International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

© International Scientific Organization

Role of Vascular Endothelial Growth Factor Gene and VEGFR in Acute Myeloid Leukemia

Naglaa Ali Khalifa[1], Rasha Mohmed Haggag[2], Manal Al-garbi[1], Rowida Mansour Soliman Slem[1]

[1]*Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt*

[2] *Medical Oncology Department, Faculty of Medicine, Zagazig University, Egypt*

Abstract

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, with an incidence of over 20 000 cases per year in the United States alone. Large chromosomal translocations as well as mutations in the genes involved in hematopoietic proliferation and differentiation result in the accumulation of poorly differentiated myeloid cells. This review is designed to provide an overview of the current literature concerning vascular endothelial growth factor (VEGF) in acute myeloid leukemia (AML). Aberrant VEGF operates in the bone marrow of AML patients and is related to a poor prognosis. The altered signaling pathway demonstrated to interfere in several autocrine and paracrine signaling pathways. VEGF promotes autocrine AML blast cell proliferation, survival, and chemotherapy resistance. In addition, VEGF can mediate paracrine vascular endothelial cell-controlled angiogenesis in AML. Both effects presumably explain the association of high VEGF levels and poor therapeutic outcome. More recently, researches focusing on bone marrow stem cell niches demonstrate a role for VEGF signaling in the preservation of several cell types within these niches. The bone marrow niches are proposed to be a protective microenvironment for AML cells that could be responsible for relapses in AML patients. This implies the need of sophisticated VEGF-targeted therapeutics in AML therapy strategies.

Keywords: Vascular Endothelial Growth Factor gene, VEGFR, Acute Myeloid Leukemia.

Mini review article **Corresponding Author*, e-mail: *rowidamansour221@gmail.com*

1. Introduction

The proliferation and survival of AML blasts are, in part, influenced by the VEGF/VEGFR signaling pathway in certain subsets of AML patients. Key biological traits of leukemic cells include their enhanced ability to self-renew and proliferate, along with a distinct survival advantage. The activation of the VEGF signaling pathway facilitates both the proliferation and survival of AML cells [1]. In vitro studies have shown that stimulation with VEGF-A significantly enhances AML blast proliferation, particularly in conjunction with stem cell factor (SCF) [2]. Additionally, the stimulation of primary AML cells with VEGF-C has been found to increase the number of viable cells in vitro, indicating that VEGF-C may also support AML cell proliferation [3]. The proliferation of AML cells induced by VEGF ligands may depend on the presence of VEGF receptors. For instance, the enforced expression of VEGFR-2 in TF-1 AML cells has been shown to promote leukemic growth in response to VEGF stimulation [4]. Subgroups of AML patients exhibiting high levels of VEGF receptor expression may rely more heavily on VEGF/VEGFR signaling for their cell proliferation. Both VEGF-A and VEGF-C have been observed to enhance the survival of AML cells in vitro [5].

The pro-survival signaling mechanisms activated by VEGF-A or VEGF-C stimulation help protect AML cells from apoptosis induced by chemotherapy, primarily through the upregulation and activation of anti-apoptotic proteins [6]. Furthermore, research on VEGF signaling in AML cells reveals that numerous downstream pathways are activated upon ligand binding. The work of Dias has shown that VEGF-A promotes AML cell proliferation and survival via signaling proteins such as NF-κβ, Akt, Erk, HSP90, and Bcl-2 [7]. VEGF-C has been shown to enhance the survival of AML cells by increasing the expression of Bcl-2 and activating downstream signaling proteins in greater detail. Specifically, VEGF-C can stimulate the transcription and protein expression of COX-2 through the activation of Erk and JNK signaling pathways. Collectively, these findings indicate that the activation of Bcl-2, HSP, MAPK, and PI3K proteins by VEGF ligands contributes to the proliferation and survival of AML cells. Furthermore, inhibiting VEGF signaling in AML cells also disrupts the activation of these downstream

signaling proteins [8]. A summarized model illustrating the classical downstream VEGF/VEGFR signaling in AML cells indicates that the VEGF receptor undergoes phosphorylation upon the binding of either VEGF-A or VEGF-C.

This phosphorylation triggers the activation of downstream signaling proteins that are integral to the PI3 kinase and MAPK pathways. Mechanisms of chemotherapy resistance are influenced by the VEGF receptor-mediated activation of Bcl-2 and HSPs. Additionally, the MAPK pathway can promote the transcription of COX-2, a pro-angiogenic factor that can further stimulate paracrine VEGF signaling. The blue proteins highlighted are recognized as crucial downstream components of the VEGF/VEGFR signaling pathway, playing significant roles in the proliferation, survival, and chemotherapy resistance of AML blast cells [9]. VEGF signaling in acute myeloid leukemia (AML) cells can occur through both internal and external pathways. The activation of these pathways may lead to distinct downstream signaling effects within AML cells, particularly when assessing the consequences of inhibiting the VEGF-A/VEGFR-2 signaling pathway, either internally or externally, in primary AML cells in vitro. The external pathway was inhibited by blocking VEGF-A, whereas the internal pathway was targeted using a specific VEGFR-2 kinase inhibitor [10].

The simultaneous inhibition of both internal and external pathways was found to significantly reduce the expression of nuclear VEGFR-2 protein. While both signaling pathways exhibit some overlap in downstream NF-κβ signaling, the inhibition of the internal pathway also influenced the downstream proteins Erk and Akt. Notably, the suppression of the internal VEGFR-2 pathway led to apoptosis in AML cell lines [11]. Furthermore, the external blockade of VEGF-A did not independently trigger apoptosis; however, it could enhance apoptotic effects when combined with VEGFR-2 inhibition in AML cell lines [12]. This observation may indicate that the internal pathway plays a more critical role in the survival of AML cells, or that VEGF-C may compensate for the role of VEGF-A in external signaling. These findings suggest that both internal and external autocrine VEGF signaling are governed by distinct signal transduction mechanisms, each of which is vital for the survival of AML cells [13]. Among the various subgroups of AML patients, those with t(8;21) translocations and MLL rearrangements exhibited the highest levels of VEGFR-2 expression, while the t(15;17) Trans located subgroup showed the highest levels of VEGFR-1 [14].

Inhibition of VEGFR-2 kinase activity in acute myeloid leukemia (AML) cells resulted in apoptosis in patients with t(8;21) and MLL rearrangements, whereas samples from patients with t(15;17) AML did not exhibit a response to VEGFR-2 kinase inhibition. Patients with other cytogenetic abnormalities displayed varied responses [15]. Patients with t(8;21) translocation or MLL rearrangement showed greater sensitivity to treatments involving anti-VEGFR-1, anti-VEGFR-2, and combined monoclonal antibodies compared to those with different cytogenetic profiles (16). Conversely, samples from patients with t(15;17) AML responded exclusively to VEGFR-1 antibody therapy. These findings indicate that both external and internal VEGF receptor-targeted therapies are most effective in AML patient subgroups exhibiting elevated expression levels of VEGF receptors. Such subgroups may rely more heavily on VEGF/VEGFR signaling for the intrinsic regulation of AML cell proliferation and survival [17]. The role of VEGF in angiogenesis associated with AML is significant. VEGF serves as a primary mediator of angiogenesis, which is the formation of new blood vessels from pre-existing ones by vascular endothelial cells. It regulates angiogenic sprouting by directing the extension of filopodia from endothelial tip cells, marking the initial step in vessel formation [18].

Vascular endothelial cells can express all VEGF receptors on their membranes at various stages of vascular development. By binding to VEGFR-2, VEGF promotes the proliferation, survival, and migration of vascular endothelial cells, thereby facilitating angiogenesis [19]. Autocrine and paracrine VEGF signaling in acute myeloid leukemia (AML) reveals two distinct pathways that work in tandem to facilitate the disease's progression. Through autocrine signaling, AML cells engage VEGF receptors, which leads to enhanced self-renewal, proliferation, survival, and resistance to chemotherapy [20]. On the other hand, paracrine VEGF signaling fosters both angiogenesis and lymphangiogenesis. These pathways enable leukemic blasts to promote vessel formation and maintain their own stem cell populations. VEGF-A and VEGF-C are capable of binding to and activating both AML cells and endothelial cells [21]. Increased angiogenesis is frequently noted in bone marrow biopsies from AML patients. Studies have shown that micro-vessel density is significantly elevated in the bone marrow of newly diagnosed AML patients compared to those who have achieved complete remission and normal bone marrow (NBM) controls [22].

This heightened micro-vessel density is linked to a poorer prognosis in AML. The vessels observed in the bone marrow biopsies of AML patients' exhibit variability in size and quantity. Three distinct vascular morphology patterns can be identified: a subgroup with "low vessel count," another exhibiting "angiogenic sprouting" characterized by a high number of small, immature capillaries, and a third group with "vessel hyperplasia," which consists of mature vessels with a large lumen [23]. Patients with "angiogenic sprouting" and "low vessel count" experience reduced event-free survival compared to those with "vessel hyperplasia" [24]. Growing evidence indicates that VEGF-A and VEGF-C play a significant role in promoting angiogenesis within the bone marrow of AML patients. The correlation between increased vessel formation and VEGF-A expression in AML patients is noteworthy [25]. A model of leukemic mice illustrates the involvement of VEGF-A in the progression of acute myeloid leukemia (AML) by promoting the development of vascular capillaries [26]. The administration of a VEGF-A antagonist was found to diminish angiogenesis and organ infiltration, thereby enhancing the survival rates of these leukemic mice. Additionally, VEGF-C has been shown to stimulate AML-related angiogenesis both in vitro and in vivo [27].

These findings indicate that AML blasts release VEGF-A and VEGF-C, facilitating angiogenesis through the activation of paracrine VEGF signaling in vascular endothelial cells [28]. The stem cell niche serves as a crucial microenvironment for hematopoietic stem cells (HSC), playing a vital role in regulating their fate and survival [29]. In vivo studies using mouse models have identified two distinct types of HSC niches within the bone marrow: a hypoxic endosteal niche located in the cancellous or trabecular bone, and a vascular niche characterized by high

oxygen levels [30]. Dormant HSCs are found in the hypoxic endosteal niche, which is essential for maintaining stem cell quiescence [31]. Conversely, active HSCs are believed to inhabit the vascular niche. These stem cell niches comprise various cell types, including mesenchymal stem cells, osteoblasts, and osteoclasts). Increasing evidence suggests that VEGF-A and VEGF-C play supportive roles within these niches. Mesenchymal cells and osteoblasts are known to produce VEGF-A [32], which is implicated in the differentiation of osteoblasts and osteoclasts from their progenitor cells. Additionally, osteoclasts secrete VEGF-C, which promotes their bone resorption activities [33].

Recent research findings provide substantial evidence supporting the hypothesis that Vascular Endothelial Growth Factor (VEGF) plays a crucial role in hematopoietic stem cell (HSC) niches and may also be significant for leukemic stem cell (LSC) niches. Additionally, studies conducted on leukemic mouse models have demonstrated that following high-dose chemotherapy, the remaining leukemic cells are predominantly found in the perivascular endothelium and within the cancellous bone [34]. It is proposed that resistant LSCs, which inhabit protective endosteal and vascular niches, contribute to the relapse of Acute Myeloid Leukemia (AML). Given that VEGF is known to support the stem cell niche and is linked to AML relapse [35], it can be posited that VEGF may play a role in relapses associated with AML niches Leukemic stem cell niches are believed to shield leukemic stem cells from the effects of therapeutic interventions. Within the endosteal bone marrow niche, stem cells exist in a quiescent state, rendering acute myeloid leukemia (AML) cells resistant to treatments aimed at proliferating cells. Additionally, cells located in vascular bone marrow niche can be mobilized by external factors, facilitating their entry into bloodstream for organ infiltration, a phenomenon frequently observed in AML patients. The secretion of VEGF-A and VEGF-C is crucial for supportive cells that constitute stem cell niches [36].

VEGF-targeted therapy in acute myeloid leukemia (AML) has emerged as a significant area of research, with various therapeutic approaches aimed at inhibiting the signaling pathways activated by VEGF. Targeting VEGF in AML patients may effectively disrupt the autocrine VEGF signaling within AML cells and mitigate the abnormal formation of blood vessels by vascular endothelial cells [37]. Bevacizumab (Avastin), a monoclonal antibody that targets VEGF-A, is currently being evaluated in clinical trials for AML treatment. A phase I clinical trial involving patients with refractory and relapsed AML indicated that monotherapy with bevacizumab did not yield any clinical responses [38]. Despite lack of partial or complete responses, treatment with bevacizumab resulted in a significant reduction in VEGF-A expression levels in bone marrow biopsies. Subsequently, a phase II clinical trial was initiated to assess the efficacy of bevacizumab in conjunction with chemotherapy. This trial has shown encouraging outcomes for both relapsed and refractory adult AML patients [39]. The variability in therapeutic responses may be attributed to several factors, including the levels of VEGF and its receptors, as well as the vascular morphology observed in the bone marrow of AML patients.

Approximately 50% of AML patients have been found to respond favorably to combination of bevacizumab and chemotherapy [40]. PTK787/ZK222584/Vatalanib (PTK) is a multi-targeted inhibitor primarily designed to selectively inhibit VEGFR-2. However, it has also been shown to affect VEGFR-1, VEGFR-3, the stem cell factor receptor (SCFR; also known as CD117 or c-Kit), and the macrophage colony-stimulating factor receptor (M-CSFR; also referred to as c-fms or CSF-1). A phase I clinical trial evaluated the efficacy of PTK in patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). The results indicated that there were no significant responses to PTK monotherapy in patients with refractory and relapsed AML. Notably, a subset of patients (4 out of 15) with secondary AML exhibited a response to PTK when combined with chemotherapy. Another multi-targeted inhibitor, semaxinib (SU5416), targets VEGF receptors, SCFR, and fms-like tyrosine kinase-3 (FLT3). In a case involving a patient experiencing a second relapse of AML that was refractory to standard treatments, semaxinib monotherapy resulted in stable remission. However, a phase II clinical trial involving patients with refractory AML revealed that none achieved complete remission, although 19% demonstrated a partial response.

An interesting correlation was identified between the patients who responded to SU5416 and elevated levels of VEGF-A mRNA at the start of treatment, suggesting that the VEGF-A mRNA levels at diagnosis may help predict which patients are likely to benefit from this therapy. The related compound sunitinib (SU11248) exhibited a modest beneficial effect as a monotherapy in a phase I clinical trial. Axitinib (AG-013736) is another multi-targeted tyrosine kinase inhibitor that targets VEGFR-2, SCFR, and platelet-derived growth factor receptor β (PDGFR-β). In a phase II clinical trial, axitinib was administered to elderly AML patients with poor prognoses, but it did not demonstrate clinical responsiveness. Sorafenib (BAY 43-9006) functions as a dual-action inhibitor, effectively targeting the RAF/MEK/Erk signaling pathway alongside upstream tyrosine kinases, including FLT3, VEGFR-2, VEGFR-3, PDGFR-β, and SCFR. Its administration has shown efficacy in treating acute myeloid leukemia (AML) patients, particularly those with a FLT3-ITD mutation, both prior to and following allogeneic stem cell transplantation [41].

Notably, all AML patients with the FLT3-ITD mutation (6 out of 6) responded positively to sorafenib treatment. Given that approximately 25% of AML patients exhibit this mutation, sorafenib presents a promising therapeutic option for this specific subset of patients [42]. Midostaurin, another multi-targeted therapeutic agent, targets FLT3, VEGFR-2, PDGF receptors, and SCFR. In a phase II clinical trial focusing on monotherapy, midostaurin demonstrated a significant rate of partial responses among AML patients. Those randomly assigned with a FLT3 mutation (74% ITD) exhibited a higher partial response rate compared to their FLT3 wild-type counterparts (75% versus 43%, respectively). However, none of the AML patients achieved complete remission [43]. Cediranib (AZD2171) serves as a multi-targeted inhibitor of VEGF receptors, SCFR, and PDGF receptors. A phase II clinical trial involving cediranib yielded unsatisfactory results in elderly AML patients (aged over 60), leading to the cessation of the study after the initial stage of enrollment [44]. Notably, none of the patients exhibited a response to cediranib, even following induction chemotherapy.

Currently, there are no studies investigating VEGF-C targeted therapy in AML and its impact on AML blast cells. Recent findings indicate that in vitro VEGF-C-targeted therapy may represent a potential new differentiation treatment for pediatric AML [45]. Among the various therapies, bevacizumab in combination therapy has shown the most promising responses in AML patients regarding VEGF-targeted treatment. While midostaurin has proven to be the most effective monotherapy for AML patients, clinical trials are ongoing to explore its combination with conventional therapies. Elevated levels of VEGF have been associated with biological responses in patients with acute myeloid leukemia (AML). To better understand the relationship between VEGF and AML responses to VEGF-targeted therapies, further research is necessary. This research should involve the assessment of VEGF ligands and receptors both prior to and following treatment. Such a clinical study design may provide insights into the reasons why certain patients respond positively to VEGF-targeted therapies and derive benefits from them, while others do not [46].

References

[1] R. Ma, L. Wang, F. Yuan, S. Wang, Y. Liu, T. Fan, F. Wang. (2018). FABP7 promotes cell proliferation and survival in colon cancer through MEK/ERK signaling pathway. Biomedicine & Pharmacotherapy. 108: 119-129.

[2] Q. Liang, L. Du, R. Zhang, W. Kang, S. Ge. (2021). Stromal cell-derived factor-1/Exendin-4 cotherapy facilitates the proliferation, migration and osteogenic differentiation of human periodontal ligament stem cells in vitro and promotes periodontal bone regeneration in vivo. Cell Proliferation. 54(3): e12997.

[3] S. Yehudai-Reshef, S. Attias, T. Gabay, R. Sabah, T. Zuckerman. (2016). Bone Marrow Stromal Cells Derived at Diagnosis and Remission Preferentially Support AML Cell Proliferation in Vitro. Blood. 128(22): 1492.

[4] M. Stevens, S. Oltean. (2019). Modulation of receptor tyrosine kinase activity through alternative splicing of ligands and receptors in the VEGF-A/VEGFR axis. Cells. 8(4): 288.

[5] A. Wenden, Y. Yang, L. Chai, R.W. Wong. (2014). Salvia miltiorrhiza induces VEGF expression and regulates expression of VEGF receptors in osteoblastic cells. Phytotherapy Research. 28(5): 673-677.

[6] Q. Chen, J. Lin, Z. Deng, W. Qian. (2022). Exosomes derived from human umbilical cord mesenchymal stem cells protect against papain-induced emphysema by preventing apoptosis through activating VEGF-VEGFR2-mediated AKT and MEK/ERK pathways in rats. Regenerative Therapy. 21: 216-224.

[7] L.E. Lamb, J.C. Zarif, C.K. Miranti. (2011). The androgen receptor induces integrin α6β1 to promote prostate tumor cell survival via NF-κB and Bcl-xL Independently of PI3K signaling. Cancer research. 71(7): 2739-2749.

[8] K. Watari, T. Shibata, A. Shinoda, H. Abe, A. Kawahara, Y. Murakami, E. Oki, J. Akiba, Y. Maehara, M. Kuwano. (2019). N-myc downstream regulated gene 1 (NDRG1) is indispensable for VEGF-A-induced tumor angiogenesis through PLCγ/ERK signaling activation in vascular endothelial cells. Cancer research. 79(13_Supplement): 183-183.

[9] T. Sandrine, P. Van Dreden, G.T. Gerotziafas, A. Larsen. (2018). Chemoresistant Colorectal Cancer (CRC) Cells Show Increased Invasive Potential Which Is Part Is Mediated By VEGF-Signaling and Can be Attenuated By VEGF-Directed Agents. In American Society of Hematology Washington, DC. Blood. 132(Supplement 1): 4974-4974.

[10] B.Z. Carter, P.Y. Mak, W. Tao, Q. Zhang, V. Ruvolo, V.M. Kuruvilla, X. Wang, D.H. Mak, V.L. Battula, M. Konopleva. (2022). Maximal Activation of Apoptosis Signaling by Cotargeting Antiapoptotic Proteins in BH3 Mimetic–Resistant AML and AML Stem Cells. Molecular Cancer Therapeutics. 21(6): 879-889.

[11] I. You, E.C. Erickson, K.A. Donovan, N.A. Eleuteri, E.S. Fischer, N.S. Gray, A. Toker. (2020). Discovery of an AKT degrader with prolonged inhibition of downstream signaling. Cell chemical biology. 27(1): 66-73. e7.

[12] S. Ly, B. Yuan, S. Grimm, M. Andreeff, H.-J. Bühring, V.L. Battula. (2019). B7-H3, an immune checkpoint protein is overexpressed in AML and the blocking monoclonal antibodies enhance NK cell-mediated apoptosis in AML cells. Cancer research. 79(13_Supplement): 3248-3248.

[13] I. Evans. (2015). An overview of VEGF-mediated signal transduction. VEGF Signaling: Methods and Protocols. 91-120.

[14] S. Qazi, F.M. Uckun. (2022). Augmented expression of the IL3RA/CD123 gene in MLL/KMT2A-rearranged pediatric AML and infant ALL. Onco. 2(3): 245-263.

[15] N.U. Katyayini, S.L. Gordon, H.A. Kuusanmäki, P.A. Durán, J.M. Enserink, K. Wennerberg. (2023). AML-027 The LD-VenEx Phase II Clinical Trial: An ex Vivo Flow Cytometry Based-Drug Screening of AML Patient Samples. Clinical Lymphoma Myeloma and Leukemia. 23: S260-S261.

[16] K.A. Urtishak, B.W. Robinson, E.F. Rappaport, M.D. Sarezky, J.A. Biegel, K.E. Nichols, D.M. Wilmoth, L.S. Wang, J.W. Stern, C.A. Felix. (2016). Unique Familial MLL (KMT2A)-Rearranged Precursor B-Cell Infant Acute Lymphoblastic Leukemia in Non-twin Siblings. Pediatric Blood & Cancer. 63(7): 1175-1180.

[17] L. An, R. Hou, H. Guan, Z. Li, T. Wu, S. Liu. (2022). CD7 CAR-T therapy for an AML patient with CD7 expression. Hematology and Oncology Discovery. 1(1): 55-59.

[18] D. Darmadi, R.H. Ruslie, C. Pakpahan, Vascular Endothelial Growth Factor (VEGF) in Liver Disease. In *Tumor Angiogenesis and Modulators*, IntechOpen: 2022.

[19] A. Salajegheh, A. Salajegheh. (2016). Vascular endothelial growth factor (VEGF). Angiogenesis in Health, Disease and Malignancy. 363-374.

[20] F. Liss, M. Frech, Y. Wang, G. Giel, S. Fischer, C. Simon, L.M. Weber, A. Nist, T. Stiewe, A. Neubauer. (2021). IRF8 is an AML-specific susceptibility factor that regulates signaling pathways and proliferation of AML cells. Cancers. 13(4): 764.

[21] D. Liu, B. Shi, W. Zhou, G. Tao. (2023). Exosomes from hypoxia-conditioned apical papilla stem cells accelerate angiogenesis in vitro through Notch/JAG1/VEGF signaling. Tissue and Cell. 84: 102197.

[22] C. Beham-Schmid, A. Schmitt-Graeff, C. Beham-Schmid, A. Schmitt-Graeff. (2020). Bone Changes Found in Bone Marrow Biopsies. Bone Marrow Biopsy Pathology: A Practical Guide. 81-90.

[23] M.Y. Jeng, D. Kong, R. Rajalingam, R.J. Lin, R.L. Olin. (2023). Lack of disease control remains a major barrier to transplant for older patients with AML. Bone marrow transplantation. 58(9): 1054-1056.

[24] A.C. Przespolewski, H.-H. Hsiao, S. Rosario, T. Cronin, M. Fos, P. Singh, E.S. Wang. (2023). Differences within the Immune Microenvironment May Account for Poorer Outcomes in African American AML Patients Compared to European American Patients with AML. Blood. 142: 5979.

[25] E.S. Wang, A. Sobczyk, J.M. Marinaro, M. Wetzler, L. Tian, G. Deeb. (2007). VEGF-A, VEGF-C, and CD31 Expression by Leukemia Cells Are Prognostic Factors for Overall Survival in Acute Myeloid Leukemia (AML). Blood. 110(11): 2392.

[26] Y. Kanno, E. Shu, H. Niwa, M. Seishima, K.-i. Ozaki. (2021). MicroRNA-30c attenuates fibrosis progression and vascular dysfunction in systemic sclerosis model mice. Molecular Biology Reports. 48(4): 3431-3437.

[27] A. Abdalla, C. Murali, A. Amin. (2022). Safranal inhibits angiogenesis via targeting HIF-1α/VEGF machinery: in vitro and ex vivo insights. Frontiers in oncology. 11: 789172.

[28] Q. Sun, T. Zhang, Q. Xiao, B. Mei, X. Zhang. (2022). Procyanidin B2 inhibits angiogenesis and cell growth in oral squamous cell carcinoma cells through the vascular endothelial growth factor (VEGF)/VEGF receptor 2 (VEGFR2) pathway. Bioengineered. 13(3): 6500-6508.

[29] S.Y. Heazlewood, S.K. Nilsson, B. Cao. (2020). The aging hematopoietic stem cell niche. Advances in Stem Cells and their Niches. 4: 1-23.

[30] H. Liu, L. Liu, C.J. Rosen. (2023). PTH and the Regulation of Mesenchymal Cells within the Bone Marrow Niche. Cells. 13(5): 406.

[31] A. Saghatelyan. (2023). Calcium signaling as an integrator and decoder of niche factors to control somatic stem cell quiescence and activation. The FEBS Journal. 290(3): 677-683.

[32] P. Kuri, G. Rice, P. Rompolas. (2019). Molecular aspects governing epidermal stem cell niches. In *Advances in Stem Cells and their Niches*. Elsevier. 3: 73-113.

[33] X. Zhao, P. Cui, G. Hu, C. Wang, L. Jiang, J. Zhao, J. Xu, X. Zhang. (2020). PIP5k1 β controls bone homeostasis through modulating both osteoclast and osteoblast differentiation. Journal of molecular cell biology. 12(1): 55-70.

[34] L. Jin, L. Wu. (2018). Recent advances in characterization of pre-leukemic/leukemic stem cells in acute myeloid leukemia. Cellular and Molecular Medicine Research. 1(1): 12-19.

[35] S. Kim, J. Choi. (2022). Restoring NK cell functions in AML relapse. Blood, The Journal of the American Society of Hematology. 140(26): 2765-2766.

[36] C.L. Pritchard, S.Y. Heazlewood, B. Cao. (2021). Acute lymphoblastic leukemia and the bone marrow microenvironment. In *Advances in Stem Cells and their Niches*. Elsevier. 5: 1-34.

[37] J.A. Taylor, C.J. Benwell, S.D. Robinson. (2022). Using Immortalized Endothelial Cells to Study the Roles of Adhesion Molecules in VEGF-Induced Signaling. In *VEGF Signaling: Methods and Protocols*. Springer. 133-141.

[38] K.-Y. Jeong, M. Park. (2021). Poly adenosine diphosphate-ribosylation, a promising target for colorectal cancer treatment. World Journal of Gastrointestinal Oncology. 13(6): 574.

[39] J. Fallah, R.T. Chaudhary, L.R. Rogers, W. Wei, C.J. Brewer, D.M. Peereboom, M.S. Ahluwalia. (2020). Clinical outcomes of the combination of bevacizumab and ttfields in patients with recurrent glioblastoma: Results of a phase II clinical trial. In American Society of Clinical Oncology. 38(15_suppl): 2537-2537.

[40] E.C. Liang, C. Chen, R. Lu, G.N. Mannis, L. Muffly. (2022). Correction to: Measurable residual disease status and FLT3 inhibitor therapy in patients with FLT3-ITD mutated AML following allogeneic hematopoietic cell transplantation. Bone marrow transplantation. 57(4): 694-694.

[41] L. Zhao, S. Zuo, K. Xing, X. Yue, H. Zhang, J. Zhang, S. Waxman, Y. Jing. (2023). Developing dual FLT3/MNK inhibitors to overcome sorafenib resistance in FLT3-ITD AML cells. Cancer research. 84(6_Supplement): 4489-4489.

[42] C. Zhou, F. Zheng, L. Xu, X. Zhang, Y. Chang, X.-D. Mo, Y. Sun, Y. Wang, X.-J. Huang. (2022). The FLT3-ITD Allelic Ratio and NPM1 Mutation Do Not Impact Outcomes in AML Patients with FLT3-ITD after Allo-HSCT: A Retrospective Propensity-Score Matching Study. Blood. 140(Supplement 1): 7689-7690.

[43] J.-w. Wang, X.-G. Yang, L.-H. Xu. (2023). NUP98::NSD1 and FLT3/ITD co-expression is an independent predictor of poor prognosis in pediatric AML patients. BMC pediatrics. 24(1): 547.

[44] M.-J. Kim, J.-Y. Byun, C.-H. Yun, I.-C. Park, K.-H. Lee, S.-J. Lee. (2008). c-Src-p38 mitogen-activated protein kinase signaling is required for Akt activation in response to ionizing radiation. Molecular Cancer Research. 6(12): 1872-1880.

[45] D. Reinhardt, C.M. Zwaan, A. Hoenekopp, J. Niolat, S. Ifrah, F. Noel-Baron, F. Locatelli. (2019). Phase II study of midostaurin+ chemotherapy in pediatric patients with untreated, newly diagnosed, FLT3-mutated acute myeloid leukemia (AML). Blood. 134 (Supplement 1): 3835.

[46] Y. Kang, H. Li, Y. Liu, Z. Li. (2023). Regulation of VEGF-A expression and VEGF-A-targeted therapy in malignant tumors. Journal of Cancer Research and Clinical Oncology. 150(5): 1-10.