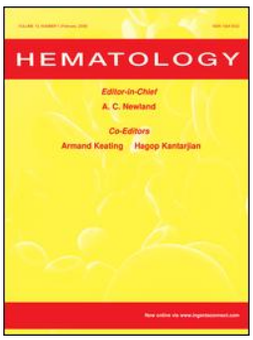

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Narrative review

Bone marrow neoplastic niche in leukemia

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Objectives: Neoplastic niche is a specific microenvironment for growth and proliferation of malignant cells. Here we review the leukemic niche and its constituent stem cells, signaling pathways and essential chemokines.

Methods: Relevant literature was identified by a PubMed search (2000–2013) of English-language literature using the terms neoplastic niche, chemokines, and leukemia.

Discussion: Leukemia is caused by malignant hematopoietic stem cells and precursors. Important molecules and signals are involved in interactions between leukemic cells and their microenvironment. MicroRNAs (miRNAs) play an important role in expression regulation of oncogenes, transcription factors, signaling molecules and in eventual fate of the cell. It seems necessary to evaluate the relationship between aberrant miRNA expression and malignant transformation of bone marrow niche.

Conclusions: Characterizing malignant leukemic cells, activated signaling pathways, and molecules involved in disease progression will result in understanding the causes of drug resistance, relapse factors, and effective treatments.

Keywords: Neoplastic niche, Bone Marrow, Signaling, Chemokine, Leukemia

Introduction

Bone marrow (BM) niche is a specific physiological microenvironment for hematopoietic and non-hematopoietic stem cells (HSCs) such as mesenchymal stem cells (MSCs). Maintaining such stem cell characteristics as pluripotency, self-renewal, control of stem cell number, proliferation, and determination of the fate of these cells is among the duties of this niche.[1,2]

BM microenvironment supporting the maintenance of HSCs is composed of two separate niches: osteoblastic (endosteal) and vascular.[3] In the osteoblastic niche, there are molecules such as bone morphogenetic protein (BMP), osteopontin, angiopoietin-1 and Notch, which appear to play important regulatory roles.[4] This niche also provides a microenvironment for long-term HSCs involved in hematopoiesis. Vascular niche composed of sinusoidal endothelial cells promotes the differentiation and proliferation of short-term HSCs.[3,4]

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MSCs are another type of stem cells in BM niche in the vicinity of endosteum, and together with osteoblasts are involved in maintenance of HSCs and regulation of osteoblastic differentiation by secretion and synthesis of important factors. Metalloproteinase-3, agrin, and BMP6 are a number of factors involved in normal bone formation, supplying survival signals to hematopoietic progenitor cells and resulting in increased osteoblastic differentiation in BM niche, respectively.[2,5,6]

Myeloid cells are of particular importance in HSC niche. In this regard, macrophages are positive regulators of MSCs and osteoblasts in BM niche by secreting such proteins as IL-1 and IGF-1, and play important roles for retention of HSCs.[5,6]

In a normal niche, BM microenvironment is formed by stromal cells such as osteoblasts and non-stromal cells like osteoclasts. Osteoclasts and osteoblasts play critical roles in remodeling and structure of niche. Osteoblasts regulate maturation and proliferation of BM cells through expression and secretion of a number of molecules and factors.[2] Typically, a normal niche maintains the balance between stasis

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expansion of stem cells.[7] Signals such as wnt/β-catenin growth inducing signal and BMP anti-growth signal are also involved in regulating the balance between stasis and expansion of niche.[2] If the stable balance of niche is egregiously influenced by activation of proliferative signals, loss of anti-growth signals, or infiltration of malignant cells such as myeloma cells, cancer stem cells (CSCs) are generated and reside in both osteoblastic and vascular niches, and this condition converts the normal niche to neoplastic one.[8–10] Leukemia is the result of malignancy of HSCs and precursors, and changes in BM niche are considered as the basis for leukemia.[2] Studies have indicated that concomitant with leukemogenic events in hematopoietic system of the niche, secretory signals of niche promote the growth and proliferation of leukemic cells.[3]

In this situation, leukemic microenvironment is created, in which leukemic cells disrupt the normal niche of hematopoietic precursor cells of BM, and create a cancerous microenvironment that can be called leukemic niche. According to investigations, leukemic cells in this niche receive antiapoptotic signals such as survivin and anti-apoptotic BCL-2 family members not only from osteoblasts but also from vascular endothelium.[3,11,12]

Metastatic niche, the growth-supportive environment for extravasated cancer cells, is created in two stages of metastasis initiation and metastatic growth, and certain factors and molecules are involved in each stage.[13,14] Metastasis initiation is triggered by cytokines and enzymes secreted by primary induced tumor. These include matrix protein fibronectin, matrix cross-linking enzyme lysil oxidase (LOX) and matrix metalloproteinase (MMP2 and MMP9).[14] Wnt and Notch signaling pathways, TGFβ along with proteolytic enzymes MMPs and cathepsin have been recognized as prominent components in metastatic outgrowth induction.[13,14]

Hypoxic conditions, growth factors, signaling molecules and secreted cytokines are different in normal as compared with malignant niche. Stem cell factor secreted by cancer stem cells leads to malignant transformation of resident cells in the niche. In addition, CD44 is involved in leukemic niche through homing and engraftment of these cells by binding selectins and hyaluronic acid.[15–17] In addition, the expression level of IL-6 as an important growth factor in BM environment is higher in malignant niche in comparison with normal BM stromal cells, which will lead to resistance to apoptosis. Excessive proliferation of cells in leukemic endosteal niche will result in expansion of hypoxic conditions in the niche.[15,18]

ATP-binding cassette (ABC) transporters are conserved transmembrane proteins highly expressed in HSCs, protecting stem cells from genetic damage due to xenobiotics.[19] In parallel with normal stem cells, malignant cells specifically express ABC transporters, which is responsible for multidrug resistance of malignant cells. ABCG2, ABCB1, and ABCC1 are three important ABC transporters known as multidrug resistance genes in malignant cells.[20] Therefore, ABC transporters play important roles in both normal and abnormal physiology. However, further studies are required in relation to the interaction among ABC transporters and drugs in neoplastic niche.[19,20]

Neoplastic niche microenvironment provides for circumstances leading to homing of normal and malignant cells. Higher expression of a number of signaling molecules like Notch is likely to result in chemoprotection and resistance to apoptosis in CSCs.[15,21]

According to the above, as HSCs niche in normal and neoplastic state of the leukemia involves complex interactions between multiple cell types and molecules, and as chemokines, cytokines, and growth factors are also secreted in niche, better understanding the nature of stem cells, leukemia types, cytokines, and chemokines secreted in normal and neoplastic niches will lead to improved treatment methods for some types of cancers and malignant tumors. In this regard, this review article will assess the factors affecting the normal and neoplastic niches in some acute and chronic leukemias such as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), chronic lymphoblastic leukemia (CLL), and multiple myeloma (MM).

Cancer stem cells in leukemic niche

CSC is a biologically distinct cell in a neoplastic clone capable of initiating tumor growth and self-renewal of cancer cells, leading to creation of heterogeneous lineages of cancer cells. In addition to progenitors and other differentiated cells, normal stem cells are the most likely targets for mutants causing CSCs due to their active self-renewal routes.[22,23] Leukemic stem cells are a type of cancer stem cell identified in leukemias with similar self-renewal capacity with normal HSCs but with some significant differences (Table 1). Leukemic niche or microenvironment of leukemic stem cells provides a site for homing of malignant leukemic cells, and plays an essential role in growth and progression of leukemia. Interactions between CSCs and their microenvironment require a number of molecules and factors. For example, CD44 is a key factor in homing and engraftment of CSCs to their leukemic niche in AML and CML.[1,24]

In addition to CD44, other molecules are involved in homing of HSCs in BM niche. Adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), E and P-endothelial selectins and integrins like very late activation antigen-4 (VLA-4) and α4-integrin are among other molecules involved in stem cell homing.

Table 1 Similarities and differences between normal stem cells and cancer stem cells in leukemia

References				
[1,28]	Self-renewal ability (pluripotency), molecular mechanisms of stem cell homing to the niche, similar antigenic features like ($CD34^+$,$CD38^-$,$CD71^-$,$HLA\text{-}DR^-$) and be quiescent of both stem cells in cell cycle			Similarities of normal stem cells and cancer stem cells in leukemia
[28,29]	LSCs surface markers:$CD33^+CD44^+CD90^+CD96^+CD123^+CD34^+CD38^-CD117^-$ Involvement of MDR1, MRP1, BCRP& lung-resistance protein in drug-resistance, activation of STAT5, RAS/MAPK & PI3K/AKT pathways as a result of mutations, highly expressed anti-apoptotic factors like Bcl-2, Bcl-x_L and Mcl-1.		AML	Differences of cancer stem cells in different types of leukemia with normal stem cells
[28–31]	LSCs surface markers:$CD34^+CD38^-CD44^+$, expression of the chimeric fusion gene BCR/ABL as a diagnostic marker, identified BCR/ABL point mutation in drug-resistance to imitanib, suppression of resistant mutants by Bcr/abl kinase inhibitors such as nilotinib and the dual Bcr/abl-Src inhibitor dasatinib		CML	
[28,29,32]	LSCs surface markers:$CD9^+CD34^+CD10^-CD19^-$, 85% of diagnosed ALL cases, BCR/ABL translocation in 5% to 25%, involvement of LRP in drug-resistance	B-Lineage	ALL	
[28,29]	LSCs surface markers:$CD34^+CD4^-CD7^-CD19^-CD90^+CD110^+$, 15% of diagnosed ALL cases	T-Lineage		

B-ALL, acute B-lymphoblastic leukemia; T-ALL, acute T-lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MRP1, multidrug resistance-associated protein; BCRP, breast cancer resistance protein; LSCs, leukemia stem cells; LRP, lung resistance-related protein.

In addition to the above molecules, soluble factors such as granulocyte colony-stimulating factor (G-CSF), granulocyte /macrophage colony stimulating factor (GM-CSF), and growth factors such as vascular endothelial growth factor, angiopoietin-1, and chemokines such as IL-8, stromal cell-derived factor 1 (SDF-1) as well as other factors play a role in homing of stem cells. Among these factors, α4-integrin/VCAM-1 play prominent roles in BM homing.[25–28]

Signaling in leukemic niche

Interactions between HSCs and their microenvironment are of particular importance to the extent that they affect the function of these cells. Therefore, regulating the activity of hematopoietic cells is a complicated process requiring moderating signals provided by the microenvironment around them.[24,33] For example, the interaction between anti-growth signal BMP and Wnt is responsible for regulating homeostatic balance of HSCs, disruption of which will lead to tumor formation.[7] Wnt/beta-catenin signaling pathway is a major signaling pathway in regulating HSC functions such as differentiation and apoptosis.[34] Moreover, SDF-1-mediated CXCR4 signaling, Notch1 activation, and B lymphoma Mo-MLV insertion region 1 homolog (BMI-1) are respectively involved in implantation and mobilization, increased self-renewal capacity and maintenance of HSCs.[35] Notch and G_s signaling pathways are among other signaling pathways playing important roles in maintenance of HSCs and osteoblastic differentiation, respectively.[36,37]Concomitant with growth of leukemic stem cells, signaling mechanisms between HSCs, and stem cell niche are hijacked by these malignant cells.[7] Aberrant activation or dysregulation of these signaling pathways and molecules involved in them can lead to a variety of malignant disorders. Disruption of Wnt signaling pathway has been observed in AML cell lines, during which decreased intracellular level of beta-catenin *in vitro* can reduce proliferation in the cell line without affecting viability of the cells.[34] Interference with the above signaling pathway has also been reported in MM, such that downregulation of beta-catenin leads to G_1/G_2 phase increase of cells and reduced S phase cells.[34,38] In MM, increased expression of DKK1 as Wnt inhibitor by BM stem cells, especially MSCs, has been reported followed by inhibition of osteoblastic differentiation of MSCs.[39] Dysregulation or activation of Wnt signaling pathway through abnormal promoter methylation of Wnt inhibitors like DKK_3 and WIF1 has also been reported in ALL patients, and is involved in pathogenesis of lymphoid leukemia. Dysregulation of this pathway in CML patients causes progression of disease from chronic phase to advanced phase.[40,41] Continuous Gs signaling leads to accumulation of osteoblast cells, resulting in reduced expression of key factors influencing the maintenance of HSCs in the BM.[37] Transcription factor genes and signaling molecules are among the most common mutated or dysregulated genes observed in leukemias (Table 2).

CXCR4/SDF-1 axis as a key chemokine/chemokine receptor interaction in leukemic niche

In addition to their role in leukocyte migration and hematopoiesis, chemokines play important roles in pathological processes such as hematological neoplasias.[57] As shown in Fig. 1, chemokine (C-X-C motif) receptor type 4 (CXCR4) plays an important role in many types of cancers indicating leukemia.[58] Most leukemic cells express CXCR4, but the expression level of this receptor is different in various types of leukemia.[59,60] Interaction between chemokines and their

Table 2 Some of important transcription factors/signaling molecules involved in leukemic niche

Transcription factor/signaling molecules	Type of involved leukemia	Mutation/ dysregulation event	miRNAs as tumor suppressor in leukemia	Inhibitors	Function	References
C/EBPα	AML	Mutations in the coding regions	miR-15a and miR-16-1	AML1-ETO fusion protein,hnRNP E2,tyrosin kinase receptor FLT3,calreticulin	Pathogenesis of AML	42–46
GATA-1	Down syndrome-associated leukemias including (AMKL) or (TMD)	Small deletions or insertions in exon 2	——	PU.1	Inhibits myeloid dif,development of certain types of myeloid leukemia	42,47
PML/RARα	APL and primary AML	Translocation (15;17) (q22;q12)	miR-15a and miR-16-1 in AML	ATRA, Tamibaroten Arsenic trioxide	Development of APL	42,43,48,49
AML1/ETO	Primary AML	Translocation (8;21) (q22;q22)	miR-15a and miR-16-1	VPA, siRNA	Inhibits dif of leukemic cells toward G, M, E cells or granulocytic sarcoma	43,49–51
AML1/EVI1	Secondary AML, most commonly blastic CML	Translocation (3;21) (q26;q22)	——	——	Progression of CML &myelodysplastic syndrome	49,52
Notch1	Pediatric & adult T-ALL	Translocation (7;9) (q34;q34)	——	DAPT,MK0752, Dibenzazepine	Inhibition of lymphoma cell apoptosis and development ofT-ALL	53–55
Wnt	AML	Aberrant activation of the Wnt pathways	miR-15a and miR-16-1	DKK_1, sFRP, Wif	Reduction of intracellular beta-catenin levels	7,34,43,56

AML, acute myeloid leukemia; AMKL, acute megakaryoblastic leukemia; TMD, transient myeloproliferative disorder; APL, acute promyelocytic leukemia; ATRA, all-trans retinoic acid; CML, chronic myeloid leukemia; T-ALL, T- acute lymphocytic leukemia; dif, differentiation; VPA, valproic acid; AME, AML1/MDS1/EVI1; DKK_1, Dickkopf1; C/EBP, CCAAT/enhancer-binding protein; G, granulocyte; M, monocyte; E, erythrocyte; OB, osteoblast; HSC, hematopoietic stem cell; OSC, osteoclast; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoblastic leukemia; CML, chronic myeloid leukemia; MM, multiple myeloma.

receptors (known as cluster) plays important roles during leukemogenesis. For example, CXCL12 (also known as SDF1) as a member of CXC chemokine family along with CXCR4 forms CXCL12/CXCR4 cluster, and during leukemogenesis in AML patients regulates migration of AML cells.[61] SDF1/CXCR4 signaling together with oncogenic proteins involved in various types of leukemia is important in prognosis of the disease, so that ITD-Flt3 signaling in AML and BCR/ABL signaling in CML along with SDF1/CXCR4 is respectively involved in development of leukemia and migration of malignant cells.[60] This chemokine receptor is essential for homing of ALL cells in bone microenvironment, the expression of which is regulated by a wide range of cytokines.[59,60] In addition to cytokines, a wide range of transcription factors affect transactivation of this chemokine receptor. FOXA2, FOXC2, and FOXH1 are among the transcription factors enhancing transactivation of this chemokine receptor, and Ying Yang 1 (YY1) is among those that reduce its transactivation.[62,63]

Interaction of leukemic stem cells with BM vasculature is strongly dependent upon CXCR4 expression and binding to SDF-1 expressed by vessel endothelium. Small peptide inhibitors of CXCR4 have been shown to be capable of overcoming BM stroma-mediated resistance to drug-induced apoptosis in AML and CLL. Therefore, CXCR4/SDF-1 can be considered as an autocrine mechanism with an indirect sanctuary role in drug resistance. In addition to the important role of this cytokine, autocrine IL-6 generation in myeloma cell clones can be a resistance mechanism against drug-induced apoptosis.[7,15]

MiRNAs, cancer stem cells, and therapeutic approach in neoplastic niche

MiRNAs as small RNA molecules affect many biological processes such as proliferation and apoptosis of the cells.[64,65] In addition, during the tumorigenesis process, miRNAs regulate important features of cancer stem cells such as migration and invasion causing increased metastatic capacity of these malignant cells. Studies conducted in this regard indicate the oncogenic role of miR-15/miR-16 cluster in CLL, such as targeting the apoptotic inhibitor Bcl-2.[65] In addition to the role of miRNA in regulating

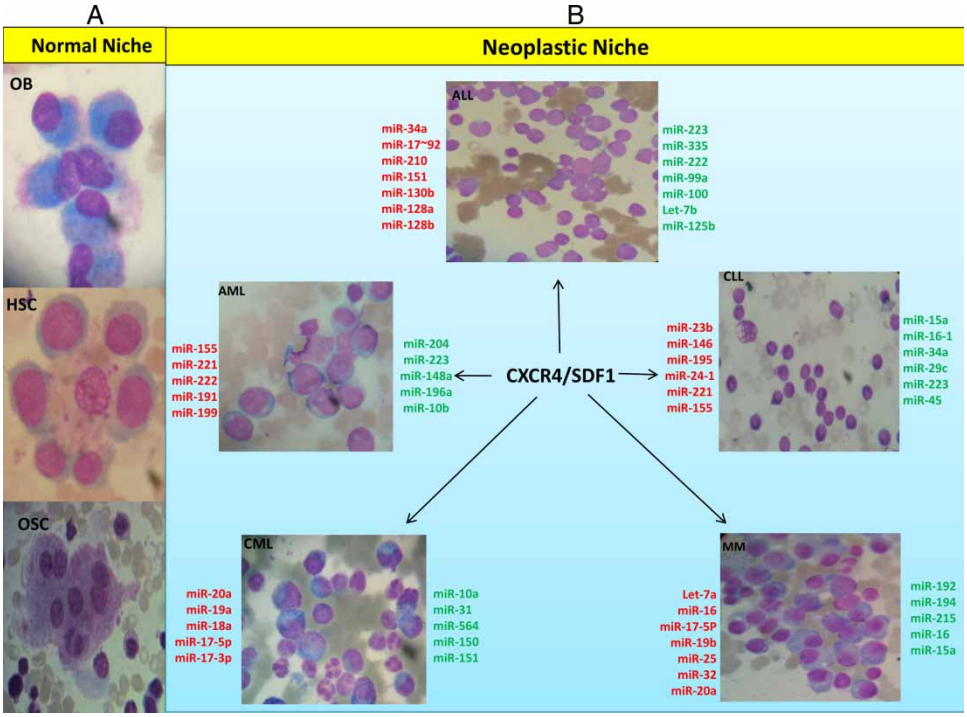

Figure 1 Schema of the relationship between changing level of miRNAs in stem cells and malignant neoplastic cells in neoplastic niche (51 and 54). (A) In normal niche respectively from top to bottom: osteoblasts, hematopoietic stem cells, among which there is a macrophage and an osteoclast is shown at the end. (B) In neoplastic niche, a variety of hematologic malignancies and miRNAs changes during the disease process has been shown, in which the upregulated miRNAs are shown in red and those downregulated in green. CXCR4/SDF1 axis has been shown as the important chemokine/chemokine receptor expressed in a variety of malignancies in neoplastic niche.

adhesion molecules, such as the role of miR-10a and miR-126 in controlling the expression of VCAM-1, the activity of adhesion-related miRNAs can be changed during development and progression of cancer metastasis. MiR-10b, miR-31 and miR-200 are among the adhesion-related miRNAs participating in metastatic progression in tumor models.[66]

As shown in Fig. 1, miRNAs are involved in a number of leukemias such as AML, ALL, CML, and CLL as well as MM. Considering the expression of MiRNAs in leukemic cells and specificity of some types of them for a number of leukemias like down regulation of miR-92 in acute leukemia, this group of small noncoding RNAs can be used as biomarkers to develop appropriate therapeutic approaches for some leukemia types.[67] Taking advantage of the tumor suppressor property of miRNAs is also possible in some types of leukemia-like tumor suppressor miR-451 in T-ALL.[64,68]

Using monoclonal antibodies conjugated with cytotoxic antibiotics against cell surface markers in leukemic cells in a variety of hematologic malignancies is also one of the important practical therapeutic strategies to eliminate leukemic stem cells. Considering the expression of CXCR4 in a variety of leukemic cell types, using the CXCR4 antagonists can be a therapeutic prospect in treatment of some leukemias.[29]

Discussion

Recent studies on neoplastic niche have indicated that Polo like kinases (PLK) as serine/threonine protein kinase family members act as important regulators of cell cycle progression and cytokinesis. However, overexpressed PLK1 results in oncoprotein neoplastic niche. Recent studies consider conventional anti-leukemic chemotherapy combined with PLK inhibitor as a promising progress in treatment of AML. In addition, development of selective histone methyltransferase inhibitors such as EZH2 has recently been considered in treatment of hematologic malignancies like AML.[69]

Normal and neoplastic niches have their specific molecules and microenvironment. Each of these niches with their own stem cells including normal and cancer stem cells along with signaling pathways, microenvironment specific chemokines and chemokine receptors are respectively involved in the growth and survival of normal stem cells and cancer progression, as observed in various types of leukemia. Accordingly, research aiming to identify molecules and factors involved in neoplastic niche is useful for therapeutic purposes.

Authors' contributions

N.S, S.B, and F.R conceived the manuscript and revised it; N.S, Sh.A, and M.Sh wrote the manuscript. N.S prepared the figure.

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