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A seed-and-soil theory for blood ageing

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Abstract

The bone marrow is the daily production site for hundreds of billions of blood cells. A new study adds evidence that, during ageing, signals emanating from bone-marrow stromal cells shift to produce inflammatory factors that skew blood-cell output, driving age-related tissue deterioration.

Blood flowing through our bodies connects and facilitates communication between all organs[1]. Notably, some recent evidence suggests that blood cells and bloodborne factors may also hold the key to youthfulness[2]. A crucial source of age-regulating bloodborne factors could be the bone marrow – a diverse network of numerous stem-cell systems that is the primary site of production of adult blood and immune cells. Throughout the body, stem cells provide a continuous source of new cells needed for development, growth, and replacement of damaged or senescent cells. Not surprisingly, therefore, disrupted tissue homeostasis resulting from stem-cell dysfunction has been postulated to drive age-related decline. In the bones, age-related factors that are intrinsic to bone-marrow stroma and blood cells have been extensively explored[3–5]. But changes in the 'soil'– extrinsic factors such as molecules involved in cellular crosstalk in stem-cell-regulating niches – remain incompletely understood[6]. In this issue of *Nature Cell Biology*, however, Mitchell et al.[7] uncover a new, drug-targetable communication pathway in the bone marrow that results in changes in blood-cell output during ageing.

More than four decades of cell-lineage tracing and functional characterization have established a detailed map of haematopoiesis – the process of blood-cell formation. At the start of the process are self-renewing haematopoietic stem cells (HSCs), which give rise to progressively more and more specialized (that is, more lineage-restricted) progenitors of the mature haematopoietic lineages, including myeloid, lymphoid and erythroid cell types. These studies have established a platform for understanding the mechanisms and genetics of normal and diseased haematopoiesis, potentially paving the way to new life-saving therapies.

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Competing interests

The authors declare no competing interests.

One key observation from studies of haematopoietic ageing has been that older individuals lose the clonal diversity of HSCs, producing a bias towards the myeloid lineage at the expense of lymphoid cells (which include B and T cells)[8]. These changes correspond to the development of a latent systemic inflammatory state as well as a weakened adaptive immune response. Mitchell et al.[7] describe this condition as ‘emergency myelopoiesis’, which not only interferes with the ability to fight infections, but also broadly impairs tissue regeneration and organ function. The bone marrow is the site of adult haematopoiesis, and bone-marrow mesenchymal stromal cells (MSCs) play a part in supporting this process (as well as in bone production). It follows, then, that age-related changes in these stromal cells might contribute to the development of myeloid-skewed haematopoiesis. Thus, the authors set out to investigate the role of the bone marrow’s microenvironment and its impact on the ageing of blood stem cells.

To uncover age-related cellular and molecular changes in bone-marrow stromal and endothelial populations, Mitchell et al.[7] isolated stromal and endothelial cells from mechanically and enzymatically dissociated bone-marrow tissue, dissected from the long bones of young and aged mice, for characterization by fluorescence-activated cell sorting. In line with the bone loss seen in the aged mice, the authors identified a reduction in the frequency of two bone-forming endosteal periarteriolar stromal populations: MSC-Ss (which express the cell-surface marker Sca1), and more-committed osteogenic-like cells (OLCs, which can express the marker Pdgfra). Molecularly, the ‘aged’ MSC-S cells lost expression of bone-related transcriptional programmes, while entering an intrinsically aged state that could not be reversed by exposure to young bone marrow in culture. Mitchell et al. further identified an increased frequency of a central marrow perisinusoidal LepR-expressing stromal population (MSC-Ls), which coincided with loss of vascular integrity. Interestingly, they also observed the emergence of a pro-inflammatory population with intermediate Sca1 expression (iMSC-Ls).

These findings were supported and extended by single-cell RNA sequencing (scRNA-seq) analyses, which refined the identity of prospectively sorted bone-marrow cells and assigned distinct transcriptional signatures to the endosteal and central-marrow stromal cells. The scRNA-seq analyses also revealed the expression of additional pro-inflammatory genes in aged bone-marrow stroma, including inflammatory cytokines and soluble ligands that mediate interactions with endothelial cells. The authors then carried out a proteomic screen for cytokines in the interstitial fluid of aged bone marrow, and specifically identified interleukin-1β (IL-1β), a known pro-inflammatory stimulator, which was also highly expressed in aged stromal-cell populations.

As expected, and as confirmed by flow cytometry and scRNA-seq, the authors found that the production of blood cells from old bone marrow was skewed towards myelopoiesis. However, blocking IL-1β in co-cultures of young blood stem cells with old stroma in vitro was sufficient to reverse age-related increases in HSC output. More importantly, the authors also showed that, under stress conditions (myeloablation), the myeloid bias in the aged blood compartment led to anaemia and thrombocytosis (abnormally high platelet production), driving enhanced mortality, which correlated with high IL-1β levels in bone-marrow fluid. They also recapitulated these ageing phenotypes by administering young

mice with systemic IL-1β for 20 days, thereby tying changes in cellular dynamics and bone-marrow composition to the pro-inflammatory actions of stroma-derived IL-1β on blood-cell production during ageing.

Mitchell et al. reasoned that normalizing IL-1β signalling in aged animals to levels seen in young mice might reinstate a youthful bone-marrow environment. They administered the potent pharmacological IL-1β blocker Anakinra to aged mice under myeloablative conditions for 14 days, and, excitingly, showed that the output of lymphoid cells could be rejuvenated.

This short-term treatment, however, was not sufficient to rescue age-related changes in HSC frequency or thrombocytosis. Thus, the authors used a genetic mouse model of lifelong loss of IL-1β receptor signalling. Excitingly, they found that old mice lacking the IL-1β receptor – unlike animals that lack another inflammatory driver, tumour necrosis factor-α – displayed features of a young bone-marrow niche, in terms of stromal-cell composition, reduced myelopoiesis and increased fitness in a regenerative setting. Strikingly, transplanting young bone marrow into aged mice lacking the IL-1β receptor yielded youthful generation of myeloid cells, underlining the importance of IL-1β signalling from the marrow microenvironment. Thus, the authors have demonstrated proof-of-concept that ablating niche-specific inflammatory signals can normalize stromal-cell composition and improve blood production in aged mice (Fig. 1).

The findings of Mitchell et al.[7] have great therapeutic implications, as they suggest that detrimental changes to blood-cell production during ageing could be prevented or reversed. Particularly exciting is the fact that this might be accompanied by improvements in musculoskeletal – and potentially even systemic – health. Nevertheless, several important questions remain. One is whether this finding can be translated to people. The composition of human bone marrow differs from that of inbred experimental mice (for example, bone marrow has a high fat-cell content in older people); moreover, high IL-1β expression has been observed in human blood cells[9]. Consequently, blood-cell-derived IL-1β might have a larger influence in humans than in mice.

Furthermore, although the IL-1β blocker Anakinra might offer a rapidly translatable method of attenuating blood ageing therapeutically, future studies will need to address whether the rejuvenative phenotype persists after withdrawing short-term treatment. If longer-term administration is necessary to maintain this state, it will be important to investigate whether and how other cell types – such as nerve or endothelial cells – are affected by this drug.

Additional experiments should also reconcile why this study could not detect previously reported age-related changes in stromal-derived pro-inflammatory and pro-bone-resorbing factors, such as Mcsf1 and interleukin-6 (or the connections between them), as well as the loss of insulin-like growth factor-1, which have all been reported to contribute to blood ageing[4,10]. This might, at least in part, be attributed to differences in how cells were fractionated and defined between different studies. Moreover, although Mitchell et al. infer some lineage relationships of their identified stromal cell types from scRNA-seq data, these lineages should be functionally validated and, ideally, integrated with published hierarchies

of the potentially overlapping skeletal stem cell lineages, especially in light of reports of functional diversity in those stem cells[11]. At the same time, combining transcriptomic/proteomic expression data with spatial information will be crucial to better dissect young and aged bone-marrow niches, in order to determine how specific IL1β-expressing stromal subsets co-localize with different blood stem and progenitor cell populations in the niche.

Finally, the work by Mitchell et al.[7] work provides further evidence that the inflammatory shift in the ageing bone-marrow stromal compartment is not directly related to cellular senescence – a hallmark of ageing that seems to have a bigger role in more-differentiated osteogenic cell types[12]. How senescent osteogenic lineages might contribute to stromal ageing will be an important issue to address. Another key question is how skeletal stromal cells acquire the aged pro-inflammatory phenotype. Although changes in the dynamics of stroma-forming skeletal stem cells due to epigenetic alterations are a possibility, the mechanisms and factors that initiate those changes will be an exciting new area to explore.

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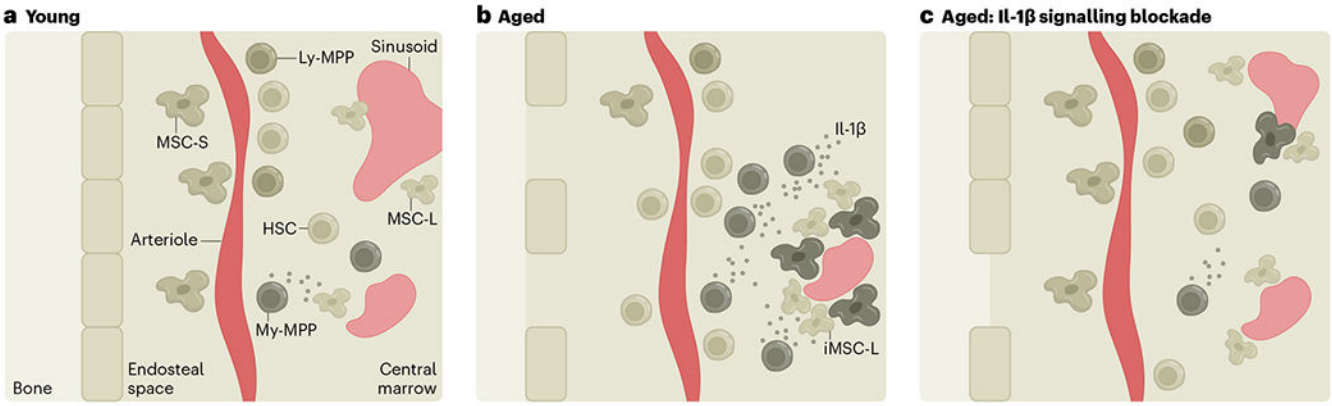

Fig. 1 |. Ageing of the stromal niche in the bone marrow affects the output of blood stem cells.
a, Defined stromal microenvironments exist within the young bone-marrow space. Periarteriolar mesenchymal stromal cells (MSC-Ss) as well as their committed downstream bone-progenitor cells (not shown) reside in the endosteal space close to bone surfaces. The central marrow is inhabited by perisinusoidal LepR-expressing stromal cells (MSC-Ls). Stromal cell types provide signals for the maintenance and cell-fate determination of blood-forming (haematopoietic) stem cells (HSCs). HSCs either give rise to lymphoid-biased multipotent progenitors (Ly-MPPs) or myeloid-biased progenitors (My-MPPs). **b**, Ageing reshapes the bone-marrow space. Mitchell et al.[7] find that bone loss coincides with loss of endosteal MSC-Ss, while MSC-Ls increase in frequency, and a pro-inflammatory stromal population accumulates in proximity to sinusoids (iMSC-Ls). The perisinusoidal stromal cell types express interleukin-1β (IL-1β), driving expansion of the HSC pool and skewing differentiation towards My-MPPs. **c**, Mitchell et al. also find that genetic ablation of signalling via the IL-1β receptor or pharmacological inhibition of IL-1β reinstates a youthful bone-marrow microenvironment by reversing the disrupted cellular dynamics.