Curcumin sensitizes human colorectal cancer xenografts in nude mice to gamma-radiation by targeting nuclear factor-κB-regulated gene products

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Preoperative chemoradiation therapy in rectal cancer has shown that only ~20% of patients achieve complete pathologic responses, mainly because of their resistance to radiation therapy. The reason behind this low response to radiation is not yet understood completely.

Nuclear factor-κB has thought to be closely related with radioresistance in multiple tumors, as suggested by various study outcomes. Hence, novel radiosensitization strategies are needed to enhance this response rate, which may permit selective avoidance of radical surgical resections for a subset of patients.

Curcumin has been found to inhibit NF-κB activation as well as down-regulate the expression of NF-κB–regulated gene products involved in survival, proliferation, angiogenesis, invasion and metastasis of the tumor. However, it is not clear whether Curcumin sensitizes colorectal tumors to radiation *in vivo.*

Objective:

To investigate the effect of Curcumin on the growth of colorectal cancer xenografts in nude mice exposed to radiation.

Study Design:

- Male athymic *nu/nu* mice (4-week old) were implanted with HCT 116 cells and randomized post one week of implantation into the following treatment groups (n= 9-10) based on the tumor volume: (a) untreated control (corn oil); (b) Curcumin alone (1 g/kg), once daily orally; (c) radiation alone (4 Gy, twice weekly); and (d) combination of Curcumin (1 g/kg), once daily orally and radiation (4 Gy, twice weekly; given 1 h after Curcumin)
- Electrophoretic mobility shift assays were performed to assess NF-κB activation by isolating nuclei out from colorectal tumor samples
- The nuclear localization of p65, COX-2, VEGF and MMP-9 was examined in tumor samples using an immunohistochemical method
- Other parameters like Ki-67 immunohistochemistry, microvessel density and western blot analysis were also carried out

Results and Discussion:

- Combination treatment showed more delayed tumor growth than the sum of growth delays caused by either alone
- Combination treatment group took ~23 days for normalized tumor volume reaching five times the original volume compared to ~5 days for vehicle and 6 days when treated with Curcumin
- Combination of Curcumin with radiation significantly ($p<0.001$) down-regulated the expression of Ki-67 in tumor tissues compared with radiation alone
- Radiation-induced NF-κB activation in tumor was inhibited by Curcumin when combined with radiation than the radiation-alone group

- Curcumin down-regulated the expression of NF-κB –regulated gene products by sensitizing the colorectal cancer to radiation

Conclusion:

Antitumor effects of radiation therapy in colorectal cancer were enhanced by Curcumin by inhibiting NF-κB and NF-κB-regulated gene products