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Role of prostaglandin E_2 in the progression of gastrointestinal cancer

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Abstract

Chronic inflammation is a well-established risk factor for several diseases, including cancer. It influences tumor cell biology and the type and density of immune cells in the tumor microenvironment (TME), promoting cancer development. While pro-inflammatory cytokines and chemokines modulate cancer development, emerging evidence has shown that prostaglandin E_2 (PGE_2) is a known mediator connecting chronic inflammation to cancerization. This review highlights recent advances in our understanding of how the elevation of PGE_2 production promotes gastrointestinal cancer initiation, progression, invasion, metastasis, and recurrence, including modulation of immune checkpoint signaling and the type and density of immune cells in the tumor/tissue microenvironment.

Keywords

Inflammation; PGE_2; colorectal cancer; gastric cancer; esophageal cancer; hepatocellular cancer; immune evasion; checkpoint inhibition

Introduction:

Inflammation is a complex process triggered by physical or chemical injury or an infectious or autoimmune disease involving numerous types of immune cells, cytokines, bioactive lipids, and chemokines. The inflammatory response is a defense mechanism needed to protect the organism from infection and injury and can be divided into at least two stages, acute and chronic. During acute inflammation, pathogens are eliminated from the host, resulting in tissue healing and repair of the affected site. In most cases, the outcome of this acute inflammation is self-limiting and resolves. However, the inability to achieve resolution leads to a continued, persistent, abnormal inflammatory state, which causes chronic

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inflammation. Chronic inflammatory processes are more indolent and prominent in auto-immune, neurodegenerative, vascular, and arthritic diseases. During chronic inflammation, the resident immune cells such as lymphocytes and macrophages continuously secrete proinflammatory cytokines and chemokines that chronically recruit, attract, and activate other immune cells (1). In the tumor microenvironment (TME), tumor cell biology is significantly influenced by surrounding fibroblasts, endothelial cells, immune cells, and mediators that they produce.

The immune system in the surrounding TME exhibits a critical influence in creating either a pro-tumorigenic or anti-tumorigenic niche, depending on the mix of cytokines, bioactive lipids, and chemokines present (2). Currently, terms such as “hot” tumors are used to describe TME with increased levels of T-cell infiltration and other components necessary for anti-tumor immunity. In contrast, “cold” tumors are described TMEs with less T-cell infiltration and with massive infiltration of immunosuppressive cells such as myeloid-derived suppressor cells (MDSC) and T regulatory cells (Tregs). While these terms are helpful for tumor characterization, they do little to explain the pro-tumorigenic immune response in cancers, which plays a critical role in the clinical outcome and has been termed “cancer-promoting inflammation”—distinct from acute and chronic forms of inflammation (3). Chronic or tumor-elicited inflammation can affect the TME resulting in tumor evasion, providing tumor-promoting signals that stimulate further tumor growth, progression, and metastatic spread (4).

Cyclooxygenase-1 (COX-1), officially named prostaglandin-endoperoxide synthase 1 (PTGS1), and cyclooxygenase-2 (COX-2), formally known as prostaglandin-endoperoxide synthase 2 (PTGS2), are enzymes that convert arachidonic acid into endoperoxide intermediates that are ultimately metabolized to prostaglandins, including PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 (prostacyclin), and thromboxane A2 (TXA_2) (1,5) (Figure 1). COX-1 is constitutively expressed in most tissues and is thought to provide basal levels of prostaglandins and thromboxanes for tissue homeostasis and platelet activation. By contrast, COX-2 is rarely expressed in healthy tissues but is highly induced in inflammatory sites and is overexpressed in certain cancers, particularly in over 85% of sporadic colorectal cancers (CRC) and 50% of colorectal adenomas (6–8). Elevated levels of COX-2 were also found in gastric cancer (GC) and esophageal cancer (EC) (9,10). The biological role of COX-2 in inflammation and cancer depends on which prostaglandins are produced in the affected tissue compartment. For example, PGE_2 is partly responsible for the cardinal signs of inflammation (1,5), and both PGE_2 and PGI_2 play critical roles in arthritis and inflammatory bowel diseases (IBD) (11). In addition, PGE_2 is the most abundant prostaglandin produced in CRC and GC (11). PGE_2 and PGI_2 were the main two prostanoids significantly increased in CRC (12). PGE_2 exerts cellular effects by binding to cell surface G-protein coupled receptors designated as PGE_2 receptors (EP1-EP4).

Elevation of PGE_2 in tumor tissues results from COX-2 and PGE_2 synthase induction and marked reduction of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) levels. 15-PGDH converts PGE_2 to an “inactive” 15-keto PGE_2 which is further metabolized to a stable end urinary PGE_2 metabolite (PGE-M). As 15-PGDH levels decrease substantially in GC, CRC, and EC (13–16), PGE-M may serve as a valuable biomarker for predicting cancer risk

and prognosis. Several studies have revealed that urinary PGE-M levels are significantly increased in CRC and GC and are associated with worse patient outcomes (17–19). The daily use of aspirin results in lower urinary PGE-M levels in healthy and cancer patients (20). Similarly, low-dose daily aspirin (100 mg per day for seven days) also led to a 46% decrease in PGE_2 levels in human colorectal mucosa (21).

In this review, we highlight the role of the COX-2-PGE_2 pathway in gastrointestinal (GI) cancers. We also explain why this pathway may serve as valuable targets for cancer prevention and treatment.

COX-2 and PGE_2 in gastrointestinal cancers:

Chronic inflammation is a well-known predisposing factor for various GI cancers. For instance, chronic viral infections such as hepatitis B or C viruses are strongly associated with hepatocellular carcinoma (HCC), and human papillomaviruses (HPV) are associated with a three-fold higher risk of esophageal squamous cell carcinoma (22,23). Importantly, it is well established that all cervical cancer and 70% of oropharyngeal cancers are caused by HPV. In addition, chronic bacterial infections such as *Helicobacter pylori* in the gastric fundus and pylorus result in increased risk and rates of GC (24). Interestingly, some changes in the gut microbiome leading to dysbiosis have been shown to increase the risk of CRC as well (25).

Furthermore, IBD caused by immune system dysfunction increases the risk for CRC (26). The observation that nonsteroidal anti-inflammatory drugs (NSAIDs) have beneficial effects on reducing the incidence, metastasis, and mortality of various solid tumors (11), including GI cancer, supports the concept that COX-2 derived prostaglandins promote cancer development because the anti-tumor effects of these agents are due, in part, to inhibition of cyclooxygenase (COX) activity. Indeed, COX-2 levels are associated with shortened survival in patients with CRC, GC, and EC (27–30). In addition, high COX-2 expression in HCC was strongly associated with decreased survival rates, enhanced lymphatic/vascular invasion, and advanced TNM stages (31).

Colorectal cancer

The effect of NSAIDs, including COX-2 selective inhibitors, on clinical outcomes has been extensively investigated in patients with CRC. In a prospective cohort study of 82,911 women over 20 years, sporadic CRC rates were shown to decrease significantly with regular, long-term NSAID use (32). A randomized controlled trial (RCT) supported the effect of sulindac on adenoma regression in FAP patients (33). In addition, an RCT revealed that treatment of a COX-2 selective inhibitor, celecoxib, significantly reduced polyp burden in FAP patients (34). In addition, three double-blind RCTs, including the Adenoma Prevention with celecoxib (APC), the Adenomatous polyp Prevention on Vioxx (APPROVe) trial, and the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trials, demonstrated significant reductions in adenoma recurrence following treatment with selective COX-2 inhibitors in patients with a history of sporadic CRC (35–37). Furthermore, several clinical trials revealed that short-term aspirin treatment minimized adenoma recurrence in patients

with a history of CRC (38–40). Another RCT showed a 24% decrease in CRC incidence and a 35% decrease in CRC mortality after 20 years of daily aspirin use (41).

Although the molecular mechanisms underlying the anti-tumor effects of NSAIDs, especially aspirin, have not been fully understood, compelling evidence demonstrates that these agents' inhibitory effects are partly due to the reduction of PGE_2 production by inhibiting COX-1 and COX-2. Indeed, cohort studies showed that regular aspirin use significantly reduced tumor recurrence in patients whose sporadic CRC expressed elevated levels of COX-2 (42), and its use after the diagnosis of CRC at stages I, II, and III improved overall survival, especially among individuals whose tumors overexpress COX-2 (43). However, a 2018 ASPREE trial showed that cancer-related mortality was 3.1% in the aspirin group compared to 2.3% in the placebo group (44) in a 5-year study. Since participants in the ASPREE had only been followed for a median of approximately five years, it has been noted that they will need to be studied for a more extended period to understand better the potential effect of aspirin on cancer diagnoses and deaths. Further studies are required to determine whether aspirin's impact on cancer in older adults is quite different from other-age adults.

Crohn's disease and ulcerative colitis predispose affected individuals to higher risk for CRC. Prolonged use of aminosalicylate in patients with ulcerative colitis has been shown to reduce CRC risk (45,46) significantly. Likewise, the use of etoricoxib in a double-blinded RCT study showed protection against CRC in IBD patients (45). Furthermore, a recent case-control study showed that long-term use of 5-aminosalicylate resulted in a dramatic reduction in CRC rates in IBD patients (46). However, there is ongoing concern about the chronic use of NSAIDs in patients with IBD, as this can cause disease flares that are sometimes quite severe.

Obesity is a risk factor for several comorbidities and cancer, and its association with CRC has been widely studied. Unlike IBD-associated CRC studies, obesity-associated CRC studies have been less conclusive regarding NSAID effects. An epidemiologic study recently demonstrated that long-term aspirin use resulted in lower colorectal adenoma recurrence rates in overweight individuals compared to normal-weight individuals (47). However, two prospective cohort studies demonstrated that the effect of aspirin on CRC risk is independent of the body mass index (48). Further studies are needed to determine whether aspirin reduces CRC risk in obese individuals.

Evidence of colorectal tumor promotion by PGE_2 was initially demonstrated in mouse models of sporadic CRC and FAP. PGE_2 treatment dramatically increased both small and large intestinal adenoma burden in $Apc^{Min/+}$ mice and significantly enhanced azoxymethane (AOM)-induced colon tumor incidence and multiplicity (49,50). PGE_2 also reverses the anti-tumor effects of NSAIDs in the $Apc^{Min/+}$ mouse model (51). Likewise, the elevation of endogenous PGE_2 by genetically deleting 15-PGDH increased tumor burden in $Apc^{Min/+}$ and AOM treated mice (52). In contrast, genetic deletion of microsomal PGE_2 synthase 1 (mPGES-1) in $Apc^{Min/+}$ and AOM mice decreased tumor formation in the small and large intestines (53). Moreover, one study revealed that loss of EP2 in $Apc^{\Delta 716}$ mice resulted in reduced intestinal tumor burden, while lack of EP1 and EP3 did not (54). Similarly,

deletion of EP1 or EP4, but not EP3, attenuates AOM-induced aberrant crypt foci (55,56). Interestingly, one report indicated that loss of EP3 promoted colon tumor development in AOM-treated mice (57). In addition, loss of EP2 in a colitis-associated CRC mouse model resulted in a decrease in colonic tumor formation, while loss of EP1 and EP3 increased tumor numbers (58). These studies concluded that the pro-tumorigenic effects of PGE_2 are mainly mediated through its activation of the EP2 and EP4 receptors and probably not EP1 or EP3.

PGE_2 binds to its receptors initiating intracellular signaling pathways that cause tumor-associated immunosuppression, angiogenesis, cell proliferation, migration, invasion, and survival (59,60) (Figure 2). For example, PGE_2 promotes intestinal adenoma formation and growth by silencing tumor suppressor genes via induction of DNA methyltransferases DNMT1/DNMT3B expression (61). In addition, PGE_2 promotes colonic cancer stem cell (CSC) formation and expansion by activation of NF-κB via the EP4-PI3K/MEK/MAPK pathway (62,63). A recent report showed that treatment of $Apc^{Min/+}$ mice with celecoxib reduces PD-L1 expression in premalignant adenomas accompanied by an influx of $CD8^+$ T cells (64). Moreover, another study showed that aspirin reduced tumor growth accompanied by reduction of PD-1 in $CD8^+$ T cells and macrophages via increasing pro-resolving mediators in a mouse model of colitis-associated tumorigenesis (65). An *in vitro* study revealed that the COX-2-PGE_2 pathway mediated the effect of bladder tumor cells on induction of PD-L1 in bone marrow-derived macrophages and MDSCs in a co-culture system (66). These PD-L1 positive cells were immunosuppressive (66). Moreover, PGE_2 also inhibited alveolar macrophage phagocytosis against bacteria (67). In addition, recent studies revealed that combined inhibition of PGE_2 signaling and PD-1 increased CTL proliferation *in vitro* (68), and EP4 antagonists enhanced antitumor efficacy of PD-1 in a syngeneic mouse model of CRC (69) and a mouse model of colitis-associated tumorigenesis (70).

Gastric cancer

Like CRC, population-based case-control and cohort have illustrated that regular and long-term use of NSAIDs, including aspirin, significantly decreased GC malignancy incidence and mortality (71,72). *In viv*o studies showed that simultaneous overexpression of both COX-2 and mPGES-1 in gastric cells was sufficient to induce hyperplastic gastric lesions (73), which progressed to tumors with simultaneous activation of Wnt signaling (74). The cooperative activation of Wnt and COX-2-PGE_2 pathways could induce $CD44^+$ slow-cycling tumor growth and expansion *in vivo* (75), indicating that PGE_2 enhances gastric CSC expansion. PGE_2 also promoted gastric tumor formation and growth by silencing tumor suppressor genes (i.e., MGMT and CNR1) via induction of DNMT3B expression *in vivo* (76). In addition, activation of the COX-2/PGE_2 pathway may induce IL-11, CXCL1, CXCL2, and CXCL5 expression in human and mouse gastric tumors (77) and modulate the type and density of immune cells in the tumor microenvironment.

Esophageal cancer

Esophageal cancer (EC) in the upper two-thirds of the esophagus is most commonly characterized by the presence of squamous cell carcinomas (SCC) that are usually due

to long-term alcohol and smoke exposure. In contrast, esophageal adenocarcinomas (EAC) in the lower one-third are generally associated with the metaplastic changes of Barrett's esophagus after prolonged gastroesophageal reflux disease (GERD) (78). These risk factors usually correlate with COX-2 elevation in these cancers (79). One meta-analysis study found that a particular COX-2 polymorphism is associated with the esophageal SCC and EAC formation in Asian populations, whereas another COX-2 polymorphism is only associated with EAC formation in Caucasian populations (80). Another recent meta-analysis revealed that aspirin use reduced incidence rates of both SCC and EAC (81). Two other studies showed that the use of aspirin and other COX-2 selective inhibitors reduced the risk of EAC (82,83). COX-2 is thought to drive Barret's esophagus (BE) and EAC formation by increasing TXA_2 (84). Interestingly, one study demonstrated that esophageal SCC patients with higher COX-2 levels in tumor tissues had lower response rates to neoadjuvant chemoradiotherapy (85).

An *in vivo* study revealed that treatment with a COX-2 inhibitor (JTE-522) significantly inhibited NMBA-induced esophageal SCC tumorigenesis (86). In addition, a selective COX-2 inhibitor attenuated GERD-induced esophagitis and BE and inhibited EAC formation accompanied by reduction of PGE_2 levels *in vivo* (87). In studies of a surgical mouse model of esophagoduodenostomy, aspirin has been shown to inhibit BE and EAC development (84). An *in vitro* study demonstrated that a novel quinoline derivative, 83b1, has anti-cancer effects on esophageal SCC cells accompanied by downregulation of COX-2 mRNA and PGE_2 (88).

Hepatocellular carcinoma

The influence of the COX-2-PGE_2 pathway on hepatocellular cancer (HCC) has become a topic of interest. COX-2 expression was elevated in HCC compared to normal tissues, and patients with high COX-2 expression in HCC tissues experienced a worse 5-year overall survival (31). Observational studies revealed that aspirin use significantly reduced the risk of HCC (89–91). One of these meta-analyses further showed that aspirin use improved liver-related mortality (91). Another that used aspirin or non-aspirin NSAIDs also reduced the risk of HCC recurrence (91). One randomized controlled trial showed that a COX-2 inhibitor significantly improved disease-free survival in liver patients without viral hepatitis after initial curative treatment (92), indicating that COX-2 inhibitors may prevent liver cancer recurrence.

Knockdown of COX-2 using RNAi reduced tumorigenicity in a xenograft model of HCCs accompanied by reduced PGE_2 levels and inhibited HCC cell proliferation *in vitro* (93). Multiple *in vitro* studies have demonstrated that the COX-2/PGE_2 axis regulates HCC cell proliferation, apoptosis, migration, invasion, and epithelial-mesenchymal transitions (EMTs) via various signaling pathways. For example, celecoxib was shown to inhibit HCC cell proliferation and induce HCC apoptosis (31). In the same study, celecoxib also suppressed HCC migration and invasion by inducing E-cadherin via targeting the COX-2-PGE2-EP2-Akt/ERK pathways (31). Another *in vitro* study revealed that a selective COX-2 inhibitor, meloxicam, inhibited HCC cell proliferation and migration, whereas PGE_2 reversed the effect of meloxicam on HCC cells via the β-catenin signaling pathway (94). Another *in*

vitro study indicated that TGFβ induced EMT in HCC via COX-2 and Akt pathways (95). Under hypoxic conditions, COX-2/PGE_2 induced HIF2α expression *in vitro* and *in vivo* (96). These pathways need to be evaluated further in spontaneous mouse models of liver cancer.

Summary:

The role of the COX-2-PGE_2 pathway in GI cancers, including CRC, GC, EC, and HCC, has been extensively investigated. Mounting evidence reveals that this pathway promotes GI tumor initiation, growth, progression, metastases by multiple signal pathways (Figure 3). Although long-term daily use of NSAIDs, including aspirin and COX-2 selective inhibitors, reduces the incidence and development of GI cancers, cardiovascular (except aspirin) and gastrointestinal side effects of NSAIDs have dampened enthusiasm for their use as chemopreventive agents. Targeting PGE_2 signaling at the EP receptor level alone may be efficacious in CRC prevention and treatment and avoid NSAIDs' unwanted side effects. Further studies are being undertaken to evaluate the efficacy of EP2 and EP4 antagonists in GI cancers, along with their long-term toxicities and impact on the immune system's ability to attack tumor cells directly. For example, one report showed that an EP4 antagonist (E7046) was safe in patients with advanced solid tumors, including GI cancers, in a phase I trial (97). Other clinical trials of EP antagonists are currently recruiting cancer patients (NCT04344795 and NCT03658772), and it will be essential to examine the safety profile once these studies have been completed. There is great interest in understanding the role of PGE_2 in modulating immune checkpoint signaling and the type and density of immune cells that reside in the tumor microenvironment. It has not escaped our attention that inhibitors of the PGE_2 signaling pathway, when combined with checkpoint inhibition, could help revert tumor cell immune evasion, enhance responsiveness to treatment, and possibly overcome resistance to therapy.

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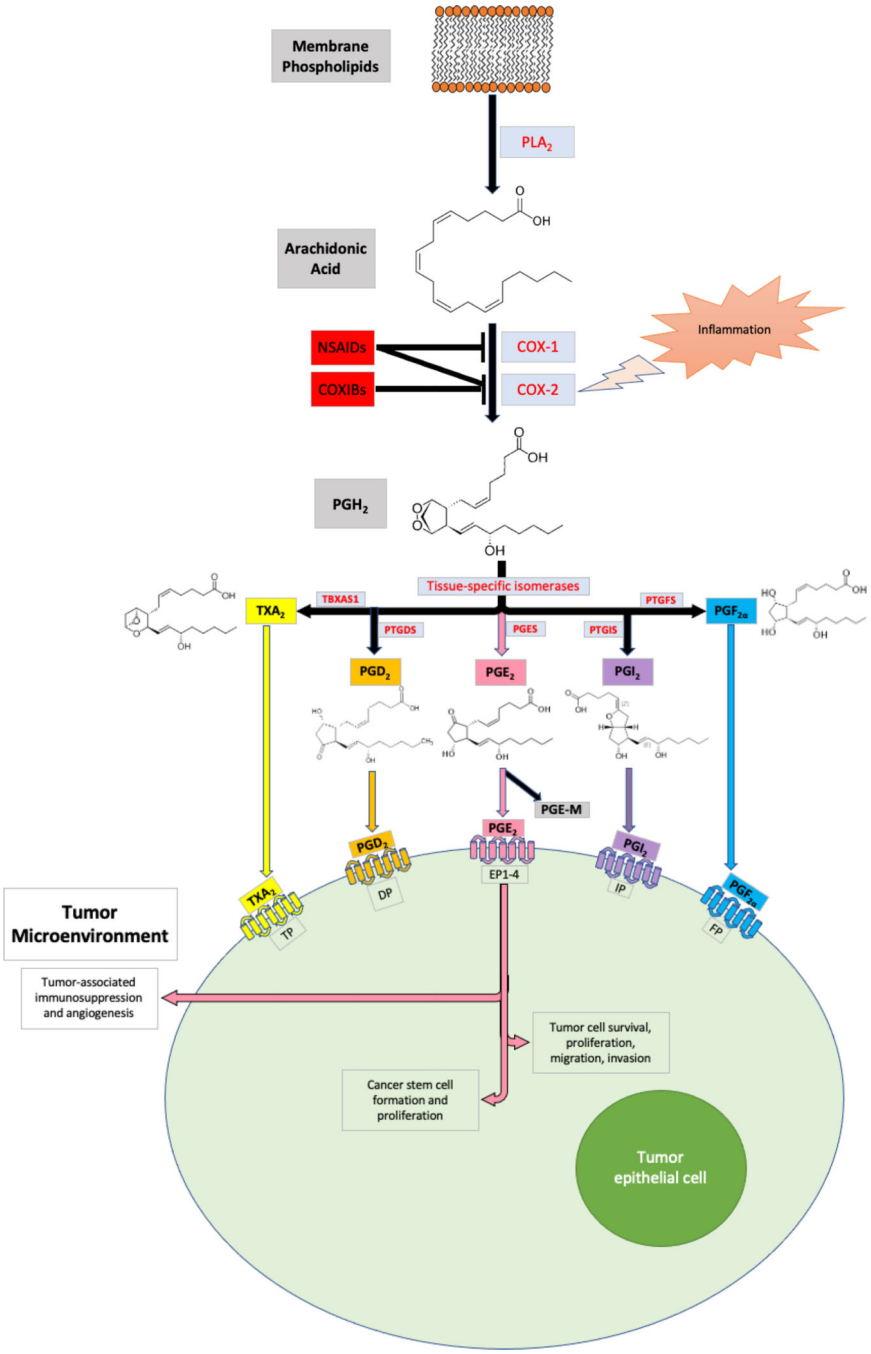

Figure 1. Prostanoid Synthesis Overview.

Free cellular AA is released after PLA_2-mediated conversion of membrane phospholipids. AA can be converted into PGH_2 via COX-1 and −2. COX-2 is upregulated only in inflamed tissues. Both COX-1 and −2 are inhibited by non-specific NSAIDs, whereas COXIB compounds may selectively target COX-2. PGH_2 may be converted into all five prostanoids via tissue-specific isomerases: TXA_2 by TBXAS1; PGD_2 by PTGDS; PGE_2 by PGES; PGI_2 by PTGIS; and $PGF_{2\alpha}$ by PTGFS. Each prostanoid may bind to its respective GPCR on the tumor epithelial cell to exert intracellular effects. Most notably, PGE_2 promotes cancer

development and progression through numerous mechanisms, as outlined by the text and figures 2 and 3.

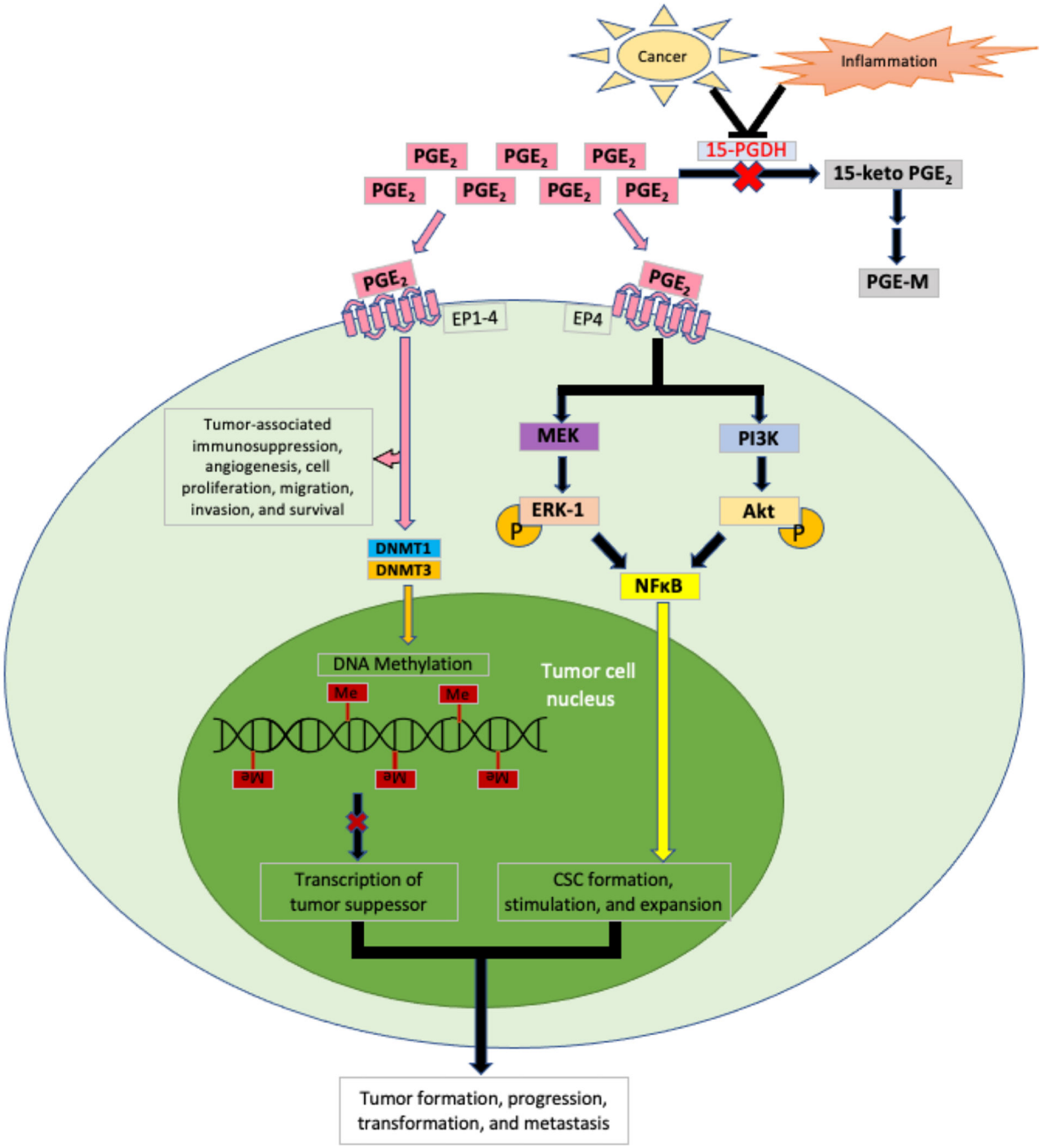

Figure 2. Regulation of tumor formation by PGE_2.

Acting through EP1–4, PGE_2 promotes tumor-associated immunosuppression, angiogenesis, and cell proliferation, as well as migration, invasion, and survival. In addition, it activates DNA methyltransferases (i.e., DNMT1/DNMT3B) to methylate and silence transcription tumor suppressor genes. Acting through EP4, PGE_2 promotes CSC formation, stimulation, and expansion via activation of NFκB through the MEK/MAPK and PI3K/AKT pathways. Overall, these processes enhance tumor formation, progression, transformation, and metastasis.

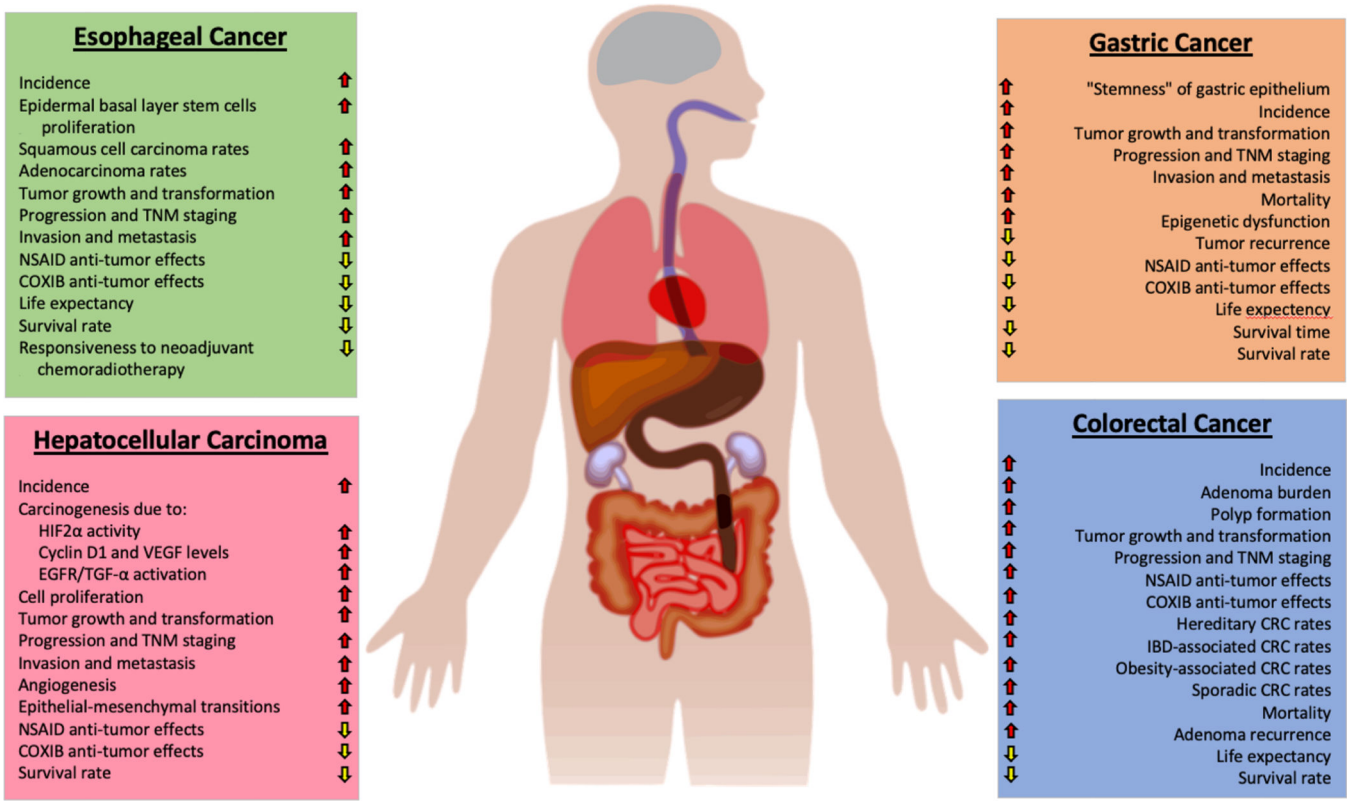

Figure 3. General effects of PGE_2 on four different gastrointestinal cancers.

PGE_2 can promote tumor initiation, progression, angiogenesis, transformation, metastasis, and recurrence in EC, GC, HCC, and CRC by activating numerous intracellular signaling pathways, as described in detail herein. In addition to blunting responsiveness to neoadjuvant chemoradiotherapy and NSAID/COXIB treatments, PGE_2 upregulation substantially worsens the overall prognosis. It also enhances epigenetic dysfunction due to DNA methylation of various tumor suppressor genes, as shown in Figure 2.