REVIEW

Celecoxib in breast cancer prevention and therapy

Jieqing Li[1,2]
Qiongyu Hao[2]
Wei Cao[2,3]
Jaydutt V Vadgama[2,4,*]
Yong Wu[2,4,*]

[1]Department of Breast Surgery, Tianjin Central Hospital of Gynecology and Obstetrics, Tianjin, China; [2]Division of Cancer Research and Training, Department of Internal Medicine, Charles R. Drew University of Medicine and Science, Los Angeles, CA, USA; [3]Department of Nuclear Medicine, Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [4]David Geffen UCLA School of Medicine and UCLA Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA, USA

*These authors contributed equally to this work

Correspondence: Jaydutt V Vadgama; Yong Wu
Division of Cancer Research and Training, Department of Internal Medicine, Charles R. Drew University of Medicine and Science, 1748 E. 118th Street, Los Angeles, CA 90059, USA
Tel +1 323 563 9397
Fax +1 323 563 4889
Email jayvadgama@cdrewu.edu; yongwu@cdrewu.edu

Abstract: Breast cancer has a high incidence worldwide. The results of substantial studis reveal that inflammation plays an important role in the initiation, development, and aggressiveness of many malignancies. The use of celecoxib, a novel NSAID, is repetitively associated with the reduced risk of the occurrence and progression of a number of types of cancer, particularly breast cancer. This observation is also substantiated by various meta-analyses. Clinical trials have been implemented on integration treatment of celecoxib and shown encouraging results. Celecoxib could be treated as a potential candidate for antitumor agent. There are, nonetheless, some unaddressed questions concerning the precise mechanism underlying the anticancer effect of celecoxib as well as its activity against different types of cancer. In this review, we discuss different mechanisms of anticancer effect of celecoxib as well as preclinical/clinical results signifying this beneficial effect.

Keywords: celecoxib, breast cancer, COX-2, inflammation

Introduction

Breast cancer (BC) is the most frequent cancer in women, the second most common cancer worldwide, and the second primary cause of cancer-related deaths.[1] One in eight women who live to age 85 years will develop BC over the course of their lifetime.[2] Previous studies suggest that inflammation is associated with cancer, and a robust correlation exists between the manifestation of inflammation and the progress of precancerous lesions at a number of anatomic sites.[3] On the other hand, cancer cells might exploit components of the inflammatory process to induce angiogenesis, inhibit apoptosis, and enhance proliferation, migration, and metastasis,[4] such as NF-κB, cytokines or cytokine receptors, chemokines or chemokine receptors, fibroblast growth factor or receptor (FGF or FGFR), and vascular endothelial growth factor (VEGF). Increasing evidence demonstrates the key role of chronic inflammation markers in increased BC risk[5]; for example, a meta-analysis suggested a significant dose–response correlation for C-reactive protein (CRP) with BC risk.[6] The pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, induce BC cells to penetrate the blood vessels, contributing to metastasis.[7]

Owing to its significant pro-tumor effects, inflammation has become a promising target for cancer prevention and treatment. Among various inflammatory factors, cyclooxygenase 2 (COX-2) is the most commonly studied anti-inflammatory/anticancer target.[8,9] Unlike COX-1, COX-2 is undetectable in normal breast tissue, but in tumor tissue, it overexpresses by 40%,[10] and in ductal carcinoma in situ (DCIS) it

overexpresses by approximately 80%.[11] The overexpression of COX-2 has been reported in different tumor cells and neovascular endothelial cells.[12] The overexpressed COX-2 converts arachidonic acid (AA) into prostaglandin E2 (PGE2),[13] which promotes BC progression through different mechanisms, for instance, suppression of antitumor immunity,[14] promotion of invasiveness,[15] migration,[15] stem-like cell (SLC) formation,[16] angiogenesis,[17] and lymphangiogenesis.[18]

Over 20 years ago, NSAIDs were reported to have anti-colon cancer effects.[19] Abundant epidemiological and preclinical/clinical studies demonstrated that celecoxib, a specific COX-2 inhibitor, was related to suppression of cancer cell proliferation and decrease in cancer incidents. In this article, different mechanisms underlying anticancer effect of celecoxib as well as preclinical/clinical results signifying this beneficial effect are discussed.

Celecoxib and BC

Celecoxib is the international nonproprietary name of 4-[5-(4-methylphenyl)–3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide, a COX-2-selective NSAID. Its oral capsule form was initially approved by US Food and Drug Administration (FDA) and marketed by Pfizer, Inc. (New York, NY, USA) in 1999. As a selective COX-2 inhibitor, celecoxib is used as an analgesic, anti-inflammatory, and antipyretic drug. Numerous preclinical evidence suggests that celecoxib may provide a strong chemopreventive activity against BC. Celecoxib treatment (500–1,500 mg/kg diet) can significantly decrease incidence, multiplicity, and tumor volume in several animal models of BC.[20,21] In addition, metastasis to the lung and brain could also be prevented.[22,23] Besides preclinical studies, clinical trials also showed positive results. Two case–control studies, including 323[24] and 18,368[25] BC cases, respectively, illustrated that a standard dose intake of celecoxib (200 mg/day) for more than 12 months was associated with significant reduced risk of BC. However, in these studies, OR was different,[25] and this might be caused by a longer duration of drug intake in the former study (more than 2 years vs more than 1 year).

Mechanisms of celecoxib's antitumor action

In spite of the encouraging efficacy mentioned earlier, the mechanisms of celecoxib's antitumor action still need to be explored. COX-2 plays an important role in tumorigenesis and development. Thus, celecoxib, as a selective COX-2 inhibitor, is believed to have several potential antitumor mechanisms, including inhibition of proliferation, induction

of apoptosis, immunoregulation, regulation of tumor microenvironment, antiangiogenic effect, and resensitization of other antitumor drugs. Meanwhile, COX-2-independent pathways also contribute to the antitumor effect of celecoxib.

Inhibition of proliferation

Celecoxib represses the proliferation of BC cells in vitro and also prevents the incidence of BC chemically induced by 7,12-dimethylben anthracene (DMBA) in rats. Thus, celecoxib shows an anticancer activity and seems to be effective in anticancer treatment.[26] Bocca et al[27] assessed the antiproliferative activity of celecoxib on human BC cells with different COX-2 expression levels. Celecoxib treatment induces a robust inhibition of cell growth in estrogen receptor (ER)α (+) MCF-7 cells, which is accompanied by a decrease in expression and activation of aromatase and ERα. The related mechanism may involve ERK and Akt inhibition as well as induction of PP2A and PTEN. In this cell line, celecoxib shows only weak effect on COX-2 level. In contrast, in ERα (−) MDA-MB-231 cells, celecoxib induces a striking suppression of COX-2, which is associated with a decrease in aromatase expression and cell proliferation. These results imply that celecoxib may exert antiproliferative activity in BC cells through COX-2-dependent or COX-2-independent pathways. A study identifying transcriptional changes in BC tissues of patients treated with celecoxib suggested that short-term COX-2 inhibition by the drug stimulates transcriptional programs that facilitate antitumor activity in primary BC tissue. The influence on proliferation-related genes is reflected by a decrease in Ki-67 (+) cells.[28] Basu et al[29] explored the mechanisms by which celecoxib affects tumor growth of two human BC cell lines such as MDA-MB-231 (highly invasive) and MDA-MB-468 (moderately invasive). They demonstrated that the distinct molecular mechanisms of celecoxib-induced growth suppression depend on the expression level of COX-2 and invasiveness in different human BC cell lines. The studies suggest that COX-2 plays an important role not only in the cancer cell growth but also in activating the angiogenic pathway via modulating levels of VEGF. Taken together, these results provide a theoretical and experimental basis for the clinical anticancer effect of celecoxib.

Induction of apoptosis

Apoptosis is an evolutionary conserved programmed cellular suicide mechanism that is vital for tissue homeostasis in multicellular organisms. It also causes the cytotoxic effects in response to standard genotoxic chemotherapy/radiotherapy.

Intriguingly, some researchers found that the tumor growth inhibition effect of celecoxib was mainly caused by inducing apoptosis[30] rather than disturbing cell proliferation.[31] Celecoxib-resistant cell lines with COX-2 overexpression[32] exhibit a reduced level of Bax, a pro-apoptosis protein, and increased levels of anti-apoptosis proteins such as Bcl-2 or Bcl-xL. COX-2 knockdown by its specific siRNA significantly decreases clonogenicity and levels of Bcl-xL and Bcl-2 in these cells. In MDA-MB-231[29,30] and MCF-7 cell lines,[33] celecoxib induces apoptosis by decreasing phosphorylation of Akt, then increasing the expression of Bax and activation of caspase 3 and caspase 7. Wang et al[34] showed that celecoxib induces apoptosis of the BC cell line, MDA-MB-231, by inhibiting the NF-κB pathway. Another mechanism of celecoxib-induced apoptosis in most cellular systems involves p53-independent mitochondrial apoptosis pathway, which is COX-2 independent and could not be inhibited by the overexpression of Bcl-2.[35,36]

Some studies suggest that the antineoplastic effects of celecoxib are attributed to its unspecific inhibitory actions on β-catenin signaling,[37,38] which is a fundamental component of the canonical Wnt pathway. Overactivation of Wnt/β-catenin signaling is associated with the progression of different types of cancer and promotion of cancer cell growth, survival, and malignant phenotype. Furthermore, recent studies suggest that Wnt/β-catenin signaling plays an important role in the modulation of cancer stem cells.[39,40] GSK-3β phosphorylates and marks β-catenin for ubiquitination and succeeding proteasomal degradation. Binding of Wnt ligands to their receptors initiates a signaling cascade that averts GSK-3β from tagging β-catenin for degradation, leading to its accumulation, translocation to the nucleus, binding to the T cell factor (TCF) family of transcription factors, and activation of Wnt target gene expression. Celecoxib treatment induces GSK-3β dephosphorylation, contributing to β-catenin phosphorylation induced by GSK-3β and suppression of the Wnt/β-catenin-dependent gene transcription, for example, c-Myc or cyclin D1, COX-2, and VEGF.[38,41] It is noteworthy that GSK-3β is a direct downstream target of Akt/PKB and activated Akt/PKB phosphorylates and consequently inactivates GSK-3β. Hence, celecoxib inhibition of Akt/PKB might at least partly be responsible for the reduction in the β-catenin levels.

Survivin is an "inhibitor of apoptosis" (IAP) protein that also functions as a mitotic regulator essential for cell division.[42] It represses apoptosis through hindering the activation of caspases. Intriguingly, celecoxib treatment downregulates survivin levels of cancer cells in vitro and in vivo.[43–47]

The degree of survivin inhibition of celecoxib correlates with its efficacy to impede cancer cell growth and to promote apoptosis among different types of cancer cells. Since prostaglandins elevate survivin expression, the downregulation of survivin may be partly attributable to celecoxib-induced suppression of COX-2.[48] In view of the role played by survivin in apoptosis resistance of cancer cells, the inhibitory effects of celecoxib on this protein might be particularly relevant to its use in anticancer treatment.[49,50] Whether the induction of apoptosis leads to clinical benefits is still debatable. A study showed that celecoxib increased apoptosis and reduced the levels of PG and VEGF expression.[51] However, this effect could not postpone tumor appearance and reduce tumor progression and development.

Immunoregulation

A thorny problem in the process of treating tumors is a repressed cell-mediated immunity, characterized by the failure of immune effector cells to induce effective antitumor responses. CD4+ or CD8+ T cells were mostly involved in local tumor suppression, while natural killer (NK) cells were involved in tumor metastasis.[52] Immunosuppressive factors, produced by the tumor, cause this problem according to tolerance. COX-2 plays an important role in BC immune escape. PGE2 has a series of adverse effects on the immune response to tumors in the body, for example, negatively influencing the activity of T/B lymphocytes, NK cells, and dendritic cells, reducing TNF-α synthesis and increasing the activity of immunosuppressive IL-10.[53] These unfavorable effects ablate the effectiveness of host defenses in monitoring and eliminating malignant cells, thus resulting in their unrestrained proliferation.[54] Previous studies demonstrate that the reduced expression of COX-2 in BC cells promotes tissue infiltration of cytotoxic T lymphocytes (CD8+), implying a role of COX-2 in immunosuppression. COX-2 inhibitors such as celecoxib regulate antitumor immunity in local and metastasis BC individually.[55] In addition, the application of celecoxib in human BCs prompts an increased number of immune cells in the tumor microenvironment.[54] A study by Gallouet et al[56] demonstrated that follicular lymphoma stromal cells release great amounts of PGE2. This production can be abolished by celecoxib treatment that targets the COX-2 isoenzyme associated with PGE2 synthesis. Interestingly, they also found that celecoxib promotes apoptosis in primary follicular lymphoma B cells cocultured with stromal cells, nonetheless, independently of the PGE2/COX-2 axis.

Substantial studies suggested that celecoxib might switch the function of immune cells to a more tumor-killing

phenotype via impeding tumors from releasing prostaglandins and via hindering COX activity in immune effector cells. Lang et al[57] suggested that cancer cells suppress the physiological function of immune cells and that celecoxib, to a certain extent, recovers this function. These results deliver an in-depth understanding of the anticancer effect of celecoxib and support its prophylactic use in high-risk patients. In a study evaluating the influence of celecoxib administration on tumor-infiltrating lymphocyte (TIL) subsets (CD3^{+}CD4^{+} CD8^{+}CD25^{+} and T cell receptor [TCR]-zeta-expressing cells) and tryptase(+) mast cells in human cervical cancers, Ferrandina et al[58] provided the first evidence that this drug can restore zeta expression by TIL in primary cervical cancers. Overall, these results suggest that a positive regulation of immune function might serve as a crucial mechanism underlying the antitumor effect of celecoxib.

Regulation of tumor microenvironment

During chronic inflammation, pro-inflammatory molecules including cytokines, ROS, NF-κB, and inducible nitric oxide synthase (iNOS) are increased and provide an advantageous microenvironment for cancer cell growth. Therefore, inflammation might result in the initiation of cancer and provide the suitable environment to support tumor growth.[59] The tumor microenvironment consists of a variety of cell and molecular components, such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinase (TIMP)-1. Tumor microenvironment has profound impacts on tumor cell proliferation, migration, and apoptosis.[60,61] Celecoxib inhibits 12-*O*-tetradecanoyl phorbol-13-acetate (TPA)-induced MMP-9 expression in a dose-dependent manner by increasing the activity of TIMP-1.[62,63]

The stimulation of constitutive expression of COX-2 is a crucial factor in the tumorigenic process. Various key risk factors associated with cancer causativeness are capable of stimulating COX-2. These factors comprise certain essential dietary fatty acids, nicotine and its metabolites, growth factors, infectious agents, hypoxia, hormones, ultraviolet B, and free radicals; oncogenic proteins; and endotoxins; etc.[64–67] Some microenvironmental stimuli, for example, bacterial lipopolysaccharides, TNF, and by-products of protein synthesis and degradation, also induce constitutive COX-2 expression. In addition, because the *COX-2* gene contains various promoter binding sites, nuclear transcription factors including NF-κβ or NF-IL6 might also mediate its upregulation.[68] Genetic induction of COX-2 in BC cells triggers local constitutive estrogen synthesis through activating the promoter II region of the aromatase gene (*CYP-19*)

in adjacent fat and muscle cells.[69] Terry et al[70] revealed a vital relationship between COX-2 overexpression and mammary tumorigenesis induced by estrogen. Hence, COX-2 tumorigenesis seems to involve synergistic interactions between many microenvironmental and genetic cofactors. Accordingly, recent studies suggested that regular use of aspirin and other coxibs has noteworthy therapeutic impact in cancer patients.[71,72] Expression of COX-2 can also be increased by large amount of collagen, which contributes to high breast density[73] and growing incidence of BC.[74,75] This effect can be inhibited by celecoxib through reducing overall collagen deposition and the levels of COX-2, PGE2, and Ki-67 expression.[76]

Tumor-associated macrophages are associated with cancer cell survival. In a microenvironment study of BC cells, Li et al[77] demonstrated that COX-2 is plentifully expressed in breast tumor-associated macrophages, which is associated with poor prognosis in BC patients. Their studies suggested that COX-2 serves as an important cancer-promoting factor through prompting a positive feedback loop between macrophages and BC cells. Apparently, COX-2 inhibitor, celecoxib, is favorable in disturbing this feedback loop in the cancer microenvironment. Accordingly, COX-2 can be exploited as a target for BC prevention and therapy. These findings provide solid molecular evidence to support the anti-BC effect of celecoxib, which has potential to raise positive expectations for clinical use.

Antiangiogenic effect

Angiogenesis refers to the generation of new blood vessels through the extension of preexisting vasculature. It is modulated by an equilibrium between the pro- and antiangiogenic factors. During tumorigenesis, the role of pro-angiogenic factors exceeds that of their counterpart and triggers the growth of new capillaries to supply more blood flow and overcome hypoxia inside the cancer microenvironment, leading to tumor growth and metastasis. At the molecular level, one of the mechanisms underlying COX-2-dependent neoplastic initiation and development in BC involves its proangiogenic activity.[78,79] Actually, COX-2 activates MMPs in an intricate mechanism involving NF-κB. This protein also promotes endothelial migration by thromboxane A2 (TXA2).[78,80] Moreover, the augmented activity of COX-2 contributes to the release of proangiogenic factors by epithelial and endothelial neoplastic cells, fibroblasts, and macrophages.[80,81] In detail, COX-2-dependent angiogenesis begins with the formation of proangiogenic prostaglandins (primarily PGE2) by tumor cells, which enhances the levels

of VEGF and bFGF. VEGF directly induces COX-2 in ECs, while bFGF induces COX-2 in fibroblasts to synthesize PGs, which can stimulate the PKA pathway via the EP2 receptor. In addition to their direct pro-angiogenic action, PGs may also induce angiogenesis indirectly, via activating monocytes that infiltrate tumor tissues. Subsequently, the activated vascular COX-2 leads to the elevated permeability, proliferation, and morphogenesis of vasculatures.[81] The high microvessel density results in the greater metastatic potential of tumor cells and poor patient prognosis.[78,81] Furthermore, PGE2 can also promote angiogenesis through activating EP4 and its second messenger PKA in ECs.[82]

Celecoxib could inhibit PGE2-induced angiogenesis and lymphangiogenesis and sequentially inhibit tumor growth and metastasis, especially in COX-2-overexpressed cell lines,[17,83] together with the reduction in microvessel density, microtubule formation, and serum VEGF level.[84,85] This inhibition effect was associated with PGE2 receptor 4 (EP4) and could be reversed by exogenous PGE2.[86] Microvascular permeability could also be reduced by celecoxib.[87,88] Tamoxifen (TAM) is an ER modulator and widely used in the treatment of BC as an adjuvant therapy against recurrence after surgery. Nevertheless, prolonged TAM administration increases VEGF levels in BC patients, stimulating new blood vessel formation and thus limiting its effectiveness. Kumar et al[89] demonstrated that celecoxib can relieve TAM-induced angiogenesis via ROS-dependent VEGF/VEGFR2 autocrine signaling. In addition, Vaish and Sanyal[90] reported that celecoxib can inhibit angiogenesis during the early neoplasm of colon through regulating PI3-K/PTEN/Akt and the canonical Wnt/β-catenin signaling pathway. In short, these findings shed light on molecular mechanisms underlying celecoxib's anticancer effect from another perspective, which enhances the positive anticipation of its clinical application.

Integrating celecoxib into BC treatment

Celecoxib has been examined for improvement in chemotherapy effectiveness in cancer clinical trials. In fact, it has been reported that celecoxib could stimulate sensitivity to chemotherapy of BC cells[91–93] via affecting the activation of multidrug resistance protein 1 (MDR1) which induces drug resistance and could be upregulated by COX-2.[94,95] Instead of affecting the pump function of MDR1, celecoxib downregulates its expression by inducing hypermethylation of MDR1 gene promoter[96] and inhibiting the DNA-binding activity and expression of nuclear transcription factors such as AP-1 and NF-κB, which can combine with putative binding sites of human MDR1 gene promoter.[97] In addition to the activation of MDR1, of pertinence to this review, celecoxib was recently demonstrated to significantly sensitize other antitumor drugs with multiple mechanisms.

Combination with chemotherapy

Considering its own antitumor competence and resensitization of other antitumor drugs, celecoxib could be a potential candidate for combination therapy. Preclinical research suggested that the antitumor effect of several agents can be enhanced by combining with celecoxib,[98] including doxorubicin[99] and 5-fluorouracil (5-FU).[100] In several Phase II studies, the combination of celecoxib and capecitabine, an orally administered pro-drug of 5-FU, could provide a clinical benefit rate at 42.1–47.5% and an unexpected lower toxicity than capecitabine alone in metastatic BC (MBC) patients.[101,102] In a single-arm, mono-institutional, nonrandomized, Phase II, two-step clinical trial, celecoxib was combined with cyclophosphamide, and the clinical benefit of this combination came to 55% in 20 advanced BC (ABC) patients.[103]

Celecoxib can also be integrated into multidrug chemotherapy regimens, in which FEC (5-FU, epirubicin, and cyclophosphamide) is the most common one. A study containing 50 patients showed that preoperative FEC with celecoxib (FECC) could provide lower intensity staining for COX-2, Ki-67, and p53 in 90% patients, while no difference was observed on tumor size, grade, or axillary lymph node status.[104] In a Phase II, multicenter, open-label, single-arm study (N001),[105] 64 invasive BC patients received four cycles of FEC (500, 100, 500 mg/m²) followed by four cycles of docetaxel (100 mg/m²) with celecoxib (200 mg twice daily) as neoadjuvant therapy (NAT). After NAT, 43 patients achieved clinical complete response (cCR) and 13 achieved clinical partial response (cPR). In addition, despite potential side effects on cardiac system, the cardiac safety of celecoxib has been declared to be acceptable.[106,107]

It has also been reported that celecoxib increases the sensitivity of drug-resistant KBV20C cancer cells to antimitotic drugs.[108] This sensitization mechanism is independent of the suppression of p-glycoprotein, indicating that the KBV20C cells are sensitized via targeting of signaling pathways by celecoxib. Moreover, it has also been observed that celecoxib intensely sensitizes KBV20C cells to vinblastine and paclitaxel, as indicated by microscopic observation, determination of Annexin V staining, and cleaved poly(ADP-ribose) polymerase (cleaved PARP). These results suggest that COX-2 inhibitors such as celecoxib can be used for cancer patients with potential resistance,

without the toxic effects of p-glycoprotein suppression. Of interest, as detailed previously,[109] celecoxib promotes (sorafenib + sildenafil) lethality in multiple ovarian cancer cell lines, concomitant with a decrease in the expression of several chaperone proteins in parallel with decreased levels of the drug efflux pumps such as ABCB1/ABCG2. The cytotoxicity by the triple combination was induced by caspase 9-dependent apoptotic pathway and RIP-1/caspases 2, 4/ AIF-dependent necroptotic pathway. In addition, the triple combination significantly reverted platinum chemotherapy resistance. Combined with the previous studies substantiating in vivo the combinations of "celecoxib + sildenafil" and "sorafenib + sildenafil" as cytotoxic to various cancer cell types, it has been suggested that the celecoxib/sorafenib/ sildenafil combination ought to be investigated in a Phase I trial in ovarian cancer.[109] Table 1 summarizes the drugs

suggested for use in combination with celecoxib for BC treatment based on preclinical data.

Not all the studies showed positive results, especially in patients with HER2-negative tumor. A multicenter randomized controlled Phase II clinical trial showed that celecoxib did not improve pathological complete response (pCR) rates in addition to epirubicin–cyclophosphamide–docetaxel (EC-D) regimen.[110] Moreover, the REMAGUS-02 multicenter randomized Phase II trial[111] demonstrated that the addition of celecoxib could not provide an increased pCR rate in HER2-negative patients. The long-term follow-up indicated that, in the HER2-negative subgroup, the addition of celecoxib led to smaller tumor size and lower expression of progesterone receptor (PgR) status, but no association of disease-free survival (DFS) benefit. In BC patients, COX-2 overexpression can be induced by HER2 oncogene activation[112] and provide

Table 1 Preclinical studies on combination of celecoxib and other therapeutic drugs in BC

Study	Combination reagent	Subject	Mechanism of action
van Wijngaarden et al[99]	Doxorubicin	MDA-MB-231 cell line	NF-κB-mediated increase in intracellular accumulation
Irie et al[100]	5-FU	BALB/c mice	Suppression of VEGF, enhancement of IFN-γ
Lim et al[108]	Paclitaxcel and vinblastine	KB and KBV20C cell lines	Increasing G2 phase cell cycle arrest, C-PARP production
Hahn et al[85]	DC-based cell vaccines GM-CSF	BALB/c mice (4T1)	Elevation of IFN-γ and IL-4 secretion by CD4+ T cells Increased infiltration of CD4+ and CD8+ T cells
Basu et al[128]	Dendritic cell-based cancer vaccine	MMTV-PyV MT mice	Reduction in IDO and survivin Increasing PTEN, Bax, and IFN-γ-producing CD8+ CTLs
Li et al[129]	PD-1 mAb	BALB/c mice (4T1)	Increasing CXCL9 and CXCL10 Suppression of IL-1, IL-6
Cho et al[130]	Nelfinavir (Viracept)	MCF7, MCF7/Dox[a], MCF7/Tax[b] BT-474, BT-1.0B and BT-1.0E[c]	Aggravation of ER stress
Mustafa and Kruger[133]	F-l-Leu	MMAC-1 cell line C3 (1)-SV40 Tag-transgenic mice	Activation of PTEN
Niu et al[134]	Minocycline hydrochloride	Nude mice (MDA-MB-435S)	Inhibition of VEGF and MMP-9 Increasing tumor cell death
Yu et al[135]	Matrine	MDA-MB-231 cell line	Impact on EGF/VEGF-VEGFR1-Akt-NF-κB signaling pathway
Wang et al[136]	Berbamine	MDA-MB-231 and MDA-MB-435S cell lines	Inhibition of Akt, NF-κB target, c-Met, Bcl-2/Bax, osteopontin, VEGF, MMP-9, and MMP-2
Jeon et al[137]	Luteolin	MCF-7, MCF7/HER18, MDA-MB-231, and SkBr3 cell lines BALB/c nude mice (MDA-MB-231)	In MCF-7 and MCF7/HER18 cells: Akt inactivation and ERK signaling inhibition In MDA-MB-231 and SkBr3 cells: Akt inactivation and ERK signaling activation
Kisková et al[139]	Resveratrol	Sprague Dawley rats MCF-7 cell line	Inducing GDF15
Thill et al[142]	Vitamin D	MDA-MB-231 and MCF-7 cell lines	Suppression of aromatase expression

Notes: [a]MCF7/Dox, a doxorubicin/multidrug-resistant variant of MCF7. [b]MCF7/Tax, a taxol-resistant variant of MCF7. [c]BT-1.0B and BT-1.0E, two trastuzumab-resistant variants of BT474.
Abbreviations: BC, breast cancer; CTLs, cytotoxic T cells; CXCL, C–X–C motif ligand; DC, dendritic cell; ER, estrogen receptor; F-l-Leu, N-(9-fluorenyl-methyloxycarbonyl)-l-leucine; 5-FU, fluorouracil; GDF, growth differentiation factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; MMAC, mammary adenocarcinoma cell; MMP, matrix metalloproteinase; PARP, poly(ADP-ribose) polymerase; PD-1 mAb, programmed death 1 monoclonal antibody; VEGF, vascular endothelial growth factor.

a positive feedback through its product PGE2 which induces HER2 expression.[113] However, the combination of celecoxib (400 mg twice daily) and trastuzumab (2 mg/kg intravenous injection weekly or 6 mg/kg intravenous injection every 3 weeks) provided no significant enhancement in a Phase II study.[114] Of note, El-Awady et al[115] explored the ability of celecoxib to sensitize different types of cancer cells (HeLa, HCT116, HepG2, MCF-7, and U251) to a number of anti-cancer drugs (5-FU, cisplatin, doxorubicin, and etoposide). Interaction of celecoxib with these chemotherapeutic drugs is antagonistic in the BC cells, MCF-7, but not in other cells,

suggesting that celecoxib exerts distinct molecular actions in different cancer cells. Mechanistic investigations demonstrated that celecoxib increases drug-triggered G2/M arrest in MCF-7 cells allowing more time to repair drug-elicited DNA damage before access into mitosis, leading to decrease in cell death and thus contributing to antagonism. These findings, if substantiated in vivo, suggest that celecoxib is not an appropriate chemo-sensitizer for BC. Therefore, the combination of celecoxib with other chemotherapeutic drugs must be customized to the cancer type. To obtain a more accurate conclusion, more in-depth and extensive clinical trials are

Table 2 Clinical trials of celecoxib on BC (ClinicalTrial.gov)

NCT number	Phase	Start date	Status	Patients	Enrollment	Interventions
NCT00075673	I	November 2003	Terminated	With recurrent or metastatic (stage IV) disease	6	Celecoxib on days 1–21, repeat every 21 days
						Vinorelbine ditartrate on days 7, 14, and 21, repeat every 21 days
NCT01425476	I/II	July 2008	Completed	With increased risk of BC	45	Celecoxib
						Cholecalciferol 400 IU or 2,000 IU/ daily for 30 days
NCT00201773	II	July 2003	Completed	With stage II–IV disease	22	Exemestane 25 mg QD for 16 weeks
						Celecoxib 200 mg BID for 16 weeks
NCT00291694	II	April 2003	Completed	With increased risk of BC	72	Celecoxib 400 mg BID for 12 months
						Placebo
NCT00056082	II	January 2003	Completed	With increased risk of BC	110	Celecoxib 400 mg BID for 12 months
NCT00291122	–	January 2003	Completed	With T1 or T2 noninvasive BC	100	Celecoxib 400 mg BID
NCT00070057	I	April 2009	Completed		75	Celecoxib for 1–3 weeks
						Celecoxib (the doses are higher than those of the aforementioned studies) for 1–3 weeks
						No Intervention
NCT01769625	I/II	January 2009	Completed	With invasive breast carcinoma (≥1 cm)	31	Placebo + cholecalciferol 400 IU
						Placebo + cholecalciferol 2,000 IU
						Celecoxib 400 mg + cholecalciferol 400 IU
						Celecoxib 400 mg + cholecalciferol 2,000 IU
NCT03185871	II	September 2017	Recruiting	With stages T1cN0 to T3N0 BC (≥1 cm), ER/PgR (+), without lymph node spread	45	Celecoxib 200 mg BID for 2 weeks
NCT01881048	I	December 2009	Active, not recruiting	With BC	42	No intervention
						Omega-3 fatty
						Celecoxib
NCT00045591	II	February 2003	Terminated	With invasive BC	39	Celecoxib 100 mg BID
						Celecoxib 400 mg BID
NCT00088972	II	November 2004	Terminated	With increased risk of BC	8	Celecoxib
						Placebo
NCT00328432	I	June 2003	Completed	With T1 or T2 noninvasive breast	100	Celecoxib 400 mg BID
NCT00305643	III	February 2003	Terminated	With metastatic colorectal cancer or MBC	11	Celecoxib 200 mg BID + standard capecitabine treatment
						Placebo with standard capecitabine treatment

Abbreviations: BC, breast cancer; ER, estrogen receptor; MBC, metastatic BC; PgR, progesterone receptor; BID, twice a day; QD, once a day.

needed. Table 2 summarizes the clinical trials of celecoxib or celecoxib combined with chemotherapy on BC patients.

Combination with endocrinal therapy

It was demonstrated that the expression of aromatase CYP19 might be potentially regulated by PGE2 through cAMP-mediated pathways, and it makes further influence on aromatase activity[116,117] and estrogen biosynthesis.[69] Linear positive correlation was shown between CYP19 and COX-2 by semi-quantitative reverse transcriptase PCR (RT-PCR), suggesting that the combination of COX-2 and aromatase inhibitors (AIs) could have synergistic effect on hormone-dependent BC.[69] The inhibition of aromatase by celecoxib was observed at transcriptional level by real-time PCR and appeared to be dose dependent.[118] Anastrozole, an AI, was combined with celecoxib to treat BC in rats.[119] The results showed that this combination might be workable for clinical therapy.

Besides laboratory investigations, clinical trials also conducted to combine celecoxib with selective ER modulator (TAM) and AIs (exemestane). In the Celecoxib Anti-Aromatase Neoadjuvant (CAAN) trial,[120] a combination of exemestane (25 mg daily) and celecoxib (400 mg twice daily) gained significantly lowered cholesterol and low-density lipoprotein (LDL) levels and higher bone mineral density (BMD) and BC subscale scores compared with single-agent groups of exemestane (25 mg daily) and letrozole (2.5 mg daily), in postmenopausal women with histologically proven local ABC (LABC). So, although the final outcomes showed no statistical difference on clinical response and tumor volume,[121] which meant that different neoadjuvant anti-aromatase therapies have similar efficacy, the combination with celecoxib may provide some additional benefits. Some other studies, including a Phase II study[122] and a Phase III study,[123] positively supported the combination of celecoxib and exemestane in postmenopausal MBC patients. A Phase II trial of neoadjuvant exemestane (25 mg daily) plus celecoxib (400 mg twice daily) demonstrated that the combination was tolerated and anticancer response was observed in the majority of postmenopausal women with BC. Statistically, noteworthy reduction could also be found in the expression of ER, PgR, Ki-67, and COX-2.[124] Nevertheless, some other research provided a different opinion. A study established by Dirix et al[125] showed that the demographic characteristics, prognostic factors, and time to progression (TTP) were all similar no matter whether celecoxib was added to endocrine therapy or not, and the lack of COX-2 expression may attribute to this result.[126] Moreover, it was suggested that the anticancer effect of combination therapy might have mainly resulted from exemestane instead of celecoxib.[127]

TAM is extensively used in BC therapy as a preventive drug against recurrence after surgical treatment, but the long-term TAM treatment enhances patients' VEGF levels, stimulates neovascularization, and thus restrains its effectiveness. Kumar et al[89] demonstrated that the combination of TAM and celecoxib at nontoxic concentrations exerted antiangiogenic effects via explicitly targeting VEGF–VEGFR2 pathway through ROS formation. In addition, their preclinical studies suggested that the TAM/celecoxib combination is a feasible strategy for the treatment of BCs with VEGF/VEGFR2 overexpression. This inventive combination exhibits encouraging effect in anti-metastasis and stimulation of apoptosis and may be a superior personalized clinical regimen vs TAM alone for BC treatment. The clinical trials on the combination of endocrine therapy and celecoxib are summarized in Table 3.

Combination with other antitumor treatments

Dendritic cell-based cancer vaccine, from tumor lysate-pulsed dendritic cell, is a popular candidate for cancer immunotherapy. Hahn et al[85] tested the antitumor immune response using the combination of celecoxib, vaccine, and GM-CSF in 4T1 cells, a cell line with COX-2 expression, poorly immunogenic, and highly metastatic ability. The triple combination therapy successfully suppressed primary tumor growth and significantly reduced the incidence of lung metastases. This effect was achieved by a tumor-specific immune response which could be observed as increased interferon (IFN)-γ and IL-4 secretion by CD4+ T cells and infiltration of CD4+ and CD8+ T cells to the tumor site. Basu et al[128] also combined celecoxib with dendritic cell-based cancer vaccine and reconfirmed that the combination gained its antitumor effect by downregulating the expression of indoleamine 2,3-dioxygenase (IDO), a negative regulator of T cell activity. A recent study by Li et al[129] using alginate hydrogel system to locally deliver celecoxib and programmed death 1 (PD-1) monoclonal antibody (mAb) to treat 4T1 MBC mouse model demonstrated a significant improvement in the anticancer activities of celecoxib, PD-1 mAb, or both combined. The persistent high levels of the drugs in peripheral circulation and within local tumor areas were observed. Importantly, the concurrent dual local delivery of celecoxib and PD-1 synergistically elevated the levels of $CD4^+$ IFN-γ^+/$CD8^+$ IFN-γ^+ T cells in the tumor and the immune system, implying that the combinatorial therapy synergistically enhances antitumor immunity. In addition, this combination treatment induces the production of two antiangiogenic chemokines such as C–X–C motif ligand (CXCL)9 and CXCL10 as well as inhibits the intra-tumoral

Table 3 Summary of clinical trials on the combination of endocrine therapy and celecoxib

Study	Year	Phase	R	Treatment	n	Clinical response (n)					Patients	Primary objective	Secondary objective
						CR	PR	SD	PD	NR			
Canney et al[122]	2006	II	No	EXE 25 mg QD + CEL 400 mg BID	53	4	12	23	8	6	Postmenopausal women, hormone receptor positive, ABC who had PD	The percentage of patients who had neither discontinued therapy nor progressed at 6 months	Response rates, duration of response, time to next progression, toxicity graded according to the CTC version 2.0 and QOL at baseline and 3 months[a]
Dirix et al[125]	2008	II	Yes	EXE 25 mg QD	55	3	8	13		6	Postmenopausal women, hormone receptor positive, ABC who had PD after treatment with TAM	The rate of clinical benefits	Tolerability, objective response rate, TTP, duration of clinical benefit
				EXE 25 mg QD + CEL 400 mg BID	56	2	10	12		5			
Chow et al[121]	2008	II	Yes	EXE 25 mg QD	24	12				2	Postmenopausal women with histologic proof of invasive BC with positive ER and/or PgR status		
				EXE 25 mg QD + CEL 400 mg BID	30	17				1			
				LET 2.5 mg QD	28	17				0			
Falandry et al[123]	2009	III	Yes	EXE 25 mg QD + celecoxib 400 mg BID	74	1	14	34	22	5	Postmenopausal women with ER- and/or PgR-positive MBC with measurable lesions >1 cm in diameter were eligible for enrollment	Progression-free survival	Assessments of tumor response and toxicities
				EXE 25 mg QD + placebo	83	0	13	44	32	6			
Lustberg et al[124]	2011	II	No	EXE (25 mg/day, 8 weeks)→EXE (25 mg/day) + CEL (800 mg/day, 8 weeks)	22	0	8	12	1	1	Postmenopausal women with ER- and/or PgR-positive stage II–III BCs		

Note: [a]Measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core - 30 version 3.0 (EORTC QLQ C-30 v3.0) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast-Cancer-Specific 23(EORTC QLQ-BR23).
Abbreviations: ABC, advanced BC; BC, breast cancer; CEL, celecoxib; CR, complete response; CTC, common toxicity criteria; ER, estrogen receptor; EXE, exemestane; LET, letrozole; MBC, metastatic BC; n, number of patients; NR, not reassessed; PD, progressive disease; PgR, progesterone receptor; PR, partial response; QOL, quality of life; R, randomized study; SD, stable disease; TAM, tamoxifen; TTP, time to progression.

formation of IL-1, IL-6, and COX2, indicating a diminished pro-cancer angiogenic and inflammatory microenvironment. This celecoxib/PD-1 mAb combination treatment provides a promising regimen for treating human BC.

By combining celecoxib with the HIV protease inhibitor, nelfinavir (Viracept), Cho et al[130] explored the aggravation of endoplasmic reticulum stress caused by this combination, which led to apoptosis in chemoresistant BC cells. Furthermore, unmethylated celecoxib (UMC), with superior COX-2 inhibitory efficacy, showed substantially weaker antitumor effect. Therefore, they speculated that the antitumor effect of celecoxib was COX-2 independent in chemoresistant BC. Chloroquine is another material that can play a role in antitumor effect with celecoxib through endoplasmic reticulum stress response.[131] In addition, treatment with the combination of anti-IL-17 antibody and celecoxib can significantly decrease bone and lung metastasis in SKG mice with mammary gland tumors and autoimmune arthritis.[132] Preclinical studies also suggested that celecoxib could be combined with peroxisome proliferator-activated receptor gamma agonist for the treatment of spontaneous BC[133] and minocycline hydrochloride for osseous metastasis in BC.[134] These combination treatments were strikingly more effective than celecoxib alone. Moreover, many plant-derived materials were combined with celecoxib and emerged synergistic effect on antitumor effect via VEGF/Akt/NF-κB signaling, including matrine,[135] berbamine,[136] and luteolin.[137,138] Resveratrol[139] can also enhance the tumor prevention effect of celecoxib, but the exact mechanism is still under investigated.

Several epidemiological studies have shown that vitamin D has beneficial effects against the carcinogenesis and development of BC.[140,141] Recent studies revealed an association between vitamin D and PGE2 metabolism. Thill et al[142] demonstrated that a synergistic growth-inhibiting effect in BC cell lines can be elicited by the combination of celecoxib and calcitriol (1,25-dihydroxycholecalciferol or 1,25-[OH]2D3), which is a biologically active form of vitamin D.[143] Calcitriol could also inhibit COX-2 expression at both protein and mRNA levels. New perspectives emerge from the growing knowledge of innovative combination of celecoxib, and other anticancer agents, which act in a complementary way, increase the efficacy and minimize toxicity.

## Side effects and clinical complications

Celecoxib is the only FDA-approved COX-2 inhibitor for use in the USA. Although celecoxib is usually a well-tolerated drug, it is not harmless. Its typical doses range from 200 to 400 mg/day; nonetheless, the dose for acute gout can reach 800 mg once, followed by 400 mg on the first day, then 400 mg twice daily for 7 days. A higher dose of celecoxib (800 mg per day) might be related to augmented cardiovascular risk according to the Adenoma Prevention with Celecoxib (APC) study.[144] The cardiotoxicity side effects may be attributed to its off-target effect, namely modulating calcium levels within the cell, according to the immediate time-dependent cell response profiles (TCRPs) for celecoxib.[145] In fact, previous studies have shown that celecoxib therapy induces an immediate increase in intracellular calcium levels.[146] In addition, clinical data indicate that chronic use of celecoxib may damage normal skeletal function resulting in reduced BMD in older male patients.[147] Serious allergic reactions to celecoxib have also been reported.[148]

When celecoxib is recommended in advanced cancer patients, the pros and cons need to be considered prudently. A meta-analysis by Chen et al[149] suggested that celecoxib has certain benefits in the treatment of cancer, but increases the risk of cardiovascular events. Specifically, they demonstrated an increase in grade 3 and 4 toxicities of cardiovascular events with the incorporation of celecoxib to the treatment of advanced cancers. Other toxicities include rash, hepatotoxicity, and gastrointestinal events, and there is no statistically significant difference among them. Of note, the risk of anemia in the celecoxib group is also significant. Although the risk of grade 3 and 4 cardiovascular events increases by 1.78 times after celecoxib use for a long time, the risk is acceptable, considering that this is a prescription for life-threatening diseases. Nevertheless, clinical monitoring of side effects, for example, cardiovascular events should be strengthened. According to these findings, it is necessary to carefully consider the benefit vs harm when recommending celecoxib in the treatment of patients with advanced cancer, especially those with a history of heart disease. Further studies are needed to confirm these results with large samples.

Conclusion

In addition to being widely used for treating inflammatory diseases such as rheumatoid arthritis and osteoarthritis,[150] celecoxib may also play an important role in the cancer prevention and treatment. Preclinical evidence demonstrates that celecoxib seems to suppress the proliferation and growth of different types of cancer through various mechanisms (Figure 1). Results of abundant clinical studies, although unconvincing, suggest that celecoxib administration is related not only to diminished incidence of cancer but also to the better prognosis in cancer patients. In view of the potential variations in response to celecoxib in cancer patients, it
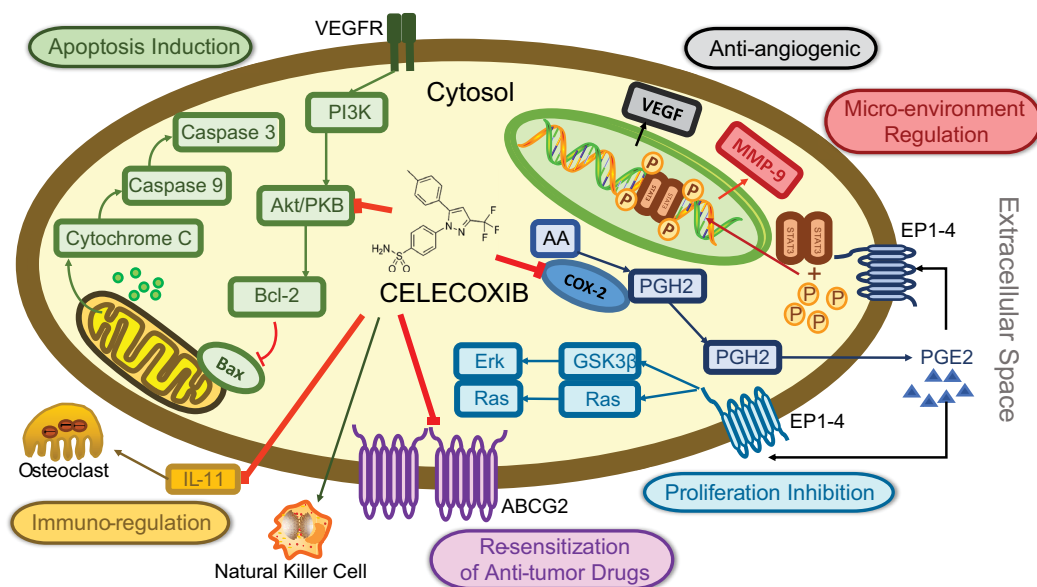
Figure 1 The identified mechanisms of anticancer effect of celecoxib.
Abbreviations: EP1, prostaglandin E2 receptor 1; MMP, matrix metalloproteinase; NK, natural killer; PEG2, prostaglandin E2; PGH2, prostaglandin E2; VEGF, vascular endothelial growth factor.

seems critical to ascertain target populations for its use. Nevertheless, factors that contribute to better outcome in celecoxib consumers are still to be explicated. The data on the effectiveness of celecoxib as neoadjuvant treatment in cancer patients are deficient. There are substantial clinical studies evaluating the role of celecoxib in the cancer treatment. The results will permit evaluation of the position of celecoxib in cancer prevention and therapy and identify the target populations in the near future. Of note, comparative studies should be designed to ascertain the optimal dosage, duration, side effects (especially the gastrointestinal and cardiovascular systems), and its cost-effectiveness. As was originally pointed out more than 10 years ago, "there exists an urgent need for clinical trials of this compound so as to accelerate its effective application in the chemoprevention and treatment of cancer." NSAIDs, and especially celecoxib, represent an inspiring proposition for repurposing as anticancer drugs with low toxicity, hence demonstrating how understanding cancer-relevant molecular signaling pathways in combination with clinical data will contribute to further development of oncology.

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Disclosure

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