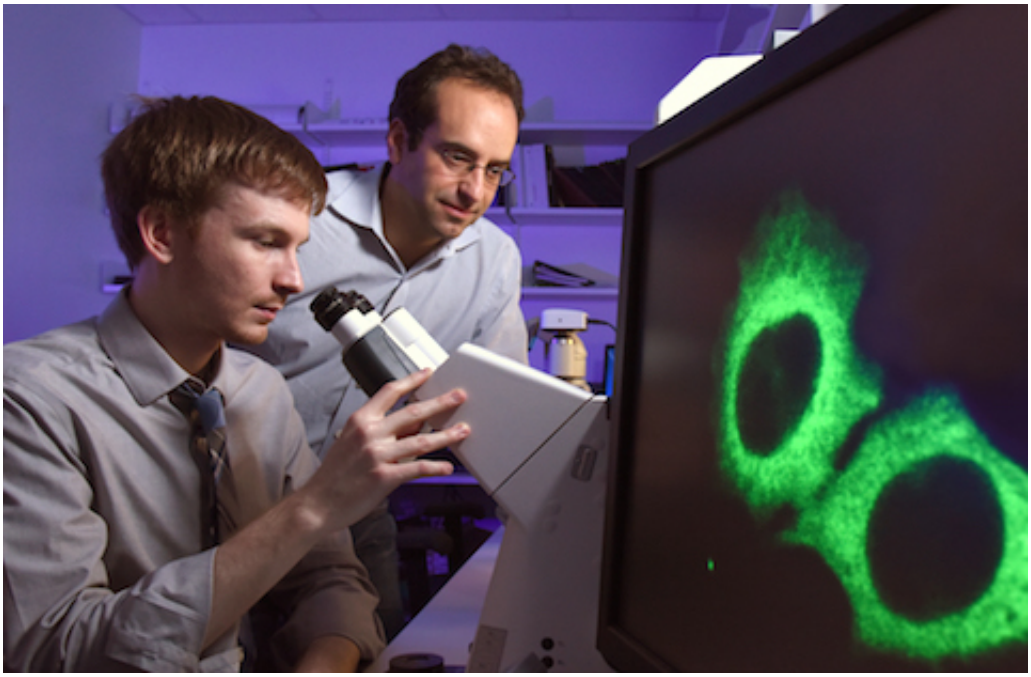
Medical Xpress

Choreographing the microRNA-target dance

January 23 2017



Ryan Golden (left) and Dr. Joshua Mendell (right) uncovered a new mechanism that allows microRNAs to engage target messenger RNAs, silence them, and then efficiently move on to the next target. The microRNA pathway is critically important to health and disease, serving as a kind of volume control for genes. Credit: UT Southwestern Medical Center

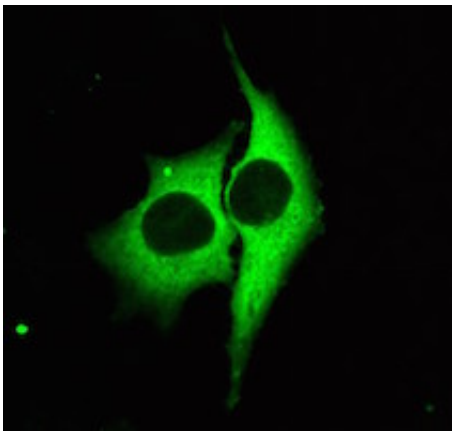
Scientists face a conundrum in their quest to understand how microRNAs regulate genes and therefore how they influence human disease at the molecular level: How do these tiny RNA molecules find their partners, called messenger RNAs, on a crowded cellular dancefloor?

MicroRNAs pair up with messenger RNAs to turn down the production of proteins. But there are far more of the messenger RNAs in the crowd, leaving scientists to ponder how the microRNAs can efficiently regulate a large excess of messenger RNA partners.

Molecular biologists at UT Southwestern Medical Center were able to uncover a new mechanism that choreographs this complex molecular dance by applying the latest in gene editing technology combined with a traditional method of making a microRNA target produce a fluorescent green protein. The successful "dance move" - called Argonaute phosphorylation - enables a microRNA to switch messenger RNA dance partners more efficiently.

"Our research addresses a fundamental question regarding how a microRNA is able to regulate a large set of target messenger RNAs, even though the microRNA is greatly outnumbered," said Dr. Joshua Mendell, Professor of Molecular Biology and a Howard Hughes Medical Institute Investigator at UT Southwestern.

The microRNA pathway is critically important to health and disease, serving as a kind of volume control for genes, dialing down the expression of specific proteins, said Dr. Mendell, a CPRIT Scholar in Cancer Research. UTSW researchers have previously found, for example, that defects in the microRNA pathway contribute to certain childhood cancers and specific microRNAs can accelerate or inhibit cancer by regulating tumor suppressor or tumor promoting genes. MicroRNAs play important roles in many other diseases including heart disease.



Glowing cells express green fluorescent protein, which scientists used along with gene-editing techniques to uncover a new microRNA mechanism. Credit: UT Southwestern Medical Center

CRISPR gene editing technology allowed the scientists to switch off a different gene in each cell across millions of cells. Cells became more fluorescent when genes that impacted the microRNA pathway were switched off, leading scientists to the discovery of the new phosphorylation mechanism involved in controlling microRNA-target interactions.

"This research uncovered a new and fundamental aspect of the microRNA pathway in which phosphate molecules are rapidly added and removed from key proteins in the pathway. We believe this mechanism allows microRNAs to engage target messenger RNAs, silence them, and then efficiently move on to the next target," said first author Ryan Golden a student in the Medical Scientist Training Program at UT Southwestern and a member of the Mendell lab.

In addition to shedding new light on the microRNA pathway, researchers say the distinctive combination of techniques used to decipher the pathway should be widely applicable to other biological questions,

allowing labs to quickly identify critical components of important genetic pathways.

"This study represents the first time this experimental strategy has been used to study the microRNA pathway on a genome-wide scale. It is a very powerful approach. This work lays out a methodology that could be used to study many different biomedical problems," said Dr. Mendell, a member of the Harold C. Simmons Comprehensive Cancer Center.

The work is published in the journal *Nature*.

More information: An Argonaute phosphorylation cycle promotes microRNA-mediated silencing, nature.com/articles/doi:10.1038/nature21025

Provided by UT Southwestern Medical Center