enzyme family COX-1 and COX-2. Cyclooxygenase-1 is a membrane-bound hemoglycoprotein that is constitutively expressed in the endoplasmic reticulum of cells in most healthy tissues and is responsible for local prostaglandin. On the other hand, COX-2, an inducible COX isoform, which is not usually detected in normal tissues [20,21]. It is only induced by proinflammatory and mitogenic stimuli and increases the synthesis of prostaglandins in inflamed and neoplastic tissues [22]. There are a number of structural differences between the COX-1 and COX-2 genes, such as differences in the cis elements within the promoter regions and 3´-untranslated domains.

The structure of the COX-2 gene indicates that it is an early gene product that occurs immediately during the inflammation [23,24]. Cyclooxygenase-2 synthesis is known as inducible and consider a variety of stimuli, such as interleukin-1 alpha and -1 beta, 25, 26 growth factors such as platelet-derived growth factor [27,28] epidermal growth factor, [29,30] and lipopolysaccharide and endothelial precursor [31,32] as in figure 1 [33].

Causative mechanism of COX 2 in cancer

COX 2 affects many important processes in carcinogenesis that makes it attractive therapeutic target. The various processes include xenobiotic metabolism, angiogenesis, apoptosis, immunosuppression and inflammation.

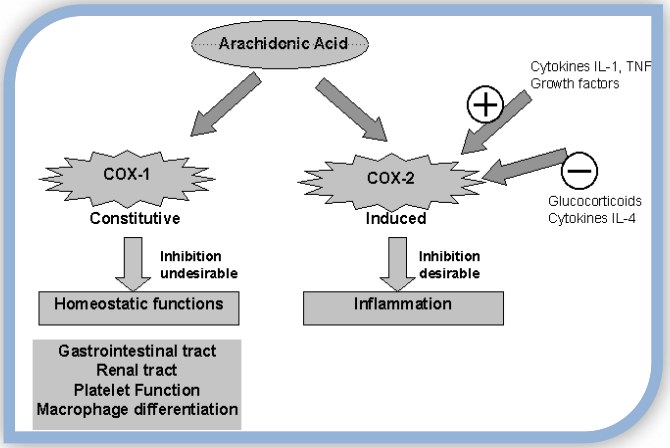

Figure 1. COX-2 is involved in the synthesis of prostaglandins that causes pain and inflammation in the body.

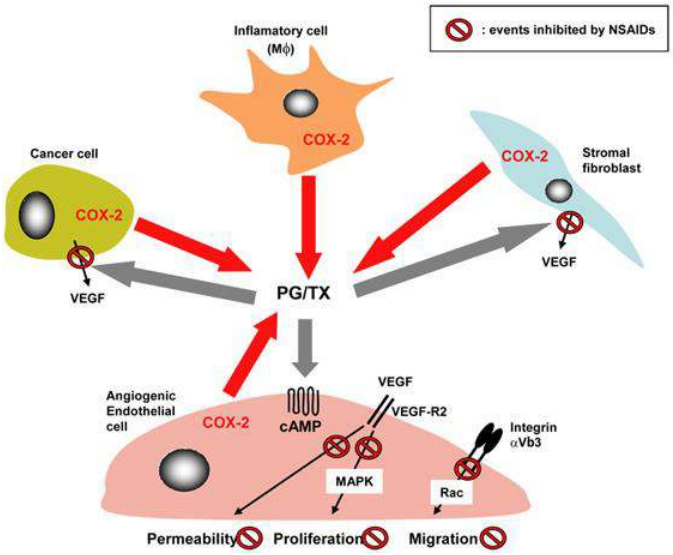

Figure 2. Representing the paradigm that expression of cyclooxygenase-2 (COX-2) and prostaglandin production which occurs during inflammation. Further, in the tumor environment COX-2/PG stimulate cell proliferation, cell survival and tumor angiogenesis; thus helps in promoting tumorigenesis [34].

Xenobiotic metabolism

The metabolism of Arachidonic acid by COX-2 produces mutagens which play a major role in carcinogenesis [35]. Malondialdehyde is a mutagen produced by isomerization of prostaglandin H2. It acts by forming adducts with deoxynucleotides, that causes frame-shifts and substitutions in base pair [36].

Wiese et. al., reported that peroxidase activity of cyclooxygenases catalyzes the formation of mutagens by the oxidation of aromatic amines, heterocyclic amines, and dihydrodiol derivatives of polycyclic hydrocarbons. Thus, overexpression of COX-2 leads to DNA damage and carcinogenesis [37].

Angiogenesis

COX-2 has also been implicated in enhancing angiogenesis which plays a role in carcinogenesis. [38]. The growth of tumors depends on an increase in blood supply. Tumor cells ensure their own growth by secreting growth factors such as vascular endothelial growth factor (VEGF) that stimulate angiogenesis. Over expression of COX 2 in colon cancer cells increases the production of vascular growth factors, the migration of endothelial cells through a collagen matrix, and the formation of capillary-like networks *in vitro* [38]. These effects can be blocked by NS-398, a selective inhibitor of COX 2. Two recent studies also showed the importance of COX- 2 in angiogenesis [39].

Apoptosis

Tumorigenic potential of initiated cells can increase by the inhibition of apoptosis. Sheng et. al., [40] showed that prostaglandin E2 may inhibit apoptosis by inducing bcl-2 (B-cell lymphoma). Recently, it was found that Celecoxib (Celebrex), a selective COX-2 inhibitor, causes inhibition of COX-2, which results in a decrease production of prostaglandin E2, TBX 2 (Thromboxane), and increase apoptosis *in vivo* [41].

Inflammation and immunosuppression

Chronic inflammation increases the risk of cancer.42 Inflammation is associated with increased synthesis of prostaglandins partly through cytokine-mediated induction of COX-2. There is a link between chronic inflammation and carcinogenesis by the over expression of COX- 2. The growth of tumor is caused by the suppression of the immune system [43].

The tumor cells releases colony-stimulating factors which activate monocytes and macrophages for the synthesis of prostaglandin E_2 (PGE2), and further causes inhibition in the production of immune regulatory lymphocytokines, proliferation of T-cell and B-cell, and the natural killer cells with its cytotoxic activity. Thus, selective inhibition of COX-2 promotes the antitumor activity by restoring the balance between IL-10 and IL-12 *in vivo*.

Therapeutic effects of COX-2 Inhibitors in various Cancers

NSAIDs act by inhibiting both COX 1 and COX 2 but primary anti-inflammatory mechanism is the inhibition of inducible isoform COX-2. The adverse effects of NSAIDs in the case of long term use are gastritis, gastrointestinal ulceration, and reversible liver and renal dysfunction [44- 46].

The over expression of COX-2 in humans has been studied in many cancer types and neoplastic precursor lesions as listed in the Table 1 below [47,48].

The data given above indicate that selective inhibition of COX-2 may contribute to be an effective strategy for preventing different types of cancers. The prevention of cancer implies multiple opportunities to inhibit the disease growth. The effective chemo preventive agents act by reducing the risk of cancer as well as by the prevention of the early and initiative stages of carcinoma through apoptosis and DNA repair in cell mutation or by preventing tumor growth during the progression stages of carcinogenesis [49]. The intervention in chemoprevention is possible at various stages of carcinogenesis starting from normal epithelium to invasive and metastatic cancer as in figure 2 [50].

Table 1. Neoplastic precursor lesions and types of cancer with the overexpression of COX-2.

Neoplastic Precursor Lesions	Overexpression of COX-2 in Cancer types
Actinic keratoses	Bladder
Atypical hyperplasia of breast	Breast
Atypical pulmonary hyperplasia	Cervical
Barrett's esophagus	Colon
Colorectal adenoma	Esophageal
Prostate intraepithelial neoplasia	Gastric
	Hepatocellular carcinoma
	Lung
	Melanoma
	Pancreatic
	Prostate
	Squamous cell carcinoma

COX-2 Inhibitor Intervention

Normal epithelium Mild dysplasia Moderate dysplasia Invasive cancer Metastatic cancer

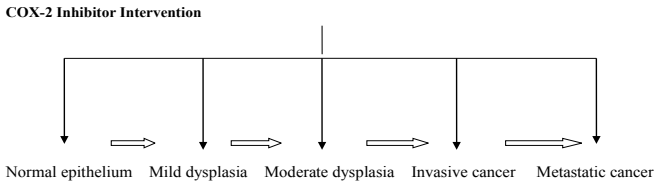

Figure 2. Process of carcinogenesis where chemoprevention intervention may be advantageous.

The proceeding clinical trials which evaluate the COX-2-specific inhibitors as chemoprevention and therapeutic agents are described in the following sections [50,51].

Colorectal Cancer

Colorectal cancer is the third leading cause of cancer death and a major health problem, with 2002 estimating 148,300 new cases and 56,000 deaths [52]. The majority of cases of colon carcinoma occur in patients who have no known susceptibility for the disease [53]. As per the estimates, currently American Cancer Society and Gastrointestinal Society colorectal cancer screening guidelines can lower the mortality rate upto 50% per annum [54].

Expression and Preclinical Data: COX-2

The chemo preventive effects of COX-2 inhibitors in the occur-

rence of colorectal cancer are the subject of intense study; animal models have been useful in investigating colorectal cancer pathogenesis.

A mutation in the Adenomatous Polyposis Coli (APC) gene results in spontaneous adenoma formation in the small intestine of APC delta716 knockout mice. Oshima and colleagues noticed that there is a cause-effect relationship between COX-2 overexpression and occurrence of gastrointestinal tumor by using the above rodent model [55]. It was shown that suppression of one allele of the COX-2 gene reduces the number of intestinal polyps by 66%, and suppression of both alleles results in a reduction of 86% [56] Further, treatment of COX-2-expressing azoxymethane-treated rats with oral Celecoxib suppressed formation of colorectal tumors by > 90%, compared with a suppression of 40% to 65% following administration of a COX inhibitor that is non selective [56,57].

Decreased occurrence of Colorectal Neoplasia

Long term use of NSAIDs causes reduction in the occurrence of colorectal adenomas, cancer and cancer mortality by 40% to 50% [58-60]. The vital study on Celecoxib for the treatment of Familial Adenomatous Polyposis (FAP) was done with 77 patients, who were randomized and given placebo or Celecoxib (100 or 400 mg twice daily) for 6 months [61]. The primary efficacy end point was the change in the number of colorectal adenomas (> 2 mm in size) at 6 months. There was a 4.5% reduction in the placebo-treated group11.9% reduction in the 100-mg Celecoxib-treated group and 28.0% reduction in the 400-mg Celecoxib-treated group. The decrease in incidence between the 400-mg Celecoxib twice-daily group and the placebo group was statistically significant (P = .003). The prevalence of adverse events was similar among the treatment groups and consisted primarily of rash, diarrhea, dyspepsia, fatigue, upper respiratory infection.

The positive results from the vital trial of Celecoxib in FAP support further investigation of COX-2 inhibitors for an overall chemoprevention strategy for colorectal tumors in other populations at risk, including patients with sporadic adenomatous polyps. There are several recently initiated clinical trials of Celecoxib in the prevention and recurrence of colorectal adenomas.

Non-melanomatous Skin Cancer

It is well-known fact that chronic sun exposure is a major cause of skin cancer .Up to the one million of new cases per year of Nonmelanomatous skin cancers such as basal cell carcinoma and squamous cell carcinoma were reported.[62] Non melanomatous skin cancer is rare in young people. Its occurrence has been reported to increase with age and to be higher in men than woman [63]. A precursor lesion of squamous cell carcinoma is actinic keratoses with 60% of squamous cell carcinomas developing from it [64].

In Vitro and Preclinical Data: COX-2

In epidermis the balance between proliferation of cells (basal layer), cell differentiation (suprabasal, spinous and granular layers) and apoptosis (transitional zone) is closely regulated. The proliferative capacity is reduced when cells undergo terminal differentiation and leave the basal cell layer.

Neufang et. al. studied in a transgenic mouse model that the overexpression of COX-2 in epidermis results in epidermal differentiation [65]. Further, there was an increase in the proliferation of the epidermal cells and number of viable cornified layers.

In vitro study by Buckman et. al., demonstrated that exposure of human keratinocytes to UV-B causes a significant increase in prostaglandin E_2 [66]. Indomethacin, a nonspecific COX inhibitor and SC58125, a COX-2 specific inhibitor acts individually by blocking UV-B induced COX-2 activity, in cultured keratinocytes of humans [67].

Clinical Data and Clinical Trials

An investigating report by Kagoura et al. showed that 4 of 16 basal cell carcinoma cases tested positive for COX-2 and 11 of 15 squamous cell carcinoma patients tested positive for COX-2 [68].

At University of Albama having sponsorship from the National Cancer institute, a phase IIB, double-blind, placebo-controlled trial is going on. The primary and secondary end point of this study are inducing actinic keratoses regression and effect of Celecoxib on potential surrogate end point biomarkers in actinic keratoses, sun-exposed skin, non-sun-exposed skin and their correlation with clinical outcome [69].

Prostate Cancer

It is the second leading cause of cancer death in men in the United States [70]. Treatment includes androgen ablation therapy, surgery, external beam radiation and radioactive seed implantation called as brachytherapy [71].

***In vitro* and Preclinical Data: COX-2**

Lim et al. demonstrated the *in vitro* study of Sulindac, a COX-1 and COX-2 inhibitor has proapoptotic activity in prostate cancer cell lines like PC3, LNCaP, and PrEC. After 48 hrs of treatment with Sulindac, 50% of PC3 cells and 40% of LNCaP cells died [72].

The studies showing the effect of COX-2 inhibitors on angiogenesis in prostate carcinoma cell lines has been well established. This study explains that cell lines LNCaP, PC3 and PrEC were treated with two COX-2 inhibitors, Etodolac and NS398. It decreases the cell proliferation in carcinoma cell lines but not in the stromal cell lines of prostate [73].

Clinical Data and Clinical Trials

The overexpression of COX-2 is noted in 86% of prostate intraepithelial neoplasia lesions and 87% of carcinomas collected during prostatectomy as reported by Kirschenbaum et. Al [74]. *In vivo* results showed that there is decrease in micro vessel activity and angiogenesis by COX-2 inhibitor.

In preclinical experiment, activity of Exisulind (phosphodiesterase/COX-1 and-2 inhibitor) is being evaluated in phase I/II clinical trials which examines prostate-specific antigen response and disease response rate of Exisulind as a single agent or in combination with docetaxel [41-43].

Breast Cancer

There is variation in the occurrence of breast cancer with age and nationality. Major etiologies implicated in breast cancer are ovarian dysfunction and abnormal hormone production [75]. The common treatment modalities are surgery, radiation and chemotherapy or their combination [76].

***In vitro* and Preclinical Data: COX-2**

Rozic et. al. reported the role of prostaglandins in the proliferation, migration, survival, angiogenic capacity and invasive behavior in murine mammary tumor cell line. Migratory and invasive behavior was done by an in vitro transwell migration assay. The COX-2 inhibitors blocked the migration and angiogenesis in *in vivo*. Thus, this study indicates that COX-2 inhibitors can be effective in preventing the development of this cancer [77].

In some studies, COX-2 inhibitors were note to act not only by preventing mammary carcinogenesis, but also by preventing multidrug resistance in breast cancer [78].

Gastric Cancer

There is variation in the occurrence of gastric cancer in different parts of the world and it is high in Japan and Chile and lowest in the Dominican Republic and Thailand [79]. The high rate of gastric cancer in Japan is due to the consumption of meat and fish.

Clinical Data: COX-2

Few studies explain that a *Helicobacter pylori* infection causes gastric cancer in a patient due to the overexpression of COX-2 [80]. There is also a direct relationship between COX-2 mRNA expressions and increased in tumor invasion. Due to this, COX-2 inhibitors are effective in preventing *H. pylori* infection and other risk factors for gastric cancer. Further clinical trials are in pipeline for testing these agents.

Bladder Cancer

It is the fourth leading cause of cancer in men and eighth in women. In US, it is the ninth cause in men and 14th cause in women of death in cancer [81]. Majorly, it arises from bladder papilloma precursors, which provides opportunities to develop chemoprevention strategies [82].

***In vitro* and Preclinical Background: COX-2**

The studies show that COX-2 inhibitors reduce the occurrence of bladder cancer caused by the chemical carcinogens [83]. Khan et. al. studied the expression of COX-1 and COX-2 in normal dogs and dogs with transitional cell carcinoma. It reveals the expression of COX-2 in carcinoma and in new blood vessels of tumor tissue but no differences in expression of COX-1between normal and malignant bladder was seen [84].

Clinical Data and Clinical Trials

At the University of Texas M. D. Anderson Cancer Center, Houston, a clinical trial on COX-2 inhibitors and incidence of bladder cancer is going on. (Table 2) [41-43]. It is designed for the comparison of time to recurrent treatment with Celecoxib or placebo in patients with high risk of superficial transitional cell carcinoma of bladder. It also correlates the modulation of biomarkers with bladder cancer.

Esophageal Cancer

There is a rapid increase in the occurrence of esophageal cancer in the patients with the premalignant condition known as Barrett's esophagus which is due to replacement of normal squamous esophageal epithelium with a columnar type) [85,86]. The patients with Barrett's esophagus have a high risk to esophageal adenocarcinoma by 30 to 40 fold [87].

In Vitro and Preclinical Background: COX-2

Li et. al., studied that aspirin decreases the cell growth in an esophageal cancer cell line [88]. The effect of COX-2 inhibitor NS398 on apoptosis and gene expression that regulate apoptosis were tested. *In vitro*, apoptosis is induced in esophageal cancer cell lines by COX-2 inhibitor through a cytochrome C-dependent pathway. Activation of caspase-9 and caspase-10 by NS398, and addition of a caspase inhibitor reverses the effect of apoptosis of COX-2 antagonist [88]. Therefore, these data refers that COX-2 inhibitors may be used for chemoprevention and treatment of esophageal cancer.

Clinical Data

Kandil et. al. studied the esophageal punch biopsy specimens in patients with Barrett's esophagus [89]. COX-2 was found in Barrett's esophagus tissue with or without dysplasia, indicating that COX-2 may play a role in the early stages of development of adenocarcinoma [90].

Currently a clinical study coordinated by the Johns Hopkins Comprehensive Cancer Center, Baltimore is going on to evaluate the efficacy and safety of Celecoxib in patients with Barrett's esophagus.

The ongoing clinical trials which evaluate the COX-nonspecific and COX-2 specific inhibitors as chemoprevention and therapeutic agents which are discussed above are mentioned in the following Table 2.

Tumor type	Trial	Contact organizations	COX inhibited
Colon	A phase II chemoprevention study of calcium and aspirin in subjects with previously resected adenomatous polyps of colon	The University of Texas M.D Anderson Cancer center	COX-1/2
Colon	Phase III trial of Celecoxib vs. placebo for prevention of new sporadic adenomatous polyps	The University of Texas M.D Anderson Cancer center	COX-2
Colon	Phase IV trial of Celecoxib for suppression of polyp formation in children and adults with FAP	Mayo Clinic	COX-2
Basal cell carcinoma	Phase II randomized study of Celecoxib for chemoprevention of basal cell carcinoma in patient with basal cell nerve	UCSF Cancer center and Cancer research institute	COX-2
Skin	Phase II/III randomized chemoprevention study of Celecoxib in patient with actinic keratoses	University of Alabama at Birmingham comprehensive cancer center	COX-2
Prostate	Phase I randomized study of neoadjuvant Celecoxib followed by prostatectomy in patient with localized prostate cancer	John Hopkins oncology center	COX-2
Prostate	Phase I/II clinical trials of combination therapy with Docetaxel and Exisulind in prostate cancer	University of Chicago	COX-1/2
Breast	Phase II trial of Celecoxib in breast DCIS	University of Kansas	COX-2
Breast	Phase II trial of Celecoxib in breast DCIS	University of Kansas	COX-2
Bladder	Phase IIB/III randomized chemoprevention study of Celecoxib in patients with superficial transitional cell carcinoma of the bladder at high risk for recurrence	The University of Texas M.D Anderson Cancer center	COX-2
Esophageal	Phase II/III randomized chemoprevention study of Celecoxib in patients with Barrett's Esophagus	Johns Hopkins Oncology Center	COX-2
Lung	Randomized phase II study of Celecoxib with Paclitaxel/carboplatin for non-small cell lung carcinoma	Comell University	COX-2
Cervical	Phase I/II study of external beam radiotherapy and brachytherapy concurrently with Celecoxib, fluorouracil, and cisplatin in patients with locally advanced cervical cancer	Radiation Therapy Oncology Group	COX-2
Cervical	Phase IIB, randomized placebo controlled trial of oral Celecoxib for high grade squamous intraepithelial lesions of the cervix	Southwest Oncology Group & University of Texas, Amarillo Medical Center	COX-2

COX- Cyclooxygenase, FAP- Familial adenomatous polyposis, DCIS- Ductal carcinoma in situ

Table 2. Clinical trials of COX inhibitors in Cancer prevention and treatment [41- 43].

COX- Cyclooxygenase, FAP- Familial adenomatous polyposis, DCIS- Ductal carcinoma in situ

Conclusion

Cyclooxygenase is a natural enzyme that mediates inflammation and other immune responses. Over expression of COX-2 is noted in various malignancies associated with chronic inflammatory conditions. The available data indicate that COX2 inhibitors can stall the progression of carcinoma at various stages, especially in tumors that take origin form nonmalignant inflammatory precursors. COX 2 inhibitors has a role both in the treatment and prevention. Recent trials noted that COX 2 inhibitors such as Celecoxib have an important role in chemoprevention of gastrointestinal carcinomas such as colon cancer, FAP and colorectal polyps. Additionally, the safety profile of COX 2 inhibitors is noteworthy when compared to chemotherapeutic agents.

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