UT SOUTHWESTERN MEDICAL CENTER NEWS

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## UT Southwestern researchers identify new targets for RNAs that regulate genes

DALLAS – July 6, 2008 – Tiny strands of genetic material called RNA – a chemical cousin of DNA – are emerging as major players in gene regulation, the process inside cells that drives all biology and that scientists seek to control in order to fight disease.

The idea that RNA (ribonucleic acid) is involved in activating and inhibiting genes is relatively new, and it has been unclear how RNA strands might regulate the process.

In a new study available online today and in a future issue of *Nature Structural and Molecular Biology,* RNA experts at UT Southwestern Medical Center found that, contrary to established theories, RNA can interact with a non-gene region of DNA called a promoter region, a sequence of DNA occurring spatially in front of an actual gene. This promoter must be activated before a gene can be turned on.

"Our findings about the underlying mechanisms of RNA-activated gene expression reveal a new and unexpected target for potential drug development," said Dr. David Corey, professor of pharmacology and biochemistry at UT Southwestern and one of the senior authors of the study.

Genes are segments of DNA housed in the nucleus of every cell, and they carry instructions for making proteins. Faulty or mutated genes lead to malfunctioning, missing or overabundant proteins, and any of those conditions can result in disease. Scientists seek to understand the mechanisms by which genes are activated, or expressed, and turned off in order to get a clearer picture of basic cell biology and also to develop medical therapies that affect gene expression.

In previous studies, Dr. Corey and Dr. Bethany Janowski, assistant professor of pharmacology at UT Southwestern and a senior author of the current study, have shown that tiny strands of RNA can be used to activate certain genes in cultured cancer cells. Using strands of RNA that they manufactured in the lab, the researchers showed that the strands regulate gene expression by somehow perturbing a delicate mixture of proteins that surround DNA and control whether or not genes are activated.

Until now, however, it was not clear exactly how the synthetic RNA strands affected that mix of regulating proteins.

In the current study, also carried out in cancer cell cultures, the UT Southwestern research team

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discovered an unexpected target for the manufactured RNA. The RNA did not home in on the gene itself, but rather on another type of RNA produced by the cell, a so-called noncoding RNA transcript. This type of RNA is found in association with the promoter regions that occur in front of the gene. Promoter regions, when activated, act essentially as a "start" command for turning on genes.

The researchers found that their man-made RNA strand bound to the RNA transcript, which then recruited certain proteins to form an RNA-protein complex. The whole complex then bound to the promoter region, an action that could then either activate or inhibit gene expression.

"Involvement of RNA at a gene promoter is a new concept, potentially a big new concept," Dr. Janowski said. "Interactions at gene promoters are critical for understanding disease, and our results bring a new dimension to understanding how genes can be regulated."

Until recently, many scientists believed that proteins alone control gene expression at promoters, but Drs. Corey and Janowski's results suggest that this assumption is not necessarily true.

"By demonstrating how small RNAs can be used to recruit proteins to gene promoters, we have provided further evidence that this phenomenon should be in the mainstream of science," Dr. Corey said.

Although using synthetic RNA to regulate gene expression and possibly treat disease in humans is still in the future, Dr. Corey noted that the type of man-made RNA molecules employed by the UT Southwestern team are already being used in human clinical trials, so progress toward the development of gene-regulating drugs could move quickly.

Other researchers from UT Southwestern involved in the research were lead author and student research assistant Jacob Schwartz; student research assistant Scott Younger; and research associate Ngoc-Bich Nguyen. Researchers from the University of Western Ontario and ISIS Pharmaceuticals also participated.

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