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# Mechanism of microRNAs deciphered

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Over 30% of our genes are under the control of small molecules called microRNAs. They prevent specific genes from being turned into protein and regulate many crucial processes like cell division and development, but how they do so has remained unclear. Now researchers from the European Molecular Biology Laboratory (EMBL) have developed a new method that uncovered the mode of action of microRNAs in a test tube.

The study, which is published in the current online issue of *Nature*, reveals that microRNAs block the initiation of translation, the earliest step in the process that turns genetic information stored on messenger RNAs into proteins.

The central dogma in molecular biology says that the genetic information stored as DNA is transcribed into molecules of messenger RNAs, which are then translated into proteins. MicroRNAs are small molecules that do not encode proteins themselves but bind to messenger RNAs that do. They function as locks for messenger RNAs and prevent their translation into proteins, but how they bring about this effect and at which stage of protein synthesis they interfere is a long-standing puzzle.

"So far it has been impossible to directly examine how and when microRNAs lock up messenger RNAs," says Matthias Hentze, Associate Director of EMBL, "because until now all we could look at were messenger RNAs that had already been locked-up within cells. To investigate the locking process itself, we developed a test tube system that recreates close to real life conditions of fruitfly embryos. Adding messenger RNAs to this system we could monitor for the first time how

they got locked-up by microRNAs."

Applying this new system Rolf Thermann, who carried out the research in Hentze's lab, discovered that miR2, an important microRNA in fruitflies, blocks translation very early on, even before the cellular machinery needed can assemble. Bound by miR2 a messenger RNA molecule is no longer accessible to ribosomes, the complexes that carry out protein synthesis.

"Strikingly, the messenger RNA locked-up in this way looks very similar to a messenger RNA that undergoes translation," Thermann says. "It is bound by big microRNA complexes that strongly resemble ribosomes, but they are not. This explains why when looking at already locked-up messenger RNA many scientists thought that translation had already started and microRNAs must interfere at a later stage of the process. It will be exciting to determine what these complexes are made of and how exactly they function."

The new approach to studying micro RNAs in action in a test tube may pave the way to similar studies of human and other microRNAs. MicroRNAs play an important role in various diseases including cancer, diabetes and viral infections. The new in vitro system will not only help shed light on the role of microRNAs in disease, but could also serve as a basis for new methods of drug discovery.

Source: European Molecular Biology Laboratory

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