

The chemopreventive agent curcumin is a potent radiosensitizer of human cervical tumor cells via increased ROS production and overactivation of the MAPK pathway.

Javvadi P, Segan AT, Tuttle SW, Koumenis C.

University of Pennsylvania School of Medicine.

Cervical cancer is the second most common malignancy among women worldwide and is highly radioresistant, often resulting in local treatment failure. For locally advanced disease, radiation is combined with low dose chemotherapy; however this modality often leads to severe toxicity. Curcumin, a polyphenol extracted from rhizomes of the plant *Curcuma longa* L, is a widely studied chemopreventive agent which was shown to have a low toxicity profile in three human clinical trials. Here, we show that pretreatment of two cervical carcinoma cell lines, HeLa and SiHa with curcumin prior to ionizing radiation (IR) resulted in significant dose-dependent radiosensitization of these cells. Notably, curcumin failed to radiosensitize normal human diploid fibroblasts. While in tumor cells, curcumin did not significantly affect IR-induced activation of AKT and NF-kappaB, we found that it caused a significant increase in the production of reactive oxygen species which further led to sustained ERK1/2 activation. The antioxidant compound N-acetyl-cysteine, (NAC) blocked the curcumin-induced increased ROS, sustained activation of ERK1/2 and decreased survival following IR in HeLa cells, implicating a ROS-dependent mechanism for curcumin radiosensitivity. Moreover, PD98059, PD184352 and U0126 specific inhibitors of MEK1/2 kinase, blocked curcumin-mediated radiosensitization demonstrating that the sustained ERK1/2 activation resulting from ROS generation leads to curcumin-mediated radiosensitization. Together, these results suggest a novel mechanism for curcumin-mediated radiosensitization involving increased ROS and ERK1/2 activation and suggest that curcumin application (either systemically or topically) may be an effective radiation modifying modality in the treatment of cervical cancer.

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