Review
Inflammation and breast cancer
Cyclooxygenase/prostaglandin signaling and breast cancer
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Abstract

Many human cancers exhibit elevated prostaglandin (PG) levels due to upregulation of cyclooxygenase-2 (COX-2), a key enzyme in eicosanoid biosynthesis. *COX-2* over-expression has been observed in about 40% of cases of invasive breast carcinoma and at a higher frequency in preinvasive ductal carcinoma *in situ* tumors, Extensive pharmacologic and genetic evidence implicates COX enzymes in neoplasia. Epidemiologic analyses demonstrate a protective effect of COX-inhibiting nonsteroidal anti-inflammatory drugs with respect to human cancer. Complementary experimental studies have established that both conventional nonsteroidal anti-inflammatory drugs and selective COX-2 inhibitors suppress mammary tumor formation in rodent breast cancer models. Furthermore, knocking out *Cox-2* reduces mammary tumorigenesis and angiogenesis, and, conversely, transgenic *COX-2* over-expression induces tumor formation. The utility of COX/PG signaling as a target for chemoprevention has been established by randomized controlled clinical trials. However, these studies also identified increased cardiovascular risk associated with use of selective COX-2 inhibitors. Thus, current efforts are directed toward identifying safer approaches to antagonizing COX/PG signaling for cancer prevention and treatment, with a particular focus on PGE_2 regulation and signaling, because PGE_2 is a key pro-tumorigenic prostanoid.

Introduction

The past few years have witnessed intense interest in the role played by the cyclooxygenase (COX) family of prostaglandin (PG) synthases in cancer. Upregulation of the inducible isoform COX-2 has been identified in many human cancers and precancerous lesions. Initially recognized in the context of colorectal cancer, *COX-2* over-expression has also been detected in approximately 40% of cases of human breast carcinoma as well as in preinvasive ductal carcinoma *in situ* (DCIS) lesions. Furthermore, epidemiologic analyses suggest a protective effect of COX inhibitory drugs with respect to both colon and breast cancer. Together, these observations have stimulated widespread enthusiasm for COX-2 as a molecular target for cancer prevention.

Substantial data support the validity of COX-2 as an anti-cancer target. Transgenic *COX-2* over-expression drives mammary tumor formation, and, conversely, knocking out *Cox-2* reduces tumor formation in rodent models of intestinal, breast, and skin cancer. Consistent with these genetic studies, selective COX-2 inhibitors (COXibs) have proven to be effective in suppressing experimental tumorigenesis. Furthermore, several recently reported randomized clinical trials have shown that COXibs significantly reduce the incidence of colorectal adenomas in humans. Dismayingly, these trials also identified an increased risk for cardiovascular events associated with COXib use, suggesting that COXibs may not be sufficiently safe for general use as cancer chemo-preventive agents. Nevertheless, the demonstrated role of COX/PG signaling in neoplasia identifies this pathway as an important anticancer target. Therefore, it behooves us to identify alternative components of the COX/PG signaling pathway, antagonism of which will achieve protection comparable to that afforded by COXibs but with minimal collateral toxicity.

Here, I review the data implicating COX/PG signaling in breast cancer, and consider alternative approaches to suppressing this pathway that may have clinical utility.

Cyclooxygenases, prostaglandins, and cancer

The COX family of enzymes comprises two members. *COX-1* (more properly *PTGS1* [PG-endoperoxide synthase 1]) is generally considered to be ubiquitously expressed, whereas *COX-2* (or *PTGS2* [PG-endoperoxide synthase 2]) is constitutively expressed in only a limited range of tissues,

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COX = cyclooxygenase; COXib = selective cyclooxygenase-2 inhibitor; DCIS = ductal carcinoma *in situ*; EP = prostaglandin E_2 receptor; ER = estrogen receptor; HER = human epidermal growth factor receptor; MMTV = mouse mammary tumor virus; mPGES = microsomal prostaglandin E synthase; NDL = *neu* deletion mutant; NSAID = nonsteroidal anti-inflammatory drug; PG = prostaglandin; 15-PGDH = 15-hydroxyprostaglandin dehydrogenase.

including placenta, brain, and kidney [1,2]. However, *COX-2* upregulation is elicited by numerous stimuli, including cytokines, growth factors and oncogenes, and is both an important component of the inflammatory response as well as an early response gene. Both COX enzymes catalyze the conversion of arachidonic acid to PGG_2 and subsequently to PGH_2, which acts as a substrate for multiple isomerases that are individually responsible for the generation of eicosanoid products, including PGE_2, prostacyclin (PGI_2), and thromboxane A_2 (Figure 1). COX-derived prostanoids contribute to many bodily functions, including hemostasis, platelet aggregation, kidney and gastric function, and several female reproductive processes [1,2]. Eicosanoids are also key mediators of pain, fever, and inflammation. Hence, COX enzymes are the targets for common painkillers of the non-steroidal anti-inflammatory drug (NSAID) class. Inhibitors that are selective for COX-2 have also been developed as anti-inflammatory agents, with the goal of minimizing the gastro-intestinal complications associated with traditional NSAIDs.

Aberrant activation of COX/PG signaling is widespread in human neoplasia [1,3]. The first indication of this was provided by the detection of elevated PG levels in cancer samples. Subsequently, it became apparent that cancer-associated increases in PG synthesis correlated with *COX-2* over-expression. *COX-2* upregulation is particularly striking in colon cancer. Thus, COX-2 protein is virtually undetectable in normal colonic mucosa, but more than 85% of colorectal adenocarcinomas have elevated COX-2 levels [1,4]. Similarly, COX-2 is undetectable in normal breast tissue by immuno-histochemistry, but it is over-expressed in about 40% of human breast carcinomas (discussed below). These and similar data from cancers of other organ sites have identified *COX-2* upregulation as a common event in human cancer, and thus they suggest that COX-2 may play a role in tumorigenesis.

A protumorigenic role for COX enzymes and COX-derived PGs has also been inferred from epidemiologic analyses. Several studies have identified an inverse relationship between colon cancer incidence and use of NSAIDs, which inhibit COX activity [4]. Similar data are also available for breast cancer [5-12]. Discrepant findings in some reports may reflect the fact that human breast cancers do not uniformly over-express *COX-2*. Nevertheless, epidemiologic data broadly support a protumorigenic role for COX enzymes in breast cancer.

Cyclooxygenase-2 expression in breast cancer

Elevated COX-2 protein levels have been detected immunohistochemically in approximately 40% of invasive breast carcinomas, with individual studies reporting frequencies ranging from 17% to 84% [13-26]. COX-2 protein is predominantly confined to the tumor epithelium, with negligible expression in normal epithelium (Figure 2). In contrast, COX-1 appears to be ubiquitously expressed in

Figure 1
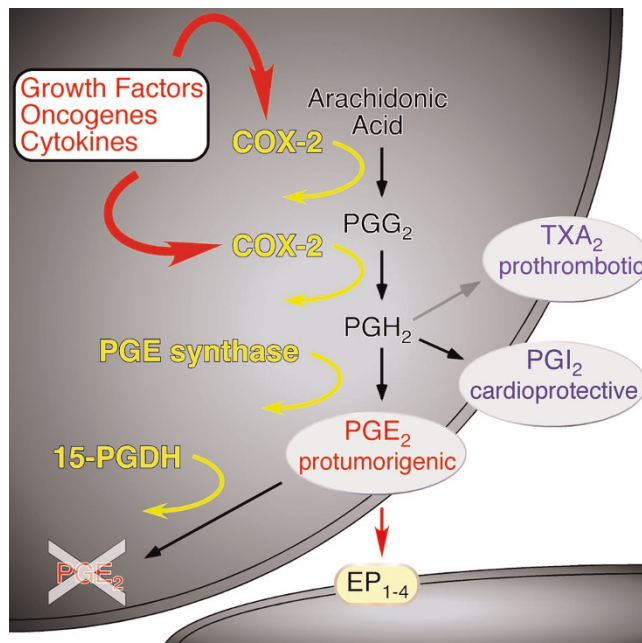
Eicosanoid metabolism and signaling. Cyclooxygenase (COX) enzymes convert arachidonic acid to the intermediate prostaglandin PGG_2, and thence to PGH_2. Subsequent enzymatic steps, catalyzed by specific isomerases, generate a variety of eicosanoid products. Thromboxane (TX) A_2 and prostacyclin (PGI_2), products of platelet COX-1 and endothelial COX-2, respectively, are thought to play opposing roles in cardiovascular biology. Most important in the context of epithelial tumorigenesis, PGE_2 is generated from PGH_2 through the action of PGE synthases. Signaling downstream of PGE_2 is initiated via interaction of PGE_2 with cognate PGE_2 receptors EP_1 to EP_4. PGE_2 signaling can be terminated via catabolism mediated by 15-hydroxyprostaglandin dehydrogenase (15-PGDH). Elevated PGE_2 levels in neoplastic tissues can thus be a consequence of *COX-2* over-expression, PGE synthase modulation, and/or loss of 15-PGDH expression.

mammary tissues [21,25]. *Cox-2* upregulation has also been detected in rodent mammary tumors, including those from both transgenic mouse and carcinogen-dependent breast cancer models [27-31]. Consistent with human observations, Cox-2 protein is present in epithelial cells in rodent tumors [30,31]. These localization data provide a marked contrast to those from colorectal cancer studies, which have identified substantial COX-2 expression in the stromal component of intestinal adenomas [32]. It remains to be determined whether stromal COX-2 expression plays a significant role in breast neoplasia.

COX-2 over-expression in human breast cancers correlates with several parameters that are characteristic of aggressive breast disease, including large tumor size, high grade, high proliferation, hormone receptor negative status, and over-expression of *HER2* (human epidermal growth factor receptor 2; also called *neu* and c-*ERBB2*) [13,24,26,33]. Consistent with these findings, Ristimaki and colleagues [26]

Figure 2
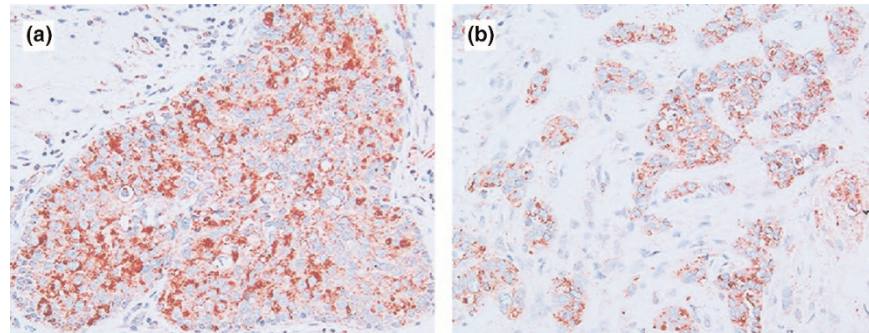
COX-2 expression in human breast tumors. Cyclooxygenase (COX)-2 protein has been detected in human breast biopsies in both **(a)** ductal carcinoma *in situ* and **(b)** infiltrating mammary carcinoma using immunohistochemistry on formalin-fixed tissue sections. Representative data are reproduced from [21] by permission of Wiley-Liss Inc., a subsidiary of John Wiley and Sons Inc. (Copyright (2000) American Cancer Society.)

have identified an inverse relationship between COX-2 protein levels and disease-free survival (Figure 3). Because HER2/neu can induce *COX-2* transcription *in vitro*, the correlation between *HER2/neu* and *COX-2* expression in breast carcinomas probably reflects a causal relationship [13,24,26,33,34]. Interestingly, both *HER2/neu* and *COX-2* are expressed at higher frequencies in DCIS (50% to 60% and 63% to 85%, respectively), which again is suggestive of a potential interrelationship. The high frequency of *COX-2* over-expression in DCIS, a common precursor to invasive breast cancer, identifies COX/PG signaling as a potentially useful target for preventing progression of DCIS to invasive disease [13,17,20,21,23,35,36]. Intriguingly, *COX-2* expression has also been detected in focal regions of normal breast in association with silencing of *CDKN2A* (p16^{INK4a}), suggesting that *COX-2* upregulation may be a very early event in breast neoplasia [37].

Cyclooxygenase-2 contributes to breast cancer: experimental evidence

Since *Cox-2* is over-expressed in mammary tumors from rodent breast cancer models, these animals provide useful experimental systems in which to evaluate the role of COX enzymes. Numerous studies have shown that experimental breast cancer can be suppressed by inhibiting Cox activity with either conventional NSAIDs or COXibs [38,39]. Furthermore, genetic ablation of *Cox-2* decreases mammary tumor formation [40]. Strikingly, transgenic over-expression of *COX-2* is sufficient to induce mammary neoplasia in multiparous animals, providing direct evidence of the *in vivo* oncogenicity of COX-2 [41]. Thus, animal-based approaches have played a pivotal role in definitively establishing that COX-2 contributes to breast cancer.

### Cyclooxygenase inhibitors suppress experimental breast cancer

The efficacy of COX inhibitors as anticancer agents has been tested in a variety of animal models (for detailed reviews, see

Howe [38], Howe and coauthors [39], Reddy [42], and Corpet and Pierre [43]). The ability of conventional NSAIDs such as indomethacin and flurbiprofen to suppress carcinogen-induced mammary tumor formation was first demonstrated more than 20 years ago. More recently, following the development of COXibs, these agents have also been tested in animal breast cancer models. Several COXibs, including celecoxib, nimesulide and rofecoxib, have demonstrated chemopreventive efficacy in chemical carcinogenesis models [30,38,39,44,45]. COX inhibitors also reduce the growth rate of implanted tumors, suggesting potential therapeutic utility. Chemically-induced tumors tend to be hormone-dependent, providing a valuable model for human breast cancers, of which approximately two-thirds are estrogen dependent. Additionally, we considered it relevant to evaluate COXib efficacy in an estrogen receptor (ER)-negative model, because several groups had reported a correlation between COX-2 over-expression and ER-negative status [13,16,24,26]. *HER2/neu* transgenic mice offer a compelling test system, because the tumors not only lack ER but also express both *HER2/neu* and *Cox-2*, thus recapitulating the relationship between HER2/neu and COX-2 in human breast cancer. Using *HER2/neu* transgenic mice, both we and others have shown that ER-negative tumor formation is significantly delayed by celecoxib administration [29,46]. These data suggest that antagonism of COX/PG signaling could be useful with respect to both ER-negative and *HER2/neu*-over-expressing breast cancers. The demonstrated chemopreventive efficacy of NSAIDs and COXibs in animal models is consistent with epidemiologic studies that show reduced breast cancer incidence in association with NSAID use [5-12].

Mammary tumorigenesis is reduced in cyclooxygenase-2-null mice

While the anticancer effects of conventional NSAIDs and COXibs strongly implicate COX enzymes in breast cancer, numerous COX-independent effects have been ascribed to NSAIDs [47,48]. Therefore, we also used a complementary

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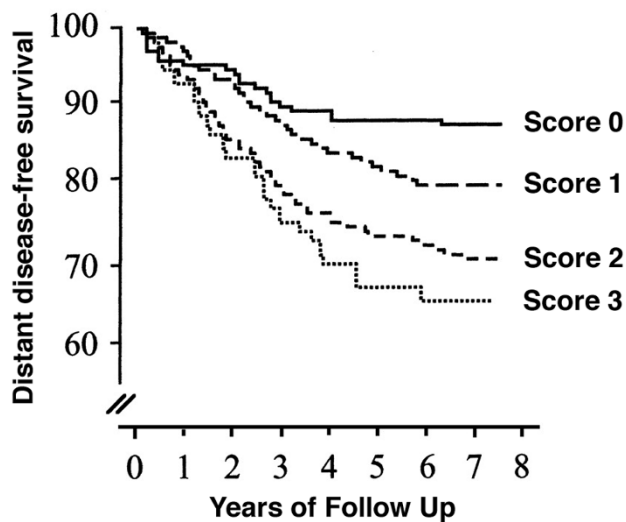
COX-2 expression in human breast cancer correlates with decreased disease-free survival. Distant disease-free survival of breast cancer patients was plotted as a function of cyclooxygenase (COX)-2 expression: score 0 = no COX-2 expression (n = 133); score 1 = weak COX-2 expression (n = 854); score 2 = moderate COX-2 expression (n = 511); and score 3 = strong COX-2 expression (n = 78). Elevated expression of COX-2 protein correlated with reduced survival (P < 0.0001; log rank test). Reproduced from [26] with permission from the American Association of Cancer Research.

genetic approach to definitively address the involvement of COX-2 in mammary tumorigenesis. Mice with targeted disruption of the *Cox-2* gene were first utilized to establish the contribution of COX-2 to tumorigenesis by Taketo and colleagues, using an intestinal cancer model [32]. We have adopted a parallel approach, crossing *Cox-2* knockout mice with the *HER2/neu* transgenic mouse mammary tumor virus (MMTV)/*neu* deletion mutant (NDL) strain, to test the role of COX-2 in breast cancer [40].

MMTV/NDL mice express a mutationally activated *HER2/neu* transgene that drives formation of multiple DCIS-like tumors in each mammary gland. These tumors subsequently progress to invasive carcinomas and ultimately metastasize to the lung, thus recapitulating the human disease [49]. Hence, we employed the MMTV/NDL strain as a breast cancer model system in which to examine the consequences of knocking out *Cox-2*. MMTV/NDL mice were crossed with *Cox-2*-deficient mice, and tumor multiplicity was compared in *HER2/neu* transgenic mice that were *Cox-2* wild type, heterozygous, and null. We found that tumor multiplicity was significantly reduced in both *Cox-2* heterozygous and null animals relative to *Cox-2* wild-type control animals (P < 0.001; Figure 4a). Complete ablation of *Cox-2* reduced the mean tumor multiplicity by approximately 50%. Additionally, an overall shift toward a higher proportion of

smaller tumors in *Cox-2* null animals relative to *Cox-2* wild-type animals was observed (P = 0.02; Figure 4b), suggesting that Cox-2 contributes not only to mammary tumor formation but also to tumor growth. PGE$_2$ levels in MMTV/NDL mammary glands correlated with *Cox-2* gene dosage. Thus, PGE$_2$ levels (ng/mg protein) in *Cox-2* wild-type, heterozygous, and null mammary tissues were 0.69 ± 0.11 (n = 7), 0.53 ± 0.15 (n = 5; P = 0.043), and 0.35 ± 0.07 (n = 5; P = 0.0001), respectively. These data provide the first genetic evidence that Cox-2 contributes to HER2/neu-induced mammary tumorigenesis [40].

Intriguingly, our *Cox-2* knockout experiment also suggested a novel role for Cox-2 in mammary gland vascularization. Specifically, we observed a striking reduction in mammary vasculature in *Cox-2* null animals relative to wild-type controls. Blood vessels were virtually absent from both dysplastic regions and areas of normal looking epithelium (Figure 5a). Consistent with the marked reduction in mammary vasculature in *Cox-2* null mammary tissues, the expression of several angiogenesis-associated genes was decreased (Figure 5b), including *VEGF* (which encodes vascular endothelial growth factor), *Ang1* and *Ang2* (which encode Tie-2 ligands), and *Flk-1* and *Flt-1* (which encode vascular endothelial growth factor receptors). Our data contrast with those obtained in studies using mouse colorectal cancer models, which suggest that *Cox-2* contributes primarily to the growth and vascularization of intestinal tumors beyond 1 mm in diameter [50,51]. Thus, in addition to its previously described role in tumor angiogenesis, Cox-2 may also contribute to blood vessel formation in nontumorous mammary tissues.

Cyclooxygenase-2 acts as an oncogene *in vivo*
As described above, mammary tumorigenesis can be suppressed by both genetic and pharmacologic ablation of Cox-2, thus clearly identifying a role for COX-2 in breast neoplasia. Furthermore, Hla and colleagues have provided definitive evidence for *in vivo* oncogenic action of COX-2 through generation of an MMTV/COX-2 transgenic mouse strain [41]. *COX-2* over-expression in mouse mammary gland induced tumor formation in more than 85% of multiparous mice [41]. Prior to visible tumor formation, COX-2 induced angiogenesis, as evidenced by increased microvessel density and expression of proangiogenic genes [52]. Furthermore, mammary gland involution after weaning was delayed in transgenic animals relative to wild-type littermates, with an accompanying decrease in apoptosis [41]. Therefore, these data suggest that COX-2 may drive tumor formation both by increasing angiogenesis and by suppressing apoptotic cell death.

Together, these genetic and pharmacologic approaches provide irrefutable evidence that COX-2 contributes to breast cancer. Furthermore, these studies offer mechanistic insights into the role of COX-2 in mammary neoplasia, indicating that COX-2 is important for angiogenesis and may also play a critical role in suppressing apoptosis. These observations are

Figure 4
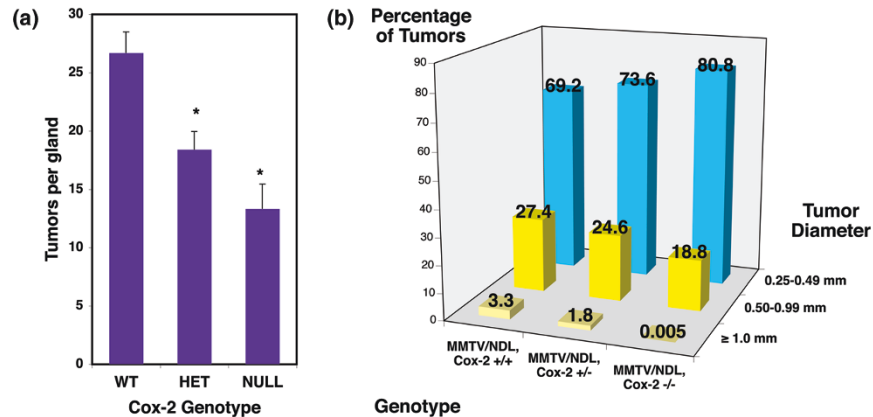
Knocking out *Cox-2* reduces mammary tumorigenesis. Mouse mammary tumor virus (MMTV)/*neu* deletion mutant (NDL) mice, which express a mammary-targeted *HER2*/*neu* transgene, were crossed with *Cox-2*-deficient mice, and mammary tumor formation was evaluated in age-matched virgin MMTV/NDL females that were *Cox-2* wild type (WT; *n* = 72), heterozygous (HET; *n* = 42), and null (NULL; *n* = 18). **(a)** Tumor multiplicity was significantly reduced in *Cox-2* deficient mice (data shown are mean ± SEM. *$P < 0.001$, by likelihood ratio test. **(b)** The percentage of tumors in each of the indicated size categories was calculated for each genotype. The proportion of large tumors was significantly reduced in *Cox-2* deficient MMTV/NDL animals relative to *Cox-2* wild-type controls ($P = 0.02$). Reproduced with permission from [40].

consistent with earlier studies in cell culture and in intestinal tumor models. Multiple additional pro-tumorigenic roles have been described for COX-derived prostanoids, including as proproliferative stimuli, immune system depressants, and promoters of cell invasiveness. COX-2 is also believed to contribute to the establishment of bone metastases. Of particular relevance to breast cancer, PGs can increase estrogen biosynthesis via upregulation of aromatase transcription (discussed below). Thus, numerous mechanisms are likely to contribute to the protumorigenic and metastasis-promoting effects of eicosanoids.

The cyclooxygenase-aromatase connection
The relationship between COX and aromatase enzymes is currently attracting considerable interest. The aromatase cytochrome P450, encoded by the *CYP19* gene, is responsible for estrogen biosynthesis and thus is extremely relevant to breast carcinogenesis, since 60% to 70% of breast cancers are hormone-dependent. Interestingly, correlations between COX and aromatase expression have been observed in human breast carcinomas [53,54]. These correlations are thought to reflect a causal link, because PG signaling can stimulate transcription of the *CYP19* gene [55-60]. PG-dependent *CYP19* induction is achieved through cAMP accumulation. At least two PGE_2 receptor (EP) isoforms signal by increasing adenylate cyclase activity [61], and *CYP19* is transcribed from cAMP-responsive promoters in breast tumor-proximal stromal tissue. Thus, both paracrine (tumor cell derived) and autocrine (stromally produced) PGE_2 may contribute to aromatase upregulation in breast cancers. Recent animal studies have demonstrated that mammary aromatase activity is significantly reduced in *Cox-2* knockout

mice, and, conversely, that aromatase expression and activity are increased by transgenic *COX-2* over-expression. Together these datasets definitively establish that Cox-2 can regulate aromatase *in vivo* in mammary tissues [56,62].

Peripheral aromatization is largely responsible for estrogen production in postmenopausal women, and mammary adipose tissue is a particularly important local estrogen source. Therefore, regulation of mammary aromatase synthesis by COX/PG signaling is most likely to be important in the context of postmenopausal breast cancer. The ability of COX-derived PGs to increase aromatase expression and hence local estrogen levels may provide a partial explanation for reports of reduced incidence of breast cancer associated with NSAID use [5-12], because COX inhibition is predicted to decrease mammary estrogen levels and hence restrict the growth of estrogen-dependent tumors. This mechanism is expected to be operative irrespective of *COX-2* expression status because *COX-1* is constitutively expressed in human breast tissues [21,25]. Importantly, the idea that both COX isoforms can impact on tumorigenesis is supported by genetic evidence obtained using *Cox-1* and *Cox-2* knockout mouse strains [32,40,63,64]. Intriguingly, Neugut and colleagues [65] have identified differential sensitivity of breast cancers to NSAID-mediated protection according to hormone receptor status. Specifically, they found that aspirin use was associated with a decreased risk of hormone receptor positive breast cancer, but did not affect the incidence of hormone receptor-negative disease, in a population-based case-control study. These data support the concept that COX inhibition reduces mammary neoplasia at least in part through suppression of estrogen biosynthesis.

Figure 5
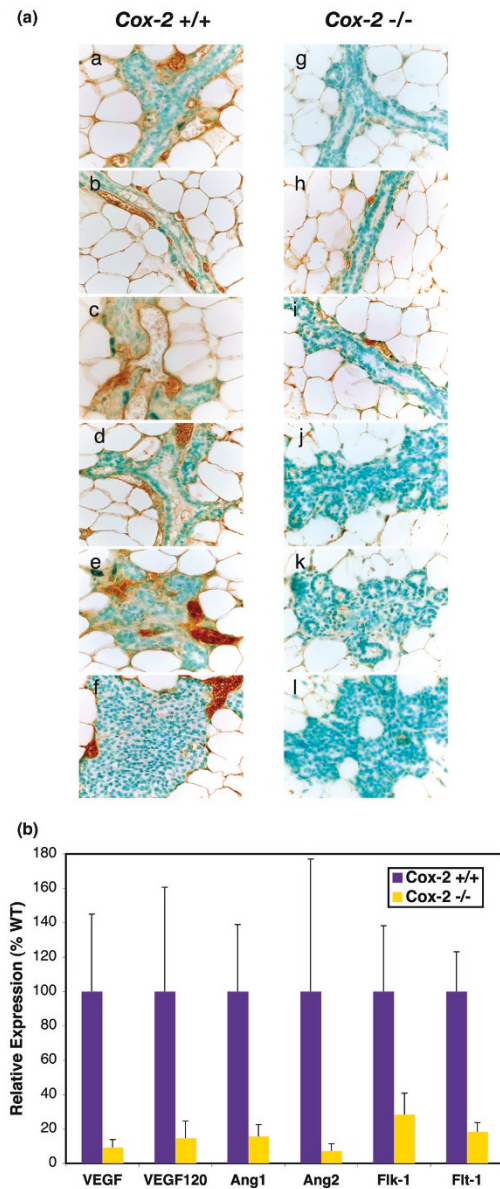
Mammary gland vascularization is reduced in *Cox-2* knockout mice.
(a) Mammary gland tissue sections from age-matched virgin mouse mammary tumor virus (MMTV)/*neu* deletion mutant (NDL) females that were *Cox-2* wild type (subpanels a to f) and *Cox-2* null (subpanels g to l) were subjected to anti-CD31 immunohistochemistry, and counterstained with methyl green. Both the number and size of blood vessels were strikingly reduced in *Cox-2* null samples. **(b)** Expression levels of angiogenesis-related genes were compared by quantitative reverse transcription polymerase chain reaction in MMTV/NDL mammary glands from *Cox-2* wild-type (blue columns) and *Cox-2* null females (yellow columns). The height of the columns indicate means normalized to the mean expression level of that gene in MMTV/NDL, *Cox-2* wild-type samples; the bars indicate the standard error. Expression of *VEGF*, *Ang1*, and *Flt1* was significantly reduced ($P = 0.016$, 0.049 and 0.010, respectively). The average of log values across all six genes for each mouse, representing a global effect, was significantly higher in wild-type tissues than in null tissues at $P = 0.025$. Reproduced with permission from [40].

Cyclooxygenase/prostaglandin signaling as an anticancer target

In combination, the data from COX-2 expression analyses, NSAID-related epidemiology, animal studies, and *in vitro* experiments strongly support a pro-tumorigenic role for COX-2 with respect to breast and other cancers. The considerable weight of evidence linking COX/PG signaling with colorectal neoplasia has stimulated evaluation of NSAIDs as preventive agents in individuals at risk for colorectal cancer. Positive results with conventional NSAIDs led to the development of similar trials to test the efficacy of COXibs, based on the expectation that these agents would have reduced gastrointestinal complications relative to conventional NSAIDs. Importantly, COXibs were found to reduce the incidence of both familial and sporadic disease, providing important proof-of-principle for targeting COX/PG signaling [66-69]. Less propitiously, some trials also identified increased cardiovascular risk associated with COXib use [70,71].

Cardiovascular toxicity of selective cyclooxygenase-2 inhibitors

The cardiovascular toxicity of COXibs has been ascribed to their selective depression of prostacyclin levels [72]. Prostacyclin (PGI_2) derived from endothelial COX-2 confers constraints on thrombogenesis, hypertension, and atherogenesis. COX-2 inhibition decreases the cardioprotection afforded by PGI_2, but, in contrast, the prothrombotic effects of thromboxane A_2, emanating from COX-1 activity in platelets, are unaffected. The cardiovascular toxicity of COXibs decreases the desirability of using this class of drugs in cancer prevention. Nevertheless, the demonstrated efficacy of COXibs as anticancer agents identifies the COX/PG signaling axis as an important target. Thus, it is incumbent on us to identify alternative components of this signaling pathway that offer safer targets for preventing cancer.

Alternative targets on the cyclooxygenase/prostaglandin signaling axis

Several potential targets have been identified through examination of eicosanoid metabolic pathways (Figure 1). Importantly in this respect, substantial data support PGE_2 as being the predominant pro-tumorigenic prostanoid. Thus, it seems reasonable to hypothesize that selective targeting of PGE_2 synthases or receptors might be useful with respect to neoplasia, and more broadly for analgesia and anti-inflammatory applications. Substantial interest is focused on microsomal prostaglandin E synthase (mPGES)-1, which is up-regulated in numerous human cancers, including breast carcinomas [73,74]. mPGES-1 ablation does not increase thrombogenesis or blood pressure [75], consistent with the hypothesis that prostacyclin suppression is a key component of COXib-induced cardiotoxicity. Thus, mPGES-1 may offer a useful alternative target to COX-2 for combating inflammation and cancer.

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The role of individual PGE_2 receptors (prostaglandin E receptors [PTGERs] 1 to 4; more usually called EP_1 to EP_4) in cancer is also under investigation. Expression of all four EPs has been identified in mouse mammary tumors [29,52]. Genetic and pharmacologic ablation approaches have been used to analyze the contributions of individual EPs to tumorigenesis in multiple animal models. No single EP has emerged as a clear favorite, with different receptors being implicated depending on the experimental system [76]. EP_1, EP_2, and EP_4 all appear to have pro-tumorigenic activity in at least one breast cancer model. Thus, it remains to be established which PGE_2 receptor(s) is the optimal candidate for anticancer applications.

Enhancing PGE_2 inactivation may provide an alternative mechanism for ameliorating COX-associated neoplasia. PGE_2 is metabolized to relatively inactive 15-keto-PGs and 15-keto-lipoxins by the enzyme hydroxyprostaglandin dehydrogenase 15-NAD, more commonly called 15-hydroxyprostaglandin dehydrogenase (15-PGDH; Figure 1). Strikingly, reduced levels of 15-PGDH have been observed in multiple tumors, including non-small-cell lung cancers, colorectal carcinomas, and breast cancers, and substantial evidence suggests that 15-PGDH acts as a tumor suppressor [77-82]. These observations suggest the intriguing possibility that PGE_2 signaling could be terminated by reversing epigenetic inactivation of the *15-PGDH* locus, and that this could offer a novel approach to targeting PGE_2-driven neoplasia.

Conclusions

The COX/PG signaling pathway offers a useful target for anti-breast cancer strategies. COX-2 is over-expressed in a significant proportion of invasive breast carcinomas, and at a higher frequency in breast pre-cancers. Both pharmacologic and genetic ablation of Cox-2 suppress experimental breast cancer, and transgenic *COX-2* over-expression drives tumor formation. Together these data strongly support the validity of COX/PG signaling as an anticancer target. The recently appreciated cardiovascular toxicity of COXibs diminishes the likely utility of this class of drugs for preventing cancer. However, analysis of the pathways by which COX-derived PGE_2 drives tumorigenesis is expected to lead to identification of novel drug targets for cancer treatment and prevention.

Competing interests

The author declares that they have no competing interests.

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