Skeleton-wide study of blood cell formation offers new ways to treat blood cancers, infections

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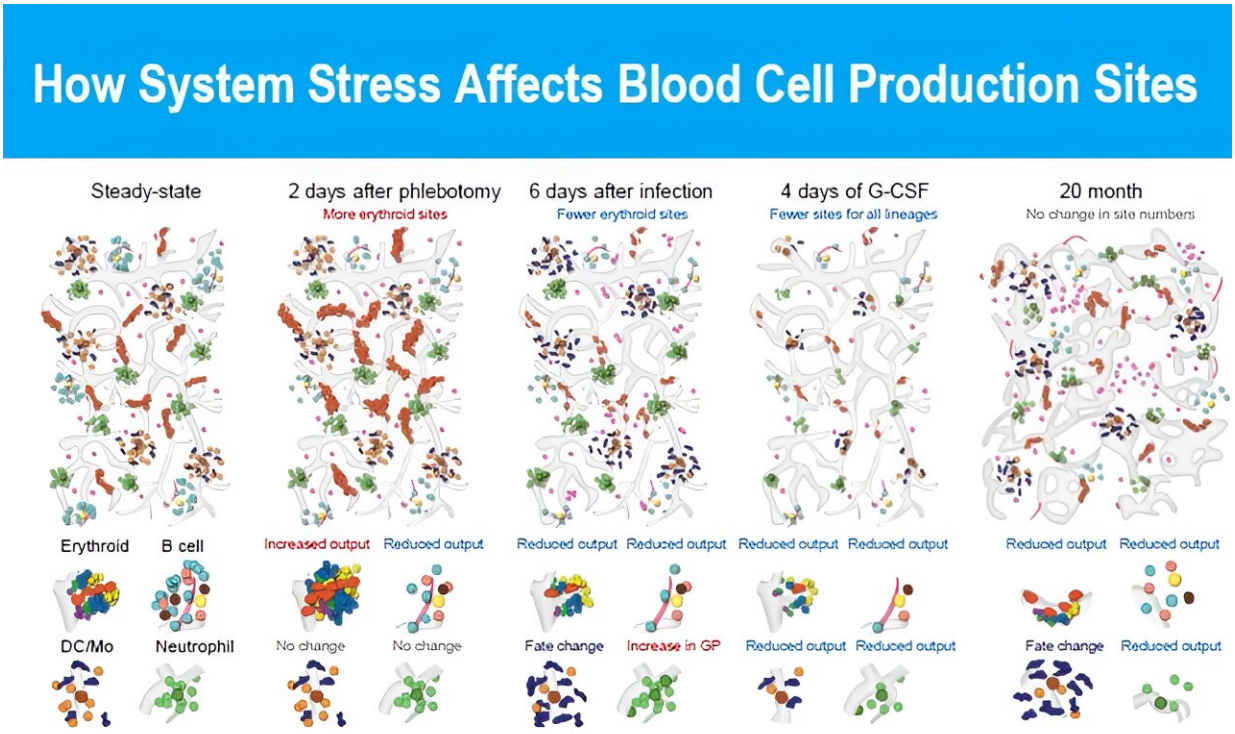

How the number of production sites in the sternum can vary significantly by the type of stress on the system, such as blood loss, infection, cancer-related treatment, and aging. Credit: *Nature* and Cincinnati Children's

Imagine being able to count the different types of blood cells being

formed inside the tiny bones of a mouse and pinpointing the strings and clusters of cells within the bone marrow that are responsible for producing specific types of blood cells.

That's exactly what a team of scientists led by experts at Cincinnati Children's achieved in a far-reaching study published March 20, 2024, in the journal *Nature*. Their work adds an unprecedented new understanding of the "elegant" and "resilient" anatomy of bone marrow while also generating evidence of unexpected variations in how the skeleton responds to stresses such as infection or blood loss.

"Stunningly, we found that the response to hematopoietic insults varies across the skeleton. We speculate that certain bones have specialized to preferentially respond to some insults, and this will be the focus of future studies," the co-authors state.

The research was led by co-first authors Qingqing Wu, Ph.D., and Jizhou Zhang, Ph.D., and corresponding author Daniel Lucas, Ph.D., all with the Division of Experimental Hematology and Cancer Biology at Cincinnati Children's. Overall, 23 researchers from five institutions contributed to this groundbreaking study.

The discovery of specific blood cell production sites within the bone marrow raises new challenges and opportunities for diagnosing and treating a number of blood-related conditions.

"For example, our data shows that biopsies that draw marrow from just one type of bone may not provide a full picture of how the blood production system has been affected by a disease or other insult," Lucas says. "Meanwhile, efforts to stimulate production of certain blood cell types may be dramatically improved by focusing on specific bone types."

Key discoveries reported in the paper include:

- New tools allowing visualization of blood production inside the bone, allowing defining the basic anatomy of blood cell formation. These revealed that bone marrow functions are highly responsive and durable, but not uniform. The paper describes how strings and clusters of cells form within the marrow to act as blood cell production factories.
- Location matters, even during normal blood cell production. The team demonstrated that different key types of progenitor cells move through different microenvironments as they mature. These microenvironments significantly influence which types of mature blood cells get produced. Different microenvironments give rise to oxygen-carrying red blood cells versus infection-fighting white blood cells, and so on.
- Unexpected variations in stress responses. The researchers compared how the system responded to three acute kinds of stress: blood loss, L. monocytogenes infection, and granulocyte-colony stimulating factor (G-CSF) treatment (often given to boost white blood cell production after chemotherapy). They also measured how aging changed the process.

The team meticulously measured how different bones responded to these insults. Among several examples: blood loss triggered rapid red blood cell production in the sternum, tibia, vertebrae, and humerus—but not in the skull. Blood loss also temporarily reduced the number of B cell production sites across the skeleton.

Meanwhile, when exposed to G-CSF, long bones rapidly increased formation of granulocyte progenitors and mature neutrophils. But in sharp contrast, the sternum from the same mice displayed "profound reductions" in these cell types as well as loss of neutrophil production sites.

"These variations are important because until now, mouse studies of

blood cell biology have depended almost entirely upon material collected from the femur and tibia," Lucas says.

Innovation required just to conduct the study

The research team first needed to conduct a research project-within-the-project to establish a method for imaging and counting the different cell types at work within the mouse bone marrow.

Counting the cells involved a process called confocal imaging microscopy. This uses specialized microscopes relying on lasers to detect specific tags in the cells. When "tagged" properly, the cells emit different colors under the laser, which allows them to be imaged and counted.

The challenge is coming up with the right tag so that the laser accurately detects the targeted cells of interest, while not counting other cells. In this study, the team started with a vast library of potential markers, then they whittled the list down to 35 promising genetic markers.

Ultimately, they found that detecting cells that express the gene marker ESAM, in combination with other markers, allowed distinguishing between six different types of blood progenitor cells. The marker also proved capable of showing information about the microenvironment, such as whether blood cell production was occurring within sinusoids or arterioles, two distinct types of blood channels found within bone marrow. Importantly, the process developed for this study allowed the team to analyze blood cell development in multiple parts of the skeleton.

Next steps

Looking ahead, Lucas says much more research will be needed to fully

detail how different parts of the skeleton become specialized producers of specific blood components. Also, more studies will be needed to confirm how much of the bone marrow stress response observed in mice also occurs in humans.

It will likely require several years of development, but understanding more about the mechanics of blood cell production may allow a wide range of improvements in the precision and effectiveness of treatments to support healthy blood cell production.

"It might even allow to build artificial bones capable of producing red blood cells for transfusion," Lucas says.

More information: Daniel Lucas, Resilient anatomy and local plasticity of naïve and stress hematopoiesis, *Nature* (2024). DOI: 10.1038/s41586-024-07186-6.
www.nature.com/articles/s41586-024-07186-6

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