MINI-REVIEW

Epidermal Growth Factor Receptor-Related DNA Repair and Radiation-Resistance Regulatory Mechanisms: A Mini-Review

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Abstract

Epidermal growth factor receptor (EGFR) overexpression is associated with resistance to chemotherapy and radiotherapy. The EGFR modulates DNA repair after radiation-induced damage through an association with the catalytic subunit of DNA protein kinase. DNA double-strand breaks (DSBs) are the most lethal type of DNA damage induced by ionizing radiation, and non-homologous end joining is the predominant pathway for repair of radiation-induced DSBs. Some cell signaling pathways that respond to normal growth factors are abnormally activated in human cancer. These pathways also invoke the cell survival mechanisms that lead to resistance to radiation. The molecular connection between the EGFR and its control over DNA repair capacity appears to be mediated by one or more signaling pathways downstream of this receptor. The purpose of this mini-review was not only to highlight the relation of the EGFR signal as a regulatory mechanism to DNA repair and radiation resistance, but also to provide clues to improving existing radiation resistance through novel therapies based on the above-mentioned mechanism.

Keywords: Epidermal growth factor receptor - signal pathway - DNA-damage repair - radiation resistance

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Introduction

The epidermal growth factor receptor (EGFR) is a type of transmembrane protein with tyrosine kinase activity, which can modulate tumor growth and cell proliferation. The EGFR signaling systems of normal cells are well regulated. However, the EGFR signaling pathway, which can modulate cell growth and death, is frequently misregulated in malignant tumors. The up-regulation of the wild-type EGFR or the expression of its mutants is associated with tumor radioresistance and poor clinical outcomes (Golding et al., 2009). Overexpression of EGFR promotes unregulated growth, inhibits apoptosis, and likely contributes to clinical radiation resistance (Tanaka et al., 2008). Radioresistance is thought to be, at least in part, the result of a strong cytoprotective response (Golding et al., 2009). However, the precise mechanism for the resistance to radiation associated with EGFR signaling and DNA repair is still unclear, and further research should be conducted. Therefore, we review relevant literature to provide some insights for future clinical research.

EGFR Expression

The overexpression or mutation of EGFR may enhance DNA repair, thereby contributing to radioresistance. EGFR overexpression has been associated with resistance to chemotherapy and radiotherapy. EGFR modulates DNA repair after radiation-induced damage by associating with the catalytic subunit (DNA-PKcs) of DNA protein kinase (DNA-PK) (Liccardi et al., 2011). Mutant EGFR has been associated with tumor resistance in many studies. For example, the type-III EGFR variant (EGFRvIII) is the most common EGFR mutation in malignant gliomas. EGFRvIII promotes both homologous recombination repair (HRR) and non-homologous end joining (NHEJ), which are probably contributory factors toward the radioresistance of malignant gliomas (Golding et al., 2009). In addition, over the last decade, accumulating evidence has indicated that the cell membrane-bound growth factor receptors of the erbB family, especially EGFR (also known as erbB1), mediate in the resistance of tumor cells to both chemo- and radiotherapy when they are mutated or overexpressed (Rodemann et al., 2007). EGFR, which is frequently expressed in tumors of epithelial origin, is an important determinant of tumor response to ionizing radiation (IR). Elevated EGFR expression and activity have been frequently correlated with tumor resistance to radiotherapy in patients (Chen and Nirodi, 2007).

DNA Damage Repair

The relationship between the reparation of DNA double strand breaks (DSBs) and the function of EGFR has been recently discussed. DSBs are the most lethal type of DNA damage caused by either IR or the chemotherapeutic drugs used to eradicate cancer cells. The ability of

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cancer cells to effectively repair DSBs can significantly influence the outcome of therapeutic regimens. NHEJ is the predominant pathway for the repair of radiation-induced DSBs (Mukherjee et al., 2010). In recent years, more evidence has revealed that EGFR may stimulate DSB rejoining due to an increase in the nuclear content of DNA-PK subunits. These subunits are key components of NHEJ in the DNA repair pathway; hence, they increase the activity of the DNA-PK-dependent non-homologous end-joining (D-NHEJ) system (Szumiel, 2006). The overall DSB repair capacity is clearly enhanced when EGFR is activated by its natural ligand, which is the epidermal growth factor (EGF); on the other hand, it was reduced when EGFR was blocked either by the specific antibody cetuximab or the tyrosine kinase inhibitor erlotinib (Kriegs et al., 2010). Recent radiosensitivity effects in clinical practice have shown that EGFR inhibitors counteract the nuclear translocation of DNA-PK subunits. Results of other studies suggest that D-NHEJ may be less active in inhibitor-treated cells, which would contribute to the enhanced lethal effects of irradiation (Szumiel, 2006). The nuclear localization of EGFR is required for the modulation of cisplatin and the IR-induced repair of DNA damage. The binding of DNA-PKcs to EGFR could be induced by cisplatin or IR, but not by EGFR nuclear translocation. Our findings have shown that EGFR subcellular distribution can modulate DNA repair kinetics (Liccardi et al., 2011). Another study (Hiro et al., 2008) has been conducted to determine the relationship between radioresistance and DNA damage repair through the repair proteins in three colon cancer cell lines. The findings suggest that the alteration of EGFR and excision repair cross-complementation group 1 (also known as ERCC1) proteins during chemoradiation in one of the three colon cancer cell lines is inversely related to that of the other radiosensitive cell lines, and that 5-FU-induced EGFR activation confers protection against radiation through the activation of DNA repair. Other data (Toulany et al., 2008) indicate that the basal expression of the X-ray repair cross-complementing group 1 (XRCC1) protein is also important for the repair of IR-induced DSBs.

DSBs, EGFR, and Radiation Resistance

Signaling pathways downstream of the EGFR invoke cell survival mechanisms that lead to resistance against radiation when abnormally activated (Toulany and Rodemann, 2010). Activation of EGFR in tumor cells stimulates a cascade of signal transduction pathways that regulate cell proliferation, cell differentiation, cell survival (apoptosis), cell cycle progression, and angiogenesis (Ono and Kuwano, 2006). The control of these cellular events at the molecular level is complicated by the fact that multiple signaling pathways may be involved, including the Ras/Raf/MEK/ERK, PKC, STAT, and PI3-K/AKT pathways (Ang et al., 2002; Sartor, 2004). Moreover, each of these pathways affects many different molecular endpoints (Carracedo and Pandolfi, 2008). Among the many downstream pathways of EGFR, the PI3K/AKT and Ras/Raf/MEK/ERK pathways are the most extensively studied in the context of radiosensitization (Meyn et al., 2009). Radioresistance is, at least in part, the result of a strong cytoprotective response fueled by signaling via AKT and ERK, which is heightened by radiation within the range of the clinical dose. Several groups, including our own, have shown that this response modulates DNA repair (Golding et al., 2009). IR has recently been demonstrated to mediate in the phosphorylation of DNA-PKcs in human tumor cells through the stimulation of the PI3K/AKT pathway. DNA-PKcs directly interact with the XRCC1 protein in base excision repair (BER). IR-induced XRCC1 expression is dependent on the expression level of DNA-PKcs and the basal activity of PI3K/AKT signaling (Toulany et al., 2008). Previous studies also support the assumption that AKT plays an important regulatory role for the activation of DNA-PKcs in irradiated cells (Toulany et al., 2008).

Conflicting Evidence of EGFR Signaling

Although AKT signaling is believed to be an important signal pathway, some data suggest that XRCC1 expression induced by irradiation is independent of PI3K/AKT signaling, but dependent of ERK1/2 of the MAPK family (Toulany et al., 2008). Likewise, other research groups have reported that high levels of the STAT1 signal render the cells resistant to IR. Results also show that resistance to radiation is associated with increased STAT1 signaling, and can be modulated by suppressors of STAT1 (Fryknäs et al., 2007; Khodarev et al., 2007; Meister et al., 2007). Thus, the molecular mechanisms by which EGFR governs the capacity for DNA repair are complex and multi-factorial. There are multiple ways by which EGFR signaling may modulate DNA repair, which are mediated by one or more signaling pathways downstream of this receptor. These mechanisms are not mutually exclusive, and the particular involvement of one or more of these signaling pathways appears to be highly dependent on the cell type and the expression level of the growth factor receptor.

Emerging data convincingly show that the signaling pathways downstream of growth factor receptors intersect with the DNA repair mechanisms that modulate cellular response to IR. Although the involvement of other pathways has not been ruled out, it appears from a review of recent literature that two signaling pathways in particular, namely, the PI3K/AKT and Ras/Raf/MEK/ERK pathways, both mediate in the signals downstream of these growth factor receptors. The novel findings on radiation-induced EGFR-signaling and its involvement in the regulation of DNA DSB repair need further investigation to elucidate the detailed mechanisms that are involved. The results from these studies may not only improve our knowledge on the basic mechanisms of radiation sensitivity and resistance, but will also promote translational approaches to testing of new strategies for clinically applicable molecular targeting. Based on the reports reviewed in this paper, more extensive investigations into the molecular mechanisms responsible for these interactions must be undertaken to fully understand how DNA repair is regulated in the context of cell growth and survival. In addition, future studies following this theme will certainly reveal more pathways

and elements of cell signaling, including those that are not downstream of receptor tyrosine kinases, which can be targeted to enhance tumor response to radiation

References

Ang KK, Mason KA, Meyn RE (2002). Epidermal growth factor receptor (EGFR) and its inhibition in radiotherapy; 7th International Meeting on Progress in Radio-OncologyICRO/PGRO; Salzburg, Austria: Medimond, Inc pp 557-67.

Carracedo A, Pandolfi PP (2008). The PTEN-PI3K pathway: of feedbacks and cross-talks. *Oncogene*, **27**, 5527-41.

Chen DJ, Nirodi CS (2007). The epidermal growth factor receptor: a role in repair of radiation-induced DNA damage. *Clin Cancer Res*, **13**, 6555-60.

Fryknäs M, Dhar S, Oberg F, et al (2007). STAT1 signaling is associated with acquired cross resistance to doxorubicin and radiation in myeloma cell lines. *Int J Cancer*, **120**, 189-95.

Golding SE, Morgan RN, Asams BR, et al (2009). Pro-survival AKT and ERK signaling from EGFR and mutant EGFRvIII enhances DNA double-strand break repair in human glioma cells. *Cancer Biol Ther,* **8**, 730-8.

Hiro J, Inoue Y, Toiyama Y, Miki C, Kusunoki M (2008). Mechanism of resistance to chemoradiation in p53 mutant human colon cancer. *Int J Oncol*, **32**, 1305-10.

Khodarev NN, Minn AJ, Efimova EV, et al (2007). Signal transducer and activator of transcription 1 regulates both cytotoxic and prosurvival functions in tumor cells. *Cancer Res*, **67**, 9214-20.

Kriegs M, Kasten-Pisula U, Rieckmann T, et al (2010). The epidermal growth factor receptor modulates DNA double-strand break repair by regulating non-homologous end-joining. *DNA Repair (Amst)*, **9**, 889-97.

Liccardi G, Hartley JA, Hochhauser D (2011). EGFR nuclear translocation modulates DNA repair following cisplatin and ionizing radiation treatment. *Cancer Res*, **71**, 1103-14.

Meister N, Shalaby T, von Bueren AO, et al (2007). Interferon-gamma mediated up-regulation of caspase-8 sensitizes medulloblastoma cells to radio- and chemotherapy. *Eur J Cancer,* **43**, 1833-41.

Meyn RE, Munshi A, Haymach JV, Milas L, Ang KK (2009). Signaling as a regulatory mechanism of DNA repair. *Radiother Oncol*, **92**, 316-22.

Mukherjee B, Choy H, Nirodi C, Burma S (2010). Targeting nonhomologous end-joining through epidermal growth factor receptor inhibition: rationale and strategies for radiosensitization. *Semin Radiat Oncol,* **20**, 250-7.

Ono M, Kuwano M (2006). Molecular mechanisms of epidermal growth factor receptor (EGFR) activationand response to gefitinib and other EGFR-targeting drugs. *Clin Cancer Res*, **12**, 7242-51.

Rodemann HP, Dittmann K, Toulany M (2007). Radiation-induced EGFR-signaling and control of DNA-damage repair. *Int J Radiat Biol*, **83**, 781-91.

Sartor CI (2004). Mechanisms of disease: Radiosensitization by epidermal growth factor receptor inhibitors. *Nat Clin Pract Oncol,* **1**, 80-7.

Szumiel I (2006). Epidermal growth factor receptor and DNA double strand break repair: the cell's self-defence. *Cell Signal*, **18**, 1537-48.

Tanaka T, Munshi A, Brooks C, et al (2008). Gefitinibradiosensitizes non-small cell lung cancer cells by suppressing cellular DNA repair capacity. *Clin Cancer Res*, **14**, 1266-73.

Toulany M, Dittmann K, Fehrenbacher B, et al (2008). PI3K-Akt signaling regulates basal, but MAP-kinase signaling regulates radiation-induced XRCC1 expression in human tumor cells in vitro. *DNA Repair (Amst)*, **7**, 1746-56.

Toulany M, Kehlbach R, Florczak U, et al (2008). Targeting of AKT1 enhances radiation toxicity of human tumor cells by inhibiting DNA-PKcs-dependent DNA double-strand break repair. *Mol Cancer Ther*, **7**, 1772-81.

Toulany M, Rodemann HP (2010). Membrane receptor signaling and control of DNA repair after exposure toionizing radiation. *Nuklearme Dizin*, **49**, S26-30.