SOUTHWESTERN NEWS

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SCIENTISTS DISCOVER PROTEIN RESPONSIBLE FOR DNA REPLICATION

DALLAS - Jan. 7, 1996 - Scientists are discovering the proteins that control the way human DNA copies itself, a breakthrough that may lead to new treatments for cancer or heart disease.

Dr. R. Sanders Williams, professor of internal medicine and chief of cardiology at UT Southwestern Medical Center at Dallas, has discovered a protein thought to function in the initiation of DNA replication. The discovery was made during his year-long sabbatical at Cold Spring Harbor Laboratory in New York where he conducted research with Dr. Bruce Stillman.

The discovery of the gene, termed $p62^{cdcd6}$, is reported in the Jan. 7 issue of *The Proceedings of the Academy of Sciences.*

"When cells divide, each of the three billion nucleotides in the entire human genome must be copied once, and only once, and this process must be completed in just a few hours," Williams said. "If the process goes awry by producing too many or too few copies of a segment of the genome, serious problems can result."

Williams said Stillman has been a major leader in the field of cell-cycle control, using yeast models to learn how DNA replication is triggered.

"A yeast protein called cdc6p proves to be a critical regulatory component that is involved in both replication licensing - preparing the chromosome to be ready to replicate - and in the process by which the cell replicates DNA precisely once in each cell cycle," Williams said.

Compared to yeasts, very little is known about what triggers DNA replication in

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higher organisms, including humans. The discovery of so-called "initiator" proteins like $p62^{cdcd6}$ in human cells opens the door to greater understanding of mechanisms of tumor development and the events by which certain cells, like those of the heart, lose the capacity to replicate DNA.

Authors Williams, Stillman and Dr. Ralph Shohet, assistant professor of internal medicine at UT Southwestern, speculate that the human DNA-replicator protein will serve a similar function as the yeast DNA-replicator counterparts.

"It appears the basic machinery of DNA replication and origin firing is conserved across all of life," Williams said.

The discovery is pertinent to cancer because mutations in yeast cdc6p cause abnormalities very similar to human malignancies. Scientists are not yet sure of the role of $p62^{cdcd6}$ in human tumors, but it could become a novel target for therapies to stop cells from replicating DNA.

Knowledge about this protein also may be useful in heart disease.

"There are some cells that don't replicate their DNA when we want them to - like heart cells after a heart attack," said Williams, who is director of the Frank M. Ryburn Jr. Cardiac Center at UT Southwestern and holder of the James T. Willerson, M.D., Distinguished Chair in Cardiovascular Diseases .

The work was communicated to the journal by Dr. James D. Watson of Cold Springs Harbor Lab and was supported by funds from the National Institutes of Health.

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