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DNA Transcription is Tuned to Specific Cells

Researchers have found a new example of how the machinery that controls the transcription of DNA to messenger RNA (mRNA) is tailored to specific cells or genes.

In studies in mice, the researchers discovered that TAFII105, a key component of the transcription machinery, is specific to egg-forming cells in ovaries. The finding emphasizes a newly emerging theme in molecular biology — that DNA transcription is not standardized throughout cells but is instead adapted to control cell-specific gene expression. The scientists believe that future research is likely to reveal other cell-specific transcription components that ensure that genes are expressed in a “customized” way according to the needs of each cell.

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— Robert Tjian

The finding that TAFII105 is specifically involved in controlling genes for egg formation also hints that some inherited forms of sterility in women may be due to mutations in the TAFII105 gene, said the scientists. In an article published in the September 14, 2001, issue of the journal *Science*, Howard Hughes Medical Institute investigator Robert Tjian and colleagues Richard N. Freiman, Shane R. Albright, Shuang Zheng, William C. Sha and Robert E. Hammer detailed how they traced the transcriptional role of TAFII105 to granulosa cells in the ovaries of mice. Granulosa cells surround the developing egg, called the oocyte, and foster its development.

The scientists also used DNA microarrays to explore which genes were switched off in knockout mice that lacked a functional copy of the TAFII105 gene. The TAFII105 protein is one of a family of TAF proteins that are

subunits of a large complex called the transcription factor TFIID.

"When TFIID and all its associated factors were discovered ten years ago, we found it in every cell we looked at," said Tjian, who is at the University of California at Berkeley. "We thought it would be invariant from cell to cell, since it was so fundamental to the cells in transcribing DNA," he said.

"So, when we discovered the TAF family of proteins, we never anticipated that there would be cell-type-specific versions," said Tjian. "But then five years or so after we made the initial discovery, I had an intuition that maybe one of the ways that metazoan [multicellular] organisms have been able to diversify their cell types was to change the transcriptional machinery."

The concept of cell-type variations in transcriptional machinery was considered radical when first proposed, said Tjian. But he believes that evidence in favor of this idea, such as the findings reported by Tjian and his colleagues in *Science*, is strengthening the case.

Tjian and his colleagues concentrated on TAFII105 as a possible cell-type-specific subunit because they had originally discovered it only in B cells of the immune system. Since the protein seemed restricted to B cells, the scientists believed that knocking out the TAFII105 gene in mice would likely not be lethal to the mice, and would enable them to explore the protein's function. When they created the knockout mice, however, they found no effect on the animals' immune system, but noticed that the female knockout mice were invariably sterile.

To pinpoint the reason for the sterility, Tjian's group collaborated with Robert E. Hammer, a mouse reproductive biology expert at the University of Texas Southwestern Medical Center. The researchers found that the defect in the knockout mice affected the granulosa cells that are part of the follicle surrounding developing eggs in the ovaries.

"While that work nailed down the physiological defect in the knockout mice, we really wanted to know which genes TAFII105 was involved in regulating," said Tjian. To do that, Tjian and his colleagues isolated mRNA from both wild-type and knockout mice and used DNA microarrays to compare gene expression in the two types of mice. The researchers treated separate DNA microarrays containing more than 11,000 mouse genes with ovarian mRNA from the two mouse strains, to determine which genes were downregulated in the knockout mice. Downregulation of a gene results in lower levels of mRNA.

"The results turned out to be interesting, because they revealed that the knockout mice had downregulated exactly the kinds of genes one would expect to be required for oocyte formation," said Tjian. "The results enabled us to actually see why knocking out TAFII105 would cause oocytes to be incorrectly developed." The findings offer a clear pathway for further exploring the action of TAFII105, said Tjian.

"We now have a very good idea of which genes we should be studying to understand the details of their transcription machinery and the role of TAFII105," Tjian said. The findings might have clinical implications in identifying the cause of some female sterility. "We suspect that if we work with clinicians to begin examining the genetic identities of the many forms of female sterility in the human population, it's likely we're going to find mutations in TAFII105," he said.

Tjian also emphasized that the lessons learned from TAFII105 offer insight into the complexity of the transcription machinery. "Our work and that of others is revealing a multitude of cell-specific differences in other components of the transcriptional machinery and in different organisms," he said. "So, I believe that the field of transcription is entering a new phase of discovery. While it is true that the transcription machinery is universal in that every cell uses it, evolution has diversified this machinery to perform important specialized functions."