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Molecular targets for altering radiosensitivity: Lessons from Ras as a pre-clinical and clinical model

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Abstract

Ras activation has been correlated with malignant and metastatic cancer phenotypes and poor prognosis for cancer patients. In the preclinical setting, Ras activation by mutation or EGFR amplification results in increased clonogenic cell survival and decreased tumor growth delay following irradiation. Activation of the Ras pathway has also been associated with increased risk of local failure and decreased overall survival in patients receiving radiotherapy. Prenyltransferase inhibitors target the post-translational processing of Ras and have been shown to increase the radiosensitivity of human cancer cell lines. In the clinical setting, these inhibitors have been used with concurrent radiotherapy in a small

Abbreviations: PTI, prenyltransferase inhibitors; FTase, farnesyltransferase; GGTase, Geranylgeranyl transferase; FTI, FTase inhibitor; GGTI, GGTase inhibitor; MAPK, mitogen activated protein kinase; PI3K, phosphatidylinositol 3′-kinase; RTK, receptor tyrosine kinase; EGFR, epidermal growth factor receptor

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number of phase I clinical trials with acceptable toxicity. Therefore, inhibiting Ras activation represents a promising molecular approach for radiosensitization in cancer therapy.

Keywords: Ras; Radiation therapy; Radiosensitization; Prenyltransferase; Farnesyltransferase; Geranylgeranyltransferase; Phosphatidylinositol 3′-kinase; Akt

1. Introduction

The objective of any anti-cancer therapy is to provide maximal cancer cell killing while at the same time minimizing the damage to normal cells and tissues. Thus, in patients receiving radiotherapy, normal tissue tolerance to ionizing radiation limits the dose that can be safely delivered and the dominant factor in probability of patient cure is the intrinsic radiosensitivity of the cancer cells. This principle has been demonstrated in multiple studies of cancer cell lines derived from patients that received radiation therapy in which the intrinsic radiosensitivity of cancer cells is strongly related to the both local tumor control and overall patient survival [1–6].

One factor known to modulate the intrinsic radiosensitivity of cancer cells is the presence of activated oncogenes such as *ras*. Mutational activation of *ras* is found in approximately 30% of human tumors and may function as a critical early step in the tumorigenesis of a variety of human cancers including thyroid, non-small cell lung, pancreatic and colon carcinomas. In addition to its effects on tumorigenesis and resistance to therapies such as ionizing radiation, Ras activation can also alter the dynamics of tumor to host interaction, promoting angiogenesis as well as tumor invasion and metastasis (reviewed in [7]). Therefore, there has been considerable hope and interest in the potential promise of Ras as a molecular target in cancer therapy.

1.1. Ras activation in tumorigenesis and malignant phenotype

Early studies of immortalized rodent fibroblast cell lines showed that expression of oncogenic (mutationally activated) *ras* could produce a transformed phenotype. In conjunction with other oncogenes such as *myc*, oncogenic *ras* is also able to transform primary cells and to produce cells with a highly metastatic phenotype [8–11]. These studies suggested that Ras activation was an important step in tumorigenesis and that Ras activation can contribute to malignant tumor phenotypes such as invasion and metastasis. This hypothesis is strongly supported by the observation that nearly 30% of human malignancies express oncogenic *ras* [12–16]. Further indirect evidence comes from experiments with carcinogen induced rodent tumors in which activating *ras* mutations are found that match the mutational spectrum of the chemical carcinogens [17,18]. To more directly address the impact of *ras* activation on tumorigenesis and phenotype, multiple investigators have used Cre/LoxP recombination to direct tissue specific expression of oncogenic *ras* in mice. In these experiments, oncogenic *ras* expression leads to tumor formation and some of these tumors display malignant and metastatic phenotypes [19–21]. Conversely, specific deletion of the mutant *ras* allele leads to reversion of the transformed phenotype and severely impairs the ability of cancer cells to form tumors in mice [22–24]. The mechanism for the effect of Ras on tumorigenesis, invasion and metastasis appears to involve Ras-mediated increases in cell growth, alterations in the apoptotic cell death, loss of cell-cell adhesion, expression of matrix metalloproteinases and alteration in expression of genes that control cell polarity [7,11,25,26].

1.2. Radiation resistance, clinical response and the Ras pathway

In addition to effects on cellular transformation, activated Ras can also promote increased cellular survival following exposure to ionizing radiation. Mutational activation of Ras has been shown to decrease the radiosensitivity of both rodent and human cells (see Section 3). Moreover, activation of wild-type Ras through amplification of receptor tyrosine kinase (RTK) signaling can also lead to decreased radiosensitivity. Downstream, the Ras radiation resistance pathway appears to signal through phosphatidylinositol 3-kinase (PI3K) and Akt kinase (see Section 5) While the direct contributions of Ras pathway mediated radioresistance to clinical outcome is difficult to measure, activation of members of the Ras signaling pathway has been correlated with increased rate of local recurrence following radiation therapy in patients with Head and Neck cancer and decreased overall survival in patients that received radiotherapy for pancreatic cancer [27,28]. Conversely, lower levels of Akt activation has been correlated with long term survival in lung cancer patients treated with radiotherapy [29].

1.3. Inhibiting Ras function

Approaches to inhibiting Ras function in pre-clinical and clinical settings have primarily focused on alteration of Ras sub-cellular trafficking. Prenylation of Ras and subsequent membrane localization appears to be required for both Ras-mediated transformation and radiation resistance. This observation led to the development of prenyltransferase inhibitors (PTI) as pharmacologic inhibitors of Ras function. These compounds can inhibit cell growth and survival and promote radiosensitization of cells with activated Ras (see Section 3). However, the mechanism for these effects is complex and remains incompletely understood, since it now seems likely