Review Article

Adipokine Role in Normal and Neoplastic Bone Marrow Niche

Behrouz Yazdanpanah, Mohammad Shahjahani[1], Faezeh Seif[1], Elahe Khodadi[1], Saeid Shahrabi[2]

Paramedicine School, Yasuj University of Medical Sciences, Yasuj, [1]Research Center of Thalassemia and Hemoglobinopathy, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, [2]Department of Biochemistry and Hematology, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran

Abstract

Bone marrow (BM) niche is an appropriate site for the growth of mesenchymal stem cells and their differentiation into adipocytes. Adipocytes are metabolically active cells affecting the function of their neighboring cells through the secretion of adipokines, growth factors, and inflammatory mediators. Although the pathological roles of adipokines have not been elucidated, the changes in their levels have been observed in various malignancies. Adipokines also affect tumor growth in the BM niche. Decreased levels of adipokines and increased levels of leptin have been reported in a number of cancers. Adipocytes can be introduced as a diagnostic marker of metastasis in some cancers. Identification of the relationship between different adipokines secreted from adipocytes and the signaling pathways activated by these adipokines, as well as the detection of molecules involved in the development of various types of malignancies, can contribute to the recognition of drug resistance factors and appropriate treatment of malignancies. In this review paper, we examine the effects of various BM-derived adipokines on the growth and metastasis of tumor cells in the neoplastic BM niche.

Keywords: *Adipokine, bone marrow, niche*

Introduction

In general, bone marrow (BM) has two different cell lines: hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). Several cells are derived from these two cell lines through cellular differentiation, and BM niche provides a good environment for supporting these stem cells.[1] MSCs are present in most tissues such as BM, neural tissue, adipose tissue, and so on. BMC MSCs are potentially capable of differentiation into osteogenic, adipogenic, and chondrogenic cell types depending on the expressions of different transcription factors.[2,3] Several transcription factors including Wingless-type MMTV integration site family member 5A, Wnt_{10b}, transduction-like enhancer of split3 (TLE3), muscle segment homeobox (Msx2), and CCAAT/enhancer binding protein beta (C/EBPB) are among the most important determinants for the entry of MSCs into either osteogenic or adipogenic pathways.[4,5] TLE3 is a protein member of Groucho/TLE family that is expressed in various tissues (including BM) and causes BM MSCs to differentiate into adipocytes. By activating the peroxisome proliferation-activated receptor (PPARy), TLE3 increases the differentiation of BMSCs into adipocytes and reduces the differentiation of BM MSCs into osteoblasts by controlling the run-related transcription factor2 (Runx2).[4,6,7]

Adipocytes can affect their adjacent cells in the BM microenvironment through the secretion of hormones, cytokines, and fatty acids. The adipocytes differentiated from BM stem cells release a wide range of inflammatory factors such as leptin, resistin, visfatin, tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, IL-6, as well as anti-inflammatory factors such as adiponectin (APN) and IL-10.[8,9] These factors can contribute to survival signaling of tumor cells, as well as the induction and proliferation of neoplastic cells.[9,10] Research has shown that adipocytes increase the differentiation of $CD34^+$ HSCs into lymphoid and myeloid lineages by providing energy and heat. Moreover, the adipokines secreted by adipocytes potentially affect the BM niche, leading to the migration of stem cells from BM to the tissue to be regenerated after injury.[11]

Recognizing the mechanism of neoplastic niche growth and survival molecules can help identify the BM microenvironment and the disorders caused by hematological diseases. Therefore, in this review paper,

How to cite this article: Yazdanpanah B, Shahjahani M, Seif F, Khodadi E, Shahrabi S. Adipokine Role in Normal and Neoplastic Bone Marrow Niche. Clin Cancer Investig J 2018;7:37-42.

Address for correspondence:
Dr. Saeid Shahrabi, Department of Biochemistry and Hematology, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran. E-mail: sshahrabi45@yahoo.com

Access this article online

Website: www.ccij-online.org

DOI: 10.4103/ccij.ccij_90_17

Quick Response Code:

the impact of adipokines secreted by adipocytes on normal and neoplastic BM niches has been discussed.

Effect of Adipokines on Normal and Malignant Bone Marrow Niche

As endocrine, paracrine, autocrine, or juxtacrine effectors, adipocytes release several adipokines that can participate in various physiological and pathological processes.[12]

Leptin

Leptin receptors are expressed by several cell types such as MSCs, hematopoietic cells, adipocytes, osteoblasts, and osteoclasts. Leptin enhances the differentiation toward osteogenesis in MSCs, decreasing the number and size of BM adipocytes and playing a protective role for the bone mass. There is a positive relationship between leptin and bone regeneration;[13,14] in other words, leptin is involved in the reconstruction and support of BM microenvironment by increasing the bone mineral density. Moreover, leptin can result in the induction and survival of cancer cells, including multiple myeloma (MM) cells, in the osteoblastic niche. Leptin enhances the proliferation of T lymphocytes, inhibiting apoptosis and inducing the production of cytokines such as TNF-α, IL-2, and IL-6 in them, the involvement of which (especially IL-6) in the growth of MM cells has been recognized.[15,16] In addition, these cytokines lead to the differentiation of T lymphocytes into Th1 cells, as well as the activation of monocytes and macrophages along with the induction of oxidative stress. Furthermore, they can be involved in the migration and metastasis of various cells in different malignancies (e.g., gastric cancer) through the upregulation of adhesion molecules such as intercellular adhesion molecule-1.[17] Leptin is effective in angiogenesis at the cellular level by increasing the expression of vascular endothelial growth factor.[18] Therefore, it seems that the leptin released by adipocyte cells in BM could play an important role in the growth, maintenance, and metastasis of cancer cells [Table 1].

Angiopoietin-1

Angiopoietin-1 (Ang-1) is an adipocyte-derived vascular growth factor that can be produced at high levels by HSCs and at lower levels by c-kit$^+$ hematopoietic progenitors, megakaryocytes, and leptin-receptor-expressing (LepR+) stromal cells. Tie2, the Ang-1 receptor, is expressed on HSCs, and Tie2 binding to its ligand appears to induce the quiescence phase and antiapoptotic effects in these cells.[18] The HSC progenitors and LepR$^+$ stromal cells release Ang-1, which reduces vascular leakiness as well as the regeneration of BM cells.[19] In addition, a higher level of Ang-1 has been shown in AML-NPM$^+$ patients, and other studies have indicated the increased expression of this adipokine in other hematological malignancies such as chronic myeloid leukemia (CML). Therefore, these findings suggest that the expression of this adipokine may play an important role in the pathogenesis of hematological malignancies.[20] Ang-1 also stimulates the angiogenesis by binding to endothelial cells, and the role of this adipokine in stimulating angiogenesis in MM patients has been demonstrated.[21,22]

Adiponectin

This molecule is mainly secreted by adipocytes. Several studies indicate that APN has a paracrine role on BM progenitor mesenchymal cells. The involvement of APN in normal hematopoiesis has recently been studied. It has been shown that the APN receptor expressed on HSCs regulates the function and proliferation of these cells through a p38-dependent pathway.[23,24] By activating the p38 MAPK pathway, APN results in the proliferation of HSCs. It can enhance bone mass by increasing the formation of bone and inhibiting bone reabsorption. APN acts as a receptor antagonist of inflammatory cytokines such as IL-1 and IL-6 and also induces the production of anti-inflammatory cytokines such as IL-10.[17,23] Studies show that APN regulates the migration of BM MSCs and recruits these cells to repair and regenerate the tissue. Through the phosphorylation and activation of SmD1-5-8 transcription factor, AdipoR-1 (the APN receptor) leads to increased expression of genes that are effective upon the migration of BM MSCs and osteoblasts into the injured site, and it can be involved in the repair of bone lesions by accelerating the regeneration and hemostasis of bone.[25] Recently, it has been shown in a meta-analysis study that the serum APN levels are increased in patients with acute

Table 1: Signaling pathways activated by adipokines

Adipokine	Chromosome	Signaling pathway	Function	References
Leptin	7	JAK-STAT, induces the expression of PI3K/ERK1, hyperphosphorylation of dcyclin, Rbp	Supporting role for bone mass	[12,18,39]
Adiponectin	3	AMPK pathway, PPAR	Supporting role for bone mass Strong anti-inflammatory effects	[12,23,25]
Omentin	1	NF-κB pathway	Important role in bone metabolism	[18]
Resistin	19	P38 MAPK pathway MEK1	Increased production of osteoclasts decreases bone mass	[12,24]

JAK: Janus kinase, STAT: Signal transducer and activator of transcription, PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase, Rbp: Retinoblastoma protein, AMPK: AMP-activated protein kinase, PPAR: Peroxisome proliferation-activated receptor, NF-κB: Nuclear factor kappa B, MEK1: MAPK and ERK kinase, MAPK: Mitogen-activated protein kinase, AMP: Adenosine monophosphate, ERK1: Extracellular signal–regulated kinase 1

leukemia, and that these increased levels could be used as a noninvasive prognostic factor [Table 1].[26]

Resistin

Although this adipokine is significantly produced by myocytes, hepatocytes, and MSCs, it is expressed in BM adipocytes to a higher extent than other tissues, which suggests that resistin may play an important role in remodeling of the bone metabolism. By activating the nuclear factor kappa B (NF-κB) signaling pathway, this adipokine increases the number of osteoclasts, followed by BM reabsorption.[23,24] In addition, resistin induces inflammatory cytokines such as TNF-α, IL-6, and IL12 through NF-κB pathway, which plays a role in the regulation of inflammatory response and vascular cell adhesion molecule-1.[27,28] The role of this factor in human hematopoiesis has been studied, and it has been shown that the level of this factor is high in the BM, liver, and umbilical cord. Moreover, it has recently been shown that resistin levels are elevated after chemotherapy and can protect the cells from chemotoxicity caused by 5-fluorouracil [Table 1].[29,30]

Omentin

This adipokine plays an important role in bone metabolism as well as in the dynamic balance between bone formation and reabsorption. Omentin inhibits the differentiation of osteoclasts *in vivo* by preventing the production of receptor activator of NF-κB ligand (RANKL), while it has no direct effect on the differentiation of osteoclasts *in vitro*. Omentin inhibits the formation of osteoclasts through induction of osteoprotegerin (OPG) and RANKL in osteoblasts [Table 1].[31,32]

Osteoprotegerin

Osteoprotegerin (OPG) is a molecule secreted by the bone that is effective on the survival and turnover of bone cells. OPG is an antibone resorption molecule and a potential candidate for inhibiting the RANKL-mediated osteolytic component, which subsequently inhibits tumor growth and development, acting as an inhibitor of human osteosarcoma. Clinical studies indicate that OPG has the potential for the treatment of bone lysis in patients with metastatic breast cancer.[33,34] Given that adipocytes, osteoblasts, and osteoclasts have a common progenitor, there is a high probability of common characteristics in these cells. Hence, it was hypothesized that OPG might also be expressed by adipocytes, which has recently been confirmed in a study.[35] In addition, this factor plays an important role in BM adipogenesis. Regarding the importance of OPG in hematopoiesis, there are reports indicating that it maintains the function of progenitors in the osteoblastic niche.[36,37]

Chemerin

Chemerin is a new adipokine secreted primarily by adipocytes. It contributes to the acceleration and progression of adipocyte differentiation, regulating adipogenesis and osteogenesis.[38] The interaction of chemerin with its CMKLR1 receptor increases the adipogenesis by MSC. Removal of the CMKLR1 receptor increases the expression of osteoblast markers such as alkaline phosphatase and type I collagen. The expression and secretion of chemerin are increased during the differentiation of adipocytes.[8,24]

Adipocyte Role in Tumor Metastasis

Metastasis to distant organs is a known feature of many tumors, which may lead to changes in various stages of cancers. In general, metastasis involves the transfer of cancer cells from their original site to other tissues of the body, which is observed in advanced stages of cancer. As an endocrine organ, BM adipose tissue has unique adipokines, including APN, leptin, resistin, and so on, giving different responses to physiological processes such as hematopoiesis and bone regeneration.[24] The tumor environment has been shown to contribute to the proliferation of adipocytes, which along with their associated inflammatory cells contributes to tumor development and progression through secretion of adipokines and cytokines, as well as the induction of vimentin polarization, the reduction of E-cadherin, and the increase of invasive cells.[11] The presence of adipocytes in tumor microenvironment (TME) increases the level of lipids such as stearic acid, which are needed for the growth of tumor cells, as well as signaling, trafficking, and migration of cells, especially when the peripheral glucose reserves are reduced.[11,40] The binding of cancer cells to BM adipocytes leads to increased translocation of fatty acids and the lipid stored in adipocytes into tumor cells, as well as the overexpression of lipid chaperones, fatty acid binding protein 4, and IL-1 in tumor cells, which causes the development of tumor metastasis.[11] Human adipocytes increase angiogenesis by activating macrophages through the (C-C motif) ligand 2 (CCL2)/IL-1/C-X-C motif chemokine ligand 12 (CXCL12) pathway.[41] In addition, the cytokines secreted by BM adipocytes turn the BM tissue into a proper environment for tumor growth. The release of factors such as APN and leptin can promote tumor growth by stimulating angiogenesis.[18]

In a process known as epithelial-mesenchymal transition, tumor cells are capable of metastasis to distant sites that are adjacent to adipocytes.[42] The interaction of tumor cells and adipocytes results in increased lipid concentrations in tumor cells, inducing inflammatory pathways in these cells and resulting in the increase in cyclooxygenase 2 and CCL2, both of which have been shown to contribute to metastasis and progression of prostate tumor to BM.[11] Various studies have shown that the reduced expression of CCL2 decreases the absorption of inflammatory monocytes to TME and inhibits the metastasis to lung and BM.[43]

Tumor growth factor (TGF) is one of the most important factors causing prostate cancer metastasis to BM. Through

the induction of TME, TGF can lead to the migration of prostate cancer cells to BM. Studies have indicated that the downregulation of miR-15 and the upregulation of miR-21 increase the migration of prostate cancer cells to bone tissue.[42]

Adipocytes in Prostate Cancer

Given that the β-oxidation of fatty acids is the main pathway for energy production in various types of prostate cancer, the metabolism of prostate cancer cells is such that aerobic glycolysis in these cells is decreased and the activity of lipogenic enzymes (including choline kinase and fatty acid synthase) in them is increased. Lipid precursors such as acetate and choline can be used as alternative tracers for PET imaging and the detection of cancerous mass.[44] In addition to their supportive function for tumors, these precursors can also have a diagnostic role.

Studies indicate that adipokines such as leptin, which are secreted through the regulation of MAPK pathway, exert mitogenic effects on prostate cancer cells. It has been argued that low levels of adipokine along with high leptin secretion result in the progression of prostate cancer by regulating the expressions of B-cell lymphoma 2 (Bcl-2) and p53. Adipokine prevents the growth and survival of prostate cancer cells through inhibiting the STAT3 signaling pathway and activating the MAPK pathway. Adipocytes with a high expression of proviral integrations of Moloney virus 2 (PIM2) kinase increase drug resistance and prevent apoptosis.[45]

Studies have shown that the metastasis from prostate cancer to BM is possible when BM is rich in adipocytes. It seems that tumor cells are juxtaposed to BM adipocytes to use the agents secreted by these cells, including a variety of growth factors, adipokines, and so on.[11,46]

Adipocytes in Breast Cancer

Research has shown that increasing serum concentrations of adipokines such as visfatin, leptin, and resistin, as well as reduced APN concentrations, can be considered as a risk factor for breast cancer among postmenopausal women.[18] The expression of leptin receptors is increased in an invasive breast carcinoma that tends to be metastatic. Increasing concentrations of leptin and decreasing APN concentrations could be considered as a diagnostic marker in patients with breast cancer.[47] By activating the signaling pathways of ERK1/2 and STAT3, leptin can inhibit the effect of tamoxifen on ER+ breast cancer cells.[48] It may be possible to measure leptin or evaluate leptin receptor expression for early detection of breast cancer along with other breast cancer diagnostic methods.

Adipokines in Leukemia and Lymphoma

The malignant transformation of HSCs is a general viewpoint on the underlying cause of leukemia; however, there are pieces of evidence indicating that the dysregulation of niche can be considered a factor of leukemogenesis.[49] BMSCs react to the presence of leukemia cancer cells by changing secretion of cytokines and chemokines. As a result, a competitive niche is created between leukemia cells and BMSCs, which is more appropriate for leukemic stem cells.[50]

According to studies, adipocytes have a supportive role for the microenvironment of ALL (acute lymphoblastic leukemia [ALL]) cells subject to treatment using asparaginase through the production of asparagine and glutamine. Alpha-linolenic acid reduces the proliferation and survival of CML cells and the expression of Bcl-2 through the phosphatidylinositol-4,5-bisphosphate 3-kinase pathway. In the presence of leptin, the effects of alpha linoleic acid on the proliferation and survival of tumor cells, as well as the expression of Bcl-2, are reduced [Figure 1].[40] Due to increase in CXCL12 production and the expression of serine/threonine-protein kinase (PIM2), adipocytes increase the survival of chronic lymphocytic leukemia, MM, and ALL cells and boost drug resistance.[51] The severity of hematologic malignancies such as MM depends on the BM microenvironment and a variety of cell types contained in it. During tumor progression, adipocytes are the primary neighboring cells of tumor cells. The adipokines such as chemokine CCL2 and CXCL12, IL-6, and TNF-α, which are released by adipocytes, have been specified as inflammatory factors in MM. Evidence suggests that a number of cytokines such as leptin in MM increase the growth of tumor cells in the BM microenvironment.[41,52] In MM, the level of IL-6 is related to disease progression. By regulating each other, TNF-α and IL-6 may support tumor growth through inducing inflammatory

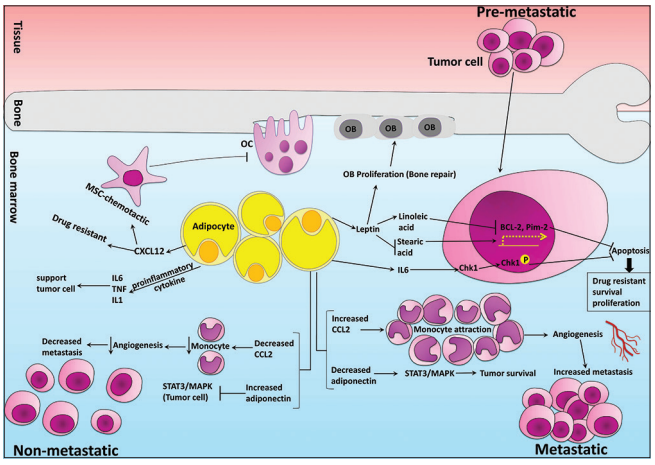

Figure 1: The role of fatty acids in metastasis and growth of cancer cells in the bone marrow niche. Alpha-linolenic acid secreted by adipocytes leads to chronic myeloid leukemia cell line proliferation and survival through the inhibition of PI3K pathway and reduces Bcl-2, while stearic acid increases the expression of Bcl-2 and subsequent tumor cell growth and proliferation. TNF-α: Tumor necrosis factor-alpha, IL-1: Interleukin 1, IL-6: Interleukin 6, CXCL12: Chemokine (C-X-C) ligand 12, CCL2: (C-C motif) ligand 2, ChK1: Checkpoint kinase 1, Bcl-2: B-cell lymphoma 2, PIM2: Proviral integrations of Moloney virus 2, PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase

chemokines such as CCL2. However, the role of TNF-α in MM progression is less pronounced than that of IL-6.[41]

Discussion

Adipocytes are among the most abundant BM cells that are associated with various diseases, including several types of cancer. It is observed that the higher the number of BM adipocytes, the higher the likelihood of metastasis from BM to other tissues and vice versa.[11,53] Adipocytes and adipocyte-secreted factors (including fatty acids and inflammatory factors) play an essential role in BM metastasis. In this regard, some adipokines have opposite effects in the metastatic process in BM. Leptin is effective in different stages of neoplastic niche changes. Conversely, since leptin is an antagonist of anti-inflammatory cytokines, increase in its levels is effective on BM restoration, and the concentration of this adipokine is decreased at different levels of cancer.[17,18,23,24] Considering the increase of adipocytes in various types of bone metastases, adipokines may be used as a metastasis diagnostic marker for malignancies such as colorectal cancer in future.[54] Recent results in some studies have suggested a negative association between leptin and colorectal cancer risk (CRC), as well as positive associations between resistin with TNF-α and CRC.[54-56]

It can be inferred that adipocytes are effective in the induction of tumor growth through secretion of various types of adipokines, which cause tumor growth and drug resistance by inducing different signaling pathways in the neoplastic niche. Recognition of the correlations among adipokines secreted from adipocytes with the signaling pathways and molecules involved in the secretion of these adipokines and the development of various types of malignancies can contribute to the identification of drug resistance factors and better treatment of malignancies.

Conclusion and Future Perspective

Adipocytes can be introduced as a diagnostic marker in hematological and nonhematological malignancies. Whether the adipokines secreted by BM adipocytes cause metastasis of tumor cells to BM and whether adipokines directly play a role in BM tumorization are ambiguities and questions that demand further investigations to evaluate the effects of adipokines on neoplastic niche and design better treatments for these patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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