

The spliceosome: Scientists are unraveling the secrets of the mechanism that snips our genes

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The single-molecule fluorescence microscope can view individual molecules.
Credit: Diana Hunt

Certain diseases such as cystic fibrosis and muscular dystrophy are linked to genetic mutations that damage the important biological process of rearranging gene sequences in pre-messenger RNA, a procedure called RNA splicing.

These conditions are difficult to prevent because scientists are still grasping to understand how the splicing process works. Now, researchers from Brandeis University and the University of Massachusetts Medical

School have teamed up to unravel a major component in understanding the process of RNA splicing.

In a recent paper published in *Cell*, research specialist Inna Shcherbakova of Brandeis and UMMS, and a team of researchers led by professors Jeff Gelles (Brandeis) and Melissa J. Moore (UMMS), explain how the molecular machine known as the [spliceosome](#) begins the process of rearranging [gene sequences](#).

In order to convey instructions for synthesizing protein to the ribosome, RNA—a transcribed copy of DNA—must be translated into mRNA. Part of the process of translating pre-messenger RNA into mRNA involves cutting out [gene segments](#) that don't contain information relevant to [protein synthesis](#), called introns, and connecting the remaining pieces together.

The spliceosome does the genetic cutting and pasting. It is a complicated complex, made up of four major parts and more than 100 accessory proteins that come together and break apart throughout the splicing process. Think of the spliceosome as an old Transformers robot—it has individual pieces that operate independently but can also come together to form a larger structure.

Sometimes, such as in the case of [cystic fibrosis](#), a mutation will cause the spliceosome to snip in the wrong place, cutting out important sequences instead of introns, and resulting in the production of a [faulty protein](#).

In studying the Transformer-like spliceosome, researchers have been unable to reconcile how the different components of the complex coordinate. To initiate the splicing process, two pieces of the spliceosome bind to the two ends of an intron. Until now, scientists believed this to be highly ordered process: first Part 1 bound, and then it

would somehow tell Part 2 to attach.

In a highly ordered process in primitive organisms such as yeast, the introns are small and it's easy for Part 1 and Part 2 to communicate. But how would that process work in humans, where introns are made up of thousands of nucleotides? How could the two parts—which jumpstart the whole splicing process—communicate?

To find out, Shcherbakova aimed a single-molecule fluorescence microscope built in the Gelles lab at the spliceosome. By tagging the different parts of the complex with fluorescent colors, the team discovered that the process is more flexible than scientists imagined.

The two first major components of the spliceosome do not need to communicate with one another to start the splicing process, nor does it matter which piece attaches to the gene first. Either of the components, called U1 and U2, can attach first and the process works equally well.

"The process is much more sensible than we originally thought," Gelles says.

Now that scientists understand how the major components of splicing can come together, they can study how the different steps of the process are orchestrated.

"We are just scratching the surface in understanding this process, but ultimately, we hope to understand how this process goes wrong and how it can be fixed," Gelles says.

Provided by Brandeis University

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