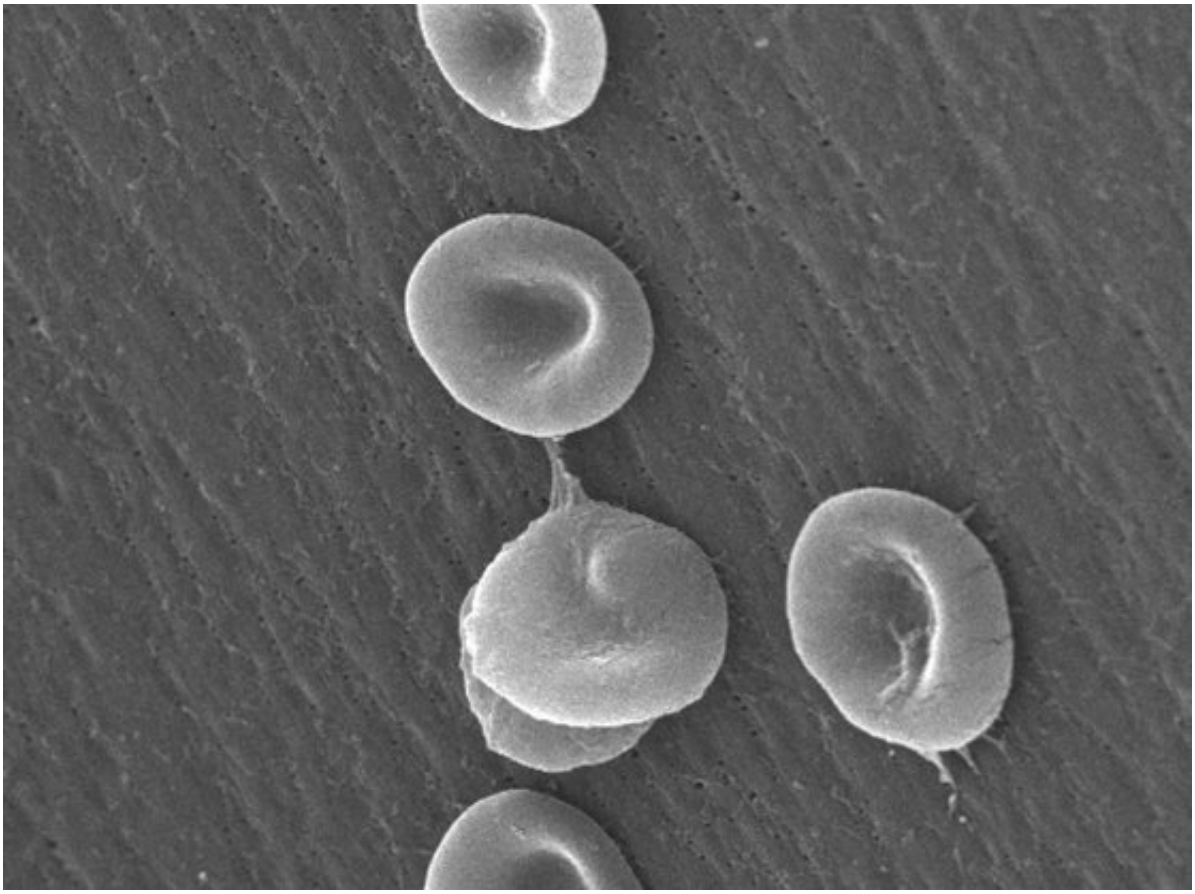
Looking beyond genes to explain blood cells' fates

March 19 2018, by Tom Ulrich



Red blood cells. Credit: CDC Public Health Image Library

Scientists often talk about cell fate and commitment in terms of mechanisms that control gene expression (transcription factors, chromatin remodeling, etc.). But by studying Diamond-Blackfan anemia

(DBA), rare genetic blood disorder, a team led by researchers from the Broad Institute of MIT and Harvard and the Dana-Farber/Boston Children's Cancer and Blood Disorders Center (DF/BC) have found a surprising mechanism that controls whether red blood cells achieve full development, one that has nothing to do with expression.

In a paper in *Cell*, the team revealed that, in red blood cells' ancestors, the number of protein-producing ribosomes available to carry out translation—but not the makeup of those ribosomes—is a major driver of their developmental fate.

Red blood cells develop from immature ancestors called erythroid progenitors. Patients with DBA carry far fewer of these precursors than normal. Researchers have long known that DBA cells carry mutations in genes related to ribosomes, the hybrid RNA/protein molecular machines that read mRNA transcripts and construct the encoded proteins.

Realizing that DBA provides a "natural experiment" for studying whether ribosomes influence cell fate, graduate student Rajiv Khajuria and associate member Vijay Sankaran of the Broad and DF/BC partnered with the Broad Proteomics Platform, the laboratories of Broad core institute member Aviv Regev and founder Eric Lander, and other collaborators to examine gene expression, protein production, and ribosome abundance and composition in normal and DBA blood progenitors.

The team showed that progenitors carrying DBA-related mutations carried far fewer ribosomes than normal. Their reduced ribosome content coincided with an interesting change in protein production. Ribosome-deficient cells, the team found, translated certain mRNAs into protein far less efficiently than normal. Those mRNAs tended to be short, produced from genes that are abundantly expressed in normal blood precursors, and have molecular features normally associated with

very efficient translation. (Notably, this group included the mRNA for GATA1, a master control switch for red blood cell development.)

Taken together, the team's results provide tantalizing clues of an expression-independent cell fate mechanism that may be active in many cell types. Indeed, they noted that there is a broad array of disorders arising from ribosomal problems, including certain neurodevelopmental disorders and various congenital defects—suggesting that with DBA they may only have scratched the surface.

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

Provided by Broad Institute of MIT and Harvard