SOUTHWESTERN NEWS

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UT SOUTHWESTERN SCIENTISTS PROVE CERTAIN PROTEINS PLAY UNEXPECTED ROLES IN GENETIC TRANSCRIPTION

DALLAS – April 19, 2002 – Researchers at UT Southwestern Medical Center at Dallas have proved that a group of proteins previously thought to have no role in turning genes on and off actually plays a part in that process, which is critical to both human development and understanding some diseases.

The work – conducted under the direction of Dr. Stephen A. Johnston, director of the Center for Biomedical Inventions, and Dr. Thomas Kodadek, professor of internal medicine and molecular biology who also works in the Center for Biomedical Inventions – is published in today's issue of *Science*. The research focuses on the proteasome, a group of proteins present in all cells.

Conventional wisdom has held that the proteasome serves one purpose: working as a unit to break down individual proteins that have done their work and are no longer needed in the cell, a process called proteolysis. The new research shows that certain proteins can break away from the proteasome to perform other functions and are involved in gene transcription, in which a gene's genetic sequence is copied into messenger RNA. Transcription is the first step in gene expression – when proteins that perform specialized functions are produced according to the gene's sequence.

"What we have shown is that a particular protein complex assembles on genes when you turn them on," Johnston said. "Only after we turned the genes on were the proteins there, and they were not involved in proteolysis."

Working with yeast cells, the researchers activated genes, then used a chemical process called chromatin immunoprecipitation assays to freeze the genetic activity. That gave them a snapshot of the genes that could be examined to find where particular proteins were when

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the freeze-framing process took place. The researchers looked for and found two proteasome proteins, called *Sug1* and *Sug2*, on the genes that had been activated.

Kodadek said yeast cells and mammalian cells, including human cells, work nearly identically at the most basic levels. This suggests that the human proteasomal proteins also are involved in gene activation, Kodadek said.

Johnston theorized about 10 years ago that proteasomes might have a role in gene expression. The theory was unpopular, but Johnston said his lab "kept banging away at it," producing circumstantial evidence to support the idea. But the latest findings reveal actual cell activity.

"It's looking directly *in vivo*," he said.

Johnston said he believes the findings eventually could help identify causes for certain diseases and targets for drug intervention, but there is not an immediate clinical application. The findings, however, could lead to a reassessment of some well-established ideas.

"Some of these proteins and processes have been associated with particular diseases, but the assumption was that the association involved proteolysis," he said. "We're going to have to reassess that. For the field, it's a surprising result."

Fernando Gonzalez, student research assistant in the Center for Biomedical Inventions, and Dr. Agnes Delahodde, a visiting scientist from Paris working in the Center for Biomedical Inventions, were lead authors of the study.

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