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Novel therapeutic strategies to target leukemic cells that hijack compartmentalized continuous hematopoietic stem cell niches

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ABSTRACT

Acute myeloid leukemia and acute lymphoblastic leukemia cells hijack hematopoietic stem cell (HSC) niches in the bone marrow and become leukemic stem cells (LSCs) at the expense of normal HSCs. LSCs are quiescent and resistant to chemotherapy and can cause relapse of the disease. HSCs in niches are needed to generate blood cell precursors that are committed to unilineage differentiation and eventually production of mature blood cells, including red blood cells, megakaryocytes, myeloid cells and lymphocytes. Thus far, three types of HSC niches are recognized: endosteal, reticular and perivascular niches. However, we argue here that there is only one type of HSC niche, which consists of a periarteriolar compartment and a perisinusoidal compartment. In the periarteriolar compartment, hypoxia and low levels of reactive oxygen species preserve the HSC pool. In the perisinusoidal compartment, hypoxia in combination with higher levels of reactive oxygen species enables proliferation of progenitor cells and their mobilization into the circulation. Because HSC niches offer protection to LSCs against chemotherapy, we review novel therapeutic strategies to inhibit homing of LSCs in niches for the prevention of dedifferentiation of leukemic cells into LSCs and to stimulate migration of leukemic cells out of niches. These strategies enhance differentiation and proliferation and thus sensitize leukemic cells to chemotherapy. Finally, we list clinical trials of therapies that tackle LSCs in HSC niches to circumvent their protection against chemotherapy.

1. Introduction

Leukemias are hematologic malignancies that are characterized by an overgrowth of white blood cells and are caused by increased monoclonal cellular proliferation in the bone marrow, resulting from (epi)genetic changes in either HSCs, lymphoid or myeloid progenitor cells [1–3]. HSCs are at the top of the hematological hierarchy as multipotent stem cells with self-renewal capacity that give rise to various types of progenitor cells and ultimately the production of mature erythrocytes, megakaryocytes, myeloid cells, and lymphocytes [4–6]. Since mature blood cells are short-lived, HSCs are required throughout life to replenish progenitor and precursor cells [5,7].

A stem cell niche is a specialized microenvironment that helps to maintain stem cell characteristics. In the bone marrow, HSCs reside in

Abbreviations: AML, acute myeloid leukemia; ANG-1, angiopoietin-1; ALL, acute lymphoblastic leukemia; AKT, protein kinase B; Ara-C, cytarabine; AXL, tyrosine kinase receptor; BCL-2, B-cell lymphoma 2; BH3, BCL-2 homology 3; BMP, bone morphogenic protein; CAR cell, CXCL12-abundant reticular cell; CBP, CREB-binding protein; c-KIT, stem cell factor receptor; CLL, chronic lymphocytic lymphoma; COX4, cytochrome c oxidase subunit 4; Ctnnb1C^{Aosb}, constitutively activated β-catenin protein; CXCR4, C-X-C receptor type 4; ECM, extracellular matrix; ERK, extracellular regulated kinases; FZ, Frizzled; GAS6, growth-arrest specific gene 6; G-CSF, colony-stimulating growth factor; GSLC, glioma stem-like cell; HA, hyaluronic acid; HHIP, human hedgehog-interacting protein; HIF-1α, hypoxia-induced factor-1α; HPC, hematopoietic progenitor cell; HSC, hematopoietic stem cell; IHH, Indian hedgehog; LSC, leukemic stem cell; LON, ATP-dependent protease; MAPK, mitogen-activated protein kinase; MDS, myelodysplastic syndromes; MER, tyrosine-protein kinase; MPL, thrombopoietin receptor; MPN, myeloproliferative neoplasms; MSC, mesenchymal stem cell; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa beta; NSC, neural stem cell; OB, osteoblast; OC, osteoclast; OM, osteomac; OPN, osteopontin; PI3K, phosphoinositide 3-kinase; OXPHOS, oxidative phosphorylation; RAS, retrovirus-associated DNA sequences; ROS, reactive oxygen species; SDF-1α, stromal derived factor-1α; SCF, stem cell factor; STAT, signal transducers and activators of transcription; TCF, T-cell factor; TGF-β, transforming growth factor-β; TIE2, tyrosine kinase receptor; TNF-α, tumor necrosis factor-α; TPO, thrombopoietin; VCAM-1, vascular cell-adhesion molecule-1; VEGF, vascular endothelial growth factor; VLA-4, very late antigen-4; WNT, wingless-type; XIAP, X-linked inhibitor of apoptosis protein

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HSC niches, which play an important role in regulating the behavior of HSCs with respect to homeostasis and stress responses [7–10]. The proliferation and differentiation of hematopoietic progenitor cells and their daughter cells are sufficient to maintain the homeostatic hematopoiesis under normal conditions, consisting of the production of one trillion (10^{12}) cells per day in healthy human adult red bone marrow. In such circumstances, HSCs are in a dormant quiescent state to prevent stem cell exhaustion [11–13]. Blood is a tissue with one of the highest regenerative capacities and the prevention of HSC exhaustion is extremely important considering the necessity to upregulate hematopoiesis in case of blood loss due to tissue damage or hematopoietic stress [5]. In these contexts, HSCs are forced to leave the niches to differentiate and proliferate in order to maintain hematopoiesis [13–15].

In the present review, molecular mechanisms are discussed of the crosstalk between HSCs and the three types of HSC niches that are recognized until now. Next, HSC niches are described in AML and ALL when AML/ALL cells use HSC niches to become LSCs that are quiescent and resistant to therapy [16–19]. We refer to this process as hijacking of HSC niches by leukemic cells. Hijacking of HSC niches by leukemic cells and their transformation into LSCs is considered to be the most prominent cause of tumor recurrence [18–20]. We describe the molecular interactions between LSCs and the main cell types of HSC niches, growth factors, cytokines and chemokines in HSC niches that facilitate adhesion, survival and quiescence of LSCs in HSC niches, ultimately resulting in therapy-resistance of LSCs [19]. Finally, therapeutic targeting of LSCs in HSC niches is discussed as a promising approach to treat AML and ALL more effectively.

2. HSC niches

HSCs are currently considered to reside in one of three types of HSC niches: endosteal, reticular or perivascular niches [21,22]. Some cell types, proteins and factors are shared between the three types of niches, others are considered to be unique for a specific niche type. A common factor of all types of niches is that they tightly regulate whether HSCs migrate into niches, are kept inside the niches or migrate out of the niches. This is crucial, because HSC stemness and quiescence are promoted in the niches, whereas migration out of the niches enables HSC differentiation and proliferation. The cell types, proteins and factors that are present in the two compartments are listed in Table 1.

2.1. The endosteal niche

The endosteum is the interface between bone and bone marrow which mainly consists of osteoblasts and, to a lesser extent, osteoclasts. Mature osteoblasts produce ECM and are responsible for bone formation whereas osteoclasts resorb bone and thus function in bone remodeling [4,21]. The endosteal niche is associated with the endosteum (Fig. 1A) and facilitates interactions between osteoblasts and HSCs, which keeps HSCs quiescent [19]. The main cell types of the endosteal niche that maintain stemness and quiescence of HSCs and affect their homing and mobilization are osteoblasts, osteoclasts [8] and osteomacs [4,23]. The functions of these 3 main cell types and the molecular mechanisms by which they maintain HSCs in the endosteal niche, will be discussed in the following Sections (2.1.1–2.1.3).

2.1.1. Osteoblasts

2.1.1.1. Osteoblast-promoted retention of HSCs in endosteal niches. Several interactions and intermediate molecules between osteoblasts and HSCs have been described for the endosteal niche. OPN is a matrix glycoprotein with cytokine and chemokine properties which is secreted by osteoblasts and binds to HSCs via CD44 or integrins containing a β1 subunit. This results in homing of HSCs in the endosteal niche and downregulation of HSC proliferation [7,24–26]. CD44 can also interact with the ECM component (HA), which results in homing of HSCs into HSC niches. HA is produced in the endosteum by stromal cells and hematopoietic cells under hypoxic conditions due to HIF-1α activity [27]. Furthermore, the chemoattractant SDF-1α (CXCL12) is produced by osteoblasts under hypoxic conditions and interacts with its receptor, CXCR4, which is expressed on HSCs, resulting in the retention of HSCs in the endosteal niche [7,25,26,28,29].

2.1.1.2. Osteoblast-promoted self-renewal of HSCs. HSCs express the receptor MPL which binds TPO after secretion by osteoblasts. Interactions between TPO and MPL result in homodimerization of MPL receptors that activate both Janus kinase 2 (JAK2) signal transduction and the signal transducers and activators of transcription (STAT) pathway, which in turn activate RAS, PI3K/AKT and mitogen-activated protein kinase (MAPK) pathways, which ultimately results in HSC self-renewal and survival [30]. Binding of TPO to MPL also upregulates HIF-1α expression and stability and may thus function in hypoxia [31]. The Notch signaling pathway also plays an important role in maintaining the HSC phenotype. Binding of osteoblastic factor Jagged-1 to its Notch-1 receptor on HSCs causes transcription of genes involved in inhibition of differentiation and an increase in self-renewal capacity of HSCs in endosteal niches. This is achieved by proteolytic cleavage of the intracellular part of Notch-1, its translocation to the nucleus and binding to cofactor recombining binding protein suppresser of hairless (RBPJ/CBF1) and co-activator Mastermind [32,33]. Osteoblasts also secrete transforming growth factor-β (TGF-β), bone morphogenic protein (BMP)-2 and BMP-7, which bind to type I and type II serine/threonine kinase receptors on HSCs. This results in SMAD translocation to the nucleus and transcription of target genes, which results in quiescence of HSCs and maintenance of the HSC phenotype [34–36]. TGF-β also activates the PI3K pathway [36] as well as the MAPK, ERK and JUN N-terminal kinase pathways via JUN and SMADs in the nucleus, resulting in transcription of target genes and subsequently HSC self-renewal and survival [37].

2.1.1.3. Osteoblasts and WNT signaling in HSCs. Osteoblasts affect both the canonical and non-canonical wingless-type (WNT) signaling pathways in HSCs that have opposite effects on HSC differentiation. The canonical WNT signaling pathway stabilizes β-catenin after binding to its receptors Frizzled (FZ) and lipoprotein receptor-related protein 5/6 (LRP5/6). Stabilized β-catenin translocates to the nucleus, where it interacts with transcription factors that promote HSC differentiation [38–41]. In the non-canonical pathways, Wnt-Ca^{2+} and Wnt-Jun N-terminal kinase pathways, β-catenin is not stabilized whereas Wnt-FZ interactions induce an increase in intracellular Ca^{2+} levels through inositol-3-phosphate or induce the Jun N-terminal kinase pathway through Rho/Rac GTPases. Non-canonical signals can then affect actin-dependent cytoskeletal reorganization and maintain the stemness of HSCs [38–42].

2.1.1.4. Effects of osteoblasts in hypoxia. Under hypoxic conditions, HSCs express the tyrosine kinase receptor TIE2 which bind to its ligand ANG-1, which are both produced by osteoblasts under the influence of HIF-1α [7,26,43]. Binding of ANG-1 to TIE2 on HSCs results in phosphorylation of TIE2 and activation of the PI3K/protein kinase B (AKT) pathway. The downstream effects are activation of p21 and nuclear factor kappa beta (NF-κB), resulting in downregulation of HSC proliferation and HSC survival, respectively [44–46]. Osteoblasts also secrete the growth factor SCF which binds to the tyrosine kinase receptor c-KIT on HSCs which downregulates HSC proliferation [21,47]. HIF-1α directly enhances the transcriptional activity of SCF [48]. SCF can also induce HIF-1α expression in HSCs which is mediated by PI3K and retrovirus-associated DNA sequences (RAS)/extracellular regulated kinases (ERK) pathways, but it is unclear whether or not SCF also plays a direct or indirect role in the stabilization of HIF-1α in hypoxic conditions [49]. The effects of hypoxia are described in more detail in Section 2.5.