News & views

Stem cells

Exercise generates immune cells in bone

Mehmet Saçma & Hartmut Geiger

A specialized type of bone-cell progenitor has been identified in the bone marrow, and shown to support the generation of immune cells called lymphocytes in response to movement. See p.438

It is pretty crowded in the bone marrow. Many types of stem and progenitor cell, including progenitors of immune cells, coexist side-by-side[1,2] and are supported by nearby cells that generate specialized protective environments for the stem cells, called niches. The interplay between the cells of the niche, also known as stromal cells, and early progenitors of immune cells in the bone marrow is poorly understood. Insight into how this interplay is coordinated would help us to better understand how progenitors of immune cells are generated. On page 438, Shen *et al.*[3] have solved part of the puzzle by identifying a role for movement in stimulating communication between one type of stromal cell and immune progenitors in mice, ultimately helping the animals to fight infection.

The various types of stem and progenitor cell in the bone marrow are highly interconnected, both physically and functionally. For instance, mesenchymal stem and progenitor cells, which give rise to bone, skeletal tissue and fat cells, are an essential part of the stromal niche for haematopoietic stem and progenitor cells (HSPCs). HSPCs, in turn, are responsible for the production of all blood-cell lineages, including immune cells[4]. In mice, some mesenchymal progenitors produce a signalling protein, called stem cell factor (SCF), that is crucial for supporting HSPCs[5]. These cells also express a cell-surface protein called the leptin receptor[5] (LepR). LepR-expressing ($LepR^+$) cells reside in several distinct locations in bone marrow, including around two types of blood vessel, arterioles and sinusoids. However, the $LepR^+$ population is a mixture of mesenchymal progenitor cell types[5]. Shen *et al.* set out to home in on the subset of $LepR^+$ cells involved in maintaining the HSPC niche.

The authors performed a gene-expression analysis of $LepR^+$ cells, which revealed that one subpopulation also expresses another marker protein, osteolectin (Oln). The group generated mice in which these Oln^+ cells fluoresced, and found that Oln^+ stromal cells reside around arterioles but not sinusoids. They then demonstrated that the cells are short-lived osteogenic progenitors, which give rise to bone-forming cells called osteoblasts that have a crucial role in bone regeneration.

Shen and colleagues then engineered mutant mice to lack the gene encoding SCF in Oln^+ cells. The resulting lack of SCF in Oln^+ cells did not affect haematopoietic stem cells or most other types of haematopoietic progenitor cell in the bone marrow. However, it did lead to a significant reduction in the number of one special type of haematopoietic progenitor — the common lymphoid progenitor (CLP), which gives rise to immune cells called lymphocytes. In support of the idea that the Oln^+ cells help to generate and maintain CLPs, the authors demonstrated that Oln^+ cells and CLPs reside close together in the bone marrow. They next infected the mutant mice with a disease-causing bacterium, *Listeria monocytogenes*, which is usually cleared from the body by lymphocytes. The mutant animals cleared the pathogen much less effectively than did controls. The animals simply did not produce enough lymphocytes to do the job, owing to the reduced number of CLPs.

Mechanical stimulation of bones, which occurs during exercise, is known to promote bone formation[6]. In a final set of experiments, Shen *et al.* placed mice in cages that had running wheels, and found that running led to a higher number of both Oln^+ cells and CLPs in bone marrow. The group found that the Oln^+ cells express the mechanosensitive ion channel protein Piezo1, and showed that CLP numbers are abnormally low in mice engineered to lack this protein. Thus, the authors have uncovered a previously unknown pathway by which exercise, sensed through the mechanosensitive protein Piezo1, triggers

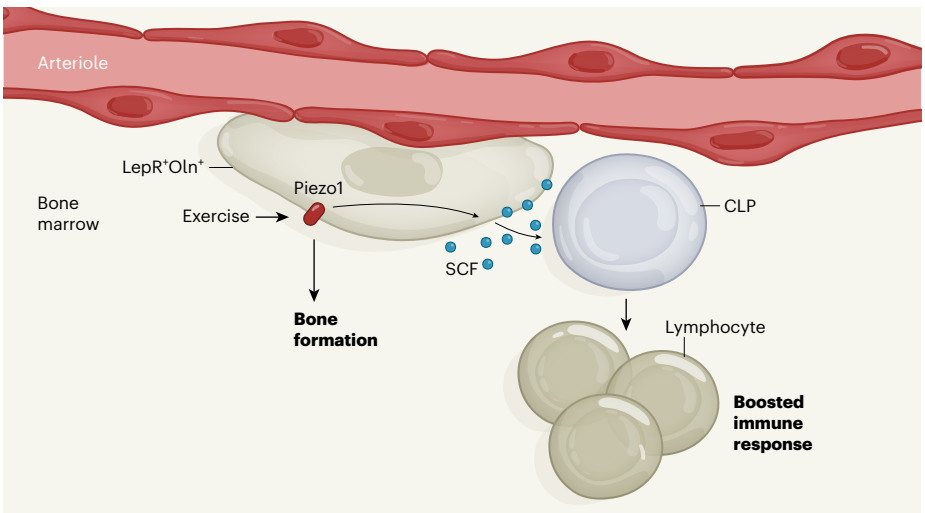

Figure 1 | From exercise to immune function. Shen *et al.*[3] have identified a population of bone-cell progenitors that resides alongside blood vessels called arterioles in the bone marrow of mice and that expresses the proteins leptin receptor (LepR) and osteolectin (Oln). Movements, such as exercise, lead to mechanical stimulation of bones, activating the mechanosensitive ion channel Piezo1 on the surface of these $LepR^+Oln^+$ cells. This has two effects. First, it triggers differentiation of the cells, leading to bone formation. Second, it leads to the expression and secretion of a signalling molecule called stem cell factor (SCF), which helps to maintain nearby common lymphoid progenitors (CLPs). Maintenance of the CLP populations renders them readily able to differentiate into cells of the immune system called lymphocytes that can fight bacterial infections.

SCF expression in osteogenic progenitors to help maintain CLPs, thereby controlling part of the function of the immune system (Fig. 1).

The discovery that mechanosensitive osteogenic progenitors have a role in fighting bacterial infections is exciting. It was known that movement can stimulate the immune system[7], but the advance in Shen and colleagues' work provides one reason why this is the case. If relevant to humans, the work could have direct clinical applications. For example, the pathway uncovered in the current study could be harnessed to develop better therapies to strengthen immune-cell output triggered by movement. A logical next step will be to test whether voluntary running can indeed improve bacterial clearance in mice. Another key question to address will be whether increasing the numbers of Oln$^+$ cells and CLPs in bone marrow would help to provide protection against other disease-causing bacteria, or even viruses, or whether it might also boost vaccination responses.

The authors also found that the number of Oln$^+$ niches, and the number of CLPs, was lower in the bone marrow of 18-month-old mice than in their 2-month-old counterparts. Aged animals are also active[8], so factors other than reduced movement might contribute to this ageing-related decline.

It would be interesting to investigate, for instance, whether the way in which Oln$^+$ niches sense mechanical stimulation changes over time, or whether epigenetic changes (modifications to DNA that can alter gene expression without changing the underlying DNA sequence) in aged Oln$^+$ cells make them less effective in generating signalling molecules such as SCF.

Mechanosensing is well established to play a part in bone physiology, but a crucial role for mechanosignalling has been also described for other cell types — for instance, pancreatic progenitor cells, intestinal stem cells and the endothelial cells that line blood vessels. Although less is known about the niches that support stem cells outside the bone marrow, the vasculature, and so endothelial cells, are prime candidates for forming such niches. It is possible, then, that mechanosensing in niche-forming endothelial cells might contribute to the maintenance of other types of stem and progenitor cell. If so, Shen and colleagues' work could have wide-ranging implications for stem-cell biology.

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Cell biology

Breaks in mitochondrial DNA rig immune response

Nandhitha Uma Naresh & Cole M. Haynes

Damage to DNA in a cellular organelle called the mitochondrion triggers an immune response in the nucleus. Mechanistic insights into this process shed light on how organelles communicate. **See p.477**

Mitochondria are membrane-bound organelles that act as hubs of metabolism and of innate immune signalling in cells. Each mitochondrion contains several copies of the mitochondrial genome (mtDNA), which can be damaged by extrinsic environmental stressors or intrinsic genetic mutations. This can cause degradation of the mtDNA, reducing the total number of mtDNA copies in the organelle and so leading to mitochondrial dysfunction. In addition, healthy mitochondrial function relies heavily on crosstalk between mitochondria and the nucleus[1,2]. Tigano *et al.*[3] uncover a mechanism on page 477 by which cells sense toxic mtDNA damage to initiate an immune response in the nucleus.

Conditions of acute stress, such as viral infection or irradiation, can lead to the activation of pro-death (apoptotic) pathways in the cell. Mitochondria have a key role in these pathways. Pore-forming proteins called BAK and BAX accumulate on the mitochondrial membrane, leading to the release of cell-death factors from the organelle into the cell's cytosolic fluid through a process called mitochondrial herniation[4]. In some instances, cell-death factors are not activated, in which case mitochondrial contents such as DNA and RNA are instead released into the cytosol[4]. The accumulation of cytosolic mtDNA and mtRNA initiates a potent antiviral response[5–7]. But precisely which aspects of mitochondrial dysfunction lead to the extrusion and accumulation of this mitochondrial material has been unclear.

Tigano *et al.* set out to examine one form of stress: cleavage of mtDNA. The group manipulated mammalian cells using 'molecular scissors' constructs called mitochondria-targeted TALENs (mTLNs), which

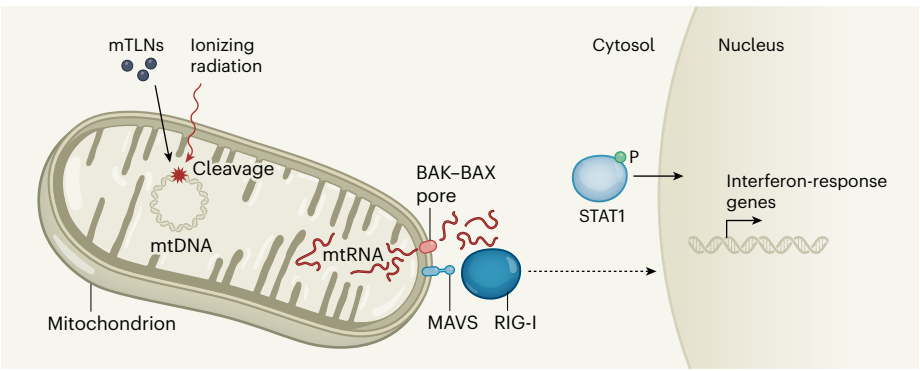

Figure 1 | Communicating damage between organelles. Tigano and colleagues[3] report a mechanism by which damage to DNA in an organelle called the mitochondrion is communicated to the nucleus. The group induced mitochondrial DNA (mtDNA) breaks, either by using 'molecular scissors' constructs called mitochondria-targeted TALENs (mTLNs) or through ionizing radiation. These treatments trigger the release of mtRNA into the cell's cytosol through pores comprising BAK and BAX proteins. Two proteins — the cytosolic RNA sensor RIG-I, acting with its adaptor protein MAVS — sense the mtRNA, triggering signalling pathways that lead to the upregulation of genes involved in an immune response called the interferon response (dashed lines indicate an indirect effect). In addition, the transcription factor STAT1 is phosphorylated (P), and moves to the nucleus, where it might have a role in activating interferon-response genes.