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COX-2 inhibitors act as radiosensitizer in tumor treatment

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Abstract

Since cyclooxygenase-2 (COX-2) is overexpressed in malignant tissues, the COX-2 mediated signaling pathway has been recognized as potential target for therapeutic intervention. In most human tumors, COX-2 overexpression has been associated with tumor aggressiveness and poor clinical outcome. In vitro studies show inhibition of cell proliferation by selective COX-2 inhibitors alone, and enhancement of the response to irradiation. In vivo experimental reports demonstrate enhanced tumor response and impediment of tumor neovascularization following radiotherapy combined with COX-2 inhibition. Clinical studies on the combination of irradiation with COX-2 inhibitors are emerging. Taken together, the perspective for the combined approach of radiotherapy with COX-2 inhibition yields clinical significance since preclinical data demonstrate selective COX-2 inhibitors to act as radiosensitizer in tumor treatment.

Keywords: COX-2 inhibition; Radiosensitization; Brain tumor

1. COX-1 and COX-2 expression in normal and malignant tissue

Prostaglandin endoperoxide synthase, commonly called cyclooxygenase (COX) is the key enzyme required for the conversion of arachidonic acid to prostaglandins. Two known isoforms are COX-1 and COX-2. COX-1 is constitutively expressed in almost all normal tissues, and is responsible for regulation of 'housekeeping' functions. The COX-2 protein mainly mediates a pro-inflammatory role, and is inducible by a number of different stimuli including irradiation [3,15]. PTGS2 alias COX-2 is an 8 kB gene composed of 10 exons located on chromosome 1q25.2–q25.3. The mRNA is 4.1–4.5 kB and encodes for a protein of approximately 68 kDa. Most normal tissues express COX-2 at undetectable or low level. COX-2 is constitutively expressed only in the kidney, stomach, uterus, ovary, pancreatic islet cells, macrophages and neuronal cells in the brains [4,7,29]. The association between cyclooxygenase-2 (COX-2) and cancer is derived from the observation that the enzyme is overexpressed in a variety of malignancies including those of the head and neck [6], breast [25], cervix uteri [12], prostate, bladder, liver, pancreas, skin, lung [11], colon, oesophagus and the brain [10,29]. The COX-2 enzyme acts, via stimulation of the prostaglandin production, anti-apoptotic and triggers tumor cell proliferation. COX-2 has been involved in the angiogenic process in tumors by various mechanisms including the increased expression of the vascular endothelial growth factor and by generating prostaglandines which stimulate endothelial cell migration and possibly the inhibition of endothelial cell apoptosis [3,16,29]. Since COX-2 was found to be overexpressed in malignant—and not or scarcely in healthy, normal tissues, the COX-2 mediated signaling pathway has been recognized as potential target for therapeutic intervention. In view of emerging clinical data on brain tumor therapy and available preclinical studies, the present overview is mainly focused on the role of COX-2 in brain tumors.

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Abbreviation: COX, cyclooxygenase.
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Literature as well as own laboratory data on COX-2 expression and modulation are presented, showing the promising perspective for the combination of radiotherapy with selective COX-2 inhibition in tumor treatment.

2. COX-2 expression in brain tumors

Glioblastoma multiforme is the most aggressive brain tumor type in humans. Standard treatment for newly diagnosed gliomas is surgical resection followed by post-operative radiation therapy. Complete surgical resection of gliomas is usually impossible due to their diffuse infiltrative growth, resulting in a high recurrence rate, and the median survival is less than 1 year after initial diagnosis [8,27]. Modification of the irradiation response by radiosensitizers is an approach with great potential in optimization of brain tumor therapy [1,9].

The expression of COX-2 was studied by immunohistochemistry both in human glioma tissue specimens and normal brain specimens [4,10,26]. The data show COX-2 positivity in cytoplasmatic neurons, macrophages, microglial cells and in a few endothelial cells in normal brain specimens. Tumor specimens also showed granular staining of the cytoplasm and COX-2 positive staining accumulated in tumor cells, in infiltrative lymphocytes and in endothelial cells. The immunoreactive score of COX-2 in human glioma specimens was related to the WHO classification grade of glioma, with a significant higher score in high grade glioma than in low grade glioma and normal brain [4,10]. High COX-2 expression in human gliomas was associated with clinically aggressiveness and predictive for a poorer survival of patients [26]. In our laboratory, we investigated the pattern and level of COX-2 expression in a series of high grade primary and recurrent malignant gliomas and correlation with time to recurrence and patients' survival following therapy. For this purpose, specimens of 14 primary gliomas and 14 recurrences (eight pairs) following surgery and full course radiation therapy were processed for immunostaining on COX-2. COX-2 positive tumor cells were found to be disseminated throughout the tumor parenchyma. The intensity and pattern of COX-2 expression were heterogeneous, with predominant expression in areas surrounding tumor necrosis (Fig. 1A). Scoring of COX-2 positivity revealed values between 1% and 80% of the tumor cells. In 17 out of 28 specimens, > 5% of tumor cells were found to be COX-2 positive. Blood vessels in the tumor showed an inter- and intra tumor variation in COX-2 staining. In some tissue sections, highly positive vascular endothelial cells with neovascularization were noticed (Fig. 1B). With regard to the clinical follow-up it was found that primary tumors with high expression of COX-2 tended to recur earlier than those with low COX-2 expression. No correlation was found between the COX-2 expression in the primary tumor with patients' survival following therapy. Because of the large variation in COX-2 expression, it was concluded that immunohistochemical screening of tumor specimens on COX-2 might be relevant for selection of those individual patients' who could benefit from adjuvant therapy with selective COX-2 inhibitors [28].

3. COX-2 inhibition and the mechanism of radiosensitization

COX-1 and COX-2 enzymes can be inhibited by non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen and indomethacin. These drugs have proven their efficacy in the suppression of inflammation, and are widely used for arthritis, cardiovascular diseases and pain. However, non-selective inhibition of the COX isoenzymes leads not only to beneficial therapeutic effects, but also to serious (gastrointestinal) adverse effects. Beneficial effects are due to inhibition of COX-2 and detrimental effects to inhibition of COX-1 [15]. Various in vitro and in vivo screening tests have been performed to discriminate between COX-1 and COX-2 inhibitory activity for a range of NSAIDs. Currently available selective COX-2 inhibitors do not inhibit constitutive COX-1, but inhibit inducible or overexpressed COX-2. Among these are celecoxib, rofecoxib, meloxicam, NS-398, SC-236 and L-743337.

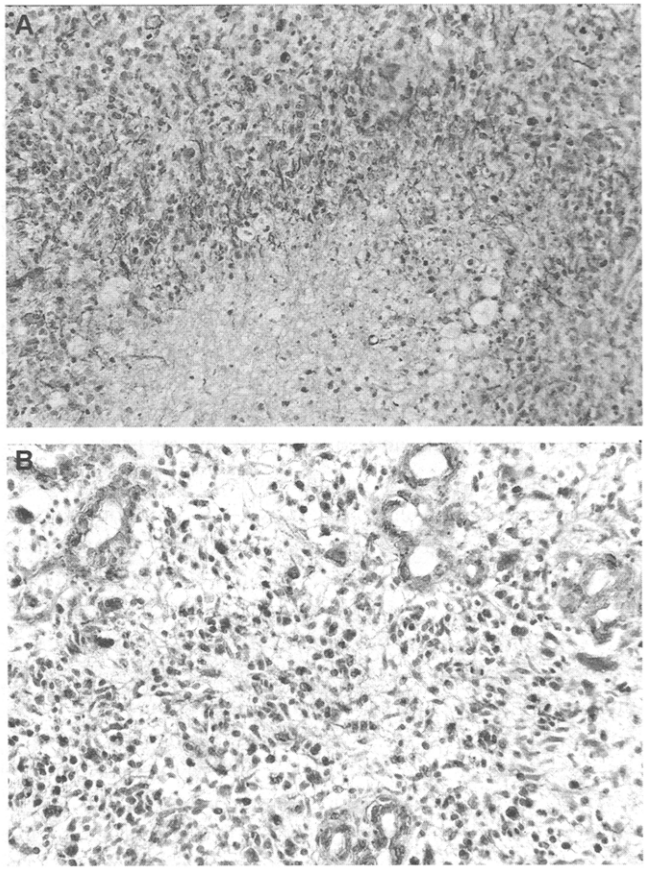

Fig. 1. Patterns of COX-2 expression in glioblastoma multiforme. (A) Tumor section with 70% of the tumor cells being positive for COX-2, and with most prominent expression in a rim surrounding an area of necrosis (×200). (B) Highly COX-2 positive vascular endothelial cells and neoangiogenesis (×200).