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Multifaceted roles of PGE_2 in inflammation and cancer[1]

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Abstract

Prostaglandin E_2 (PGE_2) is a bioactive lipid that elicits a wide range of biological effects associated with inflammation and cancer. PGE_2 exerts diverse effects on cell proliferation, apoptosis, angiogenesis, inflammation and immune surveillance. This review concentrates primarily on gastrointestinal cancers, where the actions of PGE_2 are most prominent, most likely due to the constant exposure to dietary and environmental insults and the intrinsic role of PGE_2 in tissue homeostasis. A discussion of recent efforts to elucidate the complex and interconnected pathways that link PGE_2 signaling with inflammation and cancer is provided, supported by the abundant literature showing a protective effect of NSAIDs and the therapeutic efficacy of targeting mPGES-1 or EP receptors for cancer prevention. However, suppressing PGE_2 formation as a means of providing chemoprotection against all cancers may not ultimately be tenable, undoubtedly the situation for patients with inflammatory bowel disease. Future studies to fully understand the complex role of PGE_2 in both inflammation and cancer will be required to develop novel strategies for cancer prevention that are both effective and safe.

Keywords

PGE_2; inflammation; gastrointestinal cancer; NSAIDs; COX-2; mPGES-1

1. Introduction and overview

Prostaglandin E_2 (PGE_2) is a bioactive lipid that can elicit a wide range of biological effects associated with inflammation and cancer. PGE_2 belongs to the prostanoid family of lipids, which is a subclass of eicosanoids produced by oxidation of 20-carbon essential fatty acids (EFAs) that are commonly incorporated within membrane phospholipids. Prostanoids including PGE_2, $PGF_2\alpha$, PGD_2, PGI_2 and thromboxane A_2 (TXA_2) are synthesized by the sequential actions of a panel of highly specific enzymes. Their synthesis is initiated by phospholipases (PLAs), a family of enzymes that catalyze the hydrolysis of membrane phospholipids at the sn-2 position, liberating free fatty acids, including arachidonic acid (AA), from membrane lipids. PLA_2s are grouped according to their structure and enzymatic characteristics, and are comprised of both secretory and intracellular forms. $cPLA_2\alpha$ is the best characterized isoform and the only one that is regulated by Ca^{2+} binding and phosphorylation by mitogen-activated protein kinase (MAPK). In addition, its expression is altered in cancer cells, suggesting an important role in disease development [1–3].

Membrane-released AA is rapidly oxidized into the relatively unstable metabolite, PGG_2, which is subsequently reduced to PGH_2, both steps sequentially catalyzed by the

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cyclooxygenase (COXs) enzymes. There are two major COX isoforms; COX-1 is constitutively active and present within most cells in the body, whereas constitutive COX-2 expression is largely restricted to the kidney as well as areas of the central nervous system. However, COX-2 levels are highly inducible in many tissues by pro-inflammatory and mitogenic stimuli, including cytokines and growth factors [4]. Once synthesized, PGH_2 is rapidly converted into prostanoids by a panel of terminal synthases. The metabolic steps in the formation of the PGs are summarized in Figure 1.

Three distinct synthases contribute to PGE_2 synthesis [5–7]. These terminal synthases are comprised of three isoforms that are tightly regulated under various conditions and include microsomal PGE synthase-1 (mPGES-1), mPGES-2 and cytosolic PGE synthase (cPGES) [8]. mPGES-1 is frequently induced concomitantly with COX-2 by various pro-inflammatory stimuli to generate a transient spike in PGE_2 levels [9]. On the other hand, mPGES-2 and cPGES are constitutively expressed and functionally coupled with COX-1 to maintain basal levels of PGE_2 [9]. While mPGES-1 is glutathione (GSH)-dependent, mPGES-2 and cPGES do not require co-factors for their biosynthetic activity [8].

The levels of PGE_2 can also be regulated by its metabolic turnover. The activation of two key catabolic enzymes, 15-hydroxyprostaglandin dehydrogenase (15-PGDH) and 15-keto-prostaglandin- 13-reductase (13-PGR) can essentially eliminate the biological activity of PGE_2 [10]. In particular, 15-PGDH may play a prominent role in colon carcinogenesis; in many human colorectal cancer (CRC), there is a significant reduction in the expression of 15-PGDH, suggesting a likely tumor suppressor role for this protein [11–13]. Under some conditions, 15-PGDH expression can be directly activated by TGF-β signaling [11]. Importantly, using a mouse knockout model, the Markowitz laboratory [14] has identified a role for 15-PGDH in the resistance that may develop to celecoxib during chemoprevention treatment of colon tumors. Consistent with these findings in the mouse, Yan *et al.* [14] also reported that human subjects who develop new adenomas during the course of celecoxib treatment had very low levels of 15-PGDH expression. Further mechanistic studies showed that the absence of 15-PGDH activity significantly increased intestinal tumorigenesis in Apc^{Min} mice and sensitized normally resistant C57BL/6J mice to azoxymethane (AOM) induced colon carcinogenesis [15]. Finally, Backlund *et al.* [16] examined the epigenetic regulation of 15-PGDH by histone deacetylases and reported that HDACs interact with Snail at the 15-PGDH promoter, contributing to its repression. Interestingly, treatment of colon cancer cells with HDAC inhibitors such as sodium butyrate and valproic acid can reactivate its gene expression [16]. Overall, these findings in animal models and human tissues reinforce the central role of PGE_2 in colon cancer development.

The physiological activity of PGE_2 and related prostanoids are mediated by the activation of a diverse group of downstream signaling cascades *via* seven transmembrane G-protein coupled receptors (GPCR), referred to as the EP, FP, DP, IP and TP receptors [17]. These receptors are highly selective for individual prostanoid substrates, including PGE_2 $PGF_2\alpha$, PGD_2, PGI_2 and TxA_2, respectively [17]. Each receptor has a cell type-specific expression pattern that enables tight control over their distinct but occasionally overlapping physiological functions [5]. PGE_2 binds to members of the EP family of receptors that consist of four isoforms (EP1-4) and play a major role during inflammation [5]. The EP receptors are coupled to Gα proteins that contain stimulatory ($G\alpha_S$) or inhibitory ($G\alpha_i$) subunits that can modulate the levels of Ca^{2+}, cyclic AMP (cAMP) and inositol phosphate, activating divergent downstream signaling pathways [18]. EP receptors are ubiquitously expressed within most organ systems. Coupled with the ubiquitous formation of PGE_2, EP receptor signaling accounts for the pleiotropic ability of PGE_2 to potently activate diverse biological effects, including cell proliferation, apoptosis, angiogenesis, inflammation and immune surveillance in different cell types within a wide range of tissues [7, 19, 20].

In this review, we focus on the role of PGE_2 in inflammation and cancer. PGE_2 clearly provides a pivotal connection between a number of chronic inflammatory signaling cascades and cancer pathogenesis. We will concentrate primarily on gastrointestinal (GI) cancers, where the actions of PGE_2 are most prominent, most likely due to the constant exposure to dietary and environmental insults and the intrinsic role of PGE_2 in tissue homeostasis. We will provide an overview of recent efforts to elucidate the complex and interconnected pathways that link PGE_2 signaling, inflammation and cancer.

2. Multifaceted roles of PGE_2 in inflammation

The inflammatory response is comprised of a finely orchestrated set of interconnected processes, involving a diversity of cell types and inflammatory mediators. PGE_2 plays a critical role in guiding and governing various aspects of the inflammatory response. The role of PGE_2 in driving acute inflammation is well established. However, PGE_2 also elicits powerful immunosuppressive properties that contribute to the resolution phase of acute inflammation, facilitating tissue regeneration and the return to homeostasis. These multifaceted properties of PGE_2 are both cell type and context specific. A number of comprehensive reviews focused on the regulation of the immune response by PGE_2 are available [21, 22]. In this section, we provide a brief overview of how PGE_2 impacts the inflammatory response and discuss more recent data concerning how PGE_2 intimately links chronic inflammation with cancer.

Pro-inflammatory effects of PGE_2

During the initial phase of the inflammatory response, PGE_2 and related prostanoids such as PGI_2, act as vasodilators to facilitate the tissue influx of neutrophils, macrophages and mast cells from the bloodstream leading to swelling and edema at the site of infection or tissue injury [23]. Furthermore, PGE_2 stimulates sensory nerves to increase the pain response and acts on neurons in the preoptic area to promote pyrogenic effects [23]. The contribution of PGE_2 to inflammation has been evaluated in a number of disease models, which has been facilitated by the generation of the mPGES-1 knockout (KO) mouse [24]. The mPGES-1 KO mice are generally protected against a variety of inflammatory disease phenotypes, including collagen-induced arthritis, LPS-induced bone loss and antigen-induced paw edema (reviewed by [25]). In a study employing a collagen-induced arthritis model, reduced inflammation in the mPGES-1 KO mice was associated with a failure to produce antibody against type II collagen, suggesting a role for mPGES-1 in the development of a humoral immune response [26]. Moreover, mPGES-1 KO mice displayed significantly reduced accumulation of exudate and impaired leukocyte migration into the pleural cavity during carrageenan-induced paw edema formation, confirming earlier observations that PGE_2 regulates vascular permeability during acute inflammation [25]. It is important to note that genetic deletion of mPGES-1 in mice does not adversely affect cardiovascular function (reviewed by [27]). Furthermore, mPGES-1 deletion increases tissue levels of PGI_2, which may compensate for the suppression of PGE_2 synthesis [27]. These results in pre-clinical mouse models strongly suggest the possibility that pharmacologic targeting of mPGES-1 may ultimately prove to less toxic and perhaps more effective than the traditional non-steroidal anti-inflammatory drugs (NSAIDs) for controlling acute inflammatory diseases. New drug candidates that have recently been developed for targeting mPGES-1 are discussed later in this review.

An additional pro-inflammatory effect of PGE_2 has recently been underscore by its role in promoting the activation of T_H17 cells, a subset of $CD4^+$ helper T cells that are characterized by the production of interleukin-17 (IL-17). The IL-17 family of cytokines represents a potent set of pro-inflammatory mediators that recruit monocytes and neutrophils to the site of inflammation. This has been shown to occur during the course of disease

progression in several models of autoimmunity and infection (reviewed by [28]). The maturation and activation of T_H17 cells is initiated by the binding of IL-23 to its receptor, IL-23R, present on naïve $CD4^+$ T cells, which subsequently drives the expression of the retinoic acid receptor-related orphan receptor (ROR)- t that is required for the production of IL-17 [29]. PGE_2 induces both the production of IL-23 in dendritic cells (DCs) *via* EP4 receptor signaling, and also promotes the expression of the IL-23R in naïve $CD4^+$ T cells *via* the EP2/EP4 receptors [30]. PGE_2-mediated production of IL-17 has been shown to contribute to the development of a variety of inflammatory diseases, including collagen-induced arthritis and inflammatory bowel disease (IBD) in mice [31, 32].

Anti-inflammatory activities of PGE_2

Somewhat paradoxically, PGE_2 also exerts control over a number of mechanisms that lead to the resolution of inflammation and subsequent tissue repair. Indeed, pharmacological inhibition of COX-2 during the latter phases of an inflammatory response has been shown to interfere with complete tissue recovery in the liver, lung and colon [33–36]. Among the large group of prostanoid metabolites that have been studied, PGD_2 and its metabolite PGJ_2 have received considerable interest regarding their potent anti-inflammatory properties. However, PGE_2 has also been clearly established as a key component of anti-inflammatory processes [37]. PGE_2-mediated immunosuppressive activities are associated in part with the expression of specific cytokines and chemokines, as well as their cognate receptors present on immune, stromal and epithelial cells. One important effect of PGE_2 is its ability to directly inhibit the synthesis of IL-2 and the expression of the IL-2 receptor in T cells. As reviewed by Kalinski [21], the suppression of IL-2 signaling contributes to the inhibition of effector T cell proliferation and activation. Moreover, PGE_2 suppresses the cytotoxic activities of natural killer (NK) cells, -T cells and $CD8^+$ cytotoxic T lymphocytes (CTLs), in part by down-regulating cytokine receptor expression [38–41].

In monocytes and DCs, PGE_2 has an inhibitory effect on the production of CCL19, a key chemokine for attracting naïve T cells, which interferes with the activation of effector T cells [42]. Moreover, PGE_2 has been shown to suppress the formation of an additional T cell stimulating factor, IL-12, and to induce IL-12p40 expression, a competitive inhibitor of the IL-12 receptor [21]. Most importantly, the suppression of IL-2 by PGE_2 promotes a change in the immune response from a T_H1 to a T_H2 response [43, 44]. The T_H1-type response promotes cellular immunity by stimulating the production of interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), which enhances the cytotoxic activities of macrophages and CTLs. On the other hand, the T_H2-type response is generally less tissue-destructive with cytokine profiles featuring IL-4 and IL-13.

Role of PGE_2 in the wound repair process

The T_H-type switch highlights the critical role of PGE_2 in the process of tissue repair, the final phase of the inflammatory response. As noted by Allen *et al.* [45], T_H2-type cytokines have been postulated to promote localized wound healing by enhancing M2-type macrophage activity that facilitates the production of proteins associated with accelerated tissue repair. The direct involvement of PGE_2 in wound healing has been demonstrated by Ae *et al.* [46], where mPGES-1 deficient mice exhibit delayed healing following acetic acid-induced gastric ulceration. Furthermore, the absence of inducible mPGES-1 caused an enhanced sensitivity to dextran sodium sulfate (DSS) treatment, with the development of a more severe ulcerative colitis phenotype in the KOs compared to wild-type mice [25]. A similar exacerbation of intestinal injury and ulceration has been found in EP4-deficient mice following exposure to DSS [47]. In our laboratory, we recently reported the presence of spontaneous, localized colonic ulcerations in strain A mice harboring a genetic deletion of mPGES-1 [48]. The presence of this spontaneous tissue damage provides direct evidence for

the role of inducible PGE_2 synthesis in mucosal homeostasis [48]. In addition, we have found that mPGES-1 KO mice display impaired tissue recovery in response to DSS-induced mucosal injury (unpublished results), underscoring the critical role of inducible PGE_2 synthesis in epithelial repair.

Epithelial cells play a key role in maintaining mucosal homeostasis within the gut, a tissue that is under a constant threat of inflammatory insult. Following acute injury, the tissue repair process is orchestrated by a plethora of mediators produced by a variety of cell types [49]. The inducible formation of PGE_2 is critical for maintaining epithelial barrier function within the GI tract, especially under conditions of increased stress [50]. PGE_2 has been shown to play an essential role in epithelial regeneration and reconstitution following tissue injury [51]. As part of the mechanism of tissue repair, PGE_2 directly induces epithelial cell proliferation *via* the activation of several key signaling pathways, including PI3K/Akt and the Wnt cascade [52]. In addition, PGE_2 can activate the MAPK and JNK pathways *via* transactivation of epidermal growth factor receptor (EGFR) [53]. The potent growth promoting effects of PGE_2 are discussed in detail below under 'The role of PGE_2 in cancer'.

Stromal cells also play an important role in intestinal tissue homeostasis and repair, and PGE_2 can directly affect several of these critical cellular processes. For example, recent studies have shown that PGE_2 can stimulate the expression of vascular endothelial growth factor (VEGF) in lung and stomach fibroblasts, promoting angiogenesis [54, 55]. Additional evidence for the pro-angiogenic effects of PGE_2 was demonstrated by Zhang *et al.* [56], in which PGE_2 induced *in vitro* tube formation of human microvascular endothelial cells, *ex vivo* vessel outgrowth of aortic rings and an angiogenic response *via* EP4-PKA signaling. The PGE_2-EP4 axis has also been shown to control the differentiation of endothelial cells from bone marrow-derived cells *via* the activation of AMP-activated protein kinase (AMPK) [57]. In addition, PGE_2 can affect endothelial cell migration *via* activation of the ERK signaling pathway [58].

Myofibroblasts represent a population of differentiated mesenchymal cells residing within the stroma that contribute to the coordination of tissue regeneration by secreting TGF- , epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), pro-inflammatory cytokines, and basement membrane components [59]. PGE_2 has been shown to inhibit myofibroblast differentiation and limit their collagen secretion during pulmonary fibrosis [60], in lung allografts [61] and in bleomycin-induced skin fibrosis [62]. Although the inhibitory effects of PGE_2 on myofibroblasts are protective against excessive fibrotic scar formation in the lung and skin, PGE_2 may elicit distinct effects at other sites of tissue injury. For example, Iwanage *et al.* [63] have recently shown that EP2/3/4 receptor signaling can induce the migration of intestinal sub-epithelial myofibroblasts (ISMFs) during wound closure. Moreover, PGE_2 is also capable of promoting the proliferation of cardiac fibroblasts *via* EP1/EP3 signaling [64], and inducing liver contraction *via* activation of the EP3 and FP receptors [65].

In summary, the results of these studies highlight the complex and context-dependent role of PGE_2 in contributing to epithelial homeostasis and wound healing.

3. The role of PGE_2 in cancer

Within the context of cancer, PGE_2 is generally considered to possess potent tumor-promoting activity. This inference is based on a substantial body of evidence obtained from rodent studies, as well as several decades of clinical research on the effects of NSAIDs on cancer risk [66]. In several early case-report studies, Waddell and Loughry [67, 68] showed that treatment of a small number of Gardner's syndrome patients with sulindac resulted in an almost complete regression of polyps. Epidemiological studies also demonstrated that

regular NSAID use was associated with a 50 percent reduction in risk for colon and rectal cancers [69]. In a large prospective study by Thun et al. [70], regular aspirin use at low doses was associated with a significantly reduced risk of fatal colon cancer.

The protective effects of aspirin and other NSAIDs on tumor formation are most likely due to inhibition of the COX enzymes with reduced synthesis of the prostanoid metabolites, specifically PGE_2. A direct role for PGE_2 in tumorigenesis has been demonstrated in a number of animal models as well as in *in vitro* studies. These studies are summarized in Table 1. For example, Kawamori *et al.* [71] showed that weekly *i.p.* administration of PGE_2 significantly increased the incidence and multiplicity of intestinal adenomas in F344 rats. In a subsequent mechanistic study, the Dubois laboratory [72] showed that gavage treatment of Apc^{Min} mice with PGE_2 increased epithelial cell proliferation and COX-2 expression, effects that were mediated in part by the activation of the Ras-MAPK signaling cascade. In striking contrast to these studies, administration of the stable PGE_2 analogue, 16,16-dimethyl-PGE_2, for 8 weeks to Apc^{Min} mice resulted in a surprising decrease in the size and number of tumors throughout the intestine, prompting speculation that PGE_2 may also have tumor suppressive properties [73]. Tumor suppression occurred despite increased in cell turnover demonstrated by elevated thymidine incorporation. While intriguing, these latter findings have not been reproduced by other laboratories, raising the possibility that the effect may have been environmentally influenced or perhaps the result of genetic changes occurring within the Apc^{Min} mouse colony under study.

Further evidence supporting a role for PGE_2 in tumor promotion comes from recent studies focused on mPGES-1, the terminal synthase in the formation of inducible PGE_2. Our laboratory has recently shown that genetic deletion of mPGES-1 reduces the synthesis of inducible PGE_2 and markedly suppresses (up to 70%) intestinal tumor formation in $Apc^{\Delta 14}$ mice [74]. Although neither cell turnover nor β-catenin expression was significantly affected by mPGES-1 status, the potent tumor suppressive properties are associated with impaired neovessel formation within the adenomas, consistent with a previous study of human CRC [75]. In a follow-up study to test the possibility that the potent tumor suppression in the small intestine may be extended to the colon, Nakanishi *et al.* [48, 74] backcrossed the mPGES-1 gene KO onto strain A mice that are exquisitely sensitive to colon tumorigenesis by AOM [76–78]. Consistent with the previous study in $Apc^{\Delta 14}$ mice, genetic deletion of mPGES-1 resulted in an even more dramatic (~95%) suppression in tumor size within the distal colon [48]. A role for PGE_2 in cancer has been demonstrated in other organ systems as well. For example, over-expression of COX-2 in mammary tissue by the transgenic mammary tumor virus (MMTV) was sufficient to induce breast cancer development, which was reportedly dependent on PGE_2-EP2 receptor signaling [79]. Further support for mammary tumor promotion by COX-2 was elegantly demonstrated by Smyth and colleagues [80] using mice that lack COX-2 expression selectively within mammary epithelial cells. Interestingly, breast carcinogenesis induced by medroxyprogesterone acetate and dimethylbenzanthracene (DMBA) was markedly reduced in these mice, an effect that was accompanied by a shift towards an anti-tumorigenic T_H1 type immune response [80], a finding that illustrates the complex role that PGE_2 can play in cancer promotion. In a model for gastric cancer, Oshima *et al.* [81] generated *K19-C2mE* transgenic mice that express both COX-2 and mPGES-1 in gastric epithelial cells. The *K19-C2mE* mice develop hyperplastic lesions with mucous cells in the glandular stomach, similar to *H. pylori*-induced precancerous lesions [81]. Interestingly, when the *K19-C2mE* mice were further engineered to express proteins that induce gastric epithelial cell proliferation (Wnt1 or Noggin), the compound mutant mice developed gastric adenocarcinomas [82, 83]. These observations demonstrate that gastric epithelial cells transformed by alterations in Wnt or Noggin signaling can be further driven to develop tumors in the presence of elevated levels of PGE_2, an outcome that may be induced by co-infection of mice with *H. pylori*. [84].

4. PGE_2 receptor-mediated signaling and cancer

In combination with stimulation of PGE_2 formation, EP receptors are aberrantly expressed in multiple GI cancers. In CRC, for example, EP4 is the most abundantly expressed subtype of the EP receptors, and its levels are often up-regulated during colon carcinogenesis. This was initially shown experimentally in mice by Mutoh *et al.* [85], and then in human colon cancer cell lines by Chell *et al.* [86] and later confirmed [87]. As recently demonstrated by Chandramouli *et al.* [88], EP4 is negatively regulated in human cancer cells by miR-101, a microRNA that also inhibits COX-2 expression, raising the possibility that EP4 may ultimately provide a viable chemoprevention target. To assess the functional role of the specific EP receptor subtypes in intestinal cancer, a series of studies using genetic mouse models were performed more than a decade ago. In the first study of its kind, Watanabe *et al.* [89] examined the role of EP1 and EP3 in colon carcinogenesis. The formation of carcinogen-induced colonic aberrant crypt foci (ACF) was reduced by ~ 60%, an effect that occurred only in the EP1 KO mice. On the other hand, the EP3 receptor may play an important role in later stages of colon carcinogenesis. As observed by Shoji *et al.* [90], EP3 expression was significantly reduced within the AOM-induced tumors and there was an increase in tumor incidence and multiplicity in EP3-deficient mice. Interestingly, treatment of colon cancer cells with 5-aza-2'-deoxycytidine (5-aza-dC) restored EP3 receptor expression, providing evidence that aberrant DNA methylation may contribute to the down-regulation of EP3 expression in colon cancer cells [90]. In line with this observation, Xia *et al.* [91] have recently demonstrated in both *in vitro* and *in vivo* models that PGE_2 promotes intestinal tumor growth by altering the expression of certain tumor-suppressor and DNA repair genes via epigenetic silencing. Exact mechanisms by which PGE_2 affects DNA methylation must be further addressed in future studies.

In an important study by the Taketo laboratory [92], additional proof for the key role of the EP2 receptor in small intestinal tumorigenesis was obtained. Homozygous deletion of the EP2 receptor in $Apc^{\Delta 716}$ compound mutant mice resulted in significant protection against intestinal cancer (tumor size and numbers), an effect that partially phenocopied the COX-2 KO mouse model. Genetic deletion of EP1 and EP3 were only slightly protective, whereas perhaps surprisingly, no protection was afforded to the intestine by the genetic deletion of the EP4 receptor. It was further proposed that increased cellular cAMP levels involving PGE_2–EP2 receptor signaling amplified the actions of COX-2, possibly activating the expression of VEGF within the tumor microenvironment. Finally, the Wakabayashi laboratory [85] further assessed the role of the prostanoid receptors in colon carcinogenesis using six KO mouse lines (EP2, EP4, DP, FP, IP and TP). After treatment with AOM, ACF formation was suppressed only in the EP4 KO mice to levels that were 56% of wild-type controls. The lack of protection afforded by genetic deletion of the EP2 receptor was surprising, based on the previous findings in $Apc^{\Delta 716}$ mice. This may be a result of tissue-specific actions of the EP receptors within different regions of the intestinal epithelium, or perhaps underlying differences in the initiating events that drive cancer in these two mouse models.

Several recent studies have addressed the potential role of the COX-2-PGE_2-EP signaling axis in other GI cancers. A recent study by Jimenez *et al.* [93] examined human esophageal cancers and found elevated levels of COX-2 and EP2 during the course of disease progression from Barrett's metaplasia to intra-epithelial neoplasia, and finally to adenocarcinoma formation. While the expression of the EP4 receptor was increased in esophageal adenocarcinomas, the expression levels of COX-1 and the EP3 receptor were actually decreased during disease progression. In a liver cancer cell line (HepG2), treatment with the EP1 receptor agonist, ONO-DI-004, increased their viability and migration [94]. This effect was reversed by the EP1 receptor antagonist, ONO-8711, as well as by treatment

with epigallocatechin gallate (EGCG), suggesting a novel mechanism for the chemopreventive efficacy of EGCG within the context of PGE_2 signaling. It is important to note that EP receptors exhibit highly tissue-specific functional activities. For example, EP3 has been shown to induce matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF) expression in Lewis lung carcinoma (LLC) cells, suggesting its involvement in angiogenesis and tumor metastasis [95].

EP receptor agonist and antagonist studies

In addition to the aforementioned genetic studies related to EP receptor functional activity and their impact on GI cancers, several pharmacological studies using EP receptor agonists and antagonists have also been conducted. In one of the earliest studies, administration of the selective EP1 receptor antagonist, ONO-8711, caused a dose-dependent suppression of colon ACF in response to AOM treatment [89]. The protection was extended to Apc^{Min} mice given 500 ppm ONO-8711 in the diet. Mutoh *et al.* [85] used an EP4-selective antagonist, ONO-AE2-227, to confirm the protection against AOM-induced ACF reported in the EP4 KO mice. A dose of 400 ppm ONO-AE2-227 moderately reduced the numbers of ACF, as well as the number of intestinal polyps in Apc^{Min} mice by 31% [85]. The overall reduction in ACF numbers, however, was somewhat disappointing, especially in light of the fact that the drug regimen was initiated at the start of AOM treatment and was maintained throughout the entire experimental period. Perhaps the modest response is related to pharmacokinetic factors that need to be optimized.

5. The contribution of PGE_2 to the tumor microenvironment

The tumor microenvironment is comprised of a complex array of cells, extracellular matrix (ECM) components and signaling molecules. The tumor microenvironment is established by the altered communication between stromal and epithelial cells through growth factors, cytokines and chemokines [96]. As tumors expand in size, they increasingly elicit diverse factors that can alter the host immune response, in part by exploiting the immuno-modulatory properties of PGE_2. For example, Holt *et al.* [97] have shown that in tumor-bearing mice, PGE_2 suppresses the cytotoxicity and cytokine production of natural killer (NK) cells *via* EP4 signaling. Furthermore, the polarization of tumor-associated macrophages (TAMs) towards tumor-promoting M2 macrophages is also influenced by PGE_2 in lung carcinoma cells [98]. Interestingly, Liu *et al.* [98] also reported that IL-17 is important in recruiting macrophages to the tumor microenvironment prior to their polarization, demonstrating a cooperative effect between IL-17 and PGE_2.

Fibroblasts, especially the myofibroblast cells, play a major role in the tumor microenvironment by providing oncogenic signals to facilitate tumorigenic events, including angiogenesis, cell migration and invasion [96]. However, the direct effects of PGE_2 on myofibroblasts have not yet been clearly defined. The interaction of PGE_2 with myofibroblasts appears to be context- and tissue-specific, especially during the wound-healing process (described above). Using transgenic mice that overexpress COX-2, PGE_2 and Wnt1 in stomach, Guo *et al.* [55] have shown that myofibroblasts associated with gastric tumors express high levels of the angiogenic factor, VEGF-A, suggesting a positive effect of PGE_2 signaling on a key function of myofibroblasts. However, VEGF-A expression was found to be regulated by other tumor-derived factors, suggesting that PGE_2 may not contribute a direct role in this angiogenic process [55]. Regardless, additional studies are warranted that may more clearly define the role of PGE_2 with respect to myofibroblasts.

Cancer-associated stromal reactions that contribute to the evasion of host-related immune response are the regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). The accumulation of these potent immunosuppressive cells in tumors has been well-

documented both in patients and in experimental animal models [99–101]. As reviewed by Fehervari and Sakaguchi [102], the primary role of the Tregs and MDSCs is to suppress the immune response by inducing T cell anergy and by restraining CTL proliferation and functional activity. PGE_2 plays a critical role in controlling anti-tumor immunity in part by regulating the activation and expansion of both the Tregs and MDSC.

During the past decade, a number of studies have shown that PGE_2 can modulate the proliferative capacity and effector functions of Tregs. Baratelli *et al.* [103] were the first to report that PGE_2, derived from the supernatants of lung cancer cells, can potently induce Foxp3 expression in naïve T cells, a transcription factor that is necessary for the development of Treg-associated immunosuppressive properties. Additionally, Sharma *et al.* [104] showed that tumor-reactive T cells accumulate in lung cancer tissue, but frequently fail to respond effectively to the tumor because of the large proportion of immunosuppressive Tregs that are present within the microenvironment. This study showed that PGE_2 alone was capable of inducing Foxp3 expression *in vitro*, and importantly, they further demonstrated that treatment of mice with PGE_2 increased Foxp3 expression in splenocytes [104]. In addition, COX-2 KO mice showed a reduced activity of Tregs and suppressed the growth of tumors *in vivo* [104]. In gastric cancers, Yuan *et al.* [105] showed that elevated Foxp3 levels in tumor infiltrating Tregs can suppress T-cell function via a Cox-2/PGE_2 mediated mechanism. In patients with prostate cancer, Tregs in the peripheral blood had much greater suppressive activity in comparison to Tregs harvested from healthy donors [106]. Importantly, there was a direct correlation between serum PGE_2 levels and Treg functionality in the prostate cancer patients. Lee *et al.* [107] showed that celecoxib treatment of tumor-bearing mice harboring Lewis lung (3LL) carcinomas had reduced levels of Tregs, as well as reduced expression of COX-2, indoleamine 2,3-dioxygenase (IDO) and Foxp3, a finding that was correlated with suppressed tumor growth and metastasis. These findings prompted the speculation that COX-2 inhibitors might provide a useful therapeutic strategy for overcoming Treg-induced tumor immune tolerance. In a more recent study, Mandapathil *et al.* [108] concluded that targeting COX-2 activity in combination with adenosine might provide a novel approach for improving the outcome of immune-based cancer therapies by suppressing adaptive Tregs (Tr1) cells. A study by Soontrape *et al.* [109] recently demonstrated that PGE_2 signaling, in collaboration with other immunosuppressive mediators, increases the number of $Foxp3^+$ Tregs as a consequence of EP4 receptor signaling occurring during UV-induced immunosuppression. A novel mechanism has been described by Pinchuk *et al.* [110], in which colonic myofibroblasts induce the expansion of Foxp3-expressing Tregs through both cell-contact–mediated interactions (MHC class II-TCR signaling) and stimulation of PGE_2 formation.

As discussed above, our laboratory recently examined the impact of inducible PGE_2 synthesis on colon carcinogenesis. Despite the dramatic tumor suppression associated with mPGES-1 deletion, it was also found that mPGES-1 KO mice develop spontaneous, localized colonic ulcerations within 10 weeks of age [48]. We further investigated the immunoregulatory mechanisms that may underlie this mucosal inflammation in the mPGES-1 KO mice, focusing on CD4-Foxp3 double-positive cells. Despite the active, ongoing inflammation that is present within the colon, the levels of Tregs within the mesenteric lymph nodes of the mPGES-1 KO mice were reduced by almost 50% compared to the control mice. Importantly, this effect was not systemic as the population of Tregs within the spleen was unaffected by the mPGES-1 genotype. These results highlight the importance of inducible PGE_2 formation in the expansion of Tregs *in vivo* and emphasize the critical role of inducible mPGES-1 in mediating this tumor promoting effect [48].

PGE_2 may also dampen anti-tumor immunity by triggering the functional activation of MDSC. As extensively reviewed [111, 112], MDSC represent a subgroup of immature

myeloid cells that are comprised of hematopoietic progenitor cells as well as precursors of macrophages, dendritic cells, and granulocytes. A component of normal hematopoiesis, MDSC numbers can greatly expand under a variety of pathological conditions, including cancer [113]. Upon their expansion, MDSC exert powerful immunosuppressive effects on both innate and adaptive immunity [111]. MDSC are highly active in the suppression of T-cell responses. They express high levels of a panel of immunosuppressive factors, including IDO, IL-10, arginase, nitric oxide (NO), nitric dioxide (NO_2) and reactive oxygen species (ROS) to suppress T-cell responses [112, 114].

Kalinski and co-workers [114] have recently shown that PGE_2 derived from COX-2 is a critical factor for redirecting DC development toward functionally stable MDSC. A positive feedback loop has been established between PGE_2 and COX-2 in immature monocytes within the tumor microenvironment that facilitates the redirection of DCs to MDSC [114]. This same group has shown that even short-term inhibition of COX-2 can profoundly affect the immunosuppressive activity of mature MDSC isolated from cancer patients, further demonstrating the critical role of PGE_2 in the development of functionally stable MDSC [115]. In a tumor explant study using spontaneously metastatic BALB/c-derived 4T1 mammary carcinomas, Sinha *et al.* [116] demonstrated that MDSC express EP receptors, and that receptor agonists, including PGE_2, induce the differentiation of MDSC from bone marrow stem cells. Further support for an essential role of PGE_2 in the differentiation of MDSC was obtained from a tumor explant study conducted in EP2 receptor KO mice, in which tumor growth and the accumulation of MDSC was reduced compared to wild-type mice.

Finally, the Ochoa laboratory [117] has examined the affects of PGE_2 on arginase activity in MDSC. They report that arginase production by MDSC depletes arginine from the tumor microenvironment, thereby impairing the functional activation of T cells. Focusing on T cell activity in patients with renal cell carcinomas, Ochoa and colleagues [117] found that arginase activity was markedly reduced in the peripheral blood mononuclear cells of cancer patients, associated with reduced arginine levels. It was also demonstrated that tumor-derived PGE_2 may induce arginase expression in MDSC, providing an important link between the COX-2/PGE_2 pathway and MDSC function.

6. Drug targeting of mPGES-1 for cancer suppression

While genetic inhibition of inducible mPGES-1 activity offers a reasonable approach for studying its functional role in inflammation and cancer, the development of high affinity pharmacologic agents is critical for establishing novel therapeutic approaches. In this section, we review some of the most promising studies that have attempted to uncover new inhibitors of inducible PGE_2 formation. Li *et al.* [118] have recently identified over-expression of mPGES-1 in human acute myeloid leukemia cells. As noted by these investigators, treatment of HL-60 cells with MK886 inhibited proliferation and induced apoptosis, accompanied by up-regulation of BAX expression and caspase-3 activity and reduced Bcl-2 and p-AKT. Deckmann *et al.* [119, 120] treated human cervical cancer cells (HeLa) with dimethylcelecoxib, a non-COX-2 inhibiting derivative of celecoxib. HeLa cell treatment with dimethylcoxib leads to an enhanced formation of a complex consisting of NF-κB and HDAC1 that binds to the EGR1 promoter, resulting in the down-regulation of EGR1 expression, an important mechanism for inhibition of mPGES-1 expression. Koeberle *et al.* [121] also showed that the anti-inflammatory drug licofelone suppressed PGE_2 formation by inhibiting mPGES-1 without targeting COX-2 activity. Cote *et al.* [122] identified by high-throughput screening a lead compound, phenanthrene imidzaole (MF63), as a potent, selective and orally active mPGES-1 inhibitor with both *in vitro* and *in vivo* activity. The drug shows good selectivity towards mPGES-2, with an IC50 = 0.42 uM in

A549 whole cells. In addition, several specific modifications to this chemical structure have been reported by Giroux *et al.* [123] that enhance oral bioavailability and improve the pharmacokinetic profile. More recently, as part of a highly comprehensive study, Chini *et al.* [124] have reported promising results with respect to the design and synthesis of a new generation of drugs based on the triazole scaffold that provide dual inhibition of both mPGES-1 and 5-lipoxygenase, offering the promise of safer and more effective anti-inflammatory agents. Finally, Beales and Ogunwobi [125] demonstrated with the use of either RNA interference or a small molecule inhibitor (CAY10526) the inhibition of esophogeal adenocarcinoma growth in cell culture. Many of these novel chemical structures have recently been reviewed by Chang and Meuillet [126].

Several natural compounds have also been evaluated for their ability to inhibit mPGES-1 activity. Moon *et al.* [127] showed that curcumin (diferuloylmethane) suppresses IL-1 -induced PGE_2 formation in A549 human lung epithelial cells. Interestingly, mPGES-1 inhibition actually caused a metabolite shift from PGE_2 to PGF_2 and 6-keto-PGF. The curcumin-mediated inhibition of IL-1 -induced mPGES-1 expression is mediated by suppression of the transcription factor, EGR1, with an additional role played by NF- B and JNK1/2. Koeberle *et al.* [128] also showed that curcumin blocks PGE_2 formation by direct inhibition of mPGES-1 in IL-1 stimulated A549 lung carcinoma cells with an IC_{50} = 0.2 M. The group also tested the ability of the chemopreventive agent, EGCG isolated from green tea (*Camellia sinensis*), to inhibit PGE_2 biosynthesis [129]. ECGC was relatively effective (IC_{50}=1.8 M) as an mPGES-1 inhibitor, an efficacy that was attained in the absence of inhibition of other pathway enzymes, including $cPLA_2$ or COX-2. ECGC was also effective in blocking PGE_2 synthesis in LPS-stimulated human whole blood cells [129]. Finally, Koeberle *et al.* [130] showed that myrtucommulone, a naturally occurring acylphloroglucinol derived from Myrtus communis, could efficiently suppress PGE_2 synthesis in both A549 cells and LPS-stimulated human whole blood cells by inhibiting mPGES-1. This mPGES-1 inhibition occurred independently of COX inhibition. It should be noted, however, that the majority of these pre-clincial studies, have yet to establish the therapeutic efficacy of these agents in protecting against tumorigenesis. Thus the critical and exciting studies that will further validate many of these promising therapeutic agents remain to be performed.

7. Perspectives on PGE_2 and inflammation-associated cancer

Emerging evidence places chronic inflammation directly within the pathogenetic pathway of many human cancers, particularly those affecting the GI tract [131, 132]. The notion that prolonged tissue damage contributes to cancer development has been confirmed in the case of long-standing IBD, which is a significant risk factor for CRC [133, 134]. In a recent study conducted in California (1998–2010), the incidence of CRC in patients with IBD was 60% higher than the general population [135]. In addition, the risk for developing CRC increases at a rate of approximately 0.5 – 1.0% per year in individuals with at least seven years of active disease [136]. Similar to sporadic CRC, the progression of IBD-related cancer occurs in a step-wise manner, driven to a varying extent by chromosomal instability (CIN), microsatellite instability (MSI), and mutations in key tumor-related genes, including *p53*, *KRAS*, and *APC* [136]. However, the timing of these molecular events differs with respect to the etiologies of sporadic and inflammation-associated cancers (reviewed by [136]).

As evident from this review, accumulating data suggests that PGE_2 plays an important role in the growth and progression of not only sporadic but also inflammation-related intestinal cancers. This conclusion is supported by an abundant literature showing colon cancer protection by NSAIDs, the overwhelmingly positive results associated with COX-2 or mPGES-1 deletion in pre-clinical mouse tumor models, and the efficacy of targeting EP

receptors for cancer prevention. Considering the bipartite functions of PGE_2 in inflammation and cancer (Figure 2), what role, if any, does PGE_2 play in the timing of the molecular events that occur during inflammation-associated cancer? There are few studies that have attempted to clarify the potential role of PGE_2 in the pathogenesis of IBD-related cancer. This is because the indiscriminate application of NSAIDs to IBD patients with active disease is strongly contraindicated, most likely attributable to the critical role of PGE_2 in maintaining GI epithelial barrier function. In addition, suppressing PGE_2 formation with the use of NSAIDs may further interrupt the wound-healing process, thereby exacerbating the severity of the disease. Thus, targeting PGE_2 formation within the context of IBD-related cancers presents an important clinical challenge and underscores a key paradox for successful clinical management. As postulated by Dvorak, "tumors are wounds that never heal" [137], thus underscoring the fundamental similarities that exist between tumor development and the wound healing process [138]. Ultimately, what is needed is a way to block the tumor-enhancing properties of PGE_2 without affecting its critical role in mucosal homeostasis and wound repair.

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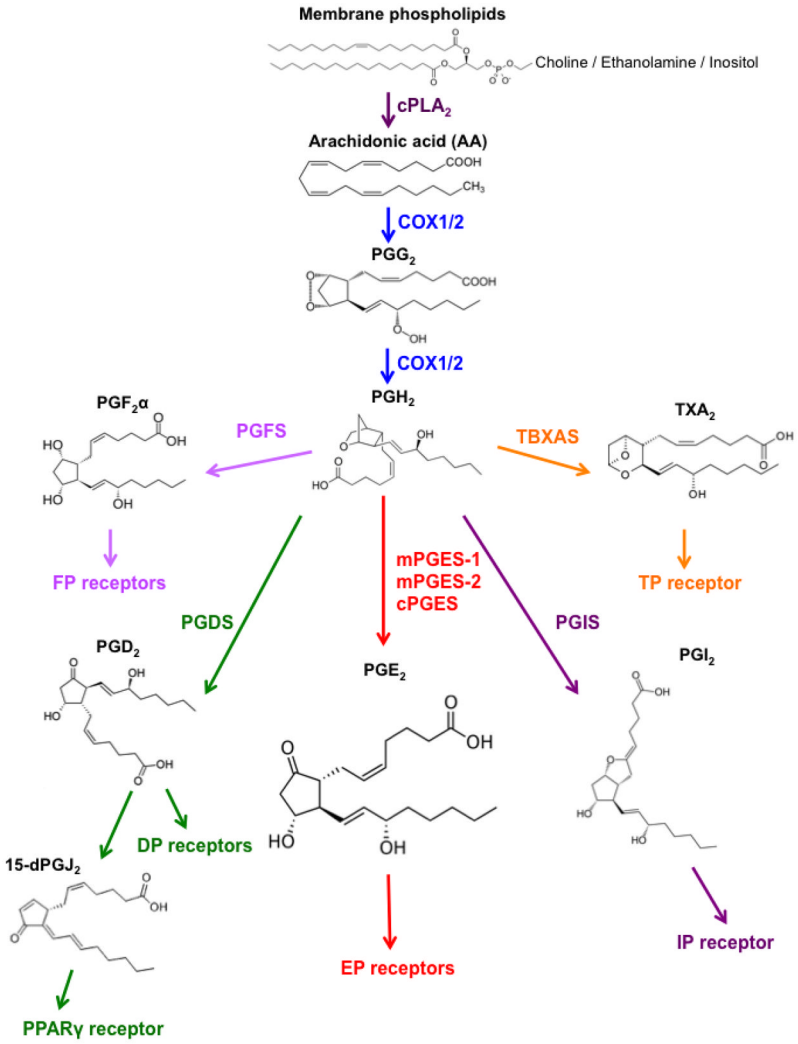

Fig. 1.
PGE_2 biosynthetic pathway

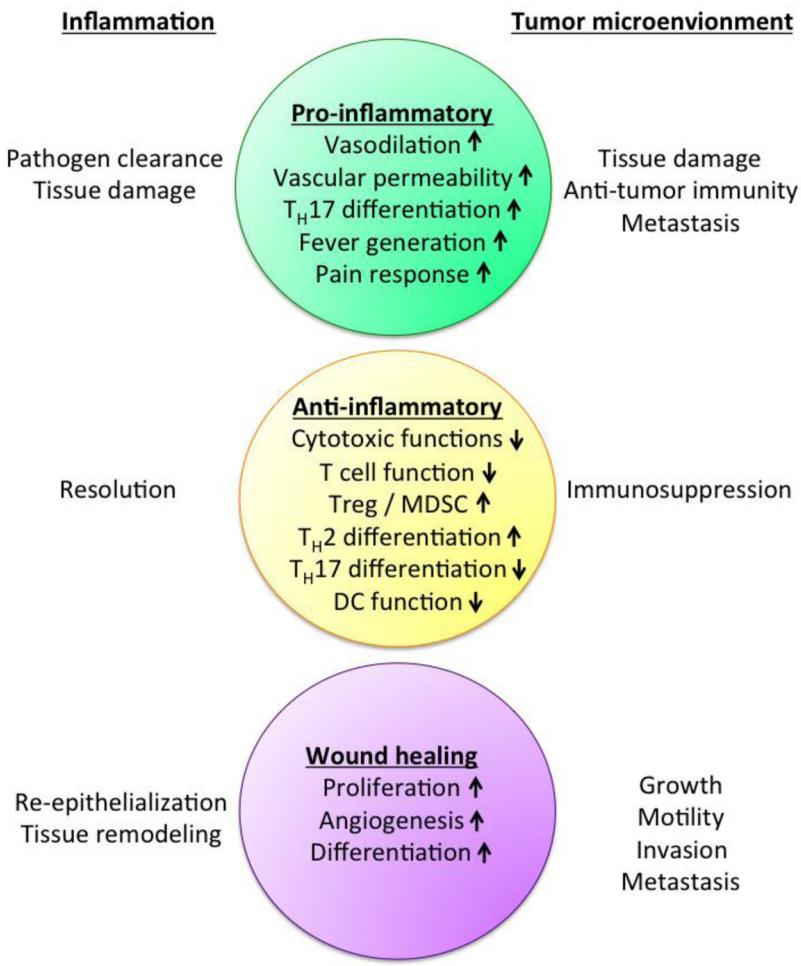

Fig. 2.
Bipartite functions of PGE_2 in inflammation and cancer

Table 1

Overview of studies that have targeted PGE_2 biosynthesis

Organ	Target gene	Model	Effects	Reference
Intestine	cPLA$_2$α KO	*Apc^{Min}*	SI tumor ↓ (83%)	[139]
	cPLA$_2$α KO	AOM	Colon tumor ↑ (5.6-fold)	[3]
	COX-1 KO	*Apc^{Min}*	SI tumor ↓ (77%)	[140]
	COX-1 KO	AOM/DSS	Tumor incidence ↓	[141]
	COX-2 KO	*Apc^{Min}*	SI tumor ↓ (84%)	[140]
	COX-2 KO	*Apc$^{\Delta 716}$*	SI tumor ↓ (86%)	[142]
	COX-2 KO	AOM/DSS	Tumor Incidence ↑	[141]
	mPGES-1 KO	*Apc$^{\Delta 14}$*	SI tumor ↓ (66%) Colon tumor ↓ (51%)	[74]
	mPGES-1 KO	*Apc^{Min}*	SI tumor ↑ (48%)	[143]
	mPGES-1 KO	AOM	ACF ↓ (40%) Colon tumor ↓ (85%)	[48]
	mPGES-1 KO	AOM	ACF ↓ Colon tumor ↓	[144]
	mPGES-1 Tg	AOM	ACF ↑	[144]
	EP1 KO	AOM	ACF ↓ (60%)	[89]
	EP1	*Apc^{Min}* ONO-8711 (antagonist)	SI tumor ↓ (57%)	[89]
	EP2 KO	*Apc$^{\Delta 716}$*	SI tumor ↓	[92]
	EP3 KO	AOM	Tumor incidence ↑ Colon tumor ↑	[90]
	EP4 KO	AOM	ACF ↓ (56%)	[85]
	EP4	AOM ONO-AE2-227 (antagonist)	ACF ↓ (67%)	[85]
	EP4	*Apc^{Min}* ONO-AE2-227 (antagonist)	SI tumor ↓ (69%)	[85]
Esophagus	EP2	Barrett's metaplasia, intraepithelial neoplasia, adenocarcinoma	Expression ↑	[93]
	EP4	Adenocarcinoma	Expression ↑	[93]
Liver	EP1	HepG2 cells ONO-D1-004 (agonist) ONO-8711 (antagonist)	Growth and migration ↓ Growth and migration ↓	[94]
Stomach	COX-2/mPGES-1 Tg in epithelial cells	*K19-C2mE*	Gastric hyperplasia and tumorous growth ↑	[81]
	EP2/4	MKN-7 MKN-28 MKN45 AGS ONO-AE1-259-01 ONO-AE1-329 (agonists)	Cell proliferation ↓	[145]
Breast	COX-2 Tg COX-2 KO HER2/neu Tg	MMTV MMTV / NDL	Tumor incidence ↑ Tumors ↓ (50%)	[146] [147]
	Floxed COX-2 in mammary epithelial cells	MPA / DMBA	Delayed onset	[80]

Organ	Target gene	Model	Effects	Reference
Skin	EP2 KO	DMBA / TPA	Tumors ↓	[148]
	EP2 Tg	DMBA / TPA	Tumors ↑	[148]

ACF, aberrant crypt foci; AOM, azoxymethane; DMBA, 7,12-Dimethylbenz(a)anthracene, KO, knockout; MMTV, mouse mammary tumor virus; MPA, medroxyprogesterone acetate; NDL, neu deletion mutant; SI, small intestine; Tg, transgenic; TPA, 12-*O*-tetradecanoylphorbol-13-acetate