Argonautes: A big turn-off for proteins

February 1 2010

Johns Hopkins scientists believe they may have figured out how genetic snippets called microRNAs are able to shut down the production of some proteins.

The issue, they say, is important because the more scientists know about how genes — the blueprints for proteins — are regulated, the more likely they are to figure out how to use that information in treating or preventing diseases linked to such regulation, including cancer.

In both computer and test-tube studies using fruit-fly protein, the Johns Hopkins researchers intensively studied a fairly large protein called Argonaute because it is known to bind to microRNA and ultimately shut down protein production.

"The question was how it did it," says Rachel Green, Ph.D., a Howard Hughes Medical Institute investigator and professor of molecular biology and genetics in the Johns Hopkins University School of Medicine.

Previous studies have been inconclusive about the mechanism by which microRNAs bound to Argonautes prevent the production of protein from a given gene.

In this study, the team discovered that when an Argonaute binds to a microRNA, it then binds more tightly to a messenger RNA thereby sequestering the message from the translation machine known as the ribosome where protein production happens.

Their research appeared in January in *Nature Structural & Molecular Biology*.

The team set out to characterize Argonautes first using computers to compare their shapes and structures with other proteins. They found striking similarities between Argonaute structures and proteins that happened to exhibit a particular kind of "cooperative binding" known as allostery.

Allostery is a condition in which the binding of one molecule stimulates the binding of a second.

By chopping up Argonaute proteins from fruit flies and testing each piece individually, the team showed that allostery stimulated tenfold the binding of the Argonaute and miRNA complex to messenger RNA.

The scientists speculate that as a result of being bound, the messenger RNA was prevented from doing its job of delivering a gene's instructions to the ribosome that translates them and manufactures proteins. These studies provide new insights into Argonaute protein function, motivating the next series of questions in the field.

"MicroRNAs are all the rage," Green says. "Suddenly, in the last 10 years, there's this whole set of genes and cellular components that we had no idea existed, and they're ubiquitous. They play roles in all manner of development, and Argonautes are the main class of protein involved in regulating them."

More information: www.nature.com/nsmb/index.html

Provided by Johns Hopkins Medical Institutions