Dokumenttyp: journal article

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Abstract: 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