In this issue of the Journal, De Bacco et al. (1) report that expression of the scatter factor/hepatocyte growth factor (SF/HGF) receptor, c-MET, is increased in response to ionizing radiation (IR) through the ataxia-telangiectasia mutated (ATM)–NF-κB signaling pathway. The authors show that c-MET contributes to radioresistance and promotes cancer invasion by autocrine and paracrine prosurvival signaling to increase cell motility and inhibit apoptosis.

The efficacy of a novel pharmacological inhibitor of c-MET as a candidate radiosensitizer was evaluated in tumor xenografts in their study.

Radiotherapy remains the most effective nonsurgical treatment for most solid tumors (2). According to the National Cancer Institute, approximately half of all cancer patients receive radiation as a part of treatment. Radiotherapy or radiochemotherapy aims to
destroy primary tumors or cancer cells in lymph nodes if malignant spread occurs. However, cancer relapse due to therapeutic resistance and development of distant metastases constitutes a major impediment to effective treatment. Enhanced tumor metastases following local tumor irradiation has been reported in the clinical literature (3). The cellular and molecular mechanisms underlying this clinical phenomenon are poorly understood.

Tumor radioresistance can be caused by extrinsic signals from the tumor niche (such as hypoxic conditions) and intrinsic mechanisms (eg, preferential checkpoint activation, increased DNA repair, evasion of apoptosis, and/or sustained prosurvival signaling) (4). Radiation mainly induces DNA double-strand breaks. In response to the IR-induced double-strand breaks, DNA damage checkpoint pathways mediated by the ATM and ATR (ATM and RAD3-related) kinases trigger cell cycle arrest and DNA repair. When the extent of DNA damage exceeds the cellular capacity for repair, the checkpoint activates proapoptotic signaling to eliminate the heavily damaged cells. Now, it is known that ATM can also induce NF-κB signaling by activation of IKK (inhibitor of κB kinase). Activated NF-κB drives the expression of genes involved in invasion and suppression of apoptosis (5,6). Although there is an undisputable link between the severity of IR-induced DNA damage and the efficacy of radiotherapy, cytoplasmic signaling is also an important contributor to radiation response. Prosurvival signaling downstream of receptor tyrosine kinases (RTKs) is mainly attributed to the phosphatidylinositol-3-phosphate kinase (PI3K)/AKT pathway that enhances expression of mitochondrial antiapoptotic proteins and caspase inhibitors. AKT signaling also contributes to NF-κB activation (7). The activation of RTKs and AKT signaling is mediated by several factors, including epidermal growth factor and SF/HGF.

The SF/HGF receptor, c-MET, has garnered particular attention because of its prominent role in radioresistance. c-MET expression is elevated in a wide variety of human cancers and is associated with increased invasiveness. Similar to other RTKs, c-MET activation by SF/HGF protects cells against ultraviolet- and IR-induced apoptosis predominantly through the PI3K/AKT pathway. The study by De Bacco et al. (1) adds a new twist to the c-MET and radioresistance story.

De Bacco et al. (1) started off by asking whether the abundance of c-MET protein is altered after exposure to therapeutic doses of IR. Using a panel of cancer cell lines, the authors show that IR induces increased expression of c-MET at the transcriptional level. They further demonstrate that NF-κB, one of important players in the induced radioresistance, is responsible for increased c-MET transcription because it can be prevented by short hairpin RNAs targeting the NF-κB subunit RELA. The finding that NF-κB activation is ATM dependent adds yet another vignette to the picture. Induction of NF-κB is linked to the secretion of soluble factors that may provide a positive feedback loop to sustain NF-κB activity. Among a large panel of growth factors and cytokines, only tumor necrosis factor-α expression was consistently increased by IR in cancer cells. In contrast to a recent study by Sheng-Hua et al. (8), this study shows that radiation-induced HGF secretion is observed in fibroblasts but not in cancer cells, suggesting a paracrine signaling mechanism between tumor and stromal cells.

How does IR-induced c-MET contribute to radioresistance? First of all, De Bacco et al. (1) show that the accumulation of c-MET not only leads to its spontaneous ligand-independent phosphorylation and activation but also enhances mitogen-activated protein kinase–mediated prosurvival signaling in response to HGF stimulation. Signaling downstream of SF/HGF is linked to the epithelial–mesenchymal transition phenotype, with enhanced motility and invasive potential. Importantly, increased cell migration and invasion through the reconstituted matrix in response to IR can be prevented by pharmacological inhibition of the kinase activity or RNA interference to decrease c-MET expression, indicating that c-MET signaling is a prerequisite for IR-induced invasive growth. IR also enhances the SF/HGF-induced branching morphogenesis in the three-dimensional tube formation assay. In keeping with activated c-MET’s stimulation of antiapoptotic and prosurvival AKT signaling, c-MET inhibition significantly reduces cell survival rate and clonogenic capacity after irradiation. Taken together, these authors’ data make c-MET an attractive target for pharmacological inhibition in vivo. Indeed, inhibition of c-MET activation with specific antibodies (9) or suppression of c-MET expression by U1/ribozymes (10) has shown promising results. De Bacco et al. (1) took advantage of a novel small-molecule inhibitor of c-MET that can be administered orally with lower toxicity. They show that the inhibitor shrinks experimental tumors in fractionated dose IR regimen.

Although delving deeper into the molecular mechanisms of induced radioresistance, the report by De Bacco et al. (1) also raises further questions for future investigation. One such question concerns the dynamics of increased c-MET expression following IR exposure. They show that the accumulation of c-MET protein is observed as early as 30 minutes after treatment of cells with IR. Such timing suggests that nontranscriptional mechanisms (such as protein stabilization) are potentially involved in the IR-induced increase in c-MET protein levels. Consistent with this hypothesis, inhibition of c-MET activity by specific short hairpin RNA to RELA fails to prevent early (1 hour after IR) accumulation of c-MET protein. Experiments to address the posttranscriptional regulation of c-MET such as protein modification would further advance our understanding on c-MET signaling and the induced radioresistance. Another obvious concern is that the authors chose cancer cell lines for all in vitro and in vivo studies. Although these cell lines are useful for the initial testing of candidate drugs, the tumor xenografts derived from these cells may not reconstitute the heterogeneity, cellular hierarchy, and complexity of solid tumors observed in the clinic. Therefore, it would be more informative to use tumor cells isolated from surgical specimens to confirm the authors’ results or to use more clinically relevant genetic mouse models of cancer to take this approach one step further. Because studies from several groups including ours have demonstrated that cancer stem cells (CSCs) are more resistant to radiation and chemotherapy (11–15), it would be interesting to determine whether c-MET expression is elevated in CSCs and contributes to CSC-mediated therapeutic resistance and invasion. We recently showed that signaling mediated by the cell surface molecule LiCAM enhances checkpoint activation and radioresistance of glioblastoma stem cells through nuclear translocation of its intracellular domain (L1-ICD) that mediates the increased expression of Nijmegen
breakage syndrome protein 1 (NBS1) via c-Myc (16), suggesting a
link between cell surface signaling and radioresistance. Because
L1CAM has been shown to be involved in the invasiveness of sev-
eral cancers (17,18), it is likely that there is an intrinsic link
between invasiveness and radioresistance of cancer cells. The ar-
ticle by De Bacco et al. (1) also supports this point.

Augmenting the sensitivity of resistant cancer cells to conven-
tional treatments has been the subject of great effort. Improved
radiotherapy with radiosensitizers is expected to increase the effi-
cacy of cancer treatment. Although the results obtained by De
Bacco et al. (1) and others show promise, our task to combat tumor
radioresistance is still incomplete. We are looking forward to
future advances in the field of radiation oncology.

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