Catalytic RNA Wins Chemistry Nobel

The discovery of catalytic RNA has changed the very meaning of "enzyme"—and the way people think about the origin of life

THE 1989 NOBEL PRIZE IN CHEMISTRY has gone to Sidney Altman of Yale University and Thomas R. Cech of the University of Colorado, Boulder, for their independent discovery that RNA molecules can act as enzymes.

The award was hailed by molecular biologists and chemists alike as being almost inevitable. By showing that RNA can cut, splice, and assemble itself without outside help, Altman and Cech revolutionized thinking about what it takes to be an enzyme. Before their work, enzymatic catalysis was thought to be the exclusive domain of proteins. But they proved that RNAs can do it, too.

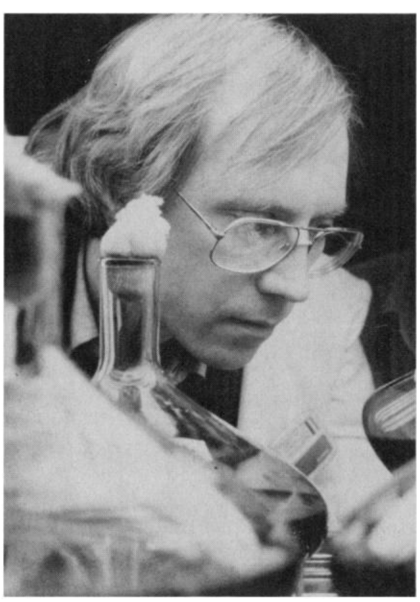
Altman and Cech's discovery also had a major impact on scientists interested in the origin of life. It had long been a mystery whether proteins or nucleic acids came first in the primordial soup. Proteins could be enzymes and catalyze the chemical reactions needed for life, but they could not store genetic information. The reverse was supposed to be true for nucleic acids. But it now seems almost certain that the Earth of 4 billion years ago was an "RNA world," in which RNA molecules carried out all the processes of life without the help of either proteins or DNA.

"I don't think there was any question whether Tom [Cech] would be involved with a Nobel prize soon," says Ohio State University biochemist Philip S. Perlman, whose own work on RNA was directly inspired by Cech's.

"I had no indication it was going to happen although my friends have been telling me to be prepared," says the elated Cech, who last year shared the prestigious Lasker prize for his work.

Cech's key finding came in 1982. He and his colleagues in Colorado had been trying to understand how nonsense sequences, or "introns," are snipped out of RNA molecules after they have been copied from the cell's DNA. The researchers were looking in particular at the RNAs that produce the ribosomes, the cell structures where protein synthesis takes place. Following the conventional wisdom that such RNA editing must be performed by protein enzymes, they isolated pre-ribosomal RNA and then added an extract from the cell nuclei, with the intention of modifying the enzyme content until the RNA editing stopped. The last enzymes out would contain their quarry.

What they actually found, however, was that removing the enzymes didn't make any difference. Something was snipping out the introns at the same rate whether the protein enzymes were there or not. "I said, This can't be right," says Cech. But it was. A careful series of experiments convinced him and his colleagues that the pre-ribosomal RNA was perfectly capable of editing itself: under the right conditions, the intron segment could twist into a convoluted knot, cut itself free, and then bring the ends of the remaining ribosomal RNA together into a perfect splice. "Tom's work was done so convincingly," says Perlman, "that within a few months, everyone was sure it was true."


University of Colorado


Wide World

Removing blinders. *Thomas Cech (left) and Sidney Altman won their Nobel prizes for a new vision of RNA.*

Intriguing as the finding was, however, Cech's self-splicing RNAs were still not full-fledged catalysts. They acted only on themselves, not on other molecules. And since they eliminated themselves in the process, they could undergo the reaction only once. The missing link was supplied a year later by Altman. He and his colleagues at Yale had been trying to understand the editing process in transfer RNA, another piece of the cell's protein-manufacturing machinery. They were focusing on an enzyme known as ribonuclease P, which cleaves off a short length of nonsense material from one end of the transfer RNA precursor. The ribonuclease is an unusual enzyme in that it contains a piece of RNA in addition to a protein. The question for Altman and his group was which component was doing all the work—the protein or the RNA?

In the beginning, at least, the answer seemed to be "Both." But in a series of in vitro experiments published in 1983 and 1984, he and his colleagues demonstrated that all the catalytic activity resides in the RNA subunit; the protein serves only to help that subunit function inside the cell.

That did it. "To see that *just* an RNA molecule could be a catalyst was a breakthrough," says Perlman. "We'd had blinders on to certain types of mechanisms in the cell." Catalytic RNA segments quickly came to be known as "ribozymes," and researchers all over the world rushed to their lab benches to see how widespread they really were.

They turned out to be very widespread indeed. Cech's work had been done with RNAs from an oddball microorganism called *Tetrahymena*, and this had caused skeptics to ask whether the RNA-splicing mechanism that he had discovered might be equally oddball. Yet it was found to be ubiquitous in the energy-producing organelles known as mitochondria, which produce RNA quite independently of the nucleus. And, while nothing has yet been proved about the editing of messenger RNA in the nucleus itself, researchers find it suggestive that RNA can be found in every one of the enzymes that does the work. (These enzymes are known as small nuclear ribonucleoprotein particles—"snurps.") By now, in fact, RNA researchers seem to be coalescing around a new paradigm: that virtually all RNA splicing is done by catalytic RNA, with proteins serving mainly in a structural role.

■ M. MITCHELL WALDROP