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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. This has two main reasons: 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 (HSCs) and non-hematopoietic stem cells and their diverse progeny[1, 2]. A critical component of this environment are bone marrow mesenchymal stromal cells (MSCs), a heterogeneous population of multipotent progenitors capable of differentiating into various skeletal lineages[1, 2]. In this review, we will 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, MSCs 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 man, describe a comparable, distinct candidate adipogenic progenitor cell population

highlighting their conserved nature (see Table 1 and Supplementary Table 1). This population is characterized by the expression of both MSC (*CXCL12* (C-X- C motif chemokine ligand 12*), LEPR (*leptin receptor*)*) and adipocyte (*LPL* (lipoprotein lipase*), ADIPOQ (*adiponectin*), PPARG (peroxisome proliferator activated receptor γ), CEBPA/D (*CCAAT enhancer-binding protein α/δ*), APOE (*apolipoprotein E*), GAS6 (*growth arrest specific-6*)*) markers. 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 murine bone marrow stroma compartment[13].

Morphologically, adipogenic progenitors in both humans and mice remain undifferentiated and lack lipid accumulation. Consistent with this, *PLIN1* (perilipin-1), 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 comprises more than 95% of their cell volume[16]. This morphology makes them very fragile[17]. Therefore, mature adipocytes are usually lost/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 (Supplementary Table 2). 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 *ESM1* expression and absence of *SCA-1*, a marker profile typical of sinusoid-associated stromal populations[3, 4]. Spatial transcriptomic analysis of a B-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, SCF* (stem cell factor, *KITLG*), *IL7* (interleukin 7)*, and ANGPT1* (angiopoietin-1), chemokines important for migration, maintenance, and survival of HSCs (See Figure 1)[14]. Consistently, HSCs 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 confirm 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 VCAM1 (vascular cell adhesion molecule 1*)*[14], an adhesion molecule implicated in HSPC homing[25]. These data demonstrate the critical involvement of adipogenic progenitors in providing support for HSCs 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 MDK–LRP1/SORL1(midkine-low density lipoprotein receptor related protein 1/sortilin related receptor 1)[4]. Notably, adipogenic progenitors express the highest levels of IL7 among all stromal subsets and constitute a major source of CCL2 and 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 HSCs. 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 *ex vivo* expand more slowly than immature MSC they 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 will focus upon 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 chapter 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 CXCL12-CXCR4 (C-X-C motif chemokine ligand 12/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 PI3K/Akt (phosphatidylinositol-4,5-bisphosphate 3-kinase/Akt)[28] and YY1/c-Myc (Yin Yang 1/c-Myc proto-oncogene) cascades[29, 30] inhibiting leukemic apoptosis; as well as MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase)[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 both pathways[14]. Although the downstream signaling underlying this protection have 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-ALLs directly triggers pro-survival PI3K/AKT signaling suppressing apoptosis[33]. In parallel, the CXCL12-CXCR4 axis induces MAPK/ERK signaling which further activates the mTOR (mechanistic target of rapamycin) pathway resulting in reduced autophagy in B-ALL cells[34]. Given that glucocorticoids like 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 MSC co-cultures. This protective effect is reversed by blocking CXCR4 with its antagonist AMD3100 (plerixafor), which also selectively reduces B-ALL viability during co-culture with adipogenic progenitors[14, 35]. These findings go 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 VLA-4 (α4β1 integrin) binding to VCAM1[36]. The VLA4-VCAM1 interaction then activates NF-κB pathway inducing 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 BIO-1211 small molecule inhibits the adipogenic progenitor-induced ALL support[14].

Intriguingly, B-ALL cells actively recruit adipogenic progenitors by secreting CCL3 (C-C motif chemokine ligand 3) chemoattractant to create a pro-tumorigenic niche[39]. Treatment of NALM-6 ALL-bearing mice with cytarabine and daunorubicin induces the formation of a protective niche for the leukemia primarily composed of Nestin+ MSCs[39]. Although not explicitly defined as such by the authors, the LepR+ NG2- profile of these cells, indicative of sinusoidal niche MSCs[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 pro-GDF15 (propeptide growth differentiation factor 15), 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 chapter.

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 MSCs display 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 *FABP4* (fatty acid binding protein 4) expression compared to healthy MSCs[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 when subjected to *ex vivo* adipogenic differentiation assays demonstrate significantly enhanced adipocyte commitment[9, 14, 46]. We also previously[14] demonstrated that the direct co-culture of MSCs with B-ALL PDXs further can 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 MSCs exposed to ALL cell line-conditioned media indicating a range of mechanisms how ALL cells are able to manipulate MSCs.

Not all studies, however, 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 MSCs 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 MSCs toward adipocyte lineage, the molecular mechanisms underlying this reprogramming are only beginning to emerge. Recently, the methyltransferase METTL3 (methyltransferase 3) has been identified as a key regulator of MSC differentiation[49]. Loss of the *METTL3* in MSCs 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 MSCs[50]. Mechanistically, METTL3 mediates m6A methylation of JAK1 (Janus kinase 1) mRNA, promoting its degradation and thereby suppressing the STAT5/C/EBPβ (signal transducer and activator of transcription 5/ CCAAT enhancer binding protein β)-induced adipogenesis under healthy physiological conditions[51]. Thus, depletion of METTL3 in MSCs enhances JAK1 signaling and promotes adipogenic differentiation.

Indeed, AML patient-derived MSCs show reduced *METTL3* and global *m6A* levels[52]. Overexpression of *METTL3* in AML patient-derived MSCs inhibits their adipogenic differentiation potency, whereas its knockdown in healthy MSCs 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 MSCs[53]. These data suggest leukemic cells may exploit METTL3 signaling pathway to reprogram MSCs 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 will henceforth use "adipocyte" specifically to refer to mature adipogenic lineage cells containing lipid droplets. It's 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 will 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 adipose tissue type[13, 57]. Human bone marrow adipocytes show lower expressions 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, and 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 or 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 (See Figure 1). As a local paracrine organ, bone marrow adipose tissue influences the HSC niche by secreting essential growth factors and cytokines, including adiponectin, stem cell factor, and leptin, that promote HSC maintenance and hematopoietic regeneration[63, 65-67]. In fact, the 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 HSCs post-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 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], see 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 *CPT1A* (carnitine palmitoyltransferase 1A), 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 the co-culture[72]. Consistently, mice injected with *CPT1A*-knock down AML cells exhibit 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 utmost importance for them to be able to switch from one metabolite to another during periods of metabolite deficiency. For instance, AML stem cells heavily rely 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 *ACADVL* expression[75]. While CD36 is involved in fatty acid transport[76], *ACADVL* (acyl-CoA dehydrogenase very long chain) 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 IL6R (interleukin 6 receptors) 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 PDXs 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 MSCs modulates leukemic chemosensitivity: overexpression of *METTL3*, which suppresses adipogenic differentiation capacity, increases AML sensitivity to chemotherapy, whereas its knockdown, which enhances adipogenesis and thus results in higher adipocyte numbers, promotes chemoresistance[52]. Consistently, knockout of *Mettl3* in murine MSCs 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 like 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 adipocyte and utilize the released fatty acids to support their proliferation and survival during chemotherapy.

In ALL, leukemic cells release pro-GDF15, IL1α, IL1β, and 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 ALL cells to compensatory fatty acid metabolic pathway[85]. Olivas-Aguirre et al[86] shows that dexamethasone reduces glycolytic activity and glutamine metabolism in ALL cells forcing them to heavily rely 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 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. The pre-treatment with adipocyte-conditioned medium reduces ALL sensitivity to chemotherapeutics[83, 87, 89, 90]. In B-ALLs, 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 like oleic acid[83, 87].

In addition, bone marrow adipocytes secrete CXCL13 (C-X-C motif chemokine ligand 13) following dexamethasone treatment in a mouse model, attracting T-ALL cells via CXCL13 receptor, CXCR5, and upregulate DLL1 (delta like canonical Notch ligand 1), 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-ALLs recovered from the adipocyte-rich tail vertebrae better survive 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 reduce leukemic burden less effectively in adipocyte-rich bone marrow than in adipocyte-poor bone marrow. Collectively, these studies indicate that T-ALLs residing in adipocyte-rich bone marrow are 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 myeloid and lymphoid leukemic cells' intrinsic transcriptional programs, metabolic dependencies, and cell cycle regulatory machinery. 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 ROS production in MSCs 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 patient 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 MSCs by upregulating *SREBF1* (sterol regulatory element binding transcription factor 1), 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 post-chemotherapy[88]. Notably, adipocyte compartment of the bone marrow is substantially depleted during both B-ALL and T-ALL development but is rapidly reconstituted after remission induction[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 MSCs primed toward adipogenesis. Consequently, the marrow stroma remains becomes enriched in adipogenic progenitors.

In summary, chemotherapeutic agents expand both adipogenic progenitors and mature adipocytes, restoring bone marrow adipose tissue post-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 MSCs towards 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 futher exploration in future research.

First is the possibility of targeting fatty acid metabolism, where 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 stromal cell differentiation. As a proof of concept indirect METTL3 pathway

targeting 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.

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

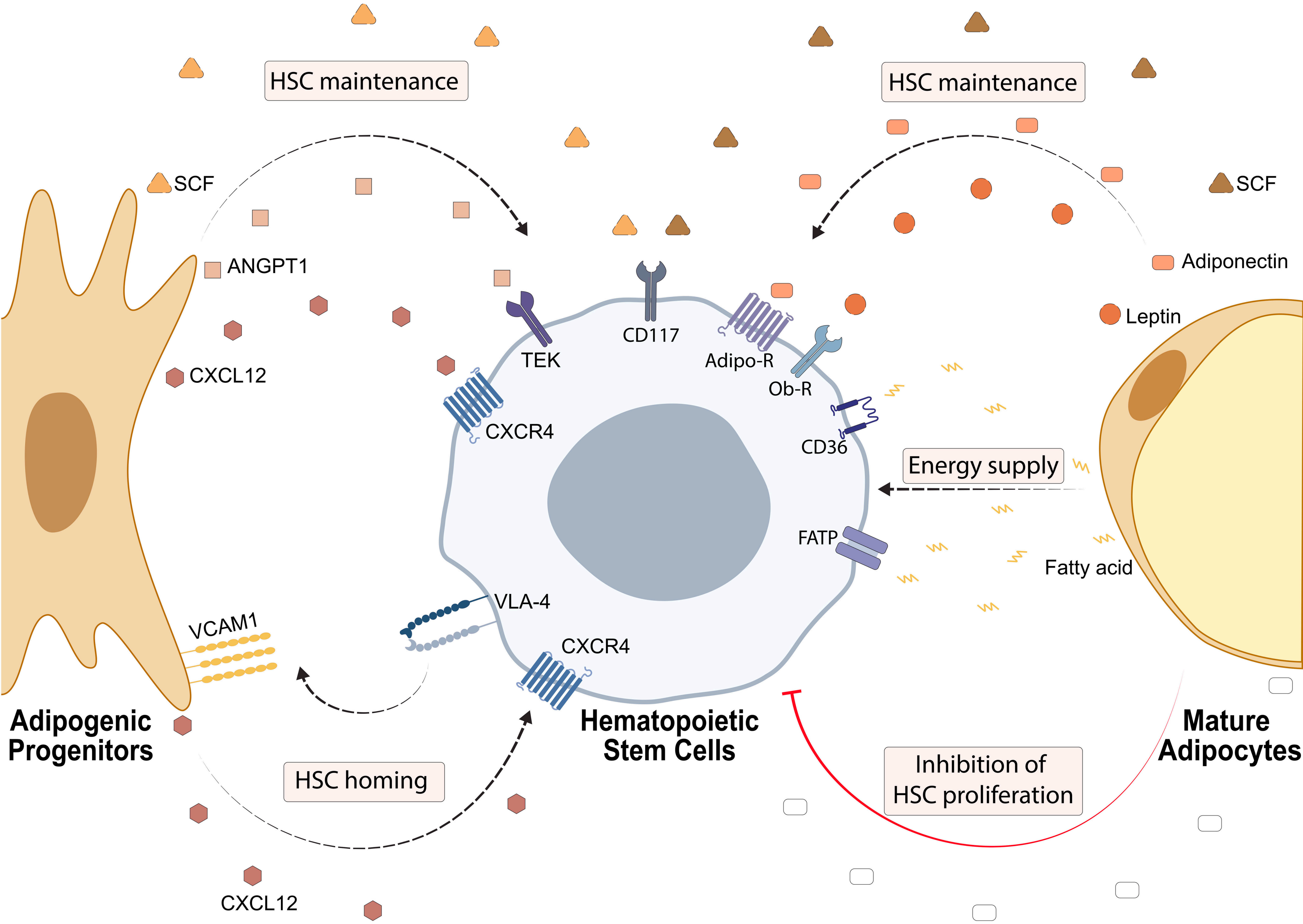
Species of origin	Source	Isolation approach	Adipogenic lineage populations	Markers	Additional markers	Hematopoietic support factors
Human	Jardine et al., 2021 [15]	The bones were cut and grinded. Samples were enriched for CD45^{+} or CD45^{-} cells and then pooled together.	Adipo-CAR (Cxcl12-Abundant 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 bone marrow from the femoral shafts was collected and bone marrow 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]♦♦	Bone marrow aspirates were sorted for either Lin^{-}/CD45^{-}/CD235^{-}/CD9^{+}/CD31^{+} or Lin^{-}/CD45^{-}/CD235^{-}/CD31^{-}/CD271^{+}/CD146$^{+/-}$ or CD146$^{+/-}$ 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 the isolation of bone marrow mononuclear cells using density gradient centrifugation. Samples were sorted for either CD45$^{low/-}$CD235a^{-} or CD45$^{low/-}$CD235a^{-}CD271^{+}.	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]	Bone marrow mononuclear cells were isolated using density gradient centrifugation from bone marrow aspirates. Samples were sorted for either CD45^{-}CD235a^{-}CD71^{-}CD31^{+} and CD45^{-}CD235A^{-}CD71^{-} cells and pooled together for sequencing.	LEPR+ Bone Marrow 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]	Bone marrow mononuclear cells were isolated using density gradient centrifugation from bone marrow aspirates. Samples were sorted for either 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*

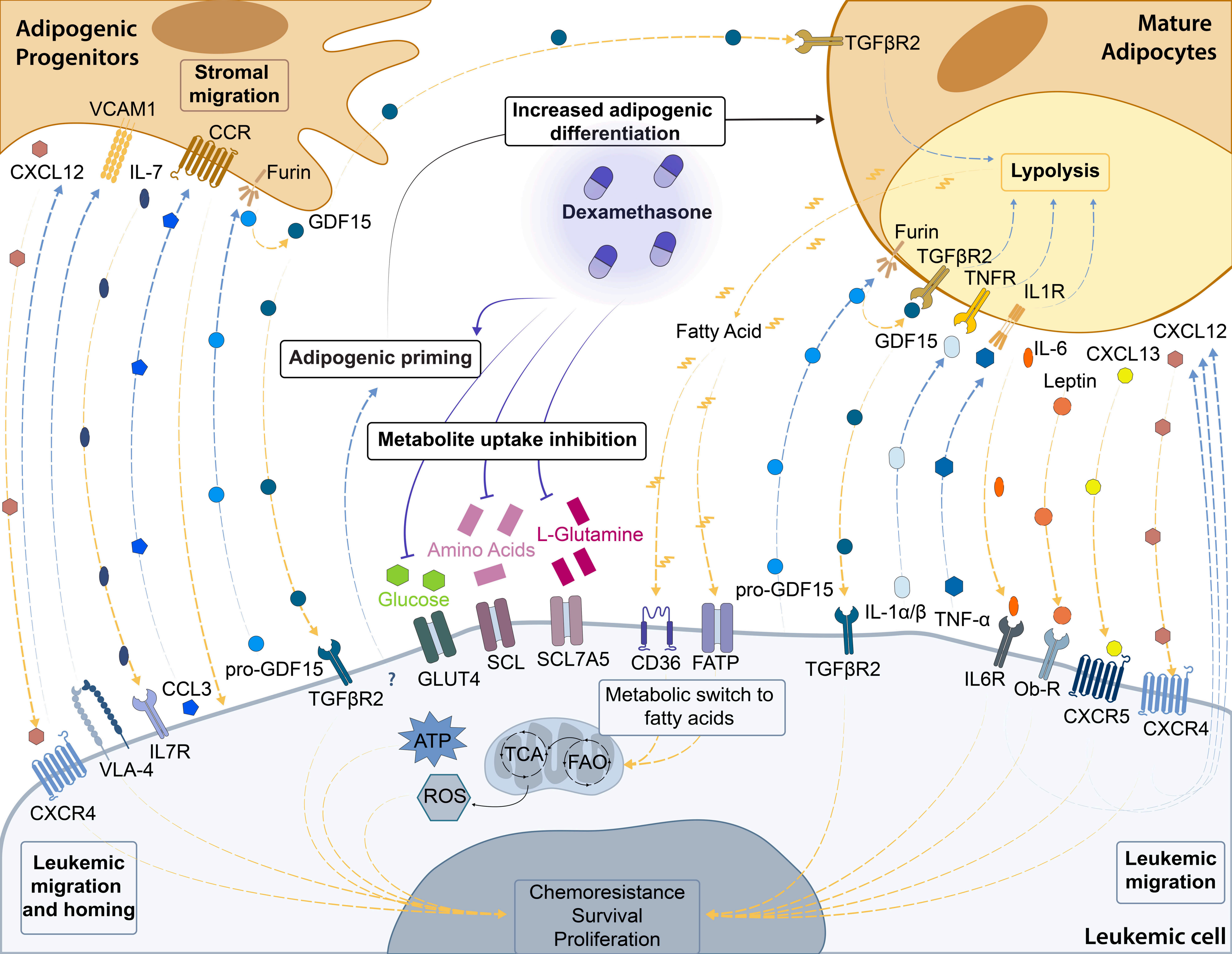
*Osteogenic markers
**Fibroblast markers
***Pericyte markers
****Authors used GAS6 as osteogenic marker in their analyses, while it is used as adipogenic marker in other studies mentioned here.
*****Stress-related transcription factors
⁎ Chondrogenic markers
♦[10] Reanalyzed data from [5] and [100]
♦♦Authors did not define the identity of the clusters from their data. Thus, we checked for the common adipogenic genes ourselves.

Figure Legends:

Figure 1. Functional roles of adipocyte lineage cells in HSC 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 HSCs through adipokine signaling (SCF, adiponectin, leptin) and metabolic substrates (fatty acids), while potentially maintaining stem cell dormancy via inhibition of proliferation.

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 MSC adipogenic differentiation, expanding this supportive niche.


HSC maintenance
HSC maintenance
SCF
SCF
ANGPT1
Adiponectin
Leptin
CXCL12
TEK
CD117
Adipo-R
Ob-R
CXCR4
CD36
Energy supply
FATP
Fatty acid
VLA-4
VCAM1
CXCR4
Adipogenic Progenitors
Hematopoietic Stem Cells
Mature Adipocytes
HSC homing
Inhibition of HSC proliferation
CXCL12



Adipogenic Progenitors
Stromal migration
VCAM1
CCR
CXCL12
IL-7
Furin
GDF15
Increased adipogenic differentiation
Mature Adipocytes
TGFβR2
Lypolysis
Dexamethasone
Furin
TGFβR2
TNFR
IL1R
Fatty Acid
GDF15
IL-6
CXCL13
CXCL12
Leptin
Adipogenic priming
Metabolite uptake inhibition
Amino Acids
L-Glutamine
Glucose
pro-GDF15
IL-1α/β
TNF-α
GLUT4
SCL
SCL7A5
CD36
FATP
TGFβR2
IL6R
Ob-R
CXCR5
CXCR4
pro-GDF15
CCL3
TGFβR2
?
IL7R
VLA-4
CXCR4
Metabolic switch to fatty acids
ATP
TCA
FAO
ROS
Leukemic migration and homing
Chemoresistance Survival Proliferation
Leukemic migration
Leukemic cell

Supplementary Table 1. Characterization of adipogenic lineage population in murine bone via single-cell RNA sequencing studies

Species of origin	Source	Isolation approach	Adipogenic lineage populations	Markers	Additional markers	Hematopoietic support factors
	Tikhonova et al., 2019 [1]	Bones were flushed and digested by Liberase and DNase I. Samples were sorted for VE-Cad⁺, LEPR⁺ and COL2.3⁺ cells.	Adipocyte-biased perivascular LEPR+	*Cxcl12, Lepr Lpl, Adipoq, Apoe, Gas6, Esm1*	(*Cd63, Cd200*)-low (*Alpl, Spp1, Wif1, Bglap, Sp7, Runx2*)*-low/neg *Mgp*⁎ –	*Cxcl12, Scf, Vcam1, Il7, Csf1, Il15, Il34, Ccl2, Ccl19, Bmp4*
	Baryawno et al., 2019 [2]	The bones were flashed, crushed and digested by STEMxyme1 and Dispase II. Samples were further sorted for Ter119-CD71-Lin-.	Lepr-MSCs	*Cxcl12, Lepr Lpl, Cebpa, Adipoq, Apoe, Grem1*	(*Thy1, Ly6a*)-neg, *Cd73, Cd105* *Sp7*, Alpl*, Runx2** (*Nes*, *Cspg4*)⸸ -neg	*Cxcl12, Scf, Vcam1, Angpt1*
	Wolock et al., 2019 [3]	Crushed bones were digested using Collagenase/Dispase and sorted for CD45-Ter119-CD31-.	adipocyte progenitor	*Cxcl12, Lepr Pparg, Cebpb, Adipoq*	*Nt5e* (*Runx2, Sp7, Alpl*)*-low and (*Bglap, Col1a1, Col1a2, Dmp1*)*-neg	*Cxcl12, Scf, Il7, Il6, Il34, Ccl2, Bmp4*
			pre-adipocyte	*Cxcl12, Lepr Pparg, Cebpb, Adipoq*	*(Fosb, Junb)*******	
	Baccin et al., 2019 [4]	Crushed bones were either enzymatically digested (Collagenase II and Dispase) or used without digestion. They were further sorted for Lin-Cd45-Cd71- cells.	Adipo-CAR (Cxcl12-abundant-reticular) cells	*Cxcl12, Lepr Lpl, Cebpb, Adipoq, Apoe*	*CD51, CD200*-mid, *CD61*-low (*Bglap, Sp7, Alpl*)*-neg	*Cxcl12, Scf, Vcam1, Il7, Csf1*
	Matsushita et al., 2020 [5]	Bone epiphyseal growth plates were cut off and the remaining part was digested by liberase and pronase followed by grinding. CD45/Ter119/CD31- tdTomato+ Cxcl12(GFP)+ cells were sorted.	Reticular Adipoq+ cells	*Cxcl12, Lepr Cebpb, Adipoq*	*Col1a1**-low (*Bglap, Spp1, Alpl, Postn*)*-neg	*Cxcl12, Scf, Fgf7, and Il7*
Mouse	Zhong et al., 2020 and 2021 [6, 7]	The epiphyses were cut off and the central bone marrow was flashed. The metaphyseal bone fragments were digested by proteases and sorted for endosteal Td⁺bone marrow cells.	Marrow adipogenic lineage precursors (MALPs)	*Cxcl12, Lepr Lpl, Cebpa, Pparg, Adipoq, Apoe, Grem1, Klf2, Ebf1, Ebf2, Ebf3*	(*Plin1*-neg, *Fabp4*-low)⁎⁎ (*Lep*-neg, *Hoxc8*-low, *Hoxc9*-low)⁎⁎⁎ (*Ucp1*-neg, *Cidea*-low, *Cox7a1*-low, *Zic1*-low)† (*Tnfrsf9*-neg, *Cited1*-low, *Shox2*-low, *Tbx1*-low) †† *Pdgfrb**** , *Lamb1**** (*Vegfa*, *Vegfc*, *Angpt4*, *Rspo3*) †††	*Cxcl12, Scf, Vcam1, Il7*, *Angpt1 Csf1*
	Dolgalev and Tikhonova, 2021 [8] Inoue et al., 2023 [9]♦	Data from Baccin et al. [4], Baryawno et al. [2], Tikhonova et al. [1], Wolock et al.[3], and Zhong et al. [6] were integrated and re-analysed.	Adipo-primed mesenchymal stem and progenitor cells (MSPC-Adipo)	*Cxcl12, Lepr Lpl, Cebpa, Pparg, Adipoq, Apoe, Grem1*	(*Bglap*, *Postn*)*-neg (*Sp7, Alpl, Col1a1, Wif1, Dmp1, and Bglap*)*-low/neg *Runx2**, *Spp1**	*Cxcl12, Scf, Vcam1, Il7, Csf1, Il15, Il34, Ccl2, Ccl19, Bmp4*
	Sivaraj et al., 2021 [10]	Bones were crushed and digested using Collagenase type II and I. CD45/CD117-neg *Pdgfrb-CreERT2 GFP*+ cells were sorted.	Lepr+ Esm1+ diaphyseal bone marrow stromal cells	*Cxcl12, Lepr Lpl, Cebpa, Cebpb, Pparg, Adipoq, Apoe, Gas6, Esm1*	(*Alpl*, *Sp7*, *Bglap2*, *Col11a2*)*-neg *Pdgfrb****	*Cxcl12, Scf*
	Ye et al., 2022 [11]	Bones were crushed and digested by Collagenase I and Dispase. Samples were sorted for Lin⁻CD45/Ter119−VDO⁺ to produce in house data which was further integrated with data from Tikhonova et al.[1] and Baryawno et al.[2]	Early mesenchymal cells (adipo-lineage committed cells)	*Cxcl12, Lepr Adipoq*	(*Bglap*, *Alpl*)*-neg, *Col1a1**-low	*Cxcl12, Vcam1*
	Pisterzi et al., 2023 [12]	Bones were crushed and digested using Collagenase. Samples were sorted for either lin⁻ CD45⁻ Ter119⁻ CD31⁺ or lin⁻ CD45⁻ Ter119⁻ CD31⁻ Sca-1⁺ CD51⁺ cells.	Lepr+ cells	*Cxcl12, Lepr Lpl, Adipoq, Apoe*	*Runx2**, *Spp1**	*Cxcl12, Scf*

*Osteogenic markers
***Pericyte markers
*****Stress-related transcription factors
⁎ Chondrogenic markers
⁎⁎ Mature adipocyte markers
⁎⁎⁎ White adipocyte markers
† Brown adipocyte markers
†† Beige adipocyte markers
††† Angiogenic markers
⸸ Perivascular MSC markers
♦[9] Reanalyzed data from [13] and [8]

Supplementary Table 2. Classification of stromal cell populations based on single-cell RNA sequencing studies.

		Early Mesenchymal Progenitor	Adipogenic progenitor	Adipo-derived osteogenic progenitor	Osteo - chondrogenic progenitor	Osteogenic progenitor	Osteoblast	Chondrogenic progenitor	Chondrocyte
Stromal markers	*CD81*	+++ 14-17	++ *13, 15, 16, 18*	++ 15, 16	+ 16	+ 15, 16	+ 15		+ 18
	LEPR	++ 16, 17	+++ 11, 13-16, 18, 19	+++ 15, 16	undetectable 16	++ 16	undetectable 15		+ 18
	CXCL12	++ 16, 17	+++ 11, 13-16, 18, 19	+++ 15, 16	undetectable 16	++ 16			+ 18
	KITLG (SCF)	undetectable 14	+++ 11, 14, 15, 18, 19	++ 15, 16	undetectable 16	++ 15, 16	+ 15		+ 18
	ANGPT1	++ 16, 17	+++ 11, 14-16, 18, 19	+++ 15, 16	undetectable 16	undetectable 15	undetectable 15		+ 18
Adipogenic markers	*LPL*	+ 14, 16	+++ 11, 13-16, 18, 19	++ 15, 16	undetectable 16	+ 15	+ 15		+ 18
	CSF1	+ 15-17	+++ 11, 15, 16	++ 15, 16	undetectable 16	+ 13, 16			+ 18
	VCAM1	undetectable 14	+++ 11, 13, 15, 16, 18	++ 15, 16	undetectable 16	++ 16			+ 18
	IL-7	undetectable 14	+++ 11, 15, 16, 19	++ 15, 16	undetectable 16	undetectable 16			+ 18
	PPARG	++ 15, 16	+++ 11, 14-16, 18	++ 15, 16	undetectable 16	undetectable 16	undetectable 15		+ 18
	FABP4	undetectable 14-16	+++ 16	++ 16	undetectable 16	undetectable 16			+ 18
	ADIPOQ	undetectable 16	++ 13, 16, 19	undetectable 16	undetectable 16	undetectable 16			+ 18
	GAS6	+ 14	++ 11, 14-16, 18, 19	++ 15, 16	undetectable 16	+ 15, 16			++ 18
	CEBPA	undetectable 16	+ 11, 15	+++ 16	undetectable 16	undetectable 16			+ 18
	CEBPB	++ 15, 17	++ 11, 15, 18	+ 15, 16	undetectable 16	+ 16			+ 18
	CEBPD	+ 15, 17	+ 11, 15, 18	+ 15, 16	undetectable 16	++ 15, 16	+ 15		+ 18
	PLIN1	undetectable 16	+ 13, 15, 18	+ 15, 16	undetectable 16	undetectable 16			+ 18
	CD36	undetectable 16	++ 11, 19	undetectable 16	undetectable 16	undetectable 15, 16			+ 18
Osteogenic markers	*COL1A1*	++ 15	++ 11, 14, 15, 18	++ 16	undetectable 16	++ 18	+++ 18	+ 13	++ 18
	COL1A2	++ 15, 16	++ 14-16, 18	+++ 15, 16	+++ 16	++ 13, 15-17	+++ 18	+ 13	++ 18
	ALPL	undetectable 14, 17	++ 11, 14-16, 18	++ 15, 16	undetectable 16	++ 13, 17	+++ 17, 18		+ 18
	BGLAP	undetectable 14, 16	undetectable 14, 16	undetectable 16	+++ 16	++ 15	+++ 15	++ 13	+ 18
	SPP1	undetectable 15, 16	undetectable 16	undetectable 16	+++ 16	undetectable 15	+++ 15	++ 13	+ 18
	POSTN	undetectable 16	undetectable 16	undetectable 16	++ 17	undetectable 16			+ 18
	CDH11	+ 14, 15	++ 14	++ 15, 16	+++ 16	+++ 15, 16	+++ 15, 16	+ 13	++ 18
	NCAM1	undetectable 14, 16	undetectable 16	undetectable 16	+++ 13, 16	+++ 15, 16	+++ 15, 16	+++ 13	+ 18
	OMD	+ 15	undetectable 16	undetectable 16	undetectable 16	+++ 15	+++ 15	+++ 13	+ 18
	RUNX2	undetectable 14	++ 11, 14, 15, 18	++ 16	+++ 16	+++ 15	+++ 15	++ 13	++ 18
	TGFb1	undetectable 15, 16	undetectable 15	undetectable 16	undetectable 16	+ 15	++ 15		+ 18
Chondrogenic markers	*WIF1*	undetectable 16	undetectable 15, 16	undetectable 16	+++ 16, 17	++ 15, 17	++ 15	+++ 13	++ 18
	ACAN	+ 15						++ 17	+++ 18
	MMP13	++ 17	undetectable 16	undetectable 16	+++ 16	+++ 17		+++ 13, 17	
	CHAD	undetectable 14, 16	undetectable 14, 16	undetectable 16	+++ 16	+ 15	++ 15		+++ 18
	COL2A1							+++ 17	+++ 18
	COL9A2/3	undetectable 16	undetectable 16	undetectable 16	undetectable 16	undetectable 16			+++ 18
	MGP	++ 15-17	++ 13, 15, 16, 18	++ 15, 16	++ 18	+ 16	+ 17	+++ 17	+++ 18
	SOX9	+ 14	undetectable 14	undetectable 16		+ 15		+ 13, 17	+++ 18

Marker gene expression levels are indicated as follows: "undetectable" denotes genes that were specifically examined but showed no detectable expression signal; "+" indicates low-level expression; "++" represents moderate expression; "+++" signifies high expression levels.

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