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Go with the flow—hidden vascular passages in bone

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Abstract

The circulatory system in long bones is incompletely understood. A new study published in *Nature Metabolism* unveils the presence of dense vascular networks in long bones that facilitate the egress of bone marrow cells and potentially the exchange of nutrients between the bone marrow and the systemic circulation.

The haemodynamics and structural basis of blood flow in bone have proven challenging to understand given the paucity of imaging modalities available to study vascular channels in this rather impenetrable microenvironment. Clues to the existence of a rich vascular supply emanated from experience on the battlefield, where resuscitation of soldiers with poor venous access is performed with inter-osseous infusions of fluid, which is followed by a rapid systemic response. Despite accumulating evidence for the presence of a complex blood supply in bone, the molecular mechanisms and anatomy underlying these rapid shifts of cells and fluid from bone marrow to the circulation have remained elusive. Writing in this issue of *Nature Metabolism*, Grüneboom et al.[1] provide important new insights into the anatomical architecture and physiology of the vascular system of long bones.

Applying several modern imaging technologies, such as light-sheet fluorescence microscopy (LSFM) and X-ray microscopy, the research team revealed canals along the entire bone shaft that cross the cortical bone perpendicularly. Aptly named trans-cortical vessels (TCVs), they form a direct connection between the endosteal and the periosteal circulation in compact bone (Fig. 1). According to the team's calculations, the majority of blood flowing in and out of bone passes through these canals.

Physiological skeletal remodelling is regulated by a continuous but asynchronous generation of osteoclasts by the differentiation factor receptor activator of NF-κB ligand (RANKL)[2],

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Competing interests

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which degrades bone, followedby the generation of new bone tissue by osteoblasts. During this process, osteoblasts can turn into osteocytes, which are fully encased in surrounding mineralized bone. Osteocytes form long cellular protrusions that run through canaliculi within bone tissue, forming direct contacts with cells on the bone surface via gap junctions[3]. The investigators demonstrate that bone resorption, from the inner bone surface (the endosteum) to the outer bone surface (the periosteum), is critical for the formation of TCVs, as pharmacological inhibition of bone-resorbing osteoclasts with bisphosphonates resulted in a substantial reduction in TCV numbers. Using mobilisation and migration assays in conjunction with intravital imaging of fluorescent neutrophils, the team also documented the passage of bone-marrow-derived neutrophils that migrated from bone marrow to the general circulation through TCVs.

To investigate whether TCVs might have a role in inflammatory and degenerative bone disorders, the authors studied mouse models of arthritis and old mice. Mice with chronic, but not acute, inflammatory arthritis developed more TCVs lined by endothelial cells providing sites for engagement of inflammatory cells. In mice aged 20–28 months, the number of TCVs was markedly reduced, which may reflect the known decrease in osteocytes with age. Using intraoperative images of human bone surfaces, high-resolution 7T high-field magnetic resonance imaging and LSFM, the research team identified canal-like structures entering compact bone along with visible nutrient arteries and vessels that structurally resemble TCVs. The presence of TCVs in human bone requires confirmation but if established will undoubtedly have important implications for health and disease.

In support of the findings by Grüneboom et al.[1], a recent study demonstrated the presence of similar microscopic channels that cross the skull and connect directly with the brain surface in a murine model of ischaemic stroke[4]. Cells infiltrating the ischaemic area were more likely to emanate from skull cortical bone adjacent to the injury than tibial bone marrow in these mice. These data corroborate the existence of vascular channels that facilitate local cellular egress from the adjacent marrow in response to injury.

Bone canals that connect bone marrow to the synovium have also been previously described in murine arthritis models and in patients with rheumatoid arthritis. These canals are likely the same TCVs as described in the Grüneboom et al.[1] study. Increased numbers of bone marrow cells and widening of subchondral bone canals were reported in murine experimental models of inflammatory arthritis[5]. In an imaging study of patients with rheumatoid arthritis, micro computed tomography (micro-CT) analysis of the bare area of the metacarpal heads in the hands, where no synovium is present, showed a marked increase in cortical micro-channels compared with healthy individuals. These channels were noted to be present in the early phases of joint inflammation[6]. The current understanding is that the immune cells observed in the synovial tissues of murine inflammatory arthritis models migrate to the inflamed synovium or pannus on the external surface of bone from the systemic circulation; this means that they come from the ‘outside’. The data provided by Grüneboom et al.[1], however, support an alternative mechanism by which cells travel to the joint from the underlying bone marrow, coming from the ‘inside’.

The implications of the newly discovered canals in bone in relation to blood flow and cell trafficking are multiple and potentially of great significance. The regulation of myeloid egress from bone marrow is critical in both the development and resolution of inflammatory arthritis[7]. For example, in inflammatory arthritis, many pro-inflammatory cytokines increase joint inflammation by inducing myelopoiesis in the bone marrow. Blocking migrationof cells from bone marrow to periosteum could thus form a viable new strategy for the treatment of inflammatory arthritis. Exploring mechanisms that promote cell transport from marrow might also be worthwhile. The localisation of hematopoietic stem cells in the bone marrow niche adjacent to blood vessels strongly suggests that bone-marrow-derived cells are mobile and regularly enter and exit the circulation. Furthermore, restricted blood flow in bones impairs osteogenesis and angiogenesis[5]. By controlling blood flow in bone, one may influence many aspects of bone biology, including bone aging, fracture repair and inflammatory arthritis as well the response to ischaemic stroke[8].

The significance of the TCVs connecting bone marrow with the general circulation in human bones also raises new questions about skeletal remodelling. Since osteocytes are a source of RANKL[9], direct contact of osteoclasts with the osteocyte canaliculi network suggests a critical role for osteocytes in bone metabolism and remodelling. Although the discovery of TCVs and the tantalising images in the study of Grüneboom et al.[1] allow us to envision a more direct interaction between osteocytes and osteoclasts than previously recognized, more definitive studies that apply the imaging modalities from this study to inflamed and damaged human bone and joint tissues are required to confirm these observations. Future work needs to address not only the interaction of osteoclasts and osteocytes, but also the role of blood flow in this closed circulatory system and its bi-directional regulation of trafficking of cells and insoluble mediators.

The results from the elegant study by Grüneboom et al.[1] prompt us to reconsider basic assumptions of bone anatomy, physiology and function and to consider interventions that regulate blood flow and cell transit in bone marrow as potential therapeutic strategies[10] to resolve inflammation and tissue injury across the disease spectrum of infammatory arthritides.

References

1. Grüneboom A et al. Nat. Metab 10.1038/s42255-018-0016-5 (2019).
2. Teitelbaum SL Bone resorption by osteoclasts. Science 289, 1504–1508 (2000). [PubMed: 10968780]
3. Stains JP & Civitelli R Biochim. Biophys. Acta 1719, 69–81 (2005). [PubMed: 16359941]
4. Herisson F et al. Nat. Neurosci 21, 1209–1217 (2018). [PubMed: 30150661]
5. Marinova-Mutafchieva L, Williams RO, Funa K, Maini RN & Zvaifler NJ Arthritis Rheum. 46, 507–513 (2002). [PubMed: 11840454]
6. Werner D et al. Arthritis Rheumatol. 69, 1580–1587 (2017). [PubMed: 28493323]
7. Ortega-Gómez A, Perretti M & Soehnlein O EMBO Mol. Med 5, 661–674 (2013). [PubMed: 23592557]
8. Ramasamy SK et al. Nat. Commun 7, 13601 (2016). [PubMed: 27922003]
9. Nakashima T et al. Nat. Med 17, 1231–1234 (2011). [PubMed: 21909105]
10. Fullerton JN & Gilroy DW Nat. Rev. Drug Discov. 15, 551–567 (2016). [PubMed: 27020098]

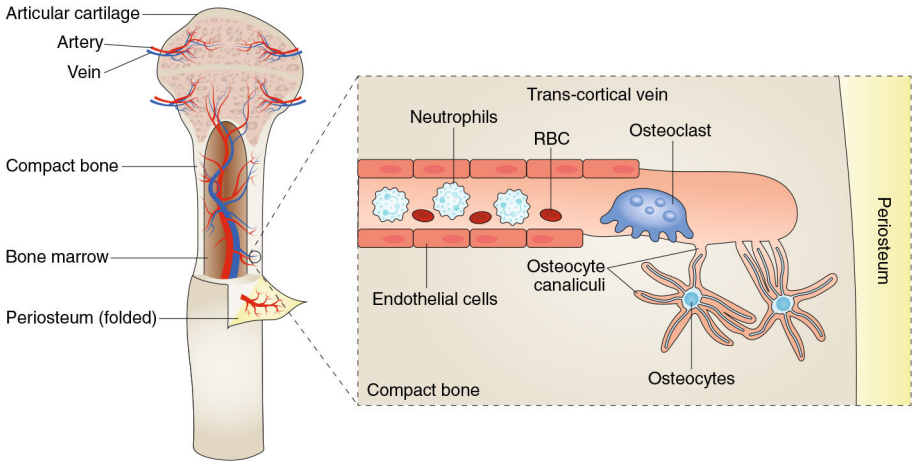

Fig. 1 |. Formation and function of trans-cortical vein canals within compact bone.

Schematic of bone microarchitecture showing the formation of trans-cortical vein canals by osteoclasts within compact bone lined by endothelial cells. This allows the egress of neutrophils and other bone marrow cells and potentially facilitates the exchange of nutrients that enter the general circulation at the periosteum interface. RBC, red blood cell.