SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS FIND ANOTHER CLUE TO SECRETS OF CELLULAR AGING

DALLAS – June 15, 2001 – A discovery by UT Southwestern Medical Center at Dallas scientists that genes near human telomeres can be silenced may help explain how and why humans age.

Telomeres are repeating sequences of DNA located at the end of each chromosome and are believed to function as a counting mechanism for cellular aging.

Dr. Jerry Shay and Dr. Woodring Wright, UT Southwestern professors of cell biology, report in today's issue of *Science* that human cells can exhibit telomere position effect (TPE), a mechanism by which genes near telomeres can be turned off, and that the strength of gene silencing is proportional to the length of nearby telomeres.

Shay and Wright, along with collaborators at UT Southwestern, have previously shown that human cells age each time they divide because their telomeres shorten. After a finite number of cell divisions – when telomeres become short – the cells stop dividing.

Most normal cells lack the enzyme telomerase, which maintains telomeres. Telomerase is activated in 90 percent of all cancers, in which cells continue to divide at a high rate. Many diseases, including Down syndrome, are characterized by premature aging. Further understanding of TPE could help researchers discover how cellular aging contributes to the overall aging process.

"This is an important step in trying to explain the connection between telomere shortening and aging," Shay said. "Normal cells will only grow for a limited time. They grow for a while, and then they go through a process called senescence, or aging. We wanted to know about the molecular memory. Are cells counting how many times they divide? We believe the telomeres are the molecular memory."

The researchers incorporated a piece of DNA containing a luciferase (the enzyme that

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allows fireflies to emit light) gene into human cells and showed that if it became located at the telomere, there was 10 times less luciferase activity than if it was located in the middle of a chromosome. They also found an even greater decrease in luciferase activity if they used telomerase to make the telomeres grow longer.

"We knew that when telomeres became too short, they caused cells to stop dividing, but there wasn't a mechanism for how a cell could sense how long its telomeres were before they became too short. TPE can do that. It can let a cell know how old it is so that it could change its behavior before it became senescent," Wright said.

TPE could help explain the differences between young and old cells. For example, if there were "aging" genes next to telomeres, they would be silent when the cells were young. As the cells aged and continued to divide, their telomeres would shorten; the silencing of the genes would be reversed; and the "aging" genes activated.

The researchers are now looking for naturally occurring human genes located near telomeres whose expression is influenced by telomere length.

Joseph A. Baur, a UT Southwestern student research assistant in cell biology, and Dr. Ying Zou, a UT Southwestern cell biology fellow, also were involved in the research.

Shay and Wright's earlier research has shown that telomerase causes human cells grown in the laboratory to retain their "youth" and continue to divide long past the time when they normally would have stopped dividing. This discovery is making the use of normal cells for tissue engineering and other therapeutic uses much easier.

The investigators' Web site can be found at www.swmed.edu/home_pages/cellbio/shay-wright.

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