

BY DAVID CAMERON



RNA grabs the driver seat

MicroRNAs found to regulate nearly one-third of human genome

FOR MANY YEARS, DNA and proteins have been viewed as the real movers and shakers in genomic studies, with RNA seen as little more than a messenger that shuttles information between the two. But researchers from Whitehead and the Massachusetts Institute of Technology have discovered that small RNA molecules called microRNAs regulate thousands of human genes—more than a third of the genome’s protein-coding regions.

“It’s exciting to see how many genes are regulated by microRNAs. We now know that this type of gene control is much more widespread than previously appreciated,” says Whitehead Member and MIT professor of biology David Bartel.

MicroRNAs interrupt a gene’s ability to make protein. These tiny, single-stranded pieces of RNA are newcomers to biological research. It wasn’t until 2000 that researchers even knew that microRNAs existed in humans. But recently in the journal *Cell*, Benjamin Lewis, a graduate student working jointly with Whitehead’s Bartel and MIT associate

“As more genome data becomes available and the technology becomes more sophisticated, I think we’ll find even more genes targeted by microRNAs.” —Benjamin Lewis

professor of biology Christopher Burge, provided the first evidence that microRNAs influence a large percentage of life’s functions.

The team developed a computational method to define the relationship between microRNAs and their target genes. In December 2003, the same group identified 400 genes in the human genome targeted by microRNAs. (Prior to this study, there were no known microRNA targets in any vertebrate.)

In their latest paper, the team has compared human genome data with that of the dog, chicken, mouse, and rat. For each of the microRNAs and protein-coding genes that are common to these five species, the team looked for correspondence between the microRNAs and the protein-coding genes.

They discovered that regulation of a third of these genes has been preserved since the last common ancestor of mammals and chickens, which lived 310 million years ago.

“This study is an excellent example of the power of comparative genomics to illuminate how human genes are regulated,” says Burge.

“As more genome data becomes available and the technology becomes more sophisticated, I think we’ll find even more genes targeted by microRNAs,” predicts Lewis.

In addition, the team discovered some hints about how microRNAs find their targets.

To produce a protein, the cell first makes a template for that protein by constructing a molecule called messenger RNA. MicroRNAs associate themselves with particular messenger RNAs, thereby reducing the amount of protein that’s ultimately produced.

In this study, the researchers determined which portion of the microRNA is most important for this process, and identified additional determinants in the messenger RNA that are likely to contribute to recognition by microRNAs.

These findings contribute to the recent interest in potential therapeutic uses of RNA.

For example, using a technique known as RNA interference, or RNAi, researchers are shutting off genes by delivering into cells artificial microRNA-like molecules called short interfering RNAs (siRNAs). RNAi has transformed the way that many labs are investigating gene functions, and siRNAs are being developed for clinical applications (see “Knockout punch” on page 10).

Learning more about how microRNAs operate in human cells should help scientists to understand how best to exploit siRNAs for treating disease.