**U0126 MEK/ERK INHIBITOR INCREASES PROSTATE CANCER CELLS RADIOSENSITIVITY IN VITRO AND IN VIVO BY DOWNREGULATING MEK/ERK/C-MYC AXYS AND AFFECTING DNA REPAIR SIGNALS.**

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Prostate cancer (PCa) is the most commonly diagnosed cancer among men in western countries. Radiotherapy (RT) is considered as the first-line treatment for localized PCa because of its non-invasiveness. It is generally accepted that the primary therapeutic effect of RT is the induction of DNA damage in the irradiated cells. However, PCa cells often show resistance to RT and the molecular mechanisms responsible for radioresistance are largely unknown. MAPK signal transduction pathways respond to extracellular and intracellular cues by activating specific cellular signaling cascades to regulate cell cycle, growth, proliferation, differentiation and survival. Uncontrolled activation of MAPKs as well as of DNA-damged repair mechanisms have been related to PCa radioresistance but no data have been yet collected on the role of MAPKs as potential therapeutical radiosensitizing target. This study was designed to examine whether the ERK pathway affects intrinsic radiosensitivity of PCa cancer cells. Exponentially growing human PCa, PC3, LnCap, and 22Rv1 cell lines were used. The specific MEK/ERK inhibitor, U0126, reduced the clonogenic potential of the three cell lines, and was affected by radiation. U0126 inhibited phospho-active ERK1/2 and reduced DNA protein kinase catalytic subunit (DNA-PKcs) suggesting that ERKs and DNA-PKcs cooperate in radioprotection of PCa cells. Interestingly we found that ERK1/2 inhibition drastically affected the expression of c-Myc, one of the most important oncogene shown to control PCa onset and progression. The PC3 cell line xenotransplanted in mice showed a reduction in tumor mass and increase in the time of tumor progression with U0126 treatment associated with reduced DNA-PKcs, an effect enhanced by radiotherapy. Thus, our results show that MEK/ERK inhibition affect transformed phenotype and enhances radiosensitivity of PCa cells, suggesting a rational approach in combination with radiotherapy.