Study finds protein is required for human chromosome production

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Scientists at the University of North Carolina at Chapel Hill School of Medicine have identified an elusive protein that performs a necessary step in the production of human chromosomes.

The study found that a protein called CPSF73 acts like scissors to cut strands of histone messenger RNA (mRNA) in the cell nucleus. This cutting action produces the mRNA needed to create histone proteins that combine with DNA to form chromosomes.

Like all other proteins, histones are made when a specialized RNA molecule is "read" by ribosomes, the cell's protein factories. The type of RNA, which relays information from the DNA (inside the nucleus) to the ribosome (outside the nucleus), is called messenger RNA.

RNA that is not cut by CPSF73 is destroyed in the nucleus and never becomes messenger RNA, said Dr. William Marzluff, senior author of the study and Kenan distinguished professor of biochemistry and biophysics in UNC's School of Medicine.

"This cutting of histone messenger RNA takes place as growing cells prepare to divide and is absolutely necessary for their eventual division," Marzluff said. Histone proteins help organize and compact within the nucleus the 6 billion nucleotides, or DNA bases, that make up the human genome – combinations of "A's," "T's," "G's" and "C's." Without histones, cells cannot survive.

Dr. Zbigniew Dominski, associate professor of biochemistry and biophysics, has been searching for the protein that cuts histone messenger RNA since joining forces with Marzluff 10 years ago. He is the corresponding and lead author of the study.

When RNA is first made from DNA, it is premature and cannot direct the synthesis of its corresponding protein until it is processed into mature messenger RNA, which includes being cut at a specific site, Dominski said.

"This is a very complex process that requires many proteins to bind to the RNA molecule and show the cutting enzyme where to cleave the RNA," he added.

Dominski was able to duplicate, in a test tube, the histone mRNA processing that takes place normally inside a cell's nucleus. However, the RNA cutting reaction was so quick that he was unable to determine which of the countless proteins inside the test tube was responsible.

"We set a trap by subtly changing the chemical makeup of the histone messenger RNA right where it is cut. This allows the protein to still come to the RNA but forces it to cut more slowly," Dominski said.

By slowing down the reaction, Dominski had enough time to irreversibly attach the RNA cutting protein, or nuclease, to the RNA itself using ultraviolet light as a cross-linking agent. Once attached to the RNA, the long-sought-after nuclease was trapped, allowing its subsequent identification.

The discovery that the RNA cutting protein is CPSF73 was unexpected. This protein was already connected with processing of a completely different class of messenger RNA, polyadenylated mRNAs. These messenger RNAs serve as blueprints for all proteins other than the

histones. "In terms of evolution, all messenger RNAs appear to be made with the aid of the same protein, CPSF73," Marzluff said. "This suggests that the two mRNA processing mechanisms, for polyadenylated and histone mRNAs, are distantly related."

The authors further demonstrate that CPSF73 not only cuts the histone messenger RNA molecule in two, but also then chews the unneeded portion of the histone mRNA molecule into pieces. It is rare to find two such activities within a single protein, Dominski said.

"From the point of view of understanding biology, our findings provide a unified mechanism for the synthesis of all messenger RNAs," Marzluff said.

UNC School of Medicine technician and co-author Xiao-cui Yang assisted Dominski and Marzluff in this study. Their work was supported by a grant from the National Institutes of Health.

Source: UNC School of Medicine