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Bone marrow microenvironment: The guardian of leukemia stem cells

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Abstract

Bone marrow microenvironment (BMM) is the main sanctuary of leukemic stem cells (LSCs) and protects these cells against conventional therapies. However, it may open up an opportunity to target LSCs by breaking the close connection between LSCs and the BMM. The elimination of LSCs is of high importance, since they follow cancer stem cell theory as a part of this population. Based on cancer stem cell theory, a cell with stem cell-like features stands at the apex of the hierarchy and produces a heterogeneous population and governs the disease. Secretion of cytokines, chemokines, and extracellular vesicles, whether through autocrine or paracrine mechanisms by activation of downstream signaling pathways in LSCs, favors their persistence and makes the BMM less hospitable for normal stem cells. While all details about the interactions of the BMM and LSCs remain to be elucidated, some clinical trials have been designed to limit these reciprocal interactions to cure leukemia more effectively. In this review, we focus on chronic myeloid leukemia and acute myeloid leukemia LSCs and their milieu in the bone marrow, how to segregate them from the normal compartment, and finally the possible ways to eliminate these cells.

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Core tip: Chronic myeloid leukemia stem cells (LSCs) and acute myeloid LSCs are resistant to common therapies due to the activation of downstream signaling pathways that guarantee their survival. In addition, they are smart enough to escape immune surveillance. Bone marrow microenvironment underlies these phenomena by providing an environment that favors leukemia development. Recent studies confirm that targeting LSCs and their crosstalk with the bone marrow microenvironment significantly reduced residual disease burden and eventuated in LSCs removal.

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INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell (HSC) disorder, emanating from t(9;22)(q34;q11.2), a translocation that involves fusion of Abelson murine leukemia viral oncogene homolog 1 (*ABL1*) on chromosome 9 and breakpoint cluster region protein (*BCR*) on chromosome 22^[1]. The encoded protein by constitutive tyrosine kinase activity stimulates downstream signaling pathways that lead to increased expansion of leukemic cells. Although the chronic phase of CML is concomitant with normal cell maturation, in the absence of appropriate treatment, a second mutation transforms the chronic phase into acute phase that mimics the same pattern as *de novo* acute leukemia^[2,3].

Acute myeloid leukemia (AML) is the most common form of leukemia in adults and is characterized by perturbed proliferation, block of differentiation, and infiltration of leukemic cells into the bone marrow and blood^[4]. Current therapies result in overall survival of about 40% in patients younger than 60 years of age, while this rate declines in older patients to 5%-15% and is associated with higher morbidity and mortality^[5]. One major concern in the treatment of AML is drug resistance, and a promising approach such as targeted therapy for relapsed or refractory AML is of the essence. While in CML the introduction of tyrosine kinase inhibitors (TKIs) as a milestone in the treatment of CML results in overall survival of about 86% and attaining treatment-free remission (TFR) seems achievable^[6].

Common treatment of AML and CML is based on the elimination of bulk disease population^[7]. As propagation of resistant leukemic cells may continue after the treatment discontinuation, the concept of cancer stem cell (CSC) came to light. Based on this theory, a cell with the self-renewal capability and leukemic related genetic alterations, which stands at the apex of the hierarchy, may be able to resist to therapy and sustain the relapse of the disease later on^[8] (Figure 1). The first approach that proved the existence of CSC was in AML, where the transplantation of a small cell population with stem cell-like properties into non-obese diabetic/severe combined immunodeficiency mice culminated in leukemia^[9]. The fact that every cell in different stages of the maturation by gaining stem cell-like features has the potential to become CSC is of paramount importance and depicts that it is not crucial for CSC to have stem cell origin^[10].

While both CML and AML leukemia stem cells (LSCs) have distinctive characteristics in case of the biology and immunophenotype, they share common properties such as drug resistance, quiescence, heterogeneity, and the microenvironment they reside. The bone marrow microenvironment (BMM) underpins normal hematopoiesis by secreting various growth factors and physical interactions with HSCs and progenitor cells^[11]. In AML and CML, the BMM boosts leukemogenesis through an interaction with LSCs, and in turn, LSCs change the BMM based on their requirements and make it less hospitable for normal stem/progenitor cells^[12]. Considering BMM as the main sanctuary for LSCs, targeting these interactions may

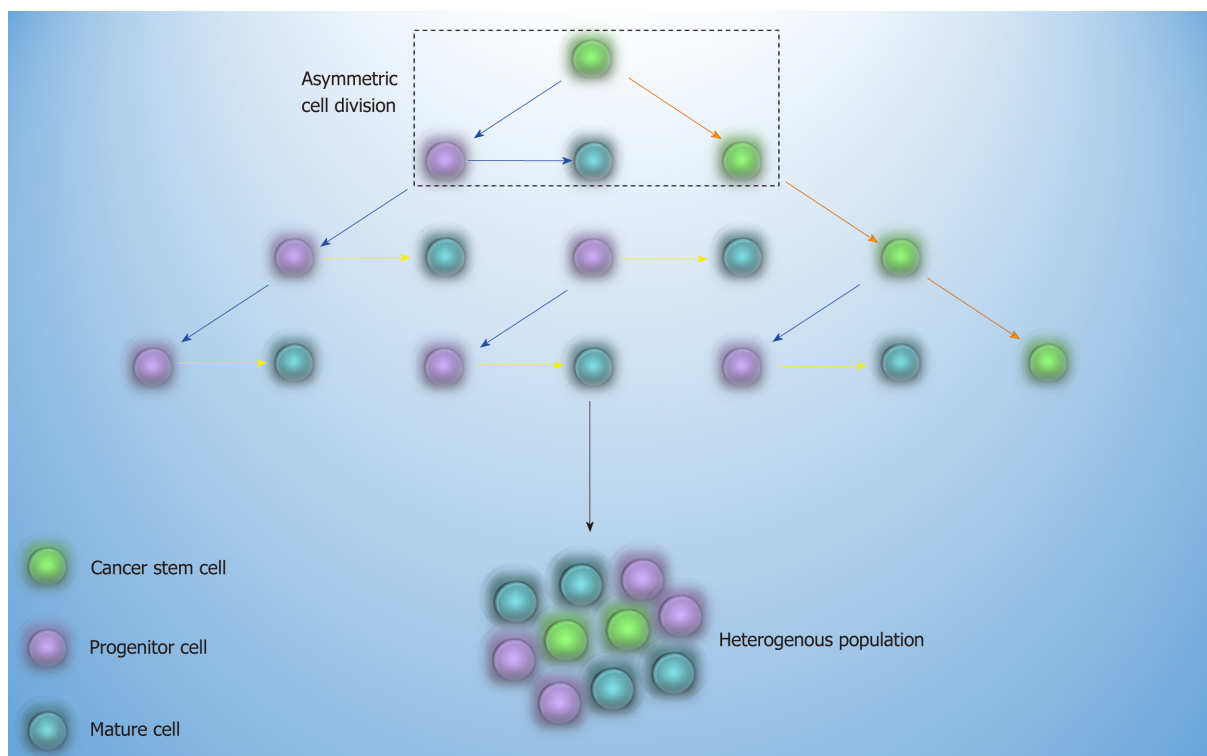


Figure 1 Cancer stem cell theory.

provide an ample opportunity to treat leukemia more effectively. In this review paper, we focus on the protective role of the BMM in the survival of CML and AML LSCs. We then move toward specific markers to identify these cells and put forward possible ways to target them within the BMM.

CML LSCs AND BONE MARROW MICROENVIRONMENT

CML LSCs, due to their resemblance to normal stem cells, reside in the same microenvironment in which a reciprocal relationship between these cells and components of the BMM is linked with enhanced proliferation, quiescence, and drug resistance. All of these mechanisms are conducted by sets of adhesion molecules or secretion of cytokines, chemokines, and growth factors *via* paracrine or autocrine mechanisms.

C-X-C motif chemokine ligand 12 (CXCL12), a known chemoattractant for the homing process, is secreted by mesenchymal stromal cells and osteoblastic cells and has a role in the localization of CML LSC and normal HSC in the BMM^[13]. However, perturbed expression of C-X-C chemokine receptor type 4 (CXCR4) by CML LSCs or CXCL12 targeting by CML LSCs impacts the homing process. Kinase activity of P210BCRABL1 and activation of downstream signaling pathways, such as phosphoinositide 3-kinases/protein kinase B [PI3K/PKB(AKT)], result in downregulation of CXCR4 by CML cells^[14]. Moreover, increased secretion of granulocyte-colony stimulating factor (G-CSF) as an antagonist of CXCL12 by CML LSCs^[15] and aberrant expression of surface marker dipeptidyl peptidase 4 (CD26) on CML LSCs with a chemokine cleavage activity favor mobilization of CML LSCs into the blood^[16]. However, TKIs, by inhibiting P210BCRABL1, contribute to the upregulation of CXCR4 and migration of CML LSCs to the BMM^[14].

The homing process for normal HSCs initiates with tethering and rolling of HSCs on endothelial cells *via* interaction with P and E-selectin. Then, a strong attachment through very late antigen-4 (VLA-4) and VLA-5 with vascular cell adhesion molecule 1 (VCAM-1) and fibronectin on endothelial cells and extracellular matrix supports the trafficking toward the BMM^[17,18]. While CML LSCs have normal expression patterns of VLA-4 and VLA-5, their impaired function demonstrates that these cells are not entirely contingent on β 1-integrins for the homing^[19]. Simultaneously, it has been reported that E and L-selectin and related ligands such as CD44 seem to be closely involved in the bone marrow lodgment of CML LSCs and are considered as the compensatory mechanisms as opposed to normal stem cells^[20]. Meanwhile, imatinib,

which is in first-line therapy for CML, increases another adhesion molecule N-cadherin in CML LSCs. Enhancement of N-cadherin promotes attachment to mesenchymal stromal cells and leads to N-cadherin- β catenin interaction^[21]. Also, secretion of exogenous WNT by mesenchymal stromal cells activates WNT- β catenin pathway in CML LSCs^[21]. WNT- β catenin is the leading signaling cascade in self-renewal and maintenance of normal HSCs and also CML LSCs, and it is important in leukemogenesis and drug resistance^[22,23]. Although TKIs may attenuate the constitutive activity of this cascade by targeting P210BCRABL1 and destabilize β catenin^[24], activation *via* the BMM may negate this inhibitory effect.

Apart from direct contacts of CML LSCs with the BMM, secretion of some soluble factors prepares a proper context for the growth of CML LSCs and confers a number of disadvantages for the growth of the normal compartment. It has been reported that enhanced secretion of some chemokines and cytokines, such as macrophage inflammatory protein 1 alpha (MIP-1 α), MIP-1 β , interleukin-1 alpha (IL-1 α), IL-1 β , and tumor necrosis factor alpha (TNF α) in the CML BMM, selectively impedes growth of normal HSCs and supports the growth of CML LSCs^[15]. Furthermore, secretion of IL-10, transforming growth factor beta (TGF- β), and IL-4 by the BMM or by CML LSCs in an autocrine manner downregulates expression of major histocompatibility complex-II (MHC-II) and helps CML LSCs to evade from the immune system and subsequent eradication^[25].

A study reported that the higher expression of bone morphogenetic protein receptor type 1b in TKI resistant CML LSCs is activated by bone morphogenetic protein 4 *via* paracrine and autocrine loops and triggers upregulation of twist family BHLH transcription factor 1, which promotes TKI resistance^[26,27]. Moreover, paracrine secretion of fibroblast growth factor 2 (FGF2) by mesenchymal stromal cells can provoke imatinib-resistance in CML patients^[28]. Direct contact of CML cells with mesenchymal stromal cells stimulates secretion of placental growth factor, which in turn increases proliferation and metabolism of leukemic cells and promotes angiogenesis within the BMM^[29].

Another secretory factor that reinforces quiescence and resistance of CML LSCs is germane to miR-126. miR-126 is considered to be the regulator of dormancy of CML LSCs as well as of normal HSCs^[30]. P210BCRABL1 kinase activity induces phosphorylation of Sprouty-related, EVH1 domain-containing protein 1, which causes reduction of mature miR-126 in CML LSCs. This depletion should be compensated by an external resource to keep up stemness features^[30]. In the BMM, endosteal Sca-1+ endothelial cells are the credible alternative by providing a high amount of miR-126 possibly through extracellular vesicles^[30]. Considering this, constraining the activity of miR-126 sensitizes LSCs to TKI and may expedite their removal^[30].

Another experiment highlighted the role of the hypoxic BMM in favor of p210BCRABL1 independent mechanisms in the survival of CML LSCs. In this milieu, a specific selection of LSC population occurs following the suppression of mature cells and stimulates TKI resistance. Sensitivity of leukemic cells to TKI is rescued by enhanced protein levels of BCRABL1 when LSCs migrate to normoxic condition^[31,32]. As HSCs reside in the hypoxic endosteal niche, enhancement of low oxygen area in the bone marrow of leukemia patients coincides with resistance and presence of minimal residual disease^[33,34]. Furthermore, it was demonstrated that hypoxia stabilizes hypoxia-inducible factor1 (HIF1), a transcription factor with a vital role in regulating proliferation, maintenance, and survival of CML LSCs^[15]. Our knowledge about the interactions of CML LSC with the putative BMM is limited and much remains to be elucidated. Interaction of CML LSCs with their environment through different molecules is described in Table 1 and Figure 2.

AML LSCs AND BONE MARROW MICROENVIRONMENT

Recent studies reported that AML LSCs are highly dependent to the leukemic BMM. *In vivo* cell tracking has specified the anatomical adjacent of these cells to the trabecular osteoblasts *via* cell adhesion molecules^[35]. Upregulation of VLA-4 in AML LSCs and its interaction with fibronectin that is distributed abundantly in endosteum facilitates AML LSCs homing to the niche. VLA-4 also has an integrity to VCAM-1 that is expressed by most of the niche cells, particularly endothelial cells^[36]. These interactions promote drug resistance in LSCs, so that the combination of cytarabine with the antibody against VLA-4 in non-obese diabetic/severe combined immunodeficiency mice prevents AML LSC lodgment to the niche and makes them an easy target^[37]. Meanwhile, similar to CML LSCs, elevated expression of CD44 on AML LSCs and high hyaluronic acid as its ligand on endosteal niche shift LSCs toward the BMM and chemoresistance state. Furthermore, this interaction promotes

Table 1 Possible molecules and their role in chronic myeloid leukemia stem cells-bone marrow microenvironment interaction

Target	Source	Role	Ref.
G-CSF	CML LSC	Mobilization	[15]
CD26	CML LSC	Mobilization	[16]
β 1-integrins	CML LSC	Homing	[19]
Selectins	CML LSC, endothelial cells	Homing	[20]
CD44	CML LSC	Homing	[20]
Chemokines (MIP-1 α , MIP-1 β , <i>etc</i>)	BMM, CML LSC	Growth of CML LSC	[15,25]
Cytokines (IL-1 α , IL-1 β , TNF α , <i>etc</i>)	BMM, CML LSC	Growth of CML LSC	[15,25]
BMP2/4	MSC, CML LSC	Drug resistance	[26]
FGF2	MSC	Drug resistance	[28]
PIGF	MSC	Proliferation, metabolism	[29]
miR-126	CML LSC, endothelial cells	Dormancy	[30]
HIF-1	CML LSC	Growth of CML LSC	[15]
Jagged-1	Osteoblast	Dormancy	[94]
Parathyroid hormone	BMM	CML LSC removal	[95]
WNT	BMM	Growth of CML LSC	[21]
N-cadherin	CML LSC	Drug resistance	[21]

CML LSC: chronic myeloid leukemia stem cell; BMM: bone marrow microenvironment; MSC: mesenchymal stromal cell; G-CSF: granulocyte-colony stimulating factor; MIP-1 α : macrophage inflammatory protein 1 alpha; MIP-1 β : macrophage inflammatory protein 1 beta; IL-1 α : Interleukin-1 alpha; IL-1 β : Interleukin-1 beta; TNF α : tumor necrosis factor alpha; BMP2/4: bone morphogenetic protein 2/4; FGF2: fibroblast growth factor 2; PIGF: placental growth factor; HIF-1: hypoxia-inducible factor1.

activation of tyrosine kinases and proto-oncogenic signals in leukemic cells including human epidermal growth factor receptor 2, non-receptor kinase Src, Rho-associated protein kinase, and Rac family small GTPase 1^[38]. While several adhesion molecules and stromal factors are involved in leukemic cell protection in the BMM, the principal mediator is related to the CXCL12-CXCR4 axis^[39]. Elevated CXCR4 level in AML cells is concomitant with a poor prognosis and causes strong adhesion of AML LSCs to the BMM^[40,41]. These cells play a bidirectional role by remarked Jagged1 expression that commences Notch1 pathway in neighbor leukemic cells and promotes autocrine signals in Jagged1 expressed stromal cells within the niche. Activation of Notch1 pathway accelerates self-renewal capacity of LSCs^[42,43].

When AML LSCs reside in this supportive milieu, secretion of some growth factors, cytokines, and chemokines is considerably important to keep leukemogenesis up in the BMM. Secretion of IL-8 in an autocrine mechanism and its receptor CXCR2 by AML LSCs supports IL8-CXCR2 interaction and triggers activation of multiple pathways, including PI3K/AKT, phospholipase C/protein kinase C, mitogen-activated protein kinase, β catenin, HIF-1, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) in AML LSCs that brings about tumor progression and survival^[44]. Moreover, CXCR2 inhibition reverses the growth of AML LSCs and enhances their removal^[44].

Another study reported that elevated parathyroid hormone signaling in osteoblastic cells controls HSC pool. While parathyroid administration increases the number of AML LSCs, it decreases the number of CML LSCs and reflects the distinct role of the BMM components in different hematologic malignancies^[45]. Activation of angiopoietin-Tie2 signaling in the osteoblastic niche preserves AML LSCs in dormancy and stimulates drug resistance^[46]. Meanwhile, release of pro-angiogenesis factors, such as vascular endothelial growth factor, hepatocyte growth factor, basic fibroblast growth factor, TNF α , and vascular endothelial growth factor receptor by LSCs increases neoangiogenesis. On the other hand, secretion of inflammatory and proliferative cytokines like TNF α , IL-6, IL-1 β , and G-CSF by leukemic cells and granulocyte-monocyte CSF by endothelial cells shares in niche neo vasculature that is considered as the major foundation of leukemia progression by providing metabolites and oxygen for AML LSC^[47-51]. In some conditions, human AML LSCs increase vascular permeability to reduce nitric oxide levels produced during the anaerobic glycolytic pathway^[52]. In a close relationship, endothelial cells also mediate proliferation and survival of LSCs by elevating the expression of CXCR4^[53].

AML LSCs are capable of maintaining long term reconstitution in the hypoxia

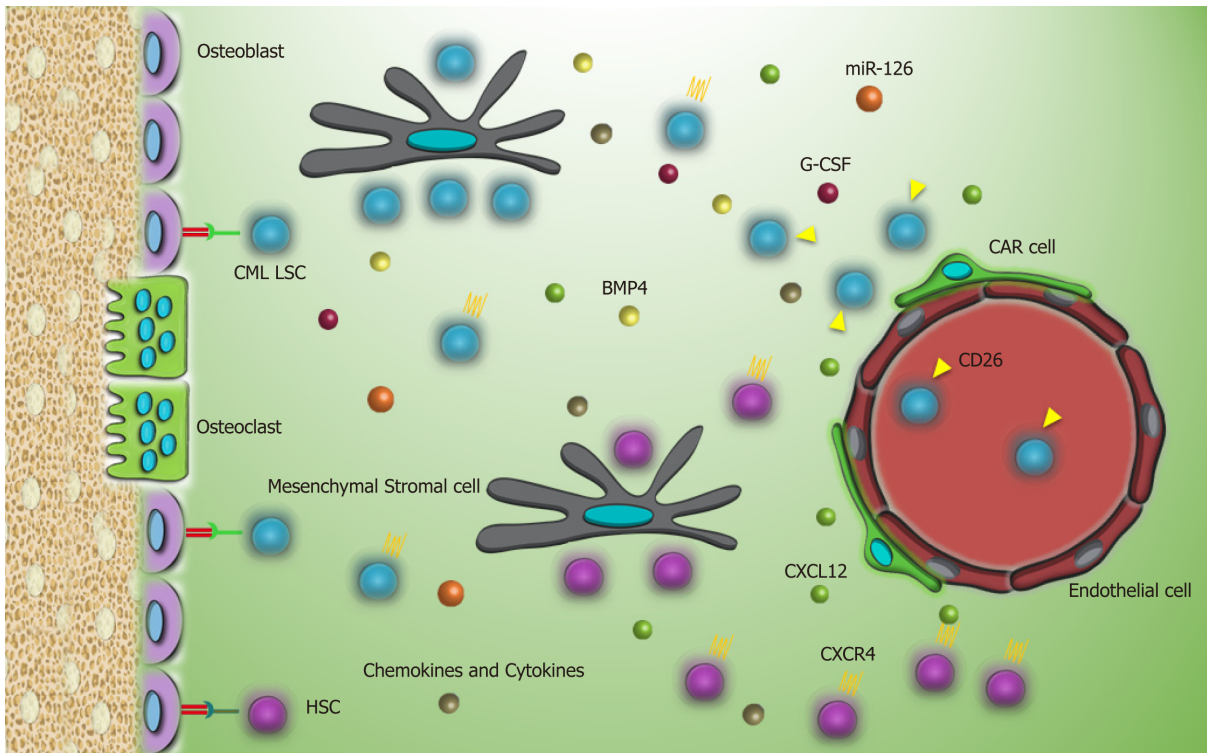


Figure 2 CML LSCs and their interaction with the bone marrow microenvironment. Expression of CXCR4 is downregulated by kinase activity of P210BCRABL1, and secretion of G-CSF and expression of CD26 by CML LSCs altogether lead to mobilization of CML LSCs into the blood. At the same time, secretion of some proteins such as bone morphogenetic protein 4, miR-126, and other chemokines and cytokines through autocrine or paracrine mechanisms may support dormancy, growth, and drug resistance of CML LSCs. CML LSC: Chronic myeloid leukemia stem cell; HSC: Hematopoietic stem cell; CAR cell: CXCL12-abundant reticular cell; G-CSF: Granulocyte-colony stimulating factor; CXCL12: C-X-C motif chemokine ligand 12; CXCR4: C-X-C chemokine receptor type 4; BMP4: Bone morphogenetic protein 4.

environment and modulate the differentiation process^[54]. This finding is in agreement with low metabolism and energy status of AML LSCs in the BMM. However, during stresses and apoptosis, high expression of CD36, a fatty acid transporter, and enhanced lipolysis by leukemic stem cells provide a compensatory source of energy that underlies their persistence^[55,56]. More investigations in LSCs and BMM crosstalk are needed to provide new insights to leukemogenesis biology and effective strategies for leukemia treatment. Interaction of AML LSCs with their environment through different molecules is summarized in Table 2 and Figure 3.

SPECIFIC MARKERS OF CML AND AML STEM CELLS

As CML LSCs reside in the CD34⁺/CD38⁻ cell fraction, finding specific markers is one step ahead for recognizing and selectively targeting these cells and to discriminate from normal HSCs. A useful CD marker should first distinguish between normal and leukemic stem cells, and, second, show lack or limited expression on the more mature population.

Many markers, such as CD44 and CD117^[57,58], have been recommended for detection of CML LSC, but shared expression with normal HSC has limited their application. On the other hand, surface markers such as CD25, IL-1 receptor accessory protein (IL-1RAP), and CD26 may offer a viable alternative in segregating CML LSCs^[16,59,60]. CD25 (IL2R α), which is expressed by CML LSCs, is regulated by signal transducer and activator of transcription 5 activity and serves as the suppressor of cell growth in CML LSCs. However, expression on the surface of progenitor cells might also be detectable^[59]. IL-1RAP as a co-receptor of IL-1 receptor participates in activation of NF- κ B and AKT signaling pathways that promote the growth of CML LSCs. As IL-1RAP expression increases with the disease progression, it seems that it may be a diagnostic marker for the advanced phase of the CML^[60]. CD26, with a chemokine cleavage activity, has a role in the mobilization of the CML LSCs into the blood by cleaving CXCL12^[16,61]. Expression of this marker in CML is just limited to CML LSCs in the chronic phase and is not expressed by normal HSCs, more mature population, and acute phase of the disease. So, CD26 may be regarded as a target

Table 2 Possible molecules and their role in acute myeloid leukemia stem cells-bone marrow microenvironment interaction

Target	Source	Role	Ref.
VLA-4	AML LSCs	Homing	[37]
CD44	AML LSCs	Homing	[38,96]
CXCR4	AML LSCs	Adhesion	[40]
Jagged-1	Osteoblast	Proliferation	[42]
CXCR2	AML LSCs	Proliferation, survival	[44]
Parathyroid hormone	BMM	OB proliferation, LSCs growth	[97]
Proangiogenesis factors (VEGF, HGF, BFGF, VEGFR)	AML LSCs, BMM	Endothelial and LSC proliferation	[47,48]
Cytokines (IL-6, IL1 β , TNF α , G-CSF, GM-CSF)	AML LSCs, BMM	Angiogenesis, LSC proliferation	[51]
Tie-2	Osteoblast	LSCs quiescent	[46]
CD36	AML LSCs	Energy source provider	[56]

AML LSC: Acute myeloid leukemia stem cell; BMM: Bone marrow microenvironment; VLA-4: Very late antigen-4; CXCR4: C-X-C chemokine receptor type 4; CXCR2: C-X-C chemokine receptor type 2; VEGF: Vascular endothelial growth factor; HGF: Hepatocyte growth factor; BFGF: Basic fibroblast growth factor; VEGFR: Vascular endothelial growth factor receptor; IL-6: Interleukin-6; IL-1 β : Interleukin-1 beta, TNF α : Tumor necrosis factor alpha; G-CSF: Granulocyte-colony stimulating factor; GM-CSF: Granulocyte-monocyte colony stimulating factor.

marker for detection of CML LSCs in newly diagnosed patients^[16]. While acute lymphoblastic leukemia LSCs with P210BCRABL1 also express CD26^[62], whether its expression in acute lymphoblastic leukemia and CML LSC is P210BCRABL1 dependent or independent remains to be discovered.

In contrast to the chronic phase of CML in which CML LSCs are defined in the CD34+/CD38- fraction, AML LSCs are composed of heterogeneous populations and except the CD34+/CD38- fraction, they also reside in CD34+/CD38+ and CD34- fractions^[63,64]. While the preleukemic state in AML initiates in HSC, they are considered non-leukemic, and progenitors are responsible for leukemia development. It has been reported that lymphoid primed multipotent progenitor cells in CD34+/CD38- fraction and granulocyte-macrophage progenitors in CD34+/CD38+ fraction are major AML LSC populations and that lymphoid primed multipotent progenitor cell like cells give rise to granulocyte-macrophage progenitor like cells (not vice versa) and show a higher self-renewal capability^[63]. However, based on the engraftment potential and transcriptomic analysis, CD34 is not a determinant marker of AML LSCs, and other markers are needed for the identification of these cells. Meanwhile, CML acute phase mimics the same pattern as acute leukemia, and LSC populations in acute phase of CML are extended to different types of progenitor cells that reflect LSCs heterogeneity^[65]. So, considering these, finding a proper marker to differentiate normal and leukemic stem cells in AML seems rather difficult and applying different markers is indispensable. For instance, some markers, such as CD96^[66], C-type lectin-like molecule-1^[67], CD123^[68], CD25^[69], CD47^[70], T-cell immunoglobulin and mucin domain-3^[71], *etc*, have been proposed for AML LSCs and are variably expressed by AML patients. In this case, a panel of markers might be helpful in dealing with AML LSCs. Apart from diagnosis, targeting of CML and AML LSCs based on these markers is already well underway, which may open up an opportunity to eliminate selectively LSCs and spare normal stem/progenitor cells. Different markers proposed for CML and AML LSCs are summarized in **Table 3** and **Figure 4**.

TARGETING LEUKEMIC STEM CELLS AND THEIR ENVIRONMENT

Clinical trials have been reported that about 40%-60% of CML patients are eligible for treatment discontinuation^[72,73]. While losing MR³ in CML patients is considered the sign of TFR failure, almost all of them achieve major molecular response and deeper molecular responses after resuming the treatment^[74,75]. Identification of the minimal residual disease is dependent on the application of quantitative real-time polymerase chain reaction, and subsequently it has been confirmed that CML LSCs are present from diagnosis, during the treatment and also in patients who are in TFR. These cells may be considered BCRABL1 negative due to undetectable transcript level of BCRABL1 in CML LSCs^[76]. Furthermore, an inverse correlation between the number of residual CD26+ CML LSCs and the probability of remaining in TFR has been

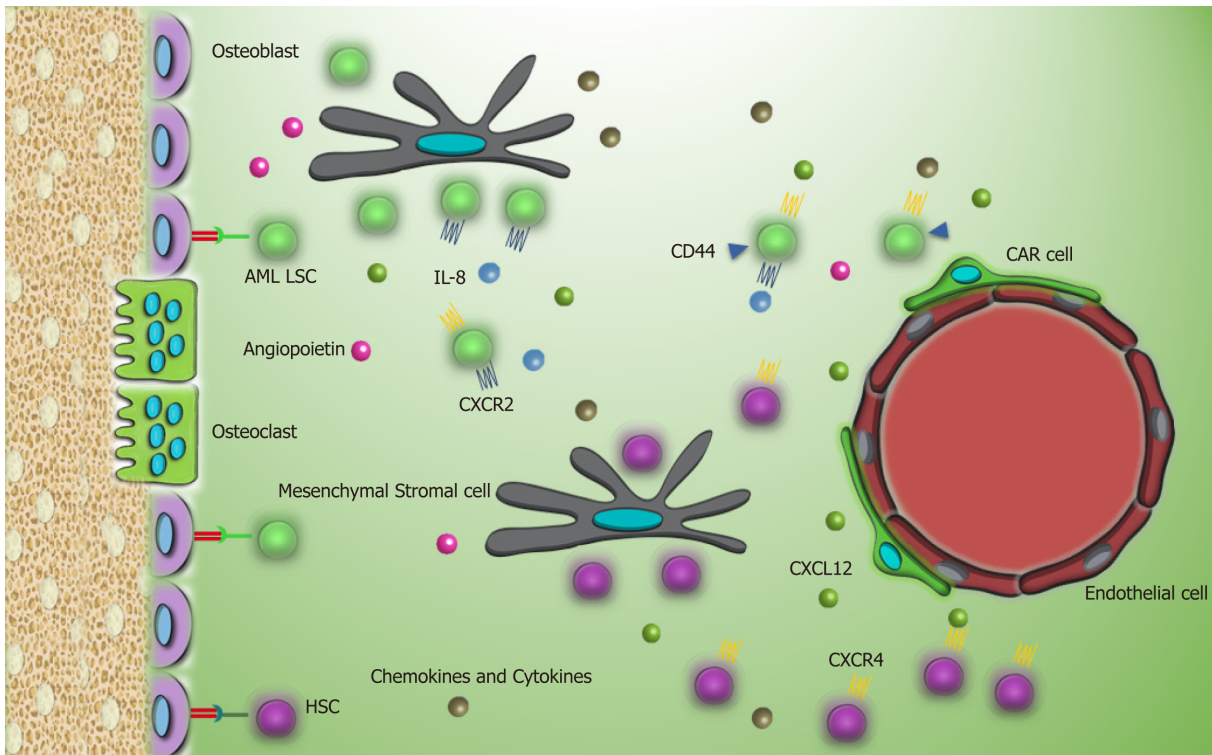


Figure 3 AML LSCs and their interaction with the bone marrow microenvironment in contrast to chronic myeloid leukemia stem cells, AML LSCs have high expression of CXCR4 that help them to reside in the bone marrow microenvironment. Meanwhile, autocrine secretion of IL-8 by AML LSCs increases their survival. Enhanced secretion of pro-angiogenesis factors *via* autocrine and paracrine mechanism extends angiogenesis, which by providing metabolites and oxygen for AML LSCs leads to leukemia progression. AML LSCs: Acute myeloid leukemia stem cell; HSC: Hematopoietic stem cell; CAR cell: CXCL12-abundant reticular cell; CXCL12: C-X-C motif chemokine ligand 12; CXCR4: C-X-C chemokine receptor type 4; CXCR2: C-X-C chemokine receptor type 2; IL-8: Interleukin-8.

Table 3 Chronic myeloid leukemia and acute myeloid leukemia stem cell markers for detection and selective targeting

Target	CD	CML LSC	AML LSC	Normal HSC	Normal progenitor	Ref.
IL-2R α	CD25	+	+	-	+/-	[59,69]
DPP4	CD26	+	-	-	-	[16]
Siglec-3	CD33	+	+	+	+	[98]
SCARB3	CD36	+	+	+/-	+	[99]
Pgp-1	CD44	+	+	+	+	[38]
IAP	CD47	+	+	+	+	[70]
Campath-1	CD52	+	+	+	+	[100]
C1qR1	CD93	+	+	+/-	+/-	[101]
Tactile	CD96	-	+	-	-	[66]
MIC2	CD99	-	+	+	+	[102]
SCFR	CD117	+	+	+/-	+/-	[64]
IL-3R α	CD123	+	+	+/-	+/-	[68]
CLL-1	-	+/-	+	+/-	+	[67]
TIM-3	-	-	+	+/-	+/-	[71]
IL-1RAP	-	+	+	-	+	[60,103]

CML LSC: Chronic myeloid leukemia stem cells; AML LSC: Acute myeloid leukemia stem cell; HSC: Hematopoietic stem cell; IL-2R α : Interleukin-2 receptor alpha; DPP4: Dipeptidyl peptidase 4; Siglec-3: Sialic acid-binding immunoglobulin-type lectin-3; SCARB3: Mast/stem cell growth factor receptor; IL-3R α : Interleukin receptor subunit α ; CLL-1: C-type lectin-like molecule-1; TIM-3: T-cell immunoglobulin mucin-3; IL-1RAP: Interleukin-1 receptor accessory protein.

overcome resistance and to eradicate LSCs more effectively^[10,84].

It was reported that blocking CXCR4 by plerixafor suppresses CXCL12-CXCR4 axis and increases the release of AML LSCs from the bone marrow to the blood^[85]. AMD3465, another CXCR4 antagonist, in combination with G-CSF and bortezomib, a proteasome inhibitor, prevents AML LSC migration toward the BMM and consequently makes them more accessible to chemotherapy agents^[86,87]. Meanwhile, in the leukemic BMM, HIF1- α and vascular endothelial growth factor modulate expression of CXCR4 and CXCL12, and targeting of these two in combination with CXCR4 antagonists significantly reduces homing of myeloid leukemia cells and reflects inducing mobilization of these cells to the blood might suppress leukemia development^[88].

On the other hand, upregulation of CD44, VLA-4, and Tie2 on AML LSCs is considered a putative target. Anti-CD44 therapy in AMLs prevents LSCs homing. Also, neutralizing VLA-4 antibody together with cytarabine treatment hampers AML development in a patient-derived xenograft mouse model^[38,89]. Adhesion of LSCs to mesenchymal stromal cells *via* VLA-4/VCAM-1 axis triggers NF- κ B activation as an anti-apoptotic factor in AML LSCs and stromal cells. AS101, a VLA-4 inhibitor that is in Phase II of a clinical trial, prevents NF- κ B activation and renders LSCs to chemotherapy^[90]. Whilst interaction of Tie2 with Ang-1 concludes LSCs quiescent, disruption of Ang-1/Tie2 interaction makes cells to cycle and recover LSCs sensitivity to cell cycle targeting agents. Ang1/2 neutralizing peptibody Trebananib (AMG 386), a combination of a peptide with an antibody, demonstrated promising results in a monotherapy program in a clinical trial^[91]. Another putative marker in AML LSCs is CD47 (SIRP α ligand), which is highly expressed by these cells. Interaction of CD47 with its ligand blocks phagocytosis, while blockade of this molecule leads to tumor cell phagocytosis and AML LSCs elimination in an efficient manner^[70]. Direct contact of AML LSCs with the BMM *via* Notch1-Jagged interaction initiates Notch signaling by intracellular domain cleavage of Notch1 following -secretase activation. Application of -secretase inhibitors like dibenzazepine in order to inhibit Notch signaling culminates in the suppression of LSC cell growth^[83]. However, in Kannan *et al*^[92], a pan-Notch inhibitor could not affect LSC proliferation, which confirms further study is needed to consider Notch signaling for targeting AML LSCs.

Inducing apoptosis also is a common approach in AML targeted therapy. O' Reilly *et al*^[93] reported that microenvironment mediated drug resistance in AML might occur following overexpression of myeloid cell leukemia 1, a BCL-2 family protein, in mesenchymal stromal cells. They confirmed that inhibition of myeloid cell leukemia 1 reverts the BMM mediated resistance against cytarabine and daunorubicin, prevents

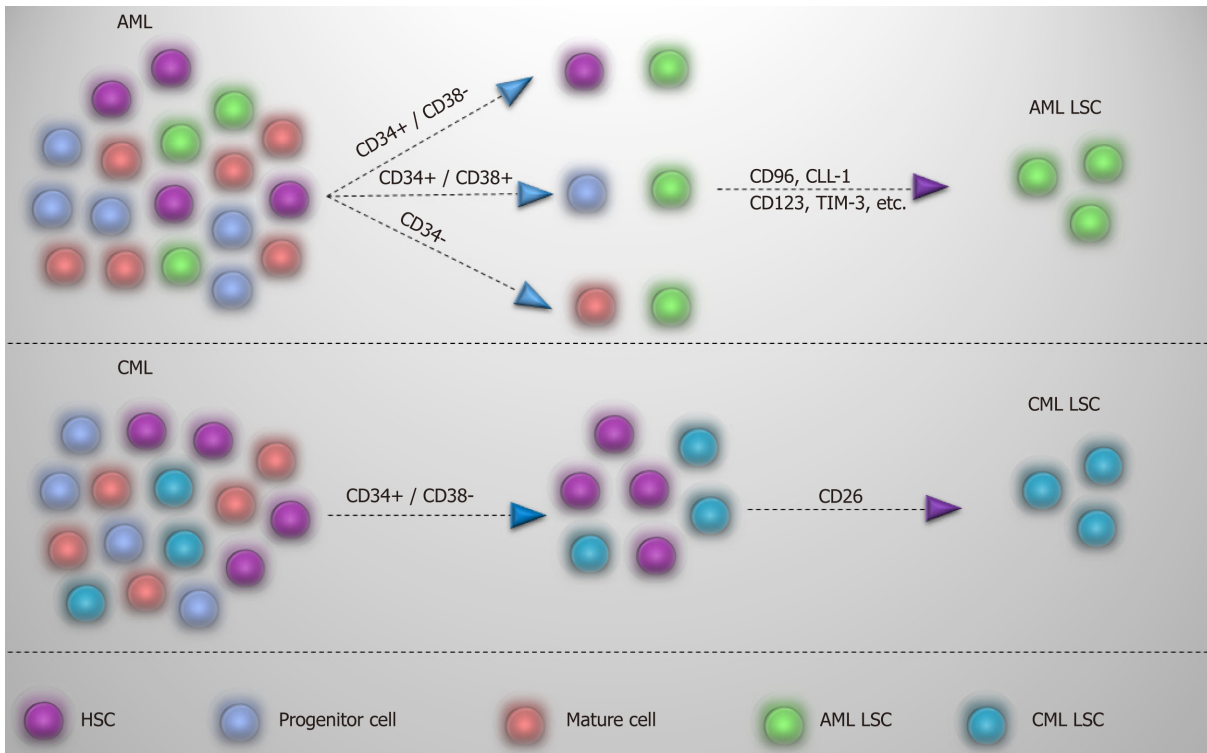


Figure 4 Detection of AML and CML LSCs. While CML LSCs in chronic phase are in CD34+/CD38-, using CD26 helps to segregate them from normal hematopoietic stem cells. In AML, CD34 is not a fixed marker for detection of AML LSCs, and due to the heterogeneity of AML LSC populations, other markers are needed to identify these cells. CLL-1: C-type lectin-like molecule-1; TIM-3: T-cell immunoglobulin and mucin domain-3; AML LSCs: Acute myeloid leukemia stem cell; HSC: Hematopoietic stem cell; CML LSCs: Chronic myeloid leukemia stem cells.

disease relapse, and ultimately improves patient survival. The proposed compounds under clinical trials related to targeting CML and AML LSCs interaction with BMM are summarized in Table 4. Other studies reported another possible target for elimination of AML LSCs by inhibiting the IL8-CXCR2 axis. This approach selectively eliminates AML LSCs while sparing normal HSCs^[44].

CONCLUSION

The therapeutic approaches that we listed above are in most cases already the object of investigational clinical trials. Many others will certainly follow, and, as far as our knowledge about the biology, the phenotypical appearance and the biochemical pathways typical of the leukemic stem cells will be better understood. It is unlikely that a single agent will be able to eliminate the leukemic stem cells. Targeted therapy will most likely be a combination of new drugs and more conventional therapeutic agents, ranging from traditional chemotherapy to new molecularly targeted agents or immune modulating agents. The final goal that we hope to achieve is to cure the vast majority of our patients and to improve their quality of their life.

Table 4 A draft of compounds under clinical trial in leukemic stem cell bone marrow microenvironment target therapy

Disease	Target	Compound	Clinical trial ID
CML	CXCR4	BL-8040	NCT02115672
CML	IL-1RAP	CAR-LMC	NCT02842320
CML	JAK-inhibitor	Ruxolitinib	NCT01702064, NCT03654768, NCT01751425, NCT03610971
AML	CXCR4	Plerixafor (AMD3100)	NCT01455025
AML	Hypoxia	TH-302	NCT01149915
AML	VEGF	Aflibercept	NCT00601991
AML	VLA-4	AS101	NCT01010373
AML	Ang-1/2	Trebananib (AMG 386)	NCT01555268
AML	CD47	SRF231, TTI-621, CC90002, Hu5F9-G4	NCT03512340, NCT02663518, NCT02367196, NCT02678338, NCT03248479
AML	Notch	LY3039478, MK0752	NCT01695005, NCT00100152
AML	XIAP	AEG35156	NCT00363974
AML	BH3	ABT-199	NCT01994837
AML	Pan FGFR	LY274455	NCT01212107

CML: Chronic myeloid leukemia; AML: Acute myeloid leukemia; CXCR4: C-X-C chemokine receptor type 4; IL-1RAP: Interleukin-1 receptor accessory protein; JAK: Janus kinase; VEGF: Vascular endothelial growth factor; VLA-4: Very late antigen-4; Ang-1/2: angiopoietin-1/2; XIAP: X-Linked inhibitor of apoptosis; FGFR: Fibroblast growth factor receptor.

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