Received: 18 January 2023 | Revised: 2 March 2023 | Accepted: 12 March 2023

DOI: 10.1002/jcla.24872

REVIEW ARTICLE

WILEY

# Adipose tissue and hematopoiesis: Friend or foe?

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## Abstract

**Aim:** Hematopoietic stem cells are the origin of all hematopoietic cells. They have the self-renewal ability and can differentiate into various blood cells. In physiological state, most of the hematopoietic stem cells are dormant, and only a few cells proliferate to maintain hematopoietic homeostasis.

**Methods:** This precise steady-state maintenance is regulated by complex mechanisms. Bone marrow adipocytes make up half of all cells in the bone marrow cavity, a feature that has attracted the attention of researchers from multiple fields. The adipocyte density within marrow increases during aging and obesity.

**Results:** Recent studies have shown that bone marrow adipocytes play important roles in regulating hematopoiesis, but the effects of bone marrow adipocytes on hematopoiesis are often conflicting. Bone marrow adipocytes, participating in the formation of bone marrow hematopoietic microenvironment, influence hematopoiesis positively or negatively. In addition, other adipose tissue, especially white adipose tissue, also regulates hematopoiesis.

**Conclusion:** In this review, we describe the role of adipose tissue in hematological malignancies, which may be useful for understanding hematopoiesis and the pathogenesis of related diseases.

KEYWORDS
adipose tissue, bone marrow, hematopoiesis

## 1 | INTRODUCTION

Hematopoietic stem cells (HSCs) are considered the most important part in the hematopoietic system. HSCs can give rise to all mature hematopoietic cells and maintain homeostasis. It is now recognized that the hematopoietic process is carried out in a stepwise and hierarchical manner. HSC is considered to be at the top of the hematopoietic system, and they have long-term self-renewal ability and multi-directional differentiation potential. Through downward differentiation step by step, they can provide various mature blood cells for the body, while maintaining their own function and quantity stability. Long-term hematopoietic stem cell (LT-HSC) located at the top are used to meet the huge daily hematopoietic demand and maintain the lifelong activity of stem cell pool meanwhile. At present, it is widely believed that this hierarchical structure can maintain the steady state and undifferentiated state of LT-HSC.[1] LT-HSC is activated only by extracellular signals and then produces cells with enhanced proliferation ability but short life span, including short-term hematopoietic stem cell (ST-HSC) and multipotent progenitor cell (MPP). ST-HSC has limited self-renewal ability, while MPP has no self-renewal ability. MPP further differentiates into myeloid common progenitor cell (CMP) and lymphoid common progenitor cell (CLP). CMP further differentiates into mononuclear progenitor cells, megakaryocyte precursor cells, and erythroid progenitor cells, while the CLP differentiates into T-lineage progenitor cells, B-lineage progenitor

cells, natural killer progenitor cell (NK cell) and dendritic cell (DC), and finally differentiates into mature terminal cells.[2,3]

Early studies suggested that the function of adipose tissue only involves storing lipids to maintain the energy balance of the body, and it has certain protective and buffering functions. In recent years, more and more studies have found that adipose tissue is the key endocrine and immune organ to regulate the body's homeostasis. Marrow adipose tissue (MAT) is located in the marrow cavity, accounting for more than 10% of the total body fat in healthy adults over 25 years old.[4] In the past, it was thought that bone marrow adipocytes (BMAds) were only used to fill the extra space of bone marrow cavity when bone mass was reduced or hematopoiesis was damaged, but increasing evidence showed that BMAds, as an important part of hematopoietic microenvironment, affect the self-renewal and differentiation of HSCs by secreting adiponectin, leptin, prostaglandin, IL-6, and other fat-derived factors.[5–10] Moreover, macrophages in white adipose tissue (WAT) can regulate metabolic homeostasis by promoting the utilization of glucose by adipocytes under normal conditions, and can affect sympathetic nerve tension, control lipid storage and release, and increase energy expenditure.[11,12] When obesity occurs, many cytokines can activate macrophages in WAT, causing the imbalance of sugar, fat and energy metabolism, and inducing insulin resistance and adipose tissue inflammation.[13,14] Therefore, this article reviews the relationship between adipocytes and hematopoietic homeostasis based on currently available data.

## 2 | CLASSIFICATION AND FUNCTION OF ADIPOCYTES

Both in rodents and in humans, adipocytes can be generally divided into five types: white, brown, beige, pink, and yellow adipocytes. They have distinct functions, including energy storage, cytokines secretion, regulating hunger and satiety, thermogenesis, and participating in the occurrence and development of various diseases (Figure 1).

### 2.1 | White adipose tissue

WAT is mainly composed of subcutaneous adipose tissue and visceral adipose tissue, accounting for about 10% of body weight. Subcutaneous adipose tissue is mainly distributed in thighs, buttocks, pubic region, abdomen. The adipose tissue in pelvic region is also a kind of typical subcutaneous adipose tissue.[15] Visceral adipose tissue refers to the adipose surrounding the inner organs. WAT is highly dynamic, plastic, and heterogeneous, and plays a key role in a series of biological processes. For example, it is the main hub of lipid storage and release, and acts as an endocrine organ regulating systemic insulin sensitivity, glucose homeostasis,[16–19] and feeding behavior through secreting various cytokines.[20,21] The best-known function of WAT is to store surplus energy in the form of triglycerides, which can be released again in case of higher demand or food shortage.[22]

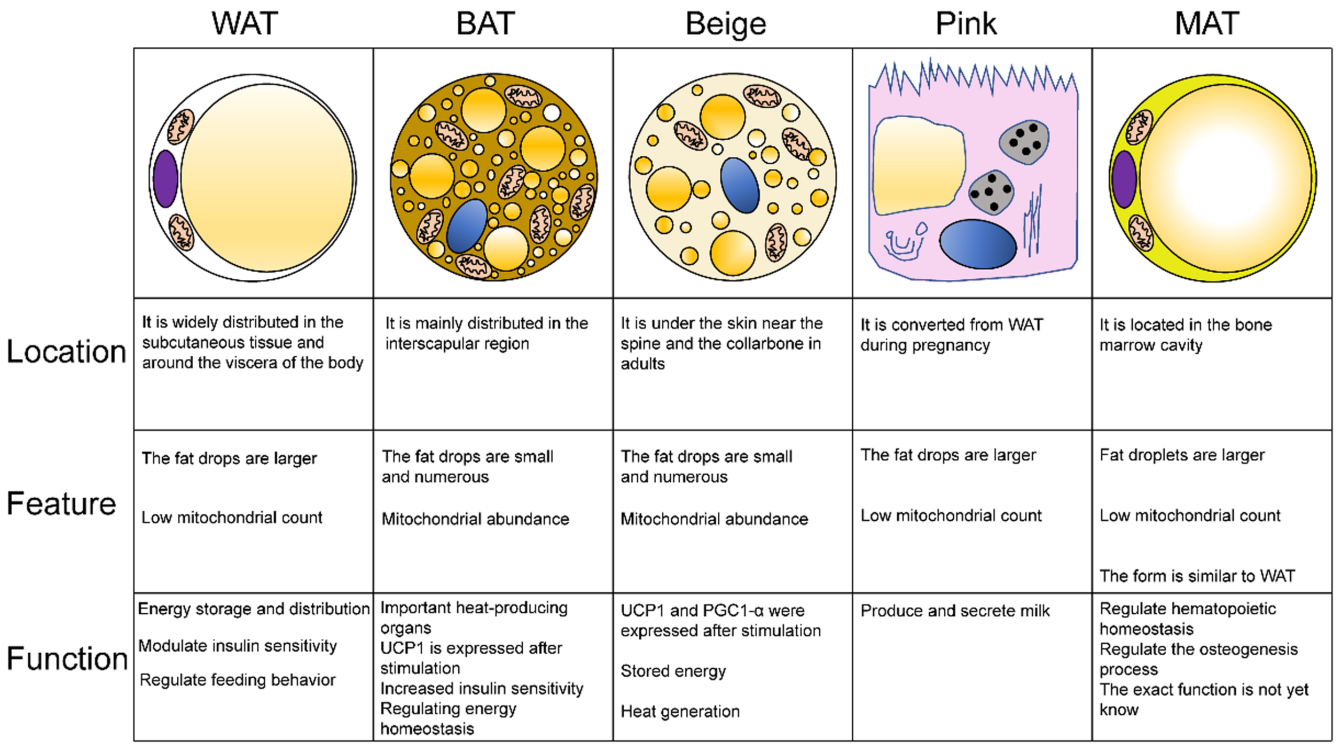


FIGURE 1 Phenotypes of WAT, BAT, Beige, Pink, and MAT. The typical phenotypic appearance of WAT, BAT, Beige, Pink, and MAT is described with the different functions of the respective adipose tissue.

### 2.2 | Brown adipose tissue , beige adipose tissue, and pink adipose tissue

Brown adipose tissue (BAT) derives from the paraxial mesoderm and is widely distributed in scapular and subscapular areas, neck, cervix, aorta, and kidney. Instead of saving fat, BAT generates heat by burning stored triglycerides in a process called nonshivering thermogenesis. This process is mediated by close coordination of uncoupling protein-1 (UCP1) and mitochondrial oxidative machinery. At the same time, BAT can also increase insulin sensitivity and improve insulin resistance, which plays an important role in regulating the balance of energy metabolism.[23–25] It has been reported that BAT activity is inversely related to body fatness. Because of its potential role in stimulating energy expenditure, BAT is protective against body fat accumulation.[26,27] Beige adipose tissue can originate from myoregulatory factor 5 negative progenitor cells (Myf5-). Beige adipose tissue is widely distributed in skeletal muscle, subcutaneous, and retroperitoneal white adipose tissues.[15,28,29] Bostrom found that the expression level of UCP1 in subcutaneous beige adipocytes of transgenic mice with high expression of PGC1-α increased after exercise. In vitro experiments showed that PGC1-α could induce the occurrence of fat beige.[24] Pink adipose tissue is an alveolar cell composed of pink adipocytes, which are transformed from white adipose tissue during pregnancy and lactation, and it produces and secretes milk.[30]

### 2.3 | Marrow adipose tissue

MAT is a unique adipose tissue within the distal skeleton including the tail, hands, and feet. The bone marrow in the marrow cavities of young children is red marrow. After the age of 5, the red marrow in the long bones is gradually replaced by adipose tissue, which becomes yellow marrow, that is, bone marrow steatosis, therefore the color yellow was assigned to MAT. Its essence is the increase in fat cells in the bone marrow, which is called MAT and also called yellow adipose tissue.[31] In normal adults over the age of 18, the red bone marrow and yellow bone marrow each account for half of the total marrow.[32] MAT shows unique biological characteristics versus other adipose tissues.[33,34] As an active participant in hematopoietic microenvironment, MAT adipocytes play a regulatory role in hematopoiesis by secreting specific factors, affecting the maintenance and reconstruction of HSCs and the differentiation of downstream hematopoietic progenitor cells.[35–38]

## 3 | DIFFERENTIATION OF HEMATOPOIETIC STEM CELLS

Hematopoietic stem cell (HSC) is the basis of the mammalian blood system, which contains over ten distinct mature cell types. HSC possesses self-renewal and multipotency capacity. Having multipotency means being able to differentiate into all types of blood cells. Self-renewal is the ability to generate itself through cell divisions. Hematopoietic homeostasis can be affected by the balance between self-renewal and differentiation. HSC are located at the top of the hematopoietic system in the bone marrow, so they are responsible for maintaining the homeostasis of the blood system.[39] There are two forms of HSC, long-term and short-term, and their self-renewal and differentiation abilities are different. ST-HSC differentiates into MPP. MPP do not have self-renewal ability, but they keep the potential to differentiate into myeloid CMP and CLP both CMP and CLP belong to relatively early hematopoietic progenitor cells, which still have strong proliferation ability and multi-lineage differentiation ability. They can further differentiate into erythroid cells, granulocyte-macrophage progenitors and megakaryocyte progenitors, and then differentiate into mature hematopoietic cells from their corresponding progenitors and enter the peripheral blood. Erythroid cells include erythroid precursor cells (protoerythrocytes, basophilic normal mother cells, polychromatic normal mother cells, and orthochromatic normal mother cells) in bone marrow, reticulocytes, and erythrocytes in bone marrow and peripheral blood flow. Granulocytic cells include lymphocytes and myeloid cells. Lymphatic system consists of T cells and B cells. Myeloid cells include the remaining white blood cells, including monocytes, macrophages, and neutrophils. Dendritic cells and natural killer cells can develop from myeloid or lymphatic system. Megakaryocytes are bone marrow progenitor cells of platelets (Figure 2).

## 4 | MARROW ADIPOSE TISSUE AFFECTS HEMATOPOIETIC HOMEOSTASIS

### 4.1 | Marrow adipose tissue negatively regulates HSC differentiation

It has long been widely believed that adipocytes inhibit the differentiation of HSCs. This is first reported by Naveiras et al., who found the negative regulatory role of MAT in hematopoiesis.[40] Their findings showed that the generation of HSC and short-term progenitors was reduced in the adipocyte-rich caudal vertebrae compared with the adipocyte-free thoracic vertebrae of mice.[40] In “fatless” A-ZIP/F1 mice, bone marrow engraftment was accelerated after irradiation in mice treated with peroxisome proliferator-activated receptor gamma (PPARγ) inhibitors compared with wild-type or untreated mice.[40] Another study found that compared with the adipocytes-increased group, the white blood cell (WBC) counts in the long bone marrow of the mice in the adipocyte inhibition group recovered faster after chemotherapy. Additionally, the number of CD45(+) bone marrow cells in the tail fatty marrow and the number of colony-forming units also increased in adipocyte-inhibited mice.[41] In obese-diabetic (db/db) and HFD-fed mice, the density of bone marrow cells decreased significantly with the accumulation of BMAds.[42] In bone marrow of high-fat diet-induced obese mice (DIO), the increase in BMAds inhibited the proliferation of lineage (–) Sca-1 (+) c-Kit (+) (LSK) cells, CLP and CMP progenitor cells.[43] More seriously, the destruction of hematopoietic function in HSCs by mouse BMAds via affecting lipid raft/TGF-β signaling pathway is also irrecoverable

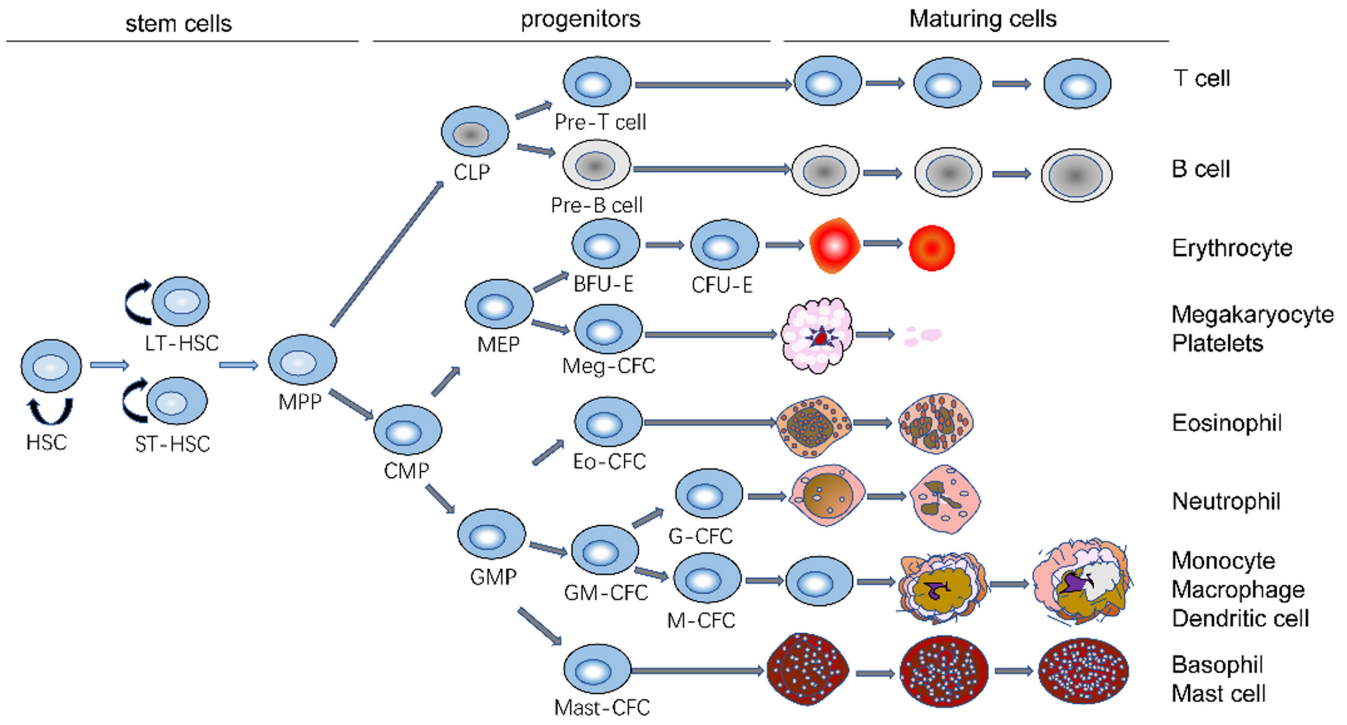


**FIGURE 2** Diagram of hematopoietic stem cell differentiation and development. Hematopoietic stem cells proliferate and differentiate into different progenitor cells which then differentiate into mature blood cells with different morphologies. The curved arrow indicates that cell self-renewal. Megakaryocyte/erythroid progenitor, BFU-E; colony-forming unit-erythroid; CFU-E; megakaryocyte colony-forming cells; Eo-CFC; granulocyte/macrophage progenitor cell; G-CFC; macrophage colony-forming cells; GM-CFC; granulocyte-colony forming cells; GMP; burst-forming unit erythroid; M-CFC; mast cell progenitors, mast-CFC; Meg-CFC; eosinophil colony-forming cell; MEP; granulocyte-macrophage progenitor.

after bone marrow transplantation (BMT).[44] These results suggest that MAT in the microenvironment of bone marrow may affect the proliferation and migration of hematopoietic cells negatively and indicate that inhibition of bone marrow adipogenesis may enhance hematopoietic recovery in clinical BMT.

## 4.2 | Marrow adipose tissue inhibits myeloid cell and lymphocyte differentiation of HSC

The development and maturation of B lymphocytes can be affected by several aspects during this process,[45] suggesting that MAT may play an important role in multi-lineage differentiation and development. Co-culture of rabbit bone marrow mononuclear cells with OP9 stromal cells and rabbit primary adipocytes in transwell conditions showed that in the presence of adipocytes, the ability of OP9 stromal cells to promote the generation of CD79a+B cells were significantly decreased, but it did not reduce the generation of CD14+ myeloid cells. These results suggest that adipocyte can secrete a soluble factor that selectively inhibits the production of B lymphocytes.[46–48] The same results were obtained in these studies.[45,49–51] The organotin compound tributyltin (TBT) can activate the apoptosis of developing B cells in vitro, induce the formation of adipocytes in bone marrow in vivo, and reduce the number of "aging-sensitive" AA4+CD19+B cells in bone marrow and B cells in spleen.[52] In addition, it has been reported that MAT can directly contact with hematopoietic cells. neuropilin-1 (NP-1) high expression level correlates with adipocytes accumulation in bone marrow of femoral, which could down-regulate granulocyte colony-stimulating factor (G-CSF) production and then lead to defective granulocytes production.[53,54] PPARγ deficient mice showed decreased MEP, increased GMP and increased granulocyte/macrophage progenitor cell ratio, but no change in CMP in BM compared with wild-type mice. Meanwhile, Sfpi/PU1 and Gata2 levels were increased while Gata1 remained unchanged in long bone of PPARγΔ/Δ mice.[55]

## 4.3 | Marrow adipose tissue positively regulates HSC differentiation

Although excessive accumulation of MAT is generally considered to be detrimental to hematopoiesis, it has also been proposed that adipocytes play a positive role in the hematopoietic niche. Zhou BO , et al. have found that the physiological hematopoietic stem cell niche, including endothelial cells and marrow stromal cells (MSCs), will be temporarily destroyed after irradiation, and MSC will urgently initiate adipogenic differentiation. In order to maintain the level of stem cell factor (SCF) in bone marrow, newly generated adipocytes become a temporary hematopoietic stem cell niche and maintain the basic hematopoietic function of the body by secreting

SCF.[8] Interestingly, contrary to previous findings,[40] mice with "fatless" A-ZIP/F1 showed delayed hematopoietic regeneration in the long bones with fewer adipocytes but not in the tail vertebrae with abundant adipocyte.[8] In addition, serious extramedullary hematopoiesis (EMH) has been showed in the mice model carrying a constitutive deletion of the gene coding for the nuclear PPARγ.[55] In a comparative study, the proportion of lymphocytes in the bone marrow of obese mice increased by 10%~18% compared with that of the control group, and the proportion of monocytes, granulocytes, erythrocytes and mixed progenitor cell lineages did not change, and the expression of leptin mRNA in bone tissue increased due to the significant increase in adipocytes in the bone marrow of obese mice, indicating that BMAds enhanced hematopoiesis by secreting leptin.[56] Other studies also support this view. Obesity induced by high-fat diet leads to an increase in the number of bone marrow precursor cells of HSCs.[57]

### 4.4 | Marrow adipose tissue in malignant hematopoiesis

There is a growing body of research examining the relationship between MAT and malignant hematological diseases. Studies have found that the expression of autophagy proteins Atg3, Atg5, and LC3-I/II in multiple myeloma (MM) cells treated with adipocyte-conditioned medium were up-regulated, demonstrating the importance of BMAds in the reduction in myeloma cells responding to chemotherapy.[58] In addition, exosomes long non-coding RNA (LncRNA), LOC606724 and SNHG1, upregulation in MM patients' adipocytes could protect MM cells from chemotherapy-induced apoptosis.[59] Bone marrow biopsy of MM patients showed significant loss of MAT, but MAT recovered after treatment. In addition, multiple myeloma cells could alter gene expression and cytokine secretion in adipocytes. This suggests a bidirectional interaction between BMAd and myeloma cells.[60]

Evidence is accumulating that MAT also influences survival and proliferation of leukemic blasts. Co-culture experiments using mouse embryo fibroblasts 3 T3-L1 and primary bone marrow MSC adipocytes with acute lymphoblastic leukemia (ALL) cells showed that the proliferation of ALL cells was inhibited.[61] MAT has been found to negatively affect the proliferation of T-ALL in vitro and in vivo, thereby mediating chemoresistance.[62] However, BMAds from the tumor microenvironment were found to support the survival and proliferation of malignant cells from acute myelocytic leukemia (AML) patients in a study on the pathogenesis of AML.[63] Knockdown of FABP4 using shRNA prevented AML blast proliferation and, in addition, FABP4 improved mouse survival in the Hoxa9/ Meis1-driven AML model.[63]

## 5 | OTHER ADIPOSE TISSUE AFFECTS HEMATOPOIETIC HOMEOSTASIS

Jinah Han et al. found that HSCs exist in the gonadal WAT, which originated from bone marrow. The results show that adipose tissue can be used as an alternative extramedullary tissue for HSC, and it is also a new resource for carrying out HSC transplantation.[64] In leptin-deficient obese mouse (ob/ob), it is found that the number of B cells in the bone marrow decreased by 70%, the absolute number of pre-B cells and immature B cells decreased to 21% and 12% of normal, and the absolute number of granulocytes and monocytes decreased by 40% and 25%, respectively, via comparing with C57BL/6 wild-type lean mice. After the treatment of ob/ob mice with recombinant leptin, the lymphocytes increased significantly. These data indicated that adipocytes suppress the production of lymphocytes and myeloid cells by secreting leptin.[65] Adiponectin is a protein hormone mainly secreted by adipocytes and abundant in the blood circulation. Adiponectin has a significant inhibitory effect on the colony formation of granulocyte-macrophage colony-stimulating factor (GM-CFU), macrophage-colony-stimulating factor (M-CFU) and granulocyte-colony-stimulating factor (G-CFU). The expression levels of anti-apoptotic genes (Bcl-xL and bcl-2) were down-regulated in M1 macrophages treated with adiponectin, especially bcl2, suggesting that adiponectin inhibits the differentiation of granulocyte-monocytic lineage by regulating bcl2.[66] Adiponectin can activate protein kinase A (PKA), resulting in a decrease in AKT activity and an increase in AMP-activated protein kinase (AMPK) activity. The level of adiponectin is decreased in obese MM patients, and adiponectin plays an anti-myeloma role in MM by regulating PKA/AMPK signaling.[67] In an earlier study, leukemia cells and lymphoma cells were found in pericardial fat and subcutaneous WAT.[68] Compared with 3/12 mice in the control group, there are 7/12 DIO mice treated with vincristine after injecting highly malignant pre-b lymphoblastic BCR/ABL+ leukemia cells developed progressive leukemia. These findings highlight that adipocytes may be responsible for the relapse of ALL resistance in obese leukemia patients.[69]

## 6 | SUMMARY AND PROSPECT

The aging and obesity are all accompanied by bone marrow steatosis.[70–73] Bone marrow steatosis is closely related to the formation of BMAds, which are derived from MSC.

Until now, the role of adipocytes in hematopoiesis is complicated and controversial, which may be mediated by various mechanisms. BMAds, as active participants in the hematopoietic microenvironment, play important roles in hematopoiesis by secreting specific factors. BMAds could affect the maintenance of HSCs as well as the differentiation of downstream hematopoietic progenitor cells. But its detailed mechanism role of BMAds in hematopoiesis has not been clarified. Age, gender, and anatomical location of BMAds are all related to the development of bone marrow fat, but little is known about their potential and process of MSCs differentiation into BMAds.[74–78] In addition, most of the data on the role of adipocytes in hematopoietic development are derived from animal experiments, through studying the life signs of obese mice or leptin deficient mice. The mysteries of hematopoietic cell evolution and the key regulatory mechanisms of blood

diseases remain to be explored. Aging accelerates bone marrow steatosis in mice and humans. Additionally, the part of red bone marrow in humans is highly fatty long before senescence, whereas mouse bone marrow remains relatively adipocytic until advanced age.[79,80] If these problems can be further studied, people will have a new understanding of the physiological function of adipocytes and its relationship with hematopoiesis.

## AUTHOR CONTRIBUTIONS

Na He contributed to the writing of the article. Yue Wu conceived and finalized the content of the article. All authors reviewed, contributed to the revisions, and finalized the drafts.

## FUNDING INFORMATION

This work was supported by the National Natural Science Foundation of China (32100614) and Natural Science Foundation of Shandong Province (ZR2021QC069).

## CONFLICT OF INTEREST STATEMENT

The authors declare there is no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## CONSENT FOR PUBLICATION

All authors agree to publish this article.

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**How to cite this article:** He N, Liu M, Wu Y. Adipose tissue and hematopoiesis: Friend or foe? *J Clin Lab Anal*. 2023;37:e24872. doi:10.1002/jcla.24872