SOUTHWESTERN NEWS

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RESEARCHERS DEVELOP ANIMAL MODEL OF HUMAN COLORECTAL CANCER

DALLAS - September 18, 1998 - The development of the first animal model for colorectal cancer by scientists at UT Southwestern Medical Center at Dallas will facilitate research into the molecular mechanisms of colorectal cancer and provide a model system for testing chemoprevention agents and new drug treatments.

One in every 20 Americans will get colorectal cancer, the second-leading cause of cancer deaths. The collaborative work of Drs. Jon Graff, Luis Parada and colleagues, published in today's issue of *Cell*, could dramatically change that prospect. Initially the researchers will use their colon cancer mouse model, which mimics the human disease in many aspects, to look at ways of preventing cancer.

"The real strength of the model is that we can use the power of modern molecular biology to alter the genetic background and look at colorectal cancer in a very specific and fundamental way," said Graff, assistant professor in UT Southwestern's Center for Developmental Biology. "We want to do pharmacological and genetic manipulations with the idea that we can use the two as a synergistic approach to really get to the basis of prevention."

The investigators were able to induce colon cancer in all of the tested mice by altering a single gene, Smad3, which belongs to a gene family known to be involved in conveying signals from the cell's surface to the cell's nucleus. Smad genes also have been characterized as tumor-suppressor genes.

"My student, Yuan Zhu, chose to look at the Smad3 gene because of previous work by Dr. Graff and because the Smad gene family conveys signals from type II transforming growth factor - (TGF). TGF mutations are seen in some types of hereditary and sporadic colon cancer," said Dr. Luis Parada, director of the Center for Developmental Biology, holder of the Diana K. and Richard C. Strauss Chair in Developmental Biology and director of the Kent Waldrep Foundation Center for Basic Neuroscience. "In mice, previous research had indicated that alterations in other genes of the Smad family did not lead to colon cancer."

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The scientists genetically inactivated the Smad3 gene to produce mice with no Smad3 gene function. They showed conclusively that the normal Smad3 gene functions as a powerful suppressor of colorectal cancer. With this cancer suppressor inactivated, mice spontaneously developed multistage colorectal cancer that had many parallels to the human disease including metastasis to lymph nodes.

As of today, no Smad3 mutations have been found in human cases of colorectal cancer. But Graff believes that since Smad2 and Smad3 are almost identical in structure, the role of Smad3 in the mouse may be analogous to the human Smad2, which has been found in a mutated state in a subset of human colorectal cancers.

"For me the joy would be to help patients and ultimately to cure this illness," Graff said.

Other UT Southwestern scientists participating in this project were first author Yuan Zhu, a doctoral student in the Center for Developmental Biology, and Dr. James Richardson, associate professor of pathology.

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