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Selected factors influencing angiogenesis and hematopoietic niche

Abstract

Angiogenesis is the vital, multistage process in which new blood vessels are created by sprouting from pre-existing vessels. It takes part in carcinogenesis and contributes to progression, metastases, and dissemination of neoplastic disease. In the bone marrow, angiogenesis influences the hematopoietic stem cells (HSC) proliferation, differentiation, and maintenance of normal hematopoiesis under both physiological and stress conditions. The bone marrow niche contains different types of cells, including macrophages, osteoblasts, mesenchymal stem cells, endothelial progenitors, and endothelial cells. All of these interact and form a unique microenvironment necessary for the appropriate function, and preservation of HSC in the quiescent state, and take a major part in the process of mobilization to peripheral blood and homing after transplantation. Cytokines active in the hematopoietic niche as well as miRNAs regulating hemato- poiesis, and angiogenesis have a significant influence on processes occurring in the bone marrow. The aim of this review was to present selected proteins, and molecules associated with angiogenesis as well as bone marrow niche processes: VEGF, ANGPT1, ANGPT2, MMP-9, SDF-1, miRNA-15a, miRNA-16, miRNA-126, miRNA-146a, and miRNA-223.

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Hematopoiesis is a complex process, which takes place in the bone marrow microenvironment in a so-called hematopoietic niche. Within the hematopoietic niche, osteoblastic, and vascular parts are distinguished. The osteoblastic part of the HSC niche is responsible for maintenance of dormant, resting HSC, while active, dividing HSCs are located mainly near endothelial cells (EC) in the vascular part of the niche [1]. The close relation of the hematopoietic cells with stromal cells is mediated by interactions of adhesive molecules with respective ligands. Hematopoiesis is influenced by processes of angiogenesis, which makes interactions much more complicated. Angiogenesis is a complex, multifactorial process leading to the formation of new vessels [2]. As a multi-step phenomenon, it comprises EC proliferation, differentiation, and organization of cells to form tubules. Microvessel formation, and spreading are crucial in the repair of tissues damaged by ischemia or injury. It is well known that angiogenesis is involved in biology, and progression of neoplastic disorders [1-6]. Levels of anti- and proangiogenic cytokines and miRNAs correspond with the activity of new vessels development. In neoplastic disorders, angiogenesis takes part in the dissemination of cancer cells and progression of the disease. The other spectrum of interest is the evaluation of proangiogenic factors in the context of their influence on the regeneration of hematopoiesis after damage caused by high dose chemotherapy and stem cells transplantation [7]. Bone marrow niche is a unique microenvironment containing growth factors, accessory cells, extracellular matrix proteins and cell-surface ligands which play important role in hematopoietic niche balance [1-3]. Hematopoietic niche plays a crucial role in engraftment after hematopoietic stem cell transplantation (HSCT). Homing is associated with the new vessel formation, primarily through the interactions of HSC cells and endothelial cell-specific factors [1-3]. Cytokines which are significant for angiogenesis control bone marrow niche and HSC trafficking via cross-talk between hematopoietic niche parts, and controlling signaling pathways [1-5].

In this review, we focused on the description of key elements of the hematopoietic niche that affect HSC traffic and angiogenesis. Most of the characterized elements were the subject of our research in patients treated with autologous HSCT.

CYTOKINES
VEGF

Vascular endothelial growth factor (VEGF) is a member of the cytokines group, which consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PGF). VEGF-A and VEGF-C play a crucial role in angiogenesis and vasculogenesis, while VEGF-B promotes EC survival [8, 9]. VEGF-D is mitogenic for EC and may contribute to the tumor development by promoting vascular and lymphatic angiogenesis [10]. PGF stimulates angiogenesis in physiological condition and during cancer development [11].

VEGF-A (hereafter referred to as VEGF) binds to vascular endothelial growth factor receptor 1 and 2 (VEGFR-1, VEGFR-2) and is a key regulator of EC proliferation, migration, and adherence [8]. Other important receptors for VEGF are neuropilin 1 and 2 receptors (NRP1 and NRP2). This cytokine stimulates angiogenesis via binding with NRP1 and enhances VEGF/VEGFR2 activation [12]. In epidermal cancer cells, VEGF/NRP1 promote invasive tumor vascularization [12].

VEGF is secreted in an autocrine and paracrine way by healthy cells (osteoblasts, stromal cells) and tumor cells as well [8, 10].

VEGF is an important factor in the development of solid tumors, and hematological malignancies, in particular non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) [13-15].

This important regulator of angiogenesis during cancer development acts in concert with other molecules: angiopoietins, hypoxia-inducible factor 1 and 2 (HIF-1, HIF-2), hepatocyte growth factor (HGF), interleukin 6 and 8 (IL-6, IL-8), [8, 16-18]. VEGF stimulates the

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formation of new blood vessels and increases vascular permeability [8]. This cytokine promotes EC survival by lowering their susceptibility to apoptosis [19]. VEGF activates phosphatidylinositol-3-kinase/ protein kinase B (PI3K/Akt) pathway and reduces the pro-apoptotic potency of chemotherapy [8, 19].

It has been shown that VEGF significantly influences the immune system, and inhibits differentiation, and maturation of dendritic cells (DC). It results in decreased expression of major histocompatibility complex (MHC) II antigens, which in turn impairs the function of T-lymphocytes [20]. This process is associated with decreased activity of NK-κB signaling pathway [8].

VEGF significantly regulates proliferation and migration of EC. By recruiting HSC and endothelial progenitor cells VEGF regulates microvessels development in the bone marrow niche and fundamentally affects hematopoiesis [15, 21].

ANGPT1 and ANGPT2

Apart from VEGF, angiopoietin 1 (ANGPT1) and angiopoietin 2 (ANGPT2), both binding to receptor tyrosine kinase Tie-2, are important players in angiogenesis regulation [22, 23].

ANGPT1, an agonist of the TIE-2 receptor is expressed in bone marrow niche by perivascular cells, osteoblasts, HSC and megakaryocytes [24-29]. During angiogenesis, ANGPT1 significantly promotes the conversion of the endothelial cell layer to multicellular vascular structures, by enhancing interaction between EC and pericytes [22, 25, 30]. ANGPT1 is associated with migration, adhesion, and survival of EC. Furthermore, it is also a very important factor for vascular maturation [25]. Expression of ANGPT1 in rat glioma model, which occurs continuously at low levels, promotes malignancy by disturbing ANGPT1/ANGPT2 balance and strengthening of the tumor vascularization [24, 25].

Through binding to the Tie-2 receptor, ANGPT1 affects the signaling pathways of the PI3K/AKT and mitogen-activated protein kinase/ extracellular signal-regulated kinase (MAPK/ERK), which significantly control the growth, proliferation, and survival related processes of EC. The inhibitory effect of ANGPT1 on NF-κB pathway results in the inhibition of proinflammatory processes, enhances survival and migration of EC, and may promote the tumor development [31-33]. In radiated mice, ANGPT1 release is involved in the recovery of suppressed bone marrow [25]. Moreover, ANGPT1 interacts with Notch signaling pathway, which is responsible for the development, differentiation, and survival of HSC [25]. Different conclusions were drawn from the study by Zhou et al. [26] who evaluated ANGPT1 expression in HSC, Leptin Receptor+ (LepR+) stromal cells and their influence on hematopoiesis recovery. It was noticed that ANGPT1 expression by these cells delays hematopoietic recovery after irradiation. ANGPT1 deletion from EC didn't affect hematopoiesis.

ANGPT2 in contrast to ANGPT1 is responsible for the induction of EC apoptosis, which leads to the regression of blood vessel [34, 35]. The mechanism of ANGPT2 activity and its role in angiogenesis is closely associated with VEGF expression. Elevated VEGF expression together with ANGPT2 promotes angiogenesis. This action is independent of Tie-2 receptor and is a non-canonical mode of action dependent on ANGPT2 binding to integrins on Tie-2-low EC. This process may occur for example under hypoxic conditions

and HIF-1 influence [5, 36]. Depending on the presence of VEGF, ANGPT2 can be both agonist and antagonist of the Tie-2 receptor. ANPT2/Tie2 axis in tumor cells induces angiogenesis. By acting on pericytes, ANGPT2/Tie-2 destabilizes blood vessels which results in EC stimulation and secretion of angiogenic cytokines, including VEGF [22, 23, 37].

ANGPT2 via receptor Tie-2 affects not only EC but also monocytes and Tie-2 expressing macrophages (TEMs). TEMs are the subset of tumor-associated macrophages (TAMs), which promote tumor angiogenesis and thus their development [22, 38].

Levels of proangiogenic cytokines were assessed during HSC mobilization in healthy donors by several authors. The kinetics of VEGF, angiopoietins level and Tie-2 receptor expression in healthy donors mobilized with granulocyte growth stimulation factor (G-CSF) were reported by Serefhanoglu et al. [39], who assessed the levels of these cytokines in the peripheral blood prior to G-CSF administration (baseline) and then 5 days after mobilization (the day of apheresis). The authors observed a decrease of Tie-2 receptor expression at the time of apheresis and stable angiopoietins level as compared to premobilization results. VEGF concentration increased during the apheresis procedure.

Another study evaluating different cytokines, including angiopoietins and Tie-2 receptor in healthy donors mobilized with G-CSF, was performed by Yang et al. [40]. The authors observed that G-CSF stimulation resulted in an increase in VEGF concentrations and a decrease in Tie-2 receptor expression, as well as angiopoietins in the bone marrow. Lysak et al. [41] evaluated several cytokines including VEGF during mobilization in healthy donors. No change in VEGF concentration was noted in their study.

Levels of VEGF, ANGPT1, and ANGPT2 change significantly during mobilization, including chemotherapy and G-CSF administration [7, 42]. In patients with lymphoproliferative disorders during CD34+ mobilization with chemotherapy and G-CSF stimulation, higher baseline VEGF levels correlated with a shorter time of G-CSF administration [7].

ANGPT1 level in the peripheral blood decreased at the time of apheresis as compared to baseline level assessed prior to chemotherapy, while ANGPT2 level increased during the mobilization procedure. Moreover, baseline ANGPT2 level was the factor predicting failure of mobilization. Additionally, the higher baseline level of ANGPT1 correlated with a shorter time of G-CSF administration. These results indicate the supportive function of bone marrow microvasculature in the mobilization of CD34+ cells to peripheral blood [42].

MMP-9

Matrix metalloproteinase 9 (MMP-9) also known as a gelatinase B or 92 kDa type IV collagenase, is a member of the zinc-containing proteolytic enzyme family [43, 44]. It is secreted by leucocytes (mainly neutrophils), HSC and tumor cells. MMP-9 is involved in the mobilization and homing of HSC, angiogenesis, tumor growth and metastasis [45, 46]. This pro-angiogenic enzyme secreted by the stromal cells, EC or HSC is also relevant to the process of hematopoiesis after myeloablative chemotherapy and HSCT [47]. MMP-9 is responsible for cleavage and release of soluble Kit-ligand

(sKitL) form bone marrow stromal cells, which promotes the transfer of EC and HSC from quiescence state to proliferation [47]. A smooth transition of hematopoietic stem cells through the blood vessel wall is necessary for their effective mobilization from the bone marrow niche and engraftment after transplantation. MMP-9 allows this transmigration through the partial degradation of the sub-endothelial basement membrane, composed primarily of type IV collagen, which results in effective diapedesis [43]. IL-10 activates tissue inhibitor of metalloproteinases 1 (TIMP-1), which downregulates expression of MMP-9 and promotes HSC adhesion to the bone marrow osteoblastic niche and hematological reconstitution [48]. In HSC mobilization, G-CSF stimulates the release of proteolytic enzymes from neutrophils, including metalloproteinases and leads to profound changes in the HSC microenvironment [49]. G-CSF exerts its activity not only by binding with its receptor on neutrophils and HSCs but also via an indirect mechanism since the presence of a G-CSF receptor is not solely required for mobilization [49]. During G-CSF-mediated mobilization neutrophil degranulation occurs leading to upregulation of the matrix metalloproteases [50].

The proteolytic environment created by MMP-9, involving G-CSF administration after transplantation or during mobilization, adjusts the level of vascular cell adhesion molecule 1 (VCAM-1) which significantly influences the effectiveness of the release of HSC from bone marrow as well as their homing after HSCT [46, 50, 51].

By signaling cross-talk with VEGF, MMP-9 regulates EC migration, endothelium permeability, formation of new blood vessels and metastasis of cancer cells [45].

SDF-1

Stromal cell-derived factor 1 (SDF-1, CXCL12) is a key protein in the migration and proliferation of cells that have a CXCR4 receptor on their surface, e.g. HSC, EC, and cancer cells [52]. Upregulated expression of CXCR4 is a predictor of poor prognosis in many malignancies. In the course of AML and B-cell ALL, overexpression of CXCR4 on CD34 positive cells is observed [53, 54]. The interaction between CXCR4 and SDF-1 ligand causes homing of the leukemic cells in a protective microenvironment of bone marrow niche, resulting in resistance to chemotherapy [53, 54].

The SDF-1/CXCR4 signaling pathway plays an important role in the mobilization of hematopoietic stem cells from the bone marrow niche to the peripheral blood [55]. When used in the mobilization of HSC, G-CSF interferes with the SDF-1/CXCR4 signaling pathway, reducing the adhesion of HSC to the hematopoietic niche [55-57]. Chemotherapy and proinflammatory cytokines cause a short-term increase in the concentration of SDF-1 in the bone marrow. Expression of this chemokine facilitates HSC homing after transplantation. SDF-1 promotes cell survival during stress and stimulates osteoclasts to produce MMP-9 [58].

The bone marrow microenvironment, containing endothelial cells, contributes to proper hematopoietic stem cell function, including regeneration after injury caused by chemotherapy. Myelosuppression resulting from cytostatic agents is accompanied by destruction of bone marrow vasculature; microvessels are then reconstructed with the recovery of hematopoiesis. Moreover, the angiogenic factors including ANGPT1, ANGPT2, and VEGF play supportive roles in

the process of mobilization of CD34+ cells to the peripheral blood. All of those observations indicate an important function of the microvasculature in the migration of hematopoietic progenitors. The expression of cytokines active in angiogenesis as well as those responsible for maintenance of the homeostasis in hematopoietic niche is modulated by miRNAs.

MicroRNAs

MicroRNAs (miRNAs) are class of small ~ 22 nucleotides (19-25), endogenous non-coding RNAs, which play an important role in post-transcriptional regulation of gene expression [59-61]. By targeting the 3' untranslated regions (UTRs) of messenger RNA (mRNA), miRNAs repress translation, which leads to mRNA degradation and therefore downregulation of gene expression [62-64].

These molecules participate in the regulation of vital processes such as cell proliferation, differentiation, and apoptosis [65-69]. Targeting the bone marrow niche gene pathways and cytokines certain miRNAs can modulate angiogenesis, mobilization of HSC and homing after transplantation [70-72]. The role of selected miRNAs in hematopoiesis is presented in table I.

miRNA-15a/-16

Variable expression of miRNA-15a/-16 influence the pathogenesis of most human cancers, like prostate, colon cancer, and hematological malignancies: multiple myeloma, B-cell lymphoma, leukemia and polycythemia vera [72-74, 76]. Development and progression of malignancies are closely associated with angiogenesis. It has been shown that VEGF activity is negatively regulated by expression of miRNA-15a/-16. In myeloma cells, miRNA-15a/-16 expression inversely correlates with VEGF. Downregulation of the miRNA-15a/-16 cluster increases the proangiogenic activity of myeloma cells [77]. MiRNA-16 is involved in normal erythropoiesis, while deregulation of this miRNA contributes to abnormal erythroid lineage in polycythemia vera [72]. Apart from the influence on the development of cancer, miRNA-15a/-16 is associated with chemoresistance. It has been shown that low level of these miRNAs reduces apoptosis, increases proliferation of tumor cells and angiogenesis [78]. Downregulation of the miRNA-15a/-16 level inversely correlates with the expression of oncogenes BCL-2 and BCL-XL in myeloma cells and neoplastic B cells [76, 79]. Deregulation of miRNA-15a/-16 expression may affect the efficacy of chemotherapy. The resistance to apoptosis, induced by a low level of miRNA-15a/-16 reduces the activity of cytarabine [80]. Interleukin 6 (IL-6) secreted by bone marrow stromal cells suppress miRNA15a/-16 in U-266 and NCI-H929 myeloma cell lines. Addition of bortezomib and melphalan significantly increases miRNA-15a/-16 expression. Hematopoietic niche protective microenvironment enhanced survival of myeloma cells preventing the drug induced apoptosis by suppression of miRNA-15a/-16 [78, 79].

miRNA-126

Cytokines and adhesion molecules regulate the migration of HSC between the hematopoietic niche and the peripheral blood.

Table I. Selected miRNAs involvement in hematopoiesis and their targeted genes/cytokines

miRNA	Regulation function	Gene target	Influence on cytokines	References
miRNA-15a/-16	Angiogenesis, apoptosis, tumorigenesis	IKKα, AKT3, BCL-2, BCL-XL	VEGF-A, IL-6	[77-79, 104, 106]
miRNA-126	HSC migration and proliferation, angiogenesis, apoptosis, tumorigenesis	ZFP91, PHIP, SPRED-1, PIK3R2	VCAM-1, VEGF-A, ANGPT1	[82-88]
miRNA-146a	HSC migration, apoptosis, inflammation, tumorigenesis	CXCR4, SOD2, IRAK1, TRAF6	SDF-1, TNF-α, IL-1, IL-6, IL-8, MMP-9	[90, 94, 97, 110]
miRNA-223	Granulopoiesis, myelopoiesis, erythroid and megakaryocyte differentiation, B-cell development, tumorigenesis, inflammation	NFI-A, IGF-1R, LMO2, IKKα, MEF2C, BCL-2, PAX6	IL-17, MMP-2, MMP-9, VEGF-A	[103-106, 111]

Genes: IKKα – inhibitors kappa B kinase α; AKT3 – serine/threonine kinase 3; BCL-2 – B-cell lymphoma 2; BCL-XL – B-cell lymphoma – extra large; ZFP91 – zinc finger protein 91; PHIP – pleckstrin homology domain interacting protein; SPRED-1 – sprouty-related, EVH1 domain-containing protein; PIK3R2 – phosphoinositide-3-kinase regulatory subunit 2; CXCR4 – C-X-C chemokine receptor type 4; SOD2 – superoxide dismutase 2; IRAK1 – interleukin-1 receptor-associated kinase 1; TRAF6 – TNF receptor-associated factor 6; NFI-A – nuclear factor I A; IGF-1R – insulin-like growth factor 1 receptor; LMO2 – LIM domain only 2; MEF2C – myocyte enhancer factor 2C; PAX6 – paired Box 6. Cytokines: VEGF-A – vascular endothelial growth factor A; IL-1/-6/-8/-17 – interleukin; VCAM-1 – vascular cell adhesion molecule 1; ANGPT-1 – angiopoietin 1; SDF-1 – stromal derived factor 1; TNF-α – tumor necrosis factor α; MMP-2/-9 – matrix metalloproteinase.

MiRNA-126 is involved in this process by targeting VCAM-1 [81]. G-CSF-stimulation during mobilization of CD34 positive cells induces accumulation of microvesicles containing miRNA-126 and leads to downregulation of VCAM-1 expression on bone marrow cells surface [81, 82]. VCAM-1 downregulation increases the hematopoietic and progenitor stem cells release from the bone marrow niche and suppresses homing after HSCT.

MiRNA-126 can influence the expression of ZFP91 gene in hematopoietic progenitor cells (HPC) which results in modulation of CD34+ cells proliferation, tumorigenesis as well as apoptosis [83]. ZFP91 gene promotes the proliferation of tumor cells through transcription factor NF-κB mediated activation of HIF-1α [84]. MiRNA-15a/-16 cluster plays also a significant role in ZFP91/NK-κB/HIF-1α pathway [85]. MiRNA-126 regulates angiogenesis and tumor development by controlling the expression of targeted VEGF signaling repressors (sprouty-related, EVH1 domain-containing protein – Spred-1 and phosphoinositide-3-kinase regulatory subunit 2 – PIK3R2) [86]. High expression of this miRNA in endothelial cells downregulates Spred-1 and PIK3R2 and promotes angiogenesis, while low expression of miRNA-126 leads to elevation of VEGF repressors, inhibition of ANGPT1 and impairment of blood vessels formation [86-89].

miRNA-146a

MiRNA-146a is an important molecule influencing inflammation and tumorigenesis. Expression of this miRNA is induced by the NF-κB protein complex, which plays a significant role in inflammatory response [90]. MiRNA-146a regulates mobilization of HSC as well as their homing after bone marrow transplantation [90-93]. Previous research has shown that under the influence of G-CSF, expression of CXCR4 chemokine receptor mRNA and protein in AML cells was decreased while the level of miRNA-146a was increased [94]. MiRNA-146a affects the CXCR4 mRNA, which leads to disruption of the SDF-1/CXCR4 signaling pathway. It results in more efficient mobilization of HSCs, and slower homing [94]. Urocinase-type plasminogen activator receptor (uPAR), known to be modulated by miRNA-146a, by binding vitronectin is involved in extracellular matrix degradation,

cell adhesion, and migration. It also allows cross-talk with CXCR4. Under GCS-F stimulation, uPAR enhances chemotactic response to SDF-1. MiRNA-146a downregulates uPAR/CXCR4 pathway, which leads to migration engraftment, and adhesion of hematopoietic stem progenitor cells (HSCPC) to the bone marrow niche [95, 96]. Through downregulating of superoxide dismutase 2 enzyme (SOD2) expression, miRNA-146a increases apoptosis and sensitivity to chemotherapy of cancer cells, by enhancement of reactive oxygen species (ROS) generation [97].

miRNA-223

MiRNA-223 is a diagnostic biomarker in the course of obesity, atherogenesis, numerous solid tumors, such as lung, colon, prostate and hematological malignancies [98-102]. Moreover, miRNA-223 expression is associated with hematopoiesis, differentiation and maturation of hematopoietic progenitor cells (HPC) [103]. MiRNA-223 stimulates granulopoiesis, erythroid, and megakaryocyte differentiation via targeting NFI-A, IGF-1R, and LMO2 genes. It is also crucial for homeostasis of mature neutrophils, and limits inflammation [103, 104]. Using transcription factors (TF) miRNA-223 is associated with regulation of network-specific signaling for HPC and differentiation of hematopoietic lines. MiRNA-223 is responsible for the appropriate development, and maturation of myeloid progenitors to granulocytic, erythroid, as well as monocyte/macrophage lines [103, 105]. During macrophage differentiation, miRNA-223 cooperates with miRNA-15a/-16 cluster targeting IKK inhibitor gene, which results in stimulation of NF-κB signaling pathway [104, 106]. Low miRNA-223 expression influence limited expansion of HSC progenitors. High-level expression of granulocyte-macrophage progenitors (GMP) is linked to a deficiency of miRNA-223 in mice [107]. In contrast, the progress of human granulopoiesis and progenitor cells differentiation is associated with higher expression of this molecule [104, 107]. Downregulation of miRNA-223 is an important factor for monocyte differentiation [108]. In hematological malignancies, miRNA-223 in bone marrow seems to be tumor-suppressive molecule [104]. MiRNA-223 is involved in neoplastic cells development. This miRNA modulates apoptosis by targeting oncogene BCL-2 and insulin

growth factor 1 receptor (IGF-1R) [109]. Upregulated expression of miRNA-223 is observed in favorable adult AML risk groups, while in B-cell malignancies (diffuse large B-cell lymphoma, Burkitt lymphoma, chronic lymphocytic leukemia) expression alterations of this miRNA may influence development of lymphoid lineage [102, 105].

We evaluated the kinetics of circulating miRNA-15a, miRNA-16, miRNA-126 and miRNA-146a as well as miRNA-223 in the group of patients with lymphoproliferative malignancies before autologous HSCT and early after transplantation [93]. We observed a correlation of miRNA-15a, miRNA-16, miRNA-126 and miRNA-146 levels assessed directly after conditioning treatment with time to engraftment. Moreover, the level of miRNA-15a/16, evaluated just after chemotherapy, positively correlated with the ANGPT1/ANGPT2 ratio. Additionally, low levels of miRNA-15a, miRNA-146a, and miRNA-223 at the nadir of aplasia were associated with faster engraftment [93]. The other interesting observation in our study was the correlation of miRNA-146a with MMP-9 level directly after chemotherapy and at the nadir of aplasia [93]. Due to a complicated network of factors, influencing cytokines and enzymes activity, it is not possible to give exact links and detailed pathways of ANGPT1/ANGPT2 regulation by miRNAs. Our results are in line with previous reports suggesting that angiogenesis contributes to proper hematopoietic stem cell function, including regeneration after injury caused by chemotherapy and transplantation.

In conclusion, it is very important to continue exploring factors that influence normal and pathological hematopoiesis. A complex network of different molecules interplaying together maintains HSCs in a quiescent state, takes part in mobilization and homing as well as in hematological malignancies. Alterations in the expression of miRNAs can affect microenvironment of the myeloid niche, especially cytokines levels. MiRNAs should also be studied as potential prognostic factors for normal or pathological angiogenesis associated with the development and treatment response of the hematological malignancies.

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The author and co-authors were responsible for the substantive part of the review and linguistic correction.

Conflict of interest/Konflikt interesu

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The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to biomedical journals.

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