Review Article

Relationship between adipocytes and hematological tumors in the bone marrow microenvironment: a literature review

Yuchun Li[1], Linlin Wang[1], Jingyu Wang[1], Yaping Xin[2], Xiaodong Lyu[1]

[1]Central Laboratory, the Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; [2]Department of Endocrinology and Metabolic Diseases, the Second Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Contributions: (I) Conception and design: X Lyu, Y Li; (II) Administrative support: L Wang; (III) Provision of study materials or patients: Y Xin; (IV) Collection and assembly of data: J Wang; (V) Data analysis and interpretation: Y Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Xiaodong Lyu, MD, PhD. Chief Physician, Central Laboratory, the Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, 127 Dongming Street, Zhengzhou 450008, China. Email: zlyyxiaodonglyu1268@zzu.edu.cn.

Background and Objective: The bone marrow microenvironment is closely related to normal hematopoiesis and hematologic tumors. Adipocytes are an important part of the bone marrow microenvironment, in which they can release free fatty acids (FFAs) through lipolysis and secrete adipocytokines, etc., and participate in normal hematopoiesis, which is closely related to the occurrence and treatment of hematological tumors. In this review, we aim to discuss how bone marrow adipocytes (BMAs) can influence the proliferation, apoptosis, and chemotherapy resistance of cancer cells by reprogramming lipid metabolism and the secretion of various adipocytokines.

Methods: Studies from 2000 to July 2024 were reviewed from PubMed, Springer Link, and the Web of Science using the keywords bone marrow microenvironment, adipocytes, lipid metabolism, adipocytokines, hematological tumor, cancer, and their combinations. Unreliable articles such as those that are old and have a low impact factor are excluded, and there is no restriction on language.

Key Content and Findings: Adipocytes can regulate the proliferation and differentiation of hematopoietic stem cells (HSCs) by secreting inflammatory factors and adipocytokines to maintain hematopoietic homeostasis. Adipocytes can also stimulate and accelerate the occurrence and progression of hematological tumors by secreting adipocytokines and mediating the reprogramming of lipid metabolism. Moreover, abundant adipocytes in bone marrow can protect tumor cells by physically blocking and/or secreting cytokines, leading to chemotherapy resistance.

Conclusions: Therefore, the targeted inhibition of related lipid metabolism pathways and adipocytokines might be a potential therapeutic target for hematological tumors, which would be helpful to inhibit tumor growth and correct chemotherapy resistance.

Keywords: Lipid metabolism; adipocytes; bone marrow microenvironment; hematological tumor; adipocytokines

Submitted Jan 09, 2024. Accepted for publication Aug 29, 2024. Published online Oct 12, 2024.
doi: 10.21037/tcr-24-52
View this article at: https://dx.doi.org/10.21037/tcr-24-52

Introduction

Bone marrow is the origin of normal hematopoietic cells and hematological tumor cells, and the growth of these cells is not isolated from the surrounding environment but occurs in close contact with the microenvironment. The bone marrow microenvironment is composed of hematopoietic stem cells (HSCs), stromal cells, and cytokines secreted by these cells, among which adipocytes are an important component of the bone marrow microenvironment (1,2). Bone marrow adipocytes (BMAs) are derived from bone marrow mesenchymal stem cells (MSCs) that transform into adipoblasts, pre-adipocytes, immature adipocytes, and

Table 1 The search strategy summary

Items	Specification
Date of search	The first search was conducted on 11/20/2023. The last search was conducted on 7/10/2024
Databases and other sources searched	PubMed, Web of Science, Springer Link
Search terms used	Bone marrow microenvironment, adipocytes, lipid metabolism, adipocytokines, hematological tumor, cancer, and their combinations
Timeframe	From 2000 to July 2024
Inclusion and exclusion criteria	Unreliable articles such as those that are old and have a low impact factor are excluded, and there is no restriction on language
Selection process	Y.L., L.W., and J.W. conducted the selection and agreed with the other authors

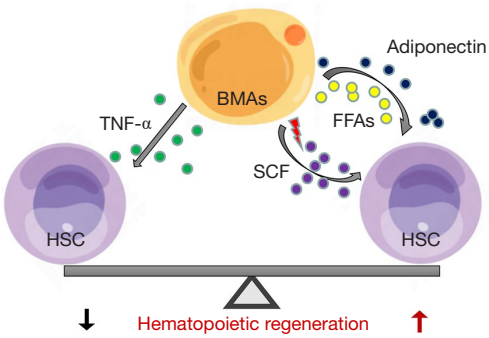

Figure 1 Dual effects of BMAs on HSCs. In the bone marrow microenvironment, BMAs can negatively regulate the proliferation of HSCs by releasing TNF-α. Nevertheless, BMAs also have a positive regulatory activity effect on HSCs through lipolysis (FFAs) and secretion (adiponectin and SCF). BMAs, bone marrow adipocytes; FFAs, free fatty acids; TNF-α, tumor necrosis factor-α; SCF, stem cell factor; HSC, hematopoietic stem cell.

lastly mature adipocytes under a series of stimuli. They are susceptible to the surrounding environment and signals promoted by aging and diseases, such as obesity, as well as drug administration (1,3). In the bone marrow microenvironment, adipocytes participate in normal hematopoiesis via the release of free fatty acids (FFAs) via lipolysis and the secretion of adipocytic factors, which are closely related to the development and treatment of hematological tumors (4). We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-52/rc).

Methods

We conducted a search of PubMed, Springer Link, and the Web of Science database for this narrative review, covering the period from 2000 to July 2024. The search strategy details are provided in *Table 1*. This review encompasses original research, review articles, and expert consensus documents. Additional literature was found through citations in articles identified in our search.

Dual role of BMAs in HSCs

BMAs have a dual effect on HSCs (*Figure 1*). The accumulation of BMAs owing to obesity or aging was found to impair hematopoietic functions (5). Moreover, the number of HSCs was found to be reduced and circulatory capacity was impaired in adipocyte-rich tail vertebrae compared to those in adipocyte-poor thorax vertebrae (6). Furthermore, during post-transplant hematopoietic reconstitution, BMAs can negatively regulate the proliferation of HSCs by releasing tumor necrosis factor (TNF)-α (7,8). Nevertheless, BMAs also have a positive regulatory effect on HSCs. FFAs released by BMAs via lipolysis were reported to be an energy source for the survival, proliferation, and differentiation of HSCs (5,9). Study has also confirmed that irradiated BMAs can secrete stem cell factors that promote HSC regeneration and hematopoietic reconstitution (5). In mouse experiments, BMAs were found to secrete adiponectin, which activates the p38 MAPK pathway and stimulates HSC proliferation. Moreover, HSCs treated with adiponectin showed enhanced hematopoietic reconstitution potential in mice, whereas adiponectin-deficient mice experienced defective hematopoietic reconstitution after chemotherapy (10,11). Furthermore, in bone marrow culture, recombinant adiponectin impedes adipocyte formation and stimulates the proliferation of HSCs (12). Therefore, BMAs can positively and negatively

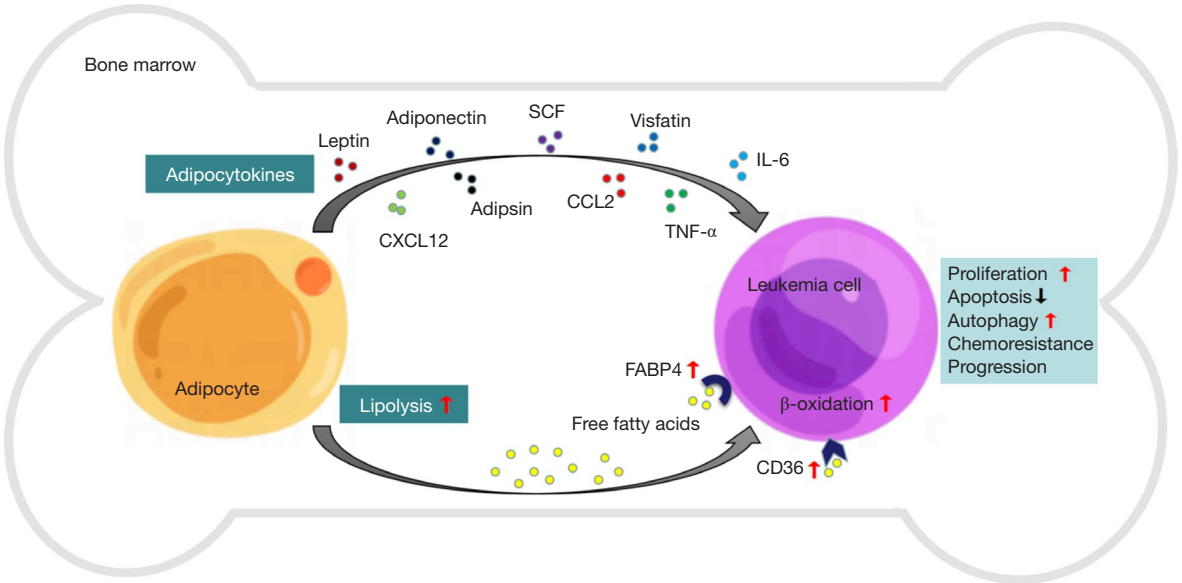

Figure 2 BMAs accelerate the occurrence and progression of hematologic tumors. The activation of adipocyte lipolysis and the upregulation of CD36 and FABP4 expression can accelerate FFA transfer to leukemia cells as an extra source of energy for β-oxidation. In addition, BMAs can also secrete some adipocytokines, such as adiponectin, leptin, and IL-6, which will affect the occurrence and progression of hematological tumors. SCF, stem cell factor; IL-6, interleukin 6; CXCL12, C-X-C motif chemokine ligand 12; CCL2, C-C motif chemokine ligand 2; TNF-α, tumor necrosis factor-α; FABP4, fatty acid-binding protein 4; BMAs, bone marrow adipocytes; FFA, free fatty acid.

regulate HSCs through different pathways to maintain hematopoietic homeostasis *in vivo*.

Adipocytes and hematological cancers in the bone marrow microenvironment

BMAs can accelerate the occurrence and progression of hematologic tumors through lipid metabolic reprogramming and the secretion of adipokines. For example, in acute myeloid leukemia (AML), enhanced levels of lipase phosphorylation and the activation of lipolysis in BMAs contribute to improving levels of FFAs in the bone marrow microenvironment, which in turn can accelerate fatty acid transfer and provide a source of energy for tumor cell β-oxidation by upregulating tumor cell surface fatty acid translocase CD36 (13). In addition, BMAs can also secrete some adipocytokines, such as adiponectin, leptin, and TNF-α, which will affect the occurrence and progression of hematological tumors (*Figure 2*) (14).

Notably, tumor cells can also regulate the differentiation and maturation of adipocytes. For example, in multiple myeloma, bone marrow biopsies showed a significant decrease in BMA numbers upon invasion of the bone marrow by myeloma cells, as well as the recovery of BMA numbers after treatment. *In vitro* and *in vivo* experiments have also indicated that myeloma cells can reduce the number of BMAs and interfere with gene expression and adipocytokine secretion in adipocytes (15).

Hematological cancer stem cells

Cancer stem cells are a group of infinitely proliferating, self-renewing, and highly heterogeneous cells. These cells are dormant for a long time, have a variety of mechanisms for drug resistance, and are responsible for the occurrence, progression, and recurrence of hematological tumors (16,17). An increased number of adipocytes contribute to the formation of lipid droplets in cancer stem cells, which can promote their tumorigenesis and self-renewal. The associated lipid saturation of the cell membrane, which can affect cell mobility, is a key factor in signal transduction, cell division, and migration (18). Therefore, BMAs might also be closely related to the leukemic stem cells (LSCs). When cocultured with AML primitive cells *in vitro*, BMAs can improve the transport capacity of fatty acids in AML blastocysts by activating adipocyte lipolysis and increasing fatty acid-binding protein (FABP)4 levels. Hence, LSCs and/or AML blastocysts can regulate adipocytes via

feedback to maintain high metabolic levels to meet the fatty acid requirements of cancer cells (19). Of note, the bone marrow adipose tissue can also protect LSCs by mediating their silencing and chemotherapy resistance, thereby representing a risk factor for poor prognosis in AML (20). In addition, unsaturated fatty acids released from adipocytes can not only directly accelerate the development of leukemia by promoting the differentiation of LSCs but also accelerate its progression by stimulating mesenchymal stromal cells to secrete angiogenic factors (21).

MSCs

MSCs play an integral role in the bone marrow niche. They provide newly differentiated osteoblasts for bone tissue regeneration and tightly control the fate of HSCs through direct interaction and secretion of growth factors, cytokines, and other soluble factors (22). Among them, C-X-C motif chemokine ligand 12 (CXCL12) abundant reticular (CAR) cells and $LepR^+$ MSCs can differentiate into adipocytes and play an important role in the HSCs ecological niche.

CAR cells, a type of MSCs, are capable of differentiating into adipocytes and osteoblasts, which are essential for maintaining the homeostasis of the bone marrow microenvironment. CAR cells are adjacent to HSCs inside and outside the endothelial zone and regulate high expression of CXCL12, interleukin (IL)-7, angiopoietin-1, and osteopontin (OPN), genes that are important for participating in HSC maintenance (23). $LepR^+$ MSCs within the bone marrow are important cellular components of the HSC niche and are critical for the maintenance of the HSCs niche. $LepR^+$ MSCs contribute to bone and adipocyte formation in adult bone marrow, and in addition, proliferation of $LepR^+$ cells was observed in bone marrow after injury (24).

The Notch signaling pathway plays a central role in maintaining homeostasis of bone marrow MSCs, and its dysregulation leads to blood tumors (25). The Notch signaling pathway plays a role in the development and progression of T-cell acute lymphoblastic leukemia (T-ALL), and more than 60% of T-ALL patients have mutations in the Notch pathway (26). The Notch signaling pathway is dysregulated in multiple myeloma through overexpression of receptors and ligands, and direct contact between multiple myeloma cells through Notch receptors and ligands can activate the signaling pathway, leading to proliferation and growth of myeloma cells (27). Currently, there are no Food and Drug Administration (FDA)-approved Notch-targeted therapeutic agents, and further studies are needed to fully elucidate the interactions between bone marrow MSCs and the Notch signaling pathway.

Osteoblasts and osteoclasts

The intraosseous cellular ecological niche includes cellular components such as osteoblast lineage cells and osteoclasts and has been recognized as critical for the successful implantation and long-term retention of regenerative HSCs and leukemia initiating cells (28,29). Recent *in vivo* imaging techniques have shown that the expansion of HSCs and AML cells is restricted at specific stages of bone remodeling. Osteoblasts, osteoclasts, and the bone marrow microenvironment synergize to regulate hematopoietic homeostasis (30). Among them, coupling factors secreted by osteoclasts, such as sphingosine 1-phosphate (S1P) regulates HSCs migration and mobilization by interacting with receptors on HSCs (31-33). S1P signaling is central to leukemia initiation, where overexpression of S1PR3 leads to leukemogenesis (34). Ephrin-B2 produced by osteoclasts interacts with EphB4 receptors on osteoblasts, potentially facilitating the expansion of HSCs and improving grafting through mechanisms that have not yet been elucidated (35,36). In addition, osteoclasts can release vascular endothelial growth factor (37) to influence the motility and maintenance of HSCs, as well as promote the mobilization of HSCs by degrading CXCL12 and stem cell factor (38-40). During the bone formation phase, osteoblasts influence the dormancy and self-renewal capacity of HSCs through secreted factors such as OPN (41). OPN is elevated and its level is associated with shorter survival in AML patients (42). These findings highlight the multifunctionality of osteoblasts, osteoclasts in the bone marrow microenvironment and how they influence the behavior and function of HSCs through different mechanisms. These interactions have important implications for understanding the treatment of hematopoietic and hematologic tumors.

Adipocytes interact with other cell types in the bone marrow microenvironment to influence the behavior of HCSs. Adipocytes influence the differentiation and function of osteoblasts by secreting various factors such as adiponectin. Adiponectin are thought to promote osteoblast activity and protect HSCs from inflammation and enhance their self-renewal capacity (43). Adipocytes also secrete factors that promote osteoclast differentiation, such as leptin, DPP4, IL-6, TNF, and CXCL1/CXCL2, which not only promote the formation of osteoclasts, but also inhibit

the differentiation of osteoblasts, which in turn promotes an inflammatory immune phenotype (44,45). With age, adipocytes tend to differentiate more, which is associated with bone aging. Aging adipocytes exacerbate the process of bone destruction by secreting factors such as RANKL (46). This information emphasizes the important role of adipocytes in bone remodeling and hematopoiesis and how they regulate osteoblast and osteoclast activity by secreting multiple factors.

Lipid metabolism

Adipocytes mediate the reprogramming of lipid metabolism in cancer cells. For example, even under aerobic conditions, the metabolism of tumor cells shifts from oxidative phosphorylation to glycolysis, a process known as the Warburg effect. Most tumor cells start to rely more on extra sources of energy precisely because of the programmed increase in glucose uptake and reduced utilization of glucose via oxidation in the tricarboxylic acid cycle. For example, through the transcription of peroxisome proliferator-activated receptor (PPAR)-γ and hypoxia-inducible factor 1-mediated expression of FABP3, FABP4, and FABP7, tumor cells can promote the uptake and utilization of extracellular fatty acids (47).

Adipocytes can mediate reprogramming of lipid metabolism in hematologic tumor cells. Indeed, BMAs were found to upregulate FABP4 levels in AML cells and accelerate the entry of FFAs into mitochondria for β-oxidation. *In vitro* experiments also confirmed that when *FABP4* was deleted in human AML cells or leukemic mice, the proliferation of leukemic cells is inhibited and the lifespan of mice is improved. Moreover, FABP4 can induce DNA methyltransferase 1 overexpression and *CDKN2B* silencing by upregulating IL-6, thereby leading to more aggressive AML (17,48). In chronic lymphocytic leukemia (CLL), increased expression of lipoprotein lipase and PPARγ facilitates cellular uptake of lipoproteins and binding to FFAs, thereby activating enzymes required for fatty acid oxidative phosphorylation, which in turn is strongly associated with disease progression and an unfavorable prognosis (49). In addition, fatty acid oxidation also interferes with the oligomerization of the pro-apoptotic proteins B-cell lymphoma (Bcl)-2-associated X and Bcl-2 homologous antagonist/killer proteins, thereby inhibiting cancer cell apoptosis (50).

Cancer cells can also induce morphological and functional adaptations in adipocytes. Experiments involving the coculture of AML cells with BMAs have indicated that growth differentiation factor-15, secreted by cancer cells, can induce cellular morphological remodeling in BMAs, whereas the calcium channel protein TRPV4 in adipocytes can negatively regulate this effect in a feedback mechanism to maintain adipocyte morphology (51,52). Adipocytes could also be stimulated to accelerate lipolysis and release fatty acids. In a hypoxic microenvironment, cancer cells can upregulate FABP4 and lipoprotein lipase levels and consequently promote adipocyte lipolysis signals, which will contribute to accelerating triglyceride hydrolysis and FFA release (49,53). In addition, adipocytes preferentially release monounsaturated fatty acids, which downregulate endogenous lipogenesis in acute lymphocytic leukemia (ALL) cells *in vitro*. Furthermore, unsaturated fatty acids secreted by adipocytes, such as oleic acid, protect ALL cells from low-dose chemotherapy (54). Notably, different types of FFAs have different effects on cells in hematologic tumor cells, ; for example, linoleic acid derivatives confer anticancer effects in AML (55), whereas polyunsaturated fatty acids can induce the apoptosis of human leukemia cells (56).

Adipocytokines

BMAs can also release a series of adipocytokines that is involved in the occurrence and progression of hematologic cancers. In contrast to FFAs, adipocytokines further stimulate the proliferation of cancer cells (57,58). Indeed, when myeloma cells were cocultured with adipocytes, it was found that myeloma cell proliferation and migration could be enhanced by leptin. Moreover, by activating the AKT/STAT3 pathway, upregulated leptin stimulates proliferation and increases chemoresistance in myeloma cells, whereas it increases Bcl-2 levels and inhibits caspase-3 enzyme activity (59). In addition, leptin can also stimulate cell proliferation and cytokine secretion and inhibit apoptosis by activating relevant receptors in myeloid and lytic cancer cells via signaling pathways such as MAPK/ERK1/2 and PI3K (60). In the study of leptin and tumor cell metabolism, leptin can promote tumor cell proliferation by increasing autophagy to promote the degradation of lipid droplets (61). Indeed, blockage of the leptin receptor signaling pathway along with the stimulation of natural killer T cells was shown to improve the outcome of multiple myeloma treatment *in vivo* (62).

Adiponectin, secreted by adipocytes, is important for the regulation of energy metabolism and hematopoietic functions. Adiponectin-activated protein kinase A reduces protein kinase B and AMP-activated protein kinase activities

and can reduce expression of the enzyme acetyl-CoA-carboxylase, thereby contributing to apoptosis and decreasing cell proliferation (63). In addition, adiponectin exerts tumor suppression by inhibiting cell proliferation and suppressing the cell regulatory cycle to induce apoptosis (64).

Lipase secreted by adipocytes can inhibit the apoptosis of myeloma cells induced by chemotherapy by increasing autophagy (65). Moreover, *in vitro* and *in vivo*, TNF-α and IL-6 can stimulate the proliferation of myeloma cells. Similarly, in myeloma cells, they can also upregulate the expression of C-C motif chemokine ligand 2 (CCL2) (66), which will in turn recruit macrophages that will support cell survival, mediate angiogenesis, and confer multidrug resistance to myeloma cells (67). The CCL2/CCR2 signaling pathway plays an important role in cancer development. When CCL2 binds to CCR2, this signaling pathway triggers the activation of multiple downstream signals with complex effects on cancer development. CCL2/CCR2 binds to and activates GPCR, leading to the activation of multiple downstream pathways. pI3K activates Akt, which in turn promotes survivin expression of G protein-coupled chemokine receptors and inhibits the cell death pathway, and the PI3K/Akt pathway is essential for cell survival and proliferation (68-70). The PI3K/Akt pathway also plays a central role in chemotaxis, promoting the expression of matrix metalloproteinase-9, which helps tumor cell migration by degrading the extracellular matrix (71). In addition, activation of MEK/ERK and JAK/STAT pathways further regulates gene expression and promotes cancer cell migration (72-74). CCL2 also enhances migration of multiple tumor cells through Smad3 and MAPK signaling (75). Overall, the CCL2/CCR2 signaling pathway affects the biological behaviors of tumor cells, such as survival, proliferation, and migration, and thus cancer development and progression, by regulating multiple downstream signaling pathways (76). This pathway could be one of the potential targets for the treatment of cancer, and its blockade may help to inhibit cancer development and metastasis.

BMAs and hematological cancer therapy

Chemotherapy resistance

There is a close relationship between BMAs and chemotherapy resistance in hematological tumor cells. The differentiation and maturation of BMAs comprise a dynamic process, which is accelerated after stimulation by external damaging signals, such as chemotherapy. By physically blocking and/or secreting cytokines, adipocytes enriched in the bone marrow protect cancer cells from the cytotoxicity of chemotherapeutic drugs (77). In ALL patients, adipocytes can secrete stromal cell-derived factor-1α, which was found to bind to chemokine C-X-C motif receptors (CXCRs) on cancer cells, thereby inducing cytoskeletal remodeling and migration to adipose tissue (78). Moreover, adipocytes can reduce the cytotoxic effect of chemotherapeutic drugs on ALL cells, leading to drug resistance, by physically blocking the lipophilic vincristine or by catabolizing erythromycin. Adipocytes can also secrete cytokines to protect leukemia cells. ALL cells, which exhibit accelerated production of intracellular reactive oxygen species, were found to promote the secretion of cytokines by adipocytes in response to oxidative stress, which would in turn protect the tumor cells from cytotoxicity and radiotoxicity (79).

Similarly, by regulating the growth and apoptosis of tumor cells, adipocytes can also induce drug resistance. Adipocytes were found to lead to cancer cell resistance to vincristine, nilotinib, and zofranil by reducing apoptosis and regulating the cell cycle in ALL cells. Moreover, In AML, Shafat *et al.* report that AML blasts cocultured with BMA show reduced apoptosis and enhanced proliferation (19). Thus, adipocytes not only physically block the cytotoxicity of chemotherapeutic drugs but also alter the balance of apoptotic signals, increase the expression of pro-survival signals, and ultimately lead to drug resistance in cancer cells, thereby increasing the risk of treatment failure (80).

Targeted therapy

Although hematological oncology chemotherapy has achieved better clinical outcomes, refractory disease, and recurrence remain the main causes of death in patients with cancer. BMAs are closely associated with the occurrence and progression of hematologic tumors; therefore, targeting the signaling pathways connecting these two cellular entities, such as targeting lipolysis and the oxidative utilization of fatty acids, blocking the energy sources of tumors, or regulating the expression/activity of adipocytokines, might represent valuable strategies for the treatment of hematological tumors (81).

Inhibitors of lipid metabolism

Fatty acid oxidation mechanisms are a potential therapeutic target for cancer. In the bone marrow microenvironment, tumor cells take up FFAs to provide energy for cell growth via mitochondrial β-oxidation. Cholesterol is thought to promote

tumor cell proliferation, migration, and invasion (82). Moreover, a study investigating lipid metabolism-targeted therapy in CLL revealed that FFAs can increase the metabolic rate of CLL blastocysts and cause resistance to cytotoxic drugs (83). In contrast, FABP4 inhibitors reduce the transfer of FFAs between BMAs and leukemia cells; thus, FABP4 could be a potential target to inhibit the proliferation of leukemia cells and improve patient survival outcomes (19). Additional study also showed that lipase and phospholipase are overexpressed in CLL cells, with the lipase inhibitor orlistat promoting the apoptosis of leukemia cells by preventing intracellular phospholipase-related signals (84). It was found that dexamethasone is effective for the treatment of CLL. By increasing the expression of PPARα and pyruvate dehydrogenase kinase subtype 4, dexamethasone can make CLL cells more dependent on FFA β-oxidation (85). Of note, inhibitors of PPARα and fatty acid oxidase increase dexamethasone-induced apoptosis in CLL cells *in vitro* and the clearance rate of CLL cells *in vivo* (83).

Study of targeted therapies related to AML lipid metabolism have demonstrated that the PPARγ agonist GW1929 promotes BMA production, inhibits AML cell growth, and improves bone marrow hematopoiesis (86). Moreover, an investigation of the role of *IDH1* mutations associated with lipid metabolism in AML cells showed that 2-hydroxyglutaric acid, a metabolite of mutant IDH1, was beneficial for adipogenesis and fatty acid oxidation, which in turn promoted the survival and metastasis of leukemia cells. Thus, this underlying mechanism could be a potential therapeutic target for leukemia patients harboring an *IDH1/2* mutation (87).

Inhibition of fatty acid oxidative phosphorylation might have a synergistic killing effect on leukemia cells when applied in combination with conventional chemotherapy or targeted therapy. For example, the fatty acid derivative AIC-47 was shown to reduce the expression of the key enzyme for fatty acid oxidation, carnitine palmitoyltransferase 1C (CTP1C), and reverse the imatinib-induced activation of CPT1C and fatty acid oxidation in chronic myeloid leukemia (CML) cells, thus effectively preventing the relapse of CML (88). Furthermore, in approximately 50% of patients with primary AML, fatty acid oxidation inhibitors, such as eamoxel and ranolazine, were shown to reduce the number of LSCs in the quiescent phase and increase the sensitivity of hematological tumor cells to the Bcl-2 inhibitor ABT-737. Moreover, when used in combination with ABT-737 or cytarabine, fatty acid oxidation inhibitors showed therapeutic effects against AML *in vivo* (89).

Adipocytokine modulators

Targeting adipocytokines might be a new therapeutic approach for hematological cancers. Leptin has cancerogenic effects and induces chemotherapy resistance via nuclear factor (NF)-κB and TGF-β signaling pathways (59,90). Leptin antagonists include leptin mutant proteins, leptin peptide antagonists, and the leptin peptide receptor antagonists Allo-aca and D-ser (91-95). For the chemokine CXCL12, CXCR4 is a specific receptor. The CXCR4 inhibitor AMD3100 was found to inhibit the affinity of ALL cells for the adipose tissue and also to increase the chemosensitivity of multiple myeloma cells (96,97). Moreover, the CXCL12 inhibitor NOX-A12 was found to increase the chemosensitivity of CLL cells (98). L-4F is an apolipoprotein analogue that increases lipocalin levels and has therapeutic effects in myeloma. Notably, the visceral lipocalin inhibitor APO866 was shown to induce apoptosis and restrain the proliferation of myeloma cells (99). In addition, adipocytes can mediate the inhibition of protein biosynthesis in ALL cells, and the stress-response kinase inhibitor GCN2iB can reduce adipocyte-mediated translational repression, activate quiescent ALL cells, and impair the protective effect of adipocytes on cancer cells (100).

Conclusions

In summary, adipocytes are a vital part of the bone marrow microenvironment, influencing the occurrence and progression of hematological cancers. By reprogramming lipid metabolism and the secretion of various adipocytokines, BMAs can influence the proliferation, apoptosis, and chemotherapy resistance of cancer cells. Therefore, targeting lipid metabolism and adipocytokines, based on the pathways of mediating crosstalk activity between cancer cells and BMAs, has the potential to be an important therapeutic approach to inhibit cancer progression, avoid chemotherapy resistance, and improve the overall outcomes of patients with hematological cancers.

Acknowledgments

Funding: This study was supported by the Key Project of Medical Science and Technology Co-Construction in Henan Province (No. SBGJ202002026).

Footnote

Reporting Checklist: The authors have completed the

Narrative Review reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-52/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-52/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-52/coif). All authors report that this study was supported by the Key Project of Medical Science and Technology Co-Construction in Henan Province (No. SBGJ202002026). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Cuminetti V, Arranz L. Bone Marrow Adipocytes: The Enigmatic Components of the Hematopoietic Stem Cell Niche. J Clin Med 2019;8:707.
2. Samimi A, Ghanavat M, Shahrabi S, et al. Role of bone marrow adipocytes in leukemia and chemotherapy challenges. Cell Mol Life Sci 2019;76:2489-97.
3. Labella R, Vujačić M, Trivanović D. Bone Marrow Adipose Tissue: Regulation of Osteoblastic Niche, Hematopoiesis and Hematological Malignancies. Stem Cell Rev Rep 2023;19:1135-51.
4. Hardaway AL, Herroon MK, Rajagurubandara E, et al. Bone marrow fat: linking adipocyte-induced inflammation with skeletal metastases. Cancer Metastasis Rev 2014;33:527-43.
5. Zhou BO, Yu H, Yue R, et al. Bone marrow adipocytes promote the regeneration of stem cells and haematopoiesis by secreting SCF. Nat Cell Biol 2017;19:891-903.
6. Wilson A, Fu H, Schiffrin M, et al. Lack of Adipocytes Alters Hematopoiesis in Lipodystrophic Mice. Front Immunol 2018;9:2573.
7. Spindler TJ, Tseng AW, Zhou X, et al. Adipocytic cells augment the support of primitive hematopoietic cells in vitro but have no effect in the bone marrow niche under homeostatic conditions. Stem Cells Dev 2014;23:434-41.
8. Glettig DL, Kaplan DL. Extending human hematopoietic stem cell survival in vitro with adipocytes. Biores Open Access 2013;2:179-85.
9. Mattiucci D, Maurizi G, Izzi V, et al. Bone marrow adipocytes support hematopoietic stem cell survival. J Cell Physiol 2018;233:1500-11.
10. Masamoto Y, Arai S, Sato T, et al. Adiponectin Enhances Antibacterial Activity of Hematopoietic Cells by Suppressing Bone Marrow Inflammation. Immunity 2016;44:1422-33.
11. Masamoto Y, Arai S, Sato T, et al. Adiponectin Enhances Quiescence Exit of Murine Hematopoietic Stem Cells and Hematopoietic Recovery Through mTORC1 Potentiation. Stem Cells 2017;35:1835-48.
12. Marinelli Busilacchi E, Morsia E, Poloni A. Bone Marrow Adipose Tissue. Cells 2024;13:724.
13. Mukherjee A, Chiang CY, Daifotis HA, et al. Adipocyte-Induced FABP4 Expression in Ovarian Cancer Cells Promotes Metastasis and Mediates Carboplatin Resistance. Cancer Res 2020;80:1748-61.
14. Wang Y, Yang C, Wan J, et al. Bone marrow adipocyte: Origin, biology and relationship with hematological malignancy. Int J Lab Hematol 2024;46:10-9.
15. Fairfield H, Dudakovic A, Khatib CM, et al. Myeloma-Modified Adipocytes Exhibit Metabolic Dysfunction and a Senescence-Associated Secretory Phenotype. Cancer Res 2021;81:634-47.
16. Vetrie D, Helgason GV, Copland M. The leukaemia stem cell: similarities, differences and clinical prospects in CML and AML. Nat Rev Cancer 2020;20:158-73.
17. Thomas D, Majeti R. Biology and relevance of human acute myeloid leukemia stem cells. Blood 2017;129:1577-85.
18. Yi M, Li J, Chen S, et al. Emerging role of lipid metabolism alterations in Cancer stem cells. J Exp Clin Cancer Res 2018;37:118.
19. Shafat MS, Oellerich T, Mohr S, et al. Leukemic blasts program bone marrow adipocytes to generate a protumoral microenvironment. Blood 2017;129:1320-32.
20. Ye H, Adane B, Khan N, et al. Leukemic Stem Cells Evade Chemotherapy by Metabolic Adaptation to an Adipose

Tissue Niche. Cell Stem Cell 2016;19:23-37.
21. Smith AN, Muffley LA, Bell AN, et al. Unsaturated fatty acids induce mesenchymal stem cells to increase secretion of angiogenic mediators. J Cell Physiol 2012;227:3225-33.
22. Crippa S, Bernardo ME. Mesenchymal Stromal Cells: Role in the BM Niche and in the Support of Hematopoietic Stem Cell Transplantation. Hemasphere 2018;2:e151.
23. Rothzerg E, Erber WN, Gibbons CLMH, et al. Osteohematology: To be or Notch to be. J Cell Physiol 2023;238:1478-91.
24. Zhou BO, Yue R, Murphy MM, et al. Leptin-receptor-expressing mesenchymal stromal cells represent the main source of bone formed by adult bone marrow. Cell Stem Cell 2014;15:154-68.
25. Cao J, Wei Y, Lian J, et al. Notch signaling pathway promotes osteogenic differentiation of mesenchymal stem cells by enhancing BMP9/Smad signaling. Int J Mol Med 2017;40:378-88.
26. Sottoriva K, Pajcini KV. Notch Signaling in the Bone Marrow Lymphopoietic Niche. Front Immunol 2021;12:723055.
27. Delgado-Calle J, Anderson J, Cregor MD, et al. Bidirectional Notch Signaling and Osteocyte-Derived Factors in the Bone Marrow Microenvironment Promote Tumor Cell Proliferation and Bone Destruction in Multiple Myeloma. Cancer Res 2016;76:1089-100.
28. Lévesque JP, Helwani FM, Winkler IG. The endosteal 'osteoblastic' niche and its role in hematopoietic stem cell homing and mobilization. Leukemia 2010;24:1979-92.
29. Schepers K, Campbell TB, Passegué E. Normal and leukemic stem cell niches: insights and therapeutic opportunities. Cell Stem Cell 2015;16:254-67.
30. Kim S, Lin L, Brown GAJ, et al. Extended time-lapse in vivo imaging of tibia bone marrow to visualize dynamic hematopoietic stem cell engraftment. Leukemia 2017;31:1582-92.
31. Raggatt LJ, Partridge NC. Cellular and molecular mechanisms of bone remodeling. J Biol Chem 2010;285:25103-8.
32. Mansour A, Abou-Ezzi G, Sitnicka E, et al. Osteoclasts promote the formation of hematopoietic stem cell niches in the bone marrow. J Exp Med 2012;209:537-49.
33. Kono M, Tucker AE, Tran J, et al. Sphingosine-1-phosphate receptor 1 reporter mice reveal receptor activation sites in vivo. J Clin Invest 2014;124:2076-86.
34. Vorbach S, Gründer A, Zhou F, et al. Enhanced expression of the sphingosine-1-phosphate-receptor-3 causes acute myelogenous leukemia in mice. Leukemia 2020;34:721-34.
35. Nguyen TM, Arthur A, Panagopoulos R, et al. EphB4 Expressing Stromal Cells Exhibit an Enhanced Capacity for Hematopoietic Stem Cell Maintenance. Stem Cells 2015;33:2838-49.
36. Furuya M, Kikuta J, Fujimori S, et al. Direct cell-cell contact between mature osteoblasts and osteoclasts dynamically controls their functions in vivo. Nat Commun 2018;9:300.
37. Hu K, Olsen BR. The roles of vascular endothelial growth factor in bone repair and regeneration. Bone 2016;91:30-8.
38. Comazzetto S, Murphy MM, Berto S, et al. Restricted Hematopoietic Progenitors and Erythropoiesis Require SCF from Leptin Receptor+ Niche Cells in the Bone Marrow. Cell Stem Cell 2019;24:477-486.e6.
39. Acar M, Kocherlakota KS, Murphy MM, et al. Deep imaging of bone marrow shows non-dividing stem cells are mainly perisinusoidal. Nature 2015;526:126-30.
40. Pinho S, Marchand T, Yang E, et al. Lineage-Biased Hematopoietic Stem Cells Are Regulated by Distinct Niches. Dev Cell 2018;44:634-641.e4.
41. Chen Q, Shou P, Zhang L, et al. An osteopontin-integrin interaction plays a critical role in directing adipogenesis and osteogenesis by mesenchymal stem cells. Stem Cells 2014;32:327-37.
42. Liersch R, Gerss J, Schliemann C, et al. Osteopontin is a prognostic factor for survival of acute myeloid leukemia patients. Blood 2012;119:5215-20.
43. Yu W, Zhong L, Yao L, et al. Bone marrow adipogenic lineage precursors promote osteoclastogenesis in bone remodeling and pathologic bone loss. J Clin Invest 2021;131:e140214.
44. Bériziat V, Mazurier C, Auclair M, et al. Systemic Dysfunction of Osteoblast Differentiation in Adipose-Derived Stem Cells from Patients with Multiple Myeloma. Cells 2019;8:441.
45. Jafari A, Fairfield H, Andersen TL, et al. Myeloma-bone marrow adipocyte axis in tumour survival and treatment response. Br J Cancer 2021;125:775-7.
46. Clar KL, Weber LM, Schmied BJ, et al. Receptor Activator of NF-κB (RANK) Confers Resistance to Chemotherapy in AML and Associates with Dismal Disease Course. Cancers (Basel) 2021;13:6122.
47. Mylonis I, Simos G, Paraskeva E. Hypoxia-Inducible Factors and the Regulation of Lipid Metabolism. Cells 2019;8:214.
48. Yan F, Shen N, Pang JX, et al. Fatty acid-binding protein FABP4 mechanistically links obesity with aggressive AML

by enhancing aberrant DNA methylation in AML cells. Leukemia 2017;31:1434-42.
49. Rozovski U, Hazan-Halevy I, Barzilai M, et al. Metabolism pathways in chronic lymphocytic leukemia. Leuk Lymphoma 2016;57:758-65.
50. Medyouf H. The microenvironment in human myeloid malignancies: emerging concepts and therapeutic implications. Blood 2017;129:1617-26.
51. Zaidi N, Lupien L, Kuemmerle NB, et al. Lipogenesis and lipolysis: the pathways exploited by the cancer cells to acquire fatty acids. Prog Lipid Res 2013;52:585-9.
52. Yang S, Lu W, Zhao C, et al. Leukemia cells remodel marrow adipocytes via TRPV4-dependent lipolysis. Haematologica 2020;105:2572-83.
53. Snaebjornsson MT, Janaki-Raman S, Schulze A. Greasing the Wheels of the Cancer Machine: The Role of Lipid Metabolism in Cancer. Cell Metab 2020;31:62-76.
54. Tucci J, Chen T, Margulis K, et al. Adipocytes Provide Fatty Acids to Acute Lymphoblastic Leukemia Cells. Front Oncol 2021;11:665763.
55. Liu S, Xu H, Li Z. Linoleic acid derivatives target miR-361-3p/BTG2 to confer anticancer effects in acute myeloid leukemia. J Biochem Mol Toxicol 2023;37:e23481.
56. Picou F, Debeissat C, Bourgeais J, et al. n-3 Polyunsaturated fatty acids induce acute myeloid leukemia cell death associated with mitochondrial glycolytic switch and Nrf2 pathway activation. Pharmacol Res 2018;136:45-55.
57. Frączak E, Olbromski M, Piotrowska A, et al. Bone marrow adipocytes in haematological malignancies. Acta Histochem 2018;120:22-7.
58. Ray A, Cleary MP. The potential role of leptin in tumor invasion and metastasis. Cytokine Growth Factor Rev 2017;38:80-97.
59. Yu W, Cao DD, Li QB, et al. Adipocytes secreted leptin is a pro-tumor factor for survival of multiple myeloma under chemotherapy. Oncotarget 2016;7:86075-86.
60. Han TJ, Wang X. Leptin and its receptor in hematologic malignancies. Int J Clin Exp Med 2015;8:19840-9.
61. Pham DV, Tilija Pun N, Park PH. Autophagy activation and SREBP-1 induction contribute to fatty acid metabolic reprogramming by leptin in breast cancer cells. Mol Oncol 2021;15:657-78.
62. Favreau M, Menu E, Gaublomme D, et al. Leptin receptor antagonism of iNKT cell function: a novel strategy to combat multiple myeloma. Leukemia 2017;31:2678-85.
63. Medina EA, Oberheu K, Polusani SR, et al. PKA/AMPK signaling in relation to adiponectin's antiproliferative effect on multiple myeloma cells. Leukemia 2014;28:2080-9.
64. Bocian-Jastrzębska A, Malczewska-Herman A, Kos-Kudła B. Role of Leptin and Adiponectin in Carcinogenesis. Cancers (Basel) 2023;15:4250.
65. Diedrich JD, Rajagurubandara E, Herroon MK, et al. Bone marrow adipocytes promote the Warburg phenotype in metastatic prostate tumors via HIF-1α activation. Oncotarget 2016;7:64854-77.
66. Birmann BM, Neuhouser ML, Rosner B, et al. Prediagnosis biomarkers of insulin-like growth factor-1, insulin, and interleukin-6 dysregulation and multiple myeloma risk in the Multiple Myeloma Cohort Consortium. Blood 2012;120:4929-37.
67. Zheng Y, Yang J, Qian J, et al. PSGL-1/selectin and ICAM-1/CD18 interactions are involved in macrophage-induced drug resistance in myeloma. Leukemia 2013;27:702-10.
68. Fei L, Ren X, Yu H, et al. Targeting the CCL2/CCR2 Axis in Cancer Immunotherapy: One Stone, Three Birds? Front Immunol 2021;12:771210.
69. Natsagdorj A, Izumi K, Hiratsuka K, et al. CCL2 induces resistance to the antiproliferative effect of cabazitaxel in prostate cancer cells. Cancer Sci 2019;110:279-88.
70. Sun C, Li X, Guo E, et al. MCP-1/CCR-2 axis in adipocytes and cancer cell respectively facilitates ovarian cancer peritoneal metastasis. Oncogene 2020;39:1681-95.
71. Tang CH, Tsai CC. CCL2 increases MMP-9 expression and cell motility in human chondrosarcoma cells via the Ras/Raf/MEK/ERK/NF-κB signaling pathway. Biochem Pharmacol 2012;83:335-44.
72. Agrawal S, Gollapudi S, Su H, et al. Leptin activates human B cells to secrete TNF-α, IL-6, and IL-10 via JAK2/STAT3 and p38MAPK/ERK1/2 signaling pathway. J Clin Immunol 2011;31:472-8.
73. Chen W, Gao Q, Han S, et al. The CCL2/CCR2 axis enhances IL-6-induced epithelial-mesenchymal transition by cooperatively activating STAT3-Twist signaling. Tumour Biol 2015;36:973-81.
74. Xu M, Wang Y, Xia R, et al. Role of the CCL2-CCR2 signalling axis in cancer: Mechanisms and therapeutic targeting. Cell Prolif 2021;54:e13115.
75. Yasui H, Kajiyama H, Tamauchi S, et al. CCL2 secreted from cancer-associated mesothelial cells promotes peritoneal metastasis of ovarian cancer cells through the P38-MAPK pathway. Clin Exp Metastasis 2020;37:145-58.
76. Iwamoto H, Izumi K, Mizokami A. Is the C-C Motif Ligand 2-C-C Chemokine Receptor 2 Axis a Promising

Target for Cancer Therapy and Diagnosis? Int J Mol Sci 2020;21:9328.
77. Sheng X, Parmentier JH, Tucci J, et al. Adipocytes Sequester and Metabolize the Chemotherapeutic Daunorubicin. Mol Cancer Res 2017;15:1704-13.
78. Cahu X, Calvo J, Poglio S, et al. Bone marrow sites differently imprint dormancy and chemoresistance to T-cell acute lymphoblastic leukemia. Blood Adv 2017;1:1760-72.
79. Sheng X, Tucci J, Parmentier JH, et al. Adipocytes cause leukemia cell resistance to daunorubicin via oxidative stress response. Oncotarget 2016;7:73147-59.
80. Shafat MS, Gnaneswaran B, Bowles KM, et al. The bone marrow microenvironment - Home of the leukemic blasts. Blood Rev 2017;31:277-86.
81. Jöhrer K, Ploner C, Thangavadivel S, et al. Adipocyte-derived players in hematologic tumors: useful novel targets? Expert Opin Biol Ther 2015;15:61-77.
82. White AM, Best OG, Hotinski AK, et al. The Role of Cholesterol in Chronic Lymphocytic Leukemia Development and Pathogenesis. Metabolites 2023;13:799.
83. Tung S, Shi Y, Wong K, et al. PPARα and fatty acid oxidation mediate glucocorticoid resistance in chronic lymphocytic leukemia. Blood 2013;122:969-80.
84. Pallasch CP, Schwamb J, Königs S, et al. Targeting lipid metabolism by the lipoprotein lipase inhibitor orlistat results in apoptosis of B-cell chronic lymphocytic leukemia cells. Leukemia 2008;22:585-92.
85. Gomes LC, Ferrão ALM, Evangelista FCG, et al. Advances in chronic lymphocytic leukemia pharmacotherapy. Biomed Pharmacother 2018;97:349-58.
86. Boyd AL, Reid JC, Salci KR, et al. Acute myeloid leukaemia disrupts endogenous myelo-erythropoiesis by compromising the adipocyte bone marrow niche. Nat Cell Biol 2017;19:1336-47.
87. Stuani L, Riols F, Millard P, et al. Stable Isotope Labeling Highlights Enhanced Fatty Acid and Lipid Metabolism in Human Acute Myeloid Leukemia. Int J Mol Sci 2018;19:3325.
88. Shinohara H, Kumazaki M, Minami Y, et al. Perturbation of energy metabolism by fatty-acid derivative AIC-47 and imatinib in BCR-ABL-harboring leukemic cells. Cancer Lett 2016;371:1-11.
89. Samudio I, Harmancey R, Fiegl M, et al. Pharmacologic inhibition of fatty acid oxidation sensitizes human leukemia cells to apoptosis induction. J Clin Invest 2010;120:142-56.
90. Gonzalez-Perez RR, Xu Y, Guo S, et al. Leptin upregulates VEGF in breast cancer via canonic and non-canonical signalling pathways and NFkappaB/HIF-1alpha activation. Cell Signal 2010;22:1350-62.
91. Shpilman M, Niv-Spector L, Katz M, et al. Development and characterization of high affinity leptins and leptin antagonists. J Biol Chem 2011;286:4429-42.
92. Rene Gonzalez R, Watters A, Xu Y, et al. Leptin-signaling inhibition results in efficient anti-tumor activity in estrogen receptor positive or negative breast cancer. Breast Cancer Res 2009;11:R36.
93. Harmon T, Harbuzariu A, Lanier V, et al. Nanoparticle-linked antagonist for leptin signaling inhibition in breast cancer. World J Clin Oncol 2017;8:54-66.
94. Otvos L Jr, Kovalszky I, Riolfi M, et al. Efficacy of a leptin receptor antagonist peptide in a mouse model of triple-negative breast cancer. Eur J Cancer 2011;47:1578-84.
95. Beccari S, Kovalszky I, Wade JD, et al. Designer peptide antagonist of the leptin receptor with peripheral antineoplastic activity. Peptides 2013;44:127-34.
96. Pramanik R, Sheng X, Ichihara B, et al. Adipose tissue attracts and protects acute lymphoblastic leukemia cells from chemotherapy. Leuk Res 2013;37:503-9.
97. Azab AK, Runnels JM, Pitsillides C, et al. CXCR4 inhibitor AMD3100 disrupts the interaction of multiple myeloma cells with the bone marrow microenvironment and enhances their sensitivity to therapy. Blood 2009;113:4341-51.
98. Hoellenriegel J, Zboralski D, Maasch C, et al. The Spiegelmer NOX-A12, a novel CXCL12 inhibitor, interferes with chronic lymphocytic leukemia cell motility and causes chemosensitization. Blood 2014;123:1032-9.
99. Venkateshaiah SU, Khan S, Ling W, et al. NAMPT/PBEF1 enzymatic activity is indispensable for myeloma cell growth and osteoclast activity. Exp Hematol 2013;41:547-557.e2.
100. Heydt Q, Xintaropoulou C, Clear A, et al. Adipocytes disrupt the translational programme of acute lymphoblastic leukaemia to favour tumour survival and persistence. Nat Commun 2021;12:5507.

Cite this article as: Li Y, Wang L, Wang J, Xin Y, Lyu X. Relationship between adipocytes and hematological tumors in the bone marrow microenvironment: a literature review. Transl Cancer Res 2024;13(10):5691-5701. doi: 10.21037/tcr-24-52