REVIEW ARTICLE

Reframing leukemia-niche interactions: the emerging role of the marrow adipocyte lineage

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Abstract

The bone marrow is a highly dynamic organ that undergoes continuous remodeling to maintain all different hematopoietic cell populations throughout life, adapting during development, aging, and disease. It serves as the primary site of both normal hematopoiesis and leukemic initiation and progression. While mesenchymal stromal cells have received substantial attention for their contribution to support acute leukemia, the bone marrow adipocyte lineage has remained largely overlooked. There are two main reasons for this: first, adipogenic progenitors are typically grouped under the broad mesenchymal stromal cell umbrella, obscuring the distinct contributions of specific stromal subsets; second, mature bone marrow adipocytes have traditionally been regarded as inert energy reservoirs rather than active components of the marrow microenvironment. Recent evidence challenges this view, demonstrating that different types of adipocyte lineage cells actively promote acute leukemia progression and chemotherapy resistance through distinct mechanisms. In this review, we summarize recent advances in defining subpopulations within the bone marrow adipocyte lineage and outline how leukemic cells exploit their functions. We further discuss how standard chemotherapy may inadvertently reshape leukemic–adipocyte lineage interactions, mediating resistance and facilitating the re-emergence of disease.

Introduction

The bone marrow is a complex network of diverse cell types functioning as the primary site for hematopoiesis. The intricate microenvironment encompasses hematopoietic stem cells (HSC), non-hematopoietic stem cells and their diverse progeny.[1,2] A critical component of this environment are bone marrow mesenchymal stromal cells (MSC), a heterogeneous population of multipotent progenitors capable of differentiating into various skeletal lineages.[1,2] In this review, we reserve the term ‘MSC’ specifically for the most primitive stromal stem cells capable of self-renewal and multi-lineage differentiation.

Within the healthy human bone marrow stroma, MSC give rise to adipogenic and osteo-chondrogenic progenitors, i.e., stromal cells with a more differentiated phenotype.[3,4] These populations further differentiate into mature adipocytes, osteoblasts, and chondrocytes, driving not only the formation and remodeling of bone tissue but also providing key components of the hematopoietic microenvironment.[4-6] Given that bone marrow adipose tissue constitutes a substantial portion of the bone marrow cavity (30-50% in children and 40-80% in adults),[7,8] adipocyte lineage cells are uniquely positioned to act as active regulators of both normal hematopoiesis and leukemia.[9]

Until now cells of the adipocyte lineage have been seen as a continuum rather than as distinct players. The advent of single-cell and spatial transcriptomic technologies allow the definition of adipogenic progenitors as a population distinct from mature adipocytes, and to map their roles within both normal hematopoietic and leukemic cell niches. Accumulating evidence indicates that both populations actively shape the bone marrow microenvironment, with the two populations creating distinct ecosystems for normal hematopoiesis and acute leukemias, including acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).

This review summarizes our current knowledge on the bone marrow adipocyte lineage focusing on three key aspects: (i) a single-cell and spatial transcriptomics-informed definition of adipogenic progenitors as a distinct niche population different from mature adipocytes; (ii) a mechanistic account on how leukemic cells (both AML and ALL) exploit the different

types of adipocyte lineage cells, revealing disease-specific dependencies that represent potential therapeutic vulnerabilities; and (iii) a discussion of therapy-induced adipogenic niche remodeling as an unintended mechanism that supports leukemic persistence and relapse. Collectively, we aim to introduce the adipocyte lineage as an underappreciated, clinically relevant and therapeutically targetable component of the leukemic microenvironment.

Adipogenic progenitors and acute leukemia

Adipogenic progenitors at single-cell resolution

The bone marrow adipocyte lineage encompasses heterogeneous, MSC-derived cells at various stages of differentiation. While adipogenic progenitors are known to give rise to mature adipocytes, a clear consensus on defining their identity has so far been lacking. Recent single-cell RNA sequencing studies in human and mouse bone marrow, however, offer a promising avenue to address this knowledge gap.

Despite differences in isolation protocols and the source of bones from which the stromal cells are derived, all single-cell RNA sequencing studies, both in mice and humans, describe a comparable, distinct candidate adipogenic progenitor cell population highlighting their conserved nature (Table 1, *Online Supplementary Table S1*). This population is characterized by the expression of markers of both MSC, e.g., C-X-C motif chemokine ligand 12 (*CXCL12*) and leptin receptor (*LEPR*), and adipocytes, e.g., lipoprotein lipase (*LPL*), adiponectin (*ADIPOQ*), peroxisome proliferator activated receptor γ (*PPARG*), CCAAT enhancer-binding protein α/δ (*CEBPA/D*), apolipoprotein E (*APOE*), and growth arrest specific-6 (*GAS6*). Similarly, studies in mice have identified a comparable adipogenic progenitor population expressing both mesenchymal and adipogenic markers[1,10-12] and forming a major component of the murine bone marrow stroma compartment.[13]

Morphologically, adipogenic progenitors in both humans and mice remain undifferentiated and lack lipid accumulation. Consistent with this, perilipin 1 (*PLIN1*), which encodes a lipid droplet–coating protein, is either undetectable or expressed at very low levels in human progenitors.[3,14,15] Murine adipogenic progenitors likewise show minimal *Plin1* expression and do not form lipid droplets prior to differentiation.[11] Mature adipocytes, on the other hand, store lipids in their cytoplasm which forms more than 95% of their cell volume.[16] This morphology makes them very fragile.[17] Therefore, mature adipocytes are usually lost or discarded during standard mononuclear cell isolation protocols[4] and are not detected in single-cell RNA sequencing data.[11,13,18]

Although adipogenic progenitors express some osteogenic, chondrogenic, and fibroblast associated genes, these transcripts are present at much lower levels than in their respective stromal counterparts (*Online Supplementary Table S2*). This pattern of co expression aligns with their multipotent nature, as *in vitro* adipogenic progenitors retain the ability to differentiate into adipocytes, osteoblasts, and chondrocytes.[4,14]

Adipogenic progenitors preferentially localize to the sinusoidal bone marrow niche. In humans, these cells are characterized by high endothelial cell-specific molecule 1 (*ESM1*) expression and absence of stem cell antigen-1 (*SCA-1*), a marker profile typical of sinusoid-associated stromal populations.[3,4] Spatial transcriptomic analysis of a B cell ALL bone biopsy supports their proximity to blood vessels.[14] Murine adipogenic progenitors show an equivalent signature, expressing *Esm1*[1,19] while lacking *Ly6a* (*Sca-1*),[1,20] and both spatial transcriptomics and immunofluorescence studies confirm their enrichment in sinusoidal regions.[1,2,19,21] These findings indicate that adipogenic progenitors predominantly occupy the sinusoidal compartment, a key site of hematopoietic regulation.

The sinusoidal positioning of adipogenic progenitors directly supports their role as active regulators of hematopoiesis, expressing the highest levels of hematopoiesis-supporting factors among stromal cells.[3] Specifically, these cells abundantly express *CXCL12*, stem cell factor (*SCF*, *KITLG*), interleukin 7 (*IL7*), and angiopoietin-1 (*ANGPT1*), chemokines important for migration, maintenance, and survival of HSC (Figure 1).[14] Consistently, HSC have been shown to be in contact with adipogenic progenitors (Lepr^{+}Cxcl12^{high}) with 85% located within 10 μm of a sinusoidal blood vessel.[22] Genetic ablation studies have confirmed the functional importance of this interaction, as deletion of *Kitl* and *Il7* in adipogenic progenitors drastically reduces the frequencies of murine hematopoietic stem and progenitor cell (HSPC) populations and impairs the production of B cells, respectively.[23,24] Adipocyte progenitors also express vascular cell adhesion molecule 1 (VCAM1),[14] an adhesion molecule implicated in HSPC homing.[25] These data demonstrate the critical involvement of adipogenic progenitors in providing support for HSC and their progeny.

Cell–cell interaction analyses suggest that adipogenic progenitors may also engage in immune communication, signaling to T cells through the IL7–IL7R axis and to monocytes via midkine-low density lipoprotein receptor related protein 1/sortilin related receptor 1 (MDK–LRP1/SORL1).[4] Notably, adipogenic progenitors express the highest levels of IL7 among all stromal subsets and constitute a major source of CCL2 and macrophage colony-stimulating factor (M-CSF), key mediators of monocyte recruitment and differentiation.[1] These features underscore their potential role in shaping the immune landscape.

In conclusion, single-cell RNA sequencing and spatial technologies have significantly advanced our understanding of bone marrow adipogenic progenitors and their lineage trajectories. They can be defined as a distinct cell population characterized by a transcriptomic profile highly

conserved across human and mice, absence of cytoplasmic lipid droplets, sinusoidal niche localization, and support for HSC. This positioning within the core of the hematopoietic niche suggests that adipogenic progenitors may be key players in acute leukemia, too.

However, it should be noted that despite the identification of adipogenic progenitor populations, only a limited number of studies have proceeded to isolate and functionally characterize these cells.[11,14] Since adipocyte progenitors expand *ex vivo* more slowly than immature MSC they

Table 1. Characterization of adipogenic lineage populations in human bone via single-cell RNA sequencing studies.

Study authors, year, ref	Isolation approach	Adipogenic lineage populations	Markers	Additional markers	Hematopoietic support factors
Jardine *et al.*, 2021[15]	The bones were cut and ground. Samples were enriched for $CD45^+$ or $CD45^-$ cells and then pooled together.	Adipo-CAR (Cxcl12-Abundant Reticular) cells	*CXCL12, LEPR LPL, PLIN1*-low, *GAS6*	*THY1 (CD90)*-low *PDGFRb*[#] *ALPL*, (BGLAP, SPP1, IBSP)**-neg *(RUNX1, RUNX2)**-low	*CXCL12, SCF, VCAM1, ANGPT1*
Wang *et al.*, 2021[5] Inoue *et al.*, 2023[10]♦	The BM from the femoral shafts was collected and BM mononuclear cells were isolated using density gradient centrifugation. $CD271^+$ cells were purified by magnetic beads.	Adipocyte precursor	*CXCL12, LEPR LPL, CEBPA, ADPOQ*	*APOD, CD167b, CD91, CD130, CD118 (CD74, CD217, CD148, CD68)*-low/absent *MGP*[§§] *CD105, CD90, CD73*	*CXCL12, SCF, CSF1*
Ye *et al.*, 2022[98]♦♦	BM aspirates were sorted for either $Lin^-/CD45^-/CD235^-/CD9^+/CD31^+$ or $Lin^-/CD45^-/CD235^-/CD31^-/CD271^+/CD146^{+/-}$ or $CD146^{+/-}$ cells which were further pooled together.	Cluster 11	*CXCL12, LEPR LPL, CEBPA, CEBPB*-low, *PPARG, GAS6, APOE*	*[BGLAP, SPP1, RUNX1, RUNX2]**-low *COL1A1*, ALPL**	*CXCL12, SCF, VCAM1, IL7, ANGPT1, CSF1*
Li *et al.*, 2023[4]	The bones were aspirated followed by isolation of BM mononuclear cells using density gradient centrifugation. Samples were sorted for either $CD45^{low/-}CD235a^-$ or $CD45l^{ow/-}CD235a^-CD271^+$ cells.	HAGEP (highly adipocytic gene-expressing progenitors) and balanced progenitors	*CXCL12, LEPR LPL, CEBPD, PPARG, ADIPOQ, GAS6,*[##] *EBF1*-low, *EBF3*-low	*(BGLAP, CHAD, SPP1, IBSP)**-neg *ALPL*, (RUNX1, RUNX2)**-low *CD63, CD81, CD56*-neg, *CD52*-neg, *CD9*-neg *MGP*[§§] *(FOS, FOSB, JUNB and EGR1)*[§]	*CXCL12, SCF, VCAM1, IL7, ANGPT1, TF, FN1, PLAUR, TNC*
Chen *et al.*, 2023[99]	BM mononuclear cells were isolated from BM aspirates using density gradient centrifugation. Samples were sorted for either $CD45^-CD235a^-CD71^-CD31^+$ and $CD45^-CD235A^-CD71^-$ cells and pooled together for sequencing.	$LEPR^+$ BM stromal cells	*CXCL12, LEPR LPL, ADIPOQ, CD36, GAS6*	*(BGLAP* and *SPP1)**-neg *(SOX9, ACAN)*[§§]-low *(S100A4* and *SEMA3C)***-low *(NG2* and *ACTA2*-low*)*[#]	*CXCL12, SCF, VCAM1, IL7, ANGPT1*
Bandyopadhyay *et al.*, 2024[3]	Bones were minced and digested with dispase II and collagenase I. Samples were either depleted for $CD45^+$ or enriched for $CD34^+$ and then pooled together.	Adipo-mesenchymal stromal cells	*CXCL12, LEPR LPL, CEBPA*-low, *CEBPB, PPARG, APOE, LBP, PLIN1*-low	*THY1 (CD90)*-low, *RUNX2*, COL1A1*, MGP*-low, *DCN***	*CXCL12, SCF, VCAM1, IL7, ANGPT1, CSF1, PTN, TGFB1, JAG1*
Ferrao Blanco *et al.*, 2025[14]	BM mononuclear cells were isolated from BM aspirates using density gradient centrifugation. Samples were sorted for either the $CD19^+$ leukemic fraction, $CD19^-CD45^+CD235A^+$ hematopoietic fraction, and $CD19^-CD45^-CD235A^-$ non-hematopoietic fraction and pooled together for sequencing.	Adipogenic progenitors	*CXCL12, LEPR, LPL, PPARG, GAS6, EBF1, MGP, CEBPD, CDH11*	*THY1*-low, *[ENG, N5E]*-neg, *COL1A2*, [ALPL, COL1A1]**-low, *[CHAD, IBSP, BGLAP]**-neg, *FOSB*[§]	*CXCL12, SCF, VCAM1, IL7*

♦Data were reanalyzed from Wang *et al.*[5] and Dolgalev *et al.*[100] ♦♦The authors did not define the identity of the clusters from their data. Thus, we checked for the common adipogenic genes ourselves. *Osteogenic markers. **Fibroblast markers. #Pericyte markers. ##The authors used *GAS6* as an osteogenic marker in their analyses, while it is used as an adipogenic marker in other studies mentioned here. §Stress-related transcription factors. §§Chondrogenic markers. BM: bone marrow; ref: reference.

have historically been neglected in most *in vitro* studies.[14] As a result, current insights into their potential role in supporting acute leukemia are largely extrapolated from studies using mixed MSC populations. Acknowledging this gap, the following sections focus on studies that have revealed generic mechanisms for the interaction of MSC and leukemic blasts that are likely to be relevant for adipocyte progenitors, considering their transcriptomic profile and location.

Adipogenic progenitor-mediated support of acute leukemia

Positioned within the sinusoidal niche and rich in signaling cues, adipogenic progenitors are well positioned to shape leukemic cell behavior. This section examines how they affect acute leukemia through soluble and contact-dependent interactions that remodel the marrow environment, promoting leukemic persistence and therapeutic resistance.[14] As the dominant source of CXCL12 in bone marrow stroma,[3] adipogenic progenitors are thought to protect AML cells primarily via the CXCL12-CXCR4 (C-X-C motif chemokine receptor 4) axis. While direct interactions between AML cells and adipogenic progenitors have not been extensively investigated, studies using CXCL12-producing stromal cells have revealed the molecular pathways through which this axis supports leukemic cells.

CXCL12-CXCR4 signaling mediates AML homing to the bone marrow,[26] with trans-well assays demonstrating potent CXCL12-induced chemotaxis of leukemic cells.[27] Beyond recruitment, CXCR4 activation triggers multiple pro-survival pathways including phosphatidylinositol-4,5-bisphosphate 3-kinase/Akt (PI3K/Akt)[28] and Yin Yang 1/c-Myc proto-onco-

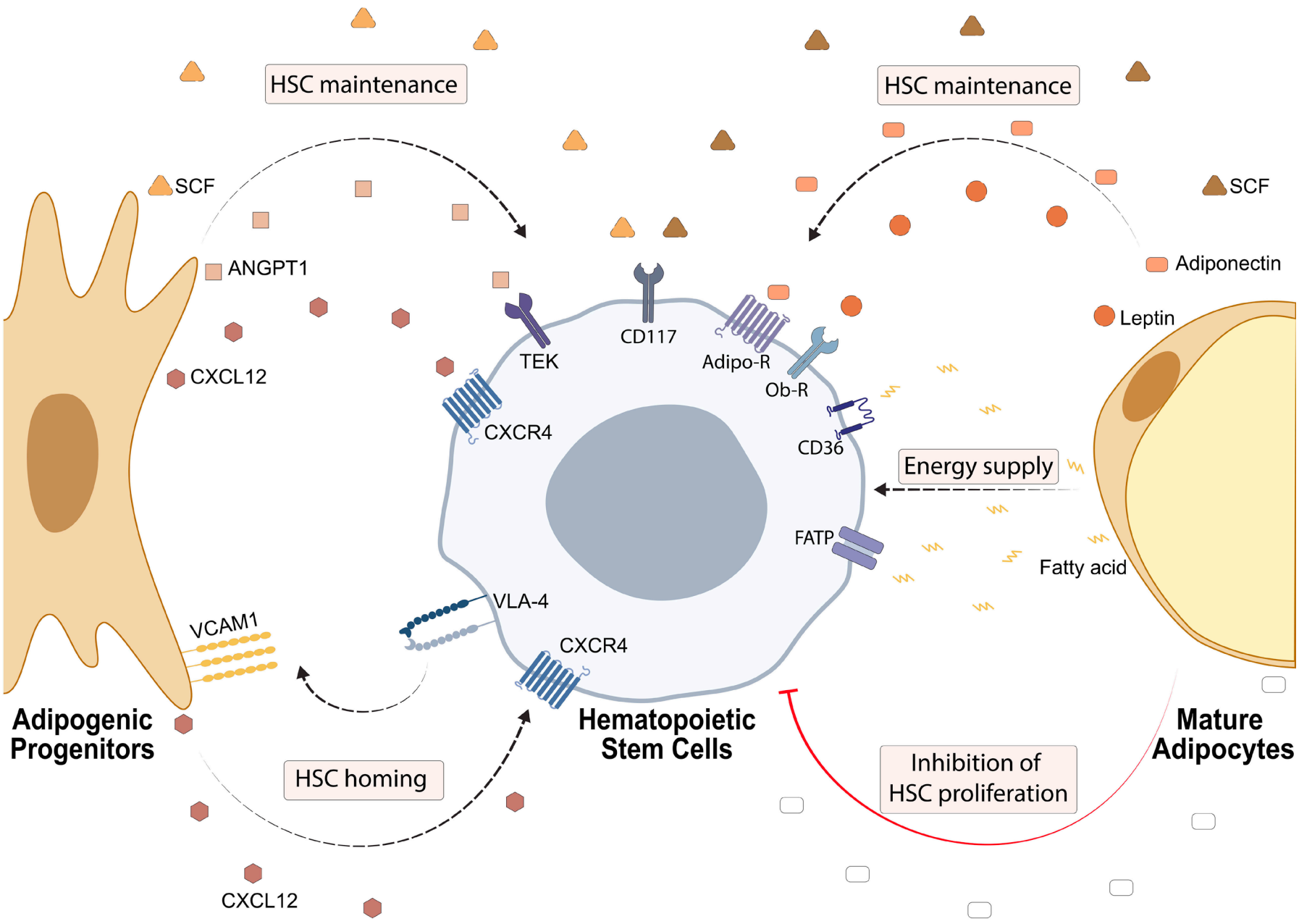


Figure 1. Functional roles of adipocyte lineage cells in hematopoietic stem cell regulation. Adipogenic progenitors serve as key niche components by producing HSC-supportive cytokines (SCF, CXCL12, ANGPT1) and providing homing receptors (CXCL12, VCAM1) that guide HSC localization. Adipocytes provide dual support for HSC through adipokine signaling (SCF, adiponectin, leptin) and metabolic substrates (fatty acids), while potentially maintaining stem cell dormancy via inhibition of proliferation. Adipo-R: adiponectin receptor; ANGPT1: angiopoietin 1; CD36: cluster of differentiation 36; CD117: cluster of differentiation 117; CXCL12: C-X-C motif chemokine ligand 12; CXCR4: C-X-C motif chemokine receptor 4; FATP: fatty acid transport proteins; HSC: hematopoietic stem cells; Ob-R: leptin receptor; SCF: stem cell factor; TEK: endothelial-specific receptor tyrosine kinase; VCAM1: vascular cell adhesion molecule 1; VLA-4: $\alpha 4\beta 1$ integrin.

gene (YY1/c-Myc) cascades[29,30] inhibiting leukemic apoptosis; as well as mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK)[31] and Wnt-β-catenin[32] pathways which promote AML proliferation. This signaling confers resistance to chemotherapeutic agents, including daunorubicin, cytarabine, and etoposide.[31] Blockade of CXCL12-CXCR4 interactions inhibits AML growth.[27] In summary, adipogenic progenitor-derived CXCL12 likely protects AML cells through sequential mechanisms: initial recruitment to the niche, retention within the protective microenvironment, and sustained anti-apoptotic and proliferative signaling counteracting chemotherapy-induced cell death.

In B-ALL, isolated adipogenic progenitors have been directly demonstrated to function as protective niche cells through two complementary mechanisms: secretion of soluble factors (IL7, CXCL12, SCF, and osteopontin) and direct cell-to-cell contact via VCAM1. Inhibition of either soluble factors or adhesion significantly reduces leukemic cell viability with considerable crosstalk between the two pathways.[14] Although the downstream signaling underlying this protection has been primarily characterized in heterogeneous MSC co-culture systems, they are likely particularly relevant to adipogenic progenitors, which exhibit the highest expression of *CXCL12* and *VCAM1*.

More specifically, CXCL12-induced CXCR4 activation in B-ALL directly triggers pro-survival PI3K/AKT signaling suppressing apoptosis.[33] In parallel, the CXCL12-CXCR4 axis induces MAPK/ERK signaling which further activates the mechanistic target of rapamycin (mTOR) pathway resulting in reduced autophagy in B-ALL cells.[34] Given that glucocorticoids such as dexamethasone induce cell death in B-ALL blasts in part by initiating autophagy and subsequently promoting apoptosis,[34] the signaling pathways that interfere with or suppress this process are understood to be contributing factors to B-ALL resistance.

Indeed, adipogenic progenitors significantly upregulate CXCL12 secretion in B-ALL co-culture compared to monoculture, with a trend toward higher concentrations than in MSC co-cultures. This protective effect is reversed by blocking CXCR4 with its antagonist AMD3100 (plerixafor), which also selectively reduces B-ALL cell viability during co-culture with adipogenic progenitors.[14,35] These findings are in line with the observations that B-ALL cells from relapsed patients have upregulated levels of CXCR4,[35] and the bone marrow is enriched for adipogenic progenitors.[14]

Beyond CXCL12-mediated signaling, bulk MSC studies have also shown that activation of CXCR4 enhances leukemic adhesion by increasing VLA4 (α4β1 integrin) binding to VCAM1.[36] The VLA4-VCAM1 interaction then activates the nuclear factor kappa B (NF-κB) pathway inducing, a pro-survival cascade.[37] The functional importance of direct cell-cell contact is demonstrated by studies showing that deletion of the α4 integrin subunit in murine *BCR-ABL*-transformed B-ALL cells increases sensitivity to chemotherapeutic drugs, including dexamethasone, vincristine, and L-asparaginase.[38] Consistently, in adipogenic progenitors, the blockade of VCAM1 with anti-VCAM1 antibody or VLA4 with the BIO-1211 small molecule inhibits the adipogenic progenitor-induced ALL support.[14]

Intriguingly, B-ALL cells actively recruit adipogenic progenitors by secreting C-C motif chemokine ligand 3 (CCL3) chemoattractant to create a pro-tumorigenic niche.[39] Treatment of NALM-6 ALL-bearing mice with cytarabine and daunorubicin induced the formation of a protective niche for the leukemia primarily composed of Nestin$^+$ MSC.[39] Although not explicitly defined as such by the authors, the LepR$^+$NG2$^-$ profile of these cells, indicative of sinusoidal niche MSC,[39] suggests they are indeed adipogenic progenitors. This is supported by their reduced self-renewal capacity and a propensity for adipogenic differentiation at the expense of osteogenic differentiation *in vitro*.[40] Furthermore, B-ALL cells secrete propeptide growth differentiation factor 15 (pro-GDF15), which is cleaved into its active form by the proconvertase furin expressed by these adipogenic progenitors. The mature GDF15 subsequently induces chemoresistance in leukemic cells.[39] Taken together, these findings underscore leukemia's ability to recruit and exploit adipogenic progenitors for their own survival, as discussed in the next section.

Leukemic cells drive adipogenesis

Recent research has revealed that leukemic cells actively skew surrounding stroma towards the adipogenic lineage as a potential mechanism of engineering a pro-tumorigenic microenvironment.

In AML, patient-derived MSC show reduced proliferation and cell cycle arrest in the G1 phase, indicative of a more differentiated, lineage-committed state.[41] Upon adipogenic induction, these cells generate a higher number of adipocytes and exhibit markedly elevated expression of fatty acid binding protein 4 (*FABP4*) compared to healthy MSC.[41,42] *FABP4* is an adipogenic marker that encodes a fatty acid transport protein.[43] Similar increases in the adipogenic differentiation potential of MSC in AML have been extensively reported in several independent studies.[44,45]

In B-ALL, patient-derived stromal cells subjected to *ex vivo* adipogenic differentiation assays demonstrate significantly enhanced adipocyte commitment.[9,14,46] We also previously[14] demonstrated that direct co-culture of MSC with B-ALL patient-derived xenografts can further increase their differentiation towards adipocytes, suggesting that leukemic cells actively drive this process. This effect disappears when trans-well inserts are used, showing that adipogenic reprogramming requires membrane-bound or short-range leukemic signaling molecules.[14] In contrast, Heydt *et al.*[9] reported enhanced adipocyte commitment in MSC exposed to ALL cell line-conditioned media indicating a range of mechanisms through which ALL cells are able to manipulate MSC.

It should be recognized that not all studies detected an

enhanced adipocyte commitment, likely reflecting differences in how different types of leukemia reprogram their microenvironment.[47,48] Altogether, however, accumulating evidence indicates that many types of acute leukemia can induce MSC towards adipocyte differentiation. Direct cell contact appears critical for this reprogramming, although soluble factors may contribute.

While the experimental evidence clearly shows that different types of leukemia can skew MSC towards the adipocyte lineage, the molecular mechanisms underlying this reprogramming are only beginning to emerge. Recently, methyltransferase-like 3 (METTL3) has been identified as a key regulator of MSC differentiation.[49] Loss of *METTL3* in MSC disrupts the balance between osteogenesis and adipogenesis, leading to impaired bone formation and increased marrow adiposity characterized by elevated adipocyte number and density.[49] This shift is accompanied by enhanced secretion of adipokines such as leptin, resistin, and growth hormone by MSC.[50] Mechanistically, METTL3 mediates m6A methylation of Janus kinase 1 (JAK1) mRNA, promoting its degradation and thereby suppressing signal transducer and activator of transcription 5 (STAT5)/CCAAT enhancer binding protein β (C/EBPβ)-induced adipogenesis under healthy physiological conditions.[51] Thus, depletion of METTL3 in MSC enhances JAK1 signaling and promotes adipogenic differentiation.

Indeed, AML patient-derived MSC show reduced *METTL3* and global *m6A* levels.[52] Overexpression of *METTL3* in AML patient-derived MSC inhibits their adipogenic differentiation potency, whereas its knockdown in healthy MSC promotes it.[52] Both processes are accompanied by reciprocal regulation of AKT and PPARγ protein levels.[52] Consistent with this, AKT inhibition reduces adipogenic differentiation of AML patient-derived MSC,[52] while PI3K/AKT1 activation enhances adipogenic differentiation in healthy MSC.[53] These data suggest that leukemic cells may exploit the METTL3 signaling pathway to reprogram MSC towards adipogenic lineage cells.

In summary, acute leukemia cells can exploit MSC plasticity to generate adipogenic progenitors that sustain a protective microenvironment promoting leukemic cell survival and resistance.

The following section explores the complementary role of mature adipocytes in these processes.

Bone marrow adipocytes and acute leukemia

Bone marrow adipose tissue: a class apart

Once differentiated from adipogenic progenitors, mature adipocytes acquire distinct physiological functions. For clarity, in this review, we henceforth use “adipocyte” specifically to refer to mature adipogenic lineage cells containing lipid droplets. It is important to note that much of the existing literature uses “adipocyte” more broadly, often encompassing both progenitors and differentiated cells, especially when interpreting data derived from *in vitro* adipogenic differentiation assays. With this clarified terminology in mind, the following sections focus on the specific functions and contributions of mature adipocytes.

Human adipose tissue can be divided into white adipose tissue and brown adipose tissue.[54] White adipose tissue, composed of subcutaneous and visceral adipose tissues, serves as an energy reserve and insulator. It is recognized as the largest endocrine organ, regulating hunger, glucose homeostasis, and energy expenditure.[54,55] In contrast, brown adipose tissue specializes in thermoregulation through uncoupling protein 1 (UCP1)-dependent heat generation.[56] Accordingly, it possesses numerous metabolically active mitochondria. Beige and pink adipose tissues, considered subtypes of white adipose tissue, arise from subcutaneous adipose tissue during chronic cold exposure and pregnancy, respectively.[55]

Recently, bone marrow adipose tissue has emerged as a distinct type of adipose tissues.[13,57] Human bone marrow adipocytes show lower expression of both brown and beige adipocyte markers (*UCP1*, *TBX1*, *TMEM26*, *CD137*),[57] firmly distinguishing them from these adipocyte depots. Consistently, murine bone marrow adipocytes do not express well-known markers of white, brown, or beige adipocytes (*Lep*, *Ucp1*, or *Tnfrsf9*, respectively).[58] These differences likely reflect the fact that bone marrow and peripheral adipocytes arise from distinct progenitor populations.

Indeed, studies on mice indicate that while peripheral adipose tissue adipocytes derive from stromal cells expressing Pdgfra, Cd34, and Sca1, bone marrow adipocytes originate from the described Lepr$^+$ adipogenic progenitors.[11,12,54,59] Integration of single-cell RNA sequencing data of murine stromal cells from bone marrow and white adipose tissue reveals some overlap between certain stromal populations.[13] However, the adipocyte progenitor cluster of white adipose tissue (CD142$^+$ population) and that of bone marrow (marrow adipogenic lineage precursor population, MALP) remain as separate clusters.[11,13] Interestingly, the expression of CSF1, a growth factor essential for osteoclast maintenance, is markedly higher in both human and murine bone marrow adipogenic progenitors, reflecting a conserved role in local bone homeostasis.[10]

Functionally, human bone marrow adipocyte tissue exhibits elevated cholesterol metabolism,[54] reduced lipolytic activity,[60,61] and diminished thermoregulation compared to brown adipose tissue.[58] It also displays reduced glucose metabolism and lower insulin responsiveness compared with white adipose tissue.[62] These features are consistent with human bone marrow adipocytes serving as a calorie reservoir of last resort.[63] Beyond this systemic role, murine studies demonstrate that bone marrow adipocytes also serve as a local energy depot, providing fatty acids to fuel the metabolic needs of bone marrow constituents during energy deficits.[64]

While initially considered passive, recent research has unveiled its active role in regulating hematopoiesis (Figure 1). As a local paracrine organ, bone marrow adipose tissue influences the HSC niche by secreting essential growth factors and cytokines, including adiponectin, SCF, and leptin, which promote HSC maintenance and hematopoietic regeneration.[63,65-67] In fact, microarray analysis showed that human bone marrow adipocytes express the majority of factors involved in hematopoietic regulation, suggesting a role in maintaining quiescent HSC.[63] Supporting this, adipocyte-rich bone marrow regions, such as the tail vertebrae in mice, exhibit reduced numbers of HSC and these HSC are non-cycling.[68] A decline in HSC proliferation is observed during aging and in obesity, also characterized by bone marrow fat expansion.[69] Pharmacological inhibition of bone marrow adipose tissue formation using the PPARγ inhibitor, bisphenol A diglycidyl ether, results in an elevated proportion of cycling HSC after chemotherapy and irradiation.[70] Collectively, these data imply that increased bone marrow adiposity could diminish signals necessary for HSC proliferation while providing factors that maintain HSC quiescence. Given this regulatory influence over normal hematopoiesis, bone marrow adipocytes may play a similar role in hematologic malignancies.

Adipocyte-mediated support and chemoresistance of acute leukemia

Bone marrow adipocytes do indeed provide essential support affecting leukemic cell survival, proliferation, and therapy resistance. Interestingly, the mechanisms of support and protection are different in AML and ALL.

In AML, leukemic cells induce pro-GDF15-dependent adipocyte lipolysis.[39,61,71] This allows the leukemic blasts to derive and consume fatty acids from bone marrow adipocytes.[72] Indeed, freshly isolated AML cells from patients exhibit high neutral lipid content, which is rapidly depleted in culture.[72] Co-culturing AML cells with adipocytes or exposing adipocytes to AML-conditioned media induces fatty acid and glycerol release, and elevated phosphorylation of hormone-sensitive lipase, indicative of adipocyte lipolysis[72,73] (Figure 2).

As a result, adipocyte-derived fatty acids fuel AML growth. Co-culturing AML cells with bone marrow adipocytes increases their proliferation, comparable to the effect of exogenous fatty acid (oleate) treatment.[72] Indeed, knocking down *FABP4*, a key fatty acid transport protein, in bone marrow adipocytes or carnitine palmitoyltransferase 1A (*CPT1A*), an enzyme catalyzing the transport of fatty acids from the cytoplasm to mitochondria, in AML cells significantly decreases the oxidative capacity of AML blasts and reduces their proliferation in co-culture.[72] Consistently, mice injected with *CPT1A*-knockdown AML cells showed improved survival.[72] This suggests that beyond supporting growth, the metabolic reliance on fatty acids may also provide AML cells with a survival advantage under chemotherapeutic stress.[61]

Since AML cells are highly dependent on various energy sources for their survival, it is of the utmost importance for them to be able to switch from one metabolite to another during periods of metabolite deficiency. For instance, AML stem cells rely heavily on amino acids to fuel oxidative phosphorylation for their proliferation by increasing fatty acid transport into their mitochondria.[74,75] Therefore, when *de novo* AML patients are treated with venetoclax and azacitidine, which inhibits amino acid uptake, it leads to leukemic stem cell eradication. However, relapsed patients exhibit low response rates to this therapy as their leukemic stem cells upregulate fatty acid oxidation to compensate for amino acid depletion.[74] Similarly, AML cells with RAS pathway mutations are also resistant to venetoclax and azacitidine due to altered energy metabolism.[75] At the transcriptional level, these leukemic cells exhibit upregulated *CD36* and acyl-CoA dehydrogenase very long chain (*ACADVL*) expression.[75] While CD36 is involved in fatty acid transport,[76] *ACADVL* encodes an enzyme essential for supplying fat-derived carbon to the tricarboxylic acid cycle.[77] Indeed, *ACADVL* knockdown selectively induces AML cell death both *in vitro* and *in vivo*.[77]

Additionally, cytarabine chemotherapy selectively favors the survival of AML cells with a high fatty acid oxidation signature.[78] Mechanistically, AML uses interleukin 6 receptors (IL6R) to activate STAT3 which further upregulates CD36 to take up fatty acids from bone marrow adipocytes, thereby supporting their growth and resistance to cytarabine.[79] Transcriptomic analysis of the resistant leukemic cells confirms elevated fatty acid metabolism and high CD36 expression following cytarabine treatment;[78] with metabolic profiling showing increased fatty acid consumption as compared with glucose, lactate, and glutamine consumption. Blocking fatty acid oxidation sensitizes AML cells to chemotherapy, highlighting the dependence of AML resistance on fatty acid metabolism.[78,80]

Moreover, AML patient-derived xenografts from older patients exhibit poorer responses to cytarabine treatment.[78] Considering the increased fat content in bone marrow of older individuals, it can be speculated that the adipocyte-rich environment provides a selective advantage to AML cells, enabling them to survive better *in vivo*. Supporting this, co-culture of AML cells with adipocytes differentiated from AML patient-derived MSC modulates leukemic chemosensitivity: overexpression of *METTL3*, which suppresses adipogenic differentiation capacity, increases the sensitivity of AML cells to chemotherapy, whereas its knockdown, which enhances adipogenesis and thus results in higher adipocyte numbers, promotes chemoresistance.[52] Consistently, knockout of *Mettl3* in murine MSC enhancing bone marrow adiposity before AML injection leads to increased chemoresistance of leukemic cells to cytarabine treatment *in vivo*.[50] On top of this, adipocytes secrete factors such as leptin, which promotes AML proliferation in a dose-related manner[81] while protecting them from doxorubicin-induced

cell death by activating STAT-3 and MAPK pathways.[82] In summary, AML cells stimulate lipolysis in bone marrow adipocytes and utilize the released fatty acids to support their proliferation and survival during chemotherapy.

In ALL, leukemic cells release pro-GDF15, interleukin 1 alpha (IL1α), interleukin 1 beta (IL1β), and tumor necrosis factor alpha (TNFα) to stimulate lipolysis in adipocytes, preferentially releasing unsaturated fatty acids such as oleate, which they utilize to fuel mitochondrial respiration.[9,39,83,84] This ALL dependency on fatty acids is further exacerbated during chemotherapy. For instance, dexamethasone suppresses the MYC transcription factor in ALL cells. This leads to decreased glucose and amino acid (glutamine, arginine, histidine, lysin, methionine, etc.) uptake, shifting

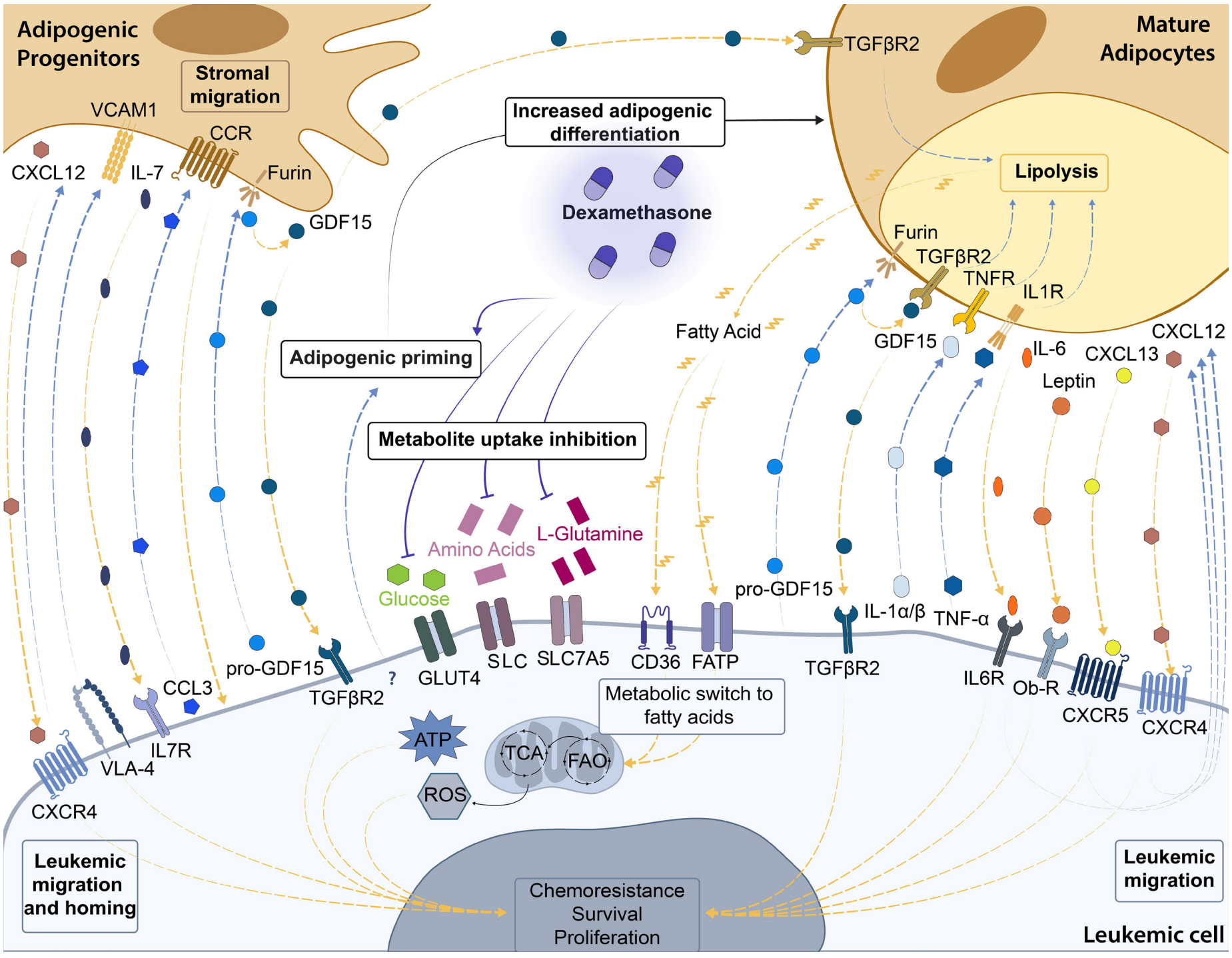


Figure 2. Chemotherapy-driven metabolic reprogramming creates leukemic cell dependency on the adipogenic niche. Dexamethasone inhibits glucose and amino acid uptake in leukemic cells, forcing them to rely on fatty acid metabolism for survival. This dependency drives leukemic cells to migrate toward adipogenic progenitors via CXCL12 and VCAM1 and toward adipocytes using chemokine signals (CXCL12, CXCL13, leptin). Leukemic cells then stimulate adipocyte lipolysis through inflammatory mediators (pro-GDF15, IL1α/β, TNFα) to consume fatty acids for energy while secreting CCL3 to recruit additional adipogenic progenitors. Adipogenic lineage cells reciprocally support survival by releasing specific cytokines that enhance chemotherapy resistance. Both chemotherapy and leukemic cells promote mesenchymal stromal cells adipogenic differentiation, expanding this supportive niche. ATP: adenosine triphosphate; CCL3: chemokine (C-C motif) ligand 3; CCR: CC chemokine receptor; CD36: cluster of differentiation 36; CXCL12/13: C-X-C motif chemokine ligand 12/13; CXCR4/5: C-X-C motif chemokine receptor 4/5; FAO: fatty acid oxidation; FATP: fatty acid transport proteins; GDF15: growth differentiation factor 15; GLUT4: glucose transporter type 4; IL: interleukin; IL1/6/7R: interleukin 1/6/7 receptor; Ob-R: leptin receptor; Pro-GDF15: propeptide growth differentiation factor 15; ROS: reactive oxygen series; SLC: solute carrier; SLC7A5: solute carrier family 7 member 5; TCA: tricarboxylic acid cycle; TGFβR2: transforming growth factor-beta receptor type 2; TNF-α: tumor necrosis factor alpha; TNFR: tumor necrosis factor receptor; VCAM1: vascular cell adhesion molecule 1; VLA-4: α4β1 integrin.

ALL cells to a compensatory fatty acid metabolic pathway.[85] Olivas-Aguirre *et al*.[86] showed that dexamethasone reduces glycolytic activity and glutamine metabolism in ALL cells forcing them to rely heavily on fatty acid oxidation instead. Interestingly, while adipocytes in AML stimulate leukemic growth, in ALL they inhibit proliferation.[87] B-ALL cells show reduced growth when exposed to an adipocyte-rich environment due to induction of G0 cell cycle arrest[9,87] which might be partly driven by adiponectin.[88] Similarly, ALL engraftment and proliferation are lower in adipocyte-rich bone marrow regions, such as tail vertebrae, compared to adipocyte-poor sites, including femoral bone marrow and thoracic vertebrae.[9,87,89] In fact, the majority of T-ALL blasts from the adipocyte-rich tail vertebrae bone marrow are quiescent CD44$^+$ leukemic cells.[90] These observations collectively indicate that bone marrow adipocytes drive the transition of ALL from a proliferating state into quiescence potentially assisting in leukemic survival.

As noted, adipocytes support chemoresistance in both B-ALL and T-ALL. Pre-treatment with adipocyte-conditioned medium reduces ALL sensitivity to chemotherapeutics.[83,87,89,90] In B-ALL, leukemic cells upregulate GAL-9 expression upon co-culture with adipocytes which enhance their cell adhesion and chemoprotection.[87] Importantly, their survival also increases upon exposure to exogenous free fatty acids such as oleic acid.[83,87]

In addition, bone marrow adipocytes secrete C-X-C motif chemokine ligand 13 (CXCL13) following dexamethasone treatment in a mouse model, attracting T-ALL cells via CXCL13 receptor, CXCR5, and upregulate delta like canonical Notch ligand 1 (DLL1), activating Notch1 signaling, which enhances adhesion and reduces chemotherapy-induced apoptosis.[91] Blocking CXCL13 or DLL1/Notch1 interactions diminishes these protective effects.[91] This explains how T-ALL recovered from the adipocyte-rich tail vertebrae survive better upon vincristine and cytarabine treatment compared to those derived from adipocyte-poor thoracic vertebrae.[89] Calvo *et al*.[90] further support this by reporting that the treatment of mice bearing T-ALL with the combination of vincristine, cytarabine, dexamethasone and L-asparaginase reduces leukemic burden less effectively in adipocyte-rich bone marrow than in adipocyte-poor bone marrow. Collectively, these studies indicate that T-ALL residing in adipocyte-rich bone marrow is less susceptible to chemotherapy, suggesting a bone marrow adipocyte-mediated protective effect.

Overall, bone marrow adipocytes play contrasting roles in acute leukemia - they promote AML proliferation while driving ALL cells into quiescence. While apparently contradictory, these divergent effects likely reflect fundamental differences between the intrinsic transcriptional programs, metabolic dependencies, and cell cycle regulatory machinery of myeloid and lymphoid leukemic cells. Nonetheless, in both types of acute leukemias, adipocyte-derived factors support leukemic survival and chemoresistance.

Chemotherapy-driven adipogenesis

Chemotherapy can directly stimulate adipogenic differentiation in the bone marrow, creating an adipocyte-rich environment that favors the persistence of acute leukemia cells. For instance, cytarabine, a standard chemotherapeutic agent for the treatment of acute leukemia,[92] induces bone marrow adipocyte hyperplasia in mice.[70] It elevates mitochondrial production of reactive oxygen species in MSC which then activates PPARγ, a major adipogenic transcription factor, resulting in the induction of adipogenesis.[93]

Dexamethasone, another anti-leukemic agent widely used in ALL therapy,[94] has similar pro-adipogenic effects. The analysis of T-ALL patients' biopsies before and after induction therapy (vincristine, idarubicin, and dexamethasone) shows a significant increase in adipocyte number following the treatment.[91] Further *in vitro* experiments indicate that this effect is indeed driven by dexamethasone, which stimulates adipogenesis in bone marrow MSC by upregulating sterol regulatory element binding transcription factor 1 (*SREBF1*), a key transcription factor regulating MSC adipogenic differentiation.[91] In fact, both knockdown of *SREBF1* with *shSREBF1* lentivirus and the blockage of SREBF1 activation with its inhibitor, fatostatin HBr, drastically reduces dexamethasone-induced adipogenesis.

These findings align with evidence that the bone marrow adipose tissue rapidly recovers after chemotherapy.[88] Notably, the adipocyte compartment of the bone marrow is substantially depleted during the development of both B-ALL and T-ALL but is rapidly reconstituted after the induction of remission.[7,9,88,95] We propose that this reconstitution of bone marrow adipocytes following chemotherapy may result not only from adipogenic priming by leukemia but, more importantly, by chemotherapy itself. While chemotherapy eliminates many cells in the bone marrow it appears to preserve and promote MSC primed toward adipogenesis. Consequently, the remaining marrow stroma becomes enriched in adipogenic progenitors.

In summary, chemotherapeutic agents expand both adipogenic progenitors and mature adipocytes, restoring bone marrow adipose tissue after treatment. This generates a microenvironment that supports residual, drug-resistant leukemia cells. Combined with chemotherapy-driven metabolic shifts toward fatty acid oxidation, these changes promote leukemia survival, chemoresistance, and potentially relapse, as a somewhat unexpected and surely unwanted "off-target" effect of chemotherapy.

Conclusion and future perspectives

The bone marrow is a complex and highly dynamic microenvironment that governs hematopoietic homeostasis. Among its diverse cellular constituents, adipocyte lineage cells have

recently emerged as critical yet underexplored components of the leukemic niche. Evidence reviewed here indicates that adipogenic progenitors and mature adipocytes are functionally distinct populations that differentially sustain leukemic cells through metabolic support and chemotherapy protection. Critically, leukemic cells actively reprogram normal MSC towards an adipogenic fate, expanding the adipogenic progenitor pool and amplifying niche-mediated chemoresistance. Chemotherapy further compounds this by driving additional adipogenesis, inadvertently generating a mature adipocyte-rich microenvironment that shelters residual resistant cells and creates permissive conditions for relapse. This dual convergence positions the adipocyte lineage as a central, clinically actionable component of leukemic persistence, and several pharmacological strategies warrant further exploration in future research.

The first possibility is to target fatty acid metabolism, with candidate compounds including SSO/SMS121 (a CD36 inhibitor),[96] BMS309403 (a FABP4 inhibitor),[72] and etomoxir (a CPT1A inhibitor)[72,78] to deprive leukemic cells of adipocyte-derived fatty acids during chemotherapy. A second option lies in disrupting leukemia-adipogenic progenitor communication, e.g., via the CXCL12-CXCR4 or VCAM1-VLA4 axes. Plerixafor (AMD3100) has already demonstrated blast mobilization and acceptable safety in a phase I/II trial (NCT00906945) in pediatric relapsed or refractory AML,[97] while VCAM1 blockade using targeted antibodies has been shown to impair ALL cell viability in adipogenic progenitor co-cultures.[14] A third potential avenue lies in the modulation of stromal cell differentiation. As a proof of concept, indirectly targeting the METTL3 pathway via the AKT inhibitor MK-2206 2HCl has been shown to reduce MSC-adipogenesis in cell culture.[52]

Future application of single cell and spatial multi-omics technologies will allow the adipocyte lineage–enriched leukemic niche to be mapped with far greater precision, uncovering critical signaling pathways and potential biomarkers of chemoresistance. Ultimately, viewing acute leukemia as a disease of a disrupted marrow ecosystem, rather than solely a malignant clone, positions adipocyte lineage cells as potentially actionable components of therapy.

Disclosures

No conflicts of interest to disclose.

Contributions

BK did the literature search and wrote the first draft of the manuscript. BK, MNFB, OH and HJV discussed and reviewed the manuscript and approved the final version.

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References

1. Tikhonova AN, Dolgalev I, Hu H, et al. The bone marrow microenvironment at single-cell resolution. Nature. 2019;569(7755):222-228.
2. Baccin C, Al-Sabah J, Velten L, et al. Combined single-cell and spatial transcriptomics reveal the molecular, cellular and spatial bone marrow niche organization. Nat Cell Biol. 2020;22(1):38-48.
3. Bandyopadhyay S, Duffy MP, Ahn KJ, et al. Mapping the cellular biogeography of human bone marrow niches using single-cell transcriptomics and proteomic imaging. Cell. 2024;187(12):3120-3140.
4. Li H, Braunig S, Dhapolar P, et al. Identification of phenotypically, functionally, and anatomically distinct stromal niche populations in human bone marrow based on single-cell RNA sequencing. Elife. 2023;12:e81656.
5. Wang Z, Li X, Yang J, et al. Single-cell RNA sequencing deconvolutes the in vivo heterogeneity of human bone marrow-derived mesenchymal stem cells. Int J Biol Sci. 2021;17(15):4192-4206.
6. Ambrosi TH, Sinha R, Steininger HM, et al. Distinct skeletal stem cell types orchestrate long bone skeletogenesis. Elife. 2021;10:e66063.
7. Tereshchenko GV, Kriventsova NA, Kupriyanov DA, et al. Quantitative bone marrow MRI in children with acute lymphoblastic leukemia. Int J Biomed. 2021;11(2):141-145.
8. Ruschke S, Pokorney A, Baum T, et al. Measurement of vertebral bone marrow proton density fat fraction in children using quantitative water-fat MRI. MAGMA. 2017;30(5):449-460.
9. 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(1):5507.
10. Inoue K, Qin Y, Xia Y, et al. Bone marrow Adipoq-lineage progenitors are a major cellular source of M-CSF that dominates bone marrow macrophage development, osteoclastogenesis, and bone mass. Elife. 2023;12:e82118.
11. Zhong L, Yao L, Tower RJ, et al. Single cell transcriptomics identifies a unique adipose lineage cell population that regulates bone marrow environment. Elife. 2020;9:e54695.
12. 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(2):e140214.
13. Zhong L, Yao L, Seale P, Qin L. Marrow adipogenic lineage precursor: a new cellular component of marrow adipose tissue. Best Pract Res Clin Endocrinol Metab. 2021;35(4):101518.
14. Ferrao Blanco MN, Kazybay B, Belderbos M, Heidenreich O, Vormoor HJ. Distinct stromal cell populations define the B-cell acute lymphoblastic leukemia microenvironment. Leukemia. 2025;39(11):2622-2639.
15. Jardine L, Webb S, Goh I, et al. Blood and immune development in human fetal bone marrow and Down syndrome. Nature. 2021;598(7880):327-331.
16. Yanina IY, Dyachenko PA, Abdurashitov AS, et al. Light distribution in fat cell layers at physiological temperatures. Sci

Rep. 2023;13(1):1073.
17. DeLuca JH, Reilly SM. Culture and differentiation of primary preadipocytes from mouse subcutaneous white adipose tissue. Methods Mol Biol. 2023;2662:11-24.
18. Zhang P, Dong J, Fan X, et al. Characterization of mesenchymal stem cells in human fetal bone marrow by single-cell transcriptomic and functional analysis. Signal Transduct Target Ther. 2023;8(1):126.
19. Sivaraj KK, Jeong HW, Dharmalingam B, et al. Regional specialization and fate specification of bone stromal cells in skeletal development. Cell Rep. 2021;36(2):109352.
20. Baryawno N, Przybylski D, Kowalczyk MS, et al. A cellular taxonomy of the bone marrow stroma in homeostasis and leukemia. Cell. 2019;177(7):1915-1932.
21. Omatsu Y, Sugiyama T, Kohara H, et al. The essential functions of adipo-osteogenic progenitors as the hematopoietic stem and progenitor cell niche. Immunity. 2010;33(3):387-399.
22. Acar M, Kocherlakota KS, Murphy MM, et al. Deep imaging of bone marrow shows non-dividing stem cells are mainly perisinusoidal. Nature. 2015;526(7571):126-130.
23. Zhang Z, Huang Z, Ong B, et al. Bone marrow adipose tissue-derived stem cell factor mediates metabolic regulation of hematopoiesis. Haematologica. 2019;104(9):1731-1743.
24. Barata JT, Durum SK, Seddon B. Flip the coin: IL-7 and IL-7R in health and disease. Nat Immunol. 2019;20(12):1584-1593.
25. Pinho S, Wei Q, Maryanovich M, et al. VCAM1 confers innate immune tolerance on haematopoietic and leukaemic stem cells. Nat Cell Biol. 2022;24(3):290-298.
26. Cho BS, Kim HJ, Konopleva M. Targeting the CXCL12/CXCR4 axis in acute myeloid leukemia: from bench to bedside. Korean J Intern Med. 2017;32(2):248-257.
27. Schelker RC, Iberl S, Muller G, et al. TGF-beta1 and CXCL12 modulate proliferation and chemotherapy sensitivity of acute myeloid leukemia cells co-cultured with multipotent mesenchymal stromal cells. Hematology. 2018;23(6):337-345.
28. Cho BS, Zeng Z, Mu H, et al. Antileukemia activity of the novel peptidic CXCR4 antagonist LY2510924 as monotherapy and in combination with chemotherapy. Blood. 2015;126(2):222-232.
29. Chen Y, Jacamo R, Konopleva M, et al. CXCR4 downregulation of let-7a drives chemoresistance in acute myeloid leukemia. J Clin Invest. 2013;123(6):2395-2407.
30. Noguera NI, Travaglini S, Scalea S, et al. YY1 knockdown relieves the differentiation block and restores apoptosis in AML cells. Cancers (Basel). 2023;15(15):4010.
31. Sison EA, McIntyre E, Magoon D, Brown P. Dynamic chemotherapy-induced upregulation of CXCR4 expression: a mechanism of therapeutic resistance in pediatric AML. Mol Cancer Res. 2013;11(9):1004-1016.
32. Zheng F, Li H, Du W, Huang S. Role of hERG1 K(+) channels in leukemia cells as a positive regulator in SDF-1a-induced proliferation. Hematology. 2011;16(3):177-184.
33. Pan C, Fang Q, Liu P, et al. Mesenchymal stem cells with cancer-associated fibroblast-like phenotype stimulate SDF-1/CXCR4 axis to enhance the growth and invasion of B-cell acute lymphoblastic leukemia cells through cell-to-cell communication. Front Cell Dev Biol. 2021;9:708513.
34. Polak A, Kiliszek P, Sewastianik T, et al. MEK inhibition sensitizes precursor B-cell acute lymphoblastic leukemia (B-ALL) cells to dexamethasone through modulation of mTOR activity and stimulation of autophagy. PLoS One. 2016;11(5):e0155893.
35. Wang S, Wang X, Liu S, et al. The CXCR4 antagonist, AMD3100, reverses mesenchymal stem cell-mediated drug resistance in relapsed/refractory acute lymphoblastic leukemia. Onco Targets Ther. 2020;13:6583-6591.
36. Shen W, Bendall LJ, Gottlieb DJ, Bradstock KF. The chemokine receptor CXCR4 enhances integrin-mediated in vitro adhesion and facilitates engraftment of leukemic precursor-B cells in the bone marrow. Exp Hematol. 2001;29(12):1439-1447.
37. Jacamo R, Chen Y, Wang Z, et al. Reciprocal leukemia-stroma VCAM-1/VLA-4-dependent activation of NF-kappaB mediates chemoresistance. Blood. 2014;123(17):2691-2702.
38. Hsieh YT, Gang EJ, Geng H, et al. Integrin alpha4 blockade sensitizes drug resistant pre-B acute lymphoblastic leukemia to chemotherapy. Blood. 2013;121(10):1814-1818.
39. Duan CW, Shi J, Chen J, et al. Leukemia propagating cells rebuild an evolving niche in response to therapy. Cancer Cell. 2014;25(6):778-793.
40. Tang C, Li MH, Chen YL, et al. Chemotherapy-induced niche perturbs hematopoietic reconstitution in B-cell acute lymphoblastic leukemia. J Exp Clin Cancer Res. 2018;37(1):204.
41. Le Y, Fraineau S, Chandran P, et al. Adipogenic mesenchymal stromal cells from bone marrow and their hematopoietic supportive role: towards understanding the permissive marrow microenvironment in acute myeloid leukemia. Stem Cell Rev Rep. 2016;12(2):235-244.
42. Sabbah R, Saadi S, Shahar-Gabay T, et al. Abnormal adipogenic signaling in the bone marrow mesenchymal stem cells contributes to supportive microenvironment for leukemia development. Cell Commun Signal. 2023;21(1):277.
43. Babbo CC, Pitere RR, Giles R, Ambele MA, Pepper MS. RT-qPCR quantification of adipogenic marker genes (PPARg, C/EBPa, FABP4, and CD36). Methods Mol Biol. 2025;2938:53-62.
44. Azadniv M, Myers JR, McMurray HR, et al. Bone marrow mesenchymal stromal cells from acute myelogenous leukemia patients demonstrate adipogenic differentiation propensity with implications for leukemia cell support. Leukemia. 2020;34(2):391-403.
45. Weickert MT, Hecker JS, Buck MC, et al. Bone marrow stromal cells from MDS and AML patients show increased adipogenic potential with reduced Delta-like-1 expression. Sci Rep. 2021;11(1):5944.
46. Vicente Lopez A, Vazquez Garcia MN, Melen GJ, et al. Mesenchymal stromal cells derived from the bone marrow of acute lymphoblastic leukemia patients show altered BMP4 production: correlations with the course of disease. PLoS One. 2014;9(1):e84496.
47. Hughes AM, Kuek V, Oommen J, et al. Characterization of mesenchymal stem cells in pre-B acute lymphoblastic leukemia. Front Cell Dev Biol. 2023;11:1005494.
48. Corradi G, Baldazzi C, Ocadlikova D, et al. Mesenchymal stromal cells from myelodysplastic and acute myeloid leukemia patients display in vitro reduced proliferative potential and similar capacity to support leukemia cell survival. Stem Cell Res Ther. 2018;9(1):271.
49. Wu Y, Xie L, Wang M, et al. Mettl3-mediated m(6)A RNA methylation regulates the fate of bone marrow mesenchymal stem cells and osteoporosis. Nat Commun. 2018;9(1):4772.
50. Liao X, Cai D, Liu J, et al. Deletion of Mettl3 in mesenchymal stem cells promotes acute myeloid leukemia resistance to chemotherapy. Cell Death Dis. 2023;14(12):796.
51. Yao Y, Bi Z, Wu R, et al. METTL3 inhibits BMSC adipogenic differentiation by targeting the JAK1/STAT5/C/EBPbeta pathway via an m(6)A-YTHDF2-dependent manner. FASEB J. 2019;33(6):7529-7544.
52. Pan ZP, Wang B, Hou DY, et al. METTL3 mediates bone marrow mesenchymal stem cell adipogenesis to promote

chemoresistance in acute myeloid leukaemia. FEBS Open Bio. 2021;11(6):1659-1672.
53. Kim J, Han D, Byun SH, et al. Neprilysin facilitates adipogenesis through potentiation of the phosphatidylinositol 3-kinase (PI3K) signaling pathway. Mol Cell Biochem. 2017;430(1-2):1-9.
54. Higos R, Saitoski K, Hautefeuille M, et al. The critical role of adipocytes in leukemia. Biology (Basel). 2025;14(6):624.
55. Machado SA, Pasquarelli-do-Nascimento G, da Silva DS, et al. Browning of the white adipose tissue regulation: new insights into nutritional and metabolic relevance in health and diseases. Nutr Metab (Lond). 2022;19(1):61.
56. Chouchani ET, Kazak L, Spiegelman BM. New advances in adaptive thermogenesis: UCP1 and beyond. Cell Metab. 2019;29(1):27-37.
57. Pham TT, Ivaska KK, Hannukainen JC, et al. Human bone marrow adipose tissue is a metabolically active and insulin-sensitive distinct fat depot. J Clin Endocrinol Metab. 2020;105(7):2300-2310.
58. Craft CS, Robles H, Lorenz MR, et al. Bone marrow adipose tissue does not express UCP1 during development or adrenergic-induced remodeling. Sci Rep. 2019;9(1):17427.
59. Hepler C, Vishvanath L, Gupta RK. Sorting out adipocyte precursors and their role in physiology and disease. Genes Dev. 2017;31(2):127-140.
60. Attane C, Esteve D, Chaoui K, et al. Human bone marrow is comprised of adipocytes with specific lipid metabolism. Cell Rep. 2020;30(4):949-958.e6.
61. Dembitz V, James SC, Gallipoli P. Targeting lipid metabolism in acute myeloid leukemia: biological insights and therapeutic opportunities. Leukemia. 2025;39(8):1814-1823.
62. Suchacki KJ, Tavares AAS, Mattiucci D, et al. Bone marrow adipose tissue is a unique adipose subtype with distinct roles in glucose homeostasis. Nat Commun. 2020;11(1):3097.
63. Mattiucci D, Maurizi G, Izzi V, et al. Bone marrow adipocytes support hematopoietic stem cell survival. J Cell Physiol. 2018;233(2):1500-1511.
64. Li Z, Bowers E, Zhu J, et al. Lipolysis of bone marrow adipocytes is required to fuel bone and the marrow niche during energy deficits. Elife. 2022;11:e78496.
65. Dias CC, Nogueira-Pedro A, Tokuyama PY, et al. A synthetic fragment of leptin increase hematopoietic stem cell population and improve its engraftment ability. J Cell Biochem. 2015;116(7):1334-1340.
66. 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(8):891-903.
67. DiMascio L, Voermans C, Uqoezwa M, et al. Identification of adiponectin as a novel hemopoietic stem cell growth factor. J Immunol. 2007;178(6):3511-3520.
68. Naveiras O, Nardi V, Wenzel PL, et al. Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment. Nature. 2009;460(7252):259-263.
69. Ambrosi TH, Scialdone A, Graja A, et al. Adipocyte accumulation in the bone marrow during obesity and aging impairs stem cell-based hematopoietic and bone regeneration. Cell Stem Cell. 2017;20(6):771-784.
70. Zhu RJ, Wu MQ, Li ZJ, Zhang Y, Liu KY. Hematopoietic recovery following chemotherapy is improved by BADGE-induced inhibition of adipogenesis. Int J Hematol. 2013;97(1):58-72.
71. Lu W, Wan Y, Li Z, et al. Growth differentiation factor 15 contributes to marrow adipocyte remodeling in response to the growth of leukemic cells. J Exp Clin Cancer Res. 2018;37(1):66.
72. Shafat MS, Oellerich T, Mohr S, et al. Leukemic blasts program bone marrow adipocytes to generate a protumoral microenvironment. Blood. 2017;129(10):1320-1332.
73. Lu W, Weng W, Zhu Q, et al. Small bone marrow adipocytes predict poor prognosis in acute myeloid leukemia. Haematologica. 2018;103(1):e21-e24.
74. Jones CL, Stevens BM, D'Alessandro A, et al. Inhibition of amino acid metabolism selectively targets human leukemia stem cells. Cancer Cell. 2018;34(5):724-740.
75. Stevens BM, Jones CL, Pollyea DA, et al. Fatty acid metabolism underlies venetoclax resistance in acute myeloid leukemia stem cells. Nat Cancer. 2020;1(12):1176-1187.
76. Perea G, Domingo A, Villamor N, et al. Adverse prognostic impact of CD36 and CD2 expression in adult de novo acute myeloid leukemia patients. Leuk Res. 2005;29(10):1109-1116.
77. Tcheng M, Roma A, Ahmed N, et al. Very long chain fatty acid metabolism is required in acute myeloid leukemia. Blood. 2021;137(25):3518-3532.
78. Farge T, Saland E, de Toni F, et al. Chemotherapy-resistant human acute myeloid leukemia cells are not enriched for leukemic stem cells but require oxidative metabolism. Cancer Discov. 2017;7(7):716-735.
79. Zhang Y, Guo H, Zhang Z, et al. IL-6 promotes chemoresistance via upregulating CD36 mediated fatty acids uptake in acute myeloid leukemia. Exp Cell Res. 2022;415(1):113112.
80. Estan MC, Calvino E, Calvo S, et al. Apoptotic efficacy of etomoxir in human acute myeloid leukemia cells. Cooperation with arsenic trioxide and glycolytic inhibitors, and regulation by oxidative stress and protein kinase activities. PLoS One. 2014;9(12):e115250.
81. Bruserud O, Huang TS, Glenjen N, Gjertsen BT, Foss B. Leptin in human acute myelogenous leukemia: studies of in vivo levels and in vitro effects on native functional leukemia blasts. Haematologica. 2002;87(6):584-595.
82. Tabe Y, Konopleva M, Munsell MF, et al. PML-RARalpha is associated with leptin-receptor induction: the role of mesenchymal stem cell-derived adipocytes in APL cell survival. Blood. 2004;103(5):1815-1822.
83. Tucci J, Chen T, Margulis K, et al. Adipocytes provide fatty acids to acute lymphoblastic leukemia cells. Front Oncol. 2021;11:665763.
84. 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(1):23-37.
85. Dyczynski M, Vesterlund M, Bjorklund AC, et al. Metabolic reprogramming of acute lymphoblastic leukemia cells in response to glucocorticoid treatment. Cell Death Dis. 2018;9(9):846.
86. Olivas-Aguirre M, Perez-Chavez J, Torres-Lopez L, et al. Dexamethasone-induced fatty acid oxidation and autophagy/mitophagy are essential for T-ALL glucocorticoid resistance. Cancers (Basel). 2023;15(2):445.
87. Lee M, Hamilton JAG, Talekar GR, et al. Obesity-induced galectin-9 is a therapeutic target in B-cell acute lymphoblastic leukemia. Nat Commun. 2022;13(1):1157.
88. Jia X, Liao N, Yao Y, et al. Dynamic evolution of bone marrow adipocyte in B cell acute lymphoblastic leukemia: insights from diagnosis to post-chemotherapy. Cancer Biol Ther. 2024;25(1):2323765.
89. 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(20):1760-1772.
90. Calvo J, Naguibneva I, Kypraios A, et al. High CD44 expression and enhanced E-selectin binding identified as biomarkers of

chemoresistant leukemic cells in human T-ALL. Leukemia. 2024:39(2):323-336.
91. Jia R, Sun T, Zhao X, et al. DEX-induced SREBF1 promotes BMSCs differentiation into adipocytes to attract and protect residual T-cell acute lymphoblastic leukemia cells after chemotherapy. Adv Sci (Weinh). 2023;10(19):e2205854.
92. Murphy T, Yee KWL. Cytarabine and daunorubicin for the treatment of acute myeloid leukemia. Expert Opin Pharmacother. 2017;18(16):1765-1780.
93. Wang W, Zhang Y, Lu W, Liu K. Mitochondrial reactive oxygen species regulate adipocyte differentiation of mesenchymal stem cells in hematopoietic stress induced by arabinosylcytosine. PLoS One. 2015;10(3):e0120629.
94. Bertoli S, Picard M, Berard E, et al. Dexamethasone in hyperleukocytic acute myeloid leukemia. Haematologica. 2018;103(6):988-998.
95. Nguyen TV, Melville A, Nath S, et al. Bone marrow recovery by morphometry during induction chemotherapy for acute lymphoblastic leukemia in children. PLoS One. 2015;10(5):e0126233.
96. Abacka H, Masoni S, Poli G, et al. SMS121, a new inhibitor of CD36, impairs fatty acid uptake and viability of acute myeloid leukemia. Sci Rep. 2024;14(1):9104.
97. Uy GL, Rettig MP, Stone RM, et al. A phase 1/2 study of chemosensitization with plerixafor plus G-CSF in relapsed or refractory acute myeloid leukemia. Blood Cancer J. 2017;7(3):e542.
98. Ye J, Calvo IA, Cenzano I, et al. Deconvolution of the hematopoietic stem cell microenvironment reveals a high degree of specialization and conservation. iScience. 2022;25(5):104225.
99. Chen L, Pronk E, van Dijk C, et al. A single-cell taxonomy predicts inflammatory niche remodeling to drive tissue failure and outcome in human AML. Blood Cancer Discov. 2023;4(5):394-417.
100. Dolgalev I, Tikhonova AN. Connecting the dots: resolving the bone marrow niche heterogeneity. Front Cell Dev Biol. 2021;9:622519.