Bone biology: vessels of rejuvenation

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Bone biology: vessels of rejuvenation

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The identification of specialized endothelial-cell populations in the blood vessels of bones, and their signalling pathways, reveals how the vasculature contributes to bone formation. See Article p.323 & Letter p.376

The different structural and metabolic requirements of organs and tissues prompt the formation of specialized blood vessels during development[1], which deliver molecules that instruct tissues on their fates[2, 3]. This process requires crosstalk between organs and the vasculature: organs generate local growth factors that attract blood vessels toward metabolically active regions, and the vessels release molecules (known as angiocrine signals) that affect cell differentiation in the developing organs. It is becoming increasingly clear that these interactions are influenced by the endothelial cells that line the inner surface of blood vessels. In two papers[4, 5] in this issue, Adams and colleagues demonstrate that the bone vasculature contains specialized endothelial cells with signalling properties that support bone maturation and regeneration. As well as providing insight into the tissue specificity of angiocrine signalling, the findings have direct clinical relevance.

In the first paper, Kusumbe et al.[4] (page 323) began by mapping gene expression, metabolic activity and cell-surface markers in the developing postnatal bone vasculature of mice. The authors distinguished two new subpopulations of endothelial cell (EC) that they term type H and type L ECs. Interestingly, they found that osteoprogenitor cells, which differentiate into bone-forming osteoblasts, preferentially associate with type H ECs because these cells are a rich source of several growth factors relevant for the survival and proliferation of osteoprogenitors (Fig. 1). With age, however, both the type H EC and the osteoprogenitor populations decline. The authors also report that type H and type L ECs express different levels of the α-subunit of hypoxia-inducible factor-1 (Hif-1α), a transcription factor that plays a central part in regulating cell metabolism and forming new blood vessels (angiogenesis)[6].

To assess the functional relevance of this protein in the endothelium, the authors genetically manipulated Hif-1α levels, and found that loss of the protein strongly reduced the number of type H ECs and osteoprogenitors, without affecting type L ECs. Conversely, enhanced Hif-1α expression increased the number of type H ECs, particularly in the metaphysis region of long bones, and this was accompanied by a significant increase in osteoprogenitor numbers and bone formation.

The observation that proliferation of type H ECs and osteoprogenitor formation positively correlates with endothelial Hif-1α levels raised the idea that Hif-1α augmentation might induce angiogenesis and osteogenesis in aged animals, in which bone formation is impaired. To test this, the authors[4] treated aged mice with deferoxamine mesylate (DFM), a chemical that inhibits Hif-1α degradation by targeting PHD enzymes, and observed a substantial expansion of type H ECs, osteoprogenitors and osteoblasts, and an increase in bone mass. These findings suggest that inducing type H ECs is key to maintaining bone remodelling during ageing.

Ramasamy et al.[5] (page 376) further investigated the crosstalk between the endothelium and osteogenesis by studying the endothelial Dll4–Notch signalling pathway, which has previously been defined as a negative regulator of angiogenesis in many organs[7]. Surprisingly, the authors found that Dll4–Notch signals positively regulate angiogenesis in postnatal long bones — highlighting the unusual properties of bone endothelium. Loss of endothelial Notch signalling in mice was associated with reduced bone mass and shortening of long bones and, conversely, activating these signals augmented osteogenesis and bone size. In line with type H ECs playing a key part in bone blood-vessel growth and osteogenesis, this cell population increased on activation of endothelial Notch.

The authors[5] next analysed factors secreted by ECs in mice that were genetically engineered to have active Notch signalling, and found a strong upregulation of Noggin, an antagonist of growth factors collectively known as bone-morphogenetic proteins. Administering Noggin to Notch-deficient mice restored angiogenesis and bone formation, and the molecular mechanism underlying this rescue was traced to effects of Noggin on restoring both local expression of the protein Sox9, which is relevant for initiating the cartilage–bone transition, and levels of vascular endothelial growth factor. Thus, Notch and the angiocrine release of Noggin link the type H endothelium to osteogenesis.

These findings generate several questions. For example, how can Notch signalling switch between negative[7] and positive regulation of angiogenesis in a tissue-specific manner? Ramasamy and co-workers suggest that this may involve Hes5, a transcription-regulating protein that acts downstream of Notch, but other environmental and tissue-specific cues may be involved. The demonstration that Hif-1α is crucial in maintaining the type H EC population, but that these cells are lost in aged animals, suggests that loss of Hif-1α signalling may be involved in age-related bone changes. If so, what regulates Hif-1α in aged animals? Obvious candidates for involvement in Hif-1α degradation are the oxygen-sensitive PHD enzymes[8]. Also, do the Notch and Hif-1α signalling cascades interdependently regulate the type H endothelium? And might changes in EC populations affect other bone cells, such as haematopoietic stem cells in the endosteum tissue layer of bones?

In addition to prompting these biological questions, Adams and colleagues' work[4, 5] has important clinical implications. Bone is continually deposited by osteoblasts, which are activated by bone fractures. But osteoblast activity declines with age, leading to bone loss and impaired fracture healing. This age-related osteoporosis is the most common cause of all bone diseases, and is associated with other health problems and deaths, especially in post-menopausal women. Osteoporosis is also a frequent complication in patients receiving long-term corticosteroid treatment following organ transplantation. The data provided by these and other[9] mouse studies suggest that DFM treatment might help to restore bone-formation deficits. DFM is registered for clinical use, currently for the treatment of iron-overloaded patients and in combination with dialysis, so clinical trials to examine the drug in the context of osteoporosis are foreseeable. DFM might also be considered as a combined therapy with bisphosphonate drugs[10], which are used to slow the loss of bone.

Excessive bone loss can also result from the reduced gravitational forces experienced during long periods of space travel. Coincidentally, the character Nog from Star Trek: Deep Space Nine shares the same name as the abbreviation for the protein Noggin, implicated by Adams and colleagues in bone formation. Only time will tell if this coincidence demonstrates foresight.

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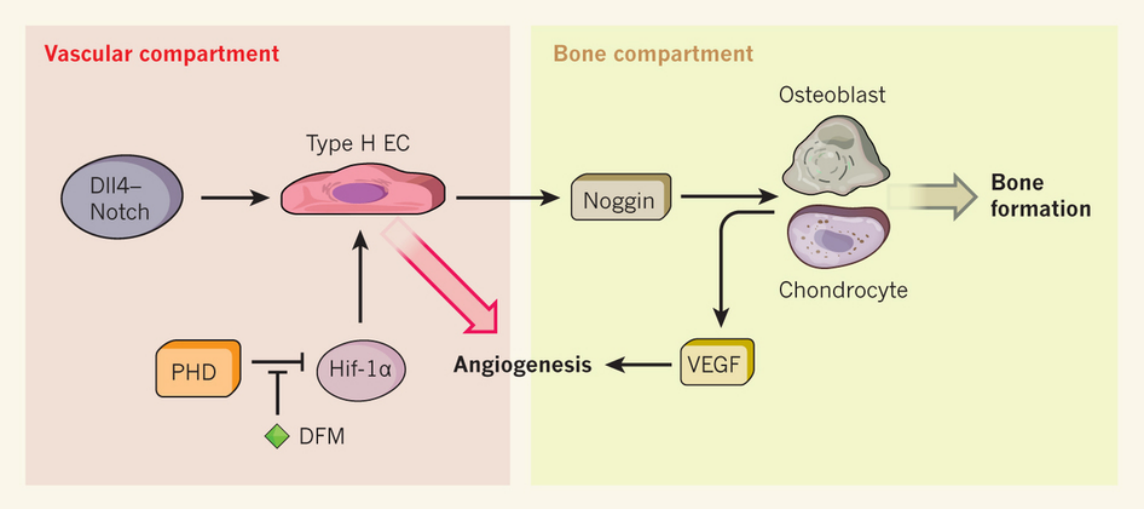

Figure 1: Type H endothelial cells couple angiogenesis to osteogenesis.

Kusumbe et al.[4] and Ramasamy et al.[5] define type H endothelial cells (ECs) as a specialized population in the bone vasculature that induces the formation of new blood vessels (angiogenesis) in bone. Type H ECs secrete the protein Noggin, which sustains the osteoblast and chondrocyte cells that are responsible for bone formation. In return, these cells secrete vascular endothelial growth factor (VEGF), which supports angiogenesis. The authors also show that the proliferation of type H ECs is positively regulated by the Hif-1α and Dll4–Notch signalling pathways. Accordingly, they find that administration of the drug DFM, which inhibits PHD enzymes that degrade Hif-1α, leads to increased numbers of type H ECs, enhanced differentiation of osteoblast-progenitor cells and increased bone formation in aged mice.