Inflammatory response and meningioma tumorigenesis and the effect of cyclooxygenase-2 inhibitors

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The term “meningioma” describes a tumor arising from the central nervous system meninges.1 The World Health Organization has identified three meningoma grades: benign, atypical, and malignant.24 Primary treatment for meningioma generally involves complete resection of the tumor, but this treatment has variable rates of success. The rate of meningioma recurrence after surgery is affected by the extent of resection (measured on the overall Simpson resection grade) and the intrinsic tumor biology.3,24,37 Recurrence rates for benign meningiomas 5 years after complete removal are 2 to 3% (median time to recurrence 3.1–7.5 years), whereas recurrence rates for atypical and anaplastic meningiomas (so-called “aggressive meningiomas”) are 38 to 50% (median time to recurrence 2.4–3.3 years) and 33 to 78% (3.5–7.7 years to recurrence), respectively.13,28 The overall 4- to 5-year survival for patients receiving multimodal treatment (that is, maximal surgical and medical management) for benign, atypical, and malignant meningiomas are 100%, 59 to 83%, and 0 to 59%, respectively.2,10,40,44 Harris et al.10 reported 10-year survival rates for atypical and malignant meningioma to be 59 and 0%, respectively. These bleak survival statistics underscore the need for new therapies for patients with atypical and malignant meningiomas. To date, medical therapies have been disappointing and radiation is limited in the number of total treatments that can be prescribed.

Cyclooxygenase-2 Expression Promotes Meningioma Formation

Clinical evidence supports the concept that meningioma formation may be associated with previous head trauma.32–34,45 In vivo and in vitro studies show Cox-2 up-regulation after head trauma, and previous work has shown that meningiomas stain extensively for Cox-2,19,21,36 which is the rate-limiting enzyme in the synthesis of prostaglandins from arachidonic acid.31 Prostaglandins have angiogenic, cell-proliferative, and antiapoptotic properties and are upregulated in a multitude of cancers (for example, breast, prostate, and lung).43 These lines of evidence suggest that meningioma formation may occur in the setting of chronic inflammation triggered by trauma.2

Of the two isoforms of cyclooxygenase, referred to as Cox-1 and Cox-2, Cox-1 is constitutively expressed in most tissues and primarily performs general “housekeeping” functions (for example, cytoprotection of the stomach and platelet aggregation). In contrast, Cox-2 is induced by migratory cells (for example, macrophages, monocytes, and microglia) responding to proinflammatory stimuli and mediates acute and chronic inflammatory states.11,27 The expression of Cox-2 is ordinarily low at baseline but surges in the context of inflammation or neoplasia.6

The head trauma–meningioma relationship may be explained by the development of neoplastic changes in meningeal tissue caused by the inflammatory state of healing and the associated release of prostaglandins and other growth factors (Fig. 1).19,21,32–34 Several studies have shown an increased incidence of meningiomas in patients with

Abbreviations used in this paper: Cox = cyclooxygenase; FDA = Food and Drug Administration; NSAIDs = nonsteroidal antiinflammatory drugs; VEGF = vascular endothelial growth factor.
previous history of head trauma, with elevated odds ratios ranging between 1.2 and 6.4 and latency periods between 14 and 24 years. In these patients, it is possible that neoplastic changes in meningeal tissue caused by healing, inflammation, and the release of growth factors may act as inciting factors in tumorigenesis.

Nonsteroidal Anti-Inflammatory Drugs and Cancer

The anti-inflammatory action of NSAIDs results from their ability to inhibit Cox enzyme activity, resulting in decreased synthesis of the proinflammatory prostaglandins. The NSAIDs decrease Cox activity through nonselective binding, selective binding, or noncyclooxygenase Cox-2 mechanisms. Among the nonselective inhibitors, aspirin irreversibly inactivates both Cox-1 and -2, whereas ibuprofen and flurbiprofen are reversible inhibitors of Cox-1 and -2 (although they act via different mechanisms; the former competes with arachidonic acid, whereas the latter forms a salt bridge). Among the selective Cox-2 inhibitors, celecoxib (Celebrex) and rofecoxib (Vioxx) are both irreversible inhibitors of Cox-2. Finally, R-flurbiprofen inhibits NF-κB and API activation of Cox-2 transcription. Selective Cox-2 inhibitors are used in cancer treatment studies because of their low side-effect profile and because they have been approved by the US FDA.

Clinically, selective Cox-2 inhibition produces antiinflammatory and analgesic effects without the side effects of gastric ulcers and platelet dysfunction. These characteristics, along with the following findings, suggest that NSAIDs may be used in the prevention of cancer and as adjuvants for treatment: 1) that Cox inhibitors promote anticancer effects in vitro; 2) that Cox inhibitors reduce the size and number of tumors in cancer animal models; 3) that Cox inhibitors reduce the incidence of colon cancer; and 4) that Cox inhibitors cause precancerous lesions (for example, the aberrant crypt foci of colorectal cancer) to regress in cohorts of patients at risk for genetic and sporadic cancers.

Interest in inhibiting Cox-2 with celecoxib in meningiomas specifically stems from the literature showing Cox-2 expression in meningioma tumor samples and from our ability to inhibit this enzyme with NSAIDs. Celecoxib is appealing because it is US FDA approved for the treatment of rheumatoid arthritis, osteoarthritis, and familial adenomatous polyposis, and it is being tracked by the National Cancer Institute in more than 30 Phase I, II, and III cancer trials in the treatment of colon, prostate, liver, lung, breast, and glioblastoma multiforme (physician’s data query at http://www.nci.nih.gov/clinicaltrials/).

Research

Cyclooxygenase-2 Inhibition in Meningiomas

Cyclooxygenase-2 is extensively expressed in meningiomas, with immunohistochemical and Western blot evidence showing cytoplasmic and nuclear localization (Fig. 2). Normal dura and dura adjacent to meningoma tu-
mors, on the other hand, do not stain for Cox-2 (Fig. 2).

Because of the selective expression of Cox-2 in meningioma tissue, its previously reported effects on other cancer cells, and FDA approval of celecoxib, this selective Cox-2 inhibitor was chosen for use in growth inhibition studies in meningiomas. Meningiomas treated both in vitro and in vivo with celecoxib showed decreased growth. In vitro studies, celecoxib showed a dose-dependent inhibition of meningioma cell growth in a malignant cell line (IOMM-Lee) and in six benign cell lines. In the IOMM-Lee cell line, this inhibition was associated with abolition of the Cox-2 enzymatic activity and a 51% reduction in prostaglandin E2 (PGE2) levels. These findings of growth inhibition in vitro coincide with other findings in the literature in which numerous cell lines, including those derived from brain tumors (for example, glioma cell lines U-87MG and U-251MG), show growth inhibition by selective Cox-2 inhibitors.

In the reported studies, celecoxib showed a dose-dependent inhibition of meningioma cell growth in a malignant cell line (IOMM-Lee) and in six benign cell lines. In the IOMM-Lee cell line, this inhibition was associated with abolition of the Cox-2 enzymatic activity and a 51% reduction in prostaglandin E2 (PGE2) levels. These findings of growth inhibition in vitro coincide with other findings in the literature in which numerous cell lines, including those derived from brain tumors (for example, glioma cell lines U-87MG and U-251MG), show growth inhibition by selective Cox-2 inhibitors.

Analysis of tumors grown in mice and treated with high-dose celecoxib showed decreased microvascular density (by 23 to 78%) and diminished Cox-2 and VEGF staining (Fig. 4), as well as increased apoptosis. Diminished Cox-2 and VEGF staining implies that celecoxib ultimately inhibits microvascular proliferation by inhibiting VEGF. This is supported by numerous studies showing that selective Cox-2 inhibition reduces blood vessel density, probably through direct inhibition of Cox-2 and downregulation of VEGF-mediated angiogenesis.

In the reported studies, celecoxib doses ranged from 500

![Fig. 2. Photomicrographs showing expression of Cox-2 in human colon cancer (A) and human meningiomas (B–F). Positive immunoreactivity appears as reddish-brown staining. A: Positive control. Strong Cox-2 immunoreactivity seen in the cytoplasm of colonic carcinoma cells (solid arrow). Note that vascular endothelium stains positively for Cox-2, as described previously in Maihofner et al. (open arrow). B: Negative control. No staining was noted when slides were incubated with serum only. C: Normal dura mater showing staining of vascular endothelium (open arrow), as well as meningioma abutting normal dura (solid arrows). D–F: Strong Cox-2 immunoreactivity noted diffusely throughout cytoplasm of meningioma (solid arrows). Note that monocyte or macrophage within blood vessel stains positive as described previously (open arrow in D). Original magnification ×10. Modified from Ragel, 2005.](https://example.com/fig2.png)
to 1500 ppm, which yielded mean plasma levels of 845 ng/ml (~0.85 μg/ml), 1540 ng/ml (~1.4 μg/ml), and 2869 μg/ml (~2.9 μg/ml) for the low-, medium-, and high-dose celecoxib doses, respectively. The peak plasma levels in various human studies of celecoxib have been reported from 0.6 μg/ml to approximately 1.2 μg/ml at recommended dosages between 200 and 800 mg a day (for the treatment of rheumatoid arthritis, osteoarthritis, and familial adenomatous polyposis). In clinical cancer trials this dose is as high as 800 mg a day. Thus, the plasma levels achieved from the low- and medium-dose celecoxib diets were within reported human ranges (Fig. 3). Although the mice on the high-dose diet achieved a plasma concentration achievable in humans, it would require ingestion of roughly 3 g of celecoxib daily (Pfizer, personal communication). Thus, although the findings in this study indicate
that celecoxib will be beneficial in the treatment of meningiomas, alternative ways of exploiting its effects should be investigated. Future studies will be used to examine celecoxib as a radiation sensitizer and in combination with other systemic therapies (for example, hydroxyurea).

Conclusions

Recurrent meningiomas, particularly those classified as aggressive, currently lack many successful treatment options; however, studies suggest that Cox-2 may offer a therapeutic target that can be inhibited by NSAIDs. Treatment with NSAIDs has been shown to curb the facilitation of tumor properties of Cox-2 in other cancers via several mechanisms. Thus, investigations of Cox-2 inhibitors may reveal benefit for the treatment of recurrent meningiomas. Studies have shown that celecoxib significantly inhibits meningioma growth in vivo at high plasma levels in a meningioma mouse model. The meningioma cell lines used in these studies showed aggressive growth with areas of necrosis on histological analysis, findings consistent with higher-grade meningiomas. Therefore, these Cox-2 inhibition results may be more applicable to higher-grade tumors and demonstrate that Cox-2 inhibition may play a role in the treatment of recurrent meningiomas.

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