Dankesrede

von

Prof. Dr. Harry Noller

anlässlich der Verleihung
des Paul Ehrlich- und Ludwig Darmstaedter-Preises
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Es gilt das gesprochene Wort!

Studies on the Structure of the Ribosome and the Molecular Basis of Protein Synthesis

2007 Paul Ehrlich and Ludwig Darmstaedter Prize Acceptance Speech

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On behalf of all of the many talented students and postdoctoral researchers who have worked with me in my laboratory at Santa Cruz over nearly four decades, it is indeed a great honor for our work to be recognized by the 2007 Paul Ehrlich-Ludwig Darmstaedter Prize. I first heard the name Paul Ehrlich in Sanford Ellberg's immunology course as an undergraduate at Berkeley. Whenever Professor Ellberg pronounced the name "Paul Ehrlich", it was in a special tone of voice that was distinct from the way in which he mentioned the other famous scientific names. In this way, he was informing us that Ehrlich's contributions were important landmarks in a field that was otherwise still a very confused and murky one. It is therefore a special honor to have our work associated with his name. With your indulgence, I would like to take this opportunity to tell you a little about the path that took us to the work that is being honored.

The ribosome, as you may know, is the molecular factory that is responsible for making proteins in all living things. Unlike almost all other such sub-cellular structures, it is made up not only of protein, but also of RNA, which comprises about two-thirds of its mass. The presence of RNA in the ribosome was a puzzle, because RNA was believed to be used mainly as an informational molecule, messenger RNA (or mRNA) or as transfer RNA, a class of small RNA that is used to read the mRNA. The idea that ribosomal RNA was some kind of messenger RNA appeared to be unlikely, and so it was concluded that its purpose was to form a molecular scaffold for holding the ribosomal proteins in place. When I began my research as a beginning assistant professor at UC, Santa Cruz in the late 1960s, I considered myself a protein chemist who worked on enzymes. Since ribosomes are enzymes of a sort, my goal was to identify one or two of the more than fifty proteins present in the ribosome, and study their biological functions in protein synthesis. Our initial approach was to treat the ribosome with specific chemicals that we expected would modify its proteins, causing loss of function. We would then identify the proteins that were associated with loss of specific functions, and study them in detail.

To our surprise, modification of the ribosomal proteins didn't have much of an effect on the ability of the ribosome to synthesize protein. But when we decided to test the effects of modifying the ribosomal RNA, we immediately observed inactivation of the ribosome. Further experiments ruled out the possibility that we were simply causing gross structural damage, and suggested that we were actually hitting functional sites in

the RNA. Although we were able to publish our work, the reaction of the scientific community at that time is best characterized by the comment of a prominent Berkeley scientist, which was related to me by a colleague: “What a crackpot idea!”

Nevertheless, we pursued the idea that the ribosomal RNAs were functional, and not merely scaffolds for proteins. Work by a brilliant graduate student, Danesh Moazed (now a professor at Harvard), showed that all of the functional molecules that interact with the ribosome, including even the antibiotics that target bacterial ribsosomes, interact with its RNA. We also found that we could remove almost all of the ribosomal proteins without affecting the enzymatic activity of the ribosome, suggesting that the ribosome was an RNA enzyme. In the course of these studies, we determined the first complete nucleotide sequences of the ribosomal RNAs, thanks mainly to the efforts of a postdoctoral researcher Jürgen Brosius, (now a professor in Münster), and found that the putative RNA functional sites that we had identified were astonishingly conserved: There were nucleotide sequences in ribosomal RNA that were identical in bacteria, plants and humans. This meant that these parts of the ribosome were unchanged over more than 3 billion years of evolution!

Determining the nucleotide sequences of the ribosomal RNAs led us into determining how they fold in three dimensions. In collaboration with Carl Woese at the University of Illinois, we figured out the base pairing, or “secondary structure” of the large ribosomal RNAs, a first step toward determining their complete three-dimensional structures. Eventually, we decided to attempt to solve the structure of the complete ribosome by x-ray crystallography. This was a very challenging undertaking, for several reasons. First, I myself had never done any x-ray crystallography, a very difficult and specialized area of biophysics. Second, no one had ever solved an asymmetric structure anywhere near the size of the ribosome, which is about one hundred times larger than typical protein structures that x-ray crystallographers were studying. Third, and equally daunting, no one had ever obtained crystals of complete ribosomes that would be useful for structure determination.

Solving the structure was made possible by the combined efforts of Marat Yusupov and Gulnara Yusupova, two Russian scientists (now at the CNRS, Strasbourg) who discovered a new crystal form of the ribosome not long after arriving in Santa Cruz, and Jamie Cate (now a professor at UC Berkeley), an exceptional young x-ray crystallographer who was able to solve the structure of the complete ribosome from the diffraction data that we collected from the Yusupovs’ crystals. Information from our earlier studies on the proteins and RNA were indispensable in fitting the final structure of the ribosome to the electron density map obtained by crystallography. Meanwhile, the structures of the ribosomal subunits were being solved in the laboratories of Ada Yonath, Venki Ramakrishnan, Tom Steitz and Peter Moore at higher resolution; these detailed structures allowed us to trace the chains of the RNA and protein molecules for the complete ribosome in three dimensions. Our structure showed not only the ribosome but how three different transfer RNAs and a messenger RNA bound to the ribosome. During the past year, using new crystals obtained by Sergei Trakhanov in our laboratory, Andrei Korostelev and Martin Lauerberg were able to solve the structure of a ribosome functional complex at increased resolution, allowing us to deduce its complete atomic structure. (As is often the case, a similar structure was solved at almost exactly the same time, by Ramakrishnan’s group.)

What have we learned about this ancient biological structure after so many years? First, our “crackpot idea” from 35 years ago, that the ribosomal RNA is the functional heart of the ribosome, has turned out to be correct. The crystal structures convincingly show that the functional sites in the ribosome are made mainly of RNA, while the ribosomal proteins appear to exist to help the RNA, rather than the other way round. Second, we can now see in great molecular detail how RNA does its jobs, and even have some suggestions as to why these jobs are not carried out by ribosomal proteins. Third, we see for the first time how antibiotics cure infectious diseases by their interactions with bacterial ribosomes, bringing us full circle back to Paul Ehrlich. In fact, the structure of the ribosome is now being used to attempt to design new antibiotics that can overcome the resistance that many pathogenic organisms have developed toward existing drugs. And finally, we now understand that the ribosome is really a molecular machine, with moving parts that enable it to carry out the many steps of protein synthesis. We are now attempting to answer the next big questions, by devising approaches to directly observe molecular movements of the ribosome in three dimensions. These challenging problems should keep us occupied for some time to come.