UT SOUTHWESTERN MEDICAL CENTER NEWS

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UT Southwestern researchers examine mechanisms that help cancer cells proliferate

DALLAS – Sept. 1, 2009 – A process that limits the number of times a cell divides works much differently than had been thought, opening the door to potential new anticancer therapies, researchers at UT Southwestern Medical Center report in the Aug. 7 issue of the journal *Cell*.

Most cells in the human body divide only a certain number of times, via a countdown mechanism that stops them. When the controlling process goes wrong, the cells divide indefinitely, contributing to cancer growth.

The number of times a cell divides is determined by special segments of DNA called telomeres, which are located at the ends of each chromosome. Every time a cell divides, the telomeres get shorter. When they are reduced to a certain length, the cell stops dividing.

In the new study, UT Southwestern researchers used both normal and cancerous human cells to examine closely how telomeres behave during cell division.

As a cell prepares to divide into two new cells, its ladder-shaped DNA "unzips," creating two halves, each resembling a single upright of a ladder with a set of half-length rungs. Fresh genetic material then fills in the rungs and a second upright. This process creates two identical sets of chromosomes that will be allotted between the two cells.

From earlier studies on model organisms such as yeast, scientists thought that all telomeres replicated late in the stage of overall DNA replication, and by the same processes. The new study suggests that telomeres replicate at various times during this stage, except for a final step that is not completed until the very end, via a different, unknown mechanism.

"Interfering with replication of telomeres might provide a way to halt uncontrolled spread of cancer cells," said Dr. Woodring Wright, professor of cell biology at UT Southwestern and co-senior author of the paper.

The researchers also examined an enzyme called telomerase, which "rebuilds" telomeres so they do not get shorter and signals the cell to stop dividing. Normally, telomerase is only active in cells such as stem cells and dividing immune cells, which must reproduce constantly.

But telomerase also has a dark side: When active in cancer cells, it enables unlimited growth, a

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hallmark of cancer.

It had been thought that telomerase only works on the shortest telomeres in a cell, but in the new study, the UT Southwestern researchers found that telomerase rebuilds most or all of the telomeres in a cell for each division, not just the shortest ones, as had been thought.

"Understanding ways to inhibit this telomerase mechanism might lead to novel anticancer therapies," said Dr. Jerry Shay, professor of cell biology and co-senior author of the paper.

Clinical trials using a drug that blocks telomerase are already under way at UT Southwestern for lung cancer and chronic lymphocytic leukemia.

The new study was possible because the researchers developed a way to examine the very ends of telomeres after a single cell division. Previous research in the field required multiple cell divisions to detect such changes.

"Now that we can look at what telomerase is doing in a single cell-division cycle, there is potential for a tremendous number of follow-up studies," Dr. Wright said.

Other UT Southwestern researchers involved in the study were lead author Dr.Yong Zhao, postdoctoral researcher in cell biology; Dr. Agnel Sfeir, former graduate student in integrative biology; Dr. Ying Zou, former graduate student in genetics and development; graduate student Christen Buseman; and graduate student Tracy Chow.

The research was funded by the National Institutes of Health, the American Federation for Aging Research and the Department of Defense Breast Cancer Program.

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