Targeting irradiation-induced mitogen-activated protein kinase activation in vitro and in an ex vivo model for human head and neck cancer.

Despite new radiotherapeutic strategies, radioresistance in head and neck squamous cell carcinoma (HNSCC) remains a major problem. Preclinical model systems are needed to identify resistance mechanisms in this heterogeneous entity. We elucidated the interplay among mitogen-activated protein kinase (MAPK)-inhibition, radiation, and p53 mutations in vitro and in a novel ex vivo model derived from vital human HNSCC samples. HNSCC cell lines (p53WT/mut) were treated with the mitogen-activated protein kinase (MEK)-inhibitor PD-0325901 and subsequently irradiated. Radiosensitization was functionally assessed and evaluated in the ex vivo model. We observed a pronounced irradiation-induced extracellular signal-regulated kinase (ERK) phosphorylation in 2 cell lines, which was independent of their p53 mutation status and associated with PD-0325901-related radiosensitization in a clonogenic assay. Heterogeneity in irradiation-induced ERK phosphorylation and in radiosensitization after MEK-inhibition was also reflected in the ex vivo model. We provide experimental evidence for radiosensitizing effects of