Editorial

Prostaglandin E_2 plays a major role in glioma resistance and progression

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Glioblastoma multiforme (GBM) is the most common primary malignant tumor of the central nervous system in adults. The prognosis for these patients remains extremely poor despite aggressive therapy including maximal surgical resection followed by radiation plus concomitant and adjuvant chemotherapy in the form of temozolomide (1). In spite of this intense therapy most patients will recur within about 7 months after the initial diagnosis and usually in or around the original site. Many studies have linked the poor response of GBM to treatment, to the presence of cancer stem/initiator cells (CSC) that are highly resistant to chemical agents and radiation because of their inability to undergo cell death (2).

Recent studies have pointed out the bioactive lipid prostaglandin E_2 (PGE_2) as a major actor in cancers including gliomas (3,4). PGE_2 belongs to the prostanoid family of lipids, which is a subclass of eicosanoids produced by oxidation of phospho-membrane lipids including arachidonic acid (AA) that is converted into PGH_2 by COX enzymes. There are two major forms of COX: COX-1 and COX-2, which is an immediate early response gene that is normally absent from most cells but is highly induced at sites of inflammation and during tumor progression (5). Several studies have demonstrated that COX-2 is over-expressed in gliomas and could be positively correlated with tumor grade. Indeed, elevated COX-2 levels correlate with earlier recurrence and shorter survival in glioma patients (5,6). COX-2, which is constitutively expressed in the central nervous system is central in the synthesis of prostanoids (7). The conversion of PGH_2 to PGE_2 is mediated by prostaglandin E synthase (PGES) that exists in three isoforms: membrane associated PGES-1 (mPGES-1), mPGES-2 and cytoplasmic PGES (cPGES). mPGES-1 is functionally associated with COX-2 and rapidly induced by various stimuli to generate a peak in PGH_2. In glioma, the overexpression of mPGES-1 and its link with enhanced apoptosis have been positively correlated to the survival of patients (3).

However, it has to be kept in mind that PGH_2 is associated with a broad range of biological effects and fulfills complex (and sometimes antagonistic) roles under both normal and pathological situations. The localization and partners of PGH_2 are important. For example, PGE_2 is pro-apoptotic when intracellular and anti-apoptotic when it is released from the cells (8). The observation that PGE_2 has potent tumor-promoting activity is centered on the considerable body of evidence obtained from rodent studies as well as research on the protective effects of non-steroidal anti-inflammatory drugs (NSAIDs) in cancer risks (9).

PGE_2 binds to members of the EP family of receptors that consists of four isoforms (EP1–4). These EP receptors are coupled to Gα proteins that contain stimulatory (GαS) or inhibitory (GαI) subunits that can modulate the levels of Ca^{2+}, cAMP and inositol phosphate thereby activating divergent downstream signaling pathways accounting for the pleiotropic actions of PGE_2 in proliferation, apoptosis, angiogenesis inflammation and immune surveillance (see *Figure 1*). In fact, mPGES-1 was found to be higher

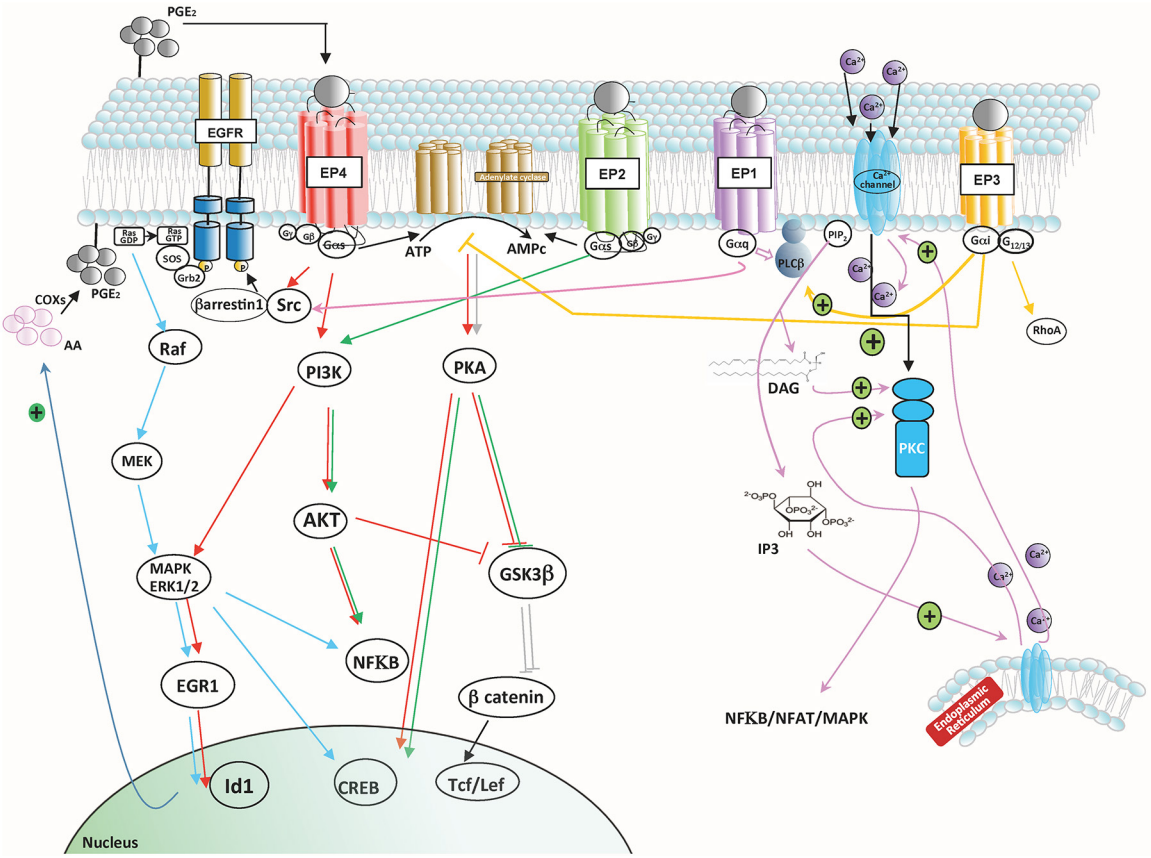

Figure 1 Signaling pathways activated by PGE_2 stimulation of the human EP receptors. EP1 receptor is coupled to Gαq proteins and signal by activation of PLC that hydrolyzes phosphatidyl inositol 4,5-bisphosphate to 1,2-diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) with an increase in intracellular Ca^{2+} and activation of PKC, which subsequently activates the MAPK pathway. EP2 and EP4 receptors are linked to Gαs proteins and initiate the induction of the adenylate cyclase, increasing the level of cAMP and activating PKA. Activation of these receptors can also trigger the PI3K signaling pathway promoting ultimately the NFκB-mediated transcription program. Activation of PKA (EP2, EP4) or PI3K (EP2) signaling pathways induce phosphorylation of the transcription factor CREB. Activation of the PI3K/ERK/MAPK pathway induces expression of EGR-1 and activation of Id1. PKA or PI3K/AKT signaling pathways inhibit GSK-3, which stabilizes β-catenin and promotes its nuclear translocation resulting in a transcriptional activity on T-cell factor/lymphoid enhance factor (Tcf/Lef)-regulated genes. The EP3 receptor coupled to Gi proteins induces the inhibition of adenylate cyclase, whereas signaling through Gs proteins results in cAMP production, couple to G12/13 proteins: activation of the small G protein Rho. EP3 receptor also activates PLCβ to increase the cytosolic Ca^{2+} concentration. Signaling through the EP1, EP2 or EP4 receptors by PGE_2 activates c-Src, which in turn transactivates the epidermal growth factor receptor (EGFR). Activation of c-Src by the EP2 and EP4 receptors involve the recruitment of β-arrestin1. Activation of the EGFR increased MAPK activity, COX-2 transcription, and stimulation of PGE_2 biosynthesis. PGE_2, prostaglandin E_2; cAMP, cyclic adenosine monophosphate; EGFR, epidermal growth factor receptor; Ras, small GTPase; Ras GDP, Ras-guanosine diphosphate complex; Ras GTP, Ras guanosine triphosphate complex; SOS, son of sevenless; Grb2, growth factor receptor-bound protein 2; Gβ, Gγ, heterotrimeric guanine nucleotide-binding proteins; GαS, stimulatory guanine nucleotide binding protein; Gαi, inhibitory guanine nucleotide binding protein; ATP, adenosine triphosphate; PLCβ, phospholipase Cβ; PIP_2, phosphatidylinositol biphosphate; G12/13, guanine nucleotide-binding protein alpha 12, 13; COXs, cyclooxygenase-1, 2; AA, arachidonic acid; Raf, serine/threonine protein kinase; Src, tyrosine kinase DAG, 1,2-diacylglycerol; PI3K, phosphatidyl-inositol 3 kinase; PKA, protein kinase A; PKC, protein kinase C; RhoA, Ras homolog gene family, member A; MEK, MAPK/Erk kinase; GSK3β, glycogen synthase kinase-3β; MAPK, mitogen-activated protein kinase; Erk1/2, extracellular signal-regulated kinase-1/2; EGR, early growth response protein; NFκB, nuclear factor κB; Id1, inhibitor of DNA binding 1; CREB, cyclic adenosine monophosphate response-element binding protein; Tcf/Lef, T-cell factor/lymphoid enhance factor.

in recurrent grade II gliomas (10). Significant crosstalk exists between the EP1, EP2 and EP4 receptors and the epidermal growth factor receptor (EGFR) signaling pathway through subsequent transactivation of the EGFR, which results in the activation of c-Src (see *Figure 1*). Activation of EGFR leads to the activation of several signal transduction cascades, engaging mitogen-activated protein kinase (MAPK), PI3K/Akt, STAT and phospholipase C (PLC) signaling pathways, culminating in cell proliferation, differentiation or migration.

In the article by Cook *et al*. (11) glioma cells obtained from a PDGF-mouse brain induced tumor using the RCAS-tva system were used to investigated the functional role of PGE_2 signaling in GBM and confirmed the over-expression of COX-2 and PGE_2. These authors underline the importance of EP2 and EP4 receptors, especially EP4.

Activation of the EP2 receptor causes the activation of several signaling pathways including activation of protein kinase A (PKA) that is responsible for activating the transcription factor cyclic adenosine monophosphate response-element binding protein (CREB) and the signaling factor extracellular signal-regulated kinase-1/2 (ERK1/2). Activation of EP2 can also lead to the formation of a β-arrestin 1-Src complex, with subsequent activation of the EGFR. Activation of the EP4 receptor triggers the same signaling pathway through activation of the transcription factor CREB, but also initiates activation of the PI3K and AKT pathway. As such, the biological outcomes of EP2 *vs*. EP4 activation are somewhat different (12). The EP1/EP1 receptor, which was shown to signal through a PLC/PKC/c-Src signaling pathway, is also involved in PGE_2-mediated GBM proliferation, and EP1 antagonists have been shown to inhibit the proliferation of glioma cell lines *in vitro* and slow tumor growth *in vivo* (13). However, the article of Cook *et al*. present the EP4 receptor as distinctively responsible for PGE_2-mediated induction of inhibitor of DNA binding 1 (Id1) and demonstrate the importance of the MAPK signal required for PGE_2-mediated induction of Id1 in GBM cells. The EP1 and EP2 receptors are low affinity receptors, compared to EP3 and EP4 and as such should be activated at low concentrations of PGE_2, but the specific connection of EP4 (and not EP2) in Id1 activation is established here. Additional survival/proliferation mechanisms by PGE_2 have been shown by Brocard *et al*. (14) who demonstrated that *in vitro* radiation-induced PGE_2 sustained human glioma cell proliferation and survival through EGFR signaling by PGE_2 mainly through EP2.

Another important point underlined in the article is the impact of the activation of Id1 on glioma cell proliferation and the self-renewal of the glioma stem cells. High Id1 levels often correlate strongly with poor prognosis, therapeutic resistance, tumor metastases and a high self-renewal of cancer stem cells. However, in another PDGF-driven tumor model, $Id1^{low}$ cells were shown to generate tumors more quickly and with higher infiltration than $Id1^{high}$ cells (15). Subsequently, targeting the Cox-2/Id1 pathway to eliminate glioma stem cells may not necessary improve the outcome of patient with GBM and it could depend on several/other factors including the glioma subgroup. Similarly, an analyses of transcriptomic results showed that $Id1^{high}$ expressing patients demonstrated a better overall survival compared to $Id1^{low}$ expressing patients suggesting that high levels of Id1 are a good prognostic factor (16). Essentially Id1 was shown to affect the efficacy of radiotherapy in GBM initiating an accumulation of cells in G_2/M and a subsequent diminution in DNA repair. This observation is particularly interesting, as the main functions of Id1–Id4 have been shown to inhibit differentiation and promote proliferation of many different cell types. However, in the brain, the expression of Id2 has been shown to be associated with cultured neural precursor cell (NPC) proliferation as well as with the proliferation of central nervous system tumors including glioblastoma (17). These results point out that the Id1/Id2 ratio could be a determinant in the control of glioma growth.

Radiotherapy remains the major treatment for GBM, the therapeutic consequence of which is the eradication of tumor cells and damage to surrounding normal tissue. However, as stated above, there is a rapid recurrence probably due to the presence of the CSC, which are radio-resistant. These CSC in the damaged tissue play a critical role in tissue regeneration and tumor recurrence. It is generally assumed that in dying cells caspase-activated pathways would release growth-promoting factors that mobilize and recruit CSC. One of these pathways is the Ca^{2+}-independent phospholipase A2, the activation of which increases the synthesis and release of AA from apoptotic cells and the consequent release of PGE_2 by these dying cells. As such, this radiation-induced release of PGE_2 would constitute the "dark side" of radiotherapy that has to be counteracted to inhibit tumor growth (18). The effect of apoptotic cells on the surrounding tissue cancer cell proliferation may be driven by inappropriate signals from these cells and modify the impact of apoptosis on tumorigenesis and cancer therapy.

It has already been described that COX-2 derived-PGE_2

could induce Id1 thereby increasing CSC self-renewal and radiation resistance. Actually, numerous studies have demonstrated that supplementing with exogenous PGE_2 recapitulates radio-resistance, thus blocking the EP2 receptor would abrogate radio-resistance (13,19). In another study it was demonstrated that radiotherapy induces a caspase-3-dependent mechanism involving PGE_2 and was responsible for the regeneration of surviving cells (20). Likewise, the role of Id1 in glioma tumorigenesis through the COX-2-PGE_2 pathway and role of Id1 in the proliferation of stem cells after radiation has been characterized (6).

Overall, the results suggest that this topic is essential in the case of fractionation radiation doses associated with chemotherapy in the treatment of GBM. If previous studies have demonstrated that CSC are selectively enriched after chemotherapy through enhanced survival and chemo-resistance. These results confirm the negative aspects of the induction of apoptosis in cancer cells by radiotherapy in glioma treatment. However, because members of the prostaglandin family have pleiotropic and often contradictory roles, the efficient targeting of the synthesis of PGE_2 by inhibitors of mPGES or the modulation of the activity of its receptors (EP2 and EP4 especially) seems to be attractive strategies.

Future investigations are needed to identify the groups of patients, defined by genomic characteristics among others that could benefit from this approach in GBM. In addition the Id1/Id2 expression could be good candidates as biomarkers to determine the tumors that would respond to these treatments.

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Footnote

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