Inflammation control in the bone marrow: HES1 at the helm

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In this issue of *Haematologica*, Zhu and colleagues[1] report that the Notch target gene HES1 safeguards bone marrow mesenchymal stromal cell (MSC) homeostasis by repressing NFATc2-driven inflammation. Their work reveals a crucial niche-extrinsic mechanism that preserves hematopoietic stem cell (HSC) function under stress, bridging classical developmental biology with emerging concepts of inflammatory control in the hematopoietic microenvironment.

The concept that the bone marrow microenvironment actively shapes hematopoiesis is now well established.[2] Advances in single-cell RNA sequencing and imaging have revealed diverse niche cell populations in both mouse and human bone marrow.[3-5] Among them, MSC represent a major component, playing key roles in regulating HSC quiescence, lineage bias, and regeneration through both direct cell-cell contact and secretion of soluble factors. Yet the inflammatory tone of the niche has received comparatively less attention. Chronic or exaggerated inflammatory signals are increasingly recognized as drivers of HSC exhaustion, myeloid skewing, and even leukemic transformation.[6] Zhu *et al*. add a new dimension by showing that HES1, previously studied for its intrinsic roles in stem/progenitor compartments,[7,8] is equally essential in non-hematopoietic niche cells. Their MSC-specific Hes1 knockout mice displayed normal steady-state hematopoiesis, but under stress (lipopolysaccharide or 5-FU), they exhibited catastrophic hematopoietic collapse. This underscores the importance of conditional resilience and that niche factors may be dispensable in homeostasis but vital under challenge.

The mechanistic centerpiece of this study is the identification of NFATc2 as a direct transcriptional target repressed by HES1. In the absence of Hes1, MSC up-regulate NFATc2 and secrete inflammatory cytokines such as TNF-α, IL-1β, and CXCL4. Pharmacological blockade of these inflammatory pathways or direct inhibition of NFATc2 restores stromal function and improves hematopoietic support (Figure 1). These findings place HES1 at the intersection of Notch signaling, metabolic regulation, and inflammatory control, establishing HES1 as a transcriptional brake on NFATc2-driven inflammation. More broadly, they suggest that stromal inflammation is not simply a byproduct of systemic infection or aging, but an actively restrained process governed by niche-specific transcriptional repressors.

These findings carry several important implications for hematology. 1) Hematopoietic aging: age-related niche inflammation ("inflammaging") is a well-recognized driver of HSC dysfunction.[9] The HES1–NFATc2 axis may represent a molecular safeguard that erodes with age, contributing to myeloid skewing and impaired regenerative capacity. 2) Bone marrow failure syndromes: in disorders such as Fanconi anemia and aplastic anemia, inflammatory cytokines exacerbate marrow collapse.[10] If HES1 is reduced or dysfunctional in patient MSC, targeting NFAT signaling could offer a novel therapeutic avenue. 3) Leukemia-niche crosstalk: leukemic cells remodel their stromal environment, frequently hijacking inflammatory circuits.[11] Given the role of NFAT in immune regulation and stromal remodeling, the HES1-NFATc2 pathway may represent a therapeutic vulnerability in malignant hematopoiesis. 4) Therapeutic targeting: NFAT inhibitors already developed in oncology and immunology might be repurposed, not only to suppress malignant cells, but also to recalibrate dysfunctional stroma, broadening their clinical potential.

As with any major advance, questions remain. Does HES1 also play roles in other stromal cell types? Is HES1 down-regulated in aged or diseased human MSC? Does HES1 interact with other niche-inflammation regulators such as IL-1R antagonists or NLRP inflammasomes? Could leukemic cells actively suppress HES1 in MSC to remodel their niche? And, importantly, what are the therapeutic windows for targeting NFAT signaling without compromising necessary immune functions? Answering these questions will require integrating mouse genetics, patient-derived MSC models, and single-cell analyses of inflammatory states across different types of stromal cells, and age and disease contexts.

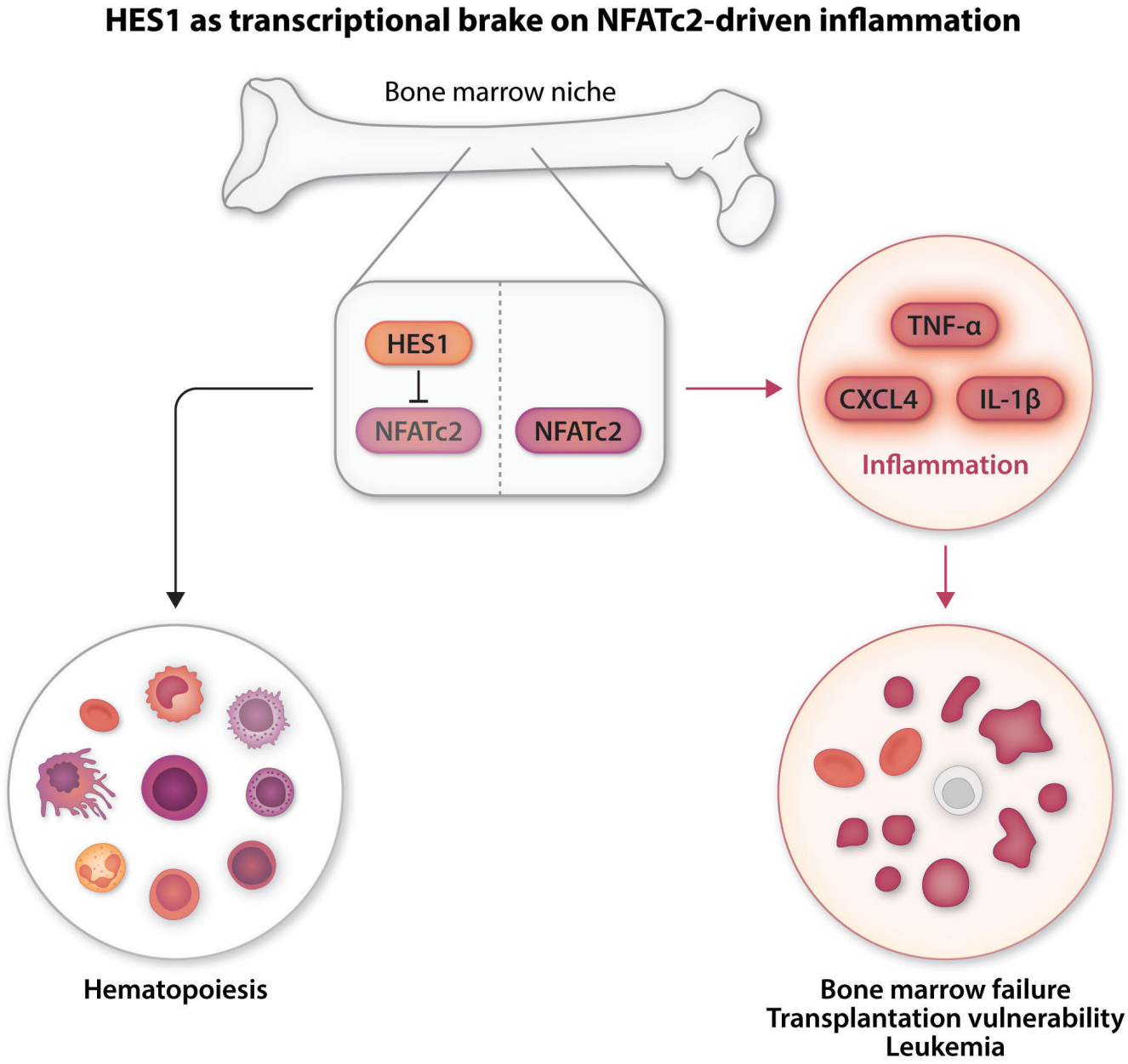

Figure 1. HES1 restrains NFATc2-driven inflammation in the bone marrow niche. Schematic model illustrating the role of HES1 in mesenchymal stromal cells (MSC). In normal MSC (black arrow), HES1 represses NFATc2, limiting cytokine output and supporting hematopoietic stem cell maintenance and balanced hematopoiesis. In the absence of Hes1 (red arrows), NFATc2 is derepressed, leading to increased production of inflammatory mediators such as TNF-α, IL-1β, and CXCL4. The resulting inflammatory milieu impairs MSC function, disrupts HSC quiescence, and contributes to hematopoietic stress, bone marrow failure, transplantation vulnerability, and leukemic remodeling.

In conclusion, the bone marrow niche is not inert soil but a dynamic ecosystem in which the balance of inflammatory cues shapes hematopoietic fate. The finding that HES1 restrains NFATc2-driven inflammation in MSC offers a new vantage point on hematopoietic stress responses. Looking ahead, targeting this pathway may open therapeutic opportunities in marrow failure, transplantation, and leukemia. More broadly, the work underscores a general principle of stem cell biology: the vitality of stem cell populations depends as much on damping inflammatory noise within their niche as on intrinsic self-renewal programs. Just as neural stem cells falter under neuroinflammation and intestinal stem cells are impaired during colitis, HSC rely on transcriptional brakes such as HES1 to buffer against inflammatory disruption.

Disclosures

No conflicts of interest to disclose.

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