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Study identifying cell of origin for large, disfiguring nerve tumors lays groundwork for development

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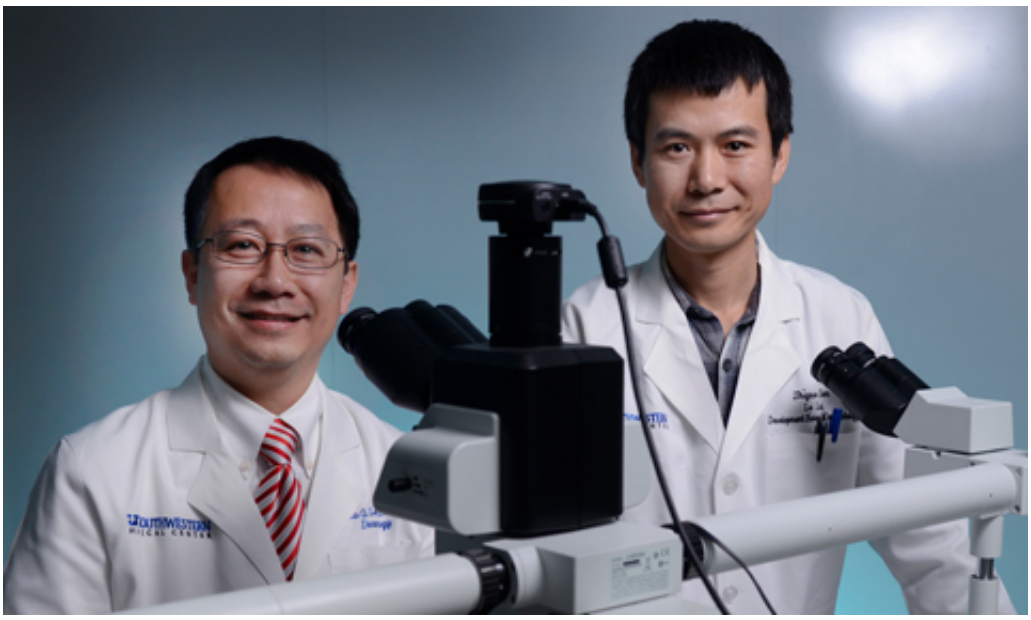

Using this multihead microscope to study large, disfiguring tumors called plexiform neurofibromas, UT Southwestern's Dr. Lu Le, left, and postdoctoral researcher Dr. Zhiguo Chen determined the cell of origin for these tumors, a finding that may assist in developing new therapies. Credit: UT Southwestern

UT Southwestern Medical Center researchers have determined the specific type of cell that gives rise to large, disfiguring tumors called plexiform neurofibromas, a finding that could lead to new therapies for preventing growth of these tumors.

"This advance provides new insight into the steps that lead to tumor development and suggests ways to develop therapies to prevent neurofibroma formation where none exist today," said Dr. Lu Le, Assistant Professor of Dermatology at UT Southwestern and senior author of the study, published online and in *Cancer Cell*.

Plexiform neurofibromas, which are complex tumors that form around nerves, occur in patients with a genetic disorder called neurofibromatosis type 1 (NF1), which affects 1 in 3,500 people. About 30 percent of NF1 patients develop this type of tumor, which is typically benign.

NF1 patients with plexiform neurofibromas, however, have a 10 percent lifetime risk of the tumors developing into malignant peripheral nerve sheath tumors (MPNSTs), a deadly, incurable type of soft-tissue cancer. In addition, due to their unusual capacity for growth, plexiform neurofibromas can be life-threatening by their physical impairment of vital organs or neural function.

While there are no currently approved therapies for either MPNSTs or plexiform neurofibromas, Dr. Le said determining the cell type and location from which these tumors originate is an important step toward discovering new drugs that inhibit tumor development.

"If we can isolate and grow the cells of origin for neurofibromas, then we can reconstruct the biological steps that lead these original cells to tumor stage," said Dr. Le, a member of the Harold C. Simmons Cancer Center. "Once we know the critical steps in the process, then we can design inhibitors to block each step in an effort to prevent or slow tumor formation."

Using a process called genetic labeling for cell fate tracing, researchers determined that plexiform neurofibromas originate from Schwann cell precursors in embryonic nerve roots.

"This study addresses a fundamental question in the neurofibromatosis field," Dr. Le said. "It points to the importance of stem cells and their immediate progenitors in the initiation of tumors, consistent with the notion that these neoplasms originate in a subset of primitive precursors and that most cells in an organ do not generate tumors."

In a related study published last year, Dr. Le's research team found that inhibiting the action of a protein called BRD4 caused tumors to shrink in a mouse model of MPNST. UT Southwestern is working with a pharmaceutical company to bring a BRD4-inhibiting drug into clinical trials for MPNST patients.

New drugs are desperately needed to treat both MPNST and plexiform neurofibromas, said Dr. Le, who also serves as co-director of UT Southwestern's Comprehensive Neurofibromatosis Clinic. The clinic, co-directed by Dr. Laura Klesse, Assistant Professor of Pediatrics and a Dedman Family Scholar in Clinical Care, is part of the Harold C. Simmons Cancer Center and serves patients with all types of hereditary neurofibromatosis.

Provided by UT Southwestern Medical Center

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