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Researchers Engineer Much-Needed Mouse Model of a Rare Vascular Sarcoma

Dr. Rubin used a novel approach to target the gene fusion that causes epithelioid hemgioendothelioma, engineering a novel, first-of-its-kind mouse model of the disease, which will help advance studies to identify new treatments.

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According to new study findings published in *Genes & Development*, Department of Cancer Biology researchers have engineered a novel mouse model of epithelioid hemangioendothelioma (EHE), a rare vascular cancer that grows from the cells that line the inside of blood vessels.

Led by Brian Rubin, MD, PhD, the team's animal model was proven indistinguishable from how EHE presents in patients. "While EHE is rare, it is highly lethal and there is unfortunately no standard treatment for the disease. One of the main factors that has limited advances in treatment options is the lack of reliable preclinical disease models for study," said Dr. Rubin, who also chairs the Robert J. Tomsich Pathology & Laboratory Medicine Institute.

Targeting a disease-driving gene fusion

While genetic analyses and *in vitro* studies are important, *in vivo* studies are critical to uncover disease pathology and drug targets.

In more than 90 percent of cases, EHE patients have a gene fusion—when two previously separate genes get rearranged as a result of chromosomal changes to become one hybrid gene. In EHE, the *WWTR1* and *CAMTA1* genes fuse together, a seminal discovery previously made by Dr. Rubin. In about 45 percent of EHE patients, the *WWTR1-CAMTA1* gene fusion is the only genetic abnormality present.

Here, Dr. Rubin and his team used a novel approach to target this gene fusion to engineer their mouse model. Their model very closely mirrors EHE in patients, including its clinical, histological, immunohistochemical and genetic manifestations.

Model points towards EHE drug targets to explore

Importantly, the researchers also determined that TAZ-CAMTA1—the protein fusion encoded by *WWTR1-CAMTA1*—is sufficient to drive EHE development and progression independent of other genetic factors.

The gene fusion acts as an over-activated form of the TAZ protein. Under normal conditions, TAZ regulates several characteristics of the cells that line blood vessels. When its activity is increased, TAZ contributes to the growth and spread of tumors.

“Taken together, this suggests that TAZ-CAMTA1 and related signaling pathways are a promising target for treating EHE,” said Dr. Rubin. “We are excited to continue exploring this line of investigation, and hope the studies for new EHE treatments by others in the field will also be advanced by our new mouse model.”

Caleb N. Seavey, MD, a general surgery resident in the Digestive Disease & Surgery Institute, is first author on the study, which was funded in part by the CRAVAT Foundation, the EHE Foundation, the Margie and Robert E. Petersen Foundation and VeloSano, Cleveland Clinic’s flagship fundraising initiative for cancer research. Dr. Seavey is also a member of Cleveland Clinic’s physician-scientist training program called PRISM (Physician Researchers Innovating in Science and Medicine), which allows residents and fellows to pursue a PhD in molecular medicine.