The Structure of the "Second Genetic Code"

Molecular biologists are hailing it as a landmark: their first clear look at a key step in the translation of the genetic code

IN THIS WEEK'S SCIENCE, biochemist Thomas A. Steitz and his colleagues at Yale University present an x-ray crystallographic structure that shows for the first time how two of the cell's key molecules interact—an achievement that other researchers are hailing as a "landmark." Says John Abelson of the California Institute of Technology, "It's a spectacularly exciting thing to people in the field."

Indeed it is. The two molecules in question—one a transfer RNA (tRNA) and the other an enzyme called tRNA synthetase—are critical components of the machinery that the cell uses to synthesize proteins. And by showing in detail how these molecules interact, the Yale group has greatly clarified a mystery that has puzzled researchers for some 30 years, ever since that machinery was first discovered.

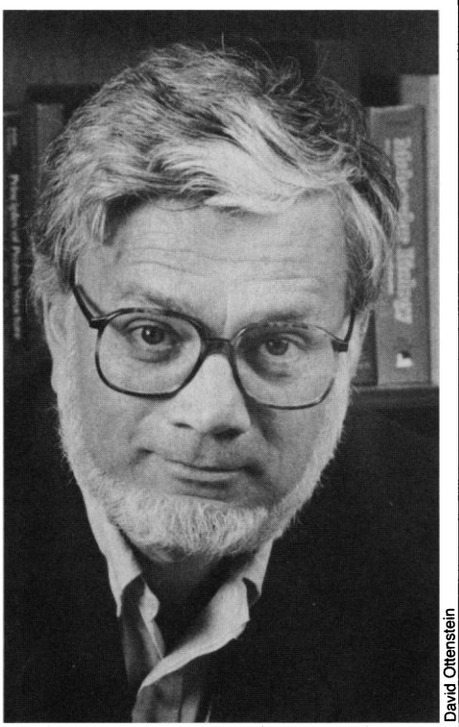
In broad outline, of course, protein synthesis is well understood. First, the genetic information encoded in a stretch of DNA is copied into messenger RNA: a kind of molecular data tape that will direct how amino acids are incorporated into the new protein. Then, a swarm of tRNA molecules brings in the amino acids, lining them up along the messenger RNA so that they can be joined in a specified order.

However, to accomplish that task each tRNA needs its synthetase, which is the enzyme that links it to the correct amino acid. And therein lies the mystery: how do a tRNA and its synthetase recognize each other? There are 20 different synthetases in a living cell, one for each of the 20 amino acids needed to make proteins. There are likewise some 45 to 50 different tRNAs, each corresponding to one or more of the three-nucleotide codewords used by DNA and RNA to specify the amino acid sequences of proteins. And worst of all, every one of those tRNAs looks virtually alike: a sequence of about 75 to 90 nucleotide bases coiled like a tangled garden hose into a crude "L."

So how does a synthetase specializing in the amino acid glutamine make sure that it isn't attaching that molecule to the tRNA for, say, methionine? How does the cell keep from getting its proteins hopelessly scrambled and thus making life impossible?

The Yale group's structure promises to provide some answers. "If there is a dictionary for the genetic code," Abelson says, "it resides here," in this tRNA-synthetase recognition process.

The recognition mechanism itself is sometimes called "the second genetic code"—the first being the set of codewords used by DNA and RNA to direct protein synthesis. But Steitz, for one, finds that phrase misleading at best. The very word "code" makes it sound as though the synthetase were functioning like a supermarket bar code reader, always looking at one particular piece of tRNA structure to see which of the tRNAs it was dealing with.



David Ottenstein

Molecular imager. *Interaction is the key to recognition, says Thomas Steitz.*

"But that's just not correct," he says. The synthetase that he and his colleagues have imaged—both it and the tRNA are specific to the amino acid glutamine in the bacterium *Escherichia coli*—is actually among the simpler ones, consisting of just a single protein. And yet its interactions with the tRNA are startlingly complex, with multiple points of contact all along the inner side of the "L."

It's going to take a long time to sort out which of these interactions are crucial for recognition and which are not, says Steitz. Nonetheless, the images are already yielding some intriguing insights. For example, the tip of the long arm of the tRNA "L" fits snugly into a deep little pocket in the protein. This was not unexpected, says Steitz, because this tip region contains the tRNA's anticodon: a sequence of three bases that recognizes the corresponding codeword on the messenger RNA during the synthesis of a protein. The anticodon was already known to be crucial for recognition of the glutamine tRNA by its synthetase. But the new data shows for the first time that the enzyme interacts mainly with two bases of the anticodon and much less strongly with the third—thus helping to explain how one synthetase can recognize two different glutamine tRNAs, which differ in the third base of the anticodon.

Another striking interaction occurs on the opposite end of the tRNA, where the tip of the short leg of the "L" is inserted into a gaping cavern in the enzyme. This is the active site where the enzyme catalyzes the formation of the link between the amino acid and the tRNA. The Yale group's structure also shows a molecule of adenosine triphosphate bound to the lower surface of the cavern, where it can supply the energy needed to make the linkage.

In any case, Steitz and his colleagues still have plenty to keep them busy for the next few years. How is the amino acid recognized, he asks? Is there an editing step to ensure that the correct amino acid has been attached? Is tRNA recognition completely idiosyncratic? Or are there features that show up in all synthetases?

For example, the cavernous active site, which is known for historical reasons as the dinucleotide fold, appears with minor variations in all synthetases whose structures are known—admittedly a small number—and in a wide variety of other enzymes. "So one of the strong statements you could make about evolution is that the synthetases all had a common precursor containing this structure," Steitz says.

If so, he adds, then this dinucleotide structure must have been deeply involved in a crucial event in evolution, the first associations between tRNA molecules and amino acids. And that means, in turn, that these synthetases are worthy of close study: they bear witness to the origin of the genetic code itself.

■ M. MITCHELL WALDROP