SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS ALTER LIFE SPAN OF HUMAN CELLS

DALLAS — March 15, 1996 — The end of a chromosome may hold the beginning of a clearer understanding of how humans age.

In the March 15 issue of the *European Molecular Biology Organization (EMBO) Journal*, Dr. Jerry Shay and Dr. Woodring Wright, both professors of cell biology and neuroscience at UT Southwestern Medical Center at Dallas, report manipulating the length of telomeres (the DNA at the ends of chromosomes) to alter the life span of human cells. Shay and Wright are the first to report this important finding. They received an AlliedSignal Award for Research on Aging to explore this line of research last year.

Telomeres are specialized structures that are important in maintaining chromosomal stability. Each time a cell divides, its telomeres shorten. Eventually, the telomeres get so short that normal cells stop dividing.

"By lengthening the telomere, we were able to extend the life of the cell hybrids," Wright explained. "This study is strong evidence that telomere length is the clock that counts cell divisions."

The expression of the enzyme telomerase maintains stable telomere length. Telomerase is not detected in normal cells and telomeres shorten and then the cells stop dividing and enter a phase called cellular senescence.

Shay and Wright have shown in earlier studies that telomeres maintain their length in almost all human cancer cell lines. This correlated with inappropriate expression of telomerase and as a consequence allowed the cell to become "immortal." Cell immortality is a critical and perhaps rate-limiting step for almost all cancers to progress. Previous work by the UT Southwestern investigators showed that in a special group of advanced pediatric cancers the lack of telomerase activity correlated with critically shortened telomeres and

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cancer remission.

Consequently, an idea gaining momentum is that the ability to measure and perhaps alter telomere length and/or telomerase activity may give physicians new diagnostic and treatment tools for managing the care of patients with cancer.

Shay and Wright tried to alter already-immortal cells by attempting to inhibit telomerase activity and cause telomeres to shorten. "Unexpectedly, we found the opposite result. Rather than inhibiting telomerase, our treatment caused the immortal cells to develop longer telomeres," Shay explained. "Although we were surprised with the result, we now know there is a causal relationship between telomere length and the proliferative capacity of cells.

"Essentially, we combined the tumor cells containing experimentally elongated telomeres with normal cells and extended the life span of those cell hybrids compared to similar hybrids using cells without experimentally elongated telomeres."

Shay and Wright said the mechanism that causes telomeres to lengthen is still unclear. However, Shay said, "Our observations increase confidence in the hypothesis that immortal cells and reactivated telomerase are essential components of human tumors. Ultimately, we may be able to regulate tumor cells by inhibiting telomerase activity."

The potential implications for research on human aging also are significant. "It is still speculative, but understanding the role of telomere shortening in cell aging may give us the information we need to increase the life span of an organism," Wright said.

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