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COMMENTARY

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Hematopoietic stem cell heterogeneity and age-related platelet bias: implications for bone marrow transplantation and blood disorders

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Abstract

Hematopoietic stem cells (HSCs) are critical for maintaining lifelong blood production and immune function, especially in the context of bone marrow transplantation, where their ability to reconstruct multiple blood lineages is essential. However, recent studies have revealed that certain HSCs exhibit a bias toward platelet differentiation, termed platelet-biased HSCs (P-HSCs). This lineage bias, particularly pronounced with aging, can lead to imbalances in post-transplant blood recovery, negatively affecting patient outcomes. Research by Claus Nerlov's team has provided key insights into the heterogeneity of HSCs, focusing on the age-related expansion of P-HSCs. Using advanced techniques such as single-cell RNA sequencing and molecular barcoding, their work highlights the evolutionary conservation of platelet bias in HSCs across species. This work delves into these findings, discussing their clinical implications for bone marrow transplantation, aging-related blood disorders, and potential therapeutic strategies. Moreover, we address limitations in current methodologies and propose future directions for research to optimize HSC-based therapies and improve clinical outcomes in hematological diseases.

Keywords Lineage bias, Platelet-biased HSCs, Bone marrow transplantation, Blood disorders, Therapeutic strategies

Main text

Hematopoietic stem cells (HSCs) are integral to the lifelong production of blood and immune cells, sustaining multilineage (ML) hematopoiesis in mammals [1]. In the clinical context of bone marrow transplantation, HSCs' capacity to regenerate multiple blood cell lineages is pivotal for patients to reestablish a fully functional blood and immune system post-transplantation [2]. However, despite this multilineage potential, HSCs can sometimes exhibit a preference for specific lineages, a phenomenon known as "lineage bias". For example, certain HSCs, such as murine fate-restricted HSCs, preferentially generate platelets. These are referred to as platelet-biased HSCs (P-HSCs) [3].

In the context of bone marrow transplantation, an elevated proportion of P-HSCs can lead to excessive platelet production, disrupting the balance of blood components, impairing overall hematopoietic function, and delaying immune system recovery. More significantly, this bias may reduce the success of the transplantation, impair long-term engraftment, and increase the risk of

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complications, ultimately threatening the patient's health and quality of life. Thus, understanding platelet bias in HSCs is crucial for improving transplantation outcomes. By unraveling the molecular mechanisms underlying platelet bias and its specific effects on HSC function, researchers aim to develop more precise treatment strategies to enhance transplantation prognosis, regulate blood cell balance, and open new avenues for treating blood disorders. It is noteworthy that the research team led by Claus Nerlov from the University of Oxford recently published significant research findings in *Science Immunology*. They conducted an in-depth analysis of the diversity of hematopoietic stem cells (HSCs), particularly focusing on the characteristics of platelet-biased HSCs (P-hHSCs) and their patterns of change with age. This study provides new perspectives and potential strategies for optimizing bone marrow transplantation outcomes and treating blood disorders [4] (Fig. 1).

The study utilized single-cell RNA sequencing to identify P-HSCs within human HSC populations. By analyzing the transcriptomes of phenotypic bone marrow HSCs, they uncovered continuous lineage biases, including those favoring platelet differentiation. This discovery aligns with previous findings in murine models, highlighting the evolutionary conservation of this trait across species [3].

To further validate the existence of P-HSCs, the research combined molecular barcoding with xenotransplantation of human HSCs into mice. This dual approach allowed for simultaneous measurement of HSC lineage

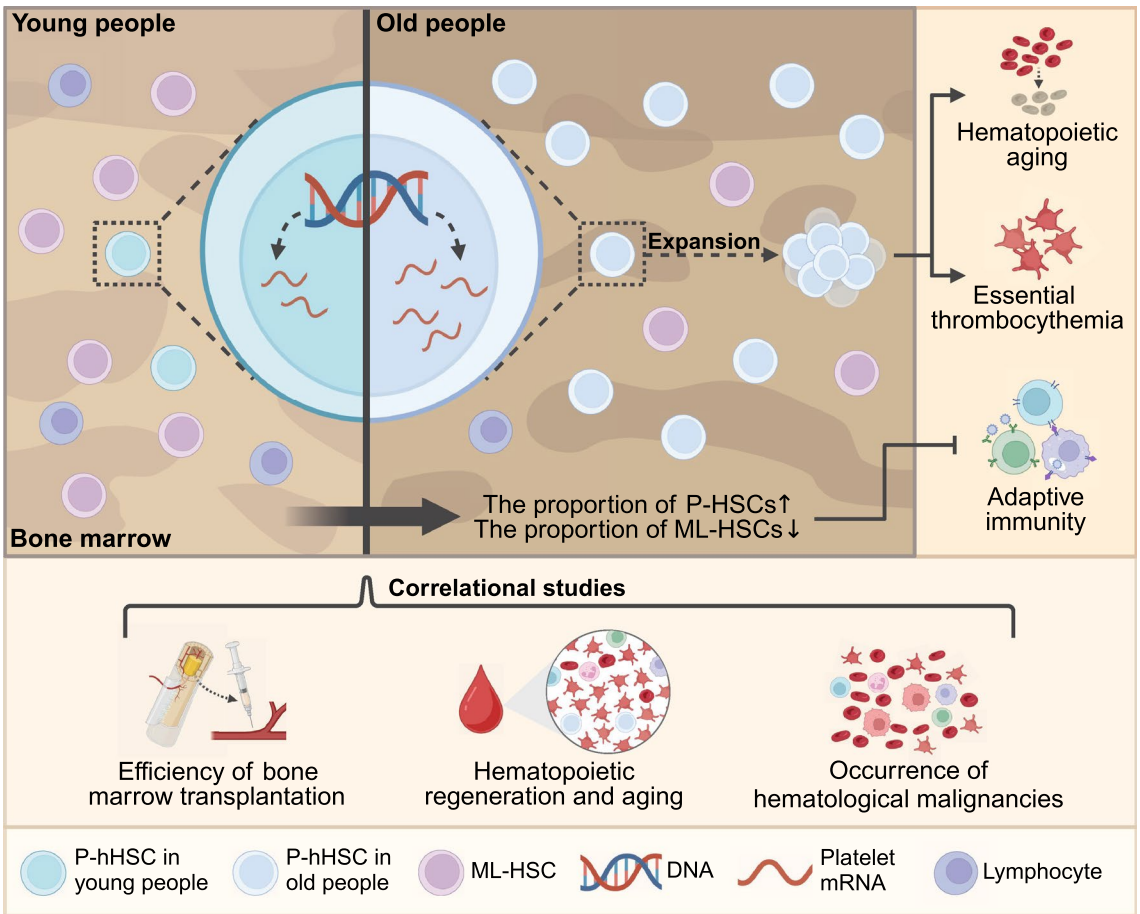

Fig. 1 Age-Related Dynamic Changes in Hematopoietic Stem Cells and Their Impact on Blood Homeostasis and Immune Function. Recent research has highlighted the complexity of hematopoietic stem cells (HSCs), particularly the emergence of platelet-biased HSCs (P-HSCs) with age. The proportion of P-HSCs increases with age, accompanied by enhanced platelet priming in their transcriptional profiles, which may disrupt blood homeostasis. This age-related shift is also associated with a decline in multilineage HSCs (ML-HSCs), contributing to diminished adaptive immune function in the elderly. The expansion of P-HSCs may lead to hematopoietic aging and the onset of conditions like essential thrombocythemia. These findings have broad implications for bone marrow transplantation, hematopoietic regeneration, and the development of hematological malignancies

output and transcriptome profiles at the single-cell level. The results confirmed that HSCs exhibit functional lineage biases, consistent with murine HSCs, and demonstrated molecular connections between P-HSCs identified by clustering and those characterized by barcoding. Differential gene expression analysis revealed significant overlap in marker genes, strengthening the molecular link between these identification methods.

Aging profoundly affects numerous biological processes, including hematopoietic stem cells. Nerlov's team investigated the impact of aging on platelet bias in HSCs by comparing single-cell transcriptomes from young and aged bone marrow. They found that P-HSCs increase with age, both in frequency and in transcriptional profiles indicating platelet priming. This shift in HSC function with aging mirrors observations in mice, further emphasizing the evolutionary conservation of this age-related bias.

The Nerlov study introduced significant innovations to the field of HSC biology, offering new insights into how HSC function evolves with age. By employing molecular barcoding and single-cell RNA sequencing, they provided a nuanced understanding of HSC heterogeneity at the single-cell level, linking transcriptomic traits to functional outcomes. This enhanced understanding of HSC complexity paves the way for deeper investigation into species-specific differences and future clinical applications. Clinically, these findings hold promise for improving bone marrow transplantation outcomes, particularly in aging populations. The study lays the groundwork for developing personalized treatment strategies by refining HSC screening techniques, thereby enhancing transplantation success and patient prognosis. Additionally, continued exploration of aging-related changes in P-HSCs could offer novel molecular targets for preventing and treating age-related hematologic disorders.

Despite its profound insights, the study does have limitations. While high-throughput single-cell RNA sequencing effectively identifies P-HSCs and their transcriptomic characteristics, the technology relies on sample quality and technical platforms, which may introduce biases, such as sample heterogeneity and limited sequencing depth. Furthermore, cross-species comparisons, though informative, may be limited by inherent biological differences. The study also primarily focused on single-cell transcriptomics, potentially overlooking the influence of cell-to-cell interactions and the microenvironment on HSC function. For example, studies have shown that aged bone marrow macrophages can expand P-HSCs through interleukin 1B signaling [5].

Moreover, the study's reliance on young and old donors limits its scope. A broader age range, as well as donors with varying health statuses, could provide a more comprehensive understanding of HSC behavior under different physiological and pathological conditions. Aging's impact on HSCs is a multifaceted process that extends beyond transcriptomic changes. Genomic instability, epigenetic alterations, and proteomic shifts are equally important factors that require investigation. Therefore, future research should integrate a wider array of experimental techniques, including proteomics and functional assays, to complement these findings.

As Nerlov's research team indicated, future studies must confirm the applicability of these results in native human hematopoietic systems and further explore the physiological roles of P-HSCs and multilineage HSCs (ML-HSCs) across age groups. Such work will deepen our understanding of HSC biology, enhance the therapeutic potential of stem cell treatments, and provide valuable insights into the mechanisms underlying hematopoietic regeneration, aging, and malignancy development.

In summary, the Nerlov team's research offers critical insights into HSC heterogeneity and its evolutionary conservation, with a particular emphasis on P-HSCs and their age-related dynamics. These findings lay the groundwork for future studies in HSC biology, particularly in aging and hematological disease. Looking ahead, we anticipate that further investigation will reveal the complex biological mechanisms governing HSC function, fostering advancements in stem cell therapy, disease prevention, and treatment strategies for related conditions.

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Author contributions
Yalu Chen and Jianqiao Shentu analyzed the literature and wrote the manuscript. Yalu Chen, Jianqiao Shentu, and Hanqi Lou drafted the figure. Yalu Chen and Jianqiao Shentu conceived the idea. Yongming Xia collected references. Shiwei Duan and Yinyan Jiang reviewed and revised the manuscript. All authors have read and approved the final the final manuscript.

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