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REVIEW ARTICLE

Bone Marrow Adipocytes and Hematology: A Literature Review

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Abstract

This review focuses on the impact of bone marrow adipocytes on hematopoiesis and the development of hematological diseases. Bone marrow fat is a metabolically active organ capable of accumulating energy required for active hematopoiesis as well as of performing endocrine functions and participating in bone formation. Adipocytes can interact with the surrounding cells both directly and indirectly via cytokines and chemokines. Apart from their active involvement in the normal hematopoiesis, BMA have also been shown to play an important role in such diseases as leukemia, multiple myeloma and aplastic anemia. The role of fat cells in hematopoiesis is still unclear and not well studied, yet it is undoubtedly important, as demonstrated by the ever increasing number of publications supporting this conclusion. (**International Journal of Biomedicine. 2021;11(2):123-130.**)

Key Words: fat cells • hematopoiesis • leukemia • multiple myeloma • aplastic anemia

Abbreviations

AA, aplastic anemia; **ALL**, acute lymphoblastic leukemia; **APL**, acute promyelocytic leukemia; **AML**, acute myeloid leukemia; **BM**, bone marrow; **BMA**, bone marrow adipocytes; **BMAT**, bone marrow adipose tissue; **cBMA**, constitutive bone marrow adipocytes; **rBMA**, regulated bone marrow adipocytes; **CLL**, chronic lymphocytic leukemia; **CML**, chronic myeloid leukemia; **3DEM**, three-dimensional electron microscopy; **DECT**, dual-energy computed tomography; **HSC**, hematopoietic stem cells; **MRI**, magnetic resonance imaging; **MM**, multiple myeloma; **MSC**, mesenchymal stem cells; **PTH**, parathyroid hormone; **RBM**, red bone marrow; **YBM**, yellow bone marrow.

Introduction

Bone marrow (BM) is one of the largest and most widely distributed organs in the human body. BM contains not only hematopoietic stem cells (HSC) but also the cells of the microenvironment, such as macrophages, endothelial cells, osteoclasts, osteoblasts and adipocytes. In the late 19th and early 20th centuries, two types of bone marrow were distinguished: "red" bone marrow (RBM) and "yellow" bone marrow (YBM).[1] Since that time, research has been conducted on BM and its components, including fat cells. The 1970s became the golden years for the studies on bone marrow adipose tissue (BMAT), or bone marrow adipocytes (BMA) as it is referred to in modern literature. These years were marked by the discovery of differences in the histogenesis of RBM and YBM, which were described by M. Tavassoli,[2] who also described the origin of BMA from unique progenitor cells, different from those of regular white fat. Furthermore, the author made an assumption that epigenetic factors could influence the differentiation and development of adipocytes, which is the subject of research carried out by many scientists at the present time.[2,3]

At the next stage in the study of bone marrow fat, fat cells were distinguished by their functions into regulated bone marrow adipocytes (rBMAs) and constitutive bone marrow adipocytes (cBMAs), which resulted in the separation of the functions of these cells and their influence on the microenvironment.[4] rBMAs are diffusely distributed in the RBM, while cBMAs

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are one of the main components of the YBM.[5] After BMAT had been classified as a separate type within the entire adipose tissue, active research on the relationship between BM and fat began. As a result, it has been shown that fat cells play an important role in the development of osteoporosis.[6]

Adipocytes originate from mesenchymal stem cells (MSC) and are an important component of the BM microenvironment.[7] Currently, many study groups are investigating the relationship between BMAT and bone metabolism. Interest in the function of fat cells has also increased among those scientists who carry out research on the pathology of BM hematopoiesis. It has been shown that adipocytes are involved in the regulation of hematopoiesis and interact with HSC via direct cell contact, affecting the secretion of growth factors and cytokines.[8,9]

BMAT is an active cellular element of the BM that stores free fatty acids and produces adipokines.[10]

Researchers delineate an important role for fat cells in oncology and oncohematology. Several studies show that fat cells contribute to the development and the continued growth of tumors, the metastasis of tumors to the BM and the development of resistance to chemotherapy through interaction with other stromal cells.[10] The increased interest in BMAT has contributed to the development of noninvasive diagnosis of BMA using modern high-tech methods. Densitometry, MRI, dual-energy computed tomography (DECT), and positron emission tomography (PETCT) open up new possibilities in the assessment of BMAT.[11]

This article is devoted to a review of the literature describing the normal development of adipose tissue in the BM, and the influence of adipose tissue on hematopoietic cells during normal BM evolution. We will elucidate the contribution of adipocytes to diseases involving the BM.

I. Normal BMA

The development of adipocytes in the BM
Bone modeling occurs during prenatal development. Bones grow not only in length, but also in diameter, and a BM cavity enlarges along with the growth of a bone itself. During fetal development, this cavity is gradually filled with RBM, and by the end of the first trimester of pregnancy, it is completely filled.[12] It has been shown that the replacement of RBM by YBM in some bones, for example, in phalanges, begins shortly before the birth of a child.[13] After birth, fatty involution of the BM occurs in different bones in different ways: in the femur and tibia, it begins at the age of 7 and ends at the age of 18; however, in the ribs and vertebrae, microscopic fat is not found until adulthood.[14] In addition, several studies have revealed some regularities in the development of adipose tissue in the BM: from the periphery to the axial skeleton, from diaphyses to metaphyses.

Regulation
Adipocytes originate from MSC of the BM. MSC also give rise to other types of cells: osteoblasts (cells forming bone tissue) and chondrocytes (cells forming cartilage). Regarding the differentiation of cells, adipocytes and osteoblasts are closely related to each other; these cells have common stages of development. A number of factors are activated during the

emergence of preosteoblasts (runt-related transcription factor 2 (RUNX2), homeobox protein 1 (Prx1) and osterix (Osx, Sp7)) and during the differentiation of preadipocytes (platelet-derived growth factor receptor beta (PDGFRb), CCAAT/enhancer binding protein alpha (C/EBP alpha), zinc finger proteins (Zfp) 423 and 467, and Prx 1). During a certain period of time, progenitor cells of adipocytes and osteoblasts can exhibit plasticity; they can mutually transform between phenotypes, a process that is regulated by microenvironmental molecules and cytokines. Type I collagen (COL1a1), osteocalcin (OCN) and RANKL stimulate osteoblast differentiation. Peroxisome proliferator-activated receptor gamma (PPARG), fatty acid-binding protein (FABP4), perilipin 2 (PLN2), and fatty acid synthase (FASN) promote adipocyte differentiation [12,15] (Fig. 1).
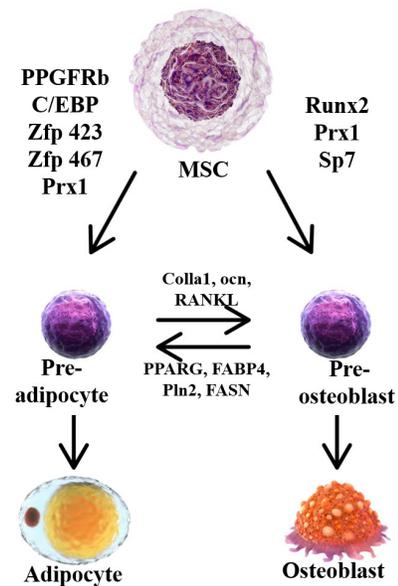

Fig. 1. *The origin and interaction between adipocytes and osteoblasts derived from mesenchymal stromal cells (MSC).*

There are also other factors that affect the amount of fat in the BM. These factors include hormones such as estrogen and parathyroid hormone (PTH). Several studies have shown that an increase in estrogen raises the number of osteoblasts and suppresses the differentiation of adipocytes in the BM.[16,17] Studies on PTH have shown that PTH can influence MSC, thereby increasing or reducing the development of adipocytes (Fig. 2).

Fig. 2*. Interaction between adipocytes and MSC: a schematic illustration.*

In those studies, the loss of PTH receptor expression in MSC increased the amount of BMA, while PTH receptor overexpression suppressed the formation of fat cells.[18]

The influence of age and gender

In healthy young adults, bone mass peaks at the age of 15 to 30. Then the amount of fat in the BM inevitably increases with age. This finding has been confirmed by numerous multiparametric studies, mainly based on new methods of quantitative MRI assessment. MRI spectroscopy has revealed that in groups of healthy controls aged 11-61, distributed by age with a 10-year interval, the amount of fat in the bones increases from 23% to 60%. During almost their entire lives, men have a higher BM fat content; however, in women, the amount of BMAT sharply increases in the postmenopausal period (over 55 years of age).[19]

Functions of adipocytes

Recently, not only the regulation of adipocyte formation in the BM has been under study, but active research has also been carried out on the functions of adipocytes and their interaction with other surrounding cells. An important function of BMA is the secretion of mediators, for example, adipokines, which can act as both paracrine and endocrine mediators. Adiponectin is the most extensively studied adipokine in the BM. Adiponectin is involved in the regulation of insulin sensitivity and energy metabolism. Adiponectin is mostly secreted by BMA, which has been shown in animal models when comparing the expression and secretion of adiponectin by BMA and by adipocytes from other peripheral fat depots.[9]

Adiponectin facilitates osteoblast differentiation *in vitro*. As evidenced by a number of clinical studies, an increase in circulating adiponectin levels is associated with the loss of bone mass. This parameter can potentially be used as a marker of increased BMAT.[20]

Furthermore, it has been demonstrated that increased adiponectin production by BMA after myeloablative chemotherapy promotes hematopoietic recovery in mice.[21] Another study showed that stem cell factors secreted by adipocytes following chemotherapy also facilitate hematopoietic recovery. The study was performed in murine models with impaired adipogenesis (A-ZIP/F1 mice) that was also accompanied by impaired hematopoiesis [22] (Figure 3).

Fig. 3. *A schematic representation of the adipocyte-secreted factors promoting hematopoietic recovery.*

D. Mattiucci et al.[23] showed *in vitro* that human BMA secrete CXCL12, which is important for hematopoietic stem cell maintenance in the BM. The co-culture of human BMA with HSC supported the survival of hematopoietic cells.

A comparison of cytokines secreted by subcutaneous adipocytes and those secreted by BMA led to the identification of 53 proteins secreted by the latter. These proteins became activated with age and affected osteoblasts by reducing bone mass.[24] This group of researchers also identified palmitate, a saturated fatty acid produced by BMA that inhibits osteoblast function.[25]

Another important function of BMA is the secretion of fatty acids that act as an additional source of energy for the surrounding cells. One of the first discovered adipokines involved in the regulation of energy metabolism was leptin.[26] In recent years, there have been a number of studies suggesting that adipocytes supply energy to osteoblasts and HSC through lipolysis. This is most evident when bone cells and hematopoietic cells are under stress; as well as in cases of trauma, diets, other forms of energy restriction, and aging. It has been shown that fatty acid oxidation in BMA may play an important role in the growth and survival of prostate cancer bone metastases.[27]

Thus, the results of many studies indicate that BMA are functionally heterogeneous. It is clear that BMA secrete factors that influence processes in the BM as well as bone remodeling and hematopoiesis. They also secrete factors that are released into the bloodstream and act outside the BM. Bone remodeling and hematopoiesis are energy-demanding processes that are tightly regulated to maintain bone mass and blood cell counts, and BMA appear to also be involved in this important process.

The role in hematopoiesis

The microenvironment of BM hematopoietic cells, also known as the "hematopoietic niche," comprises cytokines (produced by HSC themselves), BM stroma, capillaries and nerves.[28] Three-dimensional electron microscopy (3DEM) of the BM allows one to study BMA as well as their relationship with the surrounding tissues. 3DEM has revealed that BMA display features of metabolically active cells, including lipid accumulation, dense mitochondrial networks and areas of endoplasmic reticulum. It has been shown that triacylglycerol droplets containing fatty acids are absorbed and/or released in three areas: at the endothelial border, in the hematopoietic environment, and on the bone surface.[29] A group of researchers led by H. Robles [29] demonstrated that, in the hematopoietic environment of the proximal tibia, BMA interact extensively with mature cells of the myeloid lineage and are closely associated with erythroblastic islands. At the microstructural level, this directly indicates that BMAT is actively involved in many processes in the bone, and is not just some "inert filler." BMAT, as a part of the hematopoietic niche, influences the proliferation and differentiation of HSC by secreting adiponectin, leptin, prostaglandins, IL-6, and other adipocyte-related factors.[30-33] Leptin, independently or synergetically, promotes HSC proliferation,[31,32] prostaglandins inhibit HSC through the induction of apoptosis,[34] and IL-6 facilitates HSC differentiation.[33]

In vitro, BMA secrete factors that inhibit B cell lymphopoiesis, especially at the stage where lymphoid progenitor cells differentiate into pre-B cells, and at the same

time, promote the differentiation and subsequent proliferation of HSC into the myeloid lineage. BMA were also shown to negatively affect early stages of B-lymphocyte proliferation in the BM of elderly people.[35]

Kennedy et al.[36] discovered that adipocytes induce generation of myeloid suppressor cells that inhibit B cell lymphopoiesis by producing IL-1. At the same time, BMA induce inflammation via NLRP3 (NOD-like receptor 3) activation and directly inhibit B cell lymphopoiesis.[37] The activation of inflammation may also promote degeneration of the thymus,[38,39] which in turn negatively affects T-lymphocyte proliferation.[40] NLRP3 blockade enhanced B cell lymphopoiesis and prevent thymic atrophy and a decrease in T lymphocytes.[40]

Naveiras et al.[41] demonstrated that the removal of adipocytes from the BM of mice enhances hematopoiesis, including B cell lymphopoiesis. Other researchers showed that adipogenesis stimulation with the tributyltin toxicant leads to PPARγ activation in the BM, resulting in a decrease in peripheral B lymphocytes.[42]

Leptin, another mediator mentioned above, has the opposite effect on lymphopoiesis.[43] Leptin promotes differentiation and proliferation of cells of the lymphoid lineage and stimulates myelopoiesis.[26] In leptin-deficient mice, the levels of peripheral blood B cells and CD4+-expressing T cells are significantly reduced.[26,32] It has also been shown that high plasma leptin levels promote the differentiation of pluripotent CD34+ cells into granulocytes[44] (Figure 4).
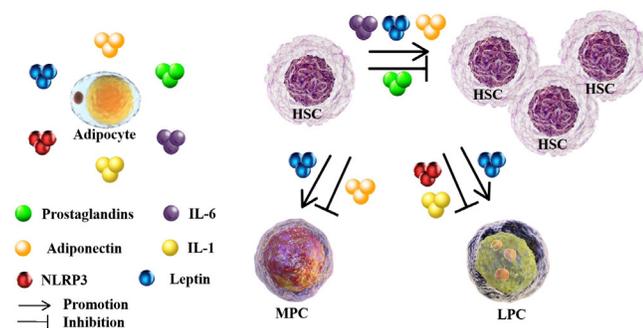

Fig. 4. *The influence of adipocyte-derived factors (adiponectin, leptin, prostaglandins, IL-6, IL-1, and NLRP3) on normal hematopoiesis in the BM, including the proliferation of HSC as well as their differentiation into myeloid (MPC) and lymphoid progenitor cells (LPC).*

As mentioned above, electron microscopy studies have shown that BMA interact closely with erythroblastic islands.[29] It has been estimated that a single adipocyte can interact with more than 100 erythropoietic cells, both directly, via cell-cell contact, and indirectly, using macrophages of erythroblastic islands.[45] Adipocytes deliver energy to maturing erythroid progenitor cells. This has been confirmed by a number of researchers in animal experiments. It has been shown that the amount of fat and the size of BMA decrease rapidly during active erythropoiesis in response to massive blood loss.[46] A recent study in mice published in the Blood journal demonstrated that stimulation with erythropoietin, which promotes differentiation of erythrocytes, leads to a decrease in BMAT.[47]

Currently, the role of BMA in hematopoiesis is controversial and yet significant. Many mechanisms of interaction between hematopoietic cells of the BM and adipocytes have not been investigated yet, so further research is needed to identify their signaling pathways.

II. BMA and Hematologic Diseases
Leukemia

There are many research groups in different countries that investigate the interaction of adipocytes, not only with normal hematopoietic cells, but also with transformed cell clones. They study these interaction effects in ALL, acute promyelocytic leukemia (APL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), multiple myeloma (MM), and aplastic anemia (AA).[48] On experimental murine models, using human ALL and AML clones, Battula et al.[49] demonstrated that leptin secreted by BMA into the microenvironment of tumor cells facilitated their engraftment, growth, and development in the BM of mice. The authors also suggested that adipocytes may play an important role in the setting of AA or hypoplastic myelodysplastic syndromes.[49]

BMA protect lymphoblasts in ALL; however, this mechanism has not been studied well. A study on a large cohort of ALL patients over age 10 revealed that, regardless of sex and age, obesity at diagnosis increases the risk of relapse by ~50% and reduces the effectiveness of treatment.[50] In murine models, it was repeatedly demonstrated that general obesity leads to an increase in the number of adipocytes in the BM.[51-53] When in the tumor environment, leptin secreted by BMAs influences cell proliferation, survival, and apoptosis. During chemotherapy, leptin protects ALL cells from drug-induced apoptosis.[54] Recent studies have shown that under treatment with daunorubicin, an antileukemic cytostatic drug, ALL cells induce oxidative stress in adipocytes. In response to oxidative stress, adipocytes secrete soluble factors, which protect ALL cells from daunorubicin.[55] BMA were also shown to confer protection against vincristine and nilotinib.[56] In APL, blast cells have a lot of leptin receptors.[54] In AML, cytokines and chemokines secreted by BMA can induce the proliferation of AML cells.[57,58] A possible mechanism of these interactions may involve the induction of lipolysis and the formation of fatty acids, which are then transported into the tumor microenvironment and serve as a good metabolic substrate for the survival and proliferation of AML cells.[59] In AML patients, leptin stimulates blast cell growth by promoting angiogenesis. It has been shown that the use of leptin receptor inhibitors in animal models leads to a reduction in angiogenesis.[60] When investigating AML cell lines and blast cells obtained from patients with AML, researchers also detected a high level of leptin isomer expression, which promotes their active proliferation.[61] A study by Yokota et al.[62] aimed at investigating the interaction between adiponectin and hematopoietic cells demonstrated that adiponectin inhibits the proliferation of myeloid cell lines and induces apoptosis in myelomonocytic leukemia lines.

Diaz-Blanco et al.[63] showed that the expression of leptin receptors is reduced in patients with CML. At the onset of the disease, BMA partially inhibit the expression of CML clones. Cytokines produced by CML cells induce the lipolysis of BMA. Then polyunsaturated fatty acids released

from the adipocytes impair CML proliferation and survival by inhibiting the PI3K pathway. However, this effect is soon inhibited by leptin released from adipocytes, which increases the lipolysis of adipocytes and protects CML cells from apoptosis by activating the PI3K pathway.[64]

In CLL, the expression of lipoprotein lipase, which is also expressed in adipocytes and prompts the hydrolysis of triglycerides into free fatty acids, is increased.[65] CLL cells accumulate these fatty acids in vacuoles and then utilize them to produce energy via oxidative phosphorylation by binding free fatty acids with receptors PPARα.[66] PPARα overexpression was demonstrated in CLL cells, and the level of the expression correlated with the disease progression.[67] Moreover, fatty acids were shown to mediate the resistance of CLL cells to treatment.[58]

Multiple myeloma

J. Caers et al. [68] showed that adipocytes in the BM microenvironment affect MM cell proliferation, apoptosis, and migration. However, fat cells were found in the BM only at the initial stages of MM. These results suggest that BMA play a significant role at the initial stages of the disease. Other researchers have found that one of the enzymes that protect MM cells against chemotherapy is resistin. Its main effect is the inhibition of chemotherapy-induced caspase cleavage.[70,71] However, resistin is expressed not only by adipocytes but also by other cells of the BM environment, so further studies are needed.[69,71]

Aplastic anemia

Aplastic anemia (AA) is the opposite of the above-mentioned BM disorders. It is characterized by a significant decrease in BM cellularity and peripheral blood pancytopenia. The BM microenvironment is one of the key pathogenetic factors in AA.[72] Normally, adipogenesis and osteogenesis are well-balanced; but in patients with pathological changes in BM, the balance between them may be seriously disrupted, resulting in the BM hypo- and hypercellularity.[73-75] In the BM of patients with AA, adipocytes are much more numerous than osteoblasts.[75] *In vitro* studies showed that MSC in patients with AA tend to differentiate into adipocytes rather than into osteoblasts.[76] Signaling pathways continue to be explored in order to improve treatment outcomes for AA patients.[77-79]

Conclusion

Over the recent years, the number of relevant studies has increased tremendously. Today, the interactions between BMA and HSC, MSC, osteoblasts, and other cells of the BM environment are being actively investigated. Apart from the exploration of processes occurring in healthy BM, many researchers have focused on the relationship between BMA and abnormal cells in the BM.

It is not always possible to determine the role of BMA in some known mechanisms of interaction between stromal and hematopoietic cells, due to the close interaction between all cells in the BM microenvironment. There is no doubt that BMA actively participate in the hematopoietic microenvironment. Adipokines, chemokines, and cytokines secreted by adipocytes are actively involved in lipolysis and thus ensure the normal functioning of hematopoietic stem cells. However, they may

also play a negative role in the abnormal transformation of the BM. In malignant hematologic diseases, adipocytes often promote the proliferation of malignant cells, provide these cells with energy, protect them against chemotherapy agents, and cause drug resistance. Active research on fat cells, adipocyte-derived mediators, and signaling pathways in the BM microenvironment, as well as their role in hematopoiesis and the development of BM disorders, may facilitate the discovery of new methods of diagnosis and treatment of hematological diseases.

Competing Interests

The authors declare that they have no competing interests.

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