Ras and Rho small GTPases as drug targets for anticancer therapy

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1. Abstract

Oncogenic forms of the small GTPase Ras increase the resistance of cells to killing by ionizing radiation (IR). Although not all of the signaling pathways for radioresistance are well defined, it is now clear that Ras-dependent signaling pathways involved in radioresistance include those mediated by phosphatidylinositol 3'-kinase (PI3-K) and Raf. Nevertheless, PI3-K and Raf together are not sufficient to reconstitute all of the resistance conferred by Ras, indicating that other effectors must also contribute. We show here that Ras-driven autocrine signaling through the epidermal growth factor receptor (EGFR) also contributes to radioresistance in Ras-transformed cells. Conditioned media (CM) collected from RIE-1 rat intestinal epithelial cells expressing oncogenic Ras increased the survival of irradiated cells. Ras-CM contains elevated levels of the EGFR ligand transforming growth factor alpha (TGF-alpha). Both Ras-CM and TGF-alpha stimulated EGFR phosphorylation, and exogenous TGF-alpha mimicked the effects of Ras-CM to increase radioresistance. Blocking EGFR signaling with the EGFR/HER-2 kinase inhibitor (KI) GW572016 decreased the postradiation survival of irradiated Ras-transformed cells and normal cells but had no effect on the survival of unirradiated cells. Ras-CM and TGF-alpha also increase PI3-K activity downstream of the EGFR and increase postradiation survival, both of which are abrogated by GW572016. Thus, Ras utilizes autocrine signaling through EGFR to increase radioresistance, and the EGFR KI GW572016 acts as a radiosensitizer. The observation that Ras-transformed cells can be sensitized to killing by ionizing radiation with GW572016 demonstrates that EGFR KIs could potentially be used to radiosensitize tumors in which radioresistance is dependent on Ras-driven autocrine signaling through EGFR.