

# Tumors resistant to radiation therapy may be controlled by the MET oncogene

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Ionizing radiation treats many cancers effectively, but in some patients a few tumor cells become resistant to radiation and go on to cause relapse and metastasis. A growth factor-receptor protein called MET may be a key player in these cells' resistance to radiation, and drugs targeting MET may help to prevent radiation-induced metastasis, according to a study published online April 4th in the *Journal of the National Cancer Institute*.

The gene that encodes MET is known as a cancer-promoting gene, or oncogene. It is expressed at high levels in many cancers and is associated with metastasis. But the exact role it plays and how it may induce radiation-resistant tumor cells is unclear.

To explore the molecular mechanisms behind radioresistance, the group led by Carla Boccaccio, M.D. and Paolo M. Comoglio, M.D., of the Institute for [Cancer Research](#) at Candiolo, University of Turin Medical School, examined the expression of the MET gene and the activity of the MET protein in human cancer cell lines before and after exposure to ionizing radiation. They also observed the effect of radiation on two proteins that regulate MET--ataxia telangiectasia mutated (ATM) and nuclear factor kappa B or NF- $\kappa$ B.

They found that after radiation treatment, MET expression increased up to fivefold due to activation of ATM and NF- $\kappa$ B. The tumor cells that survived irradiation became more invasive than previously. Moreover, inhibiting MET counteracted this increased invasiveness and promoted death of the tumor cells (apoptosis). In mice, treatment with MET

inhibitors, such as specific small-molecule kinase inhibitors, enhanced the effect of radiation, stopping growth or inducing shrinkage of tumors.

The authors conclude that [ionizing radiation](#) drives overexpression and activity of MET through the ATM and NF- $\kappa$ B signaling pathways, making some tumor cells resistant to radiation and more invasive. They also conclude that drugs that inhibit MET might counter radiation resistance.

"This has important therapeutic implications," they write, "as it suggests that the combination of radiotherapy with MET inhibition can radiosensitize cancer cells."

In an accompanying editorial, Olga Guryanova M.D., Ph.D. and Shideng Bao, Ph.D., of the Lerner Research Institute at the Cleveland Clinic, Cleveland, Ohio, note that the study adds new details to emerging knowledge of the roles of MET and NF- $\kappa$ B in therapeutic resistance. "The finding that NF- $\kappa$ B activation is ATM dependent adds yet another vignette to the picture," they write.

The editorialists point out that the study also raises questions for future investigation. One step, they suggest, would be to test human [tumor cells](#) isolated from surgical specimens to confirm the results. Another would be to determine whether MET expression is elevated in cancer stem cells, which have shown resistance to radiation and chemotherapy in some studies.

"Augmenting the sensitivity of resistant cancer cells to conventional treatments has been the subject of great effort," they write. "Improved radiotherapy with radiosensitizers is expected to increase the efficacy of [cancer](#) treatment."

Provided by Journal of the National Cancer Institute

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