Breakthrough in understanding of how red blood cells develop

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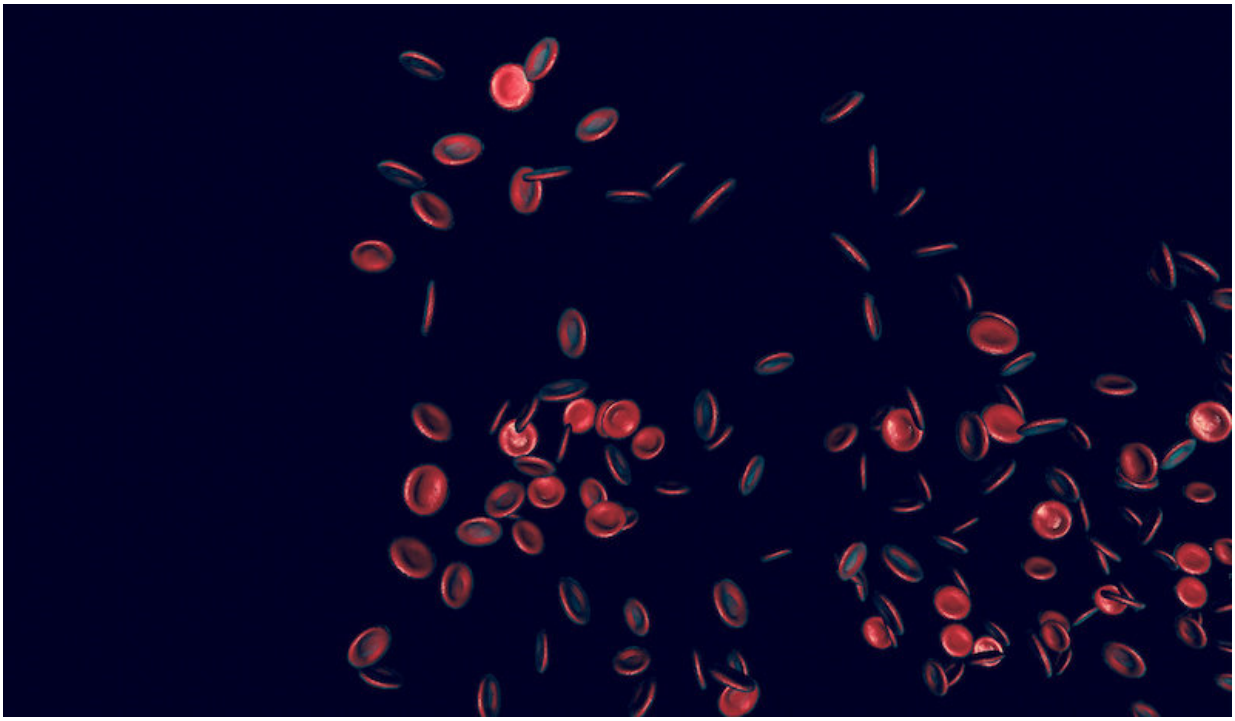

Red blood cells. Credit: Children's Hospital Boston

By taking a deep dive into the molecular underpinnings of Diamond-Blackfan anemia, scientists have made a new discovery about what drives the development of mature red blood cells from the earliest form of blood cells, called hematopoietic (blood-forming) stem cells.

For the first time, cellular machines called ribosomes—which create proteins in every cell of the body—have been linked to blood stem cell differentiation. The findings, published today in *Cell*, have revealed a potential new therapeutic pathway to treat Diamond-Blackfan anemia. They also cap off a research effort at Boston Children's Hospital spanning nearly 80 years and several generations of scientists.

Diamond-Blackfan anemia—a severe, rare, congenital blood disorder—was first described in 1938 by Louis Diamond, MD, and Kenneth Blackfan, MD, of Boston Children's. The disorder impairs red blood cell production, impacting delivery of oxygen throughout the body and causing anemia. Forty years ago, David Nathan, MD, of Boston Children's determined that the disorder specifically affects the way blood stem cells become mature red blood cells.

Then, nearly 30 years ago, Stuart Orkin, MD, also of Boston Children's, identified a protein called GATA1 as being a key factor in the production of hemoglobin, the essential protein in red blood cells that is responsible for transporting oxygen. Interestingly, in more recent years, genetic analysis has revealed that some patients with Diamond-Blackfan have mutations that block normal GATA1 production.

Now, the final pieces of the puzzle—what causes Diamond-Blackfan anemia on a molecular level and how exactly ribosomes and GATA1 are involved—have finally been solved by another member of the Boston Children's scientific community, Vijay Sankaran, MD, PhD, senior author of the new *Cell* paper.

"Much of the history of how this disorder works was written at Boston Children's," says Sankaran, who is a hematologist/oncologist and a principal investigator at the Dana-Farber/Boston Children's Cancer and Blood Disorders Center. "Now, we can move on to the next era of research—what we can do to treat it."

Learning from an error of nature

Previous studies have found that many patients with Diamond-Blackfan anemia have mutated ribosomal protein genes. But the question has remained: Do these mutations have something to do with GATA1 and why do they only impair the maturation of red blood cells? In Diamond-Blackfan, other mature blood cells—such as platelets, T cells and B cells—still fare well despite mutations of ribosomal protein or GATA1 genes.

"There has been controversy over whether a ribosomal protein mutation changes the composition of the ribosomes or the quantity of the ribosomes," Sankaran says. "We know now that it is the latter."

By closely examining human cell samples from patients with Diamond-Blackfan anemia, Sankaran and his team of collaborators found that the quantity of ribosomes within blood cell precursors directly influences their ability to produce effective levels of GATA1, which, if you remember, is needed for hemoglobin production and also for red blood cell production.

Now, finally tying all the pieces together, Sankaran and his team have definitively found that a reduced number of ribosomes slashes the output of GATA1 proteins inside blood stem cells, therefore impairing their differentiation into mature red blood cells.

An opportunity for gene therapy

Their finding supports the hypothesis that the presence of GATA1 proteins in early blood stem cells helps prime them for differentiation into red blood cells. Without enough ribosomes to produce enough GATA1 proteins, these early cells simply never receive the signal to

become red blood cells.

"This raises the question of whether we can design a gene therapy to overcome the GATA1 deficiency," Sankaran says. "We now have a tremendous interest in this approach and believe it can be done."

Although a bone marrow transplant from a matched donor can treat Diamond-Blackfan anemia, Sankaran says that a gene therapy would be advantageous since it would use a patient's own engineered cells, avoiding dangerous risks associated with graft versus host disease.

"I think what's great is that we can learn about developmental biology just by looking at our own patients very carefully," says Sankaran. "Genetic errors can give us the chance to pick apart the complex pieces of health and discover how they relate to one another."

More information: Rajiv K. Khajuria et al. Ribosome Levels Selectively Regulate Translation and Lineage Commitment in Human Hematopoiesis, *Cell* (2018). DOI: 10.1016/j.cell.2018.02.036

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