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MicroRNA works with Ago2 protein to regulate blood cell development

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MicroRNAs became the stars of the RNA universe when, in 2001, scientists found that these short RNAs can control whether or not genes are expressed. This month, scientists at Rockefeller University and the Wellcome Trust cast new light on the genesis of these key biological regulators and how they carry out their function. These provocative new findings were reported online July 12 in the journal Genes & Development.

While microRNAs are made in large amounts in every cell from plants to humans, Dónal O'Carroll, a research associate in Alexander Tarakhovsky's lab at The Rockefeller University, has focused on understanding how they regulate the development of one particular system: the hematopoietic system.

"This is a system where similar kinds of stem cells give rise to all the different types of blood cells in the body, so you can definitively address whether microRNAs are involved in the processes by which they specialize and develop," says O'Carroll.

Instead of making proteins, these snippets of RNA repress their synthesis. They bind to messenger RNAs (mRNAs) — the blueprints for proteins — and either target them for destruction or inhibit their protein-making output. In order for microRNA to find its target mRNA, it needs the help of the protein Ago2, the only member of the Argonaute family of proteins that has a "slicer" function: That is, once microRNA binds with its target, it cleaves it, effectively stopping mRNA's ability to make

proteins.

Since the “slicer” activity of Ago2 would be the most efficient way of regulating microRNA function, O’Carroll wanted to see whether it plays a role in the development of blood cells.

In the bone marrow of adult mice — where their blood stem cells reside — O’Carroll conditionally knocked out the gene that encodes Ago2. Two months later, O’Carroll observed that they had developed anemia and enlarged spleens, and noted that although the stem cells still gave rise to all blood cell types, the development of two of them was severely affected: B lymphocytes, which contribute to the production of antibodies, and red blood cells.

When he looked at the Ago2-deficient mice’s blood cells, he also saw that the microRNA levels, though not zero, were much reduced, indicating that Ago2 is essential for microRNA homeostasis during the early development of blood cells.

To specifically test the importance of Ago2’s “slicer” activity, O’Carroll then genetically reconstituted the Ago2-deficient stem cells with either wild type Ago2 or a modified version of it that rendered the “slicer” activity inactive. A few weeks later, both conditions — the anemia and the enlarged spleen — in both groups of mice were cured, suggesting that this feature of Ago2 makes only a minor contribution to its biological function. The finding was surprising since the “slicer” function is unique to Ago2.

“At least within this system, ‘slicer’ activity doesn’t have a role in the execution of microRNA function, but Ago2 does have a special role in the maintenance of microRNA levels,” says O’Carroll, who recently accepted a position at the European Molecular Biology Laboratory in Rome.

Within the blood system, low levels of microRNA are not life-threatening during development but do have a distinct effect on different blood cell lineages.

“The results have caused us to think about the differential sensitivity of distinct developmental processes to microRNA levels,” says Tarakhovsky. “It remains to be seen to what extent specialized functions of developing cells in the blood system depend on microRNA.”

Source: Rockefeller University