Prostaglandins and Cancer

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ABSTRACT
Chemoprevention has been considered as a possible approach for cancer prevention. A significant effort has been made in the development of novel drugs for both cancer prevention and treatment over the past decade. Recent epidemiologic studies and clinical trials indicate that long-term use of aspirin and similar agents, also called nonsteroidal anti-inflammatory drugs (NSAIDs), can decrease the incidence of certain malignancies, including colorectal, esophageal, breast, lung, and bladder cancers. The best-known targets of NSAIDs are cyclooxygenase (COX) enzymes, which convert arachidonic acid to prostaglandins (PGs) and thromboxane. COX-2 derived prostaglandin E$_2$ (PGE$_2$) can promote tumor growth by binding its receptors and activating signaling pathways which control cell proliferation, migration, apoptosis, and/or angiogenesis. However, the prolonged use of high dosages of COX-2 selective inhibitors (COXIBs) is associated with unacceptable cardiovascular side effects. Thus, it is crucial to develop more effective chemopreventive agents with minimal toxicity. Recent efforts to identify the molecular mechanisms by which PGE$_2$ promotes tumor growth and metastasis may provide opportunities for the development of safer strategies for cancer prevention and treatment.
INTRODUCTION

The most effective treatments for cancer, including various combinations of surgical resection, radiation, and/or toxic chemotherapy, depend on the detection of cancer at a very early-stage. Unfortunately, it has not been possible to identify all individuals who are at the highest risk for developing cancer. Most patients present to their physician with advanced cancer when standard treatment regimens for solid malignancies result in a much lower 5-year survival. It is generally agreed that an effective way to control cancer is to find better ways of preventing it. Chemopreventive approaches are definitely worth considering for health persons who have a strong family history of cancer or those who are particularly susceptible for other reasons. Therefore, the development of effective chemopreventive drugs is important for success in the field of cancer prevention. One promising group of compounds with cancer preventive activity includes nonsteroidal anti-inflammatory drugs (NSAIDs).

One promising group of compounds with cancer preventive activity includes nonsteroidal anti-inflammatory drugs (NSAIDs). A large body of evidence from population-based studies, case control studies and clinical trials indicate that regular use of NSAIDs over a 10–15 year period reduces the relative risk of developing colorectal cancer by 40-50% (1). Furthermore, long-term use of NSAID leads to the regression of preexisting adenomas in patients with familial adenomatous polyposis (FAP) (2). Since many other human cancers are reported to have elevated levels of COX-2 and overproduce prostaglandins, there is great interest for evaluating the role of NSAIDs for prevention and treatment strategies for other cancers such as breast, stomach, pancreas, urinary tract, lung, and prostate cancers. However, the prolonged use of NSAIDs is associated with side effects such as nausea, dyspepsia, gastritis, abdominal pain, peptic ulcer, gastrointestinal bleeding and/or perforation of gastroduodenal ulcers (3). It was hypothesized that NSAIDs exert their anti-inflammatory and anti-tumor effects through inhibition of the inducible cyclooxygenase-2 (COX-2) (4, 5), while unwanted side effects of these drugs such as damage to the gastric mucosa and gastrointestinal bleeding are thought to arise from the inhibition of the constitutive COX-1 (6). This hypothesis led to the development of COX-2 selective inhibitors (COXIBs) such as celecoxib, rofecoxib, and valdecoxib. Indeed, highly selective COX-2 inhibitors retain the anti-inflammatory and anti-tumor effects of the NSAIDs while not interfering with COX-1 responsible for protection of the gastroduodenal mucosa from the effects of acid from the stomach (5, 7-9). Therefore, these drugs were approved by the FDA and as novel anti-inflammatory agents and their use is associated with about a 50% reduction in gastrointestinal toxicity. Moreover, these agents have some potential for use as chemopreventives (10-12). One of them, celecoxib, was approved in December 1999 by the FDA for use in the prevention of colorectal polyp formation of patients with familial adenomatous polyposis (FAP). Unexpectedly, the prolonged use of higher doses of COX-2 selective inhibitors is associated with increased thrombotic events in humans (13-15). Now, we know that this original hypothesis was overly simplistic because of our lack of knowledge of the importance of signaling pathways which are affected downstream of COX-2. Thus it has become essential for us to understand how NSAIDs interfere with COX-2 mediated cellular functions in both normal physiology and pathological conditions.

NSAID TARGETS

Inflammation and Cancer

NSAIDs are chemically distinct compounds that share a common therapeutic action. The best known of these are aspirin, ibuprofen, piroxicam, indomethacin, and sulindac. NSAIDs are generally prescribed to ameliorate symptoms associated with acute pain and chronic inflammatory diseases like arthritis. Chronic inflammation caused by infections or autoimmune diseases is clearly associated with increased cancer risk in a number of instances. For example, it has been long known that patients with persistent hepatitis B, Helicobacter pylori infections, or an immune disorder such as ulcerative colitis have higher risk for the development
of liver or gastrointestinal tract cancer. It has been estimated that chronic inflammation contributes to the development of approximately 15% of malignancies worldwide (16). The connection between inflammation and cancer further supports the concept that anti-inflammatory drugs, NSAIDs, have anti-neoplastic activity.

COX-dependent Targets

NSAIDs were shown to exert their anti-inflammatory, analgesic and anti-pyretic effects mainly by inhibiting cyclooxygenase, a key enzyme responsible for the biosynthesis of prostaglandins from arachadonic acid (6). Aspirin is an irreversible inhibitor of the COX through blocking the approach of arachidonic acid, while indomethacin, piroxicam, ibuprofen, and sulindac are competitive inhibitors for substrate binding. When COX converts arachidonic acid to prostaglandins, the key regulatory step in this process is the enzymatic conversion of arachidonate to PGG2, which is then reduced to an unstable endoperoxide intermediate, PGH2. Specific PG synthases in turn metabolize PGH2 to at least five structurally related bioactive lipid molecules, including PGE2, PGD2, PGF2α, PGI2, and thromboxane A2 (TxA2) (17) (Figure 1).

COX exists in two isoforms commonly referred to as COX-1 and COX-2. Although both COX-1 and COX-2 are upregulated in a variety of circumstances, normally COX-1 is constitutively expressed in a broad range of cells and tissues. COX-1 expression remains constant under most physiological or pathological conditions and its constitutive enzymatic activity is linked to renal function, gastric mucosal maintenance, stimulation of platelet aggregation, and vasoconstriction. For example, COX-1-derived prostaglandins play a central role in many normal physiological processes. In the gut, COX-1-derived PGI2 (also called as prostacyclin) produced by epithelial and stromal cells in subepithelial tissues plays a key role in the cytoprotection of gastric mucosal surfaces and the normal vasculature (18). COX-1 has been shown to play an essential role in gastrulation in zebrafish and a reduction of COX-1 results in posterior mesodermal defects during zebrafish development (19, 20). In contrast, COX-2 is an immediate-early response gene and its expression is normally absent in most cells and tissues but it is highly induced in response to pro-inflammatory cytokines, hormones, and tumor promoters (21). Furthermore, COX-2 derived PGE2 is a pro-inflammatory bioactive lipid and is the major prostaglandin produced in many human solid tumors, including cancer of the colon (22), stomach (23), and breast (24). Recent research has indicated that COX-2-derived PGE2 is a key mediator of acute inflammatory responses (25, 26), arthritis (27, 28), and inflammatory bowel disease (IBD) (29, 30). Direct evidence supporting the notion that PGE2 promotes tumor growth comes from the following observations. PGE2 reversed NSAID-induced adenoma regression in ApcMin mice (31). PGE2 significantly enhanced colon carcinogen-induces tumor incidence and multiplicity in rats (32). Furthermore, our group recently reported that PGE2 accelerates intestinal adenoma growth in ApcMin mice (33).

Although COX-2 selective inhibitors suppress PGE2 production, the potential inhibition of endothelial cell–derived COX-2 activity and subsequent PGI2 production may promote platelet aggregation and lead to increased the risk of coronary thrombosis and stroke (34). Since PGI2 antagonizes the thromboxane produced by platelets, inhibition of PGI2 may shift the homeostatic balance toward more thromboxane A2 (TX A2) effects. In addition, PGI2 appears to be important in protecting cardiomyocytes from oxidative stress (35). Therefore, it will be important to develop chemopreventive agents that do not inhibit production of other prostanoids, such as the anti-thrombotic PGI2. Given that only PGE2 appears to be pro-carcinogenic, more selective pharmacological inhibition of PGE2 production downstream of COX-2 may be superior and result in fewer side effects. To achieve this goal, researchers have been investigating precisely how PGE2 promotes tumor growth and its signaling pathways.
COX-independent targets

Another explanation for anti-tumor effects of NSAIDs recently emerged, based on the studies showing that high doses of NSAIDs inhibit tumor cell growth and induce apoptosis through COX-independent mechanisms by regulating several different targets (36), such as 15-LOX-1 (37), a proapoptotic gene Par-4 (38), anti-apoptotic gene Bcl-XL (39), and NF-κB signaling (40, 41). In the above studies, higher NSAID concentrations which may be impossible to achieve in vivo without significant toxicity. For example, the pro-apoptotic effects of NSAIDs seen at concentrations above 50 µM are most likely modulated through COX-2-independent pathways. However, the best characterized biochemical target of NSAIDs at therapeutic concentrations remains the COX enzymes. It is likely that many of the chemopreventive effects of NSAIDs are carried out via inhibition of COX-2.

PGE\textsubscript{2} AND CANCER

PGE\textsubscript{2} and its receptors play a predominant role in promoting cancer progression. The only other COX-2 derived prostaglandin implicated in oncogenesis is TxA\textsubscript{2} which was reported to promote angiogenesis (42). NSAIDs have been shown to inhibit PGE\textsubscript{2}-mediated processes that play essential roles in tumor progression, such as tumor cell proliferation, invasion, angiogenesis, and immunosuppression. Therefore, we will focus on modulation of PGE\textsubscript{2} and its downstream targets that control these processes.

PGE\textsubscript{2} Regulation And Its Receptors

The steady-state cellular levels of PGE\textsubscript{2} depend on the relative rates of COX-2/PGE synthases-dependent biosynthesis and 15-hydroxyprostaglandin dehydrogenase (15-PGDH)-dependent degradation (Figure 1). For example, cytosolic or microsomal PGE\textsubscript{2} synthases are able to convert PGH\textsubscript{2} to PGE\textsubscript{2}. Two cytosolic PGE\textsubscript{2} synthases called as cytosolic glutathione transferases (GSTM2-2 and GSTM3-3) catalyze the conversion of PGH\textsubscript{2} to PGE\textsubscript{2} in the human brain (43). The two microsomal PGE\textsubscript{2} synthases characterized to date are mPGES1 and mPGES2. The mPGES1 exhibits a higher catalytic activity than the other PGES isomerases, indicating that it likely plays a key role in the synthesis of PGE\textsubscript{2} from PGH\textsubscript{2} (44, 45).

15-PGDH, a prostaglandin-degrading enzyme, catalyzes oxidization of 15(S)-hydroxyl group of PGE\textsubscript{2} to yield an inactive 15-keto PGE\textsubscript{2} (46). Genetic deletion of 15-Pgdh in mice leads to increased tissue levels of PGE\textsubscript{2} (47). Although 15-PGDH may promote certain androgen-sensitive prostate cancers (48), we and others recently reported that loss expression of 15-PGDH correlates with tumor formation, including colorectal cancer (49, 50), lung (51) and transitional bladder cancer (52). Interestingly, NASIDs have been shown to upregulate 15-PGDH expression in colorectal and medullary thyroid cancers (49, 53). Taken together, these studies suggest that the loss expression of 15-PGDH may contribute to tumor progression. The functional role of 15-PDGH in promoting tumor growth is currently under investigation in several laboratories.

PGE\textsubscript{2} exerts its cellular effects by binding to its cognate receptors (EP1-4) that belong to the family of seven transmembrane G protein-coupled rhodopsin-type receptors. The central role of PGE\textsubscript{2} in tumorigenesis has been further confirmed through homozygous deletion of its receptors. Mice with homozygous deletions in the EP1 and EP4 receptors, but not EP3, were partially resistant to colon carcinogen mediated induction of aberrant crypt foci (54, 55). EP2 disruption decreases the number and size of intestinal polyps in APC\textsubscript{Δ176} knockout mice (56). Moreover, in carcinogen-treated wild-type mice, an EP1 receptor antagonist also decreased the incidence of aberrant crypt foci, whereas Apc\textsubscript{Min} mice treated with the same EP1 receptor antagonist and an EP4 receptor antagonist developed 57% and 69% fewer intestinal polyps respectively than untreated mice (54, 55). In addition to colorectal cancer, it has been shown that EP1, 2, and 4 receptors were elevated, whereas EP3 receptor levels were decreased in...
mammary tumors in the COX-2-MMTV mice (57). Furthermore, an EP1 receptor antagonist was shown to reduce tumor burden in a carcinogen-induced rat mammary model (58). However, Amano, et al. recently reported that EP3 receptor activation is required for lung tumor associated angiogenesis and tumor growth (59). In the future it will be important to carefully determine the EP receptor profile in human cancers and to examine whether NSAIDs can modulate PGE2 receptor expression. Taken together, these findings may provide a rationale for the development of EP receptor antagonists which may offer an alternative to COX-2 selective inhibitors.

**PGE2 Signaling Pathways And Its Downstream Targets**

An increasingly large body of evidence indicates that PGE2 promotes tumor growth by stimulating EP receptor signaling with subsequent enhancement of cellular proliferation, promotion of angiogenesis, inhibition of apoptosis, stimulation of invasion/motility, and suppression of immune responses. These findings prompted research to elucidate PGE2 signaling pathways and identify PGE2 downstream targets that are involved in promoting tumor growth (Figure 2).

**EGFR pathway**

Both COX-2 and epidermal growth factor receptor (EGFR) pathways are activated in most human cancers (60). The observation that forced expression of COX-2 in human CRC cells stimulates cellular proliferation through induction of EGFR (61), indicated the likelihood of cross-talk between these two pathways. We and others have demonstrated that PGE2 can transactivate the EGFR, which results in stimulation of cell migration through increased PI3K-Akt signaling in CRC cells (62-64). Since the expression of EGFR directly correlates with the ability of human CRC cells to metastasize to the liver (65), it is possible that inhibiting both the EGFR tyrosine kinase and COX-2 at lower doses could yield additive effects blocking the spread of metastatic disease. Moreover, preclinical studies supports the notion that combined treatment of NSAIDs plus EGFR tyrosine kinase inhibitors is more effective than either single agent alone in several models. In colorectal carcinoma cells, blocking both COX-2 and the HER-2/neu pathways synergistically reduced tumor growth (66). In soft agar and xenograft assays, the combination of a COX-2 selective inhibitor, an EGFR tyrosine kinase inhibitor, and a protein kinase A antisense construct markedly reduced proliferation and angiogenesis of human colon and breast cancer cells (67). Similarly, combined treatment with inhibitors of both pathways significantly decreases polyp formation in ApcMin mice (68) since Apc deficiency is associated with increased EGFR activity in the intestinal enterocytes (69). Hence, we feel that it will be essential to examine the use of COX-2 selective inhibitors as potential agents in combination with EGFR tyrosine kinase inhibitors in clinical trials.

**Nuclear receptor pathways**

Peroxisome proliferator-activated receptors δ (PPARδ also referred to as PPARβ) is a ligand-activated nuclear transcription factor that is a member of the nuclear hormone receptor superfamily. Published data indicates that the PPARδ/β is important for regulating fat metabolism (70), inhibiting obesity induced by either genetic or high-fat-diet (70), and decreasing weight gain and insulin resistance in mice fed high-fat diets (71). However, PPARδ has been identified as a direct transcriptional target of APC/β-catenin/Tcf pathway (72). Our recent findings show that PGE2 transactivates PPARδ which in turn promotes tumor cell survival (33). PGE2 activates PPARδ via a PI3K-Akt pathway. Most importantly, we demonstrated that PGE2 promotes intestinal epithelial cell survival and colorectal adenoma growth in Apcmin mice, but not in PPARδ−/−/Apcmin mice (33), indicating that PPARδ is a critical downstream mediator in PGE2-stimulated tumor growth. Consistent with this result, a selective PPARδ agonist also
accelerates intestinal polyp growth in Apc\textsuperscript{min} mice via inhibition of tumor cell apoptosis (73). These results support the rationale for considering the development of PPAR\(\delta\) antagonists for use in cancer prevention and/or treatment and raise caution for developing PPAR\(\delta\) agonists for clinical use to treat dyslipidemia, obesity and insulin resistance.

**Ras-MAPK pathway**

Ras is an oncogene and its activation is found in a wide variety of human malignancies. Ras induces cell transformation, proliferation, and survival by triggering the downstream signaling pathways such as the Raf/MEK/ERKs and PI3K/Akt pathways. The Ras-MAP kinase cascade is one of the major intracellular signaling pathways responsible for cell proliferation. Forced expression of constitutively active Ras (mutant Ras) or MEK upregulates COX-2 expression and enhances cell proliferation in a variety of cell culture models, respectively (74-77). Nonselective NSAIDs and COX-2 selective inhibitors inhibit cell proliferation and transformation by blocking Ras-MAPK signaling pathway (78-80). Our group recently reported that PGE\(_2\) activates a Ras-MAPK pathway which in turn upregulates COX-2 expression and stimulates colorectal cancer cell proliferation (81). This finding supports a novel mechanism by which COX-2 derived PGE\(_2\) promotes human cancer cell growth by auto-regulation of COX-2 expression, which depends primarily on PGE\(_2\)-induced activation of the Ras-MAPK pathway.

**PGE\(_2\) downstream targets-angiogenic factors**

Angiogenic factors are important for the growth and survival of endothelial cells and to stimulate vascular endothelial cell migration and capillary formation (82). Overexpression of COX-2 in CRC cells induces the production of angiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) (83) and NSAIDs block the production of these angiogenic factors leading to inhibition of proliferation, migration, and vascular tube formation (83-86). The observations that PGE\(_2\) can reverse the anti-angiogenic activity of NSAIDs (87) and homozygous deletion of EP2 completely abrogated induction of VEGF in APC\(^{\Delta 716}\) mouse polyps (56) support the concept that PGE\(_2\) mediates the major role of COX-2 in inducing the expression of pro-angiogenic factors. Several reports demonstrated that PGE\(_2\) upregulates VEGF in cultured human fibroblasts (88) and increases VEGF and bFGF expression through stimulation of ERK2/JNK1 signaling pathways in endothelial cells (89). EP2/EP4 mediate PGE\(_2\) induction of VEGF in ovarian cancer cells (90) and human airway smooth muscle cells (91). Interestingly, VEGF and bFGF induce COX-2 and subsequent prostaglandin production in endothelial cells, suggesting that the effects of PGE\(_2\) on regulation of VEGF and bFGF are likely amplified through a positive feedback loop (92). However, PGE\(_2\) induction of VEGF may provide another explanation for undesired side effect of COX-2 selective inhibitors on cardiovascular complications. VEGF is implicated in cardiovascular homeostasis. For example, treatment with Avastin (bevacizumab), a humanized anti-VEGF antibody, has only marginal improvement of survival for colorectal cancer patients and is also associated with an increased risk of cardiovascular events. Therefore, it is important to identify new molecular targets that drive colorectal tumor-associated angiogenesis. Preliminary data from our laboratory indicate that PGE\(_2\) induces a pro-angiogenic chemokine expression in CRC cells (unpublished data).

**PGE\(_2\) downstream targets-anti-apoptotic factors**

Overexpression of COX-2 in rat intestinal epithelial (RIE) cells increased their resistance to undergo apoptosis and resulted in increased Bcl-2 protein expression (93). The role of COX-2 in preventing apoptosis is likely mediated by COX-2-derived PGE\(_2\), which attenuates cell death induced by the COX-2 selective inhibitor SC-58125 (94). These findings have stimulated great interest in identifying PGE\(_2\) downstream targets responsible to modulation of apoptosis.
PGE2 induces anti-apoptotic protein expression such as Bcl-2 (94) and increases NF-κB transcriptional activity (95), which is a key anti-apoptotic mediator. Since chemotherapeutic agents and radiation therapy enhance COX-2 protein expression as well as PGE2 synthesis in human cancer cells, elevated PGE2 production may increase resistance to therapy by giving cells a survival advantage. It will be important to determine whether patients treated with combinations of chemotherapy or/and radiation therapy with NSAIDs respond better than those not treated with NSAIDs. Preliminary study suggests that COX-2 selective inhibitors may increase the beneficial effects of radiotherapy (96).

**PGE2 downstream targets-chemokines and their receptors**

Although chemokines play a crucial role in immune and inflammatory reactions, recent studies indicate that they have an equally important role in the cancer (97). PGE2 has been shown to inhibit production of CC chemokines, MIP-1α and MIP-1β, in dendritic cells via binding to the EP2 receptor (98, 99) and suppress CC chemokine RANTES (Regulated upon Activation Normal T cell Expressed and Secreted) production in human macrophages through the EP4 receptor (100). These CC chemokines are crucial for macrophage and lymphocyte infiltration in human breast, cervix, pancreas, and gliomas cancers (101, 102). Moreover, a recent study showed that PGE2 mediates VEGF- and bFGF-induced CXCR4-dependent neo-vessel assembly in vivo (103). The important role of CXCR4 for cancer pharmacology is based on findings that activation of CXCR4 is involved in stimulating cancer cell migration and increasing invasion in breast, prostate, bladder, and pancreatic cancers (104-107). These pre-clinical data indicate that chemokines and their receptors are potential drug targets of PGE2 downstream signaling for cancer prevention and treatment.

**PGE2 downstream targets-immunosuppressive mediators**

The tumor microenvironment is predominantly shifted from a Th1 to a Th2-dominant response (immunosuppressive immune responses). COX-2 selective inhibitors restore the tumor-induced imbalance between Th1 and Th2 and promote anti-neoplastic responses in lung cancer (108) and metastatic spread of colorectal cancer (109). These findings led to extensive efforts to understand how PGE2 can regulate immunosuppression. PGE2 has been shown to downregulate Th1 cytokines (TNFα, IFNγ, and IL-2) (110) and upregulate Th2 cytokines such as IL-4, IL-10, IL-6 (111-113). IL-10 is an immunosuppressive cytokine. Moreover, PGE2 can modulate immune function through inhibiting dendritic cell differentiation and T-cell proliferation and suppressing the anti-tumor activity of natural killer cells and macrophages (114, 115). In addition, our group showed that PGE2 upregulates the complement regulatory protein decay-accelerating factor (DAF) which results in blocking the complement C3 into two active compounds, C3a and C3b in CRC cells (116). Thus the effects of PGE2 on the immune system may allow neoplastic cells to evade attack.

**CONCLUSIONS**

Chemoprevention is being carefully evaluated on several fronts as an effective measure to insure cancer control. NSAIDs and COX-2 selective inhibitors have been touted for their possible use as chemopreventive agents. However, concerns over the safety of COX-2 selective inhibitors have prompted researchers to develop more effective chemopreventive agents with minimal toxicity. Understanding the molecular mechanisms of COX-2 and its downstream targets will help to identify specific molecular targets for developing more safe agents which target this pathway. Preclinical studies provide evidence to demonstrate that nonselective NSAIDs and COX-2 selective inhibitors decrease the risk of colorectal cancer as well as other cancers through reduction of COX-2 derived PGE2 synthesis. Significant progress has been made in the elucidation of PGE2 downstream signaling pathways which mediate the
chemopreventive effect of NSAIDs. These cumulative data indicate that the development of agents that lower cellular levels of PGE₂ or that specifically inhibit PGE₂ downstream signaling pathway might be useful for cancer prevention. PGE synthases, 15-PDGH, and/or PGE₂ receptors may also serve as rational targets for lowering cellular levels of PGE₂ and EGFR, MAPK, chemokines, and chemokine receptors are molecular targets for specific inhibition of PGE₂ downstream signaling pathways. Moreover, another approach for decreasing the undesired side effects of COXIBs may be to lower the drug dose used. The combined use of multiple agents may allow for a lower dose of drug to be used. Taken together, efforts to develop novel chemopreventive agents with minimal toxicity and to design strategies for combinations of different agents targeting multiple pathways may yield significant benefits for cancer patients.
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A Competing Interest Statement

We (Dingzhi Wang and Raymond DuBois) declare no competing interests.

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REFERENCES


Figure legends

**Figure 1. Overview of prostaglandin synthesis and main functions.** Arachidonic acid can be metabolized through three major pathways. In the COX pathway, COX-2 derived each prostaglandin or thromboxane A2 has its unique functions.

**Figure 2. PGE₂ in carcinogenesis.** PGE₂ promote tumor growth by stimulating EP receptor downstream signaling and subsequent enhancement of cellular proliferation, promotion of angiogenesis, inhibition of apoptosis, stimulation of invasion/motility, and suppression of immune responses.
Arachidonic acid

COX-1

COX-2

PGH₂

PG & Tx Synthases

15-PGDH

TXA₂

PGI₂

PGE₂

PGD₂

PGF₂α

1. Inflammation
2. Tumor growth
1. Protection of Gastric mucosa
2. Resistance to thromboembolism
1. Inflammation
2. Tumor growth

Anti-inflammation
Loss of parturition

Thrombotic tendency

NSAIDs
COXIBs
COXIBs

PGE2

Autocrine

NSAIDs

COX-2

AA

PGE2

PI3K

Akt

PI3K

Akt

PPARδ

Ras

Raf

MEK

ERK

P

P

P

IL-10

DAF

VEGF

bFGF

P

Angiogenesis

Bcl-2

Apoptosis

Invasion

EGFR ligands

EGFR

Plasma membrane

EP1-4

Proliferation

Immuno-suppression

Invasion

PPARδ

Immuno-suppression

Proliferation

Angiogenesis

Apoptosis

Invasion

PGE2

Autocrine

NSAIDs

COXIBs

Ras

Raf

MEK

ERK

P

P

P

IL-10

DAF

VEGF

bFGF

P

Angiogenesis

Bcl-2

Apoptosis

Invasion

PPARδ

Immuno-suppression

Proliferation

Angiogenesis

Apoptosis

Invasion

PPARδ

Immuno-suppression

Proliferation

Angiogenesis

Apoptosis

Invasion

PPARδ

Immuno-suppression

Proliferation

Angiogenesis

Apoptosis

Invasion

PPARδ

Immuno-suppression

Proliferation

Angiogenesis

Apoptosis

Invasion

PPARδ