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TINY RNA MOLECULES HAVE A BIG ROLE IN DISEASE

For many years, much of the RNA—the coded copies of the information contained in our DNA—floating around our cells was thought to be "junk" that had no visible role in protein production. In particular, microRNAs (miRNAs) did not initially appear to have an important function. But recently it was discovered that these small molecules actually play a key role in helping to regulate gene expression—the process by which genetic information is turned into proteins.

Dr. Eran Hornstein

miRNAs are important in regulating the processes inside the cell, the organ, and the organism. When these components malfunction, disease may result.

They do this by binding to messenger RNA molecules, preventing them from carrying out protein synthesis. RNA interference, as this process is called, provides the cell with a way of controlling the levels of hundreds of different proteins by turning genes off at the appropriate times.

"Now we understand that miRNAs are important in regulating the processes inside the cell, inside the organ, and inside the organism," says Dr. Eran Hornstein of the Weizmann Institute of Science's Department of Molecular Genetics. "When these components are malfunctioning, you end up with a disease."

Dr. Hornstein and his team study how miRNAs regulate the activity of genes during the development of the pancreas, bone, and cartilage, and how malfunctions may contribute to diseases.

Before joining the Institute in 2006, Dr. Hornstein received his MD/PhD from the Hebrew University–Hadassah School of Medicine in Jerusalem. He started out with the goal of becoming a physician, but was ultimately drawn to basic science research and completed his postdoctoral studies in the Department of Genetics at Harvard Medical School.

While at Harvard, he helped provide some of the earliest evidence that miRNAs play a role in vertebrate development—specifically, in the development of limbs. The study of miRNAs is so new that at the time of Dr. Hornstein's postdoctoral research, the first miRNA had been identified only a decade earlier.

Dr. Hornstein's current investigations include studying the role of miRNAs in diabetes. "We know now that miRNAs are highly relevant to the regulation of insulin gene expression in beta cells that are key to controlling the body's glucose levels. And we think we also have a clue about particular miRNAs that are highly relevant to the development of diabetes in mice," he says.

Along with his colleagues, he is also looking at the role of miRNAs in amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). ALS is a neurological disorder that affects motor neurons—the nerve cells in the brain and spinal cord that control muscle movements—causing muscle weakness and paralysis. "It's a very devastating disease and the genetics of it are completely

unknown, so we don't yet know how to cure it," says Dr. Hornstein. "But we have now developed a very nice model, in mice, to show that loss of miRNA activity may generate ALS."

Research on miRNAs could lead to better understanding of neurodegenerative conditions such as ALS and Alzheimer's disease.

He believes this research could shed light on the role of miRNAs in other neurodegenerative conditions, such as Alzheimer's disease. "It seems that miRNAs are extremely relevant to the functionality of neurons," Dr. Hornstein says. He explains that miRNAs seem to work not at the cell nucleus, but at the periphery. Neurons sometimes need to regulate their functionality at a distance, very far away from the center of the cell. It now appears that regulatory RNAs—particularly miRNAs—might specialize in regulating cell functions at a distance from the center.

A better understanding of miRNAs, which are now thought to regulate more than a third of all human genes, could eventually be useful for the treatment of a wide range of illnesses ranging from osteoporosis to cancer. "Down the road, I hope the findings in my lab will come together with technologies that are being developed in order to generate new therapeutics for diseases," says Dr. Hornstein.

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At one time, miRNAs were not thought to be particularly important; however, research now shows that these small molecules were underestimated and actually perform key functions.