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Review

COX-2 and PGE_2-dependent immunomodulation in breast cancer

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ABSTRACT

COX-derived prostanoids play multiple roles in inflammation and cancer. This review highlights research examining COX-2 and PGE_2-dependent regulation of immune cell polarization and function within the tumor microenvironment, particularly as it pertains to breast cancer. Appreciating PGE_2-mediated immunomodulation is important in understanding how tumors evade immune surveillance by re-educating infiltrating inflammatory and immune cells to support tumorigenesis. Elucidation of the multiple and complex influences exerted by tumor stromal components may lead to targeted therapies in breast and other cancers that restrain microenvironmental permissiveness and maintain natural defenses against malignancies.

Contents

1. Introduction

Cyclooxygenase (COX) is the enzyme responsible for the conversion of arachidonic acid into the various prostanoids, a family of lipid mediators that have widespread and diverse biological function [1]. COX exists in two main isoforms, COX-1, which is predominantly constitutive and responsible for generation of prostanoids for "housekeeping functions", and COX-2, the inducible isoform, which contributes prostanoids involved in a variety of growth and inflammatory events [1,2]. Synthesis of eicosanoids begins after the release of arachidonic acid (AA) from membrane phospholipids through the action of cytosolic phospholipase A_2. COX-1/COX-2, also known as prostaglandin G/H synthase 1/2, converts AA into prostaglandin (PG) G_2 and then reduces PGG_2 to PGH_2. PGH_2 can be metabolized by the various PG synthases into PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane (TX) A_2, which then act via distinct downstream G protein-coupled receptors.

A large body of work describing a link between inflammation and cancer [3] has generated intense interest in targeting COX enzymes, COX-2 in particular, for cancer therapy or chemoprevention. COX-2 is upregulated in 40% of breast cancers, with up

Abbreviations: COX, cyclooxygenase; PG, prostaglandin; mPGES, microsomal prostaglandin E synthase; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; SLCO2A1, solute carrier organic anion transporter 2A1; APC, antigen-presenting cell; DC, dendritic cell; NK, natural killer; MDSC, myeloid-derived suppressor cell; TAM, tumor-associated macrophage; CTL, cytotoxic T lymphocyte; iNOS, inducible nitric oxide synthase; T_{regs}, regulatory T cells.

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to 84% increases in some studies [4]. Clinical studies have noted a reduced risk for breast, lung, prostate, and colon cancers after treatment with non-steroidal anti-inflammatory drugs (NSAIDs), which non-selectively inhibit COX-1 and COX-2, or with selective inhibition of COX-2 [5]. The beneficial effects of aspirin are less clear in part because many studies do not distinguish between consumption of low dose aspirin, whose effect is limited to inhibition of platelet COX-1 function, and higher doses that inhibit systemic function of both isozymes. In the Women's Health Initiative observational study, chronic regular use of NSAIDs was associated with reduced risk of breast cancer but subgroup analysis revealed no effect of low dose aspirin (<100 mg) [6]. Similarly, the Women's Health Study, a long term randomized trial, showed no effect of low dose aspirin every other day on breast cancer incidence [7]. Reduced risk of breast cancer death and distant recurrence, but not incidence of primary disease, was associated with regular aspirin use in the prospective observational Nurses' Health Study but dose was not reported [8]. In contrast, in another recent study, lifetime aspirin use was associated with a 32% decreased risk of breast cancer, though, again, no information on dosage was collected [9]. Analysis of eight aspirin trials revealed reduced cancer death that was independent of dose across several common cancers although scant information was available in breast cancer [10].

Certain COX-2-derived products, particularly PGE_2, are known to act via classical cancer signaling pathways in primary tumor cells to promote tumorigenesis. Recent evidence has shined a spotlight not only on the tumor cell itself, but the tumor microenvironment, or stroma, which surrounds the tumor. This is evidenced by Hanahan and Weinberg recently updating their landmark review of the hallmarks of cancer to include microenvironment specific components [11]. The microenvironment contains multiple resident and infiltrating cells, including immune cells, along with the growth factors and cytokines that they release. A supportive tumor microenvironment appears crucial for the development of a tumor as well as its transition to malignancy, and the characteristics of a protumorigenic microenvironment has been well reviewed [12]. This review will focus on tumor evasion of immune surveillance, and how COX-2-derived PGE_2 can modulate local immune responses in the tumor stroma to support progression and metastasis.

2. Metabolism and tumorigenic properties of PGE_2

PGE_2 makes up the majority of secreted prostaglandin in tumors and is thought to be the principal tumorigenic COX-2-derived product. This has been studied in a broad range of cancers, though perhaps most intensively in colorectal cancer [2]. PGE_2 is generated through the conversion of PGH_2 by microsomal PGE synthases (mPGES) 1 or 2, or cytosolic (c) PGES. Like COX-2, mPGES-1 is inducible and appears to be the dominant PGE_2-generating enzyme in tumors [13]. Functional coupling of COX-2 and mPGES-1 has been reported [14] while the constitutive cPGES couples to COX-1 (mPGES-2 has yet to be well characterized). PGE_2 acts through four distinct G-protein coupled receptors termed EP1, EP2, EP3, and EP4. Regulation of prostaglandin signaling relies not only on their synthesis, but also on their cellular transport and degradation. Solute carrier organic anion transporter 2A1 (SLCO2A1), also known as OAT2A1 or prostaglandin transporter, directs uptake of PGE_2, PGD_2, and $PGF_{2\alpha}$ from the extracellular space into the cytosol. Once there, 15-hydroxyprostaglandin dehydrogenase (15-PGDH) catalyzes the initial step in prostanoid breakdown into their inactive 13,14-dihydro-15-keto-metabolites [15]. The multidrug resistance protein 4 (MRP4) can transport PGE_2 and $PGF_{2\alpha}$ from the intracellular to the extracellular space [16] and thus may contribute to elevated PGE_2 levels and EP receptor activation. Coordinated regulation of these multiple steps in PGE_2 biosynthesis, metabolism and function, ultimately determines the biological response.

The tumorigenic properties of PGE_2 have been thoroughly reviewed elsewhere [2,4,17], including an in-depth analysis of how PGE_2 contributes to the hallmarks of cancer [18,19] – self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion/metastasis. Briefly, PGE_2 enhances Wnt signaling through EP2-mediated suppression of glycogen synthase kinase (GSK) 3β [20]. Subsequent accumulation of the β-catenin/T cell factor 4 complex leads to transactivation of perixosome proliferator-activated receptor (PPAR) δ and upregulation of pro-oncogenic genes [21]. GSK3β suppression is mediated by activation of phosphoinositide 3-kinase and Akt. In addition, $G\alpha_{s,}$ which couples to EP2, complexes with Axin, dissociating it from the β-catenin destruction complex, leading to further enhancement of the Wnt signaling pathway [20]. PGE_2 also promotes cell survival by induction of the anti-apoptotic protein Bcl-2 via Ras-MAPK signaling [22], an effect that is partially mediated by PGE_2 transactivation of extracellular growth factor receptor [23]. Multiple studies have implicated PGE_2 production in tumors or tumor cell lines in increased expression of vascular endothelial growth factor and its receptors [24,25], an effect that appears mediated by G_q-coupled EP3 [26,27] signaling through protumorigenic extracellular signaling-regulated kinase/c-Jun N-terminal kinases [28].

3. COX-2 in breast cancer

Animal and human studies report COX-2 overexpression in breast cancer [4,29–31], and strongly support a role for this enzyme in disease progression. Targeted overexpression of COX-2 gene in the mammary epithelium, via the mouse mammary tumor virus, was sufficient to induce mammary tumorigenesis in multiparous mice through a PGE_2-EP2 pathway [32,33]. Further studies in this model revealed an upregulation of cytochrome P450 aromatase that was reversed following COX-2 inhibition with celecoxib [31]. COX-2 inhibition reduced tumorigenesis across a wide range of animal breast cancer models. These have been reviewed extensively [2,4]. Briefly, celecoxib and rofecoxib, both considered selective for COX-2 inhibition, suppressed mammary tumorigenesis in rats treated with 7,12-dimethylbenzanthracene and *N*-methyl-*N*-nitrosourea [34,35]. The same inhibitors reduced disease in HER2/neu- and Lewis lung carcinoma (3LL) xenograft-induced models [36,37]. In many studies the molecular mechanism of reduced tumorigenesis has not been defined, other than to note a reduction in PGE_2 signaling on mitogenic and anti-apoptotic pathways. Reduced multiplicity and size of HER2/neu-driven mammary tumors in global COX-2 knock-out (KO) mice was attributed to a concurrent suppression in tumor angiogenesis [38], consistent with the reported contribution of COX-2-derived PGE_2 to the angiogenic switch in mammary tumors that allows disease progression [39].

We have used Cre recombinase technology to target deletion of COX-2 expression selectively to the mammary epithelium. Significantly delayed tumorigenesis was observed independent of modified angiogenesis but coincident with a change in the number and phenotype of tumor infiltrating cells [40]. These, and other studies [41], indicate a wider role for COX-2 in control of tumor progression via regulation of the microenvironment.

4. Immune regulation of tumorigenesis

In the past decade, evidence has quickly mounted that genetic mutations in classical cancer signaling pathways of tumor epithelial cells cannot fully explain differences in phenotype and clinical development of tumors [42,43]. Indeed, cancer is increasingly considered a disease of the tissue and its progression depends on