Adding crizotinib to radiation therapy may help preserve hearing in patients with NF2

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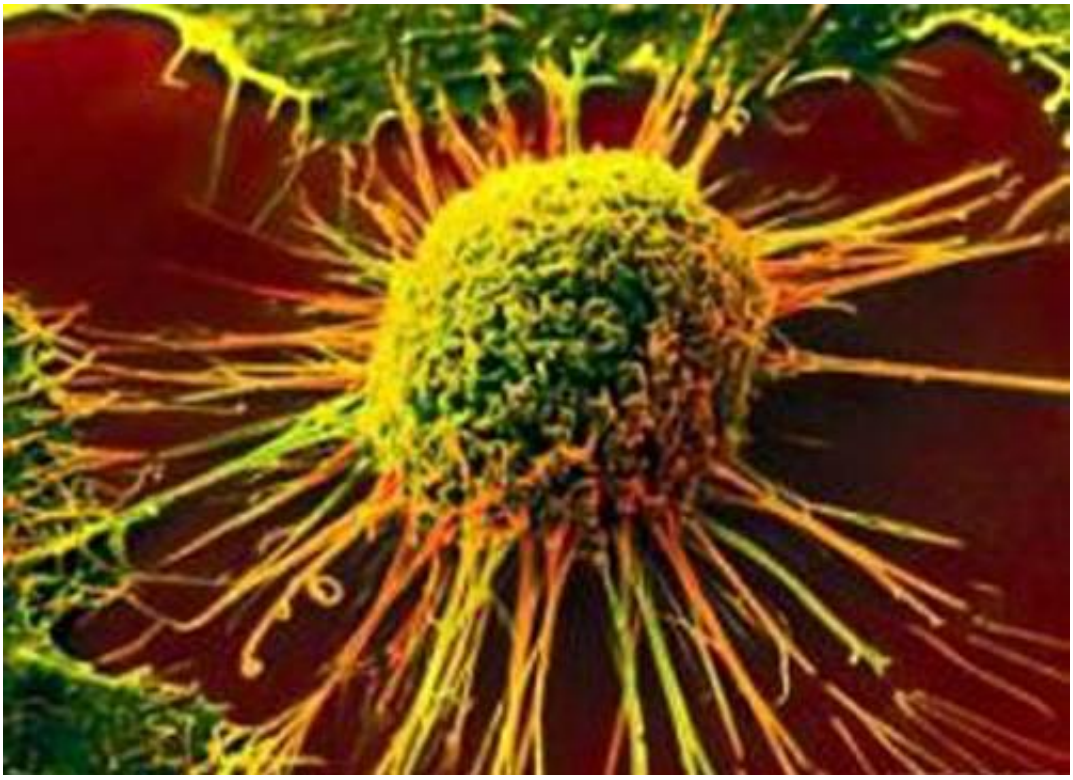

Adding the targeted cancer therapy drug crizotinib to radiation therapy for tumors associated with the genetic disorder neurofibromatosis 2 (NF2) may reduce the hearing damage that can be exacerbated by radiotherapy. A Massachusetts General Hospital (MGH) research team reports that the use of crizotinib to block a specific molecular pathway

both enhanced the radiosensitivity of tumors in mouse models of NF2, allowing a reduction in radiation dosage, and inhibited the growth of cultured tumor cells from NF2 patients. Their paper being published online in *PNAS* Plus also describes creation of a novel mouse model that mimics NF2-associated hearing loss and a better system for culturing tumor cells for NF2 patients.

"The hallmark of NF2 are intracranial tumors called vestibular schwannomas, which typically lead to profound hearing loss," explains Lei Xu, MD, PhD, of the Steele Laboratories of Tumor Biology in the MGH Department of Radiation Oncology, co-corresponding author of the report. "For most patients, hearing loss is the most disabling symptom of these tumors, and the primary treatments for growing tumors - surgery and radiation therapy - can further damage hearing. The development of a novel therapeutic strategy with enhanced efficacy and minimal treatment-related hearing loss is urgently needed."

NF2 is characterized by benign tumors that develop throughout the nervous system, most commonly on the eighth cranial nerve, which carries hearing and balance signals from the ears to the brain. These vestibular schwannomas usually lead to significant or total hearing loss by young adulthood or middle age. If the tumors press on the brain stem, they can have even more serious neurologic consequences. Previous studies from Steele Labs researchers and colleagues at the MGH Cancer Center found that treatment with the angiogenesis inhibitor bevacizumab improved hearing in some NF2 patients. But not all patients benefited, and improvement that did occur proved to be transient, indicating the need for better treatment strategies.

In 2016, Steele Labs researchers and colleagues from Johns Hopkins University found that bevacizumab treatment led to greater hearing improvement in NF2 patients who had lower circulating levels of hepatocyte growth factor (HGF), which is known to interact with the

cMET oncogene. In addition, a 2015 study led by Konstantina Stankovic, MD, PhD, of Massachusetts Eye and Ear - a co-author of the current report - had demonstrated that pathways controlled by HGF interact with pathways controlled by the angiogenesis factor VEGF in schwannomas. These and other studies suggested that the HGF-cMET pathway may play a role in schwannoma progression, response to treatment and hearing loss.

After first confirming in a standard mouse model of NF2 that radiation therapy activated cMET signaling, leading to therapy resistance, the researchers tested use of crizotinib to block cMET signaling in two mouse models - the standard model in which NF2 cells are injected into the sciatic nerve and their new model that implants schwannoma cells into the brain adjacent to the eighth cranial nerve. In collaboration with Stankovic, the MGH team confirmed that their novel model led to the same kind of hearing loss experienced by NF2 patients.

In both mouse models, the use of crizotinib to block the HGF-cMET pathway improved treatment response by enhancing radiation-induced DNA damage, significantly reducing tumor growth and extending survival. Genetic knockdown of cMET had similar results, and experiments using the novel mouse model showed that blocking cMET itself did not adversely affect the animals' hearing.

In collaboration with co-authors Scott Plotkin, MD, PhD, of the Pappas Center for Neuro-Oncology in the MGH Cancer Center and Anat Stemmer-Rachamimov, MD, MGH Pathology, Xu and co-corresponding author Rakesh Jain, PhD, director of the Steele lab, also developed a better system for culturing patient-derived schwannoma cells, which in contrast to malignant tumor cells have been difficult to culture. The improved system maintained patient-derived cells in culture for up to three weeks, and the team's experiments revealed that both HGF expression and cMET activation correlated with tumor growth and that

cMET blockade inhibited schwannoma growth.

"With this new culture model we can screen libraries of drugs for anti-tumor activity," says Jain. "These methods and tools will address a major bottleneck in the NF2 field by providing robust, expandable and biologically diverse cellular models that recapitulate the defining features of this and other human diseases."

Xu notes that, since crizotinib is FDA approved for the treatment of certain types of lung cancer, their study has the potential for rapid clinical translation. She says, "NF2 is a disease that needs new solutions, and our findings provide compelling rationale that paves the road for clinical testing of this combined therapy to treat vestibular schwannomas in human patients." Xu is an assistant professor of Radiation Oncology, and Jain is the Cook Professor of Radiation Oncology (Tumor Biology) at Harvard Medical School.

More information: Yingchao Zhao el al., "Targeting the cMET pathway augments radiation response without adverse effect on hearing in NF2 schwannoma models," *PNAS* (2018). www.pnas.org/cgi/doi/10.1073/pnas.1719966115

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