Atomic-resolution structure of a ribozyme yields insights into RNA catalysis and the origins of life

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Which came first, nucleic acids or proteins? This question is molecular biology's version of the "chicken-or-the-egg" riddle. Genes made of nucleic acids (DNA or RNA) contain the instructions for making proteins, but enzymes made of proteins are needed to replicate genes. For those who try to understand how life originated, this once seemed an intractable paradox.

The solution came with the discovery 20 years ago that certain types of RNA can act as enzymes, catalyzing reactions just as enzymes made of protein do. This means, in principle, that a single type of molecule, RNA, might be able to both encode information and replicate it. The idea that the first self-replicating molecules in a pre-biotic primordial soup were composed of RNA, known as the "RNA World" hypothesis, is one of the central tenets upon which many theories of the origin of life are now based.

Research on the structure and function of RNA enzymes, or ribozymes, has been one of the main activities in the Center for the Molecular Biology of RNA at the University of California, Santa Cruz, as well as many other laboratories throughout the world. In addition to offering glimpses into how life may have originated, ribozymes are also being engineered in many academic and industrial laboratories to be therapeutic agents for potential use in fighting infectious and chronic diseases.

Scientists at UCSC's RNA Center have now obtained a near-atomic resolution image of the three-dimensional shape of a very simple--and therefore potentially understandable--ribozyme in which the atoms are uniquely arranged and poised for catalysis in the context of an intricately twisted and folded segment of RNA. The new findings are described in a paper by graduate student Monika Martick and her adviser, William Scott, associate professor of chemistry and biochemistry, in the July 27 issue of the journal *Cell*. The paper will be available online on July 20.

Using the technique of macromolecular x-ray crystallography, Martick and Scott were able to obtain a three-dimensional picture of the spatial arrangement of the several thousand atoms that comprise the ribozyme, known as the hammerhead ribozyme. The resulting color-coded structure was recently featured on the cover of the abstract book for the annual meeting of the RNA Society held in Seattle in early June.

"The structure illustrates unambiguously how functional groups of the RNA mediate acid-base chemical catalysis, permitting us to suggest that acid-base chemistry is so fundamental to enzyme catalysis that it predates the origin of protein enzymes," Scott said.

For Scott, these results are the culmination of 19 years of research on the structure of the hammerhead ribozyme. He started work on the project as a graduate student at UC Berkeley in 1987, a few months after the ribozyme was discovered. Later, as a postdoctoral researcher at the MRC Laboratory of Molecular Biology in Cambridge, England, he achieved his first breakthrough.

Scott subsequently built an internationally-recognized research team at UCSC that has performed static and time-resolved experiments resulting in the first crystallographic time-lapse "movie" of ribozyme catalysis. His group has also elucidated structures of other RNAs, including the recent structure of a highly conserved motif from the SARS virus genome.

Scott's structural observations of the hammerhead ribozyme, however, could not explain a growing number of biochemical experimental results. The hammerhead ribozyme has been the subject of intensive investigations by researchers around the world, and Scott found his most cherished accomplishments called into question.

"In 2002, I had two very lucky breaks," he said. "The first was that I learned of a new form of this ribozyme that was 1,000 times faster than the most widely studied form. The second was that an exceptionally talented graduate student, Monika Martick, joined my research group."

The faster form includes an extended sequence of RNA building blocks that researchers had previously neglected to study. Martick and Scott set to work on this newly discovered form of the ribozyme, achieving a breakthrough in March after four years of experiments.

"Monika e-mailed me from the Stanford Synchrotron at 3 a.m. to show me the most beautiful electron density map I had ever seen," Scott said. "I was so amazed I probably didn't sleep for the next three weeks."

The new results explained the earlier discrepancies in a way that reconciled them with the previous 11 years of Scott's experiments, he said.

"Seldom do scientific research projects have this sort of fairy tale ending. It has been extremely rewarding as well as humbling," Scott said.

The RNA Center at UCSC was immensely helpful, providing support that was instrumental to the group's success, he added. Harry Noller, Sinsheimer Professor of Molecular Biology and director of the RNA Center, has assembled a world-class team of investigators that includes two members of the National Academy of Sciences and two Howard Hughes Medical Institute investigators.

"It is very inspiring to work with this collective concentration of talent," Scott said.

Source: University of California - Santa Cruz