Scientists discover new process shaping red blood cell development

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A collaboration among Drs. Daniel Kuppers, Andrew Hsieh, Beverly Torok-Storb and Patrick Paddison revealed a new process governing red blood cell development. Credit: Robert Hood / Fred Hutch News Service

Red blood cells give us life. They ferry oxygen throughout our bodies. Breakdowns in red blood cell development can be life-threatening, but scientists still have much to learn about the molecular processes that ensure these cells develop properly. Now, scientists at Fred Hutchinson Cancer Research Center have discovered a process that regulates the earliest stages of red blood cell development. The findings, published this month in the journal *Nature Communications*, could shed light on what goes wrong in certain blood cancers and anemias.

"It's a novel discovery," said Dr. Patrick Paddison, who studies how stem cells develop into cells with specialized functions. Paddison co-led the project with Hutch colleague and physician-scientist Dr. Andrew Hsieh, who studies how glitches in protein production can promote cancer.

The team showed for the first time that developing red blood cells use a particular molecular process to ensure that red blood cell-specific proteins are made. This occurs via modification to RNA, the molecular instructions that our protein-building factories "read" to create the proteins encoded by our genes. The researchers found that blocking the molecular machine that creates the modification prevents progenitor cells (which provide a renewable source of red and white blood cells) from turning into red blood cells, but not related blood cell types.

Red blood cells: essential but understudied

The work grew out of a collaboration between Paddison and Hutch colleague Dr. Beverly Torok-Storb, who studies the blood stem cells that give rise to our red and white blood cells. Dr. Daniel Kuppers, now a postdoctoral fellow co-mentored by Torok-Storb and Paddison, spearheaded the project.

Red blood cells make possible many lifesaving medical procedures that rely on blood transfusions. But they come directly from people; we haven't yet figured out how to manufacture a replacement product in a pharmaceutical factory.

"Part of the reason is we don't understand the [red blood cell developmental] process well enough," Paddison said. "A more detailed understanding of this process would allow us to actually think about clinical applications."

One major reason red blood cell development is under-researched is that

they're difficult to grow in a laboratory. Kuppers developed a lab dish-based proxy for progenitor cells that enabled him to look for genes important in red blood cell development.

RNA-based process regulates red blood cell development

Kuppers systematically screened for genes that are required for cells to signal their commitment to turning into red blood cells. The screen flagged a group of genes that encode components of a molecular machine that adds a type of molecule, or "mark," to RNA.

The molecular mark is called N6-methyladenosine, or m^6A for short. RNA marks, including m^6A, help our cells tweak how RNAs are processed and interpreted by our protein-producing factories, thereby influencing how proteins are made. Though the m^6A mark was discovered more than 40 years ago, it wasn't until recently that technological advances made studying it in detail finally possible.

At this point, Hsieh brought his expertise in protein production, or translation, to the team. "My hunch was that m^6A controlled mRNA translation," he said.

Hsieh's instinct was borne out by Kupper's experiments. Kupper knocked out genes coding for parts of this machine, preventing it from adding m^6A marks to RNA. When he did that, he saw a drop in the translation levels of 300 mRNAs involved in red blood cell development—even though the RNA levels stayed the same.

This showed that the key targets for the m^6A-adding machine were RNAs coding for proteins important to red blood cell development, Paddison explained. The targets "included a lot of key genes involved in

erythroid [red blood cell] disease: leukemias and myelodysplastic syndromes and anemia," he said.

The genes for the m^6A-adding machinery are critical for red blood cell development. Kupper removed them in blood stem cells donated by patients undergoing bone marrow biopsies. When he did so, the stem cells could no longer turn into red blood cells. But loss of m^6A didn't prevent these stem cells from turning into at least two other types of blood cell. Unexpectedly, the team also found that m^6A played an essential role in turning on a suite of other red blood cell-specific genes, including genes involved in synthesis of hemoglobin, our cells' oxygen-carrying molecule, as well as genes linked to a type of congenital anemia.

A deeper understanding of development and disease

It's often the case that diseases cannot be traced back to an obvious gene mutation. This is true for many cases of anemia. The revelation that m^6A influences production of several anemia-linked proteins could be a breakthrough in understanding the causes of anemias—and may have revealed a new treatment target, Hsieh said.

He and Paddison are working to chase down potential connections between m^6A and diseases related to red blood cell development, including anemia and cancer.

There are still a host of unanswered questions about m^6A and what it's doing on RNA, Paddison said. Scientists don't know much about how cells determine which RNAs get these marks. And in any given cell type, including red blood cell progenitors, 30% to 40% of all RNAs have m^6A marks.

"What is special about those RNAs that are regulated [by m^6A] versus those that are not?" Hsieh said.

The forces shaping cellular development are complex, and m^6A is just one player. Understanding the role it plays will also help scientists understand the bigger picture.

"There's a symphony of gene regulation that happens during [an organism's] development. Understanding its makeup and the players involved really helps you understand how an organism is put together and can provide important clues as to what can go wrong in disease," Paddison said.

More information: Daniel A. Kuppers et al. N6-methyladenosine mRNA marking promotes selective translation of regulons required for human erythropoiesis, *Nature Communications* (2019). DOI: 10.1038/s41467-019-12518-6

Read the original story here.

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