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Study suggests way to attack deadly, untreatable nerve tumors

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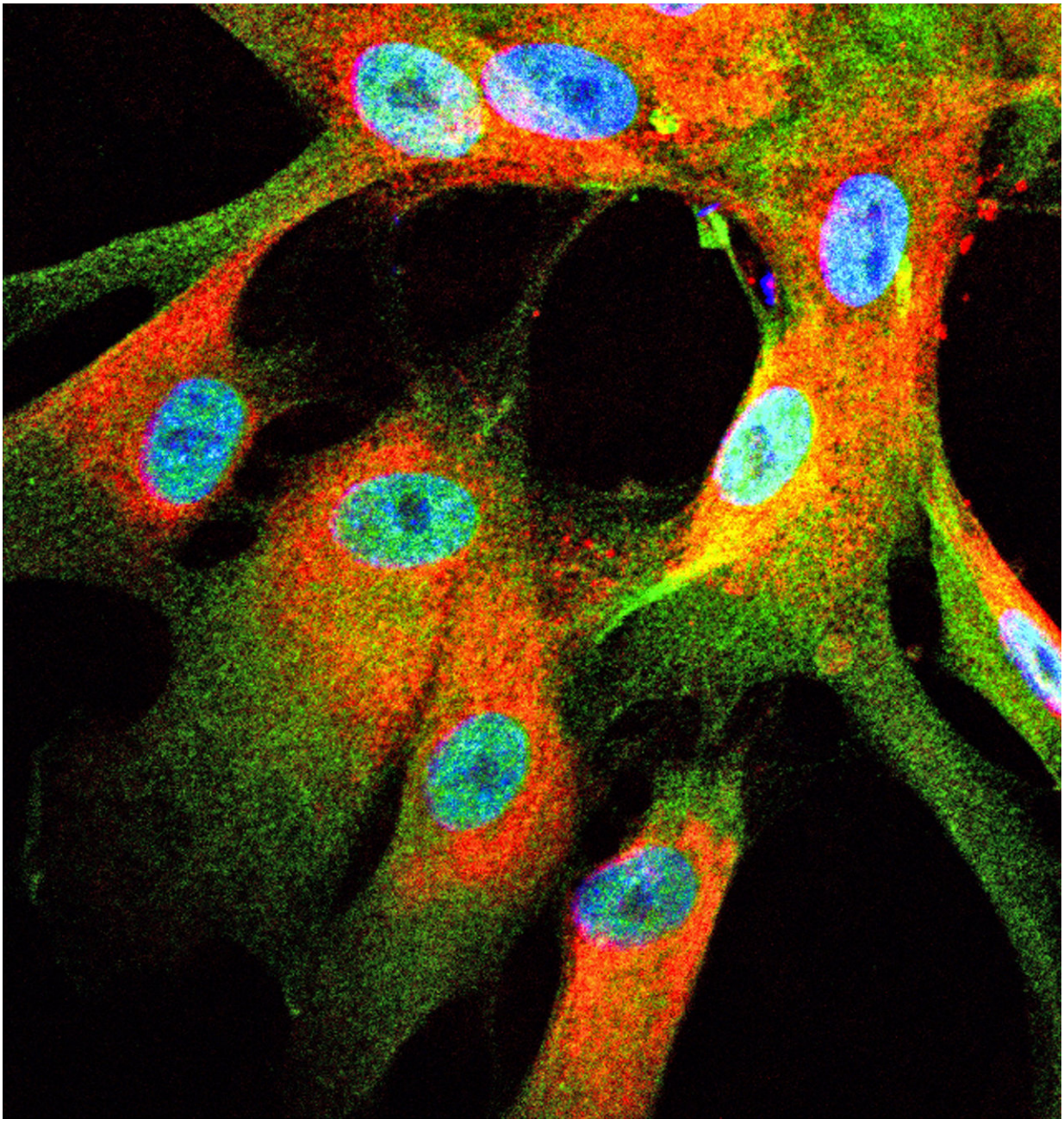

This microscopic image uses immunostaining to highlight the presence of TAZ/YAP (shown in green) in human malignant peripheral nerve sheath tumors that grew from Schwann cells. The job of Schwann cells is to form the protective nerve sheath. The cell nuclei are shown in blue. The image is from a study by scientists at Cincinnati Children's published by the journal *Cancer Cell*. Credit: Cincinnati Children's

Genomic profiling of mostly untreatable and deadly nerve sheath tumors led scientists to test a possible therapeutic strategy that inhibited tumor growth in lab tests on human tumor cells and mouse models, according to research in the journal *Cancer Cell*.

When the international team of researchers analyzed complete screens of genes and genetic material in malignant peripheral nerve sheath tumors (MPNSTs), it revealed previously unknown genetic information about the disease.

"This uncovered potential therapeutic targets we did not expect for these untreatable tumors, but our findings also need further study before knowing whether they will be relevant to patient treatment in the clinic," said Q. Richard Lu, PhD, lead author and scientific director of the Brain Tumor Center at the Cincinnati Children's Cancer and Blood Diseases Institute.

Researchers show a gene called Lats1/2 suppresses cancer, and losing the gene's expression reprograms cells so they rapidly expand and become cancerous. Loss of Lats1/2 also causes other genes in the HIPPO signaling pathway (which controls tissue growth) to become hyperactive. These hyperactive genes and their associated proteins (TAZ and YAP)

then work with the protein TEAD1 to activate molecular cancer programs that form MPNSTs.

When researchers disrupted overactive TAZ-YAP in mice bred to lack Lats1/2, they also blocked signaling from PDGF (platelet-derived growth factor receptor), which supports tissue growth. These steps reduced the size and number of MPNSTs in the mice. They also inhibited the growth of human MPNST cells in laboratory cultures.

In their future work, Lu and his colleagues want to identify small-molecule agents that will inhibit TAZ-YAP and the downstream cancer programs they activate, he said. The researchers also need to identify druggable locations on the surface of MPNST cells or HIPPO signaling cascade inside cells. This would allow small molecular inhibitors to attach to and attack the tumor cells.

Like A Car Without Brakes

MPNST's develop in what are called Schwann cells. These cells form the myelin sheath. The myelin sheath functions as a protective insulation around peripheral nerves, which connect the brain and spinal cord to extremities and organs and promote transmission of nerve impulses.

About half of MPNSTs are linked to mutation of the NF1 gene, which causes a condition called Neurofibromatosis 1, researchers say. The other half of MPNSTs have no known genetic origins, and a small proportion of cases can be caused by radiotherapy given to people for cancer treatment, according to the authors.

The NF1 gene normally helps control a balanced rate of cell growth. When it mutates, it can cause brown spots on a person or benign tumors along peripheral nerves. In some cases, NF1 mutation can lead to cases of runaway cell growth, creating very large and sometimes medically

problematic plexiform tumors which can turn into MPNSTs.

MPNSTs are biologically aggressive tumors and resistant to treatments like chemo and radiation therapy. They're also known for high relapse rates and poor prognosis, often leading to death.

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