Prostaglandin Pathways: Opportunities for Cancer Prevention and Therapy

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ABSTRACT

Because of profound effects observed in carcinogenesis, prostaglandins (PG), prostaglandin-endoperoxide synthases, and PG receptors are implicated in cancer development and progression. Understanding the molecular mechanisms of PG actions has potential clinical relevance for cancer prevention and therapy. This review focuses on the current status of PG signaling pathways in modulating cancer progression and aims to provide insights into the mechanistic actions of PGs and their receptors in influencing tumor progression. We also examine several small molecules identified as having anticancer activity that target prostaglandin receptors. The literature suggests that targeting PG pathways could provide opportunities for cancer prevention and therapy.

Introduction

The prostaglandins are physiologically active lipid compounds with diverse hormone-like effects. Prostaglandins (PG), prostaglandin-endoperoxide synthases (PTGS), and PG receptors are implicated in normal development, tissue homeostasis, inflammation, and cancer progression (1, 2). PGs are derived from the precursor 20-carbon chain fatty acid, arachidonic acid (AA), which is produced by membrane phospholipid enzymes, especially phospholipase A2. The cyclooxygenase (COX) enzymes convert AA to the precursor molecule prostaglandin H2 (PGH2; ref. 3). PGH2 is then converted to one of five primary prostanoids that include prostaglandin D2 (PGD2), prostaglandin E2 (PGE2), prostaglandin F2α (PGF2α), prostaglandin I2 (PGI2), and thromboxane A2 (TXA2). The conversion of PGH2 occurs through specific synthases, including prostaglandin D synthase (PGDS), prostaglandin E synthase (PGES), prostaglandin F synthase (PGFS), prostaglandin I synthase (PGIS), and thromboxane A synthase (TBXAS), respectively (1, 4, 5). After synthesis, PGs are rapidly transported into the extracellular microenvironment by the prostaglandin transporter (PGT), which is a protein belonging to a superfamily of 12-transmembrane anion-transporting polypeptides (6, 7). When exported to the microenvironment, the PGs bind to and activate G-protein-coupled receptors that include PGD2 receptor 1 (DP1), PGD2 receptor 2 (DP2), PGE2 receptor 1 (EP1), PGE2 receptor 2 (EP2), PGE2 receptor 3 (EP3), PGE2 receptor 4 (EP4), prostaglandin F receptor (FP), prostacyclin receptor (IP), and TXA2 receptor (TBXA2R). These receptors are classified according to their ligand specificity (8). PG binding to specific receptors leads to receptor activation and dissociation of the heterotrimeric G-protein complex. This action leads to the initiation of divergent signaling cascades (2) that mediate a variety of physiologic functions, including tumor progression.

Inhibiting COX enzymes reportedly could be effective in the prevention and treatment of multiple cancer types (9–11). However, inhibition of COX by NSAIDs or other COX inhibitors has seen limited use because these drugs are associated with various side effects, including gastrointestinal toxicity, increased risk of myocardial infarction, and cardiovascular disease (12–14). Thus, many studies have focused on the PGs downstream of COX, hoping to avoid the side effects associated with COX inhibition while retaining the potential for cancer prevention and treatment. Clarifying the function of individual receptors and development of specific inhibitors is critically important to improve the efficacy and avoid toxicity. Previously, researchers have mostly concentrated only on the EP receptors in various cancers (15). In this review, we comprehensively examine the role of PGs, their receptors, and signaling pathways involved in multiple types of cancer (Supplementary Table S1). We also discuss the potential of inhibitors of PG signaling pathways as well as their limitations and side effects in cancer treatment.

The Role and Mechanisms of PGE2 and PGE2 Receptors (EP) in Cancer

PGE2 is one of several major COX protein products detected in various physiological settings and mediates multiple functions such as inflammation, tumorigenesis, and immune responses (16, 17). PGE2 is synthesized by specific synthases. Three types of PGE synthases have been identified, including microsomal PGE synthase-1 (mPGES-1), microsomal PGES-2 (mPGES-2), and cytosolic PGE synthase (cPGES). The expression of mPGES-1 is inducible, whereas mPGES-2 and cPGES are constitutively expressed (18). 15-Hydroxyprostaglandin dehydrogenase (15-PGDH) is a prostaglandin-degrading enzyme that catalyzes oxidization of the 15(S)-hydroxyl group of PGE2 to yield an inactive 15-keto PGE2 (19). However, 15-keto-PGE2 might have an additional role as a biased and/or partial agonist capable of taking over the actions of PGE2 to gradually terminate reactions, which is significant for stopping PGE2-evoked inflammation and/or maintaining homeostasis of colorectal tissue functions (20). PGE2 exerts its cellular effects by binding to its cognate receptors (EP1, EP2, EP3, or EP4), which belong to the G-protein-coupled receptor (GPCR) family. Each of these receptors can enhance multiple physiologic functions such as carcinogenesis, inflammatory bowel disease, and Alzheimer disease (21–24). GPCRs are involved in aberrant intracellular signal transmission that is often associated with tumor growth and metastasis. Therefore, targeting the GPCRs contributing to oncogenic

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Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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Cancer Res 2022;82:949–65

doi: 10.1158/0008-5472.CAN-21-2297

signaling provides a rational approach for the development of novel anticancer therapies for cancer (25). EPs are coupled with G proteins to perform their functions by mobilizing intracellular Ca^{2+} and mediating activation of adenylyl cyclase (AC) and different downstream signaling pathways, including the PI3K, MAPK, and β-catenin signaling pathways (26–30). These signaling pathways are known to be closely associated with cancer development. Most experiments regarding the role of EP receptors in cancer are still at the cellular or animal level or in initial clinical trials. But data thus far still provides hope for application in cancer prevention or treatment. Here, we examine the roles and mechanisms of EP1, EP2, EP3, and EP4 each in the development of cancer.

EP1 promotes cancer

The EP1 receptor is highly expressed in various cancer tissues (31, 32), but shows the least affinity towards the PGE2 ligand compared with the other three EPs (33). These suggest that PGE2 must be at high levels to stimulate EP1 receptor activation, which is observed in multiple cancer types, including breast, ovarian, and colon (34–36). The EP1 receptor couples with G proteins and mediates cancer development by stimulating multiple signaling pathways in several cancer types. For example, PGE2 couples with EP1 enhancing cell growth, invasion, and migration in hepatocellular carcinoma cells (HCC) by activating the protein kinase C (PKC)/nuclear factor-kappa B (NF-κB)/Forkhead box protein C2 (FOXC2) and the EGFR/PI3K signaling pathways (37–39). Similarly, the EP1 receptor couples with Gi/o proteins promoting tumor growth and metastasis in osteoblastic (40, 41) and non–small cell lung cancer (NSCLC) cells (27) through the activation of PI3K and MAPK signaling pathways, resulting in activation of the E2F transcription factor 1 (E2F-1)/FOXC2 axis. In addition, the PGE2/EP1 signaling pathway enhances migration of oral cancer cells through intercellular adhesion molecule 1 (ICAM-1) production, which is a cell surface glycoprotein that plays an important role in tumor cell expansion or metastasis (42). Also, the upregulation of the EP1 receptor for PGE2 promotes skin tumor progression (43, 44). Collectively, PGE2 coupled with EP1 interacts with G proteins and triggers multiple signaling pathways, including EGFR, PI3K, MAPK, and NF-κB, that mediate the activation of transcription factors FOXC2 and HIF1α, resulting in enhanced cell growth and migration in cancer. (**Fig. 1A**).

Several studies have investigated the role of EP1 in cancer by evaluating the effects of EP1 antagonists. For example, the EP1 antagonist SC-51089 inhibits growth and induces apoptosis in osteosarcoma and glioma cells (44–46). This evidence suggests that the EP1 receptor might be a potential target in some cancers. However, the current studies show the potential effectiveness only in *in vitro* studies or animal models. Thus, whether targeting the EP1 receptor will benefit human cancer is still not clear.

The role of EP2 in cancer progression

The PGE2 receptor 2 subtype (EP2) is a metabolite of AA that binds with PGE2 and regulates cellular responses to PGE2. Several studies show that the EP2 receptor protein level is abnormally expressed in various cancers, including prostate, breast, colon, and liver (45–49). Also the expression level of EP2 is substantially increased in patients with high-grade cervical intraepithelial neoplasia (50). These findings suggest that EP2 might have a role in the progression of cancer.

Cancer development is known to be closely associated with inflammation (51, 52). The binding of PGE2 with EP2 is one of several major inflammatory mediators driven by COX2 that can induce several proinflammatory factors (53). For example, activation of EP2 can markedly enhance the expression of IL1β and IL6, which can increase growth, invasion, and angiogenesis in several cancer types (48, 54–56). Indeed, the activation of EP2 is critical for cancer development. PGE2 binds with EP2 to activate AC, leading to increases in cAMP levels and protein kinase A (PKA), which subsequently triggers the activation of various downstream transcription factors, including cAMP response element-binding protein (CREB; refs. 57, 58). The EP2 receptor plays a major role in skin tumor development by mediating cAMP levels (59) and also facilitates activity of the EGFR in numerous cancers (28, 60–62). For example, EP2 transactivates the EGFR to regulate the proliferation and invasion capability of esophageal squamous cell carcinoma (ESCC) cells (60). EP2 enhances the tumor promotor, survivin, through the EGFR/STAT3 pathway in UVB-exposed mouse skin (61). It can also mediate IL1α expression through the EGFR/PI3K/protein kinase B (AKT) pathway in neoplastic cervical cells (28). EP2 promotes squamous cell carcinoma growth through EGFR transactivation and the inducible nitric oxide synthase (iNOS) and the extracellular-signal-regulated kinase 1/2 (ERK1/2) pathways (62). Besides the EGFR-associated pathways, PGE2 increases EP2 receptor expression, which triggers β-arrestin 1/JNK/profilin-1 activation and induces cell migration and proliferation in human mesenchymal stem cells (63). In addition, PGE2/EP2 mediates cancer development through the β-catenin signaling pathway and PGE2 stimulates colon cancer cell growth through the G proteins/axin/β-catenin signaling axis (29). The β-catenin signaling pathway is known to be one of the most significant pathways that enhances the progression of various cancers, including colon, breast, and ovarian (64–66). EP2 can activate PI3K/AKT signaling that results in activation of the glycogen synthase kinase 3 beta (GSK3β) and β-catenin pathways, which enhances the transcription of several genes including *c-myc* and *cyclin D1* in cancer, resulting in enhanced tumorigenesis (67–71). On the basis of this evidence, the EP2 receptor can activate multiple oncogenic signaling pathways to perform its tumorigenic function in multiple cancer types.

Overall, PGE2 binding with EP2 interacts with G proteins and activates AC and EGFR, which triggers multiple signaling pathways. These pathways include β-catenin, PI3K, ERKs, and STAT3, which markedly influence inflammation, tumor growth, migration, and apoptosis (**Fig. 1B**). Compared with EP1, EP2 performs its functions through multiple signaling pathways in some cancer types. Targeting EP2 with antagonists like TG4–155, or TG6–129 inhibits cell growth and metastasis in multiple cancer types, including colorectal, prostate, and neuroblastoma (72, 73). A phase Ia/Ib study of the EP2/EP4 antagonist, TPST-1495, is being conducted in solid tumors, including colorectal, lung, head and neck, urothelial, endometrial, gastroesophageal, and gastric cancers (NCT04344795) and could provide much needed evidence for potential clinical use.

EP3 exerts duality in cancer

The function of EP3 in tumorigenesis appears to be a double-edged sword because some studies suggest that the EP3 receptor plays a critical role in tumor development (74–81) and others suggest no role for EP3. For example, as a factor in tumor development, EP3 might facilitate the migration of cervical cancer cells by activating the phosphorylated ERK1/2 and p53 signaling pathways, which modulate the expression of plasminogen activator inhibitor type 1 (PAI-1) and urokinase-type plasminogen activator receptor (uPAR). PAI-1 has a protumorigenic role in cancer enhancing angiogenesis and tumor cell survival (82). uPAR expression enhances invasion and metastasis in tumors (83). The EP3 receptor antagonist, L798,106, can reduce

proliferation and migration of SK-BR-3 breast cancer cells (75) and inhibition of EP3 attenuates migration and promotes apoptosis of NSCLC cells through the TGFβ/Smad signaling pathway (76). In addition, deletion of the EP3 receptor suppresses tumor-associated angiogenesis in the stroma by reducing VEGF and matrix metalloproteinase-9 (MMP9) expression (77–79), both of which are angiogenic activators. PGE2/EP3/c-SRC signaling regulates tumor growth and malignant progression by inducing EGFR nuclear translocation. Notably, nuclear EGFR is a hallmark of cancer aggressiveness (81). Collectively, PGE2 binds with EP3 then activates AC, EGFR, and TGFβ. The activation of these signaling pathways leads to p53, EFGR, and Smad2/Smad3 nuclear translocation enhancing tumor growth and malignant progression (**Fig. 1C**).

In contrast to these studies, some have shown that the EP3 receptor has no effect on tumorigenesis. EP1, EP2, and EP4 are highly expressed in breast cancer tissue compared with normal mammary tissue, whereas EP3 receptor expression appears to be downregulated in these cancer tissues (84). For instance, the expression level of EP3 is decreased in late-stage colon cancer compared with earlier stages (85). Similar results were observed in breast and skin cancers (84, 86, 87). These findings indicate that EP3 might exert negative or no obvious effects in mediating tumorigenesis of these cancers. Indeed, EP3 receptor expression does not appear to affect skin tumor development (59) and deletion of this receptor has no effect on colon tumor development in APC^{min} mice (88).

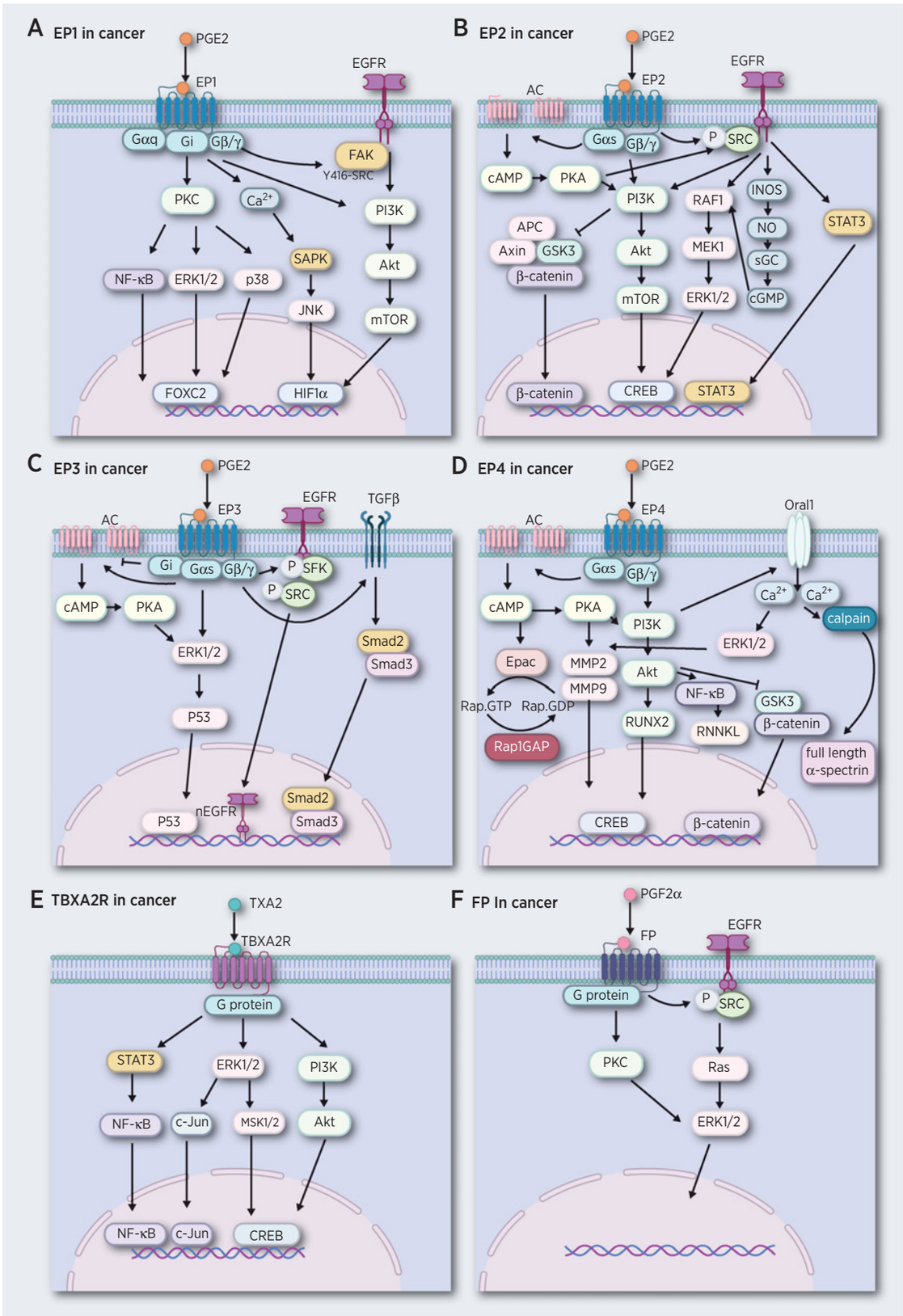
Notably, various isoforms of EP3 are generated by alternative mRNA splicing (89), which could account for the distinct effects of EP3 observed in different tumor types. The EP3 receptor has multiple splice variants differing in their C-terminal tails. In human tissue, nine mRNA and eight isoforms (EP3I, EP3II, EP3III, EP3IV, EP3V, EP3IV, EP3e, and EP3f) have been described (90–92). EP3 receptor variants are mostly expressed in clusters of multiple isoforms. For example, the human uterus expresses mRNA for the EP3V and EP3VI receptor isoforms, whereas in primary keratinocytes, the EP3I, EP3II, and EP3IV splice variants are expressed (93). These suggest that the role of the EP3 receptor is likely tumor- and cell-type specific and the different roles of the EP3 receptor in cancer might be due to the various isoforms. On the basis of these reports, the EP3 receptor does not appear to be a promising target for cancer treatment.

Targeting EP4 in cancer

The EP4 receptor is the most widely studied EP receptor in terms of its involvement in cancer development and is one of the most promising targets for the prevention and treatment of cancer. This receptor is upregulated in numerous cancers, including breast, colon, prostate, ovary, lung, and skin (89, 90, 94, 95, 96). The EP4 receptor is associated with multiple signaling pathways that are involved in cancer development and progression, including those governing proliferation, apoptosis, migration, and metastasis. EP4 plays a role in cell proliferation or apoptosis in several cancer types. EP4 can trigger the PKA/PI3K/AKT signaling pathway increasing proliferation in cells and xenograft prostate cancer models (91, 92). Inhibition of EP4 receptor-mediated signaling suppresses IGF1 and PKA-induced proliferation of pancreatic cancer cells (93, 97). EP4 antagonists hinder proliferation and induce apoptosis in cervical, colon, and oral squamous carcinoma cells by inhibiting the activation of the cyclic adenosine monophosphate/PKA/CREB axis as well as pathways involving the EGFR/Ras/MAPK/CREB and AKT/GSK3β/β-catenin pathways in human cancer cell lines (98–100). EP4 is also associated with increased migration in several cancer types by activation of the PI3K, ERKs, Rap GTPase, and arrestin1/c-Src pathways. For example, the EP4 receptor mediates migration through the activation of PI3K/Orai1/ERKs signaling in oral cancer cells (101). Activation of the EP4 receptor promotes renal cell invasion and metastasis through the Rap GTPase signaling pathway (102–105). PGE2 binding with EP4 can promote lung cancer cell migration through the EP4/β-arrestin1/c-Src pathway, which activates invasion and metastasis (106, 107). The EP4 receptor facilitates invasion of prostate cancer by mediating the cAMP/PKA/PI3K/AKT signaling pathway (92). Importantly, antagonists of EP4 suppress invasion, migration, and metastasis of prostate, breast, and colon cancer cells (96, 108–110). All these preclinical studies suggest that targeting the EP4 receptor should be one potential way to suppress cancer progression by inhibiting cell proliferation, apoptosis, invasion, and migration.

In addition, EP4 contributes to the activity of the immune system, enhancing the efficacy of immunotherapy. PGE2 activation of EP4 in natural killer (NK) cells can regulate cytokines that promote the replication and activation of cytotoxic T lymphocytes. The critical interactions between NK and dendric cells further drive both innate and adaptive antitumor responses. Each of these functions is regulated by PGE2 acting on EP4 expressed on NK cells (95, 111–113). In particular, antagonism of EP4 inhibits metastasis and enhances NK function and this inhibitory function is lost in mice lacking NK cells (111). Activation of the EP4 receptor on myeloid-derived suppressor cells mediates the p38/ERKs pathway, leading to secretion of TGFβ, which inhibits proliferation of NK cells (114). As indicated earlier, EP4 receptor antagonists are critical in cancer immunotherapy (95, 115, 116). For example, a combination of a PD-L1 antibody and an EP4 antagonist enhances immunotherapeutic efficacy, suggesting that inhibiting EP4 expression might offer a potential strategy for increasing the efficacy of immunotherapy (117, 118).

EP4 may also influence or be influenced by miRNA, which are a family of small noncoding RNAs that regulate a wide array of biological processes, including carcinogenesis (119). In cancer, some miRNAs inhibit or enhance carcinogenesis by mediating the EP4 receptor. For example, miR-92 has been shown to suppress gastric cancer cell proliferation and induce apoptosis by targeting the EP4/Notch1 axis, which plays important roles in biological processes that include proliferation and apoptosis (120, 121). Therapeutic strategies against miR-101 act by posttranscriptionally regulating the expression of the EP4 receptor in colon cancers (122). miR-155 is involved in immunomodulatory therapies through its modulation of macrophages' responses to nontuberculous mycobacteria through COX2/PGE2 signaling. Blocking EP4 can reduce bacterial survival in macrophages (123). In contrast, EP4 mediates cancer progression by targeting certain miRNAs. For example, the activation of EP4 can elevate oncogenic miR-526, which promotes breast cancer progression (124). EP4 siRNA or antagonists can impair NF-κB activity and upregulate miR-16 and miR-21 and cell proliferation in gastric cancer (125). This evidence suggests that the EP4 receptor is closely associated with some miRNAs in mediating carcinogenesis. This cumulative evidence indicates that EP4 is a potential preventive or therapeutic target, which is associated with multiple signaling pathways that include the Rap GTPase, PKA/MMPs, PI3K, ERK1/2, NF-κB, and β-catenin conduits (**Fig. 1D**). Importantly, several clinical trials are being undertaken to study the effect of EP4 antagonists in advanced cancer and metastatic tumors. For example, a phase Ib clinical study is being conducted to evaluate the safety and preliminary efficacy of E7046 in combination with pembrolizumab in patients with locally advanced/metastatic tumors (NCT04432857). Clinical studies are also evaluating the safety,


A EP1 in cancer
PGE2
EP1
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Gαq
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Gβ/γ
FAK
Y416-SRC
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Ca2+
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NF-κB
ERK1/2
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Epac
MMP2
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MMP9
NF-κB
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RUNX2
RNNKL
β-catenin
Rap1GAP
full length
α-spectrin
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CREB
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PGF2α
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EGFR
G protein
P
SRC
PKC
Ras
ERK1/2

tolerability, pharmacokinetics, efficacy, and biomarker potential of ONO-4578 in subjects with advanced or metastatic solid tumors and subjects with unresectable, advanced or recurrent gastric or colorectal cancer (NCT03661632; NCT03155061). In addition, a phase I clinical study to assess safety and tolerability of AAT-007 is being performed in patients with microsatellite stable colorectal cancer (NCT03658772). Although these clinical trials are still in their infant phase I stage, they could provide us with hope for effective targeting of EP4 in cancer therapy.

TXA2 and TBXA2R Are Potential Targets in Cancer

TXA2 synthesis is driven by the COXs and these enzymes convert AA to the precursor molecule PGH2, which is then transformed to TXA2 through the TXA2 synthase pathway and exerts its biological activities through the TBXA2 receptor (TBXA2R; refs. 1, 3). TBXA2R has two separate isoforms that are termed TBXA2Rα and TBXA2Rβ. TBXA2Rα is broadly expressed in numerous tissues whereas the splice variant, TBXA2Rβ, may have a more limited tissue distribution. The first 328 amino acids are the same for both TBXA2Rα and TBXA2Rβ isoforms, but the β isoform exhibits an extended C-terminal cytoplasmic domain. Both isoforms stimulate cells in part by activating the G proteins (126). Accumulating evidence demonstrates that TXA2-related molecules are actively involved in tumor progression (127–130).

Notably, solid evidence suggests that circulating levels of TXB2, which is the stable metabolite of TXA2, could serve as a potential biomarker for early detection of Barrett esophagus (BE) and esophageal adenocarcinoma (EAC; ref. 127). In addition, one report indicated that colorectal cancer progression is associated with higher circulating levels of TXB2 (128). Also, another group reported that TBXA2R may have significant clinical potential as a diagnostic biomarker and predictor of prostate cancer disease recurrence (131). High levels of TXA2 are associated with enhanced proliferation of various cancer cells, including esophageal, breast, lung, and colon cancer (127, 128, 129, 132). Consistent with a role in cancer progression, TXAS and TBXA2R overexpression has been observed in many tumor tissues, including breast, prostate, lung, colon, bladder, and esophageal (119–122, 127, 128, 130, 132, 133). Several studies have already studied the function of TXA2 pathways in breast, prostate, lung, and gastrointestinal cancers.

The TXA2 pathway plays a critical role in breast cancer development because TXAS or the TXA2R is required for breast cancer cell growth and invasion capabilities. The expression level of TBXA2R negatively correlates with disease-free and overall survival in human breast cancer (130). The TXA2R enhances triple negative breast cancer cell migration and invasion and activates the Rho signaling pathway, which mediates cell death in tumors (123, 124). Switching off TXA2 biosynthesis has been reported to effectively suppress either MMTV-HER-2-driven mammary tumorigenesis or breast cancer metastasis in preclinical animal models (129).

The TXA2 pathway appears to play an important role in prostate cancer because tumor suppressor genes like *Wilms's tumor (WT)1*, *Forkhead box P1 (FOXP1)*, and *NK3 Homeobox 1 (NKX3.1)* transcriptionally decrease TBXA2R expression in prostate cancer (125, 134, 135). For example, the transcriptional regulator WT1 is expressed and implicated in prostate and breast cancers and transcriptionally represses TBXA2Rα expression through GC-enrich WT1 *cis*-elements (135). TBXA2R promotes proliferation and migration in prostate cancer by activating protein kinase C-related kinase (PRK) signaling, which is associated with many physiological functions, including tumor growth and metastasis (136–139). TBXA2R is also reported to facilitate prostate cancer cell motility and cytoskeleton reorganization through the activation of Rho kinase (ROCK), which is one of the best characterized effectors of the small GTPase RhoA-regulating tumor progression (119).

The TXA2 pathway also enhances lung cancer development. 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is potent carcinogen that has been found to effectively induce various types of lung cancer in mouse models (140). NNK treatment can enhance the level of TXA2, which binds with the TBXA2R to enhance cell proliferation through the activation of CREB. CREB is downstream of the PI3K/AKT and COX2/ERKs/NF-κB pathways. The TXA2 pathway also plays a critical role in increasing gastrointestinal cancer growth as observed by TBXA2R facilitation of colorectal cancer cell growth through the activation of the cAMP and Gαq/PLC signaling pathways (128, 133, 141, 142). In addition, the COX1/2-driven TBXA2 pathway facilitates BE and EAC through the activation of the ERKs/mitogen- and stress-activated protein kinases (MSK)/CREB/c-Jun and STAT3/NF-κB pathways (127).

Agonists and antagonists of TBXA2 have also been shown to influence tumor growth in various cancers. For instance, U46619 and (Z)-7-[(1S,2R,3R,4R)-3-[(E,3R)-3-hydroxy- 4-(4-iodophenoxy) but-1-enyl]-7-oxabicyclo[2.2.1]heptan-2-yl]hept-5-enoic acid (I-BOP) are TBXA2R agonists that stimulate cell proliferation in a PKA/CREB-dependent manner (132, 143, 144). In contract, the TBXA2R antagonist, SQ29548, can effectively inhibit prostate and lung cancer cell growth (119, 121). Overall, the TBXA2R is a potential target for cancer treatment through the mediation of multiple signaling pathways, such as NF-κB, ERKs, and PI3K (**Fig. 1E**). Several studies demonstrate the concept of targeting the TBXA2 signaling pathway in cancer treatment. Increasing attention focuses on the potential of targeting TBXA2R. A phase II clinical trial is being conducted to study the TBXA2R antagonist ifetroban in treating patients with malignant solid tumors at high risk of metastatic recurrence (NCT03694249). This study could provide us with the needed information to effectively use a TBXA2R antagonist for cancer treatment in humans.

Figure 1.

PG receptors mediate cancer development by activating multiple signaling pathways. **A,** The EP1 receptor links to G proteins and mediates signaling pathways by activation of EGFR, PKC, and increasing Ca^{2+} levels, leading to activation of the PI3K/AKT, MAPK, and NF-κB signaling pathways. **B,** The EP2 receptor couples to G proteins and performs its functions by inducing the AC system and enhancing the secondary messenger cAMP, leading to activation of PKA. The EP2 receptor also can activate EGFR, leading to activation of the PI3K/AKT, GSK3/β-catenin, RAF1/MEK1/ERK1/2, and STAT3 signaling pathways. **C,** The EP3 receptor couples to G proteins and performs its functions by inducing the AC/cAMP/PKA system and activation of EGFR and TGFβ receptors, leading to activation of ERK1/2/p53, Smad2/Smad3 activation, and nuclear translocation of EGFR. **D,** The EP4 receptors link to G proteins and activate the AC/cAMP/PKA system and Oral1, leading to activation of PI3K/AKT, NF-κB/RNNKL GSK3/β-catenin, ERKs, calpain, and Epac signaling pathways. **E,** The TBXA2R receptor couples to G proteins and performs its function by mediating PI3K/AKT, ERK1/2/MSK1/2/c-Jun, and STAT3/NF-κB signaling pathways. **F,** PGF2α links to G proteins and activates EGFR and leads to Ras/ERK1/2 signaling.

The Role of PGI2 and I-prostanoid in Cancer

PGI2, also called prostacyclin, is produced by PGI synthase (PGIS) and has a single I-prostanoid (IP) receptor (145). PGIS encodes a member of the cytochrome P450 superfamily that catalyzes the metabolism of many drugs and the synthesis of lipids, such as cholesterol and various steroids. In addition, PGIS might be involved in oxidative stress, xenobiotic and drug metabolism, and prostaglandin metabolism (146, 147). The PGI2 product acts as a vasodilator and anticoagulant to maintain vascular homeostasis and is involved in inflammatory responses and activation of $CD4^+$ T cells during numerous physiologic processes such as allergic diseases and asthma (148).

PGI2 and TXA2 are known to exert opposing effects on vasculature. PGI2 is a vasodilator, which inactivates platelets and inhibits their aggregation, whereas TXA2 has opposite effects as a vasoconstrictor. In cancer, PGI2 and TXA2 and their corresponding enzymes, PGIS and TXAS, respectively, have been shown to exert markedly contrasting effects (149, 150). The PGIS/PGI2 signaling pathway acts as a tumor suppressor in cancer development. The expression of PGIS is lower in bladder, cervical, colorectal, head and neck, leukemia, lung, ovarian, and prostate cancers compared with normal tissues. Kaplan–Meier plots have shown that low PGIS is associated with poor overall and shorter progression-free survival in patients with lung, ovarian, and gastric cancer (151). Hypermethylation of the PGIS promoter has been reported to be associated with its diminished gene expression in colorectal carcinogenesis (152). Deletion of PGIS increases the number of azoxymethane (AOM)-induced colon polyps and enhances colon carcinogenesis in mice (153). Its product, PGI2, has been implicated as a potential marker, potent antimitogenic, antimetastatic agent, or chemopreventive agent in cancer (154–157). A PGI2 analog has been reported to suppress lung cancer metastasis in a mouse lung metastasis model by recruiting pericytes in tumor angiogenesis (158). PGI2 analogues can also activate PPARδ and PPARγ and have been shown to inhibit the growth of lung cancer cells (159, 160).

Collectively, the mechanisms involving the PGIS/PGI2 signaling pathway in cancer cells are still uncertain. Current information suggests that the PGI2 signaling pathway might function as a tumor suppressor. The studies focusing on PGI2 and IP in cancer are still in the early stages and further studies are still needed to clarify the functions of this signaling pathway.

PGD2 and DP1/2 Act as Tumor Suppressors

PGD2 is produced from PGH2 by lipocalin-type PGD synthase (L-PGDS) or hematopoietic PGD synthase (H-PGDS). It performs its biological functions by binding with D prostanoid receptor 1 (DP1) and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2; alternative name DP2; ref. 161). L-PGDS is mainly expressed in central nerves and is known to be associated with sleep (162) and H-PGDS has been identified as a possible drug target, due to its involvement in asthma and inflammation (163).

The PGD2 pathway reportedly acts as a tumor suppressor and gene deficiency of the DP receptor enhances angiogenesis and tumor growth in a mouse tumor transplantation model (164). *H-PGDS* gene deficiency significantly decreases the production of PGD2 and strongly accelerates the growth of implanted Lewis lung carcinoma cells (165). H-PGDS deficiency exacerbates colitis and enhances the number of adenomas in an AOM/dextran sulfate sodium-induced colon cancer model. Moreover, deletion of H-PGDS also increases intestinal polyposis in an APC mutation mouse model. Furthermore, deletion of H-PGDS can enhance inflammatory cytokine expression, especially TNFα in mouse models (166, 167). Inhibition of L-PGDS and DP2 by Yes-associated protein 1 is associated with carcinogenesis in various organs and promotes self-renewal of gastric cancer cells (168, 169). Finally, deletion of L-PGDS accelerates the growth of melanoma in mice, whereas treatment with an agonist of the DP1 receptor attenuates growth (170). This evidence demonstrates the potential of targeting PGD2 in cancer treatment. However, more clinically relevant studies should be conducted to further evaluate the function of PGD2.

The Function of PGF2α and FP in Cancer

PGF2α is produced by PGFS and binds to a cognate G-protein-coupled receptor, FP, to perform its function in biological processes as diverse as smooth muscle contraction, regulation of intraocular pressure, renal filtration, inhibition of adipocyte differentiation, and hair growth stimulation (**Fig. 1F**; ref. 171). FP is expressed as two alternatively spliced transcript variants encoding different isoforms, FPA and FPB, which have varying C-terminal lengths. FPA and FPB receptor isoforms have similar pharmacologic properties. Both isoforms are able to stimulate IP accumulation to the same degree, but the basal level of hydrolysis is 130% higher for the FPB isoform than for the FPA isoform (172). The PGF2α signaling pathway is also involved in mediating cancer development because PGF2α has been shown to promote carcinogen-induced malignant transformation (173). Studies of prostaglandin production in colon cancer have shown that the production levels of PGF2α are 30-fold higher than for PGE2 in intestinal tissue from patients with familial adenomatous polyposis (FAP; ref. 174). PGF2α might have a critical role in FAP patients. Actually, studies demonstrate that PGF2α increases chloride secretion in a cAMP-dependent manner. This observation may have implications for a variety of inflammatory disorders, including infectious colitis (i.e., clostridium difficile) as well as inflammatory bowel disease (175). PGF2α also stimulate motility and invasion of colorectal tumor cells in an animal invasion assay model (176, 177). In addition, the PGF2α-FP receptor is reported to activate EGFR and then the subsequent phosphorylation of ERK1/2 mediates angiogenesis in endometrial adenocarcinoma (178). These data show that PGF2α may play a promoting role in the malignant progression of tumors. Although the FP antagonist AL8810 can suppress prostate cancer cell proliferation, direct evidence supporting inhibition of tumor development in humans by targeting FP is still very limited. Further studies are clearly needed to understand the biological role of PGF2 in cancer development.

Inhibition of PG Pathways Provides a Potential Strategy for Attenuating Cancer Development

This review thus far has examined the role of PG pathways in tumorigenesis. The accumulated findings demonstrate that PG receptors could be potential targets for cancer prevention and therapy. In recent years, several small molecules with anticancer activity that target PG receptors have been identified in preclinical and clinical studies focusing on multiple cancer types. The effects of various antagonists

Table 1. Targeting prostaglandin signaling pathways in cancer.

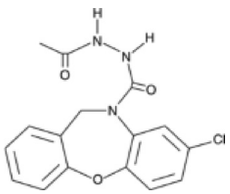
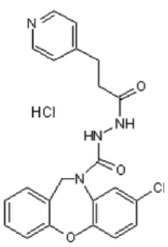
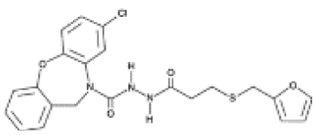
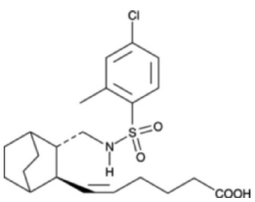
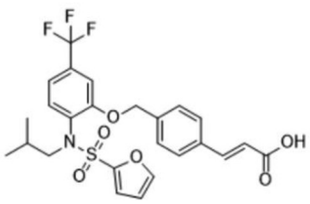
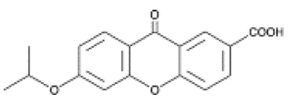
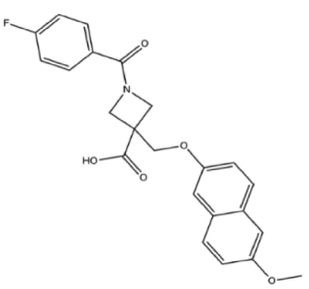
Compound	Target	Structures	Biological function	Reference or clinical trials number
---	---		Inhibits migration of metastatic breast cancer; induces colon cancer apoptosis	(109, 180)
SC-51089	EP1		Inhibits growth and induces apoptosis of osteosarcoma and glioma cells	(181, 182)
SC-51322	EP1		Inhibits proliferation in non-Hodgkin's lymphoma; Inhibits invasion of cholangiocarcinoma; induces apoptosis; mediates migration in esophageal adenocarcinoma cells	(183–185)
ONO-8711	EP1		Reduces intestinal polyp formation and colon carcinogenesis; inhibits breast and tongue carcinogenesis	(186–189)
ONO-8713	EP1		Reduces growth of colon and breast cancer cells; inhibits UVB-induced inflammation and skin cancer development	(190–193)
AH-6809	EP1/2		Inhibits migration of metastatic breast cancer	(109)
PF-04418948	EP2		Suppresses neck metastasis of hypopharyngeal cancer; suppresses colorectal tumor formation	(194, 195)

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Table 1. Targeting prostaglandin signaling pathways in cancer. (Cont'd)

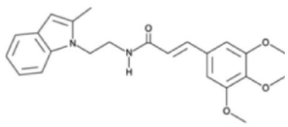
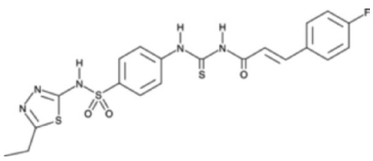
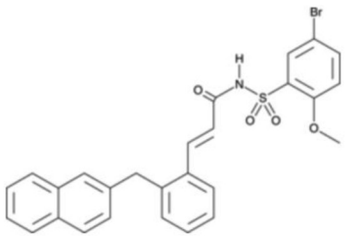
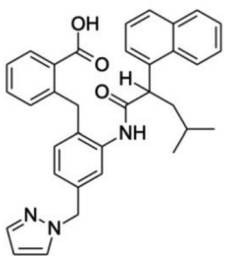
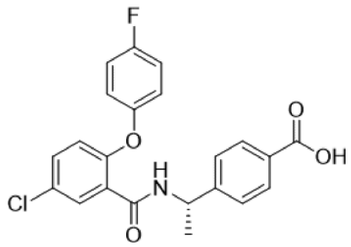
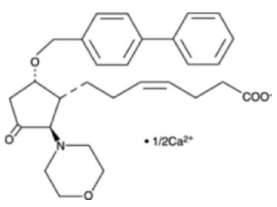
Compound	Target	Structures	Biological function	Reference or clinical trials number
TG4–155	EP2		Mediates cell proliferation, invasion and inflammation in prostate cancer	(72)
TG6–129	EP2		Inhibits tumor growth in high-risk neuroblastoma	(73)
L-798106	EP3		Inhibits migration and proliferation of human glioblastoma cells; inhibits growth of HCCs	(196, 197)
ONO-AE3–240	EP3		Reduces growth of breast cancer cells; inhibits the growth of oral squamous cell carcinoma cells	(191, 198)
RQ-15986	EP4		Reduces the tumor-initiating capacity, tumor growth, and metastasis of breast cancer; abolishes angiogenesis, lymph angiogenesis, and metastasis	(113, 199, 200)
AH23848	EP4		Inhibits migration and growth of breast and prostate cancer cells; prevents LPS-induced MMP-9 expression and invasion of colon cancer cells	(109, 110, 199, 201)

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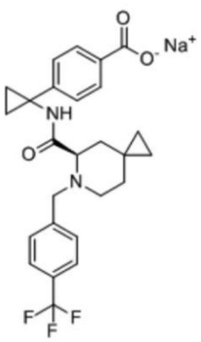
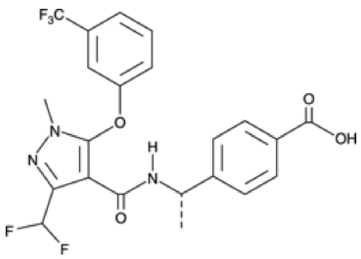
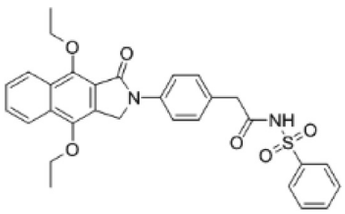
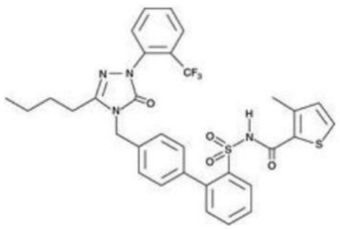
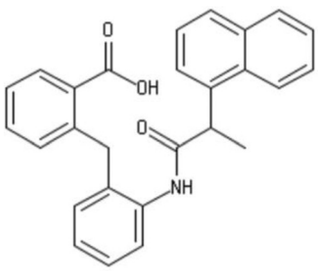
Table 1. Targeting prostaglandin signaling pathways in cancer. (Cont'd)

Compound	Target	Structures	Biological function	Reference or clinical trials number
CR6086	EP4		Inhibits tumor growth in a microsatellite stable colorectal cancer mouse model	(202)
E7046	EP4		Prevents proliferation, migration, invasion, angiogenesis, and colony formation of cancer cells; stable disease in patients with advanced malignancies; mediates protumor myeloid cell differentiation; Phase I clinical trails of EP4 antagonist E7046 in advanced solid tumors	(116, 179, 203) NCT02540291 NCT03152370 NCT04432857
GW627368X	EP4		Suppresses IGF1-induced proliferation of pancreatic cancer cells; inhibits tumor survival, motility, proliferation, and angiogenesis of cervical cancer cells; tumor reduction and induction of apoptosis in sarcoma; inhibition of proliferation and invasion of breast cancer cells	(93, 98, 204, 205)
L-161982	EP4		Enhances apoptosis of oxaliplatin-resistant HT29 cells; induces apoptosis, cell-cycle arrest, and inhibits proliferation of oral squamous carcinoma cells; induces G_0–G_1 arrest and inhibits proliferation of colon cancer cells	(99, 100, 206, 207)
ONO-AE2–227	EP4		Mediates EGFR and ERK1/2 signaling pathways in cervical adenocarcinoma cells; inhibits intestinal polyp size and colon carcinogenesis in a mouse model	(208–210)

(Continued on the following page)

Table 1. Targeting prostaglandin signaling pathways in cancer. (Cont'd)

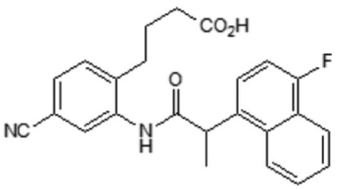
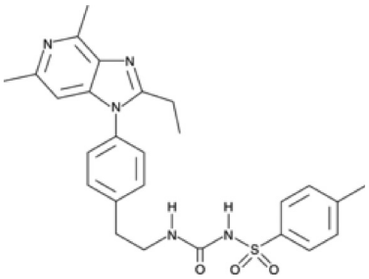
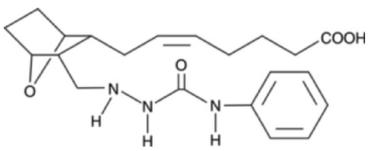
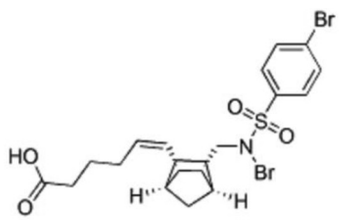
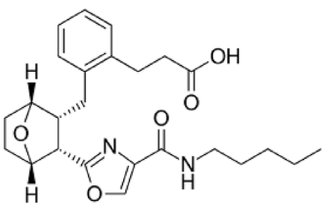
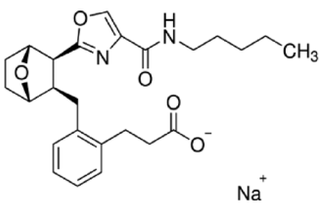
Compound	Target	Structures	Biological function	Reference or clinical trials number
ONO-AE3–208	EP4		Inhibits growth or metastasis of breast, prostate, colon cancer cells, and melanoma	(36, 96, 211–213)
AAT-007	EP4		Phase II Trials of EP4 receptor antagonist, AAT-007 (RQ-07; CJ-023,423) in advanced solid tumors	NCT02538432 NCT03658772
ONO-4578	EP4		Phase I/II clinical trails EP4 receptor antagonist ONO-4578 in advanced/metastatic tumors	NCT03155061 NCT03661632
TPST-1495	EP2/EP4		Phase 1a/1b study antitumor activity in subjects with solid tumors	NCT04344795
SQ-29548	TBXA2R		Inhibits proliferation, migration, and induces apoptosis of lung cancer, multiple myeloma, and prostate cancer cells; rescues the viability of cells, ameliorates the intracellular ROS level in neuroblastoma cells;	(119, 121, 214–217)
ONO NT-126	TBXA2R		A potent and selective TBXA2R antagonist in human astrocytoma cells; enhances the cisplatin-induced apoptosis of lung cancer cells	(218, 219)
CPI211	TBXAR2		Inhibits metastasis of breast cancer	(220)
Ifetroban sodium	TBXAR2		Ifetroban in treating patients with malignant solid tumors at high risk of metastatic recurrence (on going)	NCT03694249

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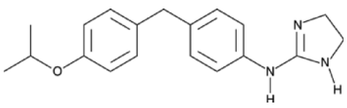
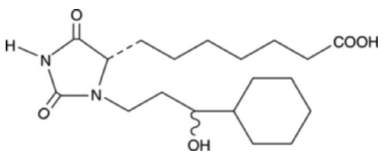
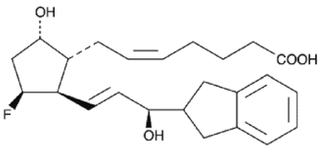
Table 1. Targeting prostaglandin signaling pathways in cancer. (Cont'd)

Compound	Target	Structures	Biological function	Reference or clinical trials number
RO1138452	IP		Suppresses migration and tube formation of tumor endothelial cells	(221)
BW245C	DP1		Inhibits colitis and colitis-associated colon cancer in mouse models; suppresses growth of ovarian cancer cells; inhibits melanoma growth in mouse models	(166, 222–224)
AL8810	FP		Mediates proliferation of prostate cancer cells	(225)

and agonists of PG receptors in cancer are summarized in **Table 1**. A number of extensive studies are focusing on the signaling pathways of PG receptors and several clinical studies are being conducted to determine the effectiveness of antagonists of EP and TXA2R against cancer development. As we partly mentioned previously, the EP receptor antagonists E7046 (NCT02540291; NCT03152370; NCT04432857), ONO-4578 (NCT03661632; NCT03155061), AAT-007 (NCT02538432; NCT03658772), and TPST-1495(NCT04344795) are being used to evaluate their inhibitory effects in advanced cancers and metastatic tumors. In addition, a clinical trial with the TBXA2 receptor antagonist, ifetroban, is being conducted in the treatment of patients with malignant solid tumors at high risk of metastatic recurrence (NCT03694249). All these studies should provide evidence as to whether targeting the PG receptors could be a promising strategy for cancer treatment.

Limitations and Adverse Effects Associated with Targeting PG Pathways

Preclinical, epidemiologic, and clinical studies have demonstrated that targeting the COX pathway could be effective in the prevention and treatment of multiple cancer types (9–11). However, suppression of COX signaling by the use of NSAIDs, or other inhibitors has been limited because the use of these drugs is associated with various side effects, including gastrointestinal toxicity and increased risk of myocardial infarction (12, 13). Extensive studies were conducted to determine the downstream signaling pathways of the PG receptors (**Fig. 1**), with the hope that targeting PG receptors might circumvent the toxic effects associated with COX inhibition while still exerting anticancer effects. Thus, several small molecules have been demonstrated to exert anticancer effects in multiple cancer types by targeting PG receptors (**Table 1**). However, whether these small molecules are effective clinically with less toxicity is still not clear although several clinical studies targeting EP receptors or the TBXA2 receptor have been conducted or are ongoing. Further studies will be needed to evaluate the effectiveness versus the unwanted side effects that have been associated with targeting PG receptors downstream of COX. Another limitation is that directly inhibiting individual PG receptors may not be as efficient as targeting COX with NSAIDS, which likely suppresses the majority of the PG pathways. Bioavailability has always been an issue with drug treatments, and thus, to improve bioavailability, multiple inhibitors might be required to attenuate cancer development. In fact, smaller doses of multiple inhibitors might be less toxic overall. For example, the TXA2:PGI2 balance is known to be critical for maintaining a healthy cardiovascular system (179). Targeting COX cannot specifically mediate the TXA2, PGI2, or other downstream signaling pathways. Thus, a combination of PG inhibitors that maintains a proper balance of TXA2 and PGI2 might have greater potential to suppress cancer development and avoid cardiovascular toxicity. Unfortunately, targeting the PG receptors has not yet made it past the stage of biological tools and future clinical studies are absolutely required to determine their potential in cancer prevention and treatment.

Summary

In this review, we examined the role the PG pathways in cancer development. Generally, PG pathways contribute to tumorigenesis by mediating cell proliferation, growth, apoptosis, invasion, migration, metastasis, and angiogenesis. PGs are critical mediators in cancer and efforts have focused on identifying the signaling pathways activated by PG receptors in multiple cancer types (**Fig. 1**; Supplementary Table S1). The PGE2/EPs, TXA2/TBXA2R, and PGF2α/FP signaling pathways mainly act as cancer promoters, whereas the PGI2/IP and PGD2/DP axes appear to primarily act as cancer suppressors. The accumulating evidence provides hope for targeting PG receptors, including EPs and TBXA2R to suppress tumorigenesis. In the extracellular microenvironment, these PGs bind with G protein receptors including EP1–4, TBXA2R, IP, DP, or FP to influence multiple cancer types. PG antagonists or antagonists interrupt binding between the PGs and receptors to suppress the development and growth of tumors (Supplementary Fig. S2). PG antagonists or agonists, in particular those targeting the EPs and TBXA2R receptors, have been successful in preclinical studies in the inhibition of tumorigenesis or metastasis (**Table 1**). Many studies have focused on the role of EPs, especially EP4, in the development of cancer. Indeed, EPs have shown their potential as biological targets in cancer. Notably, TXA2 and TBXA2R are also very promising targets for esophageal and

colon cancer prevention and treatment because of their high expression in patients with BE, EAC, and colorectal cancer compared with normal subjects. Notably, the absolute change in TXA2 in these cancers is markedly higher compared to changes in PGE2 (127, 128). These results suggest that the TXA2 pathway might be more important in gastrointestinal cancers compared with PGE2 and other PGs. On the basis of preclinical and clinical studies, targeting EP4 and TBXA2R might be a productive and effective way to treat cancer. However, as the many studies demonstrated in this review, most evidence for the role of PG receptors has been generated from *in vitro* or animal studies. In particular, whether targeting EP2 can bring benefits in the clinical treatment of cancer still remains elusive. Overall, this review examined the function of PG signaling pathways in cancer and suggest that targeting PG pathways might provide opportunities for cancer prevention and therapy.

Authors' Disclosures

No disclosures were reported.

Acknowledgments

This work was supported by The Hormel Foundation and NIH grant 1P01CA229112-01A1.

Received July 16, 2021; revised October 27, 2021; accepted December 17, 2021; published first December 23, 2021.

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