wall expansion. However, the gas leads to instabilities that result in the laser beams scattering and carrying energy back out of the hohlraum. This, in turn, reduces the hohlraum temperature, disrupting the radiation symmetry and exciting problematic energetic electrons.

Researchers have previously overcome this problem by reducing the density of the gas in the hohlraum. But the hohlraum wall expands more quickly when the gas density is lower, so a faster implosion is required, which, in turn, means that more power is needed. The team's solution to this particular problem is a feat of material and capsule engineering: a precision capsule shell made from polished polycrystalline diamond. The high-density material leads to better X-ray absorption, and requires shorter laser pulses and a thinner shell. As a result, the same size of capsule can hold a larger volume of fuel, which makes it more efficient in forming a central hotspot than capsules made from other materials[4].

Zylstra *et al*. used two strategies to optimize their experimental design. The first involved shifting the wavelength of the laser beams with the help of a photonic structure created in the plasma at the entrance to the hohlraum where the laser beams crossed, an established symmetry-tuning technique[5]. This effectively transferred energy from the laser beams focusing near the hohlraum entrance to those focusing in the interior. This energy transfer kept the hohlraum interior hot and the radiation field on the capsule uniform, thereby enabling a high-speed, symmetrical compression and resulting in efficient conversion of kinetic energy to heat.

Two of the experiments used a second strategy of changing the hohlraum from a simple cylinder to a dumb-bell shape. Having a radius slightly wider close to the laser entrance lessens the impact of hohlraum-wall expansion on the passage of the laser beams through the hohlraum. This reduces the wavelength shift needed to maintain the hohlraum temperature and radiation symmetry[6]. In the two companion papers, Kritcher *et al*. used computational models to investigate these two strategies, and Ross *et al*. detailed the thorough experimental testing of the optimized design.

The authors are confident that further improvements in performance will result in an ignited plasma, in which thermonuclear output power exceeds all loss mechanisms. And, in fact, they have already achieved this: in August last year, the NIF team announced an ignited deuterium–tritium plasma with a yield of 1.3 MJ and a gain of 0.7 (the gain represents the ratio of output energy to input laser energy). At present, the burning plasma is confined to the gaseous hot region at the centre of the fuel, and thus much higher gains will be required to convert the cooler fuel surrounding this hotspot into a burning plasma as well.

The achievements reported in the three papers advance the physics of burning and self-heating plasmas, enabling a whole range of scientific studies. Some of these pursuits will be key to national security, because the NIF is funded as part of the US programme to improve understanding of nuclear weapons and extreme environments (see *Nature* **597**, 163–164; 2021). It remains unclear whether this research will lead to a viable future power source. But the goal of developing a fuel that mitigates the dangers of climate change, while enabling us all to enjoy the benefits of electricity, is clearly worth pursuing.

Nigel Woolsey is in the Department of Physics, University of York, York YO10 5DD, UK.
e-mail: nigel.woolsey@york.ac.uk

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Physiology

Cardiac disease disrupts the bone-marrow niche

Tomer Itkin & Shahin Rafii

The production of blood cells, including some immune cells, relies heavily on the bone-marrow microenvironment. Cardiovascular diseases are now found to corrupt this niche, leading to imbalances in blood-cell production.

According to the World Health Organization, cardiovascular diseases are the world's leading cause of death (go.nature.com/3dvysp6). The development and progression of cardiovascular disease (CVD) could be influenced by a perturbation in the balance of haematopoiesis, the process by which blood cells (including immune cells) are generated from haematopoietic stem and progenitor cells (HSPCs). Indeed, inflammatory blood cells that are derived from haematopoietic progenitor cells in the bone marrow have been implicated in cardiovascular disorders such as atherosclerosis, a condition in which cholesterol builds up in the arteries; myocardial infarction (heart attack); and ischaemia, a form of heart failure that results from a lack of oxygen supply (reviewed in ref. 1). This relationship between the cardiac and haematopoietic systems was thought to be unidirectional. However, writing in *Nature Cardiovascular Research*, Rohde *et al*.[2] provide evidence from individuals with CVD, as well as from mouse models of such disease, suggesting that the crosstalk between the cardiovascular system and the bone marrow is bidirectional.

In adult mammals, haematopoiesis occurs mostly in the bone marrow, and is supported by specialized microenvironments — known as niches — in which haematopoietic stem cells and HSPCs reside and are maintained[3]. Vascular endothelial cells line the blood vessels that provide the body with oxygen and nutrients and enable the movement of immune cells from the bloodstream to the organs, and these endothelial cells also form a crucial component of stem-cell niches in various parts of the body, including in the bone marrow, thus guiding organ development and regeneration[4].

Several lines of evidence have indicated that the bone-marrow microenvironment organizes the processes of immune surveillance and immune responses in the rest of the body, by sensing stress-associated factors from other organs and mobilizing the appropriate inflammatory and immune cells to the bloodstream. The ability of bone-marrow niches to stimulate the HSPCs that give rise to the necessary inflammatory and immune cells thus enables reciprocal communication between the bone marrow and remote perturbed organs.

For example, various molecular and neural signals from the central nervous system influence the bone-marrow niche and thus modulate cell movement from the niche, as well as affecting 'decisions' about the specifications of newly formed immune cells[5]. Similarly, the collection of microorganisms living in the gut can affect bone-marrow haematopoiesis[6]. Moreover, pancreatic damage associated with diabetes alters the bone-marrow niche in a way that impairs the mobilization of HSPCs into the blood (a process that is stimulated to enable HSPC transplants for therapeutic purposes)[7].

Rohde and colleagues investigated how cardiovascular disorders can affect

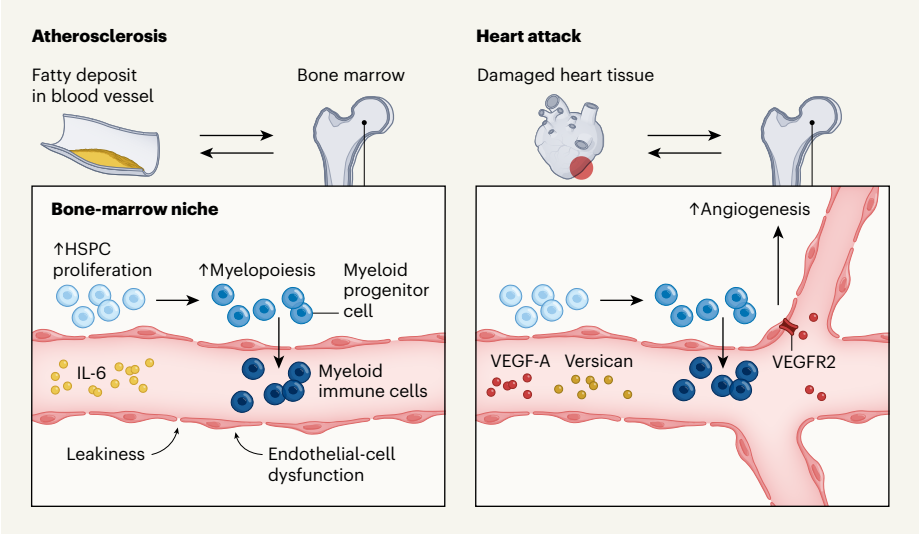

Figure 1 | Cardiovascular conditions impair the bone-marrow microenvironment and blood-cell production. An increase in the production of circulating myeloid immune cells by myelopoiesis (the proliferation of myeloid progenitor cells) worsens the outcome of cardiovascular diseases. Rohde *et al.*[2] show that such diseases, in turn, can affect haematopoiesis (the production of blood cells). They examined people with cardiovascular diseases, together with mouse models of high blood pressure (not shown), atherosclerosis (a condition in which fatty deposits build up in the arteries; left) and myocardial infarction (a heart attack; right). The authors report that, in these conditions, the bone-marrow microenvironment (niche) is disrupted, leading to increased proliferation of haematopoietic stem and progenitor cells (HSPCs) and increased myelopoeisis, accompanied by leakiness of the vascular barrier and increased mobilization of myeloid immune cells into the blood. These diseases also increase the levels of proteins such as interleukin-6 (IL-6), VEGF-A and versican that can promote the formation of new blood vessels (angiogenesis) and the leakiness of existing ones. VEGF-A does this by binding to the VEGFR2 protein, which was more highly expressed by bone-marrow endothelial cells in mice after myocardial infarction.

haematopoiesis by influencing the vascular endothelial cells that line the blood vessels in the bone marrow. The authors found that, compared with healthy control individuals, individuals with hypertension (high blood pressure), people with hypertension and atherosclerosis, or those who had recently had an acute myocardial infarction, all showed increased haematopoiesis and, more specifically, increased numbers of myeloid immune cells derived from a subtype of HSPC called myeloid progenitor cells.

They then examined haematopoiesis in three different mouse models of hypertension, which is a risk factor for severe types of CVD, such as atherosclerosis and myocardial infarction. All hypertensive mice showed increased haematopoiesis and myelopoiesis (the proliferation and differentiation of myeloid progenitor cells), indicating that changes in haematopoiesis can not only precede, but also result from, CVD.

Next, Rohde and co-workers focused on the niche formed by blood vessels in the bone marrow in mouse models of hypertension, atherosclerosis and myocardial infarction. The mice all had profound changes in the blood-vessel architecture of the bone marrow compared with healthy mice. For example, the walls of bone-marrow blood vessels in mice with hypertension or atherosclerosis were thicker than normal, and the density of blood vessels in the bone marrow (but not muscle) was increased in mice with hypertension or after myocardial infarction (Fig. 1).

A separate study[8] of endothelial cells lining the vessels in the bone marrow in mice and humans after myocardial infarction reported the loss of a specialized subtype of bone-marrow blood vessel called type-H vessels[9]; these are enriched in a tissue region called the endosteum, which lines the bone cavity containing the marrow. After myocardial infarction, endothelial cells in these vessels showed a form of inflammation-driven cell death, and had increased levels of a protein called MYC[8].

"This study describes a bidirectional regulatory loop between the bone marrow and the cardiovascular system."

Artificially increasing the expression of MYC in type-H endothelial cells resulted in the induction of their programmed cell death. However, an increase in MYC levels in other bone-marrow endothelial-cell subtypes after myocardial infarction might promote the formation of new blood vessels[10]. Indeed, in the bone marrow of mice that had had a myocardial infarction, Rohde *et al.* observed clusters of immature myeloid cells along with newly formed blood vessels. Taken together, Rohde and colleagues' findings suggest that increased myelopoiesis might occur in the vicinity of newly formed bone-marrow blood vessels after myocardial infarction, while other types of blood vessel disappear from the marrow, possibly affecting other aspects of haematopoiesis and bone homeostasis.

The authors examined the integrity of the blood-vessel wall separating the bone marrow from the bloodstream. Increasing the permeability of this barrier is known to promote the movement of immune cells into the bloodstream, while reducing the number of haematopoietic stem cells by accelerating their differentiation (particularly into myeloid cells) and by inducing their programmed cell death[11]. Consistent with this, Rohde and co-workers found that the permeability of the blood-vessel walls in the bone marrow was increased in mice with hypertension, atherosclerosis or myocardial infarction.

The activation of a receptor protein called VEGFR2 on endothelial cells by its ligand molecule, VEGF-A, not only stimulates blood-vessel formation and growth, but can also increase the permeability of existing blood vessels[12]. Rohde *et al.* show that myocardial infarction in mice leads to an increase in VEGF-A levels in the blood, and in haematopoietic myeloid and non-haematopoietic cells in the bone marrow. Furthermore, the authors show that treating mice with antibodies that block VEGFR2 prevents the increase in blood-vessel growth and myelopoiesis after myocardial infarction. These findings are consistent with a report showing that VEGFR2 in bone-marrow endothelial cells is crucial for the regrowth of bone-marrow vessels and recovery of haematopoiesis after irradiation or chemotherapeutic treatment in mice[13]. Similarly, Rohde and colleagues found that two other molecular factors that drive blood-vessel growth – interleukin-6 and versican – were increased in bone-marrow endothelial cells and promoted haematopoiesis in the mouse models of atherosclerosis and myocardial infarction, respectively.

Although this study used highly sophisticated models to uncover a two-way conversation between the bone-marrow vascular niches and the stressed cardiac tissue, there are several unknowns that need to be investigated further. For example, the source of the molecular factors that stimulate blood-vessel growth (that is, angiogenic factors) in CVDs remains to be determined. It is not clear whether these factors were released in the bone-marrow vascular niche, or by endothelial cells in the blood vessels of other organs, such as the lungs, liver and spleen. In future, it would be helpful to characterize the response to CVDs of various

subtypes of endothelial cell — in different organs as well as in the bone marrow — and to determine whether these endothelial cells modulate distinct features of haematopoiesis.

Genetic tools for specifically manipulating the expression of angiogenic factors in various bone-marrow cell types and endothelial-cell types are currently lacking. However, large, computationally analysed data sets describing the gene-expression profiles of endothelial cells in various organs[14] and of distinct endothelial-cell subtypes in the bone marrow[15], combined with genetic tools developed in mice to manipulate diverse types of cell expressing unique sets of genes[16], could potentially be used to investigate the responses of distinct subtypes of blood vessel in different tissues.

Most of the data presented by Rohde *et al.* were derived from mouse models. Therefore, whether a similarly aberrant 'conversation' between the bone marrow and the cardiac tissues occurs in humans, and whether it is mediated by similar factors, should be investigated further — for example, by using 3D systems called vascularized organoids that are made of human cells and that contain human blood vessels[17].

Overall, this study describes a bidirectional regulatory loop between the bone marrow and the cardiovascular system (Fig. 1). In a vicious circle, cardiovascular conditions disrupt the homeostatic balance of the haematopoietic niche, leading to increased production of inflammatory immune cells that, in turn, can worsen the CVD. Restoring a healthy conversation between the cardiovascular system and the bone marrow — perhaps using anti-inflammatory therapy or by restoring the normal function and homeostasis of vascular endothelial cells — could help to reset the balance of the bone-marrow niche and promote cardiac repair.

Tomer Itkin and **Shahin Rafii** are in the Division of Regenerative Medicine, Ansary Stem Cell Institute, Department of Medicine, Weill Cornell Medicine, New York, New York 10021, USA.
e-mails: toi2003@med.cornell.edu; srafii@med.cornell.edu

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