Engineers devise genetic 'on' switch made exclusively of RNA

February 2 2015

All life processes depend on genes turning on and off. Cornell University scientists have created a new "on" switch to control gene expression - a breakthrough that could revolutionize genetic engineering.

Synthetic biologists led by Julius Lucks, assistant professor of chemical and biomolecular engineering, have created a new genetic control mechanism made exclusively of ribonucleic acids (RNA). They call their engineered RNAs STARS - Small Transcription Activating RNAs - described online in *Nature Chemical Biology*, Feb. 2.

"We've created a whole new toolset of regulation," said Lucks, who describes RNA as "the most engineerable molecule on the planet."

RNA is a single-stranded version of its close cousin, DNA, which makes up the double-stranded genome of all living organisms. While DNA acts as nature's hard drive, storing the genes that make up our genome, RNA is part of the cellular computer that activates the hard drive by helping the cell tune the expression of specific genes, Lucks says. While RNA is known to do this in many ways, one thing it can't do in nature is start the process by turning on, or activating, transcription - the first step in gene expression, and the core of many cellular programs.

In the lab, Lucks and colleagues have assigned RNA this new role. They've engineered an RNA system that acts like a genetic switch, in which RNA tells the cell to activate the transcription of a specific gene. The STAR system involves placing a special RNA sequence upstream of

a target gene that acts as a blockade and prevents the cell from transcribing that gene. When the STAR is present, it removes this blockade, turning on the downstream gene by allowing transcription to take place. The effect is like a lock-and-key system for turning genes on, with STARs acting as a set of genetic keys for unlocking cellular genetic programs.

"RNA is like a molecular puzzle, a crazy Rubik's cube that has to be unlocked in order to do different things," Lucks said. "We've figured out how to design another RNA that unlocks part of that puzzle. The STAR is the key to that lock."

RNA is Lucks' favorite molecule because it's simple - much simpler than a protein - and its function can be engineered by designing its structure. In fact, new experimental and computational technologies, some developed by Lucks' lab, are now giving quick access to their structures and functions, enabling a new era of biomolecular design that is much more difficult to do with proteins.

Lucks envisions RNA-only, LEGO-like genetic circuits that can act as cellular computers. RNA-engineered gene networks could also offer diagnostic capabilities, as similar RNA circuits have been shown to activate a gene only if, for example, a certain virus is present.

"This is going to open up a whole set of possibilities for us, because RNA molecules make decisions and compute information really well, and they detect things really well," Lucks said.

More information: Creating Small Transcription Activating RNAs, DOI: 10.1038/nchembio.1737

Provided by Cornell University