J Neurosurg. 2010 Nov 5. [Epub ahead of print]

Celecoxib and radioresistant glioblastoma-derived CD133(+) cells: improvement in radiotherapeutic effects.

Ma HI, Chiou SH, Hueng DY, Tai LK, Huang PI, Kao CL, Chen YW, Sytwu HK.

Graduate Institutes of Medical Sciences and.

Abstract

Object Glioblastoma, the most common primary brain tumor, has a poor prognosis, even with aggressive resection and chemoradiotherapy. Recent studies indicate that CD133(+) cells play a key role in radioresistance and recurrence of glioblastoma. Cyclooxygenase-2 (COX-2), which converts arachidonic acid to prostaglandins, is over-expressed in a variety of tumors, including CD133(+) glioblastomas. The COX-2-derived prostaglandins promote neovascularization during tumor development, and conventional radiotherapy increases the proportion of CD133(+) cells rather than eradicating them. The aim of the present study was to investigate the role of celecoxib, a selective COX-2 inhibitor, in enhancing the therapeutic effects of radiation on CD133(+) glioblastomas. Methods Cells positive for CD133 were isolated from glioblastoma specimens and characterized by flow cytometry, then treated with celecoxib and/or ionizing radiation (IR). Clonogenic assay, cell irradiation, cell cycle analysis, Western blot, and xenotransplantation were used to assess the effects of celecoxib alone, IR alone, and IR with celecoxib on CD133(+) and CD133(-) glioblastoma cells. Three separate xenotransplantation experiments were carried out using 310 severe combined immunodeficient (SCID) mice: 1) an initial tumorigenicity evaluation in which 3 different quantities of untreated CD133(-) cells or untreated or pretreated CD133(+) cells (5 treatment conditions) from 7 different tumors were injected into the striatum of 2 mice (210 mice total); 2) a tumor growth study (50 mice); and 3) a survival study (50 mice). For these last 2 studies the same 5 categories of cells were used as in the tumorigenicity (untreated CD133(-) cells, untreated or pretreated CD133(+) cells, with pretreatment consisting of celecoxib alone, IR alone, or IR and celecoxib), but only 1 cell source (Case 2) and quantity (5 × 10(4) cells) were used. Results High levels of COX-2 protein were detected in the CD133(+) but not the CD133(-) glioblastoma cells. The authors further demonstrated that 30 μM celecoxib was able to effectively enhance the IR effect in inhibiting colony formation and increasing IR-mediated apoptosis in celecoxib-treated CD133(+) glioblastoma cells. Furthermore, reduction in radioresistance was correlated with the induction of G2/M arrest, which was partially mediated through the increase in the level of phosphorylated-cdc2. In vivo xenotransplant analysis further confirmed that CD133(+)-associated tumorigenicity was significantly suppressed by celecoxib treatment. Importantly, pretreatment of CD133(+) glioblastoma cells with a combination of celecoxib and IR before injection into the striatum of SCID mice resulted in a statistically significant reduction in tumor growth and a statistically significant increase in the mean survival rate of the mice. Conclusions Celecoxib combined with radiation plays a critical role in the suppression of growth of CD133(+) glioblastoma stemlike cells. Celecoxib is therefore a radiosensitizing drug for clinical application in glioblastoma.

PMID: 21054139 [PubMed - as supplied by publisher]