Ras signalling: Effects on radioresistance

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Successful treatment using radiotherapy is though to depend upon the size of the tumor, the intrinsic radioresistance of the tumor, the oxygenation and physiology of the tumor. In our lab we have been studying the factors that contribute to the intrinsic radiosensitivity of the tumor with the goal of developing means to improve the therapeutic outcome. We previously showed that introduction of the Hras and the myc oncogene into rat embryo fibroblasts enhanced the radiation survival of these cells. To further confirm that activation of the ras family would influence radiation survival, we compared the survival of tumor cells in which either the oncogene for N ras or for K ras had been genetically removed to the parental cells. These experiments confirmed that expression of ras oncogenes enhance radiation survival.

To identify the signalling pathways used in mediated radiosensitivity through ras, we first explored the effects of pharmacological inhibition on radiation survival of cells that had activated ras and those that did not. Inhibition of MEK, p38 or p70S had no effect on radiation survival. Inhibition of phosphatidylinositol 3-kinase (PI3-K) sensitized cells with activated ras to radiation, but did not affect cells with wild type ras. To confirm the participation of PI3-K in radiation resistance, we then introduced a plasmid coding for constitutively active PI3-K into cells without active ras or PI-3K. This resulted in enhanced radioresistance further supporting the contention that ras mediated radiosensitivity is signalled through PI3-K.

These results suggested that inhibition of ras might be used to radiosensitize tumors in vivo because ras will only be mutated in tumor cells, not in the normal host tissue. Farnesyltransferase inhibitors (FTIs) have been developed to block the action of ras. We found that treatment of mice with FTI would sensitize their tumors to radiation if those tumors had oncogenic ras, but not for tumors with wild type ras. This treatment was surprisingly effective and led us to suspect that a component in addition to the intrinsic sensitivity of the tumor cell might be involved. FTI treatment led to greatly enhanced oxygenation. Since hypoxia renders cells more radioresistant, this unexpected effect of FTI on tumor oxygenation might be contributing to the enhanced effect of FTI in vivo.

Since ras genes are mutated in many cancers including pancreatic, colon, lung and head and neck cancer (cancers that are often treated with radiation), we suggest that coupling inhibition of the ras signalling pathways with radiation might lead to more effective clinical outcomes. To pursue this concept, we have completed a Phase I clinical trial of radiation with FTI treatment and will attempt to determine clinically whether inhibition of ras could be used to enhance radiation therapy.