Editorial

Stem Cell INVESTIGATION

Reversing pathological remodelling of the bone marrow microenvironment in acute myeloid leukemia

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Comment on: Duarte D, Hawkins ED, Akinduro O, *et al.* Inhibition of Endosteal Vascular Niche Remodeling Rescues Hematopoietic Stem Cell Loss in AML. Cell Stem Cell 2018;22:64-77.e6.

Received: 05 September 2018; Accepted: 14 September 2018; Published: 26 September 2018.

doi: 10.21037/sci.2018.09.02

View this article at: http://dx.doi.org/10.21037/sci.2018.09.02

Acute myeloid leukemia (AML) remains a formidable therapeutic challenge with the majority of older patients succumbing to disease progression despite aggressive treatment. Common reasons for lack of therapeutic efficacy in AML are complications related to marrow failure caused by progressive disease or early relapse after initial chemotherapy. The genetic and functional heterogeneity observed within individual cases of AML supports the notion that cell extrinsic factors are logical therapeutic targets. Increasingly, changes within the bone marrow microenvironment have been described in AML that lead to diminished normal hematopoiesis, depletion of hematopoietic stem cells (HSCs), and the inability of healthy HSCs to compete with the accumulating leukemia cells. Greater insight regarding how leukemia may remodel the microenvironment for its own relative advantage may be crucial for the development of more effective therapies.

The bone marrow microenvironment includes vascular and endosteal niches (1) that represent distinct geographical and molecular niches (2). HSCs are maintained in endosteal niches adjacent to osteoblasts and compete with leukemia-initiating cells for saturable sites. Alterations of the endosteal niche can impair normal hematopoiesis (3). Leukemic blasts can displace healthy HSCs in protected niches and compete for space within the microenvironment. Moreover, AML blasts can alter the microenvironment and inhibit hematopoiesis directly or indirectly, through release of exosomes and other factors that change the behavior of supporting mesenchymal stromal cells (4,5). Regional differences in the bone marrow compartment have also been recently described with greater capacity to accommodate HSCs within the endosteal-enriched trabecular bone of the metaphyseal region compared to the diaphysis of long bones (2). The metaphyseal niches have greater Notch-mediated capacity to support HSCs than diaphyseal regions. AML treatment, including chemotherapy and radiation, can impair the function of the microenvironment, reduce endosteal niche capacity, deplete the vasculature, and reduce the supportive function of mesenchymal stromal cells.

In a recent paper by Duarte *et al.* (6), they describe their use of high content intravital microscopy to demonstrate the progressive remodelling of endosteal vasculature that leads to significant endothelial cell loss and spatiotemporal loss of normal HSCs through egress via perivascular transendothelial migration. Vascular destruction was limited to the endosteal region where HSC support is most abundant and was less evident in the diaphyseal region which is known to be less associated with Notch-mediated support of HSC self-renewal (2). The effects were seen only in AML and not in a murine model of Notch-driven T-ALL. Moreover, gene transcriptome analysis of endosteal leukemic cells (from crushed metaphysis) was performed by RNA-sequencing and compared with leukemic cells from the diaphysis (flushed long bones). Greater expression of genes involved in inflammation were observed in the metaphyseal region, along with members of the tumor necrosis factor signalling pathway and the anti-angiogenic cytokine Cxcl2 or MIP2-alpha. Additionally, bone marrow

imaging revealed loss of marrow stroma in areas enriched for leukemic infiltration with perturbed vascular adherence to the stroma. This was most marked in endosteal regions. They conclude that AML cells can remodel the stroma when they reach a certain threshold density. Through elegant experiments using double transgenic mice, the authors indicated that loss of endosteal vasculature preceded loss of osteoblasts and this was temporally associated with the subsequent loss of normal HSCs. Osteoblastic cells were lost in an infiltration-dependent manner and normal HSCs were only lost in late stages of leukemic infiltration and most dramatically in the metaphyseal region.

The investigators then addressed whether inhibition of vascular remodelling during AML progression in the transplanted mice could preserve HSCs and enhance their number and competitiveness during treatment with chemotherapy. They used deferoxamine (DFO) to enhance hypoxia-inducible factor 1-alpha stability and activity to induce endosteal vascular expansion. DFO-treated mice that underwent transplantation with AML cells developed similar extent of leukemic infiltration compared with control mice treated with phosphate-buffered saline (PBS) but there was a marked increase in endosteal expansion and increased co-transplanted numbers of normal HSCs in the trabecular-rich metaphysis. The flushed diaphysis was similar, however, between DFO-treated and control mice, indicating that preservation of endosteal vasculature was critical for HSC maintenance and protection, despite AML growth, and could improve HSC homing in the presence of AML.

They next hypothesized that improved endosteal vasculature could enhance the delivery of chemotherapy for leukemic stem cells and improve treatment responses in AML. They used a xenograft mouse model of AML utilizing mice mutant for Fbxw7 in which tamoxifen administration increases Notch activation in endothelial cells, thereby increasing the number of endosteal vessels and arterioles. Fbxw7 and control mice were treated with induction-like chemotherapy and the authors observed marked chemotherapy-induced vascular damage in both groups, including loss of endosteal vessels. The Fbxw7 mice, however, had fewer numbers of surviving AML cells following treatment, delayed time to relapse, and increased overall survival. They conclude that rescuing endosteal vessels prior to induction therapy can improve the efficacy of anti-leukemia treatment.

Other studies have demonstrated major changes in the marrow microenvironment in AML, including expansion of nestin-expressing MSCs with reduced differentiation capacity due to AML-induced sympathetic neuropathy (7). Moreover, MSC-derived exosomes from patients with leukemia contain a unique microRNA signature that favored leukemia cell expansion, and reduced normal hematopoiesis (4,5). Other research has demonstrated the ability of normal HSCs to progressively compete against leukemia cells for stem cell niches within the bone marrow through repeated cycles of CD34-selected HSC administration (8). Taken together, there is increasing evidence that the bone marrow microenvironment can be remodeled in AML and also by its treatment. AML hijacks the bone marrow microenvironment leading to reduced competitiveness of normal HSCs, AML progression, and marrow failure. Strategies aimed at reversing this remodelling and returning the microenvironment to a healthy state can improve the efficacy of chemotherapy and can improve the ability of normal HSCs to repopulate the marrow. This may be most relevant in the context of allogeneic blood and marrow transplant where incoming healthy HSCs need to home and repopulate the host stem cell niches. If these niches are occupied, depleted or damaged, donor HSCs have a reduced capacity to engraftment and compete against residual AML cells. Strategies to eradicate AML should consider reversing the pathological remodelling of the microenvironment, including the vascular obliteration in the endosteal niche, perhaps combined with allogeneic transplantation approaches.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. Nature 2014;505:327-34.
2. Guezguez B, Campbell CJ, Boyd AL, et al. Regional localization within the bone marrow influences the functional capacity of human HSCs. Cell Stem Cell 2013;13:175-89.
3. Raaijmakers MH, Mukherjee S, Guo S, et al. Bone progenitor dysfunction induces myelodysplasia and

secondary leukaemia. Nature 2010;464:852-7.
4. Barrera-Ramirez J, Lavoie JR, Maganti HB, et al. Micro-RNA Profiling of Exosomes from Marrow-Derived Mesenchymal Stromal Cells in Patients with Acute Myeloid Leukemia: Implications in Leukemogenesis. Stem Cell Rev 2017;13:817-25.
5. Chandran P, Le Y, Li Y, et al. Mesenchymal stromal cells from patients with acute myeloid leukemia have altered capacity to expand differentiated hematopoietic progenitors. Leuk Res 2015;39:486-93.
6. Duarte D, Hawkins ED, Akinduro O, et al. Inhibition of Endosteal Vascular Niche Remodeling Rescues Hematopoietic Stem Cell Loss in AML. Cell Stem Cell 2018;22:64-77.e6.
7. Hanoun M, Zhang D, Mizoguchi T, et al. Acute myelogenous leukemia-induced sympathetic neuropathy promotes malignancy in an altered hematopoietic stem cell niche. Cell Stem Cell 2014;15:365-75.
8. Boyd AL, Campbell CJ, Hopkins CI, et al. Niche displacement of human leukemic stem cells uniquely allows their competitive replacement with healthy HSPCs. J Exp Med 2014;211:1925-35.

doi: 10.21037/sci.2018.09.02
Cite this article as: Allan DS, De Lisio M. Reversing pathological remodelling of the bone marrow microenvironment in acute myeloid leukemia. Stem Cell Investig 2018;5:29.

