

Genes Encoding Enzymatic Activities Implicated in the Eicosanoid Cascade of Arachidonic Acid and their Receptors are Expressed at mRNA Levels in Human Meningiomas

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Abstract

In view of the important oncogenic action of lipoxygenase (LOX) and cyclooxygenase (COX) enzymatic activities we investigated, by using real time PCR, their presence in human meningiomas. Results indicated the presence of 5-LOX, 12-LOX, 15-LOX1, 15-LOX2, COX-1, COX-2, prostaglandin E (PGE) synthase, prostacyclin (PGI) synthase and thromboxane (TX) synthase transcripts in meningiomas but without relation to the tumor grade, the subtype of meningiomas, the presence of inflammatory infiltrated cells, of an associated edema, mitosis, brain invasion, vascularisation or necrosis. Similar results were found for BLT1 and BLT2 transcripts (encoding LTB₄ receptors) and for prostanoid receptor transcripts (EP₁₋₄ for PGE₂, IP for PGI₂ and TP for TXA₂). In conclusion, genes encoding enzymatic activities implicated in the eicosanoid cascade are expressed in meningiomas. LOX- and COX-derived arachidonic acid metabolites might act on tumor growth not only by acting on cell growth but also by altering the local cytokine and/or angiogenic networks.

Keywords: Meningiomas; Lipoxygenase; Cyclooxygenase; Prostanoid receptors; Arachidonic acid metabolites

Introduction

Meningiomas present clinically by causing focal or generalized seizure disorders, focal neurological deficits or neuropsychological decline (Whittle et al., 2004). Lipid mediators such as platelet-activating factor (PAF) and eicosanoids have been reported to act on the growth of various cell types (Dupuis et al., 1997a, b). A possible role for PAF has been reported in human meningiomas (Denizot et al., 2006). A role for the whole eicosanoid cascade has been suggested in meningiomas (Nathoo et al., 2004). Eicosanoids are a large family of lipid mediators with potent inflammatory and oncogenic properties. They are produced by two enzymes classes, lipoxygenases (LOX) and cyclooxygenases (COX). The LOX pathway acts on arachidonic acid (AA) to generate LTB₄, 12-HETE and 15-HETE by 5-LOX, 12-LOX and 15-LOX activities, respectively (Kuhn et al., 2002; Radmark, 2002; Yoshimoto and Takahashi, 2002). A 12S-LOX and 12R-LOX were reported. A 15-LOX1 and 15-LOX2 have been identified. Whether receptors for 12-LOX and 15-LOX metabolites are not cloned, two receptors for LTB₄ have been identified: BLT1 and BLT2. The COX pathway involves the conversion of AA to PGH₂ (Cipollone et al., 2008). The profile

of products made by cells expressing COX-1 (constitutive enzyme) or COX-2 (inducible enzyme) is therefore determined by the presence of different cell-specific downstream enzymes. PGH₂ leads to generation of prostanoids, which include prostaglandin E₂ (via a PGE synthase), thromboxane A₂ (via a thromboxane synthase, TX synthase) and prostacyclin (via a prostacyclin synthase, PGI₂ synthase). Effects of the prostanoid release are mediated by prostanoid receptors on target cells and tissues. These correspond to each of the COX metabolites: EP₁₋₄ for PGE₂, IP for PGI₂ and TP for TXA₂.

The existence of COX and 5-LOX enzymes and high levels of AA in meningiomas create a favorable environment for the efficient production of eicosanoids (Boado et al., 1992; Nathoo et al., 2004; Pfister et al., 2007). Thus TXB₂, PGE₂ and PGI₂ are produced in meningiomas (Castelli et al., 1989). Nevertheless many important questions remain unanswered. Little is known about the expression of prostanoid and LTB₄ receptors in meningiomas. Little is known about their expression of 12-LOX and 15-LOX. Little is known about the relationships between tumor LOX, COX and downstream enzymes with respect to the tumor grade. In view of the potentially important oncogenic actions of eicosanoids in human meningiomas, real time polymerase chain reaction (PCR) was utilized to quantify transcripts for the enzymatic activities implicated in the eicosanoid cascade and their receptors in intracranial meningiomas.

Patients and Methods

Patients

The procedure of the present study followed the rules edited by the French National Ethics. Ethics approval was obtained from the ethics committee of our hospital (CHU Dupuytren, Limoges, France). Twenty six patients who underwent surgery for intracranial meningiomas (from 1998 to 2004) were investi-

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gated. Tumors were from the Service d'Anatomie Pathologique of the CHU Dupuytren (France). At the time of resection, tumor samples were fixed in 4% formalin, embedded in paraffin and sections were cut and stained with hemalum phloxine saffron. On paraffin sections, histological type and grade were determined according to the WHO classification (Louis et al., 2007). There were 15 grade I meningiomas including 7 transitional (2 man, 5 women, mean age 60 years), 3 meningothelial (1 man, 2 women, mean age 60 years) and 5 fibrous (5 women, mean age 59 years). Nine tumors were grade II meningiomas: 8 atypical (6 men, 2 woman, mean age 58 years) and 1 chordoid meningioma (1 man, 54 years) Two tumors were classified as anaplastic grade III meningiomas (2 men, mean age 54 years). After undergoing the routine hospital analysis, the excess of sample was kept at -80°C until use and this in accordance with the regulations in force in France. No written or oral consent was obtained because it is a study of samples already collected and

referred to research prior the French bioethical law (2004). Thus, ethics committee explicitly approved the waiver of consent. Normal meninges were not available in our institution in the light of our ethic committee law. The low amounts (10 - 15 mg) of available tumors only permitted investigations at the mRNA level.

RNA isolation, reverse transcription and real time PCR analysis

Total RNA was extracted using the "RNeasy Lipid Tissue mini kit" (Qiagen, Courtaboeuf, France). RNA integrity was checked by capillary electrophoresis on the Bioanalyzer 2100 (Agilent Technologies, Massy, France). Total RNA was reverse transcribed in single strand cDNA using random hexamers and as described in the protocol of the "SuperScript III First-Strand Synthesis System for RT-PCR" (Invitrogen, Cergy-Pontoise, France). Reactions were frozen at -20°C until quantitative real time PCR

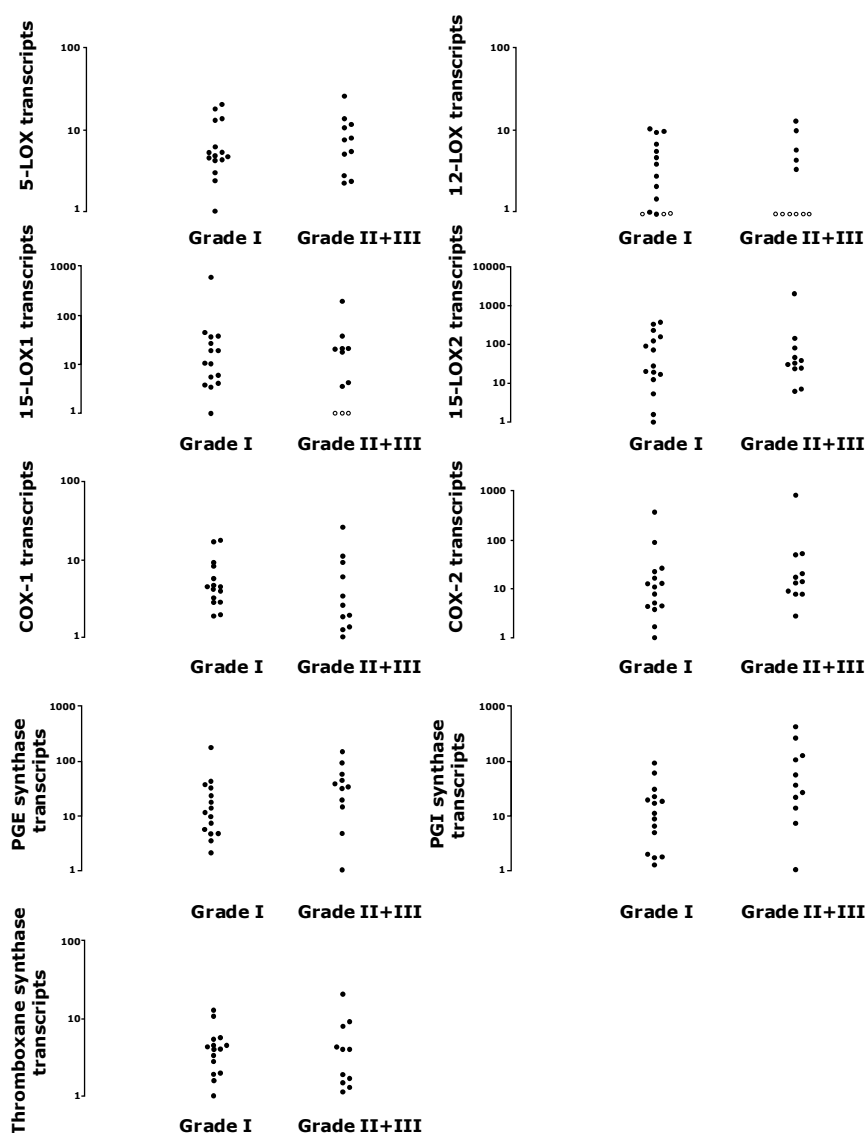


Figure 1: LOX and COX activities in human meningioma. Fifteen grade I and eleven grade II+III meningioma were investigated. Gene expression levels were normalized to 18S RNA (product reference: Hs99999901-s1). Amounts of transcripts were compared to sample with the lowest level of transcripts (a patient who was arbitrary quoted 1). (?) indicates patients with no detectable transcript. Significance was assessed by using the Kruskal-Wallis test followed by a Mann-Whitney U-test. No significant differences were documented between groups. Product references were the following: 5-LOX: Hs00386528-m1; 12S-LOX: Hs00167524-m1; 12R-LOX: Hs00153961-m1; 15-LOX1: Hs00609608-m1; 15-LOX2: Hs00153988; COX-1: Hs00277289-s1; COX-2: Hs00153133-m1; PGE synthase: Hs01115610-m1; PGI synthase: Hs00168766-m1; TX synthase: Hs00233423-m1.

realisation. PCR was performed in duplicate by using TaqMan assay reagents (Applied Biosystems, Foster City, CA) following the recommendations of the manufacturer. Amplification products were analyzed on an ABI Prism 7000 system (Applied Biosystems) (Fiancette et al., 2009; Vincent et al., 2009). Gene expression levels were normalized to 18S RNA. Amounts of various transcripts were compared to sample with the lowest level of transcripts (a patient who was arbitrary quoted 1). The relative quantification of gene expression was performed using the “relative quantitation calculation and analysis software for Applied Biosystems real-time PCR systems”.

Statistical analysis

Significance was assessed by using the Kruskal-Wallis test followed by a Mann-Whitney *U*-test. A $p < 0.05$ was considered to be significant.

Results and Discussion

LOX enzymatic transcripts in human meningiomas

We firstly investigated if LOX genes were expressed in meningiomas. 12R-LOX transcripts were not present at detectable levels (data not shown). In contrast, 5-LOX, 12S-LOX, 15-LOX1 and 15-LOX2 were detected in 100%, 65%, 88% and 100% of

tumors, respectively (Figure 1). No difference was found for LOX transcripts amounts in relation to the tumor grade (Figure 1), nor the subtype of meningiomas, the presence of inflammatory infiltrated cells, of an associated edema, mitosis, brain invasion, vascularisation or necrosis (data not shown). The technique employed in this study allowed measurement of several mRNA in the same tumor. So it was possible to evaluate the levels of each of the isoforms relative to one another. Results indicated the following rank of magnitude in human meningiomas: 5-LOX > 15-LOX1 >> 15-LOX2 > 12-LOX. Results of the present study, thus, confirm the presence of 5-LOX in human meningiomas and that 5-LOX levels did not significantly differ among different WHO grades (Pfister et al., 2007). Beside 5-LOX, we highlight for the first time the presence of 15-LOX and 12-LOX transcripts in meningiomas. The ability of 12-HETE and 15-HETE to regulate important functions of the immune system has been reported. They stimulate proinflammatory cytokine productions (Denizot et al., 1998; Denizot et al., 1999), indicating an ability of 12-HETE and 15-HETE to augment and prolong tissue inflammation. 12-LOX is found to regulate tumor angiogenesis (Hagmann, 1997). In contrast 15-LOX is a functional tumor suppressor that regulates differentiation, senescence and growth (Tang et al., 2007). The higher 15-LOX

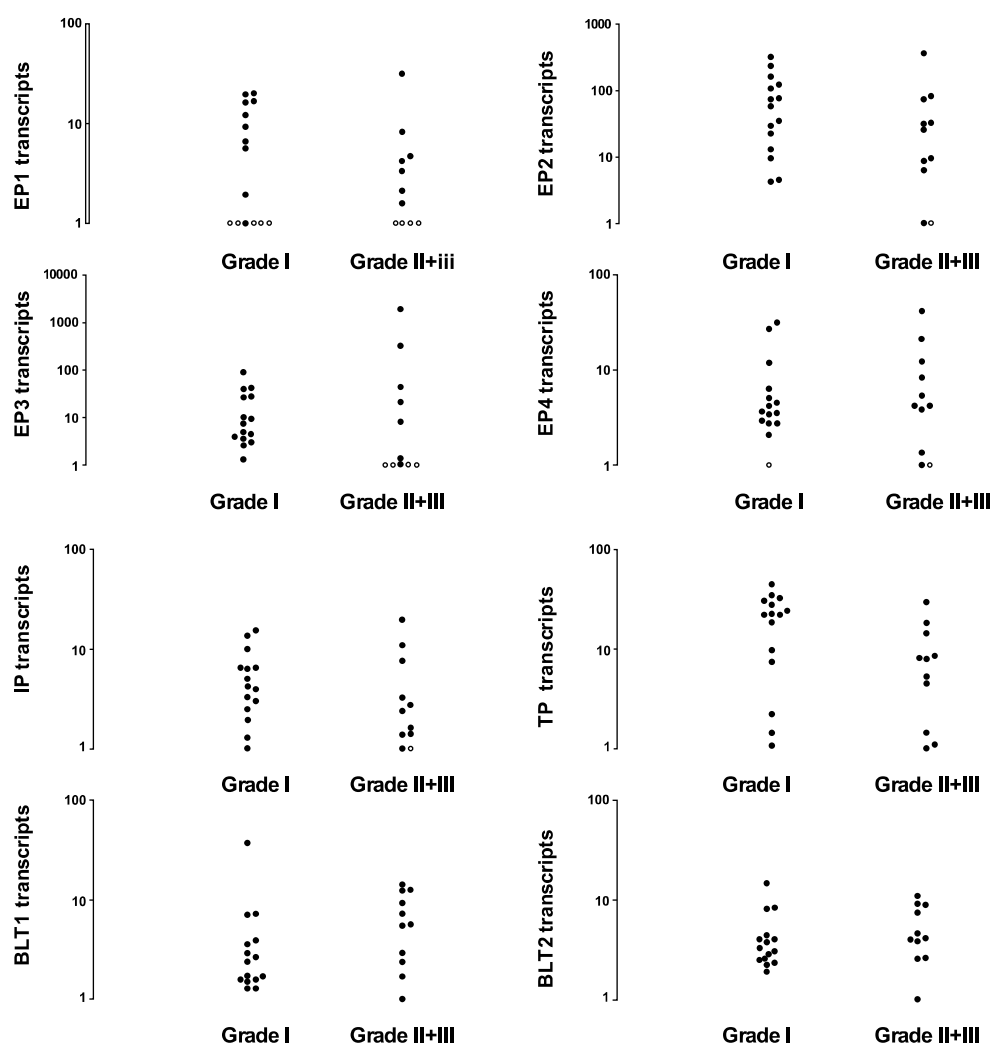


Figure 2: LTB₄ and prostanoid receptors in human meningioma. Same legend as in Figure 1. Product references were the following: EP₁: Hs00168752-m1; EP₂: Hs00168754-m1; EP₃: Hs00168755-m1; EP₄: Hs00168761-m1; IP: Hs00168765-m1; TP: Hs00169054-m1; BLT1: Hs00175124-m1; BLT2: Hs01885851-s1; 18S: Hs99999901-s1.

expression as compared with 12-LOX one is in agreement with the slow growing and low metastatic status of meningioma tumors. Investigation of 12-LOX and 15-LOX transcripts in higher growth and metastatic brain tumors such as glioblastomas and astrocytomas would be of interest to reinforce this hypothesis.

LTB₄ receptor transcripts in meningiomas

Reinforcing the putative role of 5-LOX in meningiomas, we found the presence of 5-LOX activating protein (FLAP) transcripts in 100% of meningioma samples (data not shown); FLAP functioning as a facilitator of 5-LOX activity (Radmark, 2002). We then investigated whether human meningioma tumors expressed LTB₄ receptors. Transcripts for the two LTB₄ receptors BLT1 and BLT2 were detected in 100% of human meningiomas (Figure 2). BLT1 and BLT2 play critical roles in host defense and in many inflammatory diseases by mediating the multiple activities of LTB₄ (Tager et al., 2003). Considering the critical importance of the 5-LOX/FLAP/BLT1-BLT2 signal transduction pathway in carcinogenesis (Chen et al., 2006; Nie et al., 2000), its presence in meningiomas suggest its involvement in tumor growth. Together, these observations might suggest 5-LOX inhibitors as an interesting target for drug development for meningioma therapy. However, given the ubiquitous expression of 5-LOX, drug targeting strategies must exhibit selectivity to avoid undesired side effects.

COX enzymatic-related transcripts in human meningiomas

In a second set of experiments we investigated enzymatic activities implicated in the COX cascade in meningiomas. COX-1, COX2, PGE synthase, PGI synthase and TX synthase transcripts were detected in 100% of tumors (Figure 1). No difference ($p > 0.05$, Mann Whitney *U*-test) was found for COX and downstream enzymes in relation to the tumor grade (Figure 1) nor other clinical data (data not shown). Results indicated the following rank of magnitude for COX-related enzymatic activities: COX-1 > COX-2 and PGE synthase > TX synthase > PGI synthase. Results of the current study thus highlight an ubiquitous expression of COX-1 and COX-2 in meningiomas. COX isoforms function independently and play distinct roles in regulating AA metabolism. COX-1 is constitutively expressed and responsible for the low COX metabolite production required for cell homeostasis. In contrast COX-2 is produced during the course of inflammation, cellular stress and tumorigenesis in response to a wide range of stimuli (Bhattacharya et al., 1999). We did not find a relationship between COX-2 transcript levels and the tumor grade in meningiomas. This putative link remains a conflicting question since studies documented it (Pistolesi et al., 2007; Panagopoulos et al., 2008) while others did not (Linn et al., 2003; Buccoliero et al., 2007; Pfister et al., 2007). Nevertheless the ubiquitous expression of COX-2 in meningioma tumors may suggest considering COX-2 inhibitors as a potential area of therapeutic intervention. Thus, the COX-2 inhibitor celecoxib inhibits meningioma growth in vitro (Ragel et al., 2005) and reduces meningioma tumor growth in a mouse xenograft model (Ragel et al., 2007).

Prostanoid receptor transcripts in human meningiomas

Ubiquitous expression of PGE synthase, PGI synthase and TX synthase transcripts are found in meningiomas confirming their ability to produce PGE₂, PGI₂ and TXA₂ (Castelli et al., 1989;

Constantini et al., 1993; Paoletti et al., 1989). These prostanoid metabolites are reported to play various roles in tumor progression and metastasis in several cancers (Wang et al., 2007). Reinforcing their putative roles in meningioma tumorigenesis, EP₁, EP₂, EP₃, EP₄, IP and TP transcripts were documented in the vast majority of meningiomas (65%, 96%, 80%, 92%, 96% and 100% for EP₁, EP₂, EP₃, EP₄, IP and TP transcripts, respectively) but without link with the tumor grade (Figure 2). Results indicated the following rank of magnitude for prostanoid receptor transcripts: EP₄ > EP₂ > EP₃ > EP₁ and TP > IP. PGE₂ effects are mediated through interactions with four G-protein coupled receptors. EP₁ are coupled to G_{q/p} and ligand binding induces intracellular calcium level variations. EP₂ and EP₄ are coupled to G_s and stimulate cAMP production while EP₃ are coupled to G_i and inhibit cAMP production (Bhattacharya et al., 1999; Harris et al., 2002). In meningiomas PGE₂ might act via EP₄-EP₂ receptors, thus, through a cAMP-elevating effect. PGE₂ is known to stimulate growth factor productions (Besse et al., 1999) thus acting on tumor progression by altering the tumor cytokine network. PGI₂ (reported as an anticancer metabolite) and TXA₂ (reported as a procancer metabolite) have opposing actions and the balance between these two mediators is crucial. PGI₂ modulates platelet-vascular interactions and counteracts the proliferative and platelet effects of TXA₂ in response to stress and injury (Cipollone et al., 2008).

Concluding remarks

In conclusion, genes encoding enzymatic activities implicated in the eicosanoid cascade are universally expressed in meningiomas. LOX- and COX-derived AA metabolites might act on tumor growth not only by acting directly on cell growth but also by altering the local cytokine and/or angiogenic networks. The potential role of these COX- and LOX-derived metabolites on meningiomas is reinforced by the presence of LTB₄ and prostanoid receptor transcripts in tumors. Further studies are needed to elucidate the precise contributions of each of these compounds in meningiomas and to determine their possible relevance in the targeting of new therapeutic interventions. As previously suggested for other tumors, 5-LOX and COX-2 appear as the most promising targets.

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