



# Cadherins, Selectins, and Integrins in CAM-DR in Leukemia

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The interaction between leukemia cells and the bone microenvironment is known to provide drug resistance in leukemia cells. This phenomenon, called cell adhesion-mediated drug resistance (CAM-DR), has been demonstrated in many subsets of leukemia including B- and T-acute lymphoblastic leukemia (B- and T-ALL) and acute myeloid leukemia (AML). Cell adhesion molecules (CAMs) are surface molecules that allow cell-cell or cell-extracellular matrix (ECM) adhesion. CAMs not only recognize ligands for binding but also initiate the intracellular signaling pathways that are associated with cell proliferation, survival, and drug resistance upon binding to their ligands. Cadherins, selectins, and integrins are well-known cell adhesion molecules that allow binding to neighboring cells, ECM proteins, and soluble factors. The expression of cadherin, selectin, and integrin correlates with the increased drug resistance of leukemia cells. This paper will review the role of cadherins, selectins, and integrins in CAM-DR and the results of clinical trials targeting these molecules.

**Keywords:** leukemia, cell adhesion molecules, cell adhesion-mediated drug resistance, chemoresistance, bone marrow microenvironment

## INTRODUCTION

Despite the improved overall survival of leukemia patients, relapsed and refractory leukemia still remain a problem. Chemoresistant minimal residual disease (MRD) contributes to the recurrence of the disease. Patients with relapsed leukemia in the bone marrow (BM) have worse outcomes than patients with relapses in the central nervous system or testis (1), suggesting the contribution of the BM to the progression and aggressiveness of the disease. Indeed, the BM microenvironment is known to govern leukemia quiescence (2–4), proliferation (5), drug resistance (6), and leukemogenesis (7). Leukemia cells communicate with BM through surface molecules called cell adhesion molecules (CAMs). The CAM-mediated interaction of leukemia cells with the surrounding microenvironment contributes to drug resistance, which is called cell adhesion-mediated drug resistance (CAM-DR). Surface molecule overexpression and CAM-DR have been addressed in many subtypes of leukemia, including B- and T-acute lymphoblastic leukemia (B- and T-ALL) and acute myeloid leukemia (AML). CAM-DR is one mechanism through which leukemia cells obtain chemoresistance, and resistant clones will result in the recurrence of the disease. Due to aberrant expression, CAMs serve not only as a prognostic tool for detecting MRD in leukemia but can also be targeted to sensitize drug-resistant cells to chemotherapy (8–11). CAM inhibition in

leukemia is being actively evaluated in preclinical and clinical studies. In this review, we will focus on the major groups of CAMs—cadherin, selectin, and integrin—and their role in drug resistance in leukemia.

## LEUKEMIA AND LEUKEMIA STEM CELLS

Leukemia is a type of Cancers that affects a patient's blood and bone marrow. Leukemia can be categorized into different subtypes depending on the progression of the disease (acute and chronic) or a lineage and developmental stage of cells (myeloid or lymphoblastic). Four main subtypes of leukemia that will be discussed in this review are: acute lymphoblastic leukemia (ALL) (12–14), AML (15, 16), chronic lymphocytic leukemia (CLL) (17, 18), and chronic myeloid leukemia (CML) (19, 20). Leukemic cells have been described to interact with and remodel BM to support leukemic cell expansion and survival (21).

LSCs are capable of self-renewal and thus able to maintain survival in optimized *in vitro* co-culture systems and in immunocompromised mice, which have been defined in AML and CML (22). CAMs play an important role in the interaction between LSCs and the hematopoietic niche (23, 24). Firstly, it has been shown that N-cadherin positive CD34<sup>+</sup> CD38<sup>−</sup> LSCs population has a critical role in the development of AML (25, 26). Moreover, the downregulation of E-cadherin suppressed the adhesion of AML cells to BM-derived MSCs and enhanced the anti-leukemic effect of cytarabine (27). Secondly, in an AML mouse model, LSCs adhered to the vascular niche which protected LSCs from chemotherapy through E-selectin/E-selectin ligands and this effect was ameliorated by GMI-1271 (28). Thirdly, VLA-4 is one of the most prominent integrins involved in LSCs (24). Recently a study showed that inhibition of Kindlin-3-mediated VLA-4 adhesion mobilized LSCs in the BM and prolonged survival of mice with CML (29). Furthermore, the integrin  $\alpha V\beta 3$  was expressed in particular on CD34<sup>+</sup> cells in AML with NPM1 mutation (30).

## CELL ADHESION MOLECULES IN LEUKEMIA

BM is a complex tissue with various components. Mesenchymal stromal cells (MSC) (31, 32), endothelial cells (4, 33), osteoblasts (34), adipocytes (35), neurons (36), Schwann cells (37), and megakaryocytes (38) comprise the endosteal and vascular BM niches. Soluble factors such as chemokines (39), the exosome (40, 41), or microRNA (42) facilitate crosstalk between cells in the BM (43, 44). Extracellular matrix (ECM) proteins deposited from cells provides the BM architecture and determine the stiffness of tissue, which affects the cell proliferation and chemosensitivity of leukemia (45). The BM microenvironment has been studied for its role in leukemia support and drug resistance (46, 47). A previous study examined BCR-ABL positive (Ph<sup>+</sup>) (Tom-1, Nalm-27 and Sup-B15) and BCR-ABL negative (Ph<sup>−</sup>) cell lines

(REH and Nalm-6) cultured on primary bone marrow stromal cells (BMSC) or osteoblasts (HOB) divided into three populations by relative distance to the supportive layer—S (suspended), phase bright (PB), and phase dim (PD). Out of the three populations, the PD leukemic population planted under the BMSC layer demonstrated increased quiescence; resistance to cytarabine (Ara-C), methotrexate (MTX), and vincristine (VCR); and increased glycolysis (48). This result shows the importance of crosstalk between leukemia and the surrounding microenvironment. One of the most well-known mechanisms of the BM–leukemia cell interaction is the CXCR4/CXCL12 axis (2, 49), yet there are many more surface molecules that are directly associated with adhesion and interaction (50–52). Cell adhesion molecules (CAMs) are cell surface proteins that are specialized for adhesion to other types of cells or the ECM. This review will primarily focus on leukemia-relevant adhesion receptors from four major families of CAMs - cadherin, immunoglobulin superfamily CAM (IgCAM), selectin and integrin (53).

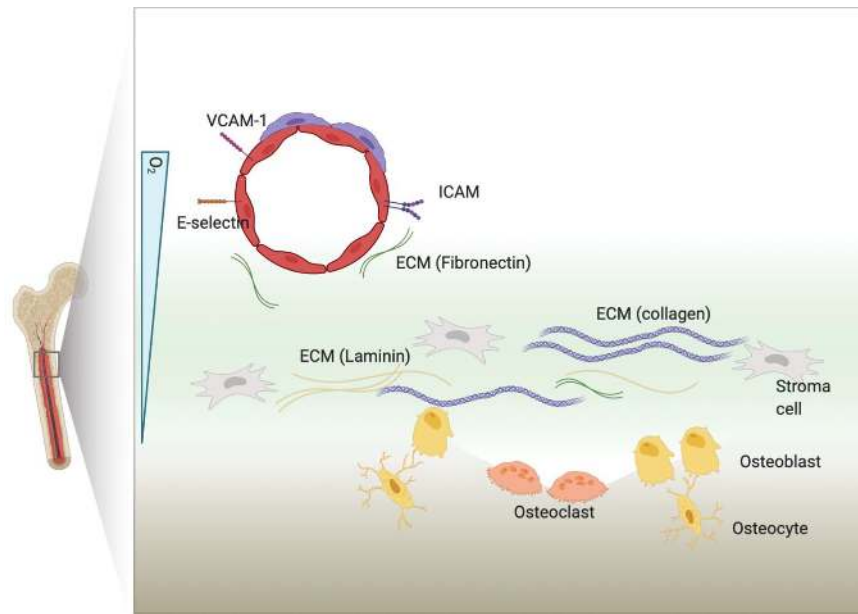
CAMs are single-pass transmembrane proteins with extracellular, transmembrane, and intracellular structures. The extracellular domain of CAMs recognizes specific ligands or counter-receptors, and the intracellular (cytoplasmic) domain translates external stimuli into intracellular signalings, while the transmembrane domain stabilizes the structure of the molecule.

While selectins act as a monomer, cadherins form a homodimer and integrins must a heterodimer in order to be fully functional. Ca<sup>2+</sup> is required for stabilization of extracellular domain (54–56), as well as in selectins for proper binding to ligands (57). Integrins are dependent and regulated by other divalent cations as well (58, 59). Ca<sup>2+</sup> binding maintains the folded and inactive conformation of integrins while the heterodimer travels from the Golgi to the cell surface, and integrin undergoes conformational changes upon replacement of Ca<sup>2+</sup> with Mg<sup>2+</sup> or Mn<sup>2+</sup> (58–60).

BM is abundant in binding partners for CAMs as each components of BM discussed above express diverse ligands and secrete ECM (61–68) (**Figure 1**). Fibronectin, collagen and laminin secreted in the BM will interact with cellular surface molecules (69, 70). Leukemia-induced BM remodeling can interrupt homeostasis and shift equilibrium towards leukemia progression by overexpressing binding partners for CAMs (71–74). At the same time, leukemia cells can aberrantly express CAM to facilitate surface molecule-mediated interaction with BM microenvironment, thereby inducing cell-adhesion mediated drug resistance (CAM-DR). Recently, the mitochondrial transfer from mesenchymal cells to leukemia has been shown to promote drug resistance in T-ALL, indicating the diverse aspects that BM can modulate to provide leukemia protection (75).

## CADHERINS IN CELL ADHESION-MEDIATED DRUG RESISTANCE IN LEUKEMIA

Cadherins are a type of CAM that participates in forming adherent junctions between adjacent cells. Cadherins can be



**FIGURE 1** | BM microenvironment. BM includes many types of cellular and non-cellular components. Cellular components express ligands or counter receptors, such as VCAM-1 or ICAM, that will bind to CAMs. Cells can also secrete extracellular matrix (ECM) proteins that will bind to CAMs.

subdivided into several different groups including Type I and Type II classical cadherins (76), desmosomal cadherins (77), proto-cadherins (78), seven-pass transmembrane cadherins, and FAT and Dachshous cadherins (79). The extracellular domain contains cadherin extracellular repeats that exert homotypic  $\text{Ca}^{2+}$  dependent adhesion, while the intracellular domain binds p120-catenin and  $\beta$  or  $\gamma$ -catenin (80–82). Furthermore,  $\beta$ -catenin will interact with  $\alpha$ -catenin, which binds actin filaments (83–85). Adherens junction complexes formed between two cells connect epithelial and endothelial cells (86) (**Figure 2**). E-cadherin, N-cadherin, and P-cadherin are classified as Type I, while VE-cadherins are Type II classical cadherins, which have been well-studied in the context of cancer biology. In metastatic epithelial tumors, the downregulation of E-cadherin compensated by the expression of other cadherins, such as N-cadherin, is a hallmark of the epithelial–mesenchymal transition (EMT). This “cadherin switching” enables tumor cells to acquire a metastatic phenotype that is different from the parental population. Indeed, E-cadherin is considered a tumor suppressor as it inhibits transformation by blocking  $\beta$ -catenin signaling (87). Therefore, dysfunctional or decreased expression of E-cadherin is associated with cancer progression and metastasis. However, cadherin switching is a late event in tumorigenesis and is context-dependent (e.g., exposure to certain soluble factors or interaction with specific ECM proteins) (88, 89).

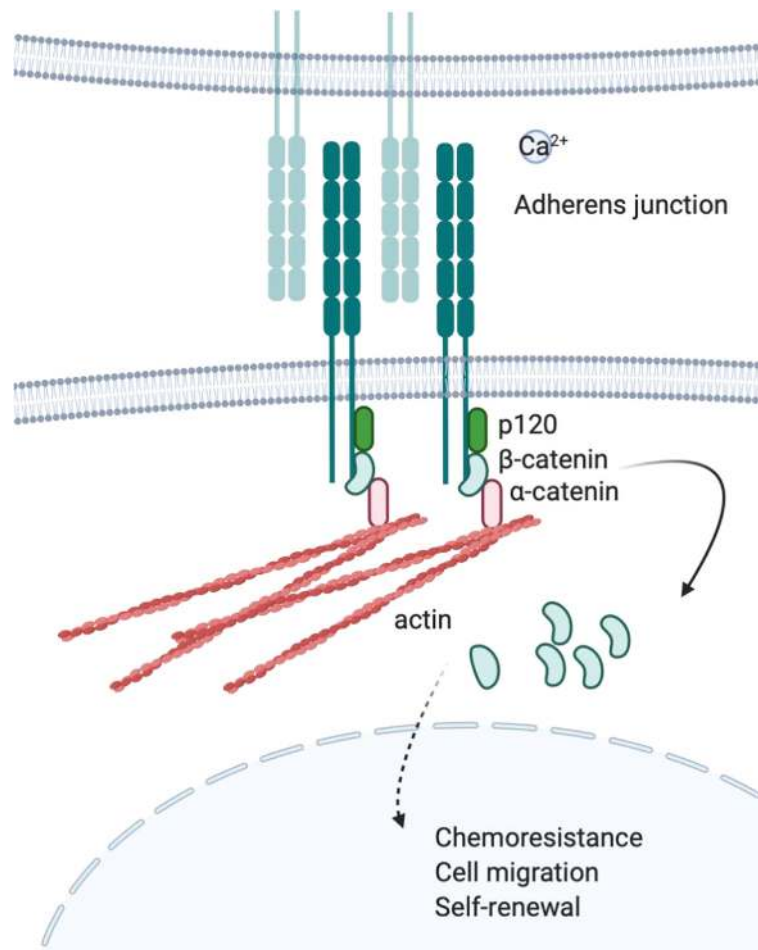
## VE-CADHERIN

Although leukemia does not necessarily undergo EMT, E-cadherin expression is reduced by hypermethylation of the E-cadherin gene promoter (90, 91), while VE-cadherin and N-

cadherin expression contributes to chemoresistance in BCR-ABL<sup>+</sup> (Ph<sup>+</sup>) ALL and CML (92, 93). VE-cadherin expression along with PECAM-1 expression on ALL enhances the adhesion of leukemia cells to human brain-derived microvasculature endothelial cells (HBMECs) and their migration through the HBMEC monolayer, suggesting a role of VE-cadherin in the central nervous system (CNS) infiltrating leukemia (94). Furthermore, stromal cells upregulate VE-cadherin expression in BCR-ABL<sup>+</sup> leukemia cell lines (K562 and SUP-B15) and increase resistance to imatinib by stabilizing  $\beta$ -catenin (95).  $\beta$ -catenin is an important component in cadherin-mediated adhesion as it bridges the cytoplasmic tail of cadherin to the actin cytoskeleton and stabilizes the adherent junction. Since  $\beta$ -catenin binds to transcription factors to initiate transcription, cadherin adhesion is often associated with the activation of Wnt/ $\beta$ -catenin intracellular signaling pathways (96). A subpopulation of the Ph<sup>+</sup> B-ALL cell line SUP-B15 presents leukemia stem cells (LSCs) and expresses stem cell markers (CD34, CD38, and c-Kit) and endothelial antigens (Flk-1 and PECAM-1); moreover, LSCs express VE-cadherin after a long-term co-culture on stromal cells (97). The overexpression of VE-cadherin on Ph<sup>+</sup>/VE-cadherin<sup>+</sup> LSC populations stabilizes  $\beta$ -catenin, maintaining  $\beta$ -catenin as constitutively active and thus promoting self-renewal independent of Wnt signaling. The same group later showed that VE-cadherin regulates apoptosis in Ph<sup>+</sup> ALL (98).

## N-CADHERIN

Apart from VE-cadherin, N-cadherin is also associated with LSCs. In AML patients treated with a HAD regimen of homoharringtonine (HHT), cytarabine (Ara-C), and daunorubicin (DNR), the N-cadherin and Tie2 expressing



**FIGURE 2** | Cadherin and adherens junction. Upon engagement in homotropic manner, cytoplasmic tail of cadherins will bind to actin through p120,  $\beta$ -catenin, and  $\alpha$ -catenin protein complex. Cadherin mediated protein complex formation is observed at adherens junction where adjacent cells are connected to each other.

CD34<sup>+</sup>/CD38<sup>−</sup>/CD123<sup>+</sup> LSC population presented higher expansion than AML patients who did not receive chemotherapy, indicating that the expression of N-cadherin and Tie2 on AML cells provides a survival benefit against the therapy (99). In addition, the N-cadherin expressing cell line KG-1 and AML patient-derived bone marrow mononuclear cells (BMMNCs) were able to form more colonies compared to an N-cadherin negative control (26). A higher percentage of N-cadherin<sup>+</sup> cells were shown to remain at the G0/G1 phases compared to N-cadherin<sup>−</sup> cells and showed higher engraftment in NOD/SCID mice compared to the negative control. Indeed, N-cadherin<sup>+</sup> cell bearing mice had a significantly shorter survival than the N-cadherin<sup>−</sup> engrafted mice. This suggests a role of N-cadherin in maintaining the stem cell-like properties and survival of LSCs, which results in relapse. Mesenchymal stromal cell (MSC)-N-cadherin adhesion in CML LSC also provides tyrosine kinase imatinib resistance by stabilizing N-cadherin/ $\beta$ -catenin complex formation and the nuclear translocation of  $\beta$ -catenin in concert with the activation of exogenous Wnt/ $\beta$ -catenin signaling (92). When the N-cadherin-mediated adhesion of

CML cells to MSCs was interrupted with anti-N-cadherin short cyclic HAV peptide (NCDH), the CML cells gained sensitivity toward imatinib treatment.

## E-CADHERIN

Another study supported E-cadherin as an important mediator for AML pathogenesis, indicated by stalled differentiation accompanied with high proliferation (100). In this study, carbohydrate-binding protein lectin LecB induced differentiation of the AML cell line THP-1 and increased apoptosis of cells in a dose and time dependent manner. LecB-induced differentiation was mediated by increased autophagy and decreased cellular  $\beta$ -catenin levels, the balance of which is a crucial factor for regulating the differentiation of AML cells. In differentiating cells, LecB was in proximity to the membrane E-cadherin and further promoted the co-localization of E-cadherin and  $\beta$ -catenin. Interestingly, fewer LecB treated THP-1 cells were suspended in the supernatant, suggesting greater adhesion to the cell culture plate, but the direct association of E-cadherin and adhesion was not investigated in this study.

Drugs developed to interrupt the interactions between malignant cells and the microenvironment decreased cadherin expression on malignant cells as a secondary effect without directly targeting cadherin. Recently, an adenosine analogue, Cordycepin, was proposed as an anti-leukemia therapeutic adjuvant. Cordycepin's anti-leukemic effect in U937 and K562 cells was achieved through the reduced attachment of leukemia cells to MSC by decreasing N-cadherin expression on leukemia cells and vascular cell adhesion molecule-1 (VCAM-1) in MSCs (101). Targeting bone marrow endothelial cells (BMECs) with combretastatin, a microtubule assembly inhibitor, increased AML cell dislodgement from BMECs (102). Combretastatin decreased VCAM-1 and VE-cadherin on BMECs, and dislodged AML cells shifted G0/G1 to G2/M in their cell cycle. A combination treatment of combretastatin and cytotoxic chemotherapy increased induction apoptosis in AML cells. Taken together, cadherins play an important role in leukemia drug resistance. Particularly, chemotherapy-resistant leukemic stem cell (LSC) populations utilize cadherin, which further stabilizes  $\beta$ -catenin and thus activates the expression of genes important for self-renewal.

## TARGETING CADHERINS IN LEUKEMIA

Cadherin inhibitors were developed based on compelling preclinical data and translated into clinical trials. A cyclic pentapeptide ADH-1 against N-cadherin is the most commonly studied cadherin inhibitor in cancer models. Thus far, this pentapeptide has been tested as a single agent or in combination with conventional chemotherapy in patients with N-cadherin expressing solid tumors (103–107). Due to N-cadherin's role in tumor metastasis, drug resistance and bone marrow homing, N-cadherin has been proposed as a potential target to treat hematological malignancies in patients (108) (Table 1).

FX06 is a naturally occurring peptide derived from the B $\beta$ <sub>15–42</sub> sequence of human fibrin that is cleaved and released from the parental fibrin and competitively binds to VE-cadherin (114). FX06 was evaluated in myocardial infarction, yet it failed to show significant baseline benefits compared to a placebo-treated group, although the necrotic core zone significantly decreased (109). FX06 has not been tested in any cancer to date.

Celecoxib is a nonsteroidal anti-inflammatory drug that inhibits prostaglandin-endoperoxide synthase 2, also known as COX-2. Interestingly, the effects of celecoxib were studied to treat calcific aortic valve disease (CAVD) because of their cadherin-11

binding properties (115, 116). Celecoxib was shown to promote anoikis by downregulating E-cadherin in osteosarcoma cell line MG-63 by decreasing PI3K/Akt (117). However, E-cadherin downregulation is a characteristic of EMT in invasive tumors when accompanied with N-cadherin expression; thus celecoxib has been proposed to induce EMT in ovarian cancer (118). Despite different views on celecoxib, there have been more than 100 related clinical trials in the U.S. for cancer patients, including two trials on leukemia and hematological malignancies (119). Celecoxib showed the inhibition of proliferation and survival by downregulating  $\beta$ -catenin in Ph<sup>+</sup> CML (120), restoring imatinib sensitivity in imatinib-resistant CML (121), and exerting an anti-tumor effect in the HL-60 AML cell line (122), yet its relationship with cadherin-11 is not yet specified. As Wnt signaling has been shown to be an aberrantly upregulated pathway in leukemia (123) and is involved with chemoresistance, this warrants further exploration of celecoxib as a viable therapy to reverse CAM-DR in leukemia.

## SELECTINS IN CELL ADHESION-MEDIATED DRUG RESISTANCE IN LEUKEMIA

Selectins (CD62) are single-chain transmembrane glycoproteins that mediate calcium-dependent carbohydrate-binding. There are three major types of selectins: L-selectins are majorly expressed on leukocytes, E-selectins are expressed on endothelial cells, and P-selectins are expressed on activated platelets (124, 125). Selectins share common structures: (1) Calcium-dependent lectin domain, (2) an epidermal growth factor (EGF)-like domain, (3) a variably-sized repeated region, (4) a transmembrane domain, and (5) a cytoplasmic domain (126). The main function of selectins is to facilitate leukocyte tethering and rolling along endothelial cells, which is an initial step of the transmigration of leukocytes through the endothelial barrier. Briefly, free floating cells expressing selectin ligands, such as P-selectin glycoprotein ligand-1 (PSGL-1), bind to P-selectin expressing endothelial cells. Upon engagement, the leukocyte movement will slow down and the cells remain in proximity to the vessel wall, while integrin-ICAM/VCAM-1 interactions and other cytokine-mediated tight adhesions between leukocytes and endothelial cells strengthen the binding for transmigration. As a result, leukocytes can travel to distant sites of inflammation, and hematopoietic stem cells (HSCs) can home into the bone marrow (127).

**TABLE 1 |** Description of cadherin inhibitors.

Drug name	Description	Indication	References
ADH-1	N-cadherin inhibitor	Solid tumors	(104–106)
FX06	Competitive inhibitor of fibrin E1 binding to VE-cadherin	Cardiac reperfusion injury and myocardial infarction	(109, 110)
Celecoxib	COX-2 inhibitor	Evaluated for anti-cancer effects by binding to cadherin-11 and regulating E-cadherin expression	(111–113)

Because the endothelium binding of leukocytes is a prerequisite of metastasis, selectins are well-known to be involved in cancer progression (128, 129). E-selectin expressed on the endothelium is the primary source of binding partners for leukocytes, and T-ALL cells were not able to adhere to interleukin-2 activated human umbilical vein endothelial cells (HUVEC) upon E-selectin inhibition with a monoclonal antibody (130). E-selectin expression in the BM vascular niche has been proposed to be regulated by Runt-related (RUNX) transcription factor, and RUNX silencing was shown to downregulate E-selectin expression and lead a subsequent decrease in AML engraftment in the BM in mice (131).

Leukemia cells interact with E-selectin through various ligands such as CD43, CD44, and PSGL-1. Particularly, myeloblasts favor PSGL-1 for interactions with endothelial selectins, while lymphoblasts express less PSGL-1. PSGL-1 expressed on the surface of the leukemia cells can bind to P-selectin along with E-selectin on endothelial cells (132). In contrast, lymphoblasts mainly use CD43 and/or CD44 to bind to endothelial selectins (133). Therefore, even though specific ligands are preferentially used in different cells, this does not mean that other molecules are less crucial in conferring CAM-DR. Indeed, myeloblasts use PSGL-1, CD44, and CD43 to various extents during E-selectin binding. Therefore, different patients show different profiles of E-selectin ligand expression levels. Interestingly, nilotinib treatment upregulated E-selectin, ICAM-1, and VCAM-1 expression on human endothelial cells (134), which may result in the increased adherence of leukemia cells to E-selectin and the evasion of chemotherapy-induced cytotoxicity. In fact, a high baseline level of soluble E-selectin along with VEGF, PAI-1, and low initial soluble ICAM-1 were proposed as prognostic factors for poor outcomes in pediatric ALL (135). Leukemia itself can express selectins on the surface to promote migration and progression. Human BCR-ABL1 (p210) retrovirus transduced murine leukemia

expressed integrin subunit alpha-6 and L-selectin, which were used to metastasize into the central nervous system, predominantly in meninges (136).

## TARGETING SELECTIN IN CANCER

Currently, selectin inhibition is actively being translated into leukemia treatments (Table 2). GMI-1271 (Uproleselan), an E-selectin antagonist, is intended to inhibit E-selectin expression on endothelial cells so that E-selectin-mediated drug resistance in leukemia can be prevented. Preclinical investigations of GMI-1271 in multiple myeloma (MM) showed the sensitization of E-selectin ligand rich in MM toward bortezomib (142). GMI-1359, a dual E-selectin and CXCR4 inhibitor, significantly decreased bone metastasis, synergized the docetaxel effect in prostate cancer cells (137), and sensitized MM toward carfilzomib (138). Currently, GMI-1271 is being investigated for its safety and efficacy in AML patients (Table 3). Crizanlizumab (Adakveo) is a monoclonal antibody against P-selectin, which is expressed on the surface of the activated endothelium and platelets. Crizanlizumab is used to reduce vaso-occlusive crises (VOC) in adult and pediatric patients with sickle cell disease (SCD). Clinical trials are open for dose confirmation and safety in both adult and pediatric SCD patients to evaluate the safety and efficacy on SCD-related complications along with a combination study of myelofibrosis with ruxolitinib. YPSL (rPSGL-Ig), a P-selectin glycoprotein ligand IgG fusion protein, binds to P-selectin and was evaluated in ischemia-reperfusion injury, liver disease, and kidney functions but has not been tested in cancer (143).

GMI-1271 is currently the only selectin inhibitor in clinical trials and is being investigated for its safety and efficacy in AML patients (Table 3). There is increasing evidence in support of the importance of targeting the BM microenvironment due to its role

**TABLE 2 |** Description of selectin inhibitors.

Drug name	Description	Indication	References
GMI-1271 (Uproleselan)	E-selectin inhibitor	Small molecule inhibitor against E-selectin on endothelial cells to treat AML and potentially other hematologic cancers	(28)
GMI-1359	E-selectin/CXCR4 dual inhibitor	Targeting E-selectin and CXCR4 to reduce tumor metastasis to bone marrow	(137, 138)
Crizanlizumab (Adakveo)	Monoclonal antibody against P-selectin	Reduction of vaso-occlusive crises in sickle cell disease patients	(139)
YPSL (rPSGL-Ig)	Recombinant P-selectin glycoprotein ligand IgG fusion protein	Myocardial infarction, red blood cell disorders, anemia, transplant, ischemic-reperfusion injury	(140, 141)

**TABLE 3 |** Clinical trials for selectin inhibitors in leukemia.

Drug	Target	Condition or disease	Phase	Intervention/treatment	References
GMI-1271	E-selectin	AML	I/II	Evaluation of GMI-1271 treatment combined with mitoxantrone, etoposide, cytarabine and idarubicin in AML patients	NCT02306291
GMI-1271	E-selectin	Relapsed/refractory AML	III	Efficacy of uproleselan (GMI-1271) in combination with mitoxantrone etoposide and cytarabine (MEC), or fludarabine, cytarabine and idarubicin (FAI) in relapsed/refractory AML patients	NCT03616470
GMI-1271	E-selectin	AML (adults 60 years and older)	II/III	Evaluation of uproleselan combined with cytarabine or daunorubicin in older AML patients receiving intensive induction chemotherapy.	NCT03701308

in therapy resistance (144–146). In these clinical trials, GMI-1271 will be administered in combination with existing chemotherapies, which highlights how targeting both the microenvironment and leukemia cells may be necessary in order to ameliorate CAM-DR.

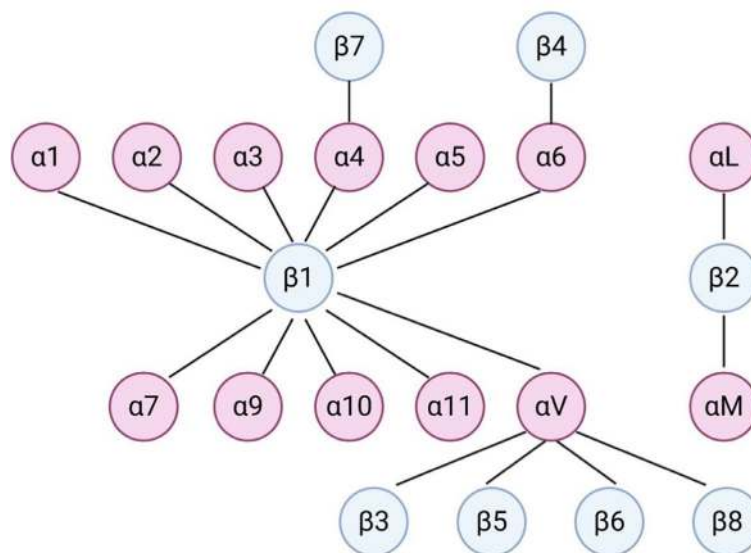
## INTEGRINS IN CELL ADHESION-MEDIATED DRUG RESISTANCE

Integrins are calcium independent type-I transmembrane proteins with a shared structure of the extracellular domain, the transmembrane domain, and the cytoplasmic domain. Composed of 18 alpha ( $\alpha$ ) and 8 beta ( $\beta$ ) subunits, integrins participate in cell–cell or cell–ECM adhesion. To date, 24 integrin heterodimers with different combinations of  $\alpha$  and  $\beta$  subunits are known and can interact with their ligands in arginine–glycine–aspartic acid (RGD) sequence dependent and independent manners (147, 148) (**Figure 3**). **Figure 3** does not represent a comprehensive list of integrin heterodimers but rather includes integrins described by currently available publications in the field of leukemia, which are reviewed in this review. During “inside-out” signaling, binding of talin to the cytoplasmic tail of the  $\beta$  subunit increases integrins’ affinity toward their ligands by undergoing conformational changes from low-affinity to high-affinity state (149, 150). On the other hand, binding of a ligand or a counter-receptor to a specific domain on the  $\alpha$  subunit or the  $\alpha\beta$  heterodimer results in spatial separation of cytoplasmic tails of  $\alpha$  and  $\beta$  subunits. This event allows adaptor proteins such as talin and vinculin to engage with  $\beta$  tail and associate with the cytoskeleton and form a protein complex called focal adhesion and integrin clustering (151–153)

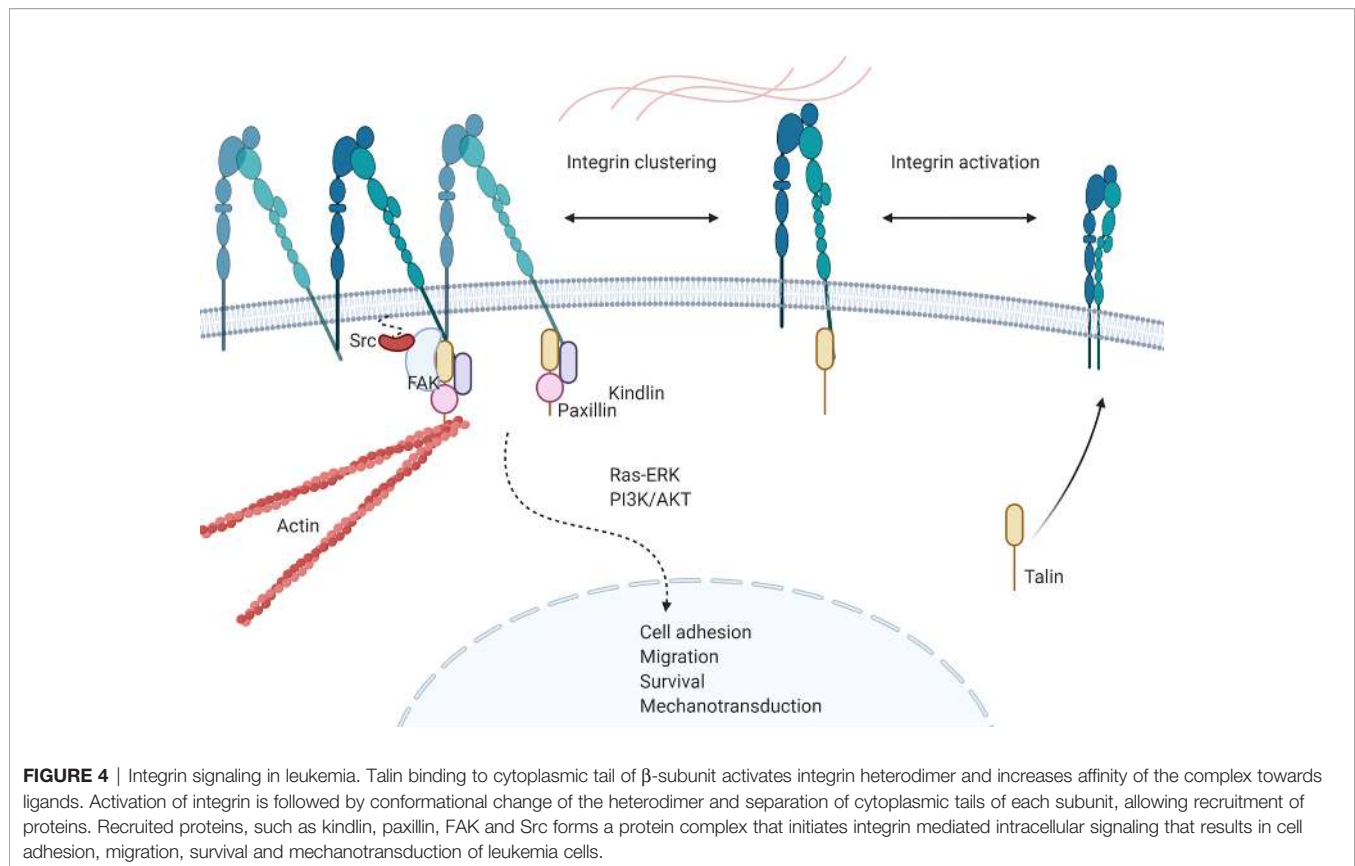
(**Figure 4**). Integrins can be internalized and recycled, thus controlling availability of integrin heterodimers on the plasma membrane (148, 154). These processes will translate external stimuli and environmental cues into intracellular signaling and mediate adhesion, cell spreading, migration, proliferation and survival in cells. Integrin-dependent adhesion to ECM can convert mechanical forces into biochemical signals, allowing cells to recognize biophysical properties of given BM microenvironment (155). Few studies analyze redundancy between integrins in CAM-DR, and how it might affect integrin targeting. Future studies will need to address this gap of knowledge. Here, we summarized integrins by name.

### INTEGRIN $\alpha$ 1 (CD49a)

Integrin alpha 1 subunit forms a heterodimer with the integrin beta 1 subunit to form  $\alpha_1\beta_1$ , which binds to collagen and laminin (156, 157).  $\alpha_1\beta_1$  is also called very late antigen 1 (VLA-1) because it is expressed on the surface of long-term activated T cells (158). VLA-1 mediates the adhesion of intraepithelial lymphocytes (IELs), such as the CD8<sup>+</sup> T cells found in the intestinal epithelium, to collagen (159).  $\alpha_1$  was also suggested to be a potential marker for stromal cells and is expressed in more than 80% of human derived non-transformed bone marrow stroma cells. In this study, only  $\alpha_1$  expressing stroma precursors was able to give rise to colony-forming unit-fibroblasts (CFU-F) compared to the  $\alpha_1$  negative subgroup of the stromal population, suggesting  $\alpha_1$  as a marker for stromal precursor cells (160). Embryonic fibroblasts derived from  $\alpha_1$  deleted mice were not able to spread or migrate to either collagen IV or laminin, suggesting their importance in cell spreading and migration (161). However, the role of VLA-1 in CAM-DR in leukemia is still unknown.



**FIGURE 3** | Dimerization of integrins in leukemia. Dimerization of  $\alpha$  and  $\beta$  integrins forms a functional heterodimer unit. This figure does not represent a comprehensive list of integrin heterodimers but rather includes integrins described by currently available publications in the field of leukemia, which are reviewed in this review.



## INTEGRIN $\alpha$ 2 (CD49b)

Integrin alpha 2 forms a heterodimer with the beta 1 subunit to form a VLA-2 molecule that binds to collagen and laminin (162). A real-time quantitative polymerase chain reaction study on 134 *de novo* AML patients revealed higher ITGA2 expression in AML patients compared to the 33 normal controls (163). Moreover, ITGA2<sup>high</sup> patients had significantly lower complete remission (CR) rates and a shorter overall survival compared to the ITGA2<sup>low</sup> groups. ITGA2 expression decreased significantly in the patients who achieved CR but increased again in relapsed patients, suggesting that ITGA2 is a marker for a poor prognosis in AML. The  $\alpha_2\beta_1$  mediated adhesion of the T-ALL cell lines Jurkat and HSB-2 and the primary T-ALL blasts toward collagen I decreased doxorubicin induced apoptosis (164).  $\alpha_2\beta_1$  mediated adhesion activates the MAPK/ERK pathway, which inhibits the doxorubicin-induced activation of c-Jun N-terminal kinase (JNK) and maintains the pro-survival protein Bcl-2 family member Mcl-1. The same group extended  $\alpha_2\beta_1$ -collagen mediated doxorubicin resistance in the AML cell lines HL-60 and U937 (165). In AML, collagen binding through  $\alpha_2\beta_1$  inhibited the activation of the pro-apoptotic protein Rac1, thereby preventing Rac1 induced DNA damage.

## INTEGRIN $\alpha$ 3 (CD49c)

VLA-3 interacts with ligands in both an RGD-dependent and RGD-independent manner. VLA-3 mediated adhesion to

fibronectin requires RGD-motif recognition, whereas binding to collagen and laminin does not require an RGD-motif in the ligands (166). VLA-3 binding to fibronectin increased in the presence of the  $Mg^{2+}$  and  $Mn^{2+}$ -divalent cations required for integrin activation, whereas binding to collagen and laminin was less affected. Integrin- $\alpha_3$  was identified as a marker for long-term repopulating hematopoietic stem cells (LT-HSCs) that expand from CD34+ human cord blood cells and retain their self-renewal ability with a long-term engraftment pattern compared to short term HSCs (SC-HSCs) (167). Furthermore, ITGA3 knockdown with short hairpin RNA against *ITGA3* did not affect the stemness of the cells but decreased the long-term reconstitution ability in NSG mice. However, the specific role of VLA-3 in CAM-DR in leukemia is still unclear.

## INTEGRIN $\alpha$ 4 (CD49d)

Integrin  $\alpha_4$  binds with either the  $\beta_1$  or  $\beta_7$  subunit to form  $\alpha_4\beta_1$  or  $\alpha_4\beta_7$  heterodimer. Integrin  $\alpha_4$  exerts physiological effects including cell adhesion and migration, while triggering intracellular signaling, thereby indicating the promotion of leukemia cell drug resistance and survival. Integrin- $\alpha_4$  knockout mice are embryonically lethal (168). There are specific relationships between integrin  $\alpha_4$ , epigenetics, metabolism, and cell surface markers. Histone deacetylase inhibitor treatment may downregulate VLA-4 for various AML cell lines, primary patient samples, and normal hematopoietic

stem cells (169). The expression of G9a, a histone methyltransferase related to gene silencing, correlates with integrin  $\alpha_4$  expression in pediatric B- and T-ALL. Furthermore, G9a depletion or inhibition with BIX01294 was shown to abrogate the ability of ALL cell migration towards the endothelial monolayer (170). Moreover, it was recently reported that tetraspanin (CD9)<sup>+</sup> B-ALL is associated with a poor prognosis. In this study, CD9 physically interacted with VLA-4 and mediated the affinity to VCAM-1. CD9 inhibition interrupted the leukemia–stroma interactions and sensitized B-ALL cells to chemotherapy (171). CD98 has been shown to interact with the cytoplasmic domains of  $\beta_1$  and  $\beta_3$  and mediate the adhesive signaling of integrin  $\alpha_4$ /VCAM-1 in AML (172). The redox modulation of adjacent thiols in VLA-4 by AS101, an IL-1 $\beta$  converting enzyme, restored the chemosensitivity of AML cells by decreasing PI3K/Akt/Bcl2 signaling (173). It has been demonstrated that integrin  $\alpha_4$  and  $\alpha_5$  are involved in Jurkat T-ALL adhesion-independent chemoresistance (174). Our studies also showed that both deletion and inhibition with natalizumab of integrin  $\alpha_4$  sensitize primary B-ALL cells to chemotherapy (175). Furthermore, the CD49d antisense drug ATL1102 efficiently downregulated the CD49d mRNA level of B-ALL *in vitro* (176). Anti-VLA-4 antibodies (SG/73, SG/17) were shown to increase chemosensitivity in human AML cells and eradicate minimal residual disease (MRD) in experimental mice when combined with chemotherapy (6). Integrin  $\alpha_4$  has been shown to be a prognostic marker of poor overall survival in B-ALL (175). Interestingly, a report from the Children's Oncology Group found that high VLA-4 expression is associated with a better clinical outcome in pediatric AML and is an independent predictor of relapse (177). Similar results were found in a study of the Southwest Oncology Group trials (178).

## INTEGRIN $\alpha_5$ (CD49e)

The integrin  $\alpha_5$  subunit can dimerize with integrin  $\beta_1$  to form  $\alpha_5\beta_1$  (VLA-5), which binds to the RGD sequence in fibronectin (179). Both murine and CD34<sup>+</sup> human HSCs were shown to bind to a recombinant peptide of the VLA-5 binding RGD-motif of fibronectin *in vitro* (180). The preincubation of B6.*Hbb<sup>d</sup>/Hbb<sup>d</sup>*, *Gpi-1<sup>a</sup>/Gpi-1<sup>a</sup>* mice-derived BM cells incubated with the fibronectin binding domain including the peptide CH-296 decreased the engraftment of BM cells in recipient mice, and the intravenous injection of the CH-296 peptide caused an increase in the percentage of progenitor cells in the spleen, suggesting the importance of VLA-5 in HSC engraftment in the BM. VLA-5 has been suggested as a therapeutic target in leukemia. A subset of ALL includes an alteration in the *IKAROS* gene, which is correlated with a poor prognosis. The exon 5 deletion of *Ikzf1* in pre-B cells arrests the cells in an “adherent phase”, where survival and proliferation depend on stable adhesion to the stroma with increased Erk1-2 MAPK activity (181). The expression of the dominant-negative Ikaros isoform IK6 in the T-ALL (Jurkat) and B-ALL cell lines (RS4;11, Nalm6) lifted the transcription suppression of FUT4, which fucosylates  $\alpha_5\beta_1$  on leukemia cells and tightens the adhesion of ALL cells to fibronectin in the ECM. This increased adhesion was achieved

*via* activation of the FAK/Akt pathway upon Lewis X (Le<sup>x</sup>, CD15, or SSEA-1) modification of  $\alpha_5\beta_1$  (182). In U937 and blasts from AML patients,  $\alpha_4\beta_1$  and  $\alpha_5\beta_1$  mediated the adhesion of cells to fibronectin, and the addition of the Wnt antagonist sFRP induced resistance to daunorubicin 16407823 (183). Both adhesion and the Wnt pathway contribute to chemoresistance in AML and require the activation of glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ). Upon serum starvation of AML U937, VLA-5 binding to fibronectin regulates specific pro-survival functions through the activation of GSK3 $\beta$  (184). VLA-5 inhibition with an anti-integrin  $\alpha_5$  antibody sufficiently decreased adhesion of the Ph<sup>+</sup> ALL cell line SUP-B15 to fibronectin, while a combination of VLA-5 inhibition with imatinib synergistically increased apoptosis in SUP-B15 cells *in vitro* (185). Furthermore, the inhibition of VLA-5 with disintegrin, an antibody, or knocking down integrin- $\alpha_5$  impaired the engraftment of SUP-B15 cells in immunodeficient mice. A combination of integrin- $\alpha_5$  inhibition with the FAK inhibitor TAE226 prolonged the survival of SUP-B15 engrafted mice, suggesting that the inhibition of VLA-5 combined with conventional chemotherapy may improve the outcome for Ph<sup>+</sup> ALL patients.

## INTEGRIN $\alpha_6$ (CD49f, VLA6)

Integrin  $\alpha_6$  dimerizes with  $\beta_1$  to form VLA-6 (186) or with  $\beta_4$  to form  $\alpha_6\beta_4$ , which is also known as TSP-180 (187).  $\alpha_6$  has been suggested to be a biomarker for minimal residual disease since it is expressed on pre-B-ALL at diagnosis, and the signal is preserved or expressed with a higher intensity after therapy (10, 188).  $\alpha_6$  was found to be expressed significantly more strongly not only in relapsed B-ALL but also in ecotropic viral integration site-1 positive (EVI1<sup>+</sup>) AML cases. In this study, the drug sensitivity of EVI1 AML cells was restored after the inhibition of integrin  $\alpha_6$  (189). Functionally,  $\alpha_6$  is suggested to play an important role in the chemoresistance and metastasis of leukemia cells. EVI1<sup>+</sup> AML cell lines and primary cells were able to bind to laminin better than cell lines with low EVI1. This adhesion is specifically mediated by ITGA6 and ITGB4 expression on EVI1 AML cells, and small-hairpin RNA against EVI1 decreased the expression of ITGA6 and ITGB4. Moreover, the inhibition of ITGA6 or ITGB4 with neutralizing antibodies restored chemosensitivity against Ara-C in EVI1<sup>+</sup> AML cells. In another study,  $\alpha_6$  on the surface of ALL was shown to facilitate the invasion of ALL cells into the central nervous system by binding to laminin during the process of migration toward the cerebrospinal fluid (190).

Since a high expression of integrin  $\alpha_6$  was found on day 29 of an MRD test on B-ALL in the Children's Oncology Group (COG) P9906 clinical trial, we proposed the drug resistance role of integrin  $\alpha_6$ . Firstly, we showed that the integrin  $\alpha_6$  blockade de-adhered the B-ALL cell from laminin-1 and OP9 stromal cells. Secondly, P5G10, an anti-integrin  $\alpha_6$  antibody, in combination with chemotherapy, prolonged the survival of B-ALL xenograft mice. Thirdly, integrin  $\alpha_6$  deletion induced apoptosis of B-ALL cells involving Src signaling (191). Recently, it has been shown that the inhibition of integrin- $\alpha_6$  is correlated with decreased cell surface deformability using

single-beam acoustic tweezers, while no changes in inhibition were shown for integrin  $\alpha 4$  (192).

## INTEGRIN $\alpha 7$ (ITGA7)

Integrin- $\alpha 7$  binds with  $\beta_1$ , which is expressed on skeletal and cardiac muscle (193–196). *ITGA7* was more significantly increased in AML patients with granulocytic sarcoma (GS) compared to patients with GS. Furthermore, integrin- $\alpha 7$  mediated the phosphorylation of ERK in the surface integrin- $\alpha 7$  expressing AML cell lines PL21 and THP1, thus promoting the proliferation of these cells (197). *ITGA7* also has been suggested to be a biomarker for AML patients as *ITGA7* expression in AML patients was significantly increased compared to the control and correlated with a poorer prognosis. Patients with either high *ITGA7* mRNA or protein expression had a shorter event-free survival (EFS) and overall survival (OS) compared to low *ITGA7* patients (198).

## INTEGRIN $\alpha 9$ (ITGA9)

Integrin- $\alpha 9$  dimerizes with the  $\beta_1$  subunit to form an  $\alpha_9\beta_1$  that is distributed in the airway epithelium, squamous epithelium, smooth and skeletal muscle, and hepatocytes (199).  $\alpha_9\beta_1$  recognizes tenascin-C (200), osteopontin (201), and VCAM-1 (202). While  $\alpha_9\beta_1$  shares nearly 40% of its amino-acid sequence homology with integrin- $\alpha 4$ , both have distinct functions. Integrin- $\alpha 9$  knockout mice develop bilateral chylothorax and die 6 to 12 days after birth due to respiratory failure (203). The roles of integrin- $\alpha 9$  in the context of leukemia have not been elucidated. Recently, the dual inhibition of  $\alpha_4\beta_1$  and  $\alpha_9\beta_1$  with BOP {[N-(benzenesulfonyl)-L-prolyl-L-O-(1-pyrrolidinylcarbonyl)tyrosine, a small molecule antagonist against integrin  $\alpha_4\beta_1$  and  $\alpha_9\beta_1$ ] demonstrated the successful HSC mobilization potential from the bone marrow to the peripheral blood. While a single dose of BOP increased the mobilization of huCD45+CD34+ cells by about 2 fold compared to the saline control, a combination of BOP with the CXCR4 inhibitor AMD3100 increased the mobilization of HSC by three fold (204). This result suggests that  $\alpha_9\beta_1$ , concomitantly with  $\alpha_4\beta_1$ , is involved in the integrin mediated adhesion of HSCs in the bone marrow. Indeed, CD34<sup>+</sup>/CD133<sup>+</sup> hematopoietic stem and progenitor cells (HSPCs) expressed  $\alpha_9$  transcripts and  $\alpha_9\beta_1$  on the surface. Integrin- $\alpha 9$  mediates the adhesion of CD34<sup>+</sup> cells to osteoblasts, and the addition of functional blocking antibody against  $\alpha_9\beta_1$  and Y9A2 significantly decreased the proliferation and differentiation of CD34+ HSPC cells (205).

## INTEGRIN $\alpha L$ (CD11a, LFA-1)

Integrin- $\alpha_L$  dimerized with a  $\beta_2$  subunit is called lymphocyte function-associated antigen-1 (LFA-1). In an early study using T cells derived from leukocyte adhesion deficient (LAD) patients with genetic defects in  $\beta_2$  showed a decreased expression of LFA-1 and LFA-1 LAD derived T cells still bound to endothelial cells similar to normal T cells *via* complementary binding through VLA-4, but their transmigration through the endothelial layer of

LAD derived T cells was significantly decreased (206). In hematological malignancies, T-cell neoplasms, including T-ALL, almost always express LFA-1, while LFA-1 expression in lymphoma and B-cell neoplasms, including T-ALL, CLL, HCL, and SLL, vary between patients (207, 208). LFA-1 on the T-ALL cell line (Sup T1 and Jurkat) and primary T-ALL were shown to play a critical role in binding T-ALL cells to the BM stroma (HS-5 and patient derived BM) and regulating the survival of T-ALL cells (209).

## INTEGRIN $\alpha M$ (CD11b)

The integrin- $\alpha_M\beta_2$  heterodimer is called Mac-1 and is known to bind to fibrinogen (210), platelet factor 4 (211), and ICAM-1 (212). The expression of Mac-1 was suggested to be a biomarker for a poor prognosis (213). The Mac-1 mediated adhesion of U937 and HL-60 cells to plastic was suggested to elicit a survival benefit in leukemia cells treated with phorbol ester, and these Mac-1 mediated adherent cells are susceptible to undergo anoikis when forced to be de-adhered, suggesting adhesion dependent survival.

## INTEGRIN $\alpha V$ (CD51, VNRA, MSK8)

Integrin- $\alpha_V$  can dimerize with  $\beta_1$ ,  $\beta_3$ ,  $\beta_5$ ,  $\beta_6$ , and  $\beta_8$ . Heterodimers including  $\alpha_V$  can bind to fibronectin (214) and vitronectin (215, 216). In AML,  $\alpha_V\beta_3$  is suggested to cooperate with the fibroblast growth factor receptor (fgf-R) to increase proliferation, especially the subset of AML that has Hox-overexpression induced by MLL fusion protein (217). In this study, the *MLL-ELL* transduction of primary murine bone marrow cells increased the expression of  $\beta_3$  integrin *via* HoxA10, and the  $\alpha_V\beta_3$ -mediated adhesion of cells to vitronectin increased Syk, Pak1, and Fak1.  $\alpha_V\beta_3$  activity was reversed through the  $\beta$ -catenin and Cdx4 dependent decrease in *ITGB3* promoter activity upon fgf-R inhibition in these cells.

## INTEGRIN $\beta 1$ (CD29)

Integrin  $\beta 1$  is the most common beta subunit heterodimer partner for integrin alpha subunits (218). In cancer, upregulated expression of  $\beta 1$  is indicative of a poor prognosis (219) and plays roles in chemoresistance by binding to ligands and eliciting downstream signaling events. Berrazouane et al. reported that  $\beta 1$  promotes chemoresistance in T-ALL primary blasts *via* ABC transporter-mediated doxorubicin efflux and the downstream activation of PYK2 (220). Integrin  $\alpha 2\beta 1$  binds to collagen and upregulates ABCC1 *via* the ERK/MAPK pathways to modulate efflux (221). Similarly, collagen-binding  $\beta 1$  integrins contribute to doxorubicin resistance in AML by reducing DNA damage through Rac1 inhibition (222).

$\beta 1$  also has roles in apoptosis inhibition. Estrugo et al. demonstrated that leukemia cell lines HL60 and Jurkat adhere to  $\beta 1$  integrin ligands fibronectin, laminin, or collagen-1 and are protected from radiation, Ara-C, and FasL-induced apoptosis (223). These  $\beta 1$  integrin-mediated cell-matrix interactions inhibit procaspase-8 activation *via* the PI3K/AKT pathway. Additionally,  $\beta 1$  integrin

ligation to fibronectin impairs both procaspase-3 and procaspase-9 activation associated with the intrinsic apoptotic pathway.

The tetraspanin superfamily is known to be associated with the activation, ligand binding, and inside-out signaling of  $\beta_1$  integrins and can promote cancer cell survival (224, 225). When  $\beta_1$  is expressed with tetraspanin CD82, chemoresistance is promoted by increasing PKC $\alpha$  activation and the downstream clustering of  $\beta_1$  integrin, leading to AML cell survival *via* the activation of p38 MAPK for DNA damage repair (226). In summary, integrin  $\beta_1$  is implicated in the chemoresistance of leukemia *via* chemotherapy efflux, intracellular signaling, and apoptosis inhibition.

## INTEGRIN $\beta_3$

It has been suggested that integrin  $\beta_3$  may have functional redundancies with  $\beta_1$  integrins (227). In AML,  $\beta_3$ -mediated signaling is required for leukemogenesis and leukemia survival (228), in part through SYK activation. To date, the function of  $\beta_3$  in the chemoresistance in leukemia has not been studied. In hepatocellular carcinoma, the upregulation of Galectin-1, which elevates  $\alpha_v\beta_3$  expression, was found to activate the PI3K/AKT pathway and is correlated with a poor sorafenib response (229). The antagonism of  $\beta_3$  with cilengitide in M2 macrophages led to the promotion of tumor cells, and the loss of integrin  $\beta_3$  signaling promoted an immunosuppressive tumor environment (230). Clearly,  $\beta_3$  signaling is important in drug response and cancer progression, which may be grounds for similar studies on leukemia.

## INTEGRIN $\beta_7$

Integrin  $\beta_7$  is present on lymphocytes as a subunit of the  $\alpha_4\beta_7$  heterodimer and mediates binding to fibronectin, VCAM-1 (231), and mucosal addressin cell adhesion molecule 1 (MAdCAM-1) (232).  $\alpha_4\beta_7$  is less well studied in the context of leukemogenesis and drug resistance and is mainly involved with lymphocyte homing and trafficking. In hematopoietic progenitor cells,  $\alpha_4\beta_7$  and MAdCAM-1 contribute to the recruitment of cells into the bone marrow following transplantation, and the inhibition of MAdCAM-1 significantly reduces homing (233). For blood cancers, it has been suggested that the expression of  $\alpha_4\beta_7$  plays a role in the leukemic evolution of T cell lymphoblastic lymphomas and the dissemination of lymphoma cells to VCAM-1-positive vascular spaces (234). In T cell leukemias with gastrointestinal involvement, it was found that the expression of  $\alpha_4\beta_7$  is linked with homing to MAdCAM-1 on endothelial cells in the intestinal mucosa (235). In summary, while  $\alpha_4\beta_7$  may not be involved with leukemogenesis, its roles in lymphocyte homing have effects on the progression of leukemia in different organs.

## TARGETING INTEGRINS

The preclinical evaluation of integrin inhibition has suggested promising results for the sensitization of leukemia cells to

chemotherapy. Knocking out *ITGA4* restored the sensitivity of BCR-ABL<sup>+</sup> murine leukemia toward nilotinib (NTB), and a blockade of integrin alpha 4 with a monoclonal antibody sensitized primary B-ALL engrafted xenograft mice to chemotherapy (175). Since the  $\beta_1$  (CD29) subunit dimerizes with many different  $\alpha$  units, blockade of  $\beta_1$  is an attractive target for leukemia therapy. In T-ALL, the  $\beta_1$  blockade with  $\beta_1$  specific antibody AIIB2 inhibited cell-matrix interactions and decreased the Matrigel effect on T-ALL colony formation. Furthermore, AIIB2 in combination with doxorubicin significantly prolonged the survival of CEM xenograft mouse models (220). OS2966, a humanized monoclonal antibody, will be used in a phase I clinical trial for glioblastoma and may also have efficacy in the treatment of hematological malignancies by targeting multiple integrins on leukemia cells and the surrounding microenvironment (236). As for other integrins, targeting the active form of the integrin  $\beta_7$  subunit, specifically the MMG49 epitope in the N-terminal region of active  $\beta_7$ , showed multiple anti-myeloma effects *in vivo* without damaging normal hematopoietic cells (237). The efficacy of chimeric antigen receptor (CAR) T cells against  $\alpha_v\beta_3$  in melanoma and  $\alpha_v\beta_6$  in ovarian, breast, and pancreatic xenograft mice models has also been evaluated (238, 239) for integrin targeting CAR T therapy in hematological malignancies.

Despite the compelling *in vitro* and *in vivo* anti-tumor effects of integrin blockades in tumor models, the preclinical evaluation of integrin targeting has not yet been successfully translated into a clinical platform. Several clinical trials evaluating integrin inhibition in solid tumors were terminated due to infusion-related reactions and non-significant anti-tumor activity (NCT00915278) (240), insufficient clinical data (NCT00684996), or low enrollment (NCT00675428). A phase II trial of abituzumab (EMD 525797) targeting  $\alpha_v$  in combination with cetuximab and FOLFIRI in metastatic colorectal cancer is expected to be completed by August 2021 (NCT03688230).

Integrin targeting is useful for the detection of cancers, and many clinical trials target integrin in the CT/PET imaging of cancer patients. A novel radiotracer <sup>99m</sup>Tc-RWY detecting integrin alpha 6 is in an early phase I clinical trial for SPECT imaging in breast cancer (NCT04289532), and the safety of the radiotracer and potential clinical applications are being evaluated. Likewise, many other types of integrin tracing molecules are being evaluated for their efficacy in imaging cancer patients (NCT04285996).

Although the inhibition of integrin has not yet been successfully translated into a clinical trial for leukemia, integrins remain a valid target for cancer therapy, as they can serve as a targetable biomarker. Targeting the active form of the integrin  $\beta_7$  subunit, specifically the MMG49 epitope in the N-terminal region of active  $\beta_7$ , showed multiple anti-myeloma effects *in vivo* without damaging normal hematopoietic cells (237). The efficacy of CAR T cells against  $\alpha_v\beta_3$  in melanoma and  $\alpha_v\beta_6$  in ovarian, breast, and pancreatic xenograft mice models has also been evaluated (238, 239) for integrin targeting CAR T therapy in hematological malignancies.

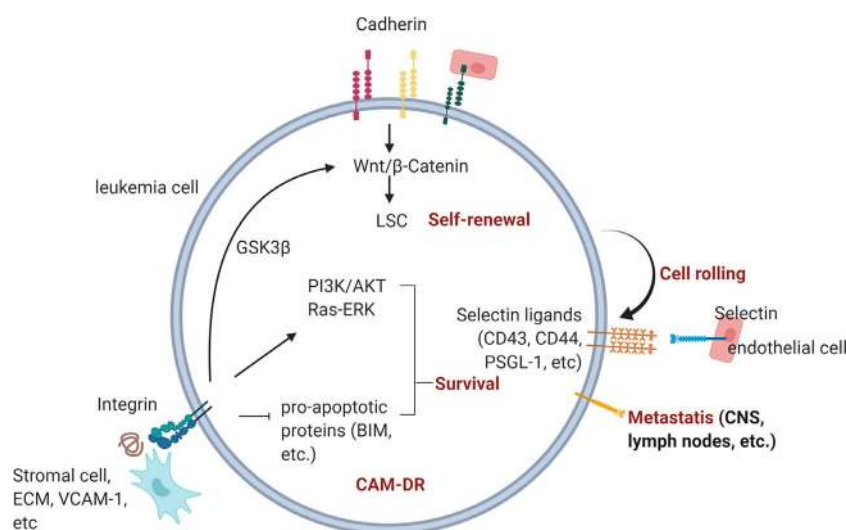
In summary, integrin blockades must be further investigated using preclinical systems that can accurately recapitulate the biological environments in patients, thus allowing the integrin blockade to exert anti-tumor effects (241) (Table 4). To overcome this challenge, integrins can serve as a good target for tumor imaging in patients or for immunotherapy, including CAR T therapy. As discussed in this section, integrin blockades have been shown to increase chemosensitivity of leukemia cells and provide support for further studies of integrins as a viable target to abolish CAM-DR in leukemia.

## CONCLUSION

Despite advances in cancer therapy and the increased overall survival rate of cancer patients, the eradication of leukemia still remains a challenge. Pediatric ALL has a good prognosis overall, yet relapse and refractory disease remain a problem. AML has a worse prognosis, and there is an unmet need for the improvement of patient outcomes. The impact of the microenvironment on cancer cell progression and drug resistance has been often neglected, yet it is apparent that

**TABLE 4 |** Description of integrin inhibitors.

Drug name	Description	Indication	References
Natalizumab (Tysabri®)	Monoclonal antibody against $\alpha_4$	Multiple sclerosis and Crohn's disease	(175)
Vedolizumab (Entvio)	Monoclonal antibody against $\alpha_4\beta_7$	severe ulcerative colitis or Crohn's disease	(242, 243)
Volociximab	Monoclonal antibody against integrin $\alpha_5\beta_1$	Solid tumors including kidney, lung, ovarian cancer, melanoma, and pancreatic cancer	(244–247)
ATN-161	non-RGD based peptide targeting $\alpha_5\beta_1$ and $\alpha_v\beta_3$	Solid tumors including prostate, colon, and hepatocellular cancers	(248–250)
Intetumumab (CNT095)	human $\alpha_v$ monoclonal antibody	Inhibition of tumor growth	(236, 251)
Etaracizumab (MEDI-522)	Monoclonal antibody against $\alpha_v\beta_3$	Psoriasis, kidney cancer	(252, 253)
Abituzumab (EMD525797)	Monoclonal antibody against $\alpha_v\beta_6$	Metastatic prostate cancer	(254, 255)
Cilengitide (EMD 121974)	first anti-angiogenic small molecule targeting the integrins $\alpha_v\beta_3$ , $\alpha_v\beta_5$ , and $\alpha_5\beta_1$	Inhibition of endothelial cell–cell and cell–ECM interactions and angiogenesis	(256–259)
GLPG0187	a small molecule inhibitor for $\alpha_v\beta_1$ , $\alpha_v\beta_3$ , $\alpha_v\beta_5$ , $\alpha_v\beta_6$ , and $\alpha_5\beta_1$	Solid tumors including high-grade gliomas and colorectal carcinoma	(260–262)
OS2966	Humanized monoclonal antibody against $\beta_1$ integrins	Glioblastoma, meningioma, ALL, and AML	(236, 263)



**FIGURE 5 |** Overview of CAM-DR in leukemia. Cadherin, selectin, and integrin contribute to drug-resistance and metastasis upon engagement with their ligands in the BM. Homotypic engagement of cadherins can protect leukemia cells from chemotherapy (reference 92, 95) by modulating Wnt signaling and promote self-renewal of LSCs (reference 96, 97, 99). Leukemia cells can also bind to E-selectin expressed on endothelial cells through expressed selectin ligands on their surface (ref 132, 133). Interruption of E-selectin mediated interaction between leukemia and endothelial cells is actively being investigated in many clinical trials (ref 20). Integrin binding to BM stromal cells, ECM or counter receptors activates pro-survival signaling pathways such as PI3K/AKT and Ras/ERK pathway (ref 164, 221, 223, 229).

leukemia cells actively communicate and interact with the surrounding microenvironment for their survival. Therefore, disrupting the interactions between leukemia cells and the surrounding cells or ECM protein may lead to apoptosis or sensitization toward chemotherapy. Cadherins, selectins, and integrins are known cell adhesion molecules that are involved in CAM-DR in leukemia (**Figure 5**). Their aberrant expression and association in CAM-DR in different types of leukemia have been studied. Furthermore, a preclinical evaluation of the efficacy of the CAM blockade was performed on subtypes of leukemia and showed promising results with an anti-leukemic effect. The FDA has granted a Breakthrough Therapy designation and Fast Track designation for the E-selectin inhibitor Uproleselan, which shows both the urgency of finding an effective drug for leukemia treatment and the importance of microenvironment–leukemia interactions in leukemia treatment. The translation of more CAM inhibitors into a clinical platform will advance leukemia therapy and eradication of the disease.

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## AUTHOR CONTRIBUTIONS

HK and YK conceptualized the study. HK wrote and prepared the original draft. HK, YR, HO, and YK wrote, reviewed, and editing. YK Supervised the study and acquired the funding. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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