Blood

Stem cells pack some chillis for the road

Anastasia N. Tikhonova & Iannis Aifantis

Pain-sensing nerve cells can mobilize blood stem cells in mice, with a component of chilli peppers being one stimulus. The finding holds the promise of improving procedures for stem-cell transplantation. See p.591

The cardinal feature of blood stem cells is their ability to regenerate the body's entire blood and immune systems. The process is known as haematopoiesis, and the cells are better known as haematopoietic stem cells (HSCs). In developing embryos, HSCs shuffle around distinct anatomical sites, with blood circulation enabling their trafficking. After birth, these cells reside in specialized niches in the bone marrow that support their quiescence and self-renewal[1]. Throughout life, HSCs are released from the bone marrow to replenish blood cells in a circadian pattern that is under the control of involuntary nerves[2]. Pain-sensing nerves also make connections with the bone marrow, but can these neurons mobilize HSCs, too? Gao *et al.*[3] address this question on page 591 and identify a surprising role for chilli peppers.

This work is of potential clinical as well as biological importance. For people who have blood cancers such as aggressive leukaemia, lymphomas and multiple myeloma, an essential part of treatment, following high-dose chemotherapy, is autologous stem-cell transplantation (ASCT)[4] — replacing damaged HSCs with healthy ones. To avoid the possibility of complications, ASCT uses an individual's own stem cells, which are collected from the blood before chemotherapy, then re-infused intravenously afterwards to regenerate damaged bone marrow.

This procedure requires a way to prompt healthy HSCs to leave their bone-marrow niche and enter the bloodstream to be collected. Since the 1990s, a secreted factor known as granulocyte-colony-stimulating factor (G-CSF) has been the most commonly used molecular prompt. The introduction of another prompt came in 2003 in the form of plerixafor, a small molecule that stops HSCs from remaining glued to the bone-marrow scaffold[4]. Since then, advances have included different routes of administration and combining G-CSF with plerixafor. But in a fraction of people, HSCs still do not mobilize sufficiently, with clinical risk factors including age, genetics and the type of cancer (up to 25% of people with lymphoma show poor mobilization), as well as repeated rounds of chemotherapy[5]. So, there is an urgent need to understand the molecular mechanisms of HSC mobilization[4].

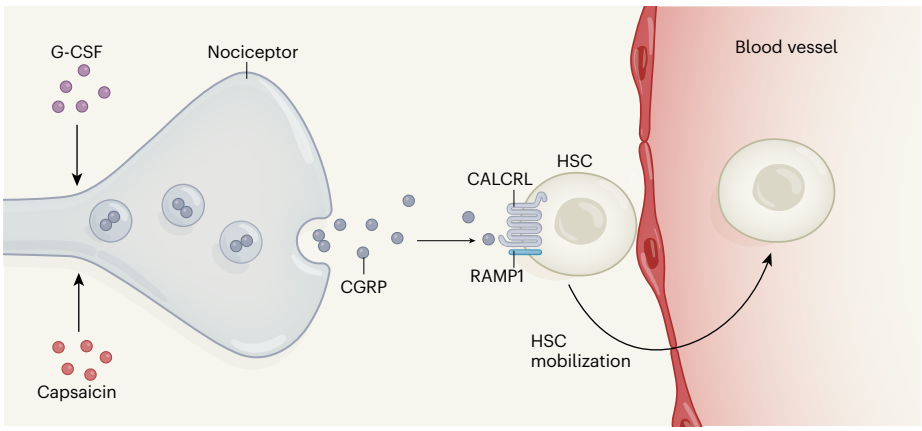

Figure 1 | Pain-sensing nerve cells regulate the mobilization of haematopoietic stem cells. Gao and colleagues[3] report that most nerves in the bone marrow are neurons called nociceptors. They find that stimulation of these nerves by the protein granulocyte-colony-stimulating factor (G-CSF), or by a component of chilli peppers called capsaicin (it is not known whether stimulation was direct or indirect), leads the cells to release the neurotransmitter molecule calcitonin-gene-related peptide (CGRP). In turn, CGRP binds directly to blood stem cells called haematopoietic stem cells (HSCs) through a receptor dimer comprising the CALCRL and RAMP1 proteins. This stimulates the HSCs to move from the bone marrow into blood vessels.

Enter Gao and colleagues. The authors began with an immunofluorescent imaging survey of the bone marrow's nerve fibres in mice, revealing most to be 'nociceptive' nerves. These nociceptors are sensory neurons that protect organisms from danger by eliciting pain in response to injury. Nociceptors can be found in any area of the body that senses noxious stimuli[6]. These neurons have been best investigated in barrier tissues such as the skin and gut. The biological role of nociceptors in non-barrier tissues, such as the bone marrow, remains poorly studied with the exception of pain perception.

To examine a possible role of nociceptors in maintaining haematopoiesis, Gao *et al.* used pharmacological and genetic strategies to eliminate these neurons. This had no effect on the maintenance of HSCs in the bone marrow. It did lead to a marked reduction of G-CSF-induced mobilization of HSCs to the bloodstream, which suggests that this class of neuron affects HSC adhesion or migration.

Calcitonin-gene-related peptide (CGRP) is a major neurotransmitter molecule secreted by nociceptor neurons[6]. Gao *et al.* found that administering CGRP greatly improved HSC mobilization following treatment with G-CSF, plerixafor, or both. They also observed that CGRP affects HSCs directly (rather than acting indirectly through the bone marrow), inducing the formation of a dimeric receptor comprising the CALCRL and RAMP1 proteins on the HSC surface (Fig. 1). Genetically engineering mice to lack either of these in bone-marrow HSCs resulted in defective HSC mobilization.

In the clinic, continuous rounds of chemotherapy often lead to a decrease in HSC mobilization — a deficit that Gao *et al.* recapitulated by treating mice with five weekly cycles of the chemotherapy drug cisplatin. Remarkably, administering CGRP restored HSC mobilization in these animals. This is a potentially crucial finding that could greatly improve protocols for HSC collection in 'poor mobilizer' individuals.

Certain types of spicy food can trigger nociceptor activation, leading Gao *et al.* to wonder whether consuming spicy food might cause HSC mobilization. To test this idea, the authors fed mice a diet rich in capsaicin — an active component of chilli peppers. This spicy fare increased the levels of CGRP in the extracellular fluid of the bone marrow, and increased the CGRP-induced mobilization of HSCs. The effect disappeared when nociceptors were blocked pharmacologically, indicating that these neurons mediated the effect of the capsaicin-rich diet.

This paper adds intriguing pieces to our

picture of the connections between the nervous system, bone marrow and blood-cell development. Early studies using photomicrographs of neurons in the bone marrow showed that it is innervated by nerve fibres[7]. During the past decade, surgical, pharmacological and genetic denervation models have established the nervous system's role in regulating the HSC niche[8]. But these studies mainly focused on sympathetic nerve fibres (those involved in involuntary actions of the body), showing that they help to maintain the functional integrity of the niche[9]. Here, Gao *et al.* have found that the adhesion of HSCs to their bone-marrow niche and their ability to mobilize to the peripheral blood is controlled by nociceptive neurons acting directly on HSCs through secretion of the neurotransmitter CGRP.

Surprisingly, the authors did not detect neuron-induced changes in the cell-surface levels of CXCR4, CD44 and VLA4 — molecules known to be expressed on HSCs and associated with their trafficking. Future studies, then, will need to delineate the precise mechanisms that mediate HSC mobilization following CALCRL–RAMP1 stimulation. It is also not known whether G-CSF affects nociceptors directly or indirectly through other cell types in the marrow. Such questions can be addressed using cell-type-specific gene targeting in animals. Moreover, findings that might be relevant to humans would need to be validated in clinical trials, because human biology is often not perfectly reflected in mice.

Finally, we should also consider stress responses in the bone marrow and their effects on neurons: for example, leukaemia induces nerve damage in the marrow[10], so it will be valuable to study the effects of blood cancers and ageing specifically on bone-marrow nociceptors. These issues notwithstanding, a robust molecular understanding of the neural regulation of haematopoiesis is now beginning to emerge.

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1. Crane, G. M., Jeffery, E. & Morrison, S. J. *Nature Rev. Immunol.* **17**, 573–590 (2017).
2. Méndez-Ferrer, S., Lucas, D., Battista, M. & Frenette, P. S. *Nature* **452**, 442–447 (2008).
3. Gao, X. *et al. Nature* **589**, 591–596 (2021).
4. To, L. B., Levesque, J.-P. & Herbert, K. E. *Blood* **118**, 4530–4540 (2011).
5. Donmez, A., Yilmaz, F., Gokmen, N. & Tombuloglu, M. *Transfus. Apher. Sci.* **49**, 485–488 (2013).
6. Dubin, A. E. & Patapoutian, A. *J. Clin. Invest.* **120**, 3760–3772 (2010).
7. Calvo, W. *Am. J. Anat.* **123**, 315–328 (1968).
8. Agarwala, S. & Tamplin, O. J. *Trends Cell. Biol.* **28**, 987–998 (2018).
9. Picoli, C. C. *et al. Stem Cells Transl. Med.* https://doi.org/10.1002/sctm.20-0284 (2020).
10. Hanoun, M. *et al. Cell Stem Cell* **15**, 365–375 (2014).

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Climate science

A seasonal solution to a palaeoclimate puzzle

Jennifer Hertzberg

Scientists have long been baffled by the mismatch of climate simulations of the past 12,000 years with temperature reconstructions from geological records. It now emerges that seasonal biases in the records explain the disparity. **See p.548**

Understanding past climate change is crucial for putting modern global warming in context. Reconstructions of climate during the Holocene — the current interglacial epoch, which began 11,700 years ago — based on geological evidence suggest that a peak in global mean annual temperatures between 10,000 and 6,000 years ago was followed by a cooling trend, which then reversed in the post-industrial era[1,2]. However, computational simulations of Holocene climate reveal only a long-term warming trend[3]. On page 548, Bova *et al.*[4] report an analysis that effectively brings Holocene climate reconstructions in line with computational simulations. This result has important implications for our understanding of the drivers of climate change during the Holocene and for the context of post-industrial warming.

To reconstruct past climates, scientists rely on proxies: geological materials that have properties that can be measured and correlated with modern climate parameters. The apparent temperature peak during the early Holocene (known as the Holocene thermal maximum) is a prominent feature in global syntheses of proxy-based climate reconstructions[1,2] (Fig. 1). Its notable absence from computational modelling has been dubbed the Holocene temperature conundrum, and has puzzled climate scientists for years[3]. The disagreement has been attributed to seasonal biases in proxy reconstructions[5] — that is, the proxies reflect the evolution of seasonal temperatures, rather than mean annual ones — and to deficiencies in modelling[6]. Notably, global proxy syntheses are dominated by sea surface temperature (SST) records (see ref. 2, for example), which are known to be seasonally biased[5].

Bova and colleagues' new method identifies seasonal biases in SST records and enables the calculation of mean annual SST from seasonal SST. It takes advantage of the characteristics of the last interglacial period (128,000–115,000 years ago), which was marked by mild global temperatures, smaller ice sheets and higher sea levels than those of

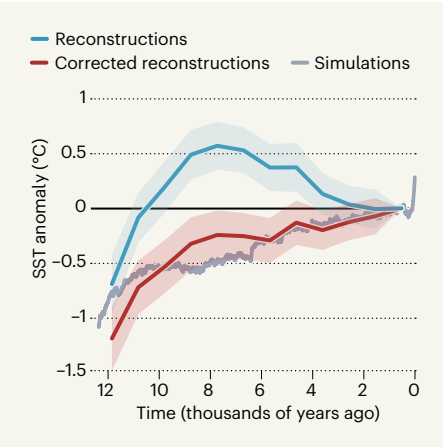

Figure 1 | Correcting seasonal bias in climate reconstructions. Average global temperatures during the Holocene (the current interglacial epoch, which began 11,700 years ago) can be reconstructed from geological records. These reconstructions (blue line) suggest that sea surface temperatures (SSTs) peaked between 10,000 and 6,000 years ago, then declined until the post-industrial period, when temperatures began to rise. However, computational simulations of Holocene SSTs don't match those reconstructions, probably because the geological records are seasonally biased — the records reflect the evolution of seasonal temperatures, rather than mean annual temperatures. Bova *et al.*[4] report a method that quantifies and corrects for seasonal bias in marine geological records, and use it to estimate mean annual SSTs (red line). The corrected data match the computational simulations, thus resolving a long-standing problem in this field. SSTs are shown as anomalies: the difference between the SST of a reference time interval and the average SST between 0 and 1,000 years ago. Shaded areas represent the bounds of one standard error.