Researchers discover how microRNAs control protein synthesis

July 9 2007

While most RNAs work to create, package, and transfer proteins as determined by the cell's immediate needs, miniature pieces of RNA, called microRNAs (miRNAs) regulate gene expression. Recently, researchers from the University of Pennsylvania School of Medicine determined how miRNAs team up with a regulatory protein to halt protein production. Results of the study were published recently in *Cell*.

Scientists estimate miRNAs have the ability to regulate the expression of approximately one third of human genes, and previous studies have linked abnormal activity of miRNAs to cancer and other diseases.

While scientists know that most miRNAs in mammals repress the translation of RNA to protein, the molecular steps by which they achieve regulation are largely unknown. By studying the relationship between human miRNAs and the regulatory protein Argonaute2 (Ago2), lead author Marianthi Kiriakidou, MD, Assistant Professor of Medicine, and others set out to uncover how miRNAs control protein synthesis.

Before interfering with protein production, miRNAs associate with proteins from the Argonaute (Ago) family. According to Kiriakidou, "Ago proteins are at the heart of the miRNA regulatory pathway, due to their engagement with miRNAs."

The miRNA and Ago protein association dictates the way that miRNA regulates gene production. While there are four different proteins in the human Ago family, Kiriakidou and colleagues from Zissimos

Mourelatos' team focused on the interaction between miRNA and Ago2. Ago2 stands out among the four mammalian Ago proteins since it is the only Ago protein able to mediate RNA interference by inhibiting gene expression.

Under normal conditions, the initiation of protein synthesis is kicked off when a protein called eIF4E binds to the front end, or cap, of messenger RNA. With eIF4E in place, a cascade of protein-protein and protein-RNA interactions allows the manufacturing of proteins to begin. However, the assembly of proteins quickly comes to a standstill when the miRNA-Ago2 complex binds near the back end of a messenger RNA. By analyzing the amino acid sequence of Ago2, Kiriakidou and others uncovered a similarity with the cap-binding domain of the EIF4E protein that offered a clue as to why the miRNA-Ago2 complex blocked protein production.

"When the miRNA-Ago2 complex pairs with a messenger RNA, Ago2 engages the cap of the RNA," explains Kiriakidou. "We believe this results in competition with eIF4E and disrupts the normal initiation process of protein synthesis."

By improving understanding about how miRNAs control protein synthesis under normal conditions, the researchers hope to identify how miRNA-mediated gene expression regulation fails in human diseases.

"Many studies show that miRNAs are differentially expressed in a wide variety of human cancers and therefore have the potential to be used as diagnostic biomarkers for cancers," says Kiriakidou. "Understanding the central role of Ago2 in the miRNA pathway provides a foundation for future studies that aim to elucidate the contribution of miRNAs to normal cellular functions and disease processes."

Source: University of Pennsylvania School of Medicine