SOUTHWESTERN NEWS

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EMBARGOED UNTIL 1 P.M. CDT, THURSDAY, MAY 2, 2002

RESEARCHERS IDENTIFY CELL, GENETIC ENVIRONMENT BEHIND NERVE-TISSUE TUMORS THAT LEAD TO CANCER

DALLAS – May 3, 2002 – Researchers at UT Southwestern Medical Center at Dallas believe they are hot on the trail of a way to prevent benign tumors that attack the nervous system and can be precursors to terminal cancer.

The research, published in today's edition of *Science*, reveals that tumors in neurofibromatosis 1 (NF-1) patients form out of a particular type of cell, the Schwann cell. Neurofibromatosis, also known as von Recklinghausen disease, is a genetic disorder that causes benign tumors to form on the nerves, skin and internal organs.

Neurofibromatosis is the most common neurological disorder caused by a single gene, and there are two distinct forms: NF-1, which affects multiple organ systems, including the central and peripheral nervous systems, and is present in about 1 in 3,500 people worldwide; and NF-2, which affects only the vestibular nerve, a cranial nerve related to hearing and balance, and the membranes around the brain and spinal cord. NF-2 is present in about 1 in 40,000 people worldwide.

The benign tumors, called neurofibromas, develop into malignant tumors, called neurofibrosarcomas, in 10 percent to 15 percent of NF-1 patients. The malignant tumors do not respond well to currently available treatments.

The new research describes genetically permissive and restrictive environments for NF-1 tumor development. The tumors grow in a permissive environment, but they are nonexistent when the environment is restrictive, researchers say.

Dr. Yuan Zhu, instructor in the Center for Developmental Biology and lead author of the study, said the findings could lead to a new approach to combating NF-1. Zhu has been studying neurofibromatosis since 1995, when as a graduate student he joined the lab of Dr. Luis Parada,

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director of the Center for Developmental Biology and senior author of the paper.

"The focus has always been on attacking the tumor cells," Zhu said. "But in our findings, killing the tumor cells is not the strategy."

Instead, the idea is to indirectly attack the tumors by creating a genetically restrictive environment. "If neurofibromatosis patients don't develop the benign tumors, they can't develop cancer from them," Parada said.

Every cell in the body carries a complete copy of the genetic code that controls human development. Included in that code are tumor suppressors whose function is to control unrestricted cell growth. People normally have two NF-1 copies (alleles), one contributed from each parent's genetic structure. NF-1 patients are born with one allele missing. The researchers discovered that when the one normal allele disappears from a particular type of cell, known as a Schwann cell, the cell can mutate and spawn a benign tumor.

In trying to develop a mouse model that replicated human NF-1, Zhu and his colleagues found that mice born with only one normal allele never develop the disorder because the odds are in their favor – they don't live as long as humans and don't have as many cells that could lose the one good allele and form tumors; however, mouse models with both alleles missing died before birth.

The researchers then genetically engineered two kinds of mice – one type with only one allele and one type with two alleles. In both, they nullified the alleles specifically in Schwann cells. But not all of the mice developed NF-1. The disease surfaced only in mice whose non-Schwann cells carried only one normal NF-1 allele. Mice that carried two normal alleles in all other cells didn't develop tumors.

"This model system demonstrates that for this type of tumor, there are two environments," Parada said. "That immediately opens the notion that it might also be true for many types of cancers."

But the focus remains on neurofibromatosis. Parada said the latest research is dedicated in memory of Elisabeth Reed Wagner, who passed away April 11, 12 days shy of her 21st

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birthday. She had battled NF-1 since age 3 and had been treated by UT Southwestern physicians at Zale Lipshy University Hospital.

The researchers already have begun pre-clinical trials using mouse models to determine if some Food and Drug Administration-approved medications can create a restrictive environment. The next step is to determine whether the permissive/restrictive condition applies to humans.

"If our ideas about how tumors form in neurofibromatosis hold true, we can envision strategies to prevent them," said Parada, who directs the Kent Waldrep Center for Basic Research on Nerve Growth and Regeneration.

Other UT Southwestern contributors to the research include Pritam Ghosh, a lab technician who is now a first-year medical student, and Dr. Dennis Burns, professor of pathology.

The research was supported by grants from the National Institute of Neurological Disorders and Stroke and the Department of Defense. Zhu also received funding as a 2001-2002 winner of a Young Investigator Award from the National Neurofibromatosis Foundation.

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