

NLS Users Help Decode RNA

Working at the National Synchrotron Light Source (NSLS), scientists from Yale University have determined the crystal structure of a section of ribonucleic acid (RNA), the molecule in cells that uses the information contained in deoxyribonucleic acid (DNA) to synthesize proteins. The work, described in the July 1, 2004 issue of *Nature*, illuminates a piece of RNA never seen before, and may lead to many discoveries, ranging from new information on how proteins behave to new ways to prevent or treat genetic disorders.



Scott Strobel

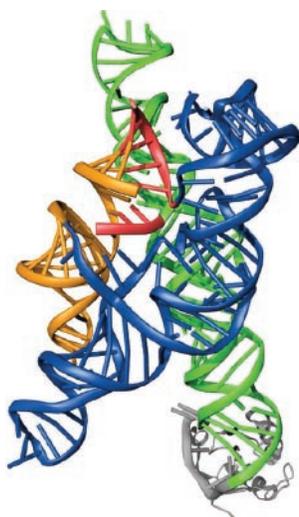
“The structure contains a number of features that have not been seen before in any structurally-determined macromolecule,” said Scott Strobel, the lead author of the paper. “This is very exciting, since there is substantially less known about RNA than protein.”

The structure contains an RNA segment called an “intron” flanked by two additional segments called “exons.” Exons are the information-carrying pieces of RNA, while introns do not carry information. The process of putting exons together and removing introns is called RNA splicing, and it is a process performed on almost all RNA molecules before they are used by cells.

Until now, however, knowledge of how splicing occurs, and what the splicing site looks like, was limited. Usually, RNA splicing is performed by a large RNA-protein complex called the spliceosome, but, in some RNA molecules, the introns can self-splice by removing themselves without the help of proteins. Strobel and his group crystallized an RNA molecule of this type to learn more about the splicing process.

“We determined the crystal structure of one of these self-splicing introns that includes both of the exons that are about to be joined, or ligated, together,” Strobel said. “This configuration displays a splicing intermediate step, where one of the exons has been severed from the intron and is about to be ligated to the second exon, which results in the release of the intron.”

Self-splicing, essentially a chemical reaction in which the intron is the catalyst, is the same reaction as that catalyzed by the spliceosome. Although self-splicing involves a much simpler mechanism than that carried out by the spliceosome, this self-splicing “snapshot” is useful because it is likely to reveal how the spliceosome removes introns during exon ligation. This, in turn, may have implications for human health and medicine, since splicing defects are responsible for many genetic disorders.



The crystal structure of the RNA section, with the exons (red) attached to the intron (orange, blue, and green). The intron catalyzes a reaction in which the red segments are joined together and the blue segment is released.

Using the structure, Strobel and his colleagues were also able to closely study the splicing site, or “active” site. They discovered that the site contains two metal ions, whose role is to promote the splicing reaction. This is very similar to the metal ions found within the active sites of the protein enzymes that catalyze the formation of RNA and DNA chains. Thus, studying the behavior of these ions may explain how these protein enzymes “learned” to perform their function.

The RNA structure was determined at NSLS beamline X25 using a technique called macromolecular crystallography, which uses intense x-rays to “see” the molecular structure of different materials. The x-rays are scattered, or diffracted, by atoms in the crystal, forming a unique pattern on a detector screen when they emerge from the sample. By analyzing this pattern, the researchers were able to determine the location of each atom in their RNA crystal.

Strobel and his group plan to continue their research by investigating how the metal ions in the active site promote the splicing reaction. They would also like to learn more about how the intron is rearranged during splicing. This research was funded by the National Science Foundation and the National Institutes of Health.

—Laura Mgrdichian