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 hematopoiesis, 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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Keywords:
miRNA, cytokines, VEGF, angiopoietins, MMP-9, bone marrow niche, hematopoiesis

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
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-kB 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-kB pathway results in the inhibition of proinflammatory processes, enhances survival and migration of EC, and may promote the tumor development [31-33]. In irradiated 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. ANP72/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]. 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          | VCM-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, PRX6 | 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 IA; IGF-1R – insulin-like growth factor 1 receptor; LMO2 – LIM domain only 2; MEF2C – myocyte enhancer factor 2C; PRX6 – paired Box 6. 
**Cytokines:** VEGF-A – vascular endothelial growth factor A; IL-1/-4/-6/-8/-17 – interleukin; VCM-1 – vascular cell adhesion molecule 1; ANGPT1 – 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 VCM-1 [81]. G-CSF-stimulation during mobilization of CD34 positive cells induces accumulation of microvesicles containing miRNA-126 and leads to downregulation of VCM-1 expression on bone marrow cells surface [81, 82]. VCM-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-223 is involved in neoplastic cells development. This miRNA is associated with higher expression of this molecule [104, 107]. 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 monocye/macrophage lines [103, 105].

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 GCSF 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 (HSPC) 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 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 monocye/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 monocye 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.

Authors’ contributions/Wkład autorów

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

Conflict of interest/Konflikt interesu

We declare no conflict of interest.

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Ethics/Etyka

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.

References/Piśmiennictwo

[1] Kopp HG, Aveillana ST, Hooper AT, Rafii S. The bone marrow vascular niche: home of HSC differentiation and mobilization. Physiology (Bethesda) 2005;20(5):349–56. doi: 10.1152/physiol.00025.2005.
[2] Colmone A, Sipkins DA. Beyond angiogenesis: the role of endothelium in the bone marrow vascular niche. Transl Res 2008; 151(1):1–9. doi: 10.1016/j.trsl.2007.09.003.
[3] Asada N, Katayama Y. Regulation of hematopoiesis in endosteal microenvironments. Int J Hematol 2012;99(6):679–84. doi: 10.1007/s12185-014-1583-1.
[4] Biel NM, Siemann DW. Targeting the Angiopoietin-2/Tie-2 axis in conjunction with VEGF signal interference. Cancer Lett 2016;380(2):525-33. doi: 10.1016/j.canlet.2014.09.035.
[5] Testa U, Saulle E, Castelli G, Pelosi E. Endothelial progenitor cells in hematologic malignancies. Stem Cell Investig 2016;3:26. doi: 10.21037/sci.2016.06.07.
[6] Hooper AT, Butler JM, Nolan DJ, et al. Engraftment and reconstitution of hematopoiesis is dependent on VEGFR2-mediated regeneration of sinusoidal endothelial cells. Cell Stem Cell 2009;4(3):263–274. doi: 10.1016/j.stem.2009.01.006.
[7] Szmigielska-Kapłon A, Krawczyńska A, Czemerska M, et al. The kinetics of hematopoietic niche cytokines and their influence on mobilization efficacy and timing in patients with hematological malignancies. J Clin Apher 2015;30(4):247–51. doi: 10.1002/jca.21369.
[8] Podar K, Anderson KC. The pathophysiologic role of VEGF in hematologic malignancies: therapeutic implications. Blood 2005;105(4):1383–95. doi: 10.1182/blood-2004-07-2909.
[9] Zhang F, Tang Z, Hou X, et al. VEGF-B is dispensable for blood vessel growth but critical for their survival, and VEGF-B targeting inhibits pathological angiogenesis. Proc Natl Acad Sci USA 2009;106(15):6152–7. doi: 10.1073/pnas.0813061106.
[10] Achen MG, Jettsch M, Kukk E, et al. Vascular endothelial growth factor D (VEGF-D) is a ligand for the tyrosine kinases VEGF receptor 2 (Flk1) and VEGF receptor 3 (Flt4). Proc Natl Acad Sci USA 1998;95(2):548–53.
[11] De Falco S. The discovery of placenta growth factor and its biological activity. Exp Mol Med 2012;44(1):1–9. doi: 10.3858/emm.2012.44.1.02.
[12] Grun D, Adhikary G, Eckert RL. VEGF-A acts via neuropilin-1 to enhance epidermal cancer stem cell survival and formation of aggressive and highly vascularized tumors. Oncogene 2016;35(33):4379–87. doi: 10.1038/onc.2015.507.
[13] Zub KA, Sousa MM, Sarno A, et al. Modulation of cell metabolic pathways and oxidative stress signaling contribute to acquired melphalan resistance in multiple myeloma cells. PLoS One 2015; 10(3):e0119857. doi: 10.1371/journal.pone.0119857.
[14] Goto H, Kudo E, Kariya R, Taura M, Katano H, Okada S. Targeting VEGF and interleukin-6 for controlling malignant effusion of primary
[15] Gerber HP, Malik AK, Solar GP, et al. VEGF regulates haematopoietic stem cell survival by an internal autocrine loop mechanism. Nature 2002;417(6892):954–8. doi: 10.1038/nature00821.

[16] Hajitou A, Grignet C, Devy L, et al. The antitumoral effect of endostatin and angiostatin is associated with a down-regulation of vascular endothelial growth factor expression in tumor cells. FASEB J 2002;16(13):1802–4. doi: 10.1096/fj.02-0109fje.

[17] Shaweik D, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. Nature 1992;359(6398):843–5. doi: 10.1038/359843a0.

[18] Jiang WG, Martin TA, Parr C, Davies G, Matsumoto K, Nakamura T. Haptocyte growth factor, its receptor, and their potential value in cancer therapies. Crit Rev Oncol Hematol 2005;53(1):35–69. doi: 10.1016/j.critrevonc.2004.09.004.

[19] Tran J, Master Z, Yu JL, Rak J, Dumont DJ, Kerbel RS. A role for survivin in chemoresistance of endothelial cells mediated by VEGF. Proc Natl Acad Sci USA 2002;99(7):4349–54. doi: 10.1073/pnas.072586399.

[20] Li YL, Zhao H, Ren XB. Relationship of VEGF/VEGFR with immune and cancer cells: staggering or forward? Cancer Biol Med 2016;13(2):206–14. doi: 10.20892/j.issn.2095-3941.2015.0070.

[21] Koch S, Claesson-Welsh L. Signal transduction by vascular endothelial growth factor receptors. Cold Spring Harb Perspect Med 2012;2(7):a006502. doi: 10.1101/cshperspect.a006502.

[22] Mazzieri R, Fucci F, Moi D, et al. Targeting the ANG2/TIE2 axis inhibits tumor growth and metastasis by impairing angiogenesis and disabling rebounds of proangiogenic myocardial cells. Cancer Cell 2011;19(4):512–26. doi: 10.1016/j.ccr.2011.02.005.

[23] Portholm M, Bono P, Saarinen-Pihkala UM, Kivivuori SM. Higher angiopoietin-2 and VEGF levels predict shorter EFS and increased non-relapse mortality after pediatric hematopoietic SCT. Bone Marrow Transplant 2013;48(1):50–5. doi: 10.1038/bmt.2012.101.

[24] Machein MR, Knedla A, Knoth R, et al. Angiopoietin-1 promotes tumor angiogenesis in a rat glioma model. Am J Pathol 2004;165(5):1557–70. doi: 10.1016/S0002-9440(10)63413-X.

[25] Sun L, Zhang H, Bi L, et al. Angiopoietin-1 facilitates recovery of tumor angiogenesis in a rat glioma model. Am J Pathol 2002;160(5):1648–56. doi: 10.1016/S0002-9440(10)63413-X.

[26] Zhou BO, Ding L, Morrison SJ. Hematopoietic stem and progenitor cells regulate the regeneration of their niche by secreting Angiopoietin-1. Elife 2015;4:e05521. doi: 10.7554/eLife.05521.

[27] Saharinen P, Alitalo K. The Yin, the Yang, and the angiopoietin-1. J Clin Invest 2011;121(6):2157–9. doi: 10.1172/JCI58196.

[28] Takakura N, Watanabe T, Suenobu S, et al. A role for hematopoietic stem cells in promoting angiogenesis. Cell 2000;102(2):99–209. doi: 10.1016/S0092-8674(00)00255-8.

[29] Sautelle E, Guerriero R, Petronelli A, et al. Autocrine role of angiopoietins during megakaryocytic differentiation. PLoS One 2012;7(7):e39796. doi: 10.1371/journal.pone.0039796.

[30] Wittenzihalcher B, Maisonneuve PC, Jones P, Yancopoulos GD, Isner JM. Chemotactic properties of angiopoietin-1 and -2, ligands for the endothelial-specific receptor tyrosine kinase Tie2. J Biol Chem 1998;273(29):18514–21. doi: 10.1074/jbc.273.29.18514.

[31] Taburyn SP, Griffioen AW. NF-κB: a new player in angiostatic therapy. Angiogenesis 2008;11(1):101–6. doi: 10.1007/s10456-008-9094-4.

[32] Makinde T, Agrawal D. Intra and extravascular transmembrane signalling of angiopoietin-1-Tie2 receptor in health and disease. J Cell Mol Med 2008;12(3):810–28. doi: 10.1111/j.1582-4934.2008.00254.x.

[33] Mitola S, Moroni E, Raveli C, Andres G, Belleri M, Presta M. Angiopoietin-1 mediates the proangiogenic activity of the bone morphogenetic protein antagonist Dmp. Blood 2008;112(4):1154–7. doi: 10.1182/blood-2007-09-111450.

[34] Burgers G, Song S. The role of pericytes in blood- vessel formation and maintenance. Neuro Oncol 2005;7(4):452–64. doi: 10.1215/ S1112851705000232.

[35] Ueda N, Chihara D, Kohno A. Predictive value of circulating angiopoietin-2 for endothelial damage-related complications in allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2014;20(9):1335–40. doi: 10.1016/j.bbtm.2014.03.030.

[36] Du R, Lu KV, Perrritsch C, et al. Ifit1a induces the recruitment of bone marrow-derived vascular modulatory cells to regulate tumor angiogenesis and invasion. Cancer Cell 2008;13(3):206–20. doi: 10.1016/j.ccr.2008.01.034.

[37] Lobov IB, Brooks PC, Lang RA. Angiopoietin-2 displays VEGF-dependent modulation of capillary structure and endothelial cell survival in vivo. Proc Natl Acad Sci USA 2002;99(17):11205–10. doi: 10.1073/pnas.172161899.

[38] Welford AF, Bizio D, Coffelt SB, et al. TIE2-expressing macrophages limit the therapeutic efficacy of the vascular-disrupting agent combretastatin A4 phosphate in mice. J Clin Invest 2011;121(5):1969–73. doi: 10.1172/JCI44562.

[39] Serefanhaglu S, Goker H, Buyukasik Y, et al. Changes in vascular endothelial growth factor, angiopoietins, and Tie-2 levels with G-CSF stimulation in healthy donors. Ann Hematol 2009;88(7):667–71. doi: 10.1007/s00277-008-0657-7.

[40] Yang JZ, Sun LX. Decreased soluble TGF-β1, Tie-2, and angiopoietins serum levels in bone marrow after treating healthy donors with granulocyte colony-stimulating factor. Transfus Apher Sci 2012;47(1):39–42. doi: 10.1016/j.transci.2012.03.007.

[41] Lysák D, Habětová M, Vrzelová J, et al. Changes of cytokine levels during granulocyte-colony-stimulating factor stem cell mobilization in healthy donors: association with mobilization efficiency and potential predictive significance. Transfusion 2011;51(2):319–27. doi: 10.1111/j.1537-2995.2010.02863.x.

[42] Szmagielska-Kaplon A, Krawczyńska A, Czermerska M, et al. Angiopoietins in hematopoietic stem cell mobilization in patients with hematological malignancies. Blood Transfus 2015;13(1):102–8. doi: 10.2450/2014.0300-14.

[43] Vande Broek I, Asosnigh K, Allegaert V, et al. Bone marrow endothelial cells increase the invasiveness of human multiple myeloma cells through upregulation of MMP-9: evidence for a role of hepatocyte growth factor. Leukemia 2004;18(5):976–82. doi: 10.1038/sj.leu.2403331.

[44] Kumar A, Collins HM, Scholefield JH, Watson SA. Increased type-IV collagenase (MMP-2 and MMP-9) activity following preoperative radiotherapy in rectal cancer. Br J Cancer 2000;82(4):960–5. doi: 10.1054/bjoc.1999.1025.

[45] Deryugina EJ, Quigley JP. Tumor angiogenesis: MMP-mediated induction of invasation and metastasis-sustaining neovascularure. Matrix Biol 2015;44–46,94–112. doi: 10.1016/j.matbio.2015.04.004.
[46] Weis SM, Cheresh DA. Tumor angiogenesis: molecular pathways and therapeutic targets. Nat Med 2011;17(11):1359–70. doi: 10.1038/nm.2537.

[47] Heissig B, Hattori K, Dias S, et al. Recruitment of stem and progenitor cells from the bone marrow niche requires MPP-9 mediated release of kit-ligand. Cell 2002;109(5):625–37. doi: 10.1016/S0092-8674(02)00754-7.

[48] Nishioka C, Ikezoe T, Furihata M, et al. CD34+/CD38- acute myelogenous leukemia cells aberrantly express CD82 which regulates adhesion and survival of leukemia stem cells. Int J Cancer 2013;132(9):2006–19. doi: 10.1002/ijc.2790.

[49] Liongue C, Wright C, Russell AP, Ward AC. Granulocyte colony-stimulating factor receptor: stimulating granulopoiesis and much more. Int J Biochem Cell Biol 2009;41(12):2372–5. doi: 10.1016/j.ijbioc.2009.08.011.

[50] Lee S, Im SA, Yoo ES, et al. Mobilization kinetics of CD34(+) cells in association with modulation of CD44 and CD31 expression during continuous intravenous administration of G-CSF in normal donors. Stem Cells 2000;18:281–6. doi: 10.1634/stemcells.18-4-281.

[51] Lévesque JP, Takamatsu Y, Nilsson SK, Haylock DN, Simmons PJ. Vascular cell adhesion molecule-1 (CD106) is cleaved by neutrophil proteases in the bone marrow following hematopoietic progenitor cell mobilization by granulocyte colony-stimulating factor. Blood 2001;98(5):1289–97. doi: 10.1182/blood.v98.5.1289.

[52] Teicher BA, Fricker SP. CXCL12 (SDF-1)/CXCR4 pathway in cancer. Clin Cancer Res 2010;16(11):2927–31. doi: 10.1158/1078-0432.CCR-09-2329.

[53] Fieg M, Samudio I, Clise-Dwyer K, Burks JK, Mnjoyan Z, Andreeff M. CXCR4 expression and biologic activity in acute myeloid leukemia are dependent on oxygen partial pressure. Blood 2009;113(7):1504–12. doi: 10.1182/blood-2008-06-161539.

[54] Zhao H, Guo L, Zhao H, Zhao J, Weng H, Zhao B. CXCR4 over-expression and survival in cancer: A system review and meta-analysis. Oncotarget 2015;6(7):5022–40. doi: 10.18632/oncotarget.3217.

[55] Rettig MP, Anstas G, DiPersio JF. Mobilization of hematopoietic stem and progenitor cells using inhibitors of CXCR4 and VLA-4. Leukemia 2012;26(1):34–53. doi: 10.1038/leu.2011.197.

[56] Szmigielska-Kaplon A, Krawczyńska A, Czemerska M, et al. Circulating endothelial cell kinetics and their potential predictive value during mobilization procedure. J Clin Apher 2013;28(5):341–8. doi: 10.1002/jca.21277.

[57] Szmigielska-Kaplon A, Krawczyńska A, Czemerska M, et al. Kinetics and apoptotic profile of circulating endothelial cells in patients undergoing autologous stem cell transplantation. Ann Haematol 2013;92:1255–62. doi: 10.1007/s00277-013-1759-4.

[58] Yu X, Huang Y, Collin-Osdoby P, Osdoby P. Stromal cell-derived factor-1 (SDF-1) recruits osteoclast precursors by inducing chemotaxis, matrix metalloproteinase-9 (MMP-9) activity, and collagen transmigration. J Bone Miner Res 2003;18(8):1404–18. doi: 10.1359/jbmr.2003.18.8.1404.

[59] He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet 2004;5:522–31. doi: 10.1038/nrg1379.

[60] Ambros V. The functions of animal microRNAs. Nature 2004;431:350–5. doi: 10.1038/nature02871.

[61] Kong YW, Ferland-McCollough D, Jackson TJ, Bushell M. MicroRNAs in cancer management. Lancet Oncol 2012;13:249–58. doi: 10.1016/S1470-2045(12)70073-6.

[62] Huntzinger E, Izaurralde E. Gene silencing by microRNAs: contributions of translational repression and mRNA decay. Nat Rev Genet 2011;12:99–110. doi: 10.1038/nrg2936.

[63] Garzon R, Fabбри M, Cimmino A, Calin GA, Croce CM. MicroRNA expression and function in cancer. Trends Mol Med 2006;12:580–7. doi: 10.1016/j.molmed.2006.10.006.

[64] Hu W, Coller J. What comes first: translational repression or mRNA degradation? The deepening mystery of microRNA function. Cell Res 2012;9:1322–4. doi: 10.1038/cr.2012.80.

[65] Fan SJ, Li HB, Cui G, et al. miRNA-149* promotes cell proliferation and suppresses apoptosis by mediating JunB in T-cell acute lymphoblastic leukemia. Leuk Res 2016;41:62–70. doi: 10.1016/j.leukres.2015.11.016.

[66] Martin EC, Qureshi AT, Dasa V, Freitas MA, Gimble JM, Davis TA. MicroRNA regulation of stem cell differentiation and diseases of the bone and adipose tissue: Perspectives on miRNA biogenesis and cellular transcriptome. Biochimie 2016;124:98–111. doi: 10.1016/j.biochi.2015.02.012.

[67] Medina PP, Nolde M, Slack FJ. OncomiR addiction in an in vivo model of microRNA-21-induced pre-B-cell lymphoma. Nature 2010;467(7311):86–90. doi: 10.1038/nature09284.

[68] Yoo JK, Kim J, Choi SJ, et al. Discovery and characterization of novel microRNAs during endothelial differentiation of human embryonic stem cells. Stem Cells Dev 2012;21(11):2049–57.

[69] Zhang L, Sankaran VG, Lodish HF. MicroRNAs in erythroid and megakaryocytic differentiation and megakaryocyte–erythroid progenitor lineage commitment. Leukemia 2012;26(11):2310–16. doi: 10.1038/leu.2012.137.

[70] Bissels U, Bosio A, Wagner W. MicroRNAs are shaping the hematopoietic landscape. Hematologica 2012;97(2):160–7. doi: 10.3324/haematol.2011.051730.

[71] Jansson MD, Lund AH. MicroRNA and cancer. Mol Oncol 2012;6:590-610. doi: 10.1016/j.molonc.2012.09.006.

[72] Guglielmelli P, Tozzi L, Bogani C, et al. Overexpression of microRNA-16-2 contributes to the abnormal erythropoiesis in polycythemia vera. Blood 2011;117(25):6923–7. doi: 10.1182/blood-2010-09-306506.

[73] Terzulli E, Donnini S, Finetti F, et al. Linking microsomal prostaglandin E Synthase-1/PGE-2 pathway with miR-15a and -16 expression: Novel mechanism of VEGF modulation in prostate cancer. Oncotarget 2016;12(7):44350–64. doi: 10.18632/oncotarget.10051.

[74] Cui X, Witalison EE, Chumanevich AA, et al. The induction of p53-dependent cell cycle arrest. PLoS One 2013;8(1):e53791. doi: 10.1371/journal.pone.0053791.

[75] Wang W, Corrigan-Cummins M, Barber EA, et al. Aberrant levels of miRNAs in bone marrow microenvironment and peripheral blood of myeloma patients and disease progression. J Mol Diagn 2015;17(6):669–78. doi: 10.1016/j.jmoldx.2015.06.006.

[76] Musilova K, Mraz M. MicroRNAs in B-cell lymphomas: how a complex biology gets more complex. Leukemia 2015;29(5):1004–17. doi: 10.1038/leu.2014.351.
[77] Sun CY, She XM, Qin Y, et al. miR-15a and miR-16 affect the angiogenesis of multiple myeloma by targeting VEGF. Carcinogenesis 2013;34(2):426–35. doi: 10.1093/carcin/bgs333.

[78] Hao M, Zhang L, An G, et al. Suppressing miRNA-15a/-16 expression by interleukin-6 enhances drug-resistance in myeloma cells. J Hematol Oncol 2011;4:37. doi: 10.1186/1756-7222-4-37.

[79] Hao M, Zhang L, An G, et al. Bone marrow stromal cells protect myeloma cells from bortezomib-induced apoptosis by suppressing microRNA-15a expression. Leuk Lymphoma 2011;52(9):1787–94. doi: 10.3109/10428194.2011.576791.

[80] Xie J, Jing R, Qi J, Lin Z, Ju S. Drug resistance-related microRNAs in hematological malignancies: translating basic evidence into therapeutic strategies. Blood Rev 2015;29(1):33–44. doi: 10.1016/j.blre.2014.09.005.

[81] Salvucci O, Jiang K, Gasperini P, et al. MicroRNA126 contributes to granulocyte colony-stimulating factor-induced hematopoietic progenitor cell mobilization by reducing the expression of vascular cell adhesion molecule 1. Haematologica 2012;97(6):818–26. doi: 10.3324/haematol.2011.056945.

[82] Harris TA, Yamakuchi M, Ferlito M, Mendell JT, Lowenstein CJ. MicroRNA-126 regulates endothelial expression of vascular cell adhesion molecule 1. Proc Natl Acad Sci USA 2008;105(5):1516–21. doi: 10.1073/pnas.0707493105.

[83] Baez A, Martin-Antonio B, Piruat JI, et al. Gene and miRNA expression profiles of hematopoietic progenitor cells vary depending on their origin. Biol Blood Marrow Transplant 2014;20(5):630–9. doi: 10.1016/j.bbmt.2014.01.022.

[84] Ma J, Mi C, Wang KS, Lee JJ, Jin X. Zinc finger protein 91 (ZFP91) activates HIF-1α via NF-κB/p65 to promote proliferation and tumorigenesis of colon cancer. Oncotarget 2016;7(24):36551–62. doi: 10.18632/oncotarget.9070.

[85] Ma X, Buscaglia LE, Barker JR, Li Y. MicroRNAs in NF-κB signaling. J Mol Cell Biol 2011;3(3):159–66. doi: 10.1093/jmcb/mjr007.

[86] van Solingen C, Seghers L, Bijkerk R, et al. Antagomir-119 targeting of FANCM during inflammation compromises genome integrity. Oncotarget 2016;19(3):205–11. doi: 10.1016/j.gde.2009.04.002.

[87] Wang S, Olson EN, AngiomiRs – key regulators of angiogenesis. Curr Opin Genet Dev 2009;19(3):205–11. doi: 10.1016/j.gde.2009.04.002.

[88] Nowicki M, Szemraj J, Wierzbowska A, Misiewicz M, Malachowski R, Pluta A, et al. miRNA-15a, miRNA-16, miRNA-126, miRNA-146a and miRNA-223 expressions in autologous hematopoietic stem cell transplantation and their impact on engraftment. Eur J Haematol 2018. doi: 10.1111/ejh.13036.

[89] Sheng X, Zhong H, Wan H, Zhong J, Chen F. Granulocyte colony-stimulating factor inhibits CXCR4/SDF-1α signaling and overcomes stromal-mediated drug resistance in the HL-60 cell line. Exp Ther Med 2012;12(1):396–404. doi: 10.3892/etm.2012.1368.

[90] Alfano D, Gorarsi A, Li Santi A, et al. Urokinase receptor and CXCR4 are regulated by common microRNAs in leukemia cells. J Cell Mol Med 2015;19(9):2262–72. doi: 10.1111/jcmm.12617.

[91] Tjwa M, Sidenius N, Moura R, et al. Membrane-anchored uPAR regulates the proliferation, marrow pool size, engraftment, and mobilization of mouse hematopoietic stem/progenitor cells. J Clin Invest 2009;119(4):1008–18. doi: 10.1172/JCI36010.

[92] Cui Y, She K, Tian D, Zhang P, Xin X. MiR-146a inhibits proliferation and enhances chemosensitivity in epithelial ovarian cancer via reduction of SOD2. Oncol Res 2016;23(6):275–82. doi: 10.3727/096504016X145627537398.

[93] Wang D, Qiao P, Wang L. Circulating microRNA-223 as a potential biomarker for obesity. Obes Res Clin Pract 2015;9(4):398–404. doi: 10.1016/j.orcp.2015.01.006.

[94] Shan Z, Qin S, Li JW, et al. An Endocrine Genetic Signal Between Blood Cells and Vascular Smooth Muscle Cells: Role of MicroRNA-223 in Smooth Muscle Function and Atherogenesis. J Am Coll Cardiol 2015;65(23):2526–37. doi: 10.1016/j.jacc.2015.03.570.

[95] Kurozumi A, Goto Y, Matsushita R, et al. Tumor-suppressive microRNA-223 inhibits cancer cell migration and invasion by targeting ITGA3/ITGB1 signaling in prostate cancer. Cancer Sci 2016;107(1):84–94. doi: 10.1111/cas.12842.

[96] Tachibana H, Sho R, Takeda Y, et al. Circulating miR-223 in oral cancer: its potential as a novel diagnostic biomarker and therapeutic target. PLoS One 2016;11(7):e0159693. doi: 10.1371/journal.pone.0159693.

[97] Zhang J, Jima DD, Jacobs C, et al. Patterns of microRNA expression characterize stages of human B-cell differentiation. Blood 2009;113(19):4586–94. doi: 10.1182/blood-2008-09-178186.

[98] Vian L, Di Carlo M, Pelosi E, et al. Transcriptional fine-tuning of microRNA‐223 inhibits cancer cell migration and invasion by targeting VEGF. Carcinogenesis 2014;35(10):1531–40. doi: 10.1093/carcin/bgu225.

[99] Shan Z, Qin S, Li JW, et al. An Endocrine Genetic Signal Between Blood Cells and Vascular Smooth Muscle Cells: Role of MicroRNA-223 in Smooth Muscle Function and Atherogenesis. J Am Coll Cardiol 2015;65(23):2526–37. doi: 10.1016/j.jacc.2015.03.570.

[100] Kurozumi A, Goto Y, Matsushita R, et al. Tumor-suppressive microRNA-223 inhibits cancer cell migration and invasion by targeting ITGA3/ITGB1 signaling in prostate cancer. Cancer Sci 2016;107(1):84–94. doi: 10.1111/cas.12842.

[101] Tachibana H, Sho R, Takeda Y, et al. Circulating miR-223 in oral cancer: its potential as a novel diagnostic biomarker and therapeutic target. PLoS One 2016;11(7):e0159693. doi: 10.1371/journal.pone.0159693.

[102] Yang M, Li W, et al. The miR-126 regulates angiopoietin-1 signaling and vessel maturation by targeting p85β. Biochim Biophys Acta 2012;1823(10):1925–35. doi: 10.1016/j.bbamcr.2012.01.022.

[103] Feng Y, Song S, Zhang L, et al. Down-regulation of CXCR4 expression identified as a mechanism for mobilization of myeloid cells. Blood 2006;108(3):812–20. doi: 10.1182/blood-2005-10-1416.

[104] Nowicki M, Szemraj J, Wierzbowska A, Misiewicz M, Malachowski R, Pluta A, et al. miRNA-15a, miRNA-16, miRNA-126, miRNA-146a and miRNA-223 expressions in autologous hematopoietic stem cell transplantation and their impact on engraftment. Eur J Haematol 2018. doi: 10.1111/ejh.13036.

[105] Sheng X, Zhong H, Wan H, Zhong J, Chen F. Granulocyte colony-stimulating factor inhibits CXCR4/SDF-1α signaling and overcomes stromal-mediated drug resistance in the HL-60 cell line. Exp Ther Med 2012;12(1):396–404. doi: 10.3892/etm.2012.1368.

[106] DiDonato JA, Mercurio F, Karin M. NF-κB and the link between inflammation and cancer. Immunol Rev 2012;246(1):379–400. doi: 10.1111/j.0105-1151.2011.00962.x.
[107] Trissal MC, DeMoya RA, Schmidt AP, Link DC. MicroRNA-223 regulates granulopoiesis but is not required for HSC maintenance in mice. PLoS One 2015;10(3):e0119304. doi: 10.1371/journal.pone.0119304.

[108] Johnnidis JB, Harris MH, Wheeler RT, et al. Regulation of progenitor cell proliferation and granulocyte function by microRNA–223. Nature 2008;451(7182):1125–9. doi: 10.1038/nature06607.

[109] Gao H, Deng H, Xu H, et al. MicroRNA-223 promote mast cell apoptosis by targeting insulin-like growth factor 1 receptor. Exp Ther Med 2016;11:2171–6. doi: 10.3892/etm.2016.3227.

[110] Bhaumik D, Scott GK, Schokrpur S, Patil CK, Campisi J, Benz CC. Expression of microRNA-146 suppresses NF-kappaB activity with reduction of metastatic potential in breast cancer cells. Oncogene 2008;27(42):5643–7. doi: 10.1038/onc.2008.171.

[111] Huang BS, Luo QZ, Han Y, Li XB, Cao LJ, Wu LX. MicroRNA-223 promotes the growth and invasion of glioblastoma cells by targeting tumor suppressor PAX6. Oncol Rep 2013;30(5):2263–9. doi: 10.3892/or.2013.2683.