Communication between bone marrow niches in normal bone marrow function and during hemopathies progression

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Abstract

Hematopoietic stem cell (HSC) chemotaxis, adhesion, proliferation, quiescence and differentiation are regulated by interactions with bone marrow (BM) niches. Two niches have been identified in the adult BM: the endosteal (close to the bone) and the perivascular niche (close to blood vessels). A vast body of literature has revealed the molecular basis for the interaction of HSCs with the two niches. However, the signals that regulate the communication between the two niches have not been well defined. Taking in consideration several clinical and experimental arguments this review highlights the molecular cues, involved in the communication between the BM niches, which regulate the basic properties of HSCs in physiological and malignant conditions. As such, it aims at clarifying the most important advances in basic and clinical research focusing on the role of different factors in the regulation of the BM microenvironment.

Introduction

Hematopoietic stem cells reside in bone marrow niches, which regulate their fate

Hematopoietic stem cells (HSCs) are self-renewing cells which give rise to all types of mature blood cells. HSCs can be subdivided into long-term HSCs (LT-HSCs) and in short-term (ST-HSCs). LT-HSCs can give rise to all blood lineages and have unlimited self-renewal capacity. LT-HSCs produce ST-HSCs which are still multipotent but with limited self-renewal capacity. ST-HSCs differentiate further into lineage-committed progenitor cells which are responsible for the large-scale production of mature blood cells.[1]

The bone marrow (BM) is the major site of adult hemopoiesis, but, in pathological conditions, hemopoiesis can also occur in extramedullary sites like thymus, spleen and liver.

HSCs are localized in specialized microenvironments within hematopoietic tissues called niches.[2-6] Within the BM, two anatomical and functional niches have been proposed, the endosteal niche[7-10] and the perivascular niche.[11] It has been suggested that about 60% of bone-marrow HSCs are adjacent to perivascular niches and up to 20% of HSCs localize in the endosteal niches; the remaining HSCs are believed to be scattered throughout the BM.[11,12]

Endosteal niches, located at the inner bone surface, contain quiescent HSCs, characterized by a low proliferative rate; whereas activated HSCs, which undergo differentiation and ultimately mobilization to the peripheral circulation, are in close contact to sinusoids of the BM microvasculature in the perivascular niche[10,13-18] Endosteal niches may thus represent a reserve of HSCs, while perivascular niches connect HSCs to the blood stream.

The endosteal niche mainly comprises endosteal cells, osteoblasts and osteoclasts, while the perivascular niche contains mainly endothelial cells. Stromal cells, including reticular and mesenchymal cells, are common components of both niches. They are scattered throughout the trabecular space of the BM and surround the endothelial cells. As these cells are a component of both endosteal and vascular niches, they may serve as a cellular link between them.[15] The cellular components of the niches interact with each other to support HSC adhesion, quiescence, chemotaxis and, in the case of the vascular niche, differentiation.[10,14,16,17,19-21] Thus, the HSC properties and functional responses depend on specific interaction with BM niches (Table 1).

Chemotaxis

Bone marrow niches recruit hematopoietic stem cells

HSC chemotaxis towards the endosteal niche has been suggested to be mediated by osteoponin (Opn) and calcium ion concentration ($[Ca^{2+}]_o$).[25] Opn, a glycoprotein expressed on endosteal bone surface by osteoblasts, promotes HSC migration, as shown *in vivo* studies with $Opn^{-/-}$ mice. In these mice, there is a long-term engraftment defect after transplantation with wild-type $Lineage^{-}Sca^{-1+}c\text{-}Kit^{+}$ cells and a compromised ability of the $Opn^{-/-}$ BM microenvironment to sustain hematopoiesis. These effects seem to be indirect, since there is no evidence, *in vitro*, of a chemotactic role for Opn on HSCs. Moreover, the high extracellular $[Ca^{2+}]_o$, maintained by the osteoclasts activity, promotes HSC localization to the endosteal niche, through calcium-sensing receptor (CaR): $CaR^{-/-}$ HSCs show a defect in the binding to collagenase I present at the bone endosteal surface.

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Key words: bone marrow niches, hematopoietic stem cell properties, molecular signals.

Acknowledgments: the authors would like to thank other members of the Angiogenesis Lab for their suggestions. Associação Portuguesa contra a Leucemia (APCL) and Liga Portuguesa Contra o Cancro (LPCC) fund our projects focusing on the bone marrow microenvironment. Sara Lamorte is funded by a fellowship from the University of Torino, Italy. Leonor Remédio is funded by an FCT (Portuguese Government) fellowship (SFRH/BD/43531/2008).

Received for publication: 26 May 2009.
Accepted for publication: 27 July 2009.

Hematology Reviews 2009; 1:e14
doi:10.4081/hr.2009.e14

Migration of HSCs from the endosteal to the perivascular niche is regulated by c-kit/Stem Cell Factor (SCF); CXC chemokine receptor 4 (CXCR4)/stromal-cell derived factor-1 (SDF-1) and granulocyte colony-stimulating factor (G-CSF), pathways.[7,22-24,42] Endothelial cells and reticular cells have been shown to produce SDF-1, generating a gradient from the perivascular to the endosteal niche, which may thus promote HSCs migration, since CXCR4 is expressed on HSC.[22-24] Mobilization of HSCs from the endosteal to the vascular niche is essential for hemopoietic recovery following myeloablation. In this case, the soluble form of membrane stem cell factor (sSCF), released from osteoblasts after cleavage by SDF-1-induced matrix metalloproteinase-9, promotes HSC homing to the perivascular niche by interacting with its receptor c-Kit.[7,22] G-CSF, produced by osteoblasts, promotes the mobilization of HSCs into the peripheral blood by up-regulating CXCR4 expression on HSCs and decreasing SDF-1 expression in the BM. G-CSF, in fact, induces the expression of proteolytic enzymes such as elastase, cathepsin G, MMP-2, and MMP-9, which cleave SDF-1.[42,43]

Adhesion

Bone marrow niche promotes hematopoietic stem cells adhesion

HSC adhesion to the endosteal niche is regulated by different molecular interactions including N-cadherin/β-catenin; Tie-2/Angio-

poietin-1 (Ang-1); Osteopontin (Opn)/ß1 integrin; Annexin II (Anxa2)/Anxa2 receptor (Anxa2r) and CaR-collagen I pathways.[10,25,28,33] The asymmetrical distribuition of N-cadherin/β-catenin on the cell surface of HSCs and osteoblasts, respectively, and, in particular, the localization of these molecules at the site of interaction of LT-HSC with spindle-shaped N-cadherin^{+}CD45^{-} osteoblastic (SNO) cells, suggested a role for N-cadherin/ß-catenin in HSCs adhesion on the endosteal niches.[10] Studies performed by Kiel and collaborators failed to show significant numbers of N-cadherin expressing HSCs, questioning whether HSC adhesion to osteoblasts is mediated by N-cadherin.[44]

Tie2, a receptor tyrosine kinase expressed by a small fraction of BM cells highly enriched for HSC activity in adult murine BM, binds its ligand, Ang-1, expressed by osteoblasts at the surface of trabecular bone.[33] Regarding Opn, its expression is restricted to the endosteal bone surface and contributes to HSCs adhesion to the endosteal region via ß1 integrin expressed by HSC.[25] Osteoblasts also express high levels of Anxa2, a calcium-dependent phospholipid-binding protein, and it has been shown, both *in vitro* and *in vivo*, that Anxa2 regulates HSCs homing and binding to the endosteal niche, through the binding to its ligand Anxa2r.[28]

Adhesion of HSCs to the perivascular niche is mediated by $\alpha^4\beta^1$ integrin/vascular cell adhesion molecule1 (VCAM1) and α^4/E-selectin interaction.[26,27,45] $\alpha^4\beta^1$ integrins, expressed by HSCs, interact with VCAM-1, constitutively expressed on BM endothelial cells.[26] Since inactivation of E-selectin and α^4 integrin reduces drastically hematopoietic progenitor and stem cell (HPSC) homing into lethally irradiated mice, it has been proposed that E-selectin ligands and α^4 integrin cooperate in HSC adhesion to perivascular niches.[27]

Proliferation versus quiescence

Endosteal niches promote HSC quiescence

The balance between HSC proliferation and quiescence is likewise regulated by several pathways. In the endosteal niche several interactions, involved in the maintenance of HSC quiescence, have been identified: Tie-2/Angiopoietin-1 (Ang-1); thrombopoietin (THPO)/MPL; Opn/OpnR; parathyroid hormone (PTH)/PTH receptor (PTHr) and Notch1/Jagged1.[14,25,29,33-35,37,46] Tie2, which is expressed by SP-HSCs, binds Ang-1^{+} expressed on osteoblasts and induces HSC quiescence.[33,34] LT-HSCs expressing MPL, the THPO receptor, are closely associated with THPO-producing osteoblasts. The THPO/MPL pathway is involved in HSC quiescence through activation of genes coding for negative regulators of cell cycle, such as *p12*^{Cip1} and *p57*^{Kip2}, and inhibition of positive regulators, such as *c-myc*.[46] This pathway is also involved in promoting HSCs proliferation in the perivascular niche.[30-32] Thus, THPO/MPL pathway exerts distinct functions on HSC, depending on cell localization. Opn/OpnR, instead, contributes to the maintenance of HSC quiescence either by inhibiting, in a dose-dependent manner, the entry into cell cycle and/or by reducing cell apoptosis.[25,29] A mouse genetic model, in which the gene *PTHr* is constitutively active in osteoblasts, showed an increase in HSCs along with osteoblasts. Moreover, there was high expression of Notch I ligand, Jagged, on osteoblasts, suggesting that the PTH/PTHr pathway can promote HSC proliferation through activation of Notch.[14,37] Several gain- and loss-of-function experiments of Notch target genes and ligands have suggested a role for Notch in HSC quiescence and self-renewal.[35] However, recently Maillard *et al.* have demonstrated rather conclusively that inactivation of the Notch pathway in HSCs does not interfere with their self-renewal; transplantation of hematopoietic progenitors with inhibited Notch signaling induced stable long-term reconstitution of irradiated hosts and a normal frequency of progenitor fractions enriched for LT-HSCs.[36]

Table 1. HSC properties are regulated by molecular cues conveyed by the bone marrow endosteal and vascular niches.

HSC properties	Molecular interactions HSC-NICHE		
	Endosteal niche		Perivascular niche
Chemotaxis	Opn[25] CaR/Ca^{2} c-Kit/SCF[22]	CXCR4/SDF-1[22-24]	G-CSF[22]
Adhesion	N-cadherin/ß-catenin[10] Tie2/Ang1[10] ß^{1} integrin/Opn[25] Anxa2/Anxa2r [28] CaR/Collagen I[25]		α^4ß^{1} integrin/VCAM1[26] α4 integrins/E-selectin[27]
Quiescence / proliferation	Tie2/Ang1[33,34] Notch1/Jagged1[35,36] Opn[25,29] PTH/PTHr[14,37]	MPL/THPO [29-32]	wnt/β catenin[47,48]
Differentiation		FGF-4[13] SDF-1/CXCR4[38] α^4ß^{1} integrin/VCAM[13] VE-Cadherin[13] Notch1/Delta[39-41]	

Perivascular niches promote hematopoietic stem cells proliferation and self-renewal

In the vascular niche, HSC proliferation is associated with (THPO)/c-mpl and Wnt/β catenin pathway. THPO is expressed on BM stromal cells and acts synergistically with erythropoietin to promote erythroid progenitors and megakaryocytes proliferation. THPO stimulates *c-myc* mRNA expression through a PI3K- and MAPK-dependent pathway, thereby promoting HSC proliferation.[30-32] Wnt proteins are expressed by BM stromal cell and exposure to Wnt was shown to stimulate proliferation and self-renewal of HSCs *in vitro*.[47,48]

Differentiation

Perivascular niches mediate hematopoietic stem cell differentiation

Differentiation of HSCs occurs only in the perivascular niches and is mediated by FGF-4; SDF-1; VCAM-1/α^4ß ; VE-cadherin and Notch1 pathway.[13,38,39,49] SDF-1 is necessary for myelopoiesis and B-lymphopoiesis, as shown by the severe reduction of B-lymphopoiesis and lack of BM myelopoiesis in CXCR4- and SDF-1 deficient mice.[49] SDF-1 and FGF-4 promote megakaryocyte maturation and platelet production: FGF-4 supports the adhesion of megakaryocytes to sinusoidal BM endothelial cells (BMECs), thereby enhancing their survival and maturation, while SDF-1 augments platelet production by promoting their migration across BMECs.[13,38] VCAM-1 enhances the interaction of α^4ß^{1} integrin $^{+}$ megakaryocytes with BMECs. VE-cadherin is essential for VCAM-1 expression in BMECs, which in turn is required for FGF-4 mediated adhesion and SDF-1-induced transendothelial migration of megakaryocytes. Neutralizing antibodies to VE-cadherin decrease the localization of megakaryocytes to the vascular niche and disrupt megakaryocyte maturation and thrombopoiesis.[13] Notch1 seems to provide a key reg-

ulatory signal in determining T- versus B-lymphoid lineage commitment. Mice transplanted with BM, transfected for retroviruses encoding a constitutively active form of Notch1, three weeks after transplantation showed immature $CD4^+CD8^+$ T cells in the BM and a block in early B-cell lymphopoiesis.[39] Notch1 activation seems to be driven by Delta-1-expressing stromal cells.[40,41]

Hemopathies require the support of aberrant bone marrow niches

Several hemopathies are characterized by a pre-malignant phase that progresses to a malignant phase. The molecular basis of this progression remains poorly understood. The data in the literature suggest the likelihood of such progression is very low and a malignant clone can remain "stable" for years. Moreover, in several diseases both phases are characterized by virtually the same genetic changes.[50,51] Taking in consideration these aspects, it is legitimate to speculate that the genetic changes are necessary for the immortalization of a malignant clone but insufficient to promote the progression to a malignant phase. So other factors must take part in the progression.

The role of the hematopoietic BM microenvironment in malignant progression has been studied extensively and its importance was well illustrated in recent, *in vivo*, studies. Widespread inactivation of retinoblastoma protein (Rb) resulted in myeloproliferative disease, characterized by extramedullary hemopoiesis and increased mobilization and differentiation of HSCs from the BM. The phenotype was not recapitulated upon inactivation of Rb in HSCs maintained in wild-type environment.[52,53] Moreover, *Mx-Cre*$^+$*Pten*$^{\Delta/\Delta}$ mice develop rapid and aggressive myeloproliferation that progressed to leukemia in 4-5 weeks post deletion. When *Pten* deletion was active in the context of a wild-type BM microenvironment, phenotypic and functional HSCs were lost without evidence of myeloproliferation or transformation.[54,55] Finally, BM from wild-type mice transplanted into mice with a deficient retinoic acid receptor γ (RARγ) microenvironment rapidly develop myeloproliferative syndromes (MPS).[56] These results strongly support the notion that the progression of the hemopathies is not entirely cell autonomous but depends on interactions between malignant cells and the BM microenvironment (BMM). As described above, BM niches support HSC properties such as adhesion, quiescence, chemotaxis and differentiation, and regulate the balance between self-renewal and differentiation. The idea outlined in this review is that alteration of the two BM niches, triggered by the aberrant expression of key molecules or cellular cues between the endosteal and the perivascular niche, impairs HSC responses, contributing to the progression of hemopathies. In chronic myeloid leukemia (CML), myelodysplastic syndromes (MDS) and multiple myeloma (MM) circulating endothelial cells (CECs), mobilized from the BM, share chromosomal aberrations with the malignant hematopoietic cells.[57-59] These malignant CECs suggest the presence of aberrant niches in the BMM. Moreover, in B-cell lymphomas, identical genetic aberration could be found both in malignant cells and in the microvascular BM endothelial cells.[60,61]

Irradiation and chemotherapy can change the BMM inducing hematopoietic and endothelial injury and allowing cells, proteins and cytokines to move between the vascular and endosteal niches.[62] Radiation-induced injury can also contribute to cell damage in the microenvironment in an indirect way, as a consequence of an inflammatory-type response.[63] Moreover, it has been shown that ionizing irradiation results in altered osteoblast differentiation ability of BM mesenchymal stem cells, destruction of the endosteal niche and consequently hematopoietic injury.[64] Another possibility is that malignant cells through direct and indirect signaling can modify the features of the vascular niche. For example, factors produced by acute lymphoblastic leukemia (ALL) cells can induce proliferation, migration and morphogenesis of human BM vascular endothelial cells.[65-67] The tumor-derived factor VEGF and tumor necrosis factor-α (TNF-α) produced in the tumor microenvironment have been shown to modify the phenotype of endothelial cells inhibiting ICAM-1 and VCAM-1 clustering on endothelial surfaces with implications for immune-cell trafficking.[68] Moreover, our own data suggests TNF-α is crucial for the onset and also for the progression of BM dysfunction, such as in MDS (*Cachaco et al., 2009, unpublished data*).

The possible mechanisms by which aberrant BM niches modify HSCs properties are discussed.

Migration/chemotaxis

Aberrant niches may promote recruitment of malignant hematopoietic stem cells

The perivascular niche expresses unique combinations of cell adhesion molecules and/or chemokines capable of attracting malignant HSCs. For example, it has been shown, *in vitro* and *in vivo*, that E-selectin and SDF-1 are expressed in vascular "hot spots" corresponding to the regions that attract leukemic cells.[69-71] Distruption of the interaction between SDF-1 and its receptor CXCR4 inhibits the homing of Nalm-6 cells, an acute lymphoblastic leukemia cell line, to the vascular niche.[71] These observations raise the possibility that E-selectin and /or SDF-1 can regulate malignant cell homing. Moreover, BM endothelial and stromal cells seem involved in the migration of ALL cells beneath BM fibroblast layers: both cell types produce SDF-1, thereby enhancing the adhesion molecules involved in the migration and homing of these cells to the BM.[72,73]

Adhesion

Aberrant niches mediate cell-adhesion-mediated drug resistance (CAM-DR)

It has been demonstrated, *in vitro* and *in vivo*, that cell-cell adhesion between hematopoietic cells and components of the BM niches, such as stromal cells, is involved in drug resistance in AML.[74,75] AML resistance to chemotherapy seems to be promoted by the adhesion-dependent secretion of WNT antagonists by osteoblasts.[76] CAM-DR is mediated by integrins α^4 and $\beta1$, as shown in MM, CML and AML cell lines.[77-79] Direct correlation has been found between the expression of integrins that mediate adhesion to FN and drug resistance.

Coculture of ALL cells lines with BM stroma cells (BMSCs) resulted in reduced apoptosis induced by etoposide. In this stroma model, drug resistance required direct cell-cell contact, since it could not be conferred by the addition of stromal conditioned media.[80] Moreover, the presence of BMSCs during treatment of myeloma cell lines significantly decreases the apoptosis during exposition of mitoxantrone, an inhibitor of topoisomerase II.[81] Notch-1 signaling seems to be involved in protection of MM from drug-induced apoptosis: overexpression of Notch-1 in Notch-1(-) myeloma cells up-regulated p21 and resulted in protection from drug-induced apoptosis.[82] BM niches may provide a survival advantage for malignant cells following initial drug exposure and facilitate the acquisition of acquired drug resistance, determining disease relapse following chemotherapy.

Aberrant niches show impaired adhesive capacity, leading to a loss of quiescence and consequently to expansion of malignant hematopoietic stem cells

It has been hypothesized that HSC mobilization results from impaired adhesion to BM niches, allowing their migration into the peripheral blood, spleen and other extramedullary sites. This could explain the increase in circulating $CD34^+$ cells reported in primary myelofibrosis (PMF) patients.[83,84]

The impaired adhesion could be explained by several mechanisms.

Altered expression of membrane adhesion molecules and integrins. For example, HSCs of CML patients have reduced adhesion molecules expression including L-selectin, CD44 and N-cadherin. This decrease correlates with, *in vitro*, reduced adhesive capacity of HSCs from CML patients.[85]

A disruption of CXCR4/SDF-1 axis. In idiopathic myelofibrosis (IM) the constitutive mobilization of $CD34^+$ cells could be the conse-

quence of the creation of a proteolytic microenvironment within the BMM. It has been shown that malignant cells and the BMM produce metalloproteinase.[86-88] Thus, the increased production of metalloproteinase-9 might disrupt adhesive interaction between CD34$^+$ HSCs and BM niches through degradation of SDF-1 or cleavage of its receptor CXCR4, leading to the release of the HSCs into the peripheral blood.[22,89]

Proliferation *vs.* quiescence

Aberrant niches determine an imbalance between proliferation and quiescence, accelerating the onset and progression of malignancy

BM cells display a different set of adhesion molecules, extracellular matrix elements, growth factors and chemokines. Spleen fibroblasts isolated from PMF patients, in contrast to primary fibroblasts purified from the spleen of healthy subjects, are able to support the proliferation of autologous patient CD34$^+$ cells, but not that of their normal counterparts.[90] Moreover, it has been shown that somatic mutations that occur in BM stromal cells, such as p53 mutations, render these cells supportive of ALL growth.[81] Finally, aberrant vascular niches produce several factors, such as VEGF; IL-6; granulocyte-macrophage and granulocyte colony-stimulating factors, that are able to support malignant hemopoiesis.[91-93] For example, it has been shown that coculture of AML cells with microvascular endothelial cells increases proliferation and inhibits apoptosis of AML cells.[93]

Providing self-renewing and proliferative cues to malignant HSCs. ALL stromal cells regulate self-renewal and proliferation of a Philadelphia-chromosome positive (Ph$^+$)/VE-cadherin$^+$ subpopulation of leukemia cells by promoting the expression of VE-cadherin, stabilizing β catenin and up-regulating BCR-abl transcripts.[94] This way, due to the stromal support, malignant cells circumvent the requirement of exogenous Wnt signaling for self-renewal. Human MM cells also become independent of the IL-6/gp130/STAT3 survival pathway when cocultured in the presence of BMSCs.[95] This evidence confirms the idea that BMSCs can provide alternative survival and proliferative signals to BM malignant cells.

Angiogenesis, the branching of new microvessels from pre-existent blood vessels, is kept at set point in which there is a balance between pro- and anti-angiogenic molecules. The angiogenic switch, unbalanced set point in favor of pro-angiogenic molecules, favors the production of new microvessels.[96] Increased angiogenesis has been described in a number of hemopathies.[97-101] The extent of BM neo-vessel formation correlates also with patient prognosis and these hemopathies are sensitive to anti-VEGF and VEGF receptor treatments.[102-105] The expanded BM endothelium may support malignant HSC growth by protecting them from chemotherapy-induced apoptosis and/or promoting their proliferation in a paracrine way through the release of factors such as G-CSF, IL-10, IL-6 and vascular endothelial growth factor-C (VEGF-C).[106,107]

Aberrant vascular niches can induce quiescence in malignant cells playing a role in tumor maintenance

Adhesion of malignant HSCs to BMSCs may induce quiescence by inhibiting cell proliferation. For example, Notch-1 activation in MM cells, after incubation on BMSCs, results in the accumulation of the cells in G0/G1 phase of cell cycle.[82,108] Aberrant niches may thus contribute to the maintenance of a malignant pool of HSCs.

Differentiation

Aberrant niches can induce malignant transformation of normal hematopoietic stem cells

The donor cell leukemia (DCL), a hemopathy following hemopoietic cell transplation, is apparently the result of malignant transformation of normal donor hematopoietic cells in the transplant recipient.[109] One of the hypotheses is that the host microenvironment in which the original malignancy developed may trigger malignant transformations in donor cells, favored by the immunocompromised status after transplantation and by perturbation of the host BMM following multiple rounds of chemotherapy.

Studies in *Drosophila Melanogaster,* by Kai *et al.,* suggest that a vacant niche can engage ectopic cells, normal hematopoietic and non-hematopoietic cells, with a resultant change in phenotype. Depending on the specific system, it seems that non-stem cells can acquire either a more proliferative phenotype or revert to a stem cell-like condition. These findings strongly support the possibility that BM niches can contribute to hemopathies, inducing aberrant transformation of normal cells, including HSCs.[110,111]

Bone marrow niches as therapeutic target

Based on the idea that the BMM has a relevant role in the progression of hemopathies, novel therapeutic approaches are being developed to revert the malignant phenotype by targeting environmental cues. The strategies used until now can be summarized into three categories.

The first strategy is to modify the niche itself. For example, Ballen and colleagues have tested the hypothesis to use parathyroid hormone (PTH) to augment the engraftment efficiency of cord blood transplant, modifying the receptivity of the endosteal niche.[112] PTH, acting also on the perivascular niche, can be used for the treatment of ischemic vascular disease.[113] Moreover, it has recently been shown that pharmacological use of PTH increases the number of HSCs mobilized into the peripheral blood for stem cell harvests, protects stem cells from repeated exposure to cytotoxic chemotherapy and expands stem cells in transplant recipients.[114]

The second strategy is to abrogate the interaction between malignant HSCs and BM niches, by blocking their physical binding or the growth factors secreted by the BMM. As described before, the chemokine axis SDF-1/CXCR4 is involved in the retention of HSCs within the BM. Thus, destruction of this interaction allows the mobilization of HSCs from the BM to the peripheral blood. This approach has been established clinically using G-CSF or antibody against CXCR4.[115-117] The combination of both result in an enhancement of HSC mobilization from the BM.[118] The proteasome inhibitor PS-341, currently used in MM therapy, blocks the growth of MM cells by decreasing their adherence to BMSCs and the related protection against drug-induced apoptosis.[119] Another strategy is the inhibition of TNF-α production by BM cells, with a monoclonal antibody against the extracellular domain of TNF-α, called infliximab. Two studies have investigated the use of infliximab in patients with low-risk MDS. In both reports, the drug showed a limited but significant activity and no particular side-effects.[120]

Another recently approved therapeutic approach involves inhibiting angiogenesis; several inhibitors of VEGF are currently used in the treatment of different hemopathies.[104, 121]

The concept behind most of these therapeutic approaches implies that to increase therapeutic efficacy it is necessary to use a strategy in which the seed (malignant HSCs) and the soil (altered BMM) must be targeted simultaneously.

Conclusions

This paper highlights the key data demonstrating that changes in the signals delivered by BM endosteal and/or perivascular niches may lead to an impairment of survival, differentiation and proliferation of HSCs. Thus, aberrant BM niches participating in HSC regulation contribute in a crucial way to the progression of hemopathies. Therefore, the molecular cues that contribute towards BM niches alteration during the onset and development of hemopathies represent a new challenging therapeutic target.

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