Celecoxib induced tumor cell radiosensitization by inhibiting radiation induced nuclear EGFR transport and DNA-repair: a COX-2 independent mechanism.

PURPOSE: The purpose of the study was to elucidate the molecular mechanisms mediating radiosensitization of human tumor cells by the selective cyclooxygenase (COX)-2 inhibitor celecoxib.

METHODS AND MATERIALS: Experiments were performed using bronchial carcinoma cells A549, transformed fibroblasts HH4dd, the FaDu head-and-neck tumor cells, the colon carcinoma cells HCT116, and normal fibroblasts HSF7. Effects of celecoxib treatment were assessed by clonogenic cell survival, Western analysis, and quantification of residual DNA damage by gammaH(2)AX foci assay.

RESULTS: Celecoxib treatment resulted in a pronounced radiosensitization of A549, HCT116, and HSF7 cells, whereas FaDu and HH4dd cells were not radiosensitized. The observed radiosensitization could neither be correlated with basal COX-2 expression pattern nor with basal production of prostaglandin E2, but was depended on the ability of celecoxib to inhibit basal and radiation-induced nuclear transport of epidermal growth factor receptor (EGFR). The nuclear EGFR transport was strongly inhibited in A549-, HSF7-, and COX-2-deficient HCT116 cells, which were radiosensitized, but not in FaDu and HH4dd cells, which resisted celecoxib-induced radiosensitization. Celecoxib inhibited radiation-induced DNA-PK activation.
in A549, HSF7, and HCT116 cells, but not in FaDu and HH4dd cells. Consequentially, celecoxib increased residual gammaH2AX foci after irradiation, demonstrating that inhibition of DNA repair has occurred in responsive A549, HCT116, and HSF7 cells only. CONCLUSIONS: Celecoxib enhanced radiosensitivity by inhibition of EGFR-mediated mechanisms of radioresistance, a signaling that was independent of COX-2 activity. This novel observation may have therapeutic implications such that COX-2 inhibitors may improve therapeutic efficacy of radiation even in patients whose tumor radioresistance is not dependent on COX-2.