Yale scientists visualize the machinery of mRNA splicing

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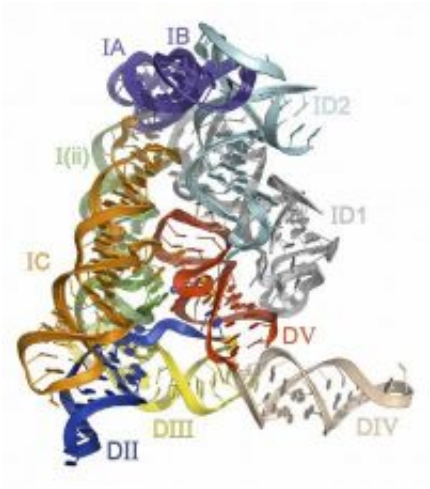

Ribbon reconstruction view of the crystal structure of an RNA group II intron -- red domain is the active site. Credit: Pyle / Yale

Recent research at Yale provided a glimpse of the ancient mechanism that helped diversify our genomes; it illuminated a relationship between gene processing in humans and the most primitive organisms by creating the first crystal structure of a crucial self-splicing region of RNA.

Genes of higher organisms code for production of proteins through intermediary RNA molecules. But, after transcription from the DNA, these RNAs must be cut into pieces and patched together before they are ready for translation into protein. Stretches of the RNA sequence that code for protein are kept, and the intervening sequences, or introns, are

spliced out of the transcript.

This work, published in *Science*, highlights a 16-year quest by Anna Marie Pyle, the William Edward Gilbert Professor of Molecular Biophysics & Biochemistry at Yale, and her research team into the nature of "group II" introns, a particular type of intron within gene transcripts that catalyzes its own removal during the maturation of RNA.

Group II introns are found throughout nature, in all forms of living organisms. Although much has been learned about their structure and how they work through biochemical and computational analysis, until now there have been no high-resolution crystal structures available. The resulting images have provided both confirmation of the earlier work and new information on the three-dimensional structure of RNA and the mechanism of splicing.

"One of the most exciting aspects of this work was that we did not need to do anything disruptive to these molecules to prepare them for structural analysis," said Pyle. "The molecules showed us their structure, their active site and their activity — all in a natural state. We were even able to visualize their associated ions."

According to Pyle, the crystal structure revealed some unexpected features — showing two sections that were most implicated as key elements of the active site and strengthening a theory that the process of splicing in humans "shares a close evolutionary heritage" with ancient forms of bacteria.

Looking to future applications of the work, Pyle said, "Group II introns hold promise in the future as agents of gene therapy. A free intron is an infectious element that is special because it targets DNA sites very specifically. We hope that further knowledge of these structures may lead to the development of new genetic tools and therapeutics."

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