Global view of blood cell development reveals new and complex circuitry

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A small pool of stem cells replenishes the human body with about 200 billion new blood cells daily. But the elaborate circuitry that determines if a cell will develop into a T cell, red blood cell, or one of the nine or more other blood cell types remains largely unknown. A research team led by scientists from the Broad Institute and Brigham and Women's Hospital has taken a systematic approach to help decipher this circuitry, compiling a comprehensive catalog of the factors that determine a blood cell's fate. Their work appears in the January 21 issue of *Cell*.

The researchers found that blood cells are directed by a multitude of transcription factors, proteins that turn on and off genes. While many previous studies have focused on individual transcription factors or types of blood cells, this study examined the expression and regulation of all transcription factors throughout blood development. The findings point to densely, interconnected circuits that control this process, suggesting that the wiring for blood cell fate is far more complex than previously thought.

"One assumption in the field had been that there are a small number of transcription factors that orchestrate this process," said Aviv Regev, a Broad Institute core member and co-senior corresponding author of the study. "Some people have always thought there would be a lot of factors and that it would just take time to find them. It turns out there are more masters than we would have thought."

The researchers looked globally at how the expression of all 20,000 or so

genes in the genome change as blood stem cells become specialized cell types (a process known as differentiation). They discovered that while a small fraction of genes are uniquely expressed in a single type of cell, other genes are more broadly expressed — present in a variety of cell types but at varying levels. Some of these genes are turned on in the blood stem cells and switched off at certain points in development while others are reused in several parallel developmental branches. The researchers found about 80 of these patterns of variable genes, called modules. Each kind of specialized cell has a unique profile, or combination, of these modules.

Looking at the genes modulated in the course of healthy cell development could give researchers clues about what events lead to blood cancers, such as leukemia, a disease where differentiation has gone wrong.

"When you look at leukemia cells beneath a microscope, they have a lack of differentiation and they look abnormal," said Broad associate member Ben Ebert, an associate physician of hematology at Brigham and Women's Hospital and a senior corresponding author of the study. "They've ended up in a place that doesn't exist in normal development." Now that the researchers have a clearer picture of the modules that normal cells exhibit, they can apply this knowledge to help identify the similarities and critical changes in leukemia cells' profiles.

"Leukemia cells have the same set of building blocks as normal blood cells – some, they keep the right way so a piece of the profile is right, and a piece of the profile is wrong," said Regev, who is also an assistant professor in the department of biology at MIT and an Early Career Scientist at Howard Hughes Medical Institute.

The research team included co-first author Noa Novershtern from the School of Computer Science at the Hebrew University of Jerusalem, co-

first author Aravind Subramanian in Todd Golub's laboratory at the Broad, and Lee Lawton and other collaborators in Richard Young's laboratory at the Whitehead Institute. All of their results will be made publicly available online through a database known as the Differentiation Map Portal (or D-Map). Ebert, Regev and their colleagues intend for D-Map to be a starting point for other researchers, empowering their investigations into the biology of blood cells as well as leukemia and other human diseases.

"Already, many people are asking for the data. Other groups can now combine their data with ours to ask new questions," said Novershtern. "What's also exciting is that people can see the power of computational models, tools that can be used to find new biological insights from the data."

More information: Novershtern N. et al. Densely interconnected transcriptional circuits control cell states in human hematopoiesis. *Cell*. Published online January 20, 2011.

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