The 2-Series Eicosanoids in Cancer: Future Targets for Glioma Therapy?

Tiberiu Moga, Sunit Das*

Division of Neurosurgery, St. Michael’s Hospital, Toronto, Canada.
Email: *DasS@smh.ca

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ABSTRACT

The 2-series eicosanoids are structurally related lipid-soluble hormones synthesized by cyclooxygenase enzymes from arachidonic acid. These compounds have well-established roles in the inflammatory response and the coagulation cascade. More recently, the eicosanoids have garnered attention for their potential roles in cancers of the lung, colon, breast, and brain. In this paper, we review the contributions of the different cyclooxygenase metabolites (i.e., prostaglandins, prostacyclins and thromboxanes) to cancer development, progression and recurrence, with special attention paid to their relevance to glioma biology. Our review suggests that 2-series eicosanoids merit further study as possible targets for therapy in patients with glioma.

Keywords: Eicosanoids; Prostaglandins; Prostacyclins; Thromboxanes; Cancer; Glioma

1. Introduction

Despite advances in surgical technique, available chemotherapies, and radiation therapy, the prognosis for patients diagnosed with a glioma remains grim. Median survival for patients with glioblastoma treated with aggressive multi-modality therapy is fourteen months [1]. While significant attention has been given to the genetic changes that underlie gliomagenesis, recent work has also focused on the importance of signalling within the tumor milieu and intratumoural communication in glioma development, progression and recurrence. In this review, we will focus on eicosanoid signalling and its possible role in glioma biology.

Eicosanoid signaling has long been a therapeutic target in inflammatory conditions. More recent research has delineated a role for eicosanoids in the development and progression of multiple cancers, including those of the breast [2], lung [3], colon [4], kidney [5], prostate [6] and brain [7]. Eicosanoids have been proposed to activate oncongenes [8] and the epithelial-to-mesenchymal transition (EMT) [9], to inhibit tumor suppressor genes [10], to participate in tumor cell evasion of the immune response [3], and to initiate angiogenesis [4]. In Table 1, we highlight the known roles of the 2-series eicosanoids in CNS and systemic cancers.

Eicosanoid synthesis begins with phospholipase A2, which releases arachidonic acid (AA) from membrane-bound phospholipids. AA is subsequently converted to prostaglandin H2 (PGH2) by the cyclooxygenase enzymes (COX-1, COX-2 and COX-3), which are also known as prostaglandin H synthase (PGHS) [11]. PGH2 subsequently serves for the substrate for the 2-series eicosanoids, a group of compounds that includes prostaglandins-D2 (PGD2), E2 (PGE2), F2α (PGF2α), and J2 (PGJ2)-prostacyclin (PGI2) and thromboxane (TxA2) (Figure 1). Owing to their inherently unstable chemical structure, eicosanoids decay rapidly and are thus only able to mediate local (i.e. paracrine or autocrine) signaling. The 2-series eicosanoids signal in one of two ways: they either activate a G protein-coupled receptor (GPCR) [3]—which in turn affects the levels of second messengers like cyclic adenosine monophosphate (cAMP) or calcium (Ca2+)—or bind to nuclear receptors that alter DNA transcription [12,13]. Given the diverse roles of eicosanoids in human disease, there has been significant research in developing new drugs that can modulate eicosanoid signaling in a selective manner.

Gliomas represent a unique therapeutic challenge in part because they are chemically isolated from the rest of the body. In the context of cancer therapy, the blood-brain barrier (BBB) is a significant obstacle as it can prevent chemotherapeutic agents that are active in the periphery from achieving therapeutic concentrations in the CNS. The drug tamoxifen, for example, is an agent that is profoundly effective in the treatment of metastatic breast cancer, but that has limited efficacy against brain...
metastases because it is excluded from the CNS by the BBB[14]. Due to their lipid-soluble structure, derivatives of 2-series eicosanoids have the potential to cross the BBB and overcome this problem. In the following sections, we discuss the signaling pathways associated with COX and each of the 2-series eicosanoids, and compare their roles in systemic cancers and glioma. In Table 2, we list pharmacologic agents that have been used to target different eicosanoid pathways.

1.1. Role of COX in Systemic Cancers

Early studies recognized that growth factors, tumor promoters, and oncogenes all induce prostaglandin synthesis [15]. More recent studies have demonstrated that COX-2 has an important role in cancer generation and progression, but that the role of prostaglandins varies in a tumor-specific manner. Analysis of normal and neoplastic human breast tissue samples has shown that COX-2 expression correlates with expression of oncogenes such as HER-2/neu [16]. COX-2 may also contribute to drug resistance in MCF-7 breast cancer cells via concomitant effects on the phosphoinositide-3-kinase (PI3K)/Akt, mitogen-activated protein kinase (MAPK), epidermal growth factor receptor (EGFR), and matrix metalloproteinase-2(MMP2) and -9(MMP9) pathways [8]. For example, pharmacologic inhibition of COX-2 decreased invasiveness of MDA-MB-231 human breast cancer cells by preventing MMP2 release [17]. Furthermore, transgenic loss of COX-2 delayed tumor progression in a mouse mammary epithelial cell model of breast cancer. These effects were driven by COX-2 genetic deletion, which resulted in an enhanced host immune response, and could be overcome by providing exogenous PGE2 (a product of COX-2 activity) [18].

Tumor-induced immune modulation is similarly relevant in colon cancer, where inhibition of the COX-2/PGE2 pathway decreases the levels of FoxP3+ regulatory T cells (Tregs) and results in an enhanced antitumor immune response [19]. Long-term COX-2 inhibition also appears to have protective benefits against non-small cell lung [20] and colon [21] cancers, suggesting a more general role for COX-2 in immune surveillance against neoplastic cells.

The role of COX-2 in tumor biology appears to extend beyond the immune response. COX-2 inhibitors can induce the expression of tumor-suppressors such as MAGI1 [22] in colorectal cancer cells (SW480 and HCT116) and 15-hydroxyprostaglandin dehydrogenase (15-PGDH) in...
Figure 1. The 2-Eicosanoid signaling family.

colon (HT29), lung (A549) and glioblastoma (T98G) cancer cells [23]. In addition, COX-2 has a direct effect on cell proliferation and survival in SGC-7901 and AGS gastric cancer cells [24]. In HepG2 human hepatocellular carcinoma cells, COX-2 inhibition also results in decreased expression of the drug efflux pumps P-glycoprotein and MRP1 [25]. Thus, COX-2 inhibitors might render tumor cells more sensitive to chemotherapy. Further, in HepG2 cells, COX-2 inhibition with nonsteroidal anti-inflammatory drugs (NSAIDs) can induce apoptosis through oxidative stress and mitochondrial toxicity [26].

The pro-apoptotic effect of COX-2 inhibition on hepatocellular carcinoma cells does not, however, hold true for all cancers. Treatment with NSAIDs appeared to protect U937 human hematopoietic cancer cells from apoptosis [27]. Furthermore, it is not universally true that COX-2 expression correlates with cell proliferation. In a T24 bladder cancer cell model of interstitial cystitis, anti-proliferative factor (APF) inhibits cell proliferation by decreasing β-catenin expression, which results in increased COX-2 expression [28]. The data from T24 cells provides the first example of a cancer cell line where increased COX-2 expression is associated with decreased proliferation. This observation stands in stark contrast to the cases of breast and colon cancers previously discussed where COX-2 activity drives cellular proliferation.

1.2. Role of COX in Glioma

Both COX-1 and COX-2 are expressed in glioma cells,
and expression levels of COX-2 increase with glioma grade [29]. COX-2 expression has been found to correlate negatively with survival in human astrocytomas and can thus be considered a poor prognostic indicator [29]. A phase II study of temozolomide, thalidomide and celecoxib combination therapy in glioblastoma patients unfortunately failed to demonstrate a statistically significant improvement in patient survival [30]. One reason why this study may not have shown a survival benefit is that patients did not receive temozolomide during radiotherapy, which is now considered the standard of care. It remains to be determined whether the combination of temozolomide, concomitant radiation therapy and a prostaglandin signaling modulator would confer a survival benefit over the current standard-of-care.

### 2. PGD₂ Signaling

PGD₂ is derived from PGH₂ via the action of prostaglandin D synthases (PGDS), of which there are lipocalin (L-PGDS) and hematopoietic (H-PGDS) subtypes. L-PGDS shares a structural homology with other members of the lipocalin family, which are extracellular proteins that bind to a lipophilic substrate. Interestingly, H-PGDS is a sigma-class glutathione transferase [31], suggesting that PGD₂ synthesis could be regulated by environmental oxidative stress through depletion of glutathione (GSH). PGD₂ can either signal directly by binding to its cognate receptor or be converted to PGJ₂, the actions of which will be discussed later. PGD₂ signaling is mediated by two receptors: DP1 (or DP) and

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**Table 2. Therapeutic modulation of eicosanoid signaling.**

<table>
<thead>
<tr>
<th>Signal Transduction Molecule</th>
<th>Associated Signal Transduction Cascades</th>
<th>Agonists</th>
<th>Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX-1</td>
<td>N/A</td>
<td>N/A</td>
<td>SC560 [112]</td>
</tr>
<tr>
<td>COX-2</td>
<td>N/A</td>
<td>12-O-tetradecanoylphorbol-13-acetate (TPA) [9] [inducer]</td>
<td>Celecoxib [9,22,72], NS398 [112], Rofecoxib [67,113], SC-236 [4]</td>
</tr>
<tr>
<td>H-PGDS</td>
<td>N/A</td>
<td>N/A</td>
<td>HQL-79 [114,115], TAS-204 [116], TFC-007 [117]</td>
</tr>
<tr>
<td>PGD₂ DP1</td>
<td>Gαs/cAMP/PKA; ERK MAPK/RSK1/CREB</td>
<td>BW245C[32]</td>
<td>BWA868C [32], Laropiprant [117], S5751 [118]</td>
</tr>
<tr>
<td>PGD₂ DP2</td>
<td>Gαs/Ca²⁺/PI3K</td>
<td></td>
<td>Cay104459 [118]</td>
</tr>
<tr>
<td>PGD₂ EP2</td>
<td>Gαs/cAMP/PKA</td>
<td>AH13205 [123], Butaprost [58,123], Misoprostol [119], ONO-AE1-259-01 [112,120,123], CP-544326/PF-04217329 [123]</td>
<td>AH6809 [3,67,121,122]</td>
</tr>
<tr>
<td>PGF₂α FP</td>
<td>Gαs/Ca²⁺/PKC; MEK/ERK/CREB</td>
<td>Fluprostenol [112,125], Latanoprost [123], latanoprost acid [126], bimatoprost acid [126], tafamido acid [126]</td>
<td>AL8810 [125]</td>
</tr>
<tr>
<td>PGIS</td>
<td>N/A</td>
<td>N/A</td>
<td>U51605 [95]</td>
</tr>
<tr>
<td>PGJ₂ IP</td>
<td>Gαs/cAMP/PKA</td>
<td>Beraprost [122], Carboprostacyclin [95,127], Cicaprost [128], Epoprostenol [129-130], Iloprost [122,131], Treprostonil [122,132]</td>
<td>CAY10441 [127], RO1138452 [122,128]</td>
</tr>
<tr>
<td>PPARδ</td>
<td>N/A</td>
<td>GW501516 [95]</td>
<td>N/A</td>
</tr>
<tr>
<td>PGJ₂ DP2</td>
<td>See PGD₂ section</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPARγ</td>
<td>N/A</td>
<td>Ciglitazone [133-135], Pioglitazone [136], Rosiglitazone [134,137,138]</td>
<td>GW9662 [44,136,139], T0070907 [48,134,135]</td>
</tr>
<tr>
<td>TXAS</td>
<td>N/A</td>
<td>N/A</td>
<td>BM-573 [140], Furegrelate [110,111,141], Ozagrel [142]</td>
</tr>
<tr>
<td>TxA₂</td>
<td>Gαs/Ca²⁺/PLC</td>
<td>U46619 [104,143,144]</td>
<td>BM-573 [140], ICI192605 [143], SQ29548 [32,145], Terutroban [146], TM30089 [117]</td>
</tr>
</tbody>
</table>
DP2 (also called CRTH2), which are both GPCRs. DP1 initiates a Gαs/cAMP/protein kinase A (PKA) cascade, while DP2 signals through Goi proteins that mobilize Ca^2+ store and activates PI3K [32].

2.1. PGD2 in Systemic Cancers

In mice implanted with Lewis lung cancer cells, administration of a synthetic DP1 agonist impairs angiogenesis [33]. PGD2 appears to inhibit prostate cancer cell proliferation in tumors expressing aldoketoreductase IC3 (AKR1C3, also called 17β-hydroxysteroid dehydrogenase (17β-HSD) type 5) [34]. Likewise, a study of tumor-prone ApcMin/+ mice showed that high levels of H-PGDS can suppress colon tumorigenesis [35]. Together, these observations establish PGD2 as a tumor-suppressing molecule that could be exploited as an anti-cancer and anti-angiogenesis therapeutic.

2.2. PGD2 in Glioma

PGD2 has long been known to inhibit cell proliferation in glioma cell lines (NCE-G 2,3,7,8,17) in vitro [7]. More recently, loss of L-PGDS expression was found to be a defining event in the progression of Grade II to Grade III astrocytomas; further, PGDS expression was noted to vary inversely with survival across all glioma grades [36]. Treatment of A172 glioma cells in culture with PGD2 inhibits cell proliferation and induces apoptosis; these effects were amplified by concomitant inhibition of COX-2 [36]. Interestingly, PKC, which is driver of EMT [37], activates PGDS in TE671 medulloblastoma cells [38]. Thus, the effect of PGD2 appears to be tumor-specific even among tumors of the CNS. Regardless, these findings establish a potential role for exogenous PGD2 analogues in the treatment of glioma.

3. PGJ2 Signaling

15-deoxy-Δ12,14-prostaglandin J2 (15-d-PGJ2) is produced in vivo by the metabolism of PGD2. 15-d-PGJ2 signals via the DP2 and PPARγ receptors, but also has direct effects on glycolytic enzymes, molecular chaperones and cytoskeletal proteins in neuronal membranes [39,40]. An unusual aspect of 15-d-PGJ2 signaling is its ability to signal by redox reactions. 15-d-PGJ2 induces Akt and Nrf2 signaling by forming a covalent adduct with GSH [41]. This does not appear to be an isolated phenomenon, but a normal process in 15-d-PGJ2 signaling. In addition, 15-d-PGJ2 oxidizes p38 at cysteine residues near the protein surface resulting in p38 inactivation [42]. Similarly, Δ^{2}-PGJ2 reacts with human serum albumin to form a covalent adduct with histidine-146, a reaction which chemically stabilizes the bound prostaglandin [43].

3.1. PGJ2 in Systemic Cancers

Of all the prostaglandins, PGJ2 exerts the broadest range of effects in cancer, echoing its biochemical diversity. 15-d-PGJ2 induces expression of the tumor suppressor, HtrA3, in 786-O and RCC4 renal cell carcinoma lines through a mechanism dependent on MEK/ERK signaling, but not PPARγ [12]. 15-d-PGJ2 also augments the anti-tumor activity of the alkylation agent, camptothecin, against Caki-2 renal cell carcinoma cells in a manner independent of topoisomerase-II and PPARγ signaling pathways [44].

In addition to its effect on tumor suppressor pathways, 15-d-PGJ targets molecular drivers of stem cell identity and proliferation. In 786-O cells, 15-d-PGJ2 inhibits expression of hypoxia-inducible factor 2α (HIF2α)—which has been implicated in modulating cancer stem cell identity [45]—by binding to iron regulatory protein-1 (IRP1) [46]. In a mouse model, 15-d-PGJ2 inhibited proliferation of embryonic stem cells by antagonizing the leukemia inhibitory factor (LIF)-Tyk2-Stat3 signal transduction pathway [47].

Moreover, 15-d-PGJ2 signaling appears to modulate cell survival and apoptosis pathways in multiple cancer types. 15-d-PGJ2 signaling induces expression of EGFR and COX-2 in MG-63 osteosarcoma cells via reactive oxygen species (ROS) and the p38 and p42/p44 MAPK pathways [48]. On the one hand, PGJ2-dependent inflammation and induction of EGFR could promote cancer genesis and survival. Conversely, ROS formation by 15-d-PGJ2 has been shown to induce apoptosis in A549 lung cancer cells [49] and synergistically enhance histone deacetylase inhibitor-driven apoptosis in DLD-1 colon cancer cells [50]. In MCF-7 breast cancer cells, 15-d-PGJ2 activates a Ca^{2+}-ERK1/2 signal transduction cascade that increases levels of the transcription factor, EGR1, which acts as an inhibitor of breast cancer cell proliferation [51]. EGR1 is also a positive regulator of the tumor suppressor gene, PTEN [52]. In MCF-7 cancer cells, 15-d-PGJ2 also reacts with GSH to form a 15-d-PGJ2-GSH conjugate, which subsequently activates Akt and Nrf2 and results in MRPI-dependent export of the 15-d-PGJ2-GSH molecules [41]. Depletion of the intracellular GSH pool is in turn believed to trigger apoptosis, while relatively moderate depletion of GSH stores is thought to augment adaptation of cancer cells to external stresses. This mechanism suggests that one could exploit the anti-cancer effects of 15-d-PGJ2 by concomitant administration of selective inhibitors of MRPI.

Studies examining the function of 15-d-PGJ2 in normal cells have revealed other novel effects of this molecule on cellular physiology that could be relevant to human disease and cancer therapy. For example, 15-d-PGJ2 signaling has been found to modulate CRM1 transporter-
Inhibitors of PGE2 synthesis, such as curcumin, are being tested in clinical trials as agents for cancer prevention. Phase Ia studies have shown that curcumin can prevent the formation of aberrant crypt foci in the colon, which are thought to precede development of colon cancer [60].

Treatment of the human colon cancer cell line HT-29 with epinephrine stimulated cell proliferation and increased PGE2 synthesis and release, which in turn increased vascular endothelial growth factor (VEGF) secretion (likely via EP4 signaling [61]) and MMP9 activity [58]. Protein kinase CK2 and the Wnt/β-catenin pathway also activate production of PGE2, with subsequent proliferation of human colon (HT29-US and DLD-1) and breast (ZR-75) cancer cells. In addition to its effects as a promoter of cell proliferation and angiogenesis in colon cancer, PGE2 has also been shown to help colon cancer cells evade the immune response and advantageously alter their energy metabolism. In LS-174T and HCT-116 colon cancer cells, PGE2 signaling activates the nuclear orphan receptor NR4A2, which increases fatty acid oxidation as an alternative fuel source to glucose [62]. This activity could promote tumor survival under conditions of starvation. Inhibition of PGE2 synthesis has also been associated with decreased incidence of colon cancer in murine studies and decreased levels of tumor-cell protective FoxP3+Tregs [19] [19].

Interestingly, NR4A2, under the regulation of PGE2, is involved in the development of drug resistance in human oral squamous cell carcinoma. In HSC3, HSC4, Ho-1- u-1 and Ca9-22 lines, PGE2 was shown to promote 5-fluorouracil resistance of EGFR-dependent tumors by induction of NR4A2 [63].

As in colon cancer, PGE2 is a stimulator of angiogenesis in breast cancer. Apoptotic MCF-7 breast cancer cells were shown to signal via the sphingosine-1-phosphate (SIP) SIP1 and SIP3 receptors in order to induce PGE2 production in macrophages. The activated macrophages then released PGE2, thereby triggering vascular endothelial cell migration and subsequent angiogenesis in breast tumors [64]. As is the case in colon cancer, PGE2 also appears to plays a role in immune evasion in breast cancer. PGE2 produced ad secreted by breast cancer cells suppresses NK cell function through activation of the EP4 receptor. PGE2 also induces expression of the onco-gene aromatase in breast adipose fibroblasts in a pathway that involves JunD and JunB [65]. Aromatase activity subsequently results in elevated levels of estradiol. This finding could explain why clinical studies have shown that COX-1 levels correlate with high levels of serum estradiol in patients with breast cancer [66]. In fact, therapeutic agents targeting the PGE2 signaling pathway have been studied as potential adjuncts for breast cancer treatment. The natural PGE2 antagonists frondoside A (which inhibits EP2 and EP4 receptors) [67] and saponin (which also acts via an AMP-activated protein kinase pathway to inhibit COX-2) [68] have been shown to slow breast cancer progression and induce apoptosis in Balb/cfC3H mouse and MCF-7 human breast cancer cells, respectively.

Current understanding of the role of PGE2 in other cancer types is more fragmented, but several recent findings are worth noting. PGE2 expression by blood mononuclear cells induced by AsPC-1 and MiaPaCa-2 pancreatic cancer cell lines is critical to generate a supportive tumor microenvironment [69]. PGE2 has also been shown to induce the crucial oncogene telomerase (hTERT) in a signaling cascade dependent on EP4 and Sp1 in both lung (H1838 and H1792) [70] and cervical (HeLa, SiHa,
Caski) [71] cancer cell lines. In renal cell carcinoma cell lines (RCC7 and Caki-1), PGE2 stimulates tumor cell migration and invasion via the EP4-Rap pathway [5]. Microsomal prostaglandin E synthase-1 (mPGES-1) is known to inhibit the tumor suppressor protein phosphate and tensin homolog (PTEN), which supports biliary tract cancer progression [10]. This effect could be an extension of the normal function of EP1, which signals via Gq, leading to Ca2+ mobilization [3] and PI3K activation, which directly antagonizes PTEN. A similar role for EP1 signaling through Ca2+ mobilization has been postulated in the development of melanoma [72]. Importantly, the biological effects of PGE2 signaling on cancer progression do not appear to be isolated from one another; rather, they appear to be related by a more fundamental process, the EMT. Vaid et al. demonstrated that natural products isolated from grape seeds can reverse EMT in melanoma cell lines (A375 and Hs294) and that this effect was duplicated by inhibiting PGE2 with celecoxib [9]. Thus, one can conclude that PGE2 signaling affects all the essential processes of tumor generation and malignant progression—from antagonizing tumor suppressor genes and activating oncogenes, to stimulating immune system evasion, angiogenesis, cell migration and the EMT.

4.2. PGE2 in Glioma

As in colon cancer, PGE2 released by glioma cells has an inhibitory effect on host immunity. Release of PGE2 by glioblastoma cells decreases induction and cytotoxicity of anti-tumor lymphocytes [73]. PGE2 secretion by MG-377 glioblastoma cells can also stimulate CD11c+ dendritic cells to induce CD4+ Treg cells, which again results in suppression of the host immune response [74]. It also appears that human U251 and T98G glioblastoma cells secrete soluble factors that drive macrophages to produce PGE2 [75]. In an induced glioma mouse model, blockade of systemic PGE2 synthesis using COX-2 inhibitors or knock-out of COX-2 inhibitors or knock-out of COX-2 suppressed gliomagenesis, possibly due to an increase in host immune surveillance [76]. Interestingly, macrophages that are capable of killing T9 rat glioma cells are resistant to the immunosuppressive effects of PGE2 [77].

The role of PGE2 in glioma biology extends beyond its effects as an immunomodulator. In U87-MG glioma xenografts, mPGES-1 drives tumor cell proliferation and tumor growth via activation of type II PKA [78], which in turn inhibits ERK and increases CREB transcriptional activity [79]. This mechanism mirrors the inhibitory effect of mPGES-1 on PTEN seen in biliary tract cancers [10]. There also seems to be a role for PGE2 in glioma cell invasion via its activation of PKC [80].

Thus far, it appears that PGE2 signaling almost universally drives cancer proliferation and migration, but this may not uniformly be the case. In one study, PGE2 was found to induce Bax-dependent apoptosis in primary glioblastoma cells, and patients expressing a high level of mPGES-1 were found longer survival times than those with low levels of mPGES-1 [81]. In principle, this trend could be explained by pro-apoptotic PGE2 signaling through the EP4 receptor [59]. Whereas the EP4 receptor may mediate the clinically important effects of PGE2 in gliomas, in medulloblastoma it appears that the EP1 and EP3 receptors are more crucial. Specifically, EP1 and EP3 drive proliferation of medulloblastoma cells [82]. These differing roles of PGE2 in different cancers and contexts speak to the intricacy of prostaglandin signaling, and how development of prostaglandin-based therapies will require an appreciation of this complexity.

Finally, these observations suggest that EP1 and EP3 modulators could provide a novel means of treating gliomas by augmenting the host anti-tumor immune response, similar to the use of ipilimumab in the treatment of metastatic melanoma [83].

5. PGF2α Signaling

In humans, aldokeotoreductase (AKR) 1B1 is the primary enzyme that produces PGF2α from PGH2 [84], while AKR1C3 plays a minor role in PGF2α synthesis [34]. The PGF2α receptor FP is a GPCR linked to Gq, which affects Ca2+ homeostasis and regulates smooth muscle cell contraction, most notably in the intestines [85] and uterus [86]. PGF2α analogues (e.g. latanoprost) are also used clinically to lower intraocular pressure in the treatment of glaucoma [87].

5.1. PGF2α in Systemic Cancers

The PGF2α metabolite 8-isoPGF2α has been found to be a reliable marker of cancer progression in a rat breast cancer model [88]. Levels of 8-isoPGF2α have also been monitored to track cellular damage associated with renal oxidative stress [89] and bladder obstruction [90], which are considered risk factors for the development of renal cell and uroepithelial cancers, respectively.

5.2. PGF2α in Glioma

In NG108-15 hybrid neuroblastoma-glioma cells, PGF2α (and also PGD2 and PGE2) raises intracellular Ca2+ levels via a cGMP-dependent mechanism [91]. Since these early studies, very little attention has been given to the role of PGF2α in CNS cancers. The few described effects of PGF2α in glioblastoma have focused on its role in tumor-associated vasculature. Glioma cells appear to synthesize high levels of both PGF2α and TxA2, but the disproportionate increase in TxA2 synthesis over PGF2α synthesis is believed to contribute to the changes seen in...
vascular permeability and the resulting cerebral edema [92]. It appears that PGF₂α signaling is also involved in the remodeling of cerebral vascular architecture: in SV40-transfected microglial cells, PGF₂α acts via a Ras/Raf- and Tcf-pathway dependent to increase production of the CYR61 protein [93], which induces physiologic angiogenesis in the corpus luteum [94]. Thus, building on the work of Kesari et al. [30], modulators of PGF₂α signaling might be good targets as angiogenesis inhibitors in the treatment of glioblastoma multiforme.

6. PGI₂ Signaling

PGI₂ is synthesized in vascular endothelial cells by prostanycin synthase (PGIS) through the catalysis of PGH₂. The PGI₂ receptor (IP) is a rhodopsin-like GPCR that signals via Gα to activate cAMP synthesis. PGI₂ may also signal through Gαq, Gαi, and the PPARδ pathways [13]. A recent mouse model has shown that maternal PGI₂ signaling through fetal PPARδ is key for blastocyst hatching and subsequent implantation [95].

6.1. PGI₂ in Systemic Cancers

The PGI₂ analogue iloprost has been investigated as a potential agent for lung cancer prevention. A phase II placebo-controlled randomized study showed that iloprost significantly reduced dysplasia in lung tissue biopsies obtained from former smokers [96]. Whether PGI₂ signaling levels have a meaningful effect on cancer survival remains unclear. An observational study of patients in Ireland with various forms of lung cancer showed that overall PGI₂ synthase (PGIS) expression was decreased in lung cancer, but PGIS expression levels did not correlate with survival [97]. On the other hand, a recent case study showed that a patient with lung cancer treated with iloprost showed no evidence of cancer progression in the absence of conventional chemotherapy [98].

6.2. PGI₂ in Glioma

The role of PGI₂ signaling in gliomas is not well understood. Many CNS tumors express endogenous PGI₂ receptors (IP). PGI₂ signaling results in cAMP and cGMP accumulation in N4TG3 murine neuroblastoma cells, but not in 1321N1 human astrocytoma cells [99]. Angiotensin is known to induce release of PGI₂ from rat C6 glioma cells [100] and the IP receptor can generate inward Ca²⁺ currents in hybrid rodent NG108-15 glioma-neuroblastoma cells [101]. Activation of the IP receptor, however, is subject to desensitization in response to prolonged stimulation in these cells [102]. Surprisingly, the IP receptor in NG108-15 cells does not activate the ERK1/2 pathways, as would be expected from IP-driven cAMP production [103]. In these experiments, PI3K- and PKC-dependent currents were observed in CHO but not glioma cells. Further work is needed to determine whether PGI₂ signaling has functional relevance in glioblastoma.

7. TxA₂ Signaling

Thromboxane A₂ (TxA₂) is produced by the thromboxane synthase enzyme (TXAS) and signals via the TP receptor, a GPCR linked to Gαq. Like some of the other prostaglandin receptors, TxA₂ exerts its effects by mobilizing Ca²⁺ stores, most notably in the processes of coagulation and regulation of vascular smooth muscle tone [104].

7.1. TxA₂ in Systemic Cancers

Binding of TxA₂ to the TP receptor results in enhanced activity of the protein kinase C-related kinase (PRK)1. PRK1 signals downstream of RhoA and is implicated in the development and progression of prostate cancer [6]. Though not as extensively described as a therapeutic target as PGE₂, TxA₂ has shown promise for as a target for investigation in lung [105] and prostate [6] cancers.

7.2. TxA₂ in Glioma

TxA₂ synthesis is known to be elevated in gliomas, and increases with increasing tumor grade [106]. TxA₂ signaling results in CREB-dependent induction of IL-6 by human 1321N1 astrocytoma cells through activation of the p38 MAPK and PKA pathways [107]. Furthermore, TxA₂ induces cell swelling in 1321N1 cells in a mechanism dependent on Gαq, RhoA, the Na⁺/H⁺ exchange pump, and aquaporins [108]. Since aquaporins are known to be involved in migration and proliferation of human glioma cell lines (D54, D65, STTG1, U87, U251) [109], this discovery regarding the role of TxA₂ in astrocytoma cells raises the question of whether TxA₂ inhibition could be used to inhibit glioma invasion. Inhibition of TxA₂ signaling by blocking TXAS also renders glioma cells more sensitive to apoptosis when subjected to γ-radiation [110] or alkylating chemotherapy (U87 glioblastoma cells) [111]. Thus, inhibition of TxA₂ signaling may be a valuable adjunct to radiation therapy in glioma.

8. Conclusion

The 2-series eicosanoids have diverse roles in the biology of systemic cancers and glioma. These effects vary drastically in a cancer- and context-specific manner. The list of cancer cell processes affected by prostaglandin signaling is impressive and includes modulation of the immune system, induction of the EMT, modulation of tumor cell migration and invasion, changes in the cell metabolic state, and alterations in the balance between oncogene and tumor-suppressor activity. New therapies based on eicosanoid biology could provide valuable
therapies to currently intractable cancers. One possible strategy would be to combine the purported anti-proliferative and pro-apoptotic effects of PGD₂, PG₁, and PGJ₂ while inhibiting the oncogenic effects of the other 2-series eicosanoids. Our current knowledge suggests that the 2-series eicosanoids merit further study as possible therapeutic targets in patients with glioblastoma and other cancers.

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