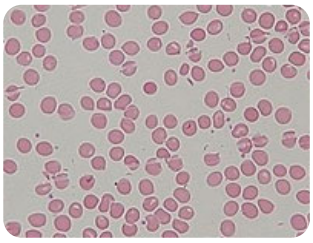
Global view of blood cell development reveals new and complex circuitry

A small pool of stem cells replenishes the human body with about 200 billion new blood cells dai
However, 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 catalogue of the factors th
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 tur
on and off genes. While many previous studies have focused on individual transcription factors or types o
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 th
the wiring for blood cell fate is far more complex than previously thought.

'More masters than we thought'

"One assumption in the field had been that there are a small number of transcription factors that orchestrat
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 a
blood stem cells become specialised cell types (a process known as differentiation). They discovered tha
while a small fraction of genes are uniquely expressed in a single type of cell, other genes are more broad
expressed - present in a variety of cell types but at varying levels. Some of these genes are turned on in th
blood stem cells and switched off at certain points in development while others are reused in several para
developmental branches. The researchers found about 80 of these patterns of variable genes, called
modules. Each kind of specialised 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 leukaemia, a disease where differentiation has gone
wrong.

"When you look at leukaemia cells beneath a microscope, they have a lack of differentiation and they look
abnormal," said Broad associate member Ben Ebert, an associate physician of haematology at Brigham a
Women's Hospital and a senior corresponding author of the study. "They've ended up in a place that does

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 leukaemia cells' profiles.

'Same set of building blocks as normal cells'

"Leukaemia cells have the same set of building blocks as normal blood cells - some, they keep the right w 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. A of their results will be made publicly available online through a database known as the Differentiation Map Portal (or D-Map) (www.broadinstitute.org/dmap). Ebert, Regev and their colleagues intend for D-Map to b a starting point for other researchers, empowering their investigations into the biology of blood cells as we as leukaemia 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 computationa models, tools that can be used to find new biological insights from the data."

This work was supported by the Richard Merkin Foundation for Stem Cell Research at the Broad Institute, the Damon Runyon-Rachleff Foundation, the Searle Scholar Program, the Burroughs Wellcome Fund, the Smith Family Foundation, the Howard Hughes Medical Institute, and the National Institutes of Health.

Paper cited:

Novershtern N. et al. *Densely interconnected transcriptional circuits control cell states in human haematopoiesis. Cell*. Published online 20 January 2011.

The Broad Institute of Harvard and MIT

The Eli and Edythe L. Broad Institute of Harvard and MIT was launched in 2004 to empower this generatio of creative scientists to transform medicine. The Broad Institute seeks to describe all the molecular components of life and their connections; discover the molecular basis of major human diseases; develop effective new approaches to diagnostics and therapeutics; and disseminate discoveries, tools, methods a data openly to the entire scientific community.

Founded by MIT, Harvard and its affiliated hospitals, and the visionary Los Angeles philanthropists Eli and Edythe L. Broad, the Broad Institute includes faculty, professional staff and students from throughout the MIT and Harvard biomedical research communities and beyond, with collaborations spanning over a hundred private and public institutions in more than 40 countries worldwide. For further information about tl Broad Institute, go to www.broadinstitute.org.

The Richard Merkin Foundation for Stem Cell Research at the Broad Institute

The Richard Merkin Foundation for Stem Cell Research at the Broad Institute seeks to fund Broad Institute

affiliated scientists to develop a novel and comprehensive "toolbox" of experimental methods and computational algorithms and to apply those tools to understand cellular circuitry in stem cells, with the goa of being able to manipulate those circuits for both biological knowledge and medical applications.

Brigham and Women's Hospital

Brigham and Women's Hospital (BWH) is a 793-bed non-profit teaching affiliate of Harvard Medical Schoc and a founding member of Partners HealthCare, an integrated health care delivery network. BWH is the home of the Carl J. and Ruth Shapiro Cardiovascular Centre, the most advanced centre of its kind. BWH is committed to excellence in patient care with expertise in virtually every specialty of medicine and surgery.

The BWH medical pre-eminence dates back to 1832, and today that rich history in clinical care is coupled with its national leadership in quality improvement and patient safety initiatives and its dedication to educati and training the next generation of health care professionals. Through investigation and discovery conduct at its Biomedical Research Institute (BRI), BWH is an international leader in basic, clinical and translational research on human diseases, involving more than 900 physician-investigators and renowned biomedical scientists and faculty supported by more than $ 537 M in funding. BWH is also home to major landmark epidemiologic population studies, including the Nurses' and Physicians' Health Studies and the Women's Health Initiative.

For more information about BWH, go to www.brighamandwomens.org.

For more, visit: https://www.bizcommunity.com