Radiation-induced signalling: pathways, RAS proteins, receptors and paracrine factors

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1. Abstract

The mechanisms by which cellular radiosensitivity is regulated are not fully understood. Initial portions of the presentation will describe what is known about the mechanisms of ionizing radiation-induced signaling in human tumor cells. The RAS oncogene family of GTP binding proteins is known to enhance radiation resistance; however no studies have been performed in isogenic carcinoma cells to determine the relative effects of RAS isoform function on radiosensitivity. By using HCT116 cells (which express a single allele of activated K-RAS D13), HCT116 cells genetically deleted for expression of K-RAS D13, and HCT116 cells deleted for expression of K-RAS D13 stably transfected with H-RAS V12, we have explored the role of K-RAS and H-RAS in human carcinoma cell radiosensitivity. In isogenic HCT116 cells we determined that radiation preferentially activated the ERK1/2 pathway over the PI3K/AKT pathway whereas in HCT116 cells expressing H-RAS V12 radiation preferentially activated PI3K/AKT signaling over that of ERK1/2. In agreement with these findings, radiation resistance mediated by K-RAS D13 was dependent on ERK1/2 signaling whereas resistance mediated by H-RAS V12 was mediated via paracrine signaling from heregulin to the PI3K / AKT pathway. Although H-RAS V12 promoted PI3K translocation into the plasma membrane, the actions of the paracrine factor heregulin in promoting AKT activation and radio-resistance were essential to H-RAS V12 radioresistance. The use of clinically relevant inhibitors of AKT and PDK-1 also radiosensitized cells expressing H-RAS V12 to a greater extent than in cells expressing K-RAS D13. Thus H-RAS and K-RAS generate qualitative and quantitative differences in cellular radiation resistance.