cycles, one might expect the ACC to be weaker today than it was during an epoch known as the Pliocene (5.3 million to 2.6 million years ago). This is because elevated atmospheric greenhouse-gas concentrations during the Pliocene made Earth much warmer than it is now. Instead, Lamy and colleagues' ACC records show the opposite relationship — the strength of the ACC increased overall as Earth cooled between 5 million and 3 million years ago. The authors attribute this discrepancy to processes resulting from the climatic conditions that characterized the warm Pliocene, before the establishment of a larger ice sheet on Antarctica and increased sea-ice extent at the end of the Pliocene. These processes led to a strengthening of north–south density gradients and Southern Ocean wind forcing in response to the global cooling that occurred throughout the Pliocene.

As well as these million-year ACC trends, Lamy *et al.* also observed 400,000-year cycles, which they ascribe to the impact that Earth's orbital changes have had on tropical atmospheric circulation and, in turn, on westerly winds in the Pacific sector of the Southern Ocean. The authors discuss how their records complement other reconstructions of oceanic and atmospheric changes that have taken place across the past five million years. Together, the combined reconstructions help to establish key connections between the strength of the ACC, the supply of nutrients to the surface ocean, the marine carbon cycle and the storage of carbon dioxide in the Southern Ocean.

Although Lamy and co-authors' reconstructions provide insights into the evolution of the ACC and its relationship with the changes in Earth's climate, questions remain. First, how representative are the South Pacific records of the other sectors of the Southern Ocean? For example, are the 400,000-year cycles common to all sectors? Second, can the relative contribution of changes in wind versus density gradients be more explicitly untangled by using robust reconstructions of the evolution of north–south density gradients across sectors of the Southern Ocean? Finally, to what extent has the depth dependence of ocean current speeds in the ACC changed over time?

Over the past century, human activity has driven a rise in atmospheric greenhouse-gas concentrations from the relatively low values characteristic of the rest of the Holocene to the much higher levels associated with the Pliocene, setting Earth's climate on a trajectory towards Pliocene warmth. This begs the question: will the ACC strengthen with warming, as it does on the timescale of glacial–interglacial cycles, or weaken, as suggested by the long-term Pliocene trend?

There are two important aspects that need to be kept in mind when using past climate change to inform our understanding of the ocean's response to future global warming. The first is the direction of change. Earth's climate is currently going from cold to warm, and not warm to cold, as it did during the Pliocene. The second is the timescale on which the ocean adjusts to climatic changes, which is on the order of thousands of years for the deep ocean.

Taking these points into account, the glacial–interglacial timescale of past changes in ACC strength might be considered the closest analogue for future climate change, suggesting that the current's strength will increase as westerly winds shift towards the South Pole and as Southern Ocean density gradients strengthen. That said, this picture will probably be complicated by mechanisms in the atmosphere, ocean and cryosphere (regions of Earth covered by snow and ice), acting on shorter timescales. These uncertainties aside, it's clear that detailed reconstructions such as the records reported by Lamy *et al.* will improve our understanding of these powerful climatic players.

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Haematology

Powerful imaging shows blood cells made in bone

M. Carolina Florian

A method for imaging the production of blood cells in the bones of mice has revealed the organization of cell lineages, both in a steady state and in response to stressors, such as bleeding and infection. **See p.839**

Blood cells constantly renew throughout life, in a process called haematopoiesis. In adult mammals, blood cells are produced in bone marrow, which is a semi-solid tissue found in most bones in the body. Because haematopoiesis is a dynamic process that can readily adjust to face challenges such as stress and infection, bone marrow must also be dynamic. The tissue is packed with different cells in various stages of development, ready to be released into the bloodstream to maintain homoeostasis of the blood. Given the semi-solid and highly dynamic nature of bone marrow, it has so far been difficult both to tell how cells are organized in the tissue, and to resolve the production of blood cells at a single-cell level. On page 839, Wu *et al.*[1] describe a powerful method for visualizing various steps of haematopoiesis throughout the skeletons of mice.

In 2021, researchers in the same lab as Wu *et al.* established tools for imaging myelopoiesis — the production of myeloid cells, which are a family of immune cells that includes granulocytes, such as neutrophils[2]. In the latest study, Wu and colleagues build on these tools and describe a protocol for imaging the most immature haematopoietic stem and progenitor cells (those that have the potential to give rise to all blood cells); the production of red blood cells (erythropoiesis); and the production of another family of immune cells, which includes dendritic cells and B lymphocytes (lymphopoiesis). The method allows them to see where each of these processes happens in bone marrow, how they intermingle and how they remodel in the face of stress. The detailed images that the authors generate show that bone marrow has a defined architecture with many haematopoietic processes happening in specific anatomical locations.

The authors start by using a technique called flow cytometry to define combinations of five proteins expressed on the surface of bone-marrow cells, referred to as

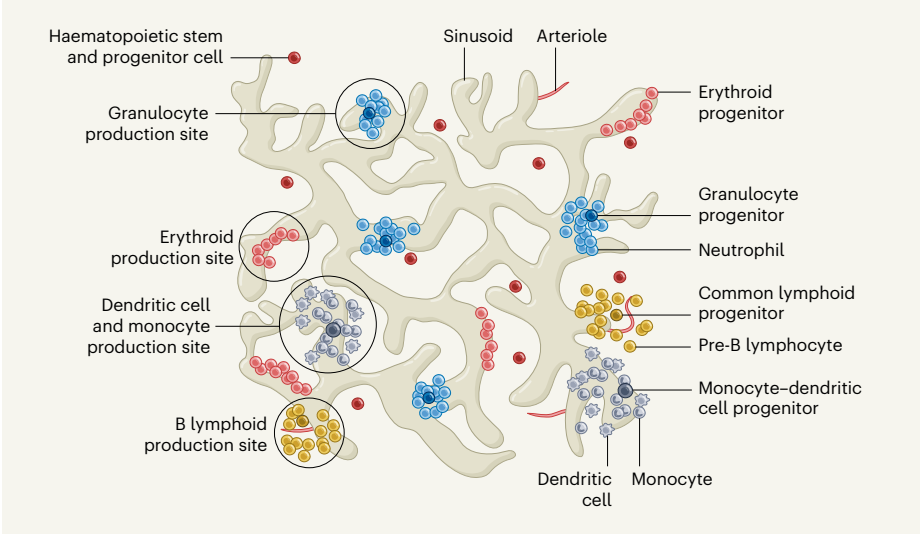

Figure 1 | Organization of blood-cell production in bone marrow. Wu *et al.*[1] have developed a powerful imaging technique to visualize various stages of blood-cell production (haematopoiesis) in bone marrow. In steady-state haematopoiesis, haematopoietic stem and progenitor cells – the most immature cells that have the potential to give rise to multiple cell lineages – are distributed away from each other. Cells of each lineage are clustered into non-overlapping production sites near small vessels called sinusoids and arterioles. Each production site consists of lineage-committed progenitor cells surrounded by their daughter cells: granulocyte progenitors give rise to neutrophils; common lymphoid progenitors give rise to pre-B lymphocytes; monocyte–dendritic cell progenitors give rise to monocytes and dendritic cells; and erythroid progenitors later give rise to red blood cells (not shown).

surface markers, that enable six types of haematopoietic stem and progenitor cell to be identified by fluorescence microscopy of intact bone-marrow tissue. Using these surface-marker combinations, they investigate the spatial organization of stem cells and different haematopoietic progenitor cells, with respect to both each other and structures in the bone marrow, including small blood vessels (sinusoids and arterioles) and the inner layer of bone tissue (endosteum). They find that production sites for different blood-cell populations exist in specific, non-overlapping areas, and that the relative number of production sites per bone is remarkably consistent between samples – for example, erythroid and neutrophil production sites are about twice as abundant as lymphoid and dendritic production sites (Fig. 1).

Interestingly, stem cells are always found as single cells, distributed far away from each other, whereas progenitors that are committed to a particular lineage form clusters with their daughter cells. This property is intrinsic to these stem cells and the authors show that they separate from each other *in vitro* when isolated from other bone-marrow cells.

Finally, the authors imaged bone marrow after mice were subjected to different stressors, such as bacterial infection, excessive blood loss and ageing. Together, the data show that blood-cell-production sites are flexible and can adjust their output on the basis of the demand of the system. Each type of blood-cell-production site is regulated independently, and the anatomy (size, number and architecture of production sites) returns to its baseline state once the acute insult (bleeding or infection) is resolved. Notably, some insults were shown to elicit different responses across the skeleton, with specific bones more engaged than others – for example, blood loss leads to an increase in erythropoiesis in the breastbone (sternum), limb bones (tibia and humerus) and vertebrae, but not in the skull.

The preferred experimental approaches for investigating the function of cells in bone marrow have conventionally been flow cytometry and single-cell profiling, because these approaches rely on dissociating cells from tissue and analysing them in suspension, which is relatively easy to do for bone marrow. Although the anatomy of many tissues in the body has been characterized for decades using imaging techniques, bone marrow has historically been challenging to prepare and image – especially compared with other tissues such as epithelial tissue, which consists of a thin, continuous layer of compactly packed cells. For this reason, the complexity of the 3D architecture of bone marrow has largely been underestimated.

Although Wu and colleagues overcome the challenges associated with imaging bone marrow, the wider application of this technology could be challenging. This is because it requires fluorescently labelled antibodies specific to each surface marker that would each need to emit light at a separate wavelength, as well as highly performing microscopes for image acquisition and analysis. Moreover, the improvement in imaging capacity provided by this technique must be followed by an improvement in image analysis. Annotating single cells in images of bone marrow can be extremely error prone because of the complex combinations of surface markers and the high density of cells. Manual annotation is usually necessary, but this is slow and limits the capacity of the technique.

One of the most exciting directions for investigations of the physiology and pathology of bone marrow will be improving software for image analysis, and possibly coupling this to single-cell molecular profiling techniques – including RNA sequencing to examine gene expression and 'ATAC sequencing' to identify regions of DNA that are accessible to transcriptional machinery[3]. It is likely that deep-learning-based approaches will boost the capabilities of these tools and aid in their translation to clinical applications (see *Nature* **623**, 1095–1097; 2023).

A limitation of the study is that the imaging is carried out at discrete time points, which does not allow cells to be tracked over time. Therefore, it cannot be ruled out that the observed architecture of bone-marrow-cell populations is transient. This is because time-lapse fluorescence imaging of large areas of live bone-marrow tissue, using microscopes that can detect more than two or three wavelengths emitted by fluorescently labelled surface markers, cannot yet be carried out. However, it is very unlikely that these observations depict transient dynamics, given the robust reproducibility of the localization and number of production sites over different samples.

Furthermore, it will be interesting to see how these insights into bone-marrow anatomy could help scientists' understanding of disease progression, particularly when it is divergent – for example, when the progression and outcome of leukaemia differs between patients, despite being caused by the same genetic mutation[4]. The work by Wu *et al.* could also bring fresh perspectives to the biology of infections sustained by different pathogens, or responses to different stressors that might heavily involve the spatial remodelling of the bone marrow.

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