SOUTHWESTERN NEWS

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## SCIENTISTS GETTING CLOSER TO UNDERSTANDING HOW CELLS AGE

DALLAS – November 11, 1997 – Understanding how normal human cells age should help scientists develop new tools to stop the growth of cancer cells, which bypass the aging process.

Normal human cells undergo a finite number of cell divisions before they "age" and can no longer divide. On the other hand, cancer cells divide indefinitely and are often referred to as immortal cells. In normal cells a biological clock keeps track of the number of cell divisions by checking the length of telomeres, special structures on the ends of chromosomes that protect the tips from degradation.

In the November issue of the journal *Genes and Development,* Drs. Jerry Shay and Woodring Wright, UT Southwestern professors of cell biology and neuroscience, and Dr. Valerie Tesmer, a cell biology and neuroscience research fellow, offer new information about human telomere structure and regulation.

"If we can more fully understand how the biological clock and timing mechanism works, we may be able to manipulate cancer and aging," Shay said.

Chromosomes are made up of double-stranded deoxyribonucleic acid (DNA). During replication the strands separate and each strand is copied to make a new double-stranded molecule. One strand is the leading strand, the other the lagging strand. Because of the way DNA replicates, the enzyme that copies the lagging strand is unable to copy the DNA all the way to the end of the chromosome; therefore, the newly synthesized daughter strand is shorter than the parental strand.

"It is like a painter in a closed room. He can paint the entire floor except for the square where he is standing," said Shay. For this reason there are no genes at the ends of the chromosomes; instead there are thousands of telomeric repeats.

Scientists used to speculate that there were long telomere overhangs, or tails, on both ends of the chromosome. The new data dispute this finding and strongly point to a long telomere tail at

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only one end of the chromosome; the other end of the chromosome is blunt or has a short end. This is important because, in human cells, the way in which the telomere tail is generated during DNA replication is likely to regulate the rate of telomere shortening.

"It is extremely important to understand the rate of telomere shortening if we are to understand some of the pathologies of aging and if we are going to develop new therapeutics for cancer," Wright said.

Drs. Shay, Wright and their colleagues now are closer to understanding how telomeres erode. Reproductive cells and cancer cells have an enzyme, telomerase, that adds telomeric sequences to the chromosomal ends. This counters the shortening of the telomeres, so that these cells continue to divide and are in a sense immortal. In addition, different cells shorten their telomeres at different rates.

Acceleration of telomere erosion in cancer cells, as well as inhibiting telomerase, may be a means of cancer therapy. "Since there are different rates of telomere shortening, it means that the rates are not fixed and immutable, and so we might be able to intervene and change those rates," Wright said.

Drs. Stephen Levene and Kenneth Huffman of UT Dallas also contributed to the research.

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