Gene's function may give new target for cancer drugs

September 12 2012, by Brian Wallheimer

(Phys.org)—Purdue University scientists have determined that a gene long known to be involved in cancer cell formation and chemotherapy resistance is key to proper RNA creation, an understanding that could one day lead to new therapies and drug targets.

The human gene p68 has long been recognized as an oncogene, one associated with cancer formation, but its function was unknown. Elizabeth Tran, a Purdue biochemist, found that misregulation of p68 causes problems with RNA formation and arrangement, possibly leading to chromosomal abnormalities.

Tran, whose findings were published in the Journal of Biological Chemistry, used a gene in baker's yeast - Dbp2 – as a model to understand p68's function.

"Our results show that Dbp2, and likely p68, functions in proper formation of RNA. Our evidence suggests that Dbp2 keeps the RNA from folding improperly," Tran said. "We think that misfolded RNA may not be released from the DNA, causing problems with the DNA itself."

Genes send instructions to proteins to carry out functions. To do that, DNA is decoded into RNA, which then take that code to proteins.

Tran found that Dbp2 is a crucial part of that RNA creation process. Both Dbp2 and p68 encode an enzyme called an RNA helicase. The

RNA helicase enzyme controls the structure and arrangement of RNA, which must be separated from DNA before it takes instructions to proteins.

In this case, Tran showed that misregulated Dbp2 and p68 cause defects in DNA, most likely from incorrect separation of RNA from the DNA. DNA that doesn't fold properly is vulnerable to chromosomes breaking or fusing, problems known to cause a host of diseases.

"The hallmark of cancer is aberrant or even broken DNA," Tran said. "If this process is important for RNA structure and DNA integrity, we may have found a clue as to why misregulation of P68 causes cancer."

Although the study does not address the connection between p68 and cancer, it lays the foundation for future studies. Next, Tran plans to use biochemical experiments to determine exactly how Dbp2 works in a cell and what changes it makes to RNA.

"We need to know what RNAs are recognized by Dbp2 to find how specific genes are affected," Tran said. "We also need to discover what other proteins may function in similar processes and simply haven't been discovered to date."

More information: The DEAD-box RNA Helicase Dbp2 Connects RNA Quality Control with Repression of Aberrant Transcription, Sara C. Cloutier, Wai Kit Ma, Luyen T. Nguyen, and Elizabeth J. Tran, *Journal of Biological Chemistry*, 2012.

Abstract:
DEAD-box proteins are a class of RNA-dependent ATP hydrolysis enzymes that rearrange RNA and RNA-protein (ribo- nucleoprotein) complexes. In an effort to characterize the cellular function of individual DEAD-box proteins, our laboratory has uncovered a previously

unrecognized link between the DEAD-box protein Dbp2 and the regulation of transcription in Saccharomyces cerevisiae. Here, we report that Dbp2 is a double-stranded RNA-specific ATPase that associates directly with chromatin and is required for transcriptional fidelity. In fact, loss of DBP2 results in multiple gene expression defects, including accumulation of noncoding transcripts, inefficient end formation, and appearance of aberrant transcriptional initiation products. We also show that loss of DBP2 is synthetic lethal with deletion of the nuclear RNA decay factor, RRP6, pointing to a global role for Dbp2 in prevention of aberrant transcriptional products. Taken together, we present a model whereby Dbp2 functions to cotranscriptionally modulate RNA structure, a process that facilitates ribonucleoprotein assembly and clearance of transcripts from genomic loci. These studies suggest that Dbp2 is a missing link in RNA quality control that functions to maintain the fidelity of transcriptional processes.

Provided by Purdue University