How Mammals Get the Message

Messenger RNA is a mysterious maverick in mammalian cells

by Joan Arehart-Treichel

So much has been learned about gene expression in bacteria during the past 20 years that some biologists now profess a "molecular biology is dead" philosophy. "Not so!" counter biologists enamored with the conversion of genes into molecules of messenger RNA into proteins, in mammalian cells. The mammalian cell is a thousand times larger than the bacterium and has thousands more genes, messenger RNA molecules and proteins than the bacterium does. What's more, gene expression in mammalian cells is frontier research territory.

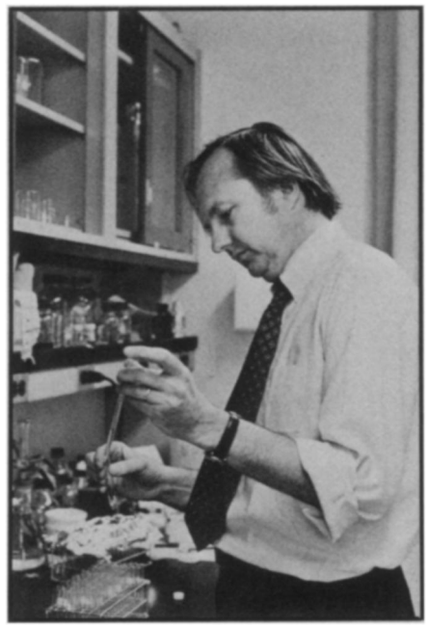
If anything inflames those studying mammalian-gene expression, it is the manufacture of messenger RNA. They're becoming more and more convinced that the manufacture in mammals differs dramatically from the manufacture in bacteria.

In the bacterium, the conversion of a gene (DNA) into a molecule of messenger RNA and then into a protein is immediate and automatic. The reason is that the bacterium has no nucleus and its manufacturing equipment sits cozily together in the cytoplasm. But in the mammalian cell, the process is more than a humdrum assembly line.

Evidence building for a decade suggests that DNA in the nucleus of the mammalian cell makes large RNA molecules. As one of the discoverers recalls, "We had no idea what in the hell the cell was doing to make molecules of such monstrous size." These large nuclear molecules give rise to much, much smaller (some 10 times as small) molecules of messenger RNA. The molecules of messenger RNA are then catapulted from the nucleus of the cell into the cell's cytoplasm, where they hook up with ribosomes and get on with protein production.

Molecular biologists are now tackling the manufacture of messenger RNA molecules from the large nuclear RNA molecules, what properties they share or don't share and why. A property that has them especially intrigued is poly (A)—a string of nucleotides that contains adenylic acid only as its base composition.

Two years ago, for instance, Mary Edmonds of the University of Pittsburgh and some other molecular biologists found that large molecules of RNA and molecules of messenger RNA have the same chemical handle on their right ends (the so-called 3′ ends). The handle is added to each kind of molecule after it is made. Because both kinds of molecules have a poly (A) handle on their right ends, and because the handle is added only after they're transcribed, it appears that messenger RNA molecules might be made from the nucleotides toward the right ends of the large RNA molecules. Now another, shorter poly (A) sequence has been found within large RNA molecules, but not in messenger RNA molecules. And this shorter poly (A) sequence is nowhere near the right (3′) end of the large RNA molecules, Edmonds and her colleagues reported in the January PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.



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Consequently Edmonds does not think that this shorter poly (A) is involved in messenger RNA production. Yet she thinks that it will allow biologists "to map areas of the large RNA molecules." And the ultimate unraveling of the chemistry of the large RNA molecules, of course, should in turn shed light on which parts of the molecules become messenger RNA molecules.

Meanwhile James Darnell and his co-workers at Columbia University are taking a different tack to unravel the large RNA molecules. They've used the large poly (A) handle on the right ends of the large RNA molecules to determine specific nucleotides within the molecules. They reported in the January CELL, the first determination of the location of specific nucleotides in the large RNA molecules that definitely do not become messenger RNA molecules. "The game by and large," Darnell says, "is trying to see who sits next to whom on the line."

Only by identifying all the nucleotides that make up the large RNA molecules, Darnell believes, will scientists then be able to determine which nucleotides become messenger RNA molecules and which, if any, might serve as regulators of messenger RNA production—just as strips of DNA serve as regulators of mRNA production in the bacterium.

While Edmonds, Darnell and other molecular biologists are trying to understand the role of poly (A) in the large RNA molecules and to use poly (A) to unravel the chemistry of the large RNA molecules, George Brauerman of Tufts University School of Medicine and Julio Diez of the Children's Cancer Foundation in Boston are zeroing in on the poly (A) handle on messenger RNA molecules.

Poly (A) appears necessary for the expulsion of messenger RNA molecules from the cell nucleus into the cell cytoplasm. But most provocative, after messenger RNA molecules are ejected, their poly (A) handles deflate to half their size. Now Brauerman and Diez have found that while poly (A) on messenger RNA molecules decreases at the time of ejection, it later mushrooms to full size. "We don't know what it means," Brauerman admits, "but it must mean something since the cell goes to the trouble of cleaving it, then remaking it."

Poly (A) does not seem to be necessary for messenger RNA translation into proteins, Brauerman says, but it may give messenger RNA molecules the shape they need to function. There is evidence that both bacterial and mammalian messenger RNA molecules are not just long chains of nucleotides but chains arranged in elaborate structures.

Obviously more has to be learned about the chemistry of the large RNA molecules and the role of poly (A) in messenger RNA manufacture and function before the reason for the evolution of messenger RNA from the large RNA becomes apparent. Considering how thrifty nature usually is, it's hard to see why mammalian cells make so much RNA, then throw it away. Yet, as a correspondent writes in the February 15 NATURE: ". . . the maturation process may be part of a system for gene control . . . rather than simply a feature of the mechanism of messenger RNA production." □