Study reveals key step in protein synthesis

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Scientists at the University of California, Santa Cruz, have trapped the ribosome, a protein-building molecular machine essential to all life, in a key transitional state that has long eluded researchers. Now, for the first time, scientists can see how the ribosome performs the precise mechanical movements needed to translate genetic code into proteins without making mistakes.

"This is something that the whole field has been pursuing for the past decade," said Harry Noller, Sinsheimer Professor of Molecular Biology at UC Santa Cruz. "We've trapped the ribosome in the middle of its movement during translocation, which is the most interesting, profound, and complex thing the ribosome does."

Understanding ribosomes is important not only because of their crucial role as the protein factories of all living cells, but also because many antibiotics work by targeting bacterial ribosomes. Research on ribosomes by Noller and others has led to the development of novel antibiotics that hold promise for use against drug-resistant bacteria.

Noller's lab is known for its pioneering work to elucidate the atomic structure of the ribosome, which is made of long chains of RNA and proteins interlaced together in complicated foldings. Using x-ray crystallography, his group has shown the ribosome in different conformations as it interacts with other molecules. The new study, led by postdoctoral researcher Jie Zhou, is published in the June 28 issue of *Science*.

To make a new protein, the genetic instructions are first copied from the DNA sequence of a gene to a messenger RNA molecule. The ribosome then "reads" the sequence on the messenger RNA, matching each three-letter "codon" of genetic code with a specific protein building block, one of 20 amino acids. In this way, the ribosome builds a protein molecule with the exact sequence of amino acids specified by the gene. The matching of codons to amino acids is done via transfer RNA molecules, each of which carries a specific amino acid to the ribosome and lines it up with the matching codon on the messenger RNA.

"The big question has been to understand how messenger RNA and transfer RNA are moved synchronously through the ribosome as the messenger RNA is translated into protein," Noller said. "The transfer RNAs are large macromolecules, and the ribosome has moving parts that enable it to move them through quickly and accurately at a rate of 20 per second."

The key step, called translocation, occurs after the bond is formed joining a new amino acid to the growing protein chain. The transfer RNA then leaves that amino acid behind and moves to the next site on the ribosome, along with a synchronous movement of the messenger RNA to bring the next codon and its associated amino acid into position for bond formation. The new study shows the ribosome in the midst of a key step in this process.

"This gives us snapshots of the intermediate state in the movement," Noller said. "We can now see how the ribosome does this with a rotational movement of the small subunit, and we can see what look to be the 'pawls' of a ratcheting mechanism that prevents slippage of the translational reading frame."

Many antibiotics interfere with the function of the bacterial ribosome by preventing or retarding this translocational movement. Understanding

the structural and dynamic details of this movement could help researchers design new antibiotics.

Translocation involves two steps (as Noller's lab showed back in 1989). Step one is the movement of the tRNA's "acceptor end" (where it carried the amino acid). This leads to a hybrid state, with the two ends of the tRNA in two different sites on the ribosome: the "anticodon end" is still lined up with the matching mRNA codon in one site, while the acceptor end has moved on to the next site. Step two is the movement of the tRNA's anticodon end together with the messenger RNA, which advances by one codon. Step two requires a catalyst called elongation factor G (EF-G). The new study shows the ribosome in the middle of step two, with EF-G bound to it and the tRNA halfway between the hybrid state and the final state.

Noller has spent decades working to understand how the ribosome works. Being able to see how it moves, he said, is an exciting moment.

"This is one of the most fundamental movements in all of biology, at the root of the whole mechanism for translation of the genetic code, and we now understand it all the way down to the molecular level," Noller said. "This mechanism had to be in place around the origin of life as we know it."

Provided by University of California - Santa Cruz