Adding antiangiogenesis increases effectiveness of radiation against NF2-associated tumors

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Treatment with antiangiogenesis drugs may improve the effectiveness of radiation treatment of nervous system tumors that interfere with the hearing of patients with the genetic disorder neurofibromatosis 2 (NF2). A team of Massachusetts General Hospital (MGH) investigators reports in *PNAS* Early Edition that use of an antiangiogenesis drug reduced the radiation dose required to shrink tumors in animal models of the NF2-associated tumors called vestibular schwannomas. They also discovered several mechanisms behind this effect and determined the time window during which radiation therapy produces the best results in the tested model.

"We found that treatment with an antibody blocking the angiogenic factor VEGF improves neurologic function in our mouse model by alleviating tissue edema, which may further improve neurologic function by decreasing muscle atrophy and increasing nerve regeneration, both of which we observed," says Lei Xu, MD, PhD, of the Steele Laboratory of Tumor Biology in the MGH Radiation Oncology Department, corresponding author of the *PNAS* report. "Combining anti-VEGF with radiation therapy allows use of a lower radiation dose, which can achieve better tumor control and minimize radiation-related neurological damage."

NF2 is characterized by benign tumors that develop throughout the nervous system. The most common site of these tumors is the eighth

cranial nerve, which carries hearing and balance information from the ears to the brain. Although vestibular schwannomas grow slowly, they usually lead to a significant or total hearing loss by young adulthood or middle age. The tumors can also press on the brain stem, leading to headaches, difficulty swallowing and other serious neurologic symptoms. While the tumors can be surgically removed or destroyed with radiation treatment, both approaches can also damage hearing.

Several previous investigations had suggested that - unlike other benign tumors - vestibular schwannomas induce the formation of new blood vessels, as malignant tumors do. A 2009 New England Journal of Medicine study led by Scott Plotkin, MD, PhD, of the Pappas Center for Neuro-Oncology in the MGH Cancer Center reported that treatment with the antiangiogenesis drug bevacizumab caused shrinkage of NF2 schwannomas in most of the treated patients and improved hearing in more than half. But the limitations of that approach - the fact that not all patients responded, that the hearing improvement was often transient and that some patients could not tolerate long-term bevacizumab treatment - indicated the need to better understand the mechanisms behind the effects of antiangiogenesis on the function of tumor-bearing nerves.

To investigate that question, Xu and Steele laboratory director Rakesh Jain, PhD, collaborated with Plotkin and with Anat Stemmer-Rachamimov, MD, of MGH Molecular Pathology to conduct the current study. In a series of experiments using several mouse models of nerve tumors they found that treatment with an experimental anti-VEGF drug produced more improved neurologic function than did radiation alone and that treatment reduced tissue edema, alleviating swelling that may compress nearby nerves. They also found evidence that anti-VEGF treatment enhanced the regeneration of damaged nerves and decreased atrophy in muscles connected to tumor-bearing nerves.

Careful observation of tumor vasculature in a mouse model of NF2 revealed that anti-VEGF treatment reduced the number of abnormal blood vessels within the tumor, a key mechanism behind the successful use of antiangiogenesis drugs to treat several types of cancer. As also seen in those applications, this normalization of the tumor's blood supply proved to be temporary, beginning around day 2 of treatment and starting to diminish on day 5. Administering radiation therapy during that normalization window had significantly greater effects than did either anti-VEGF or radiation therapy alone, while radiation given outside that time had no additive effect. Giving radiation during the normalization window also increased its effectiveness, producing the same beneficial results with half the radiation dosage.

"NF2 is a disease that needs new solutions, and we demonstrated that combining anti-VEGF with radiation therapy can achieve better tumor control, allowing a reduction in radiation dose that can minimize neurological toxicity," says Xu, who is an assistant professor of Radiation Oncology at Harvard Medical School. "Our study provides compelling rationale and paves the way for further testing of combined therapy in human patients, and we are currently planning a clinical trial."

More information: X. Gao et al. Anti-VEGF treatment improves neurological function and augments radiation response in NF2 schwannoma model, *Proceedings of the National Academy of Sciences* (2015). DOI: 10.1073/pnas.1512570112

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