

EGFR Upregulation by Ionizing Radiation and Cisplatin

Question: What is the evidence for the upregulation of EGFR by ionizing radiation (IR)?

Answer: EGFR (HER-1) and other genes contain radiation-responsive regulatory domains in their promoter regions, which facilitate rapid and direct induction by IR (Bristow et al 1998). EGFR and its downstream cascades are also major components of the network of cellular response pathways induced by radiation exposure, as it could be demonstrated that EGFR activity is inducible by ionizing radiation even in the absence of ligand binding. Two EGFR-dependent pathways seem to be primarily involved in resistance to chemo- and radiotherapy due to their regulatory role in stimulating cell survival by inhibiting apoptosis (PI3K-AKT) and promoting cell proliferation (Ras-MAPK), reviewed in Rodemann et al, 2007.

It has been shown that radiation can increase EGFR expression in cancer cells up to 9 fold (Schmidt-Ulrich et al, 1994), that this expression increases over time (Peter et al, 1993), and that the increase in EGFR expression occurred in parallel to the acceleration of cellular repopulation after radiation damage (Peterson et al, 2003). This is consistent with the role of EGFR in the repair of radiation damage and being implicated in radioresistance.

Question: What is the effect of radiation on EGFR expression in skin?

Answer: Ionizing radiation has been shown to increase the expression of EGFR in keratinocytes (Peter et al, 1993), although the expression of EGFR in keratinocytes is transient returning to baseline at 48 hrs post exposure. In A431 epidermoid cancer cells EGFR expression increased over time after a single dose exposure of radiotherapy with 48 hr expression greater than 24 hr expression. Therefore the expression patterns differ significantly between cancer and normal cells, and likely reflect that EGFR, like other oncogenes, is tightly regulated in normal tissues.

Question: What is the evidence for the similar effect of cisplatin on EGFR?

Answer: EGFR expression has been shown to be increased in resistance to various chemotherapies (vincristine, actinomycin), and in multi-drug resistant cancer cells. Recently, it was shown that cisplatin can directly activate the EGFR receptor (Yoshida et al, 2008), and that EGFR can be overexpressed in cancer cells resistant to cisplatin (Michaelis et al 2008). Similar to what was seen with exposure to ionizing radiation, the upregulation of EGFR increased over a period of time, and EGFR upregulation was transient in cisplatin-sensitive cells and durable in cisplatin-resistant cells (Michaelis et al, 2008). Also relatively recently, Dittmann et al, 2005, showed that cisplatin forces the cell to use the same EGFR pathway as with ionizing radiation, to function in the repair of DNA damage.

Question: If use of an EGFR targeting therapy like nimotuzumab eradicates the high-density EGFR cells, what will become of the low-EGFR expressing cells and how can nimotuzumab result in the eradication of these cells given its density-selective mode of action?

Answer: Radiation treatment by itself is extremely effective at eliminating tumor cells, and recurrences often occur from only one or a few surviving cells. Preclinical and clinical studies have shown that over-expression of the EGFR in tumors is associated with decreased local tumor control after radiotherapy (Baumann and Krause, 2004). EGFR overexpression is generally associated with rapid tumor repopulation due to intrinsic radioresistance. Nimotuzumab binding could target cells that are intrinsically radioresistant (have a high expression of EGFR) or which develop into radioresistant cells (also with a high expression of EGFR).

Therefore, based on the available literature, the mechanism of action from combining radiation therapy and nimotuzumab should result in improved eradication of cells which can repopulate the tumor, resulting in improved responses and overall survival.

Indeed this is observed clinically, as in the BEST head and neck trial, which showed that combining nimotuzumab with radiotherapy improved the locoregional control rate from 37% in the control arm to 76%, while nimotuzumab with chemoradiotherapy improved locoregional control rates from 70% in the control arm to 100% with nimotuzumab.

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