# Loss of tumor supressor gene essential to transforming benign nerve tumors into cancers

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Researchers at UCLA's Jonsson Comprehensive Cancer Center showed for the first time that the loss or decreased expression of the tumor suppressor gene PTEN plays a central role in the malignant transformation of benign nerve tumors called neurofibromas into a malignant and extremely deadly form of sarcoma.

The work, a collaboration between the Institute for Molecular Medicine, the Department of Molecular and Medical Pharmacology and the cancer center's Sarcoma Program, could lead to the development of new therapies that target the cell signaling pathway regulated by PTEN. A novel mouse model of neurofibromatosis type 1 (NF1) developed at UCLA first illustrated the importance of PTEN tumor suppressor in malignant transformation and this finding was validated in human malignant peripheral nerve sheath tumors, the deadly sarcomas.

The study will be published this week in the early online edition of the peer-reviewed journal Proceedings of the National Academy of Sciences .

"The loss of expression of PTEN in the human sarcomas we studied mirrored the loss of PTEN in mice, and we anticipate being able to target this pathway abnormality for the development of new methods of diagnosis and treatment" said Dr. Fritz Eilber, director of the Sarcoma Program and an assistant professor of surgical oncology. "Within the

sarcoma world, malignant peripheral nerve sheath tumors are one of the most lethal sub-types, so this is a significant finding and may lead to new and more effective treatments."

NF1 is one of the most common genetically inherited disorders, with an incidence of about 1 in every 2,500 births, said, Dr. Hong Wu, associate director of the molecular medicine institute, a Jonsson Cancer Center researcher and senior author of the study.

"Patients with NF1 have an about 10 percent lifetime risk of developing this lethal sarcoma sub-type," Wu said.

The study also showed that Positron Emission Tomography (PET) scanning with the glucose analogue FDG - both in the mice and in humans - is a highly accurate way to distinguish between the benign tumors and the malignant ones, indicating that this non-invasive imaging technology is valuable in assessing therapeutic response to new treatments.

Wu created the mouse model with two of her graduate students, Caroline Gregorian and Jonathan Nakashima, co-first authors of this paper. It was created by altering two cell signaling pathways that are commonly activated in peripheral and central nervous system cancers, the RAS/RAF/MAPK & PTEN/P13K/AKT pathways, known to regulate cell proliferation, survival and differentiation.

"When we began to generate mouse models to mimic different human cancers, we usually did gene-based analysis to see the relevance of a specific gene in the development of the cancer," Wu said. "But we realize that sometimes targeting the cell signaling pathways that organize and instruct cells to function, both for normal functions of our body and also in abnormal ways in disease, are more important and informative than the individual gene"

The mouse model developed benign neurofibromas, but then progressed to the deadly sub-type of sarcoma. The neurofibromas had half the normal levels of PTEN and the sarcomas had a complete loss of PTEN. Since PTEN is an important factor in suppressing cells from becoming malignant, this could provide an explanation for the sequence of the normal cells transforming into benign neurofibromas that could then transform into cancer.

Wondering if this was also the case in people, Dr. Wu collaborated with Eilber and pathologist Dr. Sarah Dry, director of the Institute of Molecular Medicine's Pathway Pathology Center, and a multidisciplinary team of physician-scientists to determine if people with this sarcoma sub-type also had little or no PTEN.

"This type of collaboration is the hallmark of the work at the Jonsson Cancer Center and molecular medicine institute - translating discoveries in a basic science lab into discoveries in patients," Wu said.

Currently, there are no effective treatments to prevent the benign NF1 tumors from transforming into cancer. The genetically engineered mouse model will be used to screen drugs that may be able to target the signaling pathway regulated by PTEN, to block signals that instruct the cells to change from a benign state to a malignant one, providing treatment options for patients with the deadly form of cancer.

"I think these findings will help us provide a better diagnosis that can determine if the neurofibroma is becoming a malignant tumor or not," Eilber said. "But more importantly, the loss of the PTEN and its associated signaling pathways gives us targets for therapy and it may lay the foundation for treatment in other sarcomas as well."

Source: University of California - Los Angeles