Modulation of Molecular Targets to Enhance Radiation

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The potential for modern molecular radiobiology to provide meaningful contributions to cancer therapeutics has never been brighter. The classic radiobiology framework assembled over the last three to four decades has not only provided critical insights regarding cell cycle kinetics, DNA damage/repair systems, and the biological basis for fractionation but now affords the opportunity to exploit new molecular targets which may prove particularly valuable in cancer therapy when manipulated in concert with the delivery of ionizing radiation (1–3)

To highlight one arena in which modern molecular biology appears to hold particular promise for cancer therapeutics, consider the recent logarithmic expansion in our appreciation and understanding regarding the importance of cellular growth factors and signal transduction systems. There is perhaps no more fertile area of translational cancer research at present than that reflected by the collaborative and sometimes competitive efforts of academia and industry to identify, develop, test, and market new growth factor and signal transduction inhibitors for cancer therapy. Inhibitors for virtually every two- to four-letter growth factor or signal transduction acronym are currently under investigation including CDK (cyclin-dependent kinase), PKC (protein kinase C), EGF (epidermal growth factor), MAPK (mitogen-activated protein kinase), FT (farnesyl transferase), MEK (mitogen-activated protein kinase kinase), and VEGF (vascular endothelial growth factor) to name only a very popular few! How valuable these signal transduction inhibitors ultimately prove to be in cancer therapy may depend not only on the traditional characteristics of agent design and delivery but also on the manner in which they are combined with other cytotoxic or cytostatic agents.

A theoretical rationale regarding the value of combining radiation with specific growth factor or signal transduction inhibitors is easy to portray. Many of the inhibitors are primarily cytostatic (antiproliferative) without the capacity to effectively eradicate malignant cells on their own. Seldom have single agents delivered alone proven as fully effective in human cancer therapy as carefully crafted combinations of agents with complementary activities and mechanisms of action. Notable recent advances in our capacity to deliver high precision, three-dimensional/conformal radiation underscore an anticipation that combining molecular-based systemic therapies with radiation will selectively enhance toxicity, primarily within the confines of the tumor itself, precisely where oncologists have always wished to deposit toxicity in the first place.

One particular growth factor receptor family and signal transduction system that has received considerable recent attention in oncology therapeutics involves the ErbB receptor tyrosine kinase family (4, 5). The story of Herceptin, which targets the ErbB-2 receptor (HER-2/neu), in the treatment of women with breast cancer is a testament for bench-to-bedside translational molecular cancer research (6, 7). Recent preclinical data further suggest that combining radiation with monoclonal antibody blockade of the HER-2/neu receptor can enhance radiation response and inhibit DNA repair in breast cancer cells (8). A remarkably similar picture is now emerging regarding the ErbB-1 receptor (EGFR), in which development of the monoclonal antibody C225 shows promise across a spectrum of epithelial tumors, particularly for those that overexpress EGFR such as squamous cell carcinoma of the head and neck. Blockade of the EGFR with C225 enhances the in vitro radiosensitivity of human squamous cell carcinomas (9), and phase II clinical trials are now examining the capacity of C225 to enhance tumor control rates in patients with advanced head and neck cancers treated with radiation or cisplatin chemotherapy.

The article by Milas et al. (10) in this issue of Clinical Cancer Research provides additional promising preclinical data regarding the in vivo activity of EGFR blockade with C225 in conjunction with ionizing radiation. A greater than 3-fold enhancement in tumor response after single-fraction radiation exposure is demonstrated in athymic mice bearing squamous cell carcinoma xenografts when they receive systemic C225. The potency of the in vivo antitumor effect observed (more potent than that observed in cell culture) using the combination of C225 and radiation suggests that mechanisms beyond simple proliferative growth inhibition are operational in the in vivo setting.

Several distinct lines of inquiry are currently under investigation in an attempt to better understand specific cellular mechanisms of action that may contribute to the antitumor potency of EGFR blockade plus radiation in vivo model systems (Table 1 and Fig. 1). Recent data from several laboratories suggest that EGFR blockade with C225 may serve to inhibit tumor angiogenesis (10–13), and this result appears to be augmented when effected in combination with radiation (10, 13). In addition to the established data demonstrating an antiproliferative effect of EGFR blockade with C225, with resultant G1 cell cycle arrest (14, 15) data are now emerging regarding the capacity of C225 to modulate apoptosis, inhibit cellular repair of...
radiation-induced damage, and influence cellular migration capacity and possibly metastases (9, 12, 16, 17). It may be that molecular down-regulation of certain mitogenic signal transduction pathways, including the EGFR system cascade, can disrupt cellular recovery processes after radiation damage, although precise mechanisms for this are only beginning to be unraveled.

The natural evolution from classic radiobiology to molecular radiobiology achieved in recent years is possible in large part because of the meticulous experimentation of our radiobiology predecessors. Molecular techniques and targets that are so readily accessible today often can be best understood and exploited within the context of established basic principles regarding cellular and tissue responses to radiation derived over past years. The judicious application of specific growth factor receptor and signal transduction inhibitors delivered in combination with ionizing radiation represents a promising new frontier in molecular cancer therapeutics.

REFERENCES

Table 1  Postulated C225/radiation interactions

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<thead>
<tr>
<th>C225:G1 phase</th>
<th>Radiation:G2/M phase</th>
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<tr>
<td>Inhibits tumor cell proliferation</td>
<td>Promotes radiation-induced apoptosis</td>
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<td>Induces cell cycle arrest</td>
<td>Inhibits radiation-induced damage repair</td>
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<td>Inhibits tumor angiogenesis</td>
<td>Effects on invasion, metastases</td>
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Fig. 1  Simplified schematic illustration of the EGFR system depicting EGFR, mitogen-activated protein kinase signal transduction cascade to the nucleus, and stimulation of cell cycle machinery. Potential interactions and resultant effects of radiation and selected chemotherapeutic agents on the EGFR system are referred to within the text [reproduced with permission from Huang and Harari (5)].