SOUTHWESTERN NEWS

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IMMORTALIZING ENZYME DOES NOT MAKE HUMAN CELLS CANCEROUS

DALLAS — December 29, 1998 — Scientists at UT Southwestern Medical Center at Dallas have shown that human cells grown in the laboratory and immortalized by the introduction of the enzyme telomerase are not transformed into cancer cells, perhaps clearing the way for safe, future medical applications.

Drs. Jerry Shay and Woodring Wright, UT Southwestern professors of cell biology and neuroscience, and their colleagues will report in the January 1999 issue of *Nature Genetics* that cells immortalized with telomerase, now more than 220 generations past their normal life span of 75 to 80 divisions, remain young and vigorous.

The cells exhibited none of the characteristics associated with cancer cells, such as chromosome instability, serum-independent growth, loss of contact inhibition and loss of cell-cycle checkpoint controls. In an accompanying article, collaborators at the Geron Corporation and academic colleagues demonstrate that the cells with introduced telomerase do not produce tumors in mice.

The fear that telomerase may cause cancer resulted because telomerase activity is a marker of cancer cells. While most normal cells, which have finite life spans, do not contain telomerase, more than 90 percent of cancer cells, which divide indefinitely, do.

"We clearly demonstrate that the expression of telomerase in cultured human cells does not cause cancer progression," said Wright, thereby reducing concerns that telomerase might act as an oncogene, a gene that can induce a cell to become malignant. "The abnormalities seen in cancer cells are due to other mutations; telomerase merely allows the cells to keep dividing."

A year ago the same researchers reported in *Science* (279:349-52, 1998) that telomerase introduced into human cells grown in the laboratory was sufficient to immortalize them. Their report proved that progressive shortening of telomeres – specific short pieces of

(MORE)

deoxyribonucleic acid (DNA) that the enzyme telomerase adds back to the tips of chromosomes – is the biological clock that governs how many divisions a cell will go through.

With the new findings, the way now seems clear for research into new therapies for age-related diseases and for cancer – two ends of the same spectrum. The scientists emphasize, however, that additional studies will be necessary before the concepts are applied to humans.

"In the future I predict we will be attacking cancer by new combinatorial therapeutic approaches using DNA synthesis inhibitors, angiogenic inhibitors and telomerase inhibitors," Shay said. "The combination of these inhibitors would not only prevent the tumor from getting bigger, but each time the tumor cells divided, their telomeres would shorten. Eventually the cells would be unable to divide, and die."

The ability to immortalize human cells and retain normal behavior holds promise in several areas including biopharmaceutical research and transplantation medicine. The scientists believe this new technology has the potential to produce unlimited quantities of normal human cells of virtually any tissue type. Permanent, stable sources for normal human cells – instead of the animal cells or abnormal transformed human cells now available – may help in drug development, screening and testing. Genetic engineering of telomerase-immortalized cells also could help develop cellular models of human disease.

In the future it should be feasible to immortalize a patient's own blood stem cells, eliminating the need for donor bone marrow and avoiding immune rejection. The same technology could be applied to the production of insulin-producing cells for patients with insulin-dependent diabetes mellitus; cartilage cells for those with osteoarthritis and rheumatoid arthritis; blood vessel-forming cells for cardiac patients with angina, stroke or arterial insufficiency; skin cells for burn patients and patients with severe wounds; muscle stem cells for treating muscular dystrophy patients; and the cosmetic production of collagen.

"The goal of our research is to increase our health span, not necessarily our life span, by finding out how to keep our aging – but healthy – cells growing and how to make our cancer cells senescent," said first author Dr. Carmela Morales, a research fellow in internal medicine and a Robert Wood Johnson scholar. "We believe that telomerase is an important target both for the potential treatment of age-related disease and for cancer."

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Other UT Southwestern investigators involved in this research included former research fellow Dr. Shawn Holt; cell biology and neuroscience research fellows Dr. Michel Ouellette and Dr. Kiran Kaur; pharmacology research fellow Dr. Ying Yan; Dr. Michael White, assistant professor of cell biology and neuroscience; and Dr. Kathleen Wilson, assistant professor of pathology.

The investigators' Web site is at: www.swmed.edu/home_pages/cellbio/shay/

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