How blood and immune systems form in developing bone marrow

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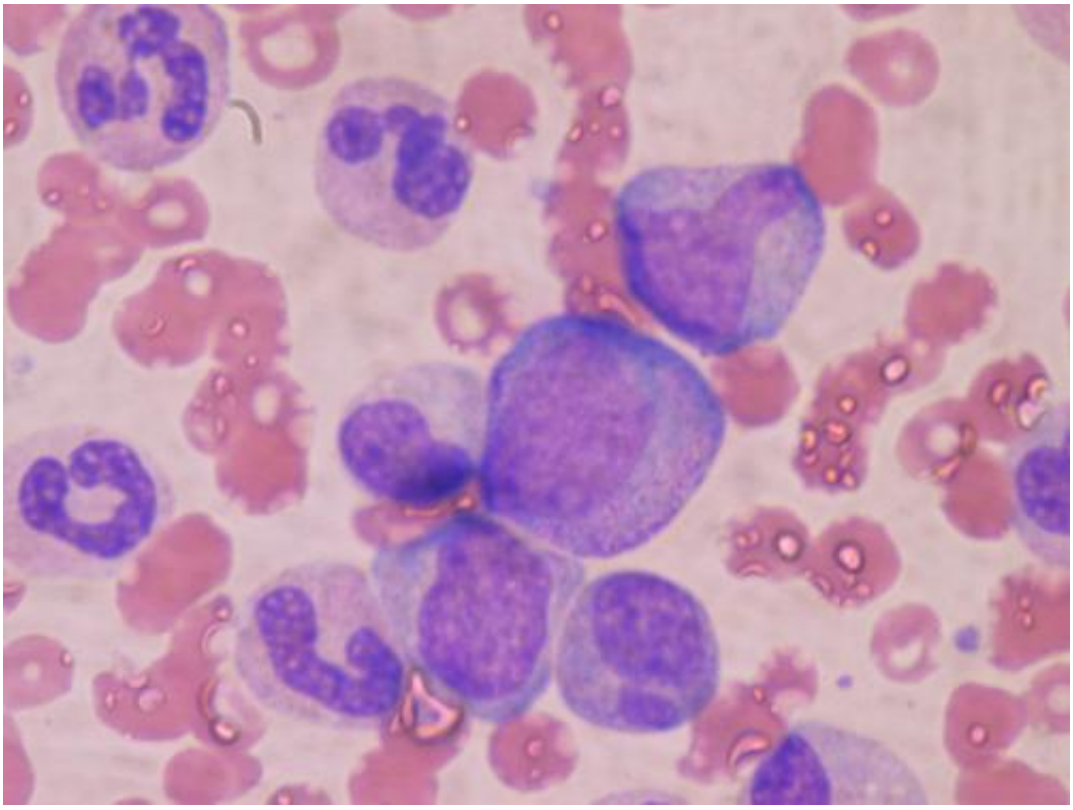

Hematopoietic precursor cells: promyelocyte in the center, two metamyelocytes next to it and band cells from a bone marrow aspirate. Credit: Bobjgalindo/Wikipedia

Researchers have found that in the space of just a few weeks, numerous blood and immune cell types emerge from developing bone marrow, including key white blood cells that protect against bacteria.

The first comprehensive analysis of how the blood and immune systems develop in prenatal bone marrow has been conducted by scientists at Newcastle University, the Wellcome Sanger Institute and collaborators.

The study, published today in *Nature*, is part of the Human Cell Atlas (HCA) initiative to map every cell type in the human body, to transform our understanding of health, infection and disease. It will be an important reference for understanding how the blood and immune systems develop in bone marrow, and how this can go wrong in disorders such as leukemia, with important implications for diagnoses and treatments.

A previous HCA study described how the human blood and immune systems begin to develop in the yolk sac and liver, a process known as haematopoiesis. But until now, it was unknown how haematopoiesis continued in bone marrow, which produces blood and immune cells for the rest of the individual's life.

Although the human blood and immune system generally protects us from infection and disease, the system can go wrong and lead to immune deficiencies and cancers such as leukemia, a cancer that affects white blood cells.

Protection from bacteria

In this study, researchers from the Wellcome Sanger Institute, Newcastle University, University of Cambridge and University of Oxford, used single cell RNA technology to analyze developing bone marrow tissue samples, in order to identify the cell types present and which genes those cells expressed.

The team observed the rapid diversification of blood and immune cells into specialist types, including white blood cells called neutrophils that

protect against bacteria. This diversification occurred over six to seven weeks early in the second trimester of pregnancy. Compared to fetal liver, there were a large number of B-lymphoid cell types, which are needed both to help combat infection and to mount an effective response to vaccines.

Dr. Laura Jardine, a first author on the paper from Newcastle University, said: "For the first time, we were able to identify all the blood and immune cells in developing bone marrow. This even allowed us to see the stromal cells—the environment that the immune cells develop in—which never been characterized in detail before. This atlas will be a huge resource for researchers."

Professor Muzlifah Haniffa, a senior author of the paper from the Wellcome Sanger Institute and Newcastle University, said: "However much we may have thought that we understood the immune system, it is actually far more complex than we had realized. Data like this provides the resolution needed to properly understand what is happening at a molecular level during development."

The researchers also studied Down syndrome bone marrow, identifying notable differences in gene expression that may help to shed light on why individuals with Down syndrome are more prone to developing immune disorders and leukemia.

Professor Irene Roberts, a senior author of the paper from the MRC Molecular Haematology Unit at the University of Oxford, said: "We know that children with Down syndrome have a higher risk of developing leukemia but we don't know why. This study characterizes some of the differences in gene expression in their bone marrow, which will allow us to start figuring out whether these differences are significant and in what way. We hope this will ultimately help researchers develop better ways of treating, or even preventing, leukemia

in these children."

This research is part of the Human Developmental Cell Atlas (HDCA), which is creating an atlas of all cells that are important for healthy human development. Key to understanding what happens in early development and how this can affect health or lead to disease, the HDCA is likely to lead to transformations in healthcare.

Dr. Sarah Teichmann, a senior author of the study from the Wellcome Sanger Institute and co-chair of the Human Cell Atlas Organising Committee, said: "This first detailed map of developing bone marrow is another important contribution to the international Human Cell Atlas initiative, which aims to create an openly available human 'Google map' of the body to understand health and disease. It is helping to transform our understanding of how the human immune system develops in early life and is likely to lead to new ways of diagnosing and treating patients with immune diseases, including the potential for regenerative medicine."

More information: Laura Jardine et al, Blood and immune development in human fetal bone marrow and Down syndrome, *Nature* (2021). DOI: 10.1038/s41586-021-03929-x

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