

# Protein found to regulate red blood cell size and number

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The adult human circulatory system contains between 20 and 30 trillion red blood cells (RBCs), the precise size and number of which can vary from person to person. Some people may have fewer, but larger RBCs, while others may have a larger number of smaller RBCs. Although these differences in size and number may seem inconsequential, they raise an important question: Just what controls these characteristics of RBCs?

This question is particularly relevant for the roughly one-quarter of the population that suffers from [anemia](#), which is often caused by flawed RBC production. A better understanding of how RBC production is controlled may offer greater insight into the development and potential treatment of anemia.

By analyzing the results of genome-wide association studies (GWAS) in conjunction with experiments on mouse and [human red blood cells](#), researchers in the lab of Whitehead Institute Founding Member Harvey Lodish have identified the protein cyclin D3 as regulating the number of cell divisions RBC progenitors undergo, which ultimately affects the resulting size and quantity of RBCs. Their findings are reported in the September 14 issue of [Genes and Development](#).

"This is one of the rare cases where we can explain a normal human-to-human variation," says Lodish, who is also a professor of biology and [bioengineering](#) at MIT. "In a sense, it's a window on [human evolution](#). Why this should have happened, we have no idea, but it does."

Lodish likens cyclin D3's role in RBCs to that of a clock. In some people, the clock triggers RBC progenitors to mature after four rounds of cell division, resulting in fewer but larger RBCs. In others it goes off after five cell division cycles, which leads to production of a greater number of smaller RBCs. In both cases, the blood usually has the same ability to carry oxygen to distant tissues.

The initial hint of cyclin D3's importance came from GWAS, genetic surveys of large numbers of people with or without a particular trait. Researchers compare the groups in an attempt to identify genetic variations.

"The problem with most GWAS is that you get a bunch of potentially interesting genes, but that doesn't tell you anything about the functional biology, so you really have to figure it out," says Leif Ludwig, a Lodish graduate student and co-author of the *Genes and Development* paper. "You only know something has a role, but you don't know how it can cause variation. This work on cyclin D3 is a really nice example of how functional follow-up on a GWAS association can really teach us something about underlying biology."

In the case of RBC size and number, a mutation affecting cyclin D3 production bubbled to the surface from the GWAS's murky genetic data. Ludwig and co-author Vijay Sankaran then confirmed that reduced or inhibited cyclin D3 expression in mice and in human RBC [progenitors](#) caused those cells to halt [cell division](#) and mature earlier, producing larger and fewer [red blood cells](#) than mice and cells with uninhibited cyclin D3 production.

As one of only a handful of studies that have successfully used GWAS to produce definitive biological results, Sankaran is excited that this work confirms the value of such genetic studies.

"Can genetics teach us about biology?" asks Sankaran, also a postdoctoral researcher in the Lodish lab. "Yes! This work tells us that as genetic studies identify new genes, there will probably have been a lot of things biologists may have ignored. Genetics allows you to shine a spotlight on something interesting and then home in on it see what can be learned."

**More information:** "Cyclin D3 coordinates the cell cycle during differentiation to regulate erythrocyte size and number" *Genes and Development*, 2012.

Provided by Whitehead Institute for Biomedical Research

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