

UC Irvine

UC Irvine Previously Published Works

Title

New insights into the normal and leukemic stem cell niche: a timely review.

Permalink

<https://escholarship.org/uc/item/8bc3j677>

Journal

Cytometry. Part B, Clinical cytometry, 84(1)

ISSN

1552-4957

Author

Van Etten, Richard A

Publication Date

2015-01-08

Peer reviewed

Editorial

New Insights into the Normal and Leukemic Stem Cell Niche: A Timely Review

The concept that tissue stem cells develop within specialized microenvironments or niches originated from genetic studies of germ cell development in *Drosophila* (1), but much of what we know about stem cell niche biology has emerged from studies of the hematopoietic stem cell (HSC) niche, first conceptualized over 30 years ago by Schofield (2). In this issue of *Clinical Cytometry*, Krause et al. provide a comprehensive update on this rapidly moving field (3). Recent studies have demonstrated that the niche for normal HSC is complex, dynamic, and composed of multiple cellular components including osteoblasts, osteoclasts, mesenchymal stem cells, fibroblasts, adipocytes, macrophages, perivascular and endothelial cells, and sympathetic neurons and glial cells. Most of the new knowledge has emerged from sophisticated *in vivo* imaging techniques such as two-photon confocal microscopy (4), use of genetically modified mice that either lack critical niche signaling (5) or adhesion (6) molecules or express fluorescent reporter proteins in different niche lineages (7), and increasingly sophisticated flow cytometric analysis and cell purification (8). Krause et al. summarize the current state of knowledge of the HSC niche, the relationship between the vascular and osteoblastic niches within the bone marrow microenvironment, and emerging efforts to manipulate the niche in clinical HSC transplantation.

By contrast, the study of the influence of the bone marrow microenvironment on the pathogenesis of hematopoietic malignancies is less well understood. Transplantation studies in mouse models of chronic (CML) and acute (AML) myeloid leukemias and xenotransplantation of the corresponding human leukemias into immunodeficient mice have identified populations of malignant progenitors that are capable of initiating and sustaining these leukemias (9). These so-called leukemia stem cells (LSC) are postulated to be the cause of relapse following induction of remission with chemotherapy. By analogy to normal HSC, LSC are thought to reside in specific bone marrow niches that regulate their self-renewal, quiescence, and sensitivity to chemoradiotherapy. Until quite recently, we had little insight into the nature of these LSC niches (10) or whether they could represent a novel target for leukemia therapy. Early studies identified CD44 as an adhesion molecule binding selectins and hyaluronic acid that is expressed on both CML (11) and AML (12) stem cells, mediating homing, engraftment, and maintenance of LSC in transplanted mice. Other studies showed a dependence of AML LSC on $\beta 1$ integrins (13) and the chemokine

CXCL12 (14), contributing to chemotherapy resistance. Importantly, both anti-CD44 (Hoffmann-La Roche) and anti-CXCR4 (the receptor for CXCL12; Sanofi-Genzyme) therapies are currently in clinical trials for AML. Krause et al. discuss the rapid progress in this area, including exciting recent studies suggesting that the CML and AML stem cell niches are distinct and can be manipulated pharmacologically (15).

What can we expect from this field in the future? A better understanding of the normal HSC niche should inform clinical strategies to improve HSC mobilization for both autologous and allogeneic transplantation, and to improve engraftment of recipients. Conversely, targeting the LSC niche has the promise to increase the response to cytotoxic and tyrosine kinase inhibitor therapy and eliminate residual leukemia, increasing the probability of cure. The review by Krause et al. illuminates both the progress made and the road ahead for translational and clinical investigators in this exciting arena.

Richard A. Van Etten

LITERATURE CITED

- Papagiannouli F, Lohmann I. Shaping the niche: Lessons from the *Drosophila* testis and other model systems. *Biotechnol J* 2012;7:723–736.
- Schofield R. The relationship between the spleen colony-forming cell and the haematopoietic stem cell. *Blood Cells* 1978;4:7–25.
- Krause DS, Scadden DT, Preffer FI. The hematopoietic stem cell niche—Home for friend and foe? *Cytometry B Clin Cytom* 2013;84B:7–20.
- Lo Celso C, Fleming HE, Wu JW, Zhao CX, Miake-Lye S, Fujisaki J, Cote D, Rowe DW, Lin CP, Scadden DT. Live-animal tracking of individual haematopoietic stem/progenitor cells in their niche. *Nature* 2009;457:92–96.
- Fulzele K, Krause DS, Panaroni C, Saini V, Barry KJ, Liu X, Lotinun S, Baron R, Bonewald L, Feng JQ, et al. Myelopoiesis is regulated by osteocytes through Gsalpha-dependent signaling. *Blood* 2012. DOI: 10.1182/blood-2012-06-437160 (in press).
- Goncharova V, Seroby N, Iizuka S, Schraufstatter I, de Ridder A, Povaliy T, Wacker V, Itano N, Kimata K, Orlovskaja IA, et al. Hyaluronan expressed by the hematopoietic microenvironment is required for bone marrow hematopoiesis. *J Biol Chem* 2012;287:25419–25433.
- Park D, Spencer JA, Koh BI, Kobayashi T, Fujisaki J, Clemens TL, Lin CP, Kronenberg HM, Scadden DT. Endogenous bone marrow MSCs are dynamic, fate-restricted participants in bone maintenance and regeneration. *Cell Stem Cell* 2012;10:259–272.

*Correspondence to: Richard A. Van Etten, M.D., Ph.D., Molecular Oncology Research Institute and Division of Hematology/Oncology, Tufts Medical Center, 800 Washington Street, Box 5609, Boston, MA 02111. E-mail: Rvanetten@tuftsmedicalcenter.org

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/cyto.b.21071

8. Preffer F, Domkowski D. Advances in complex multiparameter flow cytometry technology: Applications for stem cell research. *Cytometry B Clin Cytom* 2009;76B:295-314.
9. Krause DS, Van Etten RA. Right on target: Eradicating leukemic stem cells. *Trends Mol Med* 2007;13:470-481.
10. Lane SW, Scadden DT, Gilliland DG. The leukemic stem cell niche: Current concepts and therapeutic opportunities. *Blood* 2009;114:1150-1157.
11. Krause DS, Lazarides K, von Andrian UH, Van Etten RA. Requirement for CD44 in homing and engraftment of BCR-ABL-expressing leukemic stem cells. *Nat Med* 2006;12:1175-1180.
12. Jin L, Hope KJ, Zhai Q, Smadja-Joffe F, Dick JE. Targeting of CD44 eradicates human acute myeloid leukemic stem cells. *Nat Med* 2006;12:1167-1174.
13. Matsunaga T, Takemoto N, Sato T, Takimoto R, Tanaka I, Fujimi A, Akiyama T, Kuroda H, Kawano Y, Kobune M, et al. Interaction between leukemic-cell VLA-4 and stromal fibronectin is a decisive factor for minimal residual disease of acute myelogenous leukemia. *Nat Med* 2003;9:1158-1165.
14. Nervi B, Ramirez P, Rettig MP, Uy GL, Holt MS, Ritchey JK, Prior JL, Piwnica-Worms D, Bridger G, Ley TJ, et al. Chemosensitization of acute myeloid leukemia (AML) following mobilization by the CXCR4 antagonist AMD3100. *Blood* 2009;113:6206-6214.
15. Krause DS, Fulzele K, Catic A, Hurley M, Lezeau S, Attar EC, Wu JY, Lin HYF, Divieti-Pajevic P, Hasserjian RP, et al. Differential regulation of myeloid leukemia by the bone marrow microenvironment. *Blood* 2012;120:1245a.