We have recently reported a possible regulation of VEGF-165 messenger RNA (mRNA) and protein expression in two human epidermoid carcinoma cell lines (A-431 and SCC-9) by a COX-2 pathway as well as a statistically significant association between COX-2 pathway up-regulation (increase in COX-2 mRNA and protein expression, and prostaglandin E2 biosynthesis) and angiogenesis in human head and neck cancers. Moreover, we demonstrated that COX-2 inhibition, by nonselective and more selective drugs, i.e., indomethacin and nimesulide, respectively, are able to reduce the synthesis of VEGF165 in A-431 and SCC-9 cell lines in vitro (3). An analogous role of COX-2 metabolites in controlling tumor angiogenesis in colon cancer cell lines has been also reported (4). Based on these findings, it is likely that the antiangiogenic effect of SC-’236, potentially responsible for the enhancement of tumor response to ionizing radiation (1), was mainly due to a reduced VEGF production by tumor cells. More recently, Jones et al. (5) also suggested an inhibition of angiogenesis by anti-COX-2 drugs through direct effects on endothelial cells.

Taken together, these results further support the hypothesis that different antiangiogenic therapies are able to increase the antitumor effects of ionizing radiation (6); however, the exact mechanism(s) responsible for this effect remains to be elucidated. Gorski et al. (2) have postulated a model in which irradiation is able to induce a stress response in irradiated cells characterized by VEGF production. The stress-related VEGF release might protect tumor blood vessels from radiation-mediated cytotoxicity and, thus, contribute to tumor resistance. The pretreatment with selective COX-2 inhibitors or with a neutralizing antibody to VEGF might counteract the biologic effects of radiation-induced VEGF release with lack of protection of tumor blood vessels resulting in a decreased tumor vascularization and increased tumor radiosensitivity.

Furthermore, the recently reported proapoptotic effect of COX-2 inhibition in human tumor xenografts suggests alternative mechanism(s) (7) by which COX-2 inhibitors might improve the efficacy of tumor response to radiotherapy in vivo, currently under investigation in our laboratory. It is possible to postulate that COX-2 inhibitors increased sensitivity to radiation because of a direct proapoptotic effect on tumor cells or, alternatively, because of an indirect proapoptotic effect on tumor cells stressed by an alteration of tumor blood supply.

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REFERENCES


NOTE

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RESPONSE

We are pleased to see that Dr. Gallo provided additional experimental data that indirectly support the hypothesis we advanced recently (1), that inhibition of tumor angiogenesis might be involved in the dramatic enhancement of tumor radioreponse when tumor-bearing mice were treated with SC-’236, a selective inhibitor of cyclooxygenase-2 (COX-2). Our hypothesis was based on the observation that SC-’236 inhibited formation of new vessels induced by tumor cells.
We attributed the effect of SC-236 to its inhibition of the synthesis of prostaglandins (PGs), which possess proangiogenic activities. The findings by Gallo, presented above, show that COX-2 can stimulate tumor angiogenesis by substances other than PGs, i.e., by increasing the production of vascular endothelial growth factor (VEGF) by tumor cells. He also reports that inhibition of COX-2 resulted in the inhibition of VEGF synthesis in tumor cells. It was reported earlier that inhibition of COX-2 by the selective inhibitor celecoxib can suppress corneal angiogenesis induced by fibroblast growth factor (FGF) (4). Thus, these findings imply that the biologic role of COX-2, at least in the regulation of angiogenesis, is broader than simple mediation through PG synthesis.

Although attributing the antitumor effects of COX-2 inhibitors to the inhibition of tumor angiogenesis alone is easy to understand, its link to the enhancement of tumor radioresponse by these agents is much less clear. Solid tumors have defective microcirculation and, as a result, contain many hypoxic cells, which are considerably more radioresistant than well-oxygenated cells. In theory, inhibition of angiogenesis would result in increased tumor hypoxia and, hence, in tumor radioresistance. Yet, recent studies report enhancement of tumor radioresponse when radiation was combined with antiangiogenic agents (2,3,5). A number of possibilities may account for this. For example, severe inhibition of angiogenesis and vessel damage could lead to vascular collapse in tumors and result in massive necrosis of tumor cells, as is the case for combretastatin (6) and C225 antiepidermal growth factor receptor antibody (7). Also, some angiogenic factors, such as VEGF, FGF, and certain PGs, can act as radioprotectors and, therefore, their reduction would enhance radiation effects on both endothelial and tumor cells. These radioprotectors may influence cell radioresponse by physiologic means or may regulate intrinsic cell radiosensitivity. We recently showed (unpublished data) that SC-236 enhanced in vitro intrinsic radiosensitivity of human glioma cells. Although this compound alone induced apoptosis, it did not enhance radioresponse by rendering tumor cells more sensitive to radiation-induced apoptosis. However, the role of apoptosis in enhancement of tumor radioresponse by COX-2-selective inhibitors requires further investigation.

In addition, other mechanisms dependent on and independent of COX-2 may be involved in the potentiation of tumor radioresponse by compounds designed to inhibit COX-2. They include immunologic mechanisms and interaction with growth factors and their signaling pathways. The biology of COX-2 and the role of this enzyme in tumor growth and tumor response to cytotoxic therapy is a rapidly evolving field in cancer research. As our understanding of the interaction between COX-2 and radiotherapy increases, we will be better able to assess the full potential of this therapeutic strategy.

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