Review article

The leukemic stem cell niche: current concepts and therapeutic opportunities

Steven W. Lane,1,2 David T. Scadden,3-5 and D. Gary Gilliland1,4-6

1Division of Hematology, Brigham and Women’s Hospital, Boston, MA; 2University of Queensland, Brisbane, Australia; 3Massachusetts General Hospital, Boston; 4Harvard Stem Cell Institute, Boston, MA; 5Harvard University Department of Stem Cell and Regenerative Biology, Boston, MA; and 6Howard Hughes Medical Institute, Boston, MA

The genetic events that contribute to the pathogenesis of acute myeloid leukemia are among the best characterized of all human malignancies. However, with notable exceptions such as acute promyelocytic leukemia, significant improvements in outcomes based on these insights have not been forthcoming. Acute myeloid leukemia is a paradigm of cancer stem (or leukemia initiating) cells with hierarchy analogous to that seen in hematopoiesis. Normal hematopoiesis requires complex bidirectional interactions between the bone marrow microenvironment (or niche) and hematopoietic stem cells (HSCs). These interactions are critical for the maintenance of normal HSC quiescence and perturbations can influence HSC self-renewal. Leukemia stem cells (LSCs), which also possess limitless self-renewal, may hijack these homeostatic mechanisms, take refuge within the sanctuary of the niche during chemotherapy, and consequently contribute to eventual disease relapse. We will discuss the emerging evidence supporting the importance of the bone marrow microenvironment in LSC survival and consider the physiologic interactions of HSCs and the niche that inform our understanding of microenvironment support of LSCs. Finally, we will discuss approaches for the rational development of therapies that target the microenvironment.

Cell autonomous contributions to acute myeloid leukemia

As for many cancers, acute myeloid leukemia (AML) has been extensively characterized as a cell autonomous disorder—that is, the genetic events leading to transformation of the normal hematopoietic cell are found within that cell and are both necessary and sufficient for the generation of leukemia. For example, leukemogenic fusion proteins, such as MLL-AF9 or MLL-ENL1 that are expressed as a consequence of translocations involving chromosome t(9;11)(p22;q23)2 or MOZ-TIF2 observed in AML with inv(8)(p11q13),3 are present in leukemic blasts derived from patients with AML. Furthermore, introduction of these alleles into normal hematopoietic cells can be transformed by MLL-AF9 in xenograft transplantation assays5 or through conditional deletion of PTEN in hematopoietic stem and progenitor cells.6 Each of these observations demonstrates the central importance of cell-autonomous contributions to the AML phenotype.

AML is a stem cell disease with a hierarchy analogous to normal hematopoietic development

Although all AML cells are thought to harbor the cell-autonomous mutations that are causally implicated in disease pathogenesis, there is emerging evidence for functional heterogeneity among AML cells. In particular, it is thought that there is a subpopulation of AML cells referred to as “leukemia stem cells” (LSC) that alone have long-term repopulating potential and the ability to propagate and maintain the AML phenotype. The existence of a leukemia stem cell, and contributions of stem cells to other cancers, has long been postulated.7 Formal proof for the existence of this subpopulation of cells was enabled by the emergence of technologies that allowed for prospective isolation of hematopoietic stem and progenitor cell populations using high-speed multiparameter flow cytometry by Spangrude and colleagues.8 Application of this technology to AML by Bonnet and Dick9 and Lapidot and colleagues10 identified a subpopulation of CD34+CD38− human AML cells that can serially transplant leukemia in a mouse xenograft model. In contrast, more committed progenitors that are CD34+CD38− lacked such potential. Furthermore, it was estimated that as few as one in a million AML cells possessed leukemia initiating activity. It is thus thought that leukemia has a hierarchical organization similar to that of normal hematopoiesis in which there is a rare subpopulation of cells with limitless self-renewal potential that gives rise to progeny that lack such potential. The LSC in certain types of murine AML, such as those induced by MLL-AF9,2 MOZ-TIF2,3 or MLL-ENL15 have characteristics of progenitor cells with an immunophenotype similar to normal granulocyte-macrophage precursors, that is, lineage-, cKit+, Sca-1−, CD34+, and FcγRII+1,13 These leukemia-initiating cells have an immunophenotype that is more mature than that seen in normal hematopoietic stem cells (HSCs)2,11 but have acquired limitless self-renewal through oncogenic transformation, leading to the activation of a stem cell–like gene expression program.2 These observations raise questions about the origin of LSCs that is beyond the scope of this review, but cumulative data suggest that LSCs may arise from mutations occurring in either the HSCs or committed progenitor compartments, at least in murine models of disease.1,3
Therapeutic implications of cell-autonomous contributions to leukemia: the failure of current therapies

The insights that specific disease alleles—which now number in the hundreds for AML—are causally implicated in disease pathogenesis has provided numerous targets for molecularly targeted therapeutic interventions. Advances have been made in targeting cell-autonomous defects in AML, including recent efforts to inhibit FLT3 in the subset of AML patients with activating mutations in this receptor tyrosine kinase,12 or targeting BCR-ABL with ABL-selective tyrosine kinase inhibitors in BCR-ABL–positive AML.13 Nonetheless, response to such therapies as single agents is short-lived and is not curative. Furthermore, many cell-autonomous disease alleles are considered “undruggable” using conventional approaches to drug design. These include alleles such as mutant KRAS or NRAS, as well as the majority of “nonkinase” disease alleles in AML that include transcription factor fusions such as RUNX1-ETO and MLL fusions, as well as NPM mutations among many others. There is promise in pursuing these targets, but thus far these alleles have proven remarkably resistant to drug targeting using conventional approaches.14,15 Several approaches hold promise, such as identification of synthetic lethal interactions between the leukemia-causing alleles and more “druggable” targets,16 but such approaches are still in the earliest stages of development.

Against this backdrop, there is compelling emerging evidence that cell nonautonomous contributions to leukemia play a pivotal role in disease maintenance and propagation. These data evoke innovative approaches to treatment of leukemia, as well as solid tumors, that focus on the microenvironment—the niche—in support of the leukemia phenotype.

Microenvironmental regulation of normal hematopoiesis

To begin to understand the role of the hematopoietic niche in support of leukemogenesis, it is first important to fully elaborate the role of the microenvironment on normal HSC maintenance and development, and how these support mechanisms differ between HSCs and LSCs. The HSC niche, a term first coined in Schofield’s prescient observations,17 comprises supportive bone marrow microenvironment structures that are essential for the long-term maintenance of a stable HSC pool.18 This niche is anatomically and functionally defined, and has an endosteal19,21 and perivascular compartment22,23 within the bone marrow. Within the niche, there are critical bidirectional signals that ensure the regulation of normal HSC numbers24,25 and maintenance of the quiescent long-term HSC pool.26 The quiescent fraction of immunophenotypically defined HSCs has been previously demonstrated to correlate with long-term repopulating ability of bone marrow;27,28 and loss of this fraction is associated with inability to sustain serial transplantation, the most stringent in vivo assay of self-renewal.26

The endosteal niche is defined anatomically by immediate proximity to trabecular or cortical bone, and can be recapitulated in vitro by osteoblast coculture.20,29,30 Elegant imaging studies by Nilsson and colleagues showed that primitive hematopoietic cells resided close to the endosteal bone surface.30 Osteoblastic lineage cells were first shown to participate in HSC regulation in vivo by 2 concurrent studies. In one, osteoblastic cells were shown specifically to be involved by the use of transgene system in which the 2.3-kb promoter of collagen 1α (a promoter that is activated in osteoblasts and preosteoblasts) drove expression of a constitutively active parathyroid hormone (PTH) receptor in mice. In this setting, HSC increased approximately 2-fold, a magnitude of increase similarly seen in another genetic model in which multiple cell types in the marrow were altered by activating the interferon-inducible Mx1 promoter driving Cre recombinase and deleting the BMP1a receptor. Both osteoblasts and stem cells were shown to increase in this and the PTH receptor model. The converse experiment of decreasing osteoblastic cells was subsequently performed using a transgenic model in which the 2.3-kb collagen 1α promoter was used to express herpes thymidine kinase and ganciclovir was given to ablate osteoblasts. In this setting, a 3- to 10-fold decrease in primitive hematopoietic cells was seen in the bone marrow, and extramedullary hematopoiesis was observed.31 However, other studies have indicated that osteoblastic cells may not be critical for stem cell function. Biglycan-deficient mice have reduced osteoblasts but demonstrate normal HSC number and function,32 and strontium chloride exposure increased osteoblasts without increased HSC number.33 Reconciling these studies is difficult unless there is heterogeneity to the osteoblastic lineage, and some, but not all, are involved in the hematopoietic niche and may have differential sensitivity to biglycan or strontium.

The endosteal niche may not be limited to cellular components as extracellular matrix components, as osteopontin (OPN)24,34 or calcium ions that signal through the calcium sensing receptor29 or input from the sympathetic nervous system35 have all been shown to affect HSC function. For example, calcium-sensing receptor null mice have defective homing to the endosteal niche and reduced in vivo long-term repopulating capacity.19 OPN negatively regulates HSC numbers, as evidenced by increased HSC numbers in the OPN null microenvironment and hypersensitivity to exogenous stimuli.24,36 Osteoclasts also play a role in regulating this niche and are important in stem cell mobilization.37 Conditions associated with altered trabecular bone alter the capacity of the bone marrow to support HSCs. For example, conditional deletion of the tumor suppressor gene neurofibromatosis 2 leads to altered HSC localization and increased regenerative capacity in a non–cell-autonomous manner.38 Furthermore, there is evidence that HSCs may regulate mesenchymal stromal cell differentiation into osteoid lineage cells, thus providing a bidirectional element of control to the endosteal niche.39 The role of specific molecules in the endosteal niche can be elucidated in transgenic systems by conditional expression or deletion by osteoblastic lineage-specific promoters or inducible systems (eg, Osterix-Cre, 2.3-kb collagen 1α promoter26 or Osteocalcin-Cre inducible systems representing promoters activated in respective order during osteoblast lineage differentiation). Perivascular structures, defined by proximity to sinusoidal vascular endothelium, and surrounding supportive structures such as stromal cells, also have essential roles in the bone marrow niche. These observations are based on in vivo immunofluorescence using the “SLAM code” (signaling lymphocyte activation molecule: CD150 positive and CD48 negative) that demonstrates high proportion of HSCs located adjacent to or within 5 cell diameters from endovascular structures.22 Stem cells also associate with vascular structures that are abundant on the surface of trabecular bone.40,41 Functional studies for endothelium analogous to those
performed with osteoblast specific promoters have proved challenging, although this can be achieved through conditional expression with vascular specific regulatory sequences such as Tie-2. 2−4 Cells that are of presumed mesenchymal origin, so-called adventitial reticular cells, have been shown to alter stem cell function. These cells express high levels of the CX chemokine ligand 12 (CXCL12) also stromal-derived factor-1, SDF1) 3 and are located between vessels and bone. Targeted deletion of CXCR4 (the ligand for CXCL12) led to a severe reduction in HSC numbers 4 and increased sensitivity to 5-fluorouracil–induced myelotoxic stress. 2−4 It has also been shown that mesenchymal cells located adjacent to blood vessels and expressing CXCL12 can recapitulate a hematopoietic microenvironment in a xenograft transplantation model. 4−6 The apparent contradictions within the literature may be explained by recent findings that suggest the vessels and endosteal surfaces are intimately entwined within trabecular bone, where most HSCs reside. 30−41 Initial localization studies derived from static 2-dimensional images are now refined by real-time 3-dimensional imaging indicating that the cells reside in a complex meshwork, with the vascular and mesenchymal components of bone potentially playing a coordinated and interrelated role rather than acting as binary options. These illustrate that the niche has close relationships between endosteal and vascular structures that may not be mutually exclusive; however, this remains a point of ongoing debate and active discussion 2−4 in the field.

The interactions between CXCR4 and CXCL12 (SDF-1) are important in the localization and retention of HSCs and progenitor cells, and chemokine interactions through CXCL12 can lead to up-regulation of vascular cell adhesion molecule-1 (VCAM-1) and very late antigen-4 (VLA-4) expression. 45 CXCL12 has a critical role in colonization of the bone marrow by HSCs during early development, as CXCL12-deficient embryos have severely reduced HSC numbers and function. 42 This can be overcome by enforced CXCL12 expression from vascular endothelial cells, a fact that speaks to the importance of both CXCL12 and the endovascular niche. Furthermore, the bone marrow niche is a dynamic system, in part mediated by circadian oscillations in sympathetic nervous system tone. Adrenergic inputs effect stem cell mobilization through down-regulation of CXCR4 during daytime and up-regulation of CXCR4 4 expression on HSC at night, 37 with consequent changes in mobilization of HSC into the peripheral blood. Genetic or pharmacologic ablation of sympathetic nerve signaling may contribute to failure of HSC egress from bone marrow. 35 Recent data also implicate sinusoidal endothelial cells, regulated by vascular endothelial growth factor receptors (VEGFR2 and VEGFR3), in hematopoietic reconstitution after transplantation and myelotoxic chemotherapy, although not in steady-state hematopoiesis. 48 Megakaryocytes have also been linked to bone homeostasis and may regulate osteoblast development within the endosteal niche. 49 Megakaryocytes may interact with sinusoidal bone marrow endothelial cells in response to cytokine signals through CXCL12 and FGF4, leading to up-regulation of adhesion molecules such as VCAM-1 and VLA-4. 45 These adhesion molecules have been described in the localization and retention of normal HSCs within the bone marrow niche. VLA-4 is essential in fibronectin-mediated adhesion to the extracellular matrix of bone, 50 and both have roles in chemokine/CXCR4-mediated homing to perivascular niche cells. 45

In addition to the aforementioned regulators of normal hematopoietic niche function, there are several other key interactions of note. Interactions between angiopoietin-1 (Ang1) and the receptor tyrosine kinase Tie2 promote HSC quiescence and are important for the maintenance of long-term repopulation in vivo. 51 This quiescence was shown to protect against myelotoxic stress. The Wnt and Notch pathways are evolutionarily conserved and have important developmental roles. Expression of the Wnt inhibitor Dickkopf-1 from an osteoblast-specific promoter resulted in reduced in vivo repopulating ability, loss of stem cell quiescence, and stem cell burnout. This effect was irreversible and non-cell-autonomous (that is, defined by the microenvironment). 25 A Notch ligand, Jagged 1, was expressed by endosteal cells and was up-regulated in cells in which the parathyroid hormone receptor was activated. In that specific setting, Notch activation appears to play a role in increasing HSC numbers. 25 Cytokine signals, including stem cell factor, 52 are also important for HSC survival, and they may be regulated in part through microenvironmental factors. 52 Thrombopoietin is present in the circulation, and in the niche it is thought to positively regulate HSC survival through the Mpl receptor expressed on those cells. A block in thrombopoietin signaling leads to reduced HSC numbers. 53 Finally, the membrane Rho GTPase Cdc42 regulates HSC quiescence, and consequently, Cdc42 null mice are unable to sustain long-term hematopoietic reconstitution. 54 The closely related Rac proteins have important cell-autonomous effects in homing, retention, and engraftment of HSCs. 55

The niche may also protect HSCs from the effect of reactive oxygen species. 56 This has previously been shown to be important in the long-term repopulating potential of HSCs. 57 The important regulatory factors in bone marrow microenvironment signaling are summarized in Table 1.

<table>
<thead>
<tr>
<th>Molecular pathways implicated in HSC-niche interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-sensing receptor(3)</td>
</tr>
<tr>
<td>Parathyroid hormone receptor(2) (potentially as a function of increased osteoblast numbers)</td>
</tr>
<tr>
<td>Bone morphogenetic protein receptor 1α(3) (also potentially as a function of increased osteoblast numbers)</td>
</tr>
<tr>
<td>Osteopontin(3,4)</td>
</tr>
<tr>
<td>CX chemokine ligand 12 (also known as stromal-derived factor-1)–CX chemokine receptor 4 interactions(4,5)</td>
</tr>
<tr>
<td>Angiopoietin-Tie2 interactions(6)</td>
</tr>
<tr>
<td>Canonical Wnt signaling(26)</td>
</tr>
<tr>
<td>Notch activation (with osteoblast parathyroid hormone receptor activation)(25)</td>
</tr>
<tr>
<td>Mpl receptor, thrombopoietin(21)</td>
</tr>
<tr>
<td>cKit receptor, stem cell factor (SCF)(37)</td>
</tr>
<tr>
<td>Cdc42(20) and Rac proteins(45)</td>
</tr>
<tr>
<td>Insulin-like growth factor 2(20)</td>
</tr>
<tr>
<td>N-cadherin (conflicting data exist)(31,32,36)</td>
</tr>
<tr>
<td>VLA-4(10)</td>
</tr>
<tr>
<td>VCAM-1(45)</td>
</tr>
</tbody>
</table>

**Hematopoietic microenvironment perturbations that contribute to hematopoietic dyscrasias**

Recent studies have provided insights into the role of aberrant microenvironment signaling leading to disease pathology. Selective gene targeting within the microenvironment leading to deletion of the retinoic acid gamma receptor (RARγ) 6 is or retinoblastoma (Rb) 6 gene leads to a condition reminiscent of a myeloproliferative disorder in vivo. In parallel with this, the mice show reduced HSC...
numbers with concomitant reduction in trabecular bone volume, further implicating the microenvironment in control of stem cell numbers. Most importantly, these results demonstrate that perturbations in niche signaling can mimic human diseases. There is mounting evidence that microenvironment perturbations may be important and pathogenic in idiopathic myelofibrosis (one of the myeloproliferative disorders) leading to enhanced stem cell mobilization and the creation of alternate niches (for a recent, comprehensive review see Lataille and et al). The microenvironment has been extensively studied in multiple myeloma. For example, self-renewal pathway activation in the niche (such as the canonical Wnt pathway) has been postulated to result in enhanced myeloma cell survival. Myeloma cells also directly disrupt the endosteal niche by secretion of Dickkopf-1, an endogenous Wnt inhibitor leading to impaired osteoblast differentiation. For a complete review of the microenvironment in myeloma, see Podar and et al.

Finally, WHIM syndrome is a rare cause of congenital neutropenia that is often caused by mutations in CXCR4 with increased sensitivity to CXCL12. This rare disorder provides some fascinating insights into leukocyte trafficking through the niche. It has not been linked to progressive malignant disease.

The influence and therapeutic potential of the microenvironment on leukemogenesis

There is mounting evidence that LSCs occupy and receive important signals from the microenvironment that support self-renewal and may exploit the normal homeostatic mechanisms that preserve long-term HSCs. Recent studies have also provided some insight that the microenvironment is linked with primary LSC resistance to therapy. Xenograft transplantation assays have been able to support the role of niche signaling in LSC engraftment, chemotherapy resistance, and cell-cycle regulation. In a series of elegant experiments, human AML stem cells (CD34^+; CD38^-) were demonstrated to home to the endosteal niches of NOD/SCID/IL2rnull mice that lack the common γ chain of the IL2 receptor. Furthermore, these cells were highly enriched for quiescent cells and were resistant to cytosine arabinoside chemotherapy. Similar results were seen in an in vitro model of acute lymphoblastic leukemia whereby resistance to asparaginase was conferred by mesenchymal cell secretion of asparagine synthetase. These observations need to be supported by prospective targeting of candidate genes using murine transgenic models to provide functional in vivo validation. However, they offer the tantalizing possibility that perhaps primary disease resistance can be overcome by altering the microenvironment.

Leukemias generated by retroviral transduction with candidate oncogenes (eg, MLL-AF9 from the t(9;11)(p22;q23) chromosome translocation and found in patients with AML) appear to require microenvironment cues for immunophenotypic differentiation. For example, human CD34^+ cord blood transformed with the MLL-AF9 oncogene caused acute lymphoblastic leukemia or acute biphenotypic leukemia when transplanted into NOD/SCID/β2microglobulin null mice but uniformly produced AML when transplanted into NOD/SCID mice transgenic for the cytokine genes KITLG (also known as SCF), CSF2 (also known as GM-CSF), and IL-3. This article provided the first clear evidence that lineage fate can be determined by the host microenvironment, although phenotypic differences have also been shown in myeloproliferative disorders due to host factors.

Homing to the microenvironment appears important in sustaining LSC survival. LSC may also hijack these pathways in a number of ways, for example, up-regulation of the α4β1 integrin, VLA-4. Patients with undetectable VLA-4 levels on leukemic blasts had an excellent response to chemotherapy, perhaps indicating that this pathway may mediate a stromal influence on sensitivity to chemotherapy. Correlating these clinical data, therapeutic targeting with a neutralizing VLA-4 antibody, in conjunction with cytarabine chemotherapy, was able to prevent the development of AML in a SCID xenograft transplantation model. As discussed in “Translation into therapeutic applications,” CD44 antibody therapy may also prevent LSC homing and engraftment in vivo.

The interaction between CXCR4 and CXCL12 appears to be used by leukemia cells. Elevated CXCR4 levels have been described in AML and are found to portend a poor prognosis. Furthermore, these interactions have been implicated in Nalm-6 homing in xenograft models of acute lymphoblastic leukemia and provide a more direct example of hijacking the niche. In this model, CXCL12 (SDF-1) was localized to perivascular hot spots, correlating with Nalm-6 acute lymphoblastic leukemia, normal HSC, and progenitor cell homing. The leukemia cells were able to directly modulate the niche at the expense of normal hematopoietic stem and progenitor cells by down-regulating CXCL12 levels in areas of leukemia infiltration. Stem cell factor, a niche regulator, was secreted by the leukemia cells leading to normal HSC and progenitor cell homing. The leukemia cells also hijack these pathways in a number of ways, for example, up-regulation of the α4β1 integrin, VLA-4. Patients with undetectable VLA-4 levels on leukemic blasts had an excellent response to chemotherapy, perhaps indicating that this pathway may mediate a stromal influence on sensitivity to chemotherapy.

Translation into therapeutic applications: creating a nonpermissive hematopoietic microenvironment that favors support of normal versus leukemic stem cells

The opportunity and challenge of stem cell biology is to translate the expansion of biological insights into clinically meaningful improvements for patients with leukemia and related disorders. For example, niche-targeted approaches have been suggested in the context of regenerative medicine and may have direct applications following chemotherapy to optimize supportive care and improve efficacy of stem cell mobilization. However, there is also emerging evidence that the complex interactions between LSCs and their niche may also be targeted to selectively deplete the repopulating (or regenerative) ability of LSCs as opposed to their normal HSC counterparts. Moreover, niche-targeted therapy might mitigate against cell intrinsic mechanisms of resistance such as increased expression of the multidrug resistance efflux pump, MDRI, and the selection of mutants that are insensitive to directly targeted therapy.

A recurring theme in niche regulation of HSCs involves the maintenance of a quiescent state, allowing long-term self-renewal
Based in part on these insights, it is likely that quiescence is important for LSCs as well. For example, it was recently shown that targeting of the promyelocytic leukemia tumor suppressor through genetic approaches or pharmacologically with arsenic trioxide leads to loss of self-renewal within the LSC in chronic myeloid leukemia, possibly through interfering with the quiescent fraction of chronic myeloid leukemia stem cells.

What are the characteristics of a niche-targeted therapy that might result in LSC eradication and translate successfully into the clinic? These agents would need to selectively limit the growth of the LSC clone in vivo by interacting with and disrupting the bidirectional interactions detailed in Figure 1. This could plausibly include inhibition of candidates such as cytokine signaling, self-renewal pathways (eg, Notch or Wnt), homing mechanisms, or cell adhesion molecules. In particular, there are data supporting the role of the Notch pathway in AML stem cells and evidence that both of these pathways are regulated, in part by the niche. Adhesion molecules are attractive candidates for LSC targeted therapies, and 2 recent studies have shown proof of principle that this approach may be successful. CD44 is important for homing and engraftment of BCR-ABL–positive CML and AML stem cells in a NOD/SCID xenograft transplantation model. It is also a receptor for the known niche component osteopontin. In both of the leukemia studies, antibody blockade of CD44 led to failed engraftment of these leukemias, although the ability to instigate leukemia when directly injected into medullary long bones remained. Proteasome inhibitors are an attractive consideration, given the diverse effects in targeting cytokine signaling networks. For example, bortezomib has been shown to inhibit the migration of AML blasts to stromal cell–derived CXCL12. Direct targeting of CXCR4 with chemical compounds may also represent another promising strategy. The CXCR4 antagonist AMD3465 has been shown to prevent the chemoprotective effects of stromal cell–leukemia interaction. Further studies have also shown leukemia mobilization and increased chemosensitivity in acute promyelocytic leukemia after treatment with AMD3100, another CXCR4 antagonist that has been studied extensively in normal HSC mobilization. This appears to be analogous to the beneficial effect seen with GCSF therapy in human AML, although it remains unclear whether either of these effects is mediated through synergistic cytotoxicity, prevention of stromal cell–derived chemoprotection, or the specific targeting of putative LSCs by some other means (such as enforced cell cycling and loss of quiescence). Finally, epigenetic chromatin modifiers (such as histone deacetylase inhibitors) have myriad effects including repression of self-renewal pathway target genes and induction of antiangiogenic molecules and may also prove appealing candidates.
Niche-targeted therapy must also respect the essential homeostatic mechanisms for HSCs and permit or promote normal HSC regeneration. As LSCs appear to use shared self-renewal pathways with HSCs, achieving this requirement may be extremely challenging.

Heterotypic cell coculture, initially developed using whole bone marrow on a supportive stromal cell layer, allows an in vitro readout of long-term self-renewal that correlates with long-term hematopoietic reconstitution in vivo. Evidence is emerging that the same techniques can be used to isolate and analyze LSCs and may prove a useful platform for drug screening and validation.

This rapidly developing field poses many more questions that require careful consideration before one can postulate niche targeted therapeutics in AML. For example, do AML stem cells respect and require the conventional bone marrow niche, or are they able to create and inhabit new niches (such as spleen or liver)? Spleens harvested from diseased mice with AML are enriched for leukemia-initiating activity and efficiently transplant disease, whereas normal mice have few immunophenotypically defined HSCs in the spleen, suggesting that LSCs may find ways to escape the normal regulatory signals and niche requirements or that they can manipulate other cell types to form new microenvironments. These are critical issues that we can define only as we unravel the detailed nature of the niche–stem cell interrelationship. Another consideration for niche-targeted therapy would be the optimal timing of this approach. As mentioned, it is likely that these compounds could have overlapping toxicity with chemotherapy and could potentially have devastating effects on normal HSC reconstitution or engraftment of allogeneic stem cells in the transplantation setting.

The complex cellular, humoral, and environmental controls presented in this review offer the potential to target LSCs independently of their substantial cell autonomous mechanisms of resistance to conventional therapies. Identification of candidate genes or compounds that are specific for LSCs will require well-designed heterotypic cell culture screens and careful in vivo validation to provide mechanistic insight and prevent against overlapping HSC toxicity.

Acknowledgments

We acknowledge the insightful comments and critical review of the manuscript provided by Drs. S. Frohling and S. Sykes.

D.G.G. received funding support from the US National Institutes of Health (NIH; Bethesda, MD), the Howard Hughes Medical Institute (Boston, MA), the Leukemia & Lymphoma Society (White Plains, NY), the Doris Duke Charitable Foundation (New York, NY), and the Myeloproliferative Disorders Foundation (Chicago, IL). D.T.S. received funding from NIH (National Heart, Lung and Blood Institute; National Cancer Institute; and the National Institute of Diabetes and Digestive and Kidney Diseases), the Ellison Medical Foundation, and the Harvard Stem Cell Institute. S.W.L. has received funding support from the Haematology Society of Australia and New Zealand, Royal Brisbane and Women’s Hospital Foundation, and the Australia/US Fulbright Commission.

Authorship

Contribution: S.W.L. wrote the paper; and D.T.S. and D.G.G. reviewed and provided critical revisions to the paper.

Conflict-of-interest disclosure: D.T.S. is a consultant and shareholder in Fate Therapeutics. S.W.L. and D.G.G. declare no competing financial interests.

Correspondence: Steven W. Lane, Division of Hematology, Karp Family Research Bldg, 5th Floor, 1 Blackfan Cir, Boston, MA 02115; e-mail: swlane@partners.org.

References


68. For personal use only.


The leukemic stem cell niche: current concepts and therapeutic opportunities

Steven W. Lane, David T. Scadden and D. Gary Gilliland

Updated information and services can be found at:
http://www.bloodjournal.org/content/114/6/1150.full.html

Articles on similar topics can be found in the following Blood collections
- Free Research Articles (4463 articles)
- Myeloid Neoplasia (1666 articles)
- Review Articles (697 articles)

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml