Review Article

The Effect of Stem Cells and Vascular Endothelial Growth Factor on Cancer Angiogenesis

Nahid Moradi-Gharibvand[1,2], Batool Hashemibeni[2]

[1]Abadan University of Medical Sciences, Abadan, Iran, [2]Department of Anatomical Sciences and Molecular Biology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

The formation of new vessels from pre-existing vessels is known as angiogenesis. The process is controlled by stimuli and inhibitors. Angiogenesis starts as a result of the unbalance of these factors, where balance has a tendency toward the stimulus. One of the most important factors promoting angiogenesis is the vascular endothelial growth factor (VEGF). In addition to being involved in vascular regeneration in normal tissues, VEGF also takes part in tumor tissue angiogenesis. These factors affect endothelial cells (ECs) directly as well as differentiate tumor cells from endothelial cells and play an active role in tumor tissue angiogenesis. Angiogenesis partakes in the growth and proliferation of tumor tissue. Because anti-angiogenic treatment is favorable in existing cancer therapies, the potential benefits should be considered. One of these new therapies is cell therapy using mesenchymal stem cells (MSCs). Research on MSCs remains controversial because much of the earlier research on MSCs has shown their effectiveness, but more recent research has identified harmful effects of these cells. This article reviews the role of stem cells and their secretions in the angiogenesis of tumor tissues.

Keywords: Angiogenesis, cancer, mesenchymal stem cells, vascular endothelial growth factor

Address for correspondence: Prof. Batool Hashemibeni, Department of Anatomical Sciences and Molecular Biology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: hashemibeni.batool69@gmail.com
Submitted: 02-Dec-2021; **Revised:** 17-Apr-2022; **Accepted:** 24-Apr-2022; **Published:** 15-May-2023

Introduction

Angiogenesis is a highly complex process involving a range of cell types and signaling pathways. Neovascularization requires the activation and proliferation of endothelial cells (ECs). Activation of Ecs by factors such as the vascular endothelial growth factor (VEGF) gives rise to new blood vessel formation. Studies have indicated that VEGFs induce angiogenesis *in vitro* as well as in vivo.[1-4] In addition to normal tissue, angiogenesis can also occur in tumor tissue.[5-9] The development of new vessels begins in pre-malignant conditions as the demand for oxygen and nutrients by the growing cancer cell mass increases.[10] The developing vessels in tumors are unlike normal vessels. In tumors, vessels are irregular in diameter, have thin walls, and are leaky.[11,12] Cancer can be treated with surgery, chemotherapy, or radiation therapy.[13] The abnormal vascularity can make tumors resistant to chemotherapeutic agents. Anti-angiogenic therapy suppresses tumor growth.[14] One of the new methods for treating cancer is the use of stem cells.[15] Some studies have indicated that stem cells have therapeutic effects on tumor tissue, whereas others have provided evidence of the negative effects of these cells.[16] Mesenchymal stem cells (MSCs) are involved in tumorigenesis, including induction of angiogenesis,[17] stimulation of epithelial–mesenchymal transition (EMT) and tumor metastasis,[18] and inhibition of tumor cell apoptosis.[19] MSCs suppress tumor growth by inhibiting angiogenesis,[20] inducing cell cycle arrest and apoptosis[21] [Figure 1]. This article provides an overview of the role of stem cells and vascular endothelial growth factors in cancer angiogenesis.

Data Acquisition

Scientific publications, journals, and textbooks were excluded from the search. *In vivo* and *in vitro* studies were both evaluated

Access this article online

Quick Response Code:

Website: www.advbiores.net

DOI: 10.4103/abr.abr_378_21

How to cite this article: Moradi-Gharibvand N, Hashemibeni B. The effect of stem cells and vascular endothelial growth factor on cancer angiogenesis. Adv Biomed Res 2023;12:124.

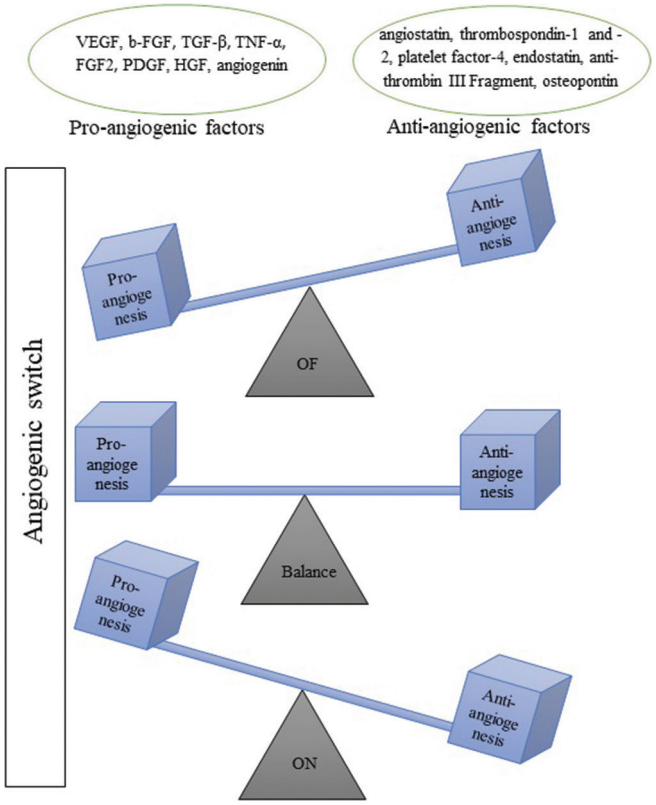

Figure 1: Schematic image of angiogenesis switch

equally. Two independent researchers reviewed the included data, abstracts, titles, and full texts to determine their relevance for inclusion in the study. The search terms used were "cancer," "angiogenesis," "stem cell," "paracrine secretions," "vascular endothelial growth factor," TGF-β, TGF-α, FGF2, PDGF, BFGF, granulocyte colony-stimulating factor, granulocyte colony-stimulating factor, interleukin-8 (IL-8), hepatocyte growth factor, epidermal growth factor, and other factors. No methodological search filter was applied. Scientists in related fields were contacted to assess the findings and conclusions of the related literature. In the event that additional information was needed, the authors were contacted whenever possible.

Angiogenesis

New blood vessels develop through vasculogenesis, angiogenesis, arteriogenesis, and collateral growth.[17] Angiogenesis is known as the process by which new blood vessels form from pre-existing blood vessels.[5] It is a complex four-step process involving the destruction of the basement membrane, the activation of ECs, the proliferation of ECs, and the continuation of the process under the influence of angiogenic (pro-angiogenic) factors.[18] The reason for the complexity of the process is the requirement for a variety of biological interactions, including several cell types, angiogenic factors, and extracellular matrix. Typically, angiogenesis occurs in the fetal and adult stages. In adulthood, it plays a vital role in wound healing and the female reproductive cycle, such as ovulation, follicle development, corpus luteum formation, progesterone release, endometrial growth, and embryo implantation. In addition, this process plays an important role in the progression of cancer.[5,19,20] In 1971, Folkman was the first person to propose that tumor growth depends on the induction of angiogenesis. Subsequently, studies have shown the essential role of angiogenesis in tumor metastasis because it can provide the basis for tumor cells to metastasize farther away.[20] It also diminishes tumor access to chemotherapy drugs.[14] Many factors are involved in regulating angiogenesis, which are secreted by cells such as ECs, cancer cells, stromal cells, blood, and extracellular matrix.[5] These factors consist of pro-angiogenic factors including BFGF, VEGF,[21,22] TGF-β, TNF-α, FGF2, PDGF, epidermal growth factor, angiogenin, angiopoietin,[23] granulocyte colony-stimulating factor, interleukin-8 (IL-8),[24] and hepatocyte growth factor.[25] Anti-angiogenic factors consist of angiostatin, thrombospondin-1 and -2, platelet factor-4, endostatin, anti-thrombin III fragment, osteopontin, collagen, kininogen domains, vasostatin, calreticulin, soluble, and the tissue inhibitors of metalloproteinases.[5] Interaction and balance between pro-angiogenic and anti-angiogenic factors regulate angiogenesis[26] [Figure 1]. When the balance between the factors is disturbed in such a way that the balance moves toward the stimulus, the ECs become active, a change in the expression of genes and proteins occurs, and eventually, angiogenesis starts. Therefore, in angiogenesis, it is not sufficient to increase pro-angiogenic factors, but also a reduction in the expression of anti-angiogenic factors is required.[20] Hypoxia stimulates angiogenesis in tumor tissue by increasing the expression of the VEGF and other angiogenic stimuli.[5] The VEGF plays a major role in pathological angiogenesis, such as macular degeneration, diabetic retinopathy, inflammatory processes, tumor growth, and metastasis.[27]

Effect of the Vegf on Cancer Cells

The role of the VEGF in tumor angiogenesis was established via stimulation of VEGFRs on the tumor endothelium. However, there is increasing evidence that the VEGF may have an additional role in cancer via the stimulation of VEGFRs in tumor cells.[28] Several studies have demonstrated the presence of VEGFRs in cancer cells, such as breast cancer, pancreatic, prostate, and lung cancer cells.[29-32] Therefore, the expression of VEGFRs by tumor cells involves the major role of VEGF/VEGFR signaling in these tumors. Yanga *et al*. (2015) demonstrated that VEGF-B is a vascular remodeling factor promoting cancer metastasis and that targeting VEGF-B may be an important therapeutic approach for cancer metastasis[33] Positive regulation of the VEGF/neuropilin-1 axis in breast cancer tumorigenesis and metastasis may be associated with enhanced EMT and NF-B and catenin signaling.[34] Zhao *et al*. (2015) showed that VEGF promotes tumor-initiating cells' (primary breast and lung cancers) self-renewal through VEGFR-2/STAT3 signaling[35] Myeloid-derived suppressor cells (MDSCs) induced through VEGF signaling play

important roles in tumor immune evasion in ovarian cancer, and the targeting of VEGF-induced MDSCs represents a promising treatment for ovarian cancer.[36] Kong *et al*. (2020) showed that VEGF-C mediates tumor growth and metastasis by promoting EMT-epithelial breast cancer cells.[37] Tomida *et al*. (2018) indicated that VEGF/VEGF-R inhibitors directly act on colon cancer cells and activate their evasive adaptation via various mechanisms.[38]

Effect of Mscs on Cancer Cells

One of the important steps in angiogenesis is the differentiation of progenitor ECs into ECs and the proliferation of the resulting cells. Several different signaling control this process.[5] The tumor microenvironment consists of different types of cells that affect tumor angiogenesis.[28] A lack of balance between angiogenic factors results in the pathogenesis of many diseases. For example, insufficient angiogenesis causes ischemic disease, and high levels of it can lead to cancer.[29] Small vessels only contain ECs, but larger vessels contain mural cells (pericyte and vascular smooth muscle).[17] Nowadays, angiogenic therapy is just as important as surgical treatments, chemotherapy, and radiation therapy. Cancer anti-angiogenesis treatments have an advantage over chemotherapy. They do not cause toxicity and have a synergistic effect in the use of other treatments such as chemotherapy, radiation therapy, and gene therapy.[20] Therefore, the advantage of anti-angiogenesis therapy resulted in promoting researchers to come up with new anti-angiogenesis treatments for cancer. One of the new methods in the treatment of cancer is the use of MSCs.[15]

One of the cells used to treat breast cancer is the stem cell.[30] Stem cells are a group of undifferentiated cells that can discriminate into different types of specialized cells.[31] MSCs are a population of stem cells with self-renewal and multipotentiality that hold great promise for regenerative medicine.[32] MSCs move to tumor sites and then incorporate between the tumor stroma.[34,39] These cells interact with cancer cells.[40,36] MSCs have been isolated from bone marrow, adipose tissue, and umbilical cord blood. MSCs promote tumor growth and suggest that the crosstalk between tumor cells and MSCs increased the expression of pro-angiogenic factors, which may have induced tumor cell proliferation and angiogenesis thereby increasing solid tumor growth.[41] Adipose tissue-derived stem cells (ADSCs) significantly promoted the proliferation and invasion of ovarian cancer cell (EOC) in both direct and indirect co-culture assays. In addition, after co-culture with ADSCs, EOC cells secreted higher levels of matrix metalloproteinases (MMPs), and inhibition of MMP2 and MMP9 partially relieved the tumor-promoting effects of ADSCs in vitro. Omental ADSCs play a promotive role during ovarian cancer progression.[42] IL-8 secreted by MSCs promotes colorectal cancer angiogenesis and growth and can therefore serve as a potential novel therapeutic target.[43] MSCs promote the progression of colorectal cancer via AMPK/mTOR-mediated NF-κB activation.[44] CXCL1/8 secreted by hADSCs could promote breast cancer angiogenesis and therefore provide better understanding of safety concerns regarding the clinical application of hADSCs and suggestions for further novel therapeutic options.[45] Human adipose-derived mesenchymal stromal cells may promote progression and metastatic spread in breast cancer through a switch to a more malignant phenotype with worse prognosis.[46]

MSCs and Their Differentiation into ECs

To create a vascular network, it is necessary to have a source of ECs, which are usually taken from blood vessels and umbilical cords. Because it is difficult to access these resources, the production of these cells is very limited. Therefore, searching for a better source to obtain these cells is essential. Stem cells are often used to differentiate into EC. Angiogenic factors are frequently used to differentiate MSCs from ECs.[47] MSCs can have quasi-endothelial properties in pro-angiogenic environments,[48] allowing them to participate in the processes of proliferation, migration, endothelial tube formation, and ultimately angiogenesis.[49] Expression of endothelial markers shows MSC differentiation into ECs.[47] *In vitro* and *in vivo* studies have shown that MSCs that invade ECs are able to form blood vessels.[47,49] MSCs could potentiate angiogenesis due to their ability to migrate and create capillary-like structures, and this is achieved through growth factors.[50] MSCs present in cancerous tissue stroma play a key role in the proliferation of cancer cells, metastases, and resistance to chemotherapy.[51] MSCs are found in many tissues such as the umbilical cord, peripheral blood, skeletal muscle, adipose tissue,[52] dermis,[53] and synovial membrane.[54] MSCs are positive for CD105, CD73, and CD90, and negative for CD45, CD34, CD14, or CD11b, CD79, or CD19, and HLA-DR molecules.[55,56] The umbilical cord MSCs do not express MHC types 1 and 2, so they are good candidates for clinical use.[57] Studies have shown that MSCs stimulate the growth and metastasis of tumors, whereas other studies have reported that MSCs suppress tumor growth and metastasis.[16,39] However, in connection with the role of tumor suppression, MSCs can suppress tumor growth through the AKT signaling pathway.[58] MSCs can also prevent cancer of human liver cancer cells and breast cancer cells by inhibiting the Wnt signaling pathway.[46,59] In addition, MSC inhibits tumor growth through anti-angiogenic activity,[60] low expression of the X-dependent apoptotic protein inhibitor (XIAP),[61] PI3K signaling pathway molecules,[58] and inhibition of cell cycle progression.[62] MSCs secrete angiopoietin 2, VEGF, IL8, BFGF,[63] PDGF,[64] and IL6.[65] Uterine endometrial stem cells secrete angiogenic factors such as MMP3, MMP10, GM CSF, angiopoietin 2, and PDGF-BB.[66] Stem cells derived from fat, uterine endometrium, and placenta secrete angiogenic factors including VEGF, HGF, BFGF, TGFB, IGF1, PDGF, MMP3, and MMP10.[64,67] MSCs isolated from different tissues, depending on their origin, may have different potentials for clinical applications and there are differences in regression.[64] ADSCs secrete more angiogenic agents and are more capable

of forming new blood vessels than endometrial and umbilical cord-derived stem cells.[68] Likewise, fat-derived MSCs have more vascular potential than bone-derived MSCs and umbilical cords.[69,70] ADSCs promote the development of breast cancer by releasing cytokines such as CXCL1 and CXCL8.[43,47-68,70-72] MSCs with IL6 secretion increase endothelin 1 in the tumor, thereby stimulating ECs and causing angiogenesis.[65] ADSCs secrete angiogenic factors such as HGF.[64] ADSC are affected by containing FGF2 receptors and are differentiated into ECs.[73] A 2017 study found that direct cell-to-cell contact between stem cells and ECs caused stem cells to differentiate into ECs.[74] TGF-β also differentiates stem cells into ECs and lymph vessels.[75] In addition to growth factors, the suitability and effectiveness of the culture medium is a complementary approach to cell growth because it can have a major impact on cellular behavior and cell differentiation.[47] The most common ship environment used for ECs is EGM2. When bone marrow-derived stem cells are cultured in the medium containing EGM2, the expression of endothelial markers such as CD31, VWF, and VEGFR2 increases.[76] Factors such as KDR, CD34, CD31, FLT1, V-cadherin, and VCAM1 are some of the signs that differentiate ECs from stem cells.[77] SOD1 is a factor secreted by MSCs through paracrine pathways that improves the damage and dysfunction of ECs due to lung cancer chemotherapy.[78] FGF is a growth factor involved in angiogenesis, wound healing, embryonic development, and a number of other endocrine signaling pathways. Cultivated ADSCs in the culture medium containing FGF showed that ADSCs were differentiated into ECs, and markers represent ECs.[79] FGF has a multiplier effect on MSCs and, most prominently, controls ADSC differentiation and plays a role in the migration of ECs.[79] Zhang *et al*. have found that an EGM2 culture medium containing VEGF increased the levels of the mRNA VEGF and eNos in ADSCs. The BFGF also stimulates ECs.[71,62,63,69,70,73-78,80]

VEGF: A Key Factor in Cancer Angiogenesis and MSC Differentiation into ECs

The VEGF is a major factor in angiogenesis, stimulating the growth of new blood vessels from previous vessels and providing access to oxygen and nutrients for tumors.[81] The VEGF is an important pro-angiogenic factor in breast cancer and is involved in the growth, survival, and invasion of tumor cells through autocrine pathways.[82] Studies have shown that the suppression of tumor suppressor genes such as P53 and the activation of oncogenic genes such as Kras, Hras, v-Src, human epidermal growth factor HER 2, HER1/EGFR, FOS, trkB, V-p3K, PTTG1, and Bcl2 increase VEGF expression in tumor cells.[83] Family members of the VEGF include five glycoproteins (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E) and placenta growth factors 1, 2, and 3. VEGF-A is the most important member of the VEGF family, which mainly targets ECs.[82] PDGF and HIF-1α induce VEGF expression in the tumor cells.[84] The VEGF is then attached to its receptor on the surface of ECs, causing the cells to grow and proliferate. However, it increases MMP expression in tumor cells.[82] There is also a VEGF receptor on tumor cells.[85] This growth factor is involved in the migration, proliferation, and differentiation of MSCs into ECs.[86] The study by Sami G in 2017 showed that the VEGF is involved in the differentiation of MSCs into ECs.[87] The study by SG Ball *et al*. revealed that the VEGF stimulates the proliferation and migration of MSCs by activating the PDGF (5).[88] One of the signaling pathways through which the VEGF can play a role in distinguishing MSCs from ECs is MAPK, which is an intracellular pathway.[89] ERK1/2-c-jun NH2 and P38 are members of the cascade MAPK.[90] When VEGFR2 is activated, PLC-γ phosphorylates and activates the MAPK signaling pathway.[87] In 2008, J Xu demonstrated that VEGF mediates the differentiation of bone-derived MSCs into ECs by activating the MAPK pathway.[91] VEGF is the most common growth factor for distinguishing bone marrow MSCs from ECs. The NFKB pathway regulates VEGF secretion from MSCs. Inhibition of this pathway reduces its secretion.[6] The VEGF, along with FGF, induces c-Kit, IL-3R, M-CSF, CSFR1, Flt3L, Flt3, and CXCR4 receptors in ECs, resulting in an increased ability of the VEGF and FGF to form vascular tubes. STAT3 and P38 MAPK pathways cause VEGF secretion from MSCs.[7] The Rho family plays an important role in the migration and angiogenesis of VEGF-induced ECs. The VEGF activates the Rho/ROCK messaging pathway and stimulates nuclear translocation of myocardin-related transcription factor-A (MRTE-A) and differentiates MSCs into ECs.[7] Therefore, VEGF production by MSCs may be a crucial factor responsible for the angiogenic potential of MSCs and can promote angiogenesis in cancer.[79-91]

Conclusions

Whereas the potential of MSCs to induce angiogenesis leading to tissue regeneration has been well documented in preclinical and clinical studies, the effect of paracrine factors secreted by these MSCs is currently under investigation. Considering cancer as a common cause of death worldwide, the use of stem cells to treat the disease requires serious contemplations and observations. Therefore, more studies should be done in relation to the secretory factors of stem cells and the mechanism of action of these factors.

Abbreviations are used: VEGF: vascular endothelial growth factor, ECs: endothelial cells, MSCs: mesenchymal stem cells, TGF-β: transforming growth factor-beta, TGF-α: transforming growth factor-alpha, FGF2: fibroblast growth factor 2, PDGF: platelet-derived growth factor, BFGF: basic fibroblast growth factor, TNF-α: tumor necrosis factor α, TIMPs: tissue inhibitors of metalloproteinases, CD: cluster differentiation, MHC: major histocompatibility complex, HLA-DR: human leukocyte antigen—DR isotype, XIAP: X-dependent apoptotic protein inhibitor, PI3 K: phosphatidylinositol-3-kinase, MMP3: matrix metalloproteinases, GM CSF: granulocyte–macrophage

colony-stimulating factor, PDGF-BB: platelet-derived growth factor-BB, HGF: hepatocyte growth factor, IGF1: insulin-like growth factor, CXCL: chemokine (C-X-C motif) ligand, ADSC: adipose tissue-derived stem cells, EGM: endothelial growth medium, vWF: von Willebrand factor, VCAM: vascular cell adhesion molecule, SOD1: superoxide dismutase, EGM2: endothelial cell growth medium 2, MAPK: mitogen-activated protein kinase, ERK1: extracellular signal-regulated kinase.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Olfert IM, Howlett RA, Wagner PD, Breen EC. Myocyte vascular endothelial growth factor is required for exercise-induced skeletal muscle angiogenesis. Am J Physiol Regul Integr Comp Physiol 2010;299:R1059-67.
2. Karali E, Bellou S, Stellas D, Klinakis A, Murphy C, Fotsis T. VEGF signals through ATF6 and PERK to promote endothelial cell survival and angiogenesis in the absence of ER stress. Mol Cell 2014;54:559-72.
3. Silva EA, Mooney DJ. Effects of VEGF temporal and spatial presentation on angiogenesis. Biomaterials 2010;31:1235-41.
4. Pinto MP, Badtke MM, Dudevoir ML, Harrell JC, Jacobsen BM, Horwitz KB. Vascular endothelial growth factor secreted by activated stroma enhances angiogenesis and hormone-independent growth of estrogen receptor–positive breast cancer. Cancer Res 2010;70:2655-64.
5. Rajabi M, Mousa SA. The role of angiogenesis in cancer treatment. Biomedicines 2017;5:34.
6. Cook KM, Figg WD. Angiogenesis inhibitors: Current strategies and future prospects. CA Cancer J Clin 2010;60:222-43.
7. Vasudev NS, Reynolds AR. Anti-angiogenic therapy for cancer: Current progress, unresolved questions and future directions. Angiogenesis 2014;17:471-94.
8. Welti J, Loges S, Dimmeler S, Carmeliet P. Recent molecular discoveries in angiogenesis and antiangiogenic therapies in cancer. J Clin Invest 2013;123:3190-200.
9. Hellsten Y, Hoier B. Capillary growth in human skeletal muscle: Physiological factors and the balance between pro-angiogenic and angiostatic factors. Biochem Soc Trans 2014;42:1616-22.
10. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996;86:353-64.
11. Badraoui R, Boubakri M, Bedbabiss M, Ben-Nasr H, Rebai T. Walker 256/B malignant breast cancer cells improve femur angioarchitecture and disrupt hematological parameters in a rat model of tumor osteolysis. Tumor Biol 2014;35:3663-70.
12. Jain RK. Normalizing tumor microenvironment to treat cancer: Bench to bedside to biomarkers. J Clin Oncol 2013;31:2205-18.
13. Waks AG, Winer EP. Breast cancer treatment: A review. JAMA 2019;321:288-300.
14. Teng L-S, Jin K-T, He K-F, Wang H-H, Cao J, Yu D-C. Advances in combination of antiangiogenic agents targeting VEGF-binding and conventional chemotherapy and radiation for cancer treatment. J Chin Med Assoc 2010;73:281-8.
15. Zhang Q, Xiang W, Yi D-Y, Xue B-Z, Wen W-W, Abdelmaksoud A, *et al*. Current status and potential challenges of mesenchymal stem cell-based therapy for malignant gliomas. Stem Cell Res Ther 2018;9:1-9.
16. Klopp AH, Gupta A, Spaeth E, Andreeff M, Marini III F. Concise review: Dissecting a discrepancy in the literature: Do mesenchymal stem cells support or suppress tumor growth? Stem Cells 2011;29:11-9.
17. Fang S, Salven P. Stem cells in tumor angiogenesis. J Mol Cell Cardiol 2011;50:290-5.
18. Viallard C, Larrivée B. Tumor angiogenesis and vascular normalization: Alternative therapeutic targets. Angiogenesis 2017;20:409-26.
19. Tahergorabi Z, Khazaei M. A review on angiogenesis and its assays. Iran J Basic Med Sci 2012;15:1110-26.
20. Tiwari M. Apoptosis, angiogenesis and cancer therapies. J Cancer Ther Res 2012;1:3.
21. Chao Y, Wu C-Y, Kuo C-Y, Wang JP, Luo J-C, Kao C-H, *et al*. Cytokines are associated with postembolization fever and survival in hepatocellular carcinoma patients receiving transcatheter arterial chemoembolization. Hepatol Int 2013;7:883-92.
22. Petrillo M, Patella F, Pesapane F, Suter MB, Ierardi AM, Angileri SA, *et al*. Hypoxia and tumor angiogenesis in the era of hepatocellular carcinoma transarterial loco-regional treatments. Future Oncol 2018;14:2957-67.
23. Zimta A-A, Baru O, Badea M, Buduru SD, Berindan-Neagoe I. The role of angiogenesis and pro-angiogenic exosomes in regenerative dentistry. Int J Mol Sci 2019;20:406.
24. Gatsiou A, Sopova K, Tselepis A, Stellos K. Interleukin-17A triggers the release of platelet-derived factors driving vascular endothelial cells toward a pro-angiogenic state. Cells 2021;10:1855.
25. Fan G-C. Hypoxic exosomes promote angiogenesis. Blood J Am Soc Hematol 2014;124:3669-70.
26. Goel S, Wong AH-K, Jain RK. Vascular normalization as a therapeutic strategy for malignant and nonmalignant disease. Cold Spring Harb Perspect Med 2012;2:a006486.
27. Melincovici CS, Boşca AB, Şuşman S, Mărginean M, Mihu C, Istrate M, *et al*. Vascular endothelial growth factor (VEGF)-key factor in normal and pathological angiogenesis. Rom J Morphol Embryol 2018;59:455-67.
28. Weis SM, Cheresh DA. Tumor angiogenesis: Molecular pathways and therapeutic targets. Nat Med 2011;17:1359-70.
29. Herbert SP, Stainier DY. Molecular control of endothelial cell behaviour during blood vessel morphogenesis. Nat Rev Mol Cell Biol 2011;12:551-64.
30. Chu D-T, Nguyen TT, Tien NLB, Tran D-K, Jeong J-H, Anh PG, *et al*. Recent progress of stem cell therapy in cancer treatment: Molecular mechanisms and potential applications. Cells 2020;9:563.
31. Mirabdollahi M, Haghjooyjavanmard S, Sadeghi-Aliabadi H. An anticancer effect of umbilical cord-derived mesenchymal stem cell secretome on the breast cancer cell line. Cell Tissue Bank 2019;20:423-34.
32. Yang C, Lei D, Ouyang W, Ren J, Li H, Hu J, *et al*. Conditioned media from human adipose tissue-derived mesenchymal stem cells and umbilical cord-derived mesenchymal stem cells efficiently induced the apoptosis and differentiation in human glioma cell lines in vitro. BioMed Res Int 2014;2014.
33. Yang X, Zhang Y, Hosaka K, Andersson P, Wang J, Tholander F, *et al*. VEGF-B promotes cancer metastasis through a VEGF-A–independent mechanism and serves as a marker of poor prognosis for cancer patients. Proceedings National Academy Sci 2015;112:E2900-E9.
34. Jiang Y, Wells A, Sylakowski K, Clark AM, Ma B. Adult stem cell functioning in the tumor micro-environment. Int J Mol Sci 2019;20:2566.
35. Zhao D, Pan C, Sun J, Gilbert C, Drews-Elger K, Azzam D, *et al*. VEGF drives cancer-initiating stem cells through VEGFR-2/Stat3 signaling to upregulate Myc and Sox2. Oncogene 2015;34:3107-19.
36. Mandel K, Yang Y, Schambach A, Glage S, Otte A, Hass R. Mesenchymal stem cells directly interact with breast cancer cells and promote tumor cell growth *in vitro* and in vivo. Stem Cells Dev 2013;22:3114-27.
37. Kong D, Zhou H, Neelakantan D, Hughes CJ, Hsu JY, Srinivasan RR, *et al*. VEGF-C mediates tumor growth and metastasis through promoting EMT-epithelial breast cancer cell crosstalk. Oncogene 2021;40:964-79.
38. Tomida C, Yamagishi N, Nagano H, Uchida T, Ohno A, Hirasaka K, *et al*. VEGF pathway-targeting drugs induce evasive adaptation by activation of neuropilin-1/cMet in colon cancer cells. Int J Oncol 2018;52:1350-62.
39. Rhee KJ, Lee JI, Eom YW. Mesenchymal stem cell-mediated effects of tumor support or suppression. Int J Mol Sci 2015;16:30015-33.
40. Melzer C, Yang Y, Hass R. Interaction of MSC with tumor cells. Cell Commun Signal 2016;14:1-12.
41. Zhang T, Lee YW, Rui YF, Cheng TY, Jiang XH, Li G. Bone marrow-derived mesenchymal stem cells promote growth and angiogenesis of breast and prostate tumors. Stem Cell Res Ther 2013;4:1-15.

42. Chu Y, Tang H, Guo Y, Guo J, Huang B, Fang F, *et al*. Adipose-derived mesenchymal stem cells promote cell proliferation and invasion of epithelial ovarian cancer. Exp Cell Res 2015;337:16-27.
43. Wang J, Wang Y, Wang S, Cai J, Shi J, Sui X, *et al*. Bone marrow-derived mesenchymal stem cell-secreted IL-8 promotes the angiogenesis and growth of colorectal cancer. Oncotarget 2015;6:42825-37.
44. Domenis R, Cifù A, Quaglia S, Pistis C, Moretti M, Vicario A, *et al*. Pro inflammatory stimuli enhance the immunosuppressive functions of adipose mesenchymal stem cells-derived exosomes. Sci Rep 2018;8:1-11.
45. Wang Y, Liu J, Jiang Q, Deng J, Xu F, Chen X, *et al*. Human adipose-derived mesenchymal stem cell-secreted CXCL1 and CXCL8 facilitate breast tumor growth by promoting angiogenesis. Stem Cells 2017;35:2060-70.
46. Kamat P, Schweizer R, Kaenel P, Salemi S, Calcagni M, Giovanoli P, *et al*. Human adipose-derived mesenchymal stromal cells may promote breast cancer progression and metastatic spread. Plastic Reconstr Surg 2015;136:76-84.
47. Takeda K, Sowa Y, Nishino K, Itoh K, Fushiki S. Adipose-derived stem cells promote proliferation, migration, and tube formation of lymphatic endothelial cells *in vitro* by secreting lymphangiogenic factors. Ann Plastic Surg 2015;74:728-36.
48. Kwon HM, Hur S-M, Park K-Y, Kim C-K, Kim Y-M, Kim H-S, *et al*. Multiple paracrine factors secreted by mesenchymal stem cells contribute to angiogenesis. Vascul Pharmacol 2014;63:19-28.
49. Comşa S, Ciuculescu F, Raica M. Mesenchymal stem cell-tumor cell cooperation in breast cancer vasculogenesis. Mol Med Rep 2012;5:1175-80.
50. Brown C, McKee C, Bakshi S, Walker K, Hakman E, Halassy S, *et al*. Mesenchymal stem cells: Cell therapy and regeneration potential. J Tissue Eng Regen Med 2019;13:1738-55.
51. Castro-Manrreza M, Bonifaz L, Castro-Escamilla O, Monroy-García A, Cortés-Morales A, Hernández-Estévez E, *et al*. Mesenchymal stromal cells from the epidermis and dermis of psoriasis patients: Morphology, immunophenotype, differentiation patterns, and regulation of T cell proliferation. Stem Cells Int 2019;2019.
52. Bami M, Sarlikiotis T, Milonaki M, Vikentiou M, Konsta E, Kapsimali V, *et al*. Superiority of synovial membrane mesenchymal stem cells in chondrogenesis, osteogenesis, myogenesis and tenogenesis in a rabbit model. Injury 2020;51:2855-65.
53. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, *et al*. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8:315-7.
54. Mizuno H, Tobita M, Uysal AC. Concise review: Adipose-derived stem cells as a novel tool for future regenerative medicine. Stem Cells 2012;30:804-10.
55. Choi M, Lee HS, Naidansaren P, Kim HK, O E, Cha JH, *et al*. Proangiogenic features of Wharton's jelly-derived mesenchymal stromal/stem cells and their ability to form functional vessels. Int J Biochem Cell Biol 2013;45:560-70.
56. Lu L, Chen G, Yang J, Ma Z, Yang Y, Hu Y, *et al*. Bone marrow mesenchymal stem cells suppress growth and promote the apoptosis of glioma U251 cells through downregulation of the PI3K/AKT signaling pathway. Biomed Pharmacother 2019;112:108625.
57. Hou L, Wang X, Zhou Y, Ma H, Wang Z, He J, *et al*. Inhibitory effect and mechanism of mesenchymal stem cells on liver cancer cells. Tumor Biol 2014;35:1239-50.
58. Li M, Cai H, Yang Y, Zhang J, Sun K, Yan Y, *et al*. Perichondrium mesenchymal stem cells inhibit the growth of breast cancer cells via the DKK-1/Wnt/β-catenin signaling pathway. Oncol Rep 2016;36:936-44.
59. Rosenberger L, Ezquer M, Lillo-Vera F, Pedraza PL, Ortúzar MI, González PL, *et al*. Stem cell exosomes inhibit angiogenesis and tumor growth of oral squamous cell carcinoma. Sci Rep 2019;9:1-12.
60. Dasari VR, Velpula KK, Kaur K, Fassett D, Klopfenstein JD, Dinh DH, *et al*. Cord blood stem cell-mediated induction of apoptosis in glioma downregulates X-linked inhibitor of apoptosis protein (XIAP). PloS One 2010;5:e11813.
61. Kalamegam G, Sait KHW, Ahmed F, Kadam R, Pushparaj PN, Anfinan N, *et al*. Human Wharton's jelly stem cell (hWJSC) extracts inhibit ovarian cancer cell lines OVCAR3 and SKOV3 *in vitro* by inducing cell cycle arrest and apoptosis. Front Oncol 2018;8:592.
62. Lu H, Wang F, Mei H, Wang S, Cheng L. Human adipose mesenchymal stem cells show more efficient angiogenesis promotion on endothelial colony-forming cells than umbilical cord and endometrium. Stem Cells Int 2018;2018:7537589.
63. Huang W, Chang M, Tsai K, Hung M, Chen H, Hung S. Mesenchymal stem cells promote growth and angiogenesis of tumors in mice. Oncogene 2013;32:4343-54.
64. Meng X, Ichim TE, Zhong J, Rogers A, Yin Z, Jackson J, *et al*. Endometrial regenerative cells: A novel stem cell population. J Transl Med 2007;5:1-10.
65. Kong P, Xie X, Li F, Liu Y, Lu Y. Placenta mesenchymal stem cell accelerates wound healing by enhancing angiogenesis in diabetic Goto-Kakizaki (GK) rats. Biochem Biophys Res Commun 2013;438:410-9.
66. Lin R-Z, Moreno-Luna R, Zhou B, Pu WT, Melero-Martin JM. Equal modulation of endothelial cell function by four distinct tissue-specific mesenchymal stem cells. Angiogenesis 2012;15:443-55.
67. Kim YJ, Kim HK, Cho HH, Bae YC, Suh KT, Jung JS. Direct comparison of human mesenchymal stem cells derived from adipose tissues and bone marrow in mediating neovascularization in response to vascular ischemia. Cell Physiol Biochem 2007;20:867-76.
68. Tan K, Zheng K, Li D, Lu H, Wang S, Sun X. Impact of adipose tissue or umbilical cord derived mesenchymal stem cells on the immunogenicity of human cord blood derived endothelial progenitor cells. PloS One 2017;12:e0178624.
69. Ning H, Liu G, Lin G, Yang R, Lue TF, Lin C-S. Fibroblast growth factor 2 promotes endothelial differentiation of adipose tissue-derived stem cells. J Sex Med 2009;6:967-79.
70. Joddar B, Kumar SA, Kumar A. A contact-based method for differentiation of human mesenchymal stem cells into an endothelial cell-phenotype. Cell Biochem Biophys 2018;76:187-95.
71. Lin C-H, Lee S-Y, Lin Y-M. Plasma treatment in conjunction with EGM-2 medium increases endothelial and osteogenic marker expressions of bone marrow mesenchymal stem cells. J Mater Sci 2016;51:9145-54.
72. Bekhite MM, Finkensieper A, Rebhan J, Huse S, Schultze-Mosgau S, Figulla H-R, *et al*. Hypoxia, leptin, and vascular endothelial growth factor stimulate vascular endothelial cell differentiation of human adipose tissue-derived stem cells. Stem cells Dev 2014;23:333-51.
73. Igarashi Y, Chosa N, Sawada S, Kondo H, Yaegashi T, Ishisaki A. VEGF-C and TGF-β reciprocally regulate mesenchymal stem cell commitment to differentiation into lymphatic endothelial or osteoblastic phenotypes. Int J Mol Med 2016;37:1005-13.
74. Janeczek Portalska K, Leferink A, Groen N, Fernandes H, Moroni L, van Blitterswijk C, *et al*. Endothelial differentiation of mesenchymal stromal cells. PLoS One 2012;7:e46842..
75. Oswald J, Boxberger S, Jørgensen B, Feldmann S, Ehninger G, Bornhäuser M, *et al*. Mesenchymal stem cells can be differentiated into endothelial cells in vitro. Stem Cells 2004;22:377-84.
76. Klein D, Steens J, Wiesemann A, Schulz F, Kaschani F, Röck K, *et al*. Mesenchymal stem cell therapy protects lungs from radiation-induced endothelial cell loss by restoring superoxide dismutase 1 expression. Antioxid Redox Signal 2017;26:563-82.
77. Khan S, Villalobos MA, Choron RL, Chang S, Brown SA, Carpenter JP, *et al*. Fibroblast growth factor and vascular endothelial growth factor play a critical role in endotheliogenesis from human adipose-derived stem cells. J Vasc Surg 2017;65:1483-92.
78. Zhang P, Moudgill N, Hager E, Tarola N, DiMatteo C, McIlhenny S, *et al*. Endothelial differentiation of adipose-derived stem cells from elderly patients with cardiovascular disease. Stem Cells Dev 2011;20:977-88.
79. Shibuya M. Vascular endothelial growth factor and its receptor system: Physiological functions in angiogenesis and pathological roles in various diseases. J Biochem 2013;153:13-9.
80. Lee SH, Jeong D, Han Y-S, Baek MJ. Pivotal role of vascular endothelial growth factor pathway in tumor angiogenesis. Ann Surg Treat Res 2015;89:1-8.
81. Carmeliet P. VEGF as a key mediator of angiogenesis in cancer. Oncology 2005;69(Suppl. 3):4-10.
82. Rashid M, Zadeh LR, Baradaran B, Molavi O, Ghesmati Z, Sabzichi M,

et al. Up-down regulation of HIF-1α in cancer progression. Gene 2021;798:145796.
83. Roskoski R Jr. Vascular endothelial growth factor (VEGF) and VEGF receptor inhibitors in the treatment of renal cell carcinomas. Pharmacol Res 2017;120:116-32.
84. Wang N, Zhang R, Wang S-J, Zhang C-L, Mao L-B, Zhuang C-Y, *et al*. Vascular endothelial growth factor stimulates endothelial differentiation from mesenchymal stem cells via Rho/myocardin-related transcription factor-A signaling pathway. Int J Biochem Cell Biol 2013;45:1447-56.
85. Almalki SG, Agrawal DK. ERK signaling is required for VEGF-A/VEGFR2-induced differentiation of porcine adipose-derived mesenchymal stem cells into endothelial cells. Stem Cell Res Ther 2017;8:1-14.
86. Ball SG, Shuttleworth CA, Kielty CM. Vascular endothelial growth factor can signal through platelet-derived growth factor receptors. J Cell Biol 2007;177:489-500.
87. Fearnley GW, Smith GA, Abdul-Zani I, Yuldasheva N, Mughal NA, Homer-Vanniasinkam S, *et al*. VEGF-A isoforms program differential VEGFR2 signal transduction, trafficking and proteolysis. Biol Open 2016;5:571-83.
88. Gomes E, Rockwell P. p38 MAPK as a negative regulator of VEGF/VEGFR2 signaling pathway in serum deprived human SK-N-SH neuroblastoma cells. Neurosci Lett 2008;431:95-100.
89. Xu J, Liu X, Jiang Y, Chu L, Hao H, Liua Z, *et al*. MAPK/ERK signalling mediates VEGF-induced bone marrow stem cell differentiation into endothelial cell. J Cell Mol Med 2008;12:2395-406.
90. Novotny NM, Markel TA, Crisostomo PR, Meldrum DR. Differential IL-6 and VEGF secretion in adult and neonatal mesenchymal stem cells: Role of NFkB. Cytokine 2008;43:215-9.
91. Wang M, Zhang W, Crisostomo P, Markel T, Meldrum KK, Fu XY, *et al*. STAT3 mediates bone marrow mesenchymal stem cell VEGF production. J Mol Cell Cardiol 2007;42:1009-15.