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New research shows how cells control splicing, the process of removing extra pieces of RNA

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Before living organisms can use the genetic instructions encoded in DNA, they must first transcribe genes into RNA, which carry instructions for building proteins that will carry out the work to be done in a cell. But the process isn't straightforward. Frequently, pieces of RNA need to be removed along the way, a process called splicing.

Jonathan Staley, PhD, professor and chair of the Department of Molecular Genetics and Cell Biology at the University of Chicago, just published a new study in the journal *Genes & Development* that delves more into how the splicing process works. We spoke to him about what he and his colleagues discovered.

Can you describe splicing and how it's involved in the process of gene expression?

Splicing is an intermediate step in the process when our genes are decoded into proteins, the workhorses of the cell. In this process, the DNA of our genes are transcribed into "messenger" RNA, a molecule similar to DNA that serves as the blueprint for constructing proteins. However, before messenger RNA can be used to build proteins, some segments of the message, called introns, must be removed. Although introns have been described as junk, they can be removed from a single RNA strand in different ways to modify the blueprint and the resulting protein, with consequences of differing function in the cell. Changes in splicing patterns allow organisms to adapt as they grow and respond to their environments. Mistakes in splicing also underlie numerous diseases.

How does splicing work?

A kind of molecular machine called the spliceosome actually cuts out the introns. It's similar to the ribosome, the machinery that decodes messenger RNA to make proteins, because it's built from both protein components as well as functional, non-coding RNA molecules that play a role distinct from messaging. It's actually an RNA component of the spliceosome, rather than a protein part, that accelerates the splicing reaction so that it occurs on a timescale that is relevant to the cell. This RNA component, named U6, resembles an ancient self-splicing intron that may have emerged from the RNA world during the origin of life. The spliceosome has to be dismantled, or turned off, to release the excised intron and begin subsequent rounds of splicing. The spliceosome can also be shut down prematurely to make sure only correct messages are read by the ribosome to make proteins.

What were you looking to learn about splicing in the new study?

We have known for some time that splicing is turned off by one of a large family of RNA helicases, which are energy-consuming proteins that move along RNA like trains on a track. They can displace items bound to this RNA "track," just as a cow-catcher functions on a train. We know that an RNA helicase called Prp43 terminates splicing, but we have not known what RNA it moves along to terminate splicing. Identifying the RNA that this helicase interacts with is critical to understanding the mechanism and regulation of splicing termination.

What were the key findings of the study?

We saw that Prp43 terminates splicing by acting on the tail of the U6 RNA, indicating that spliceosome termination starts by disassembling the catalytic core itself. Secondly, our data imply a model in which Prp43 simply pulls on the tail of U6, thereby building up tension on the catalytic core

and ultimately disrupting it from a distance. This mechanism for “turning off” the spliceosome is significant because the tail of U6 is protected until the spliceosome is turned on, so at the same time the spliceosome turns on it also becomes primed to turn off, implying a need for tight control of splicing activity in the cell.

What does this tell you about the machinery involved in RNA splicing?

Curiously, this RNA helicase not only helps in the production of messenger RNA for translation into proteins but also helps in the synthesis for the ribosome, the machinery that executes translation. That links the production of the translation substrate with the translation catalyst. This work will provide insight into how this RNA helicase promotes ribosome synthesis and more broadly how many RNA helicases function to trigger rearrangements at all stages of gene expression.

For full activity though, Prp43 needs help in the form of an activator that binds to Prp43 and helps propel it along RNA. Two of these activators have been linked to cancers such as breast cancer. Our insight into how this works provides a potential pathway for interrupting the activity of such activators.

The study, “Termination of pre-mRNA splicing requires that the ATPase and RNA unwindase Prp43p acts on the catalytic snRNA U6,” was supported by the National Institutes of Health. Additional authors include Rebecca Toroney and Klaus H. Nielsen from the University of Chicago.

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