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Eviction from the sanctuary: development of targeted therapy against cell adhesion molecules in acute lymphoblastic leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) is a malignant hematological disease afflicting hematopoiesis in the bone marrow. While 80-90% of patients diagnosed with ALL will achieve complete remission at some point during treatment, ALL is associated with high relapse rate, with the 5-year overall survival rate of 68%. The initial remission failure and the high rate of relapse can be attributed to intrinsic chemoprotective mechanisms that allow persistence of ALL cells despite therapy. These mechanisms are mediated, at least in part, through the engagement of cell adhesion molecules (CAMs) within the bone marrow microenvironment. This review assembles CAMs implicated in protection of leukemic cells from chemotherapy. Such studies are limited in ALL. Therefore, CAMs that are associated with poor outcomes or are over-expressed in ALL and have been shown to be involved in chemoprotection in other hematological cancers are also included. It is likely that these molecules play parallel roles in ALL because the CAMs identified to be a factor in ALL chemoresistance also work similarly in other hematological malignancies. We review the signaling mechanisms activated by the engagement of CAMs that provide protection from chemotherapy. Development of targeted therapies against CAMs could improve outcome and raise the overall cure rate in ALL.

Keywords

acute lymphoblastic leukemia; cell adhesion molecules; targeted therapy; chemoresistance; bone marrow

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant hematological disease characterized by the accumulation of immature, abnormal white blood cells that replace normal marrow

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elements within the bone marrow and inhibit the production of functional blood cells. Of those diagnosed, 80–90% will have complete remission at some point during treatment (1). However, about half of these patients will experience a recurrence of the disease, making the overall 5-year survival rate about 40% for adults and 85% for children. Nearly 60% of patients diagnosed are age 20 or younger, but patients older than 20 account for approximately 85% of deaths from ALL (2,3).

Remission is defined as lack of clinical evidence of the disease and restoration of normal hematopoiesis. However, this does not guarantee a cure. Leukemic cells may still be dispersed throughout the body or have resisted the chemotherapy treatments and persisted in the bone marrow. The detectable presence of leukemic cells within the bone marrow following induction therapy is termed minimal residual disease (MRD), and can be considered a measure of drug resistance *in vivo*. A patient's prognosis is inversely proportional to their MRD level (Fig. 1) (4,5). These leukemic cells that resist chemotherapy are responsible for the high recurrence and less than optimal long-term survival rates in ALL (6). Therefore, sensitization to chemotherapy is important for disease eradication to prolong survival in ALL patients.

Chemotherapy Resistance Mechanisms in ALL

Chemotherapy resistance in ALL is extensively studied and a variety of mechanisms have been identified as contributing factors (Table 1). An exhaustive examination of all chemotherapy resistance mechanisms in ALL is beyond the scope of this review, which focuses on the microenvironment-induced protection of leukemic cells from the effects of chemotherapeutic drugs. This mechanism of resistance is a major contributor of intrinsic chemoresistance, and pre-exists prior to exposure of the leukemic cells to chemotherapeutics. The intrinsic chemoresistance afforded by the microenvironment is often referred to as 'chemoprotection' because it shields neoplastic cells from chemotherapy. The bone marrow microenvironment comprises osteoblasts, endothelial cells, fibroblasts, adipocytes, macrophages and stromal cells (also called bone marrow mesenchymal stem cells) with their associated extracellular matrix (ECM) components and secreted soluble factors (Fig. 2). The bone marrow microenvironment provides a sanctuary for leukemic cells similar to hematopoietic stem cells (HSCs). Leukemic cells modify this environment making it more habitable while leading to HSC dysfunction (7).

Several studies have reported that ALL cells co-cultured with osteoblasts or stromal cells, to mimic the bone marrow microenvironment, have improved survival and reduced sensitivity to chemotherapy (8–14). These effects required direct cell-cell contact and were not replicated in cells contacting ECM or in cells cultured in conditioned medium from stromal cells, indicating the contribution of the ECM and soluble factors was secondary (9). The absence of a change in the expression of drug transporters, has suggested a reliance on adhesion for chemoprotection (15). These adhesive interactions are mediated by cell-cell and cell-matrix contacts via cell adhesion molecules (CAMs) such as integrins, cadherins, selectins, immunoglobulin-like superfamily, and other CAMs on the cell surface (10,14,16) (Fig. 3, 4). The interactions between CAMs on two contacting cells not only serve as glue to bind the two cells together but also activate signaling pathways that regulate a wide array of

cellular functions including cell survival, evasion of apoptosis, and cell dormancy resulting in defense against chemotherapy (17). Understanding the role of CAMs in conferring chemoprotection provides the basis for possible development of targeted therapeutics for ALL.

CAMs involved in chemoprotection in ALL

Integrins

Integrins are one of the most extensively studied classes of CAMs in the activation of cell survival pathways and induction of chemoresistance. Integrins are expressed on the cell surface as heterodimers consisting of α and β chains. Different combinations of these subunits as well as alternative splicing allows integrins to bind to a variety of ligands on the cell surface, ligands in the ECM, and even soluble ligands. Different intracellular signaling pathways can be activated upon integrin ligation leading to outcomes such as cell survival, cell migration or cell proliferation and differentiation (18). The physiological role of integrins that play a role in chemoresistance is summarized in Table 2.

Integrin $\alpha_4\beta_1$ or VLA-4 (very late antigen-4) has been widely identified as a key mediator of chemotherapy resistance (Table 3). Therefore, it was not surprising that high VLA-4 expression in children with relapsed B-ALL was associated with unfavorable prognosis (19). Thus, blocking of VLA-4/VCAM-1 binding by a humanized antibody targeting VLA-4 (natalizumab) or a ligand-mimetic small molecule inhibitor of integrin α4 (TBC3486) not only sensitized B-ALL cells to chemotherapy, but also prolonged survival in leukemia bearing mice in preclinical studies (20,21).

Although less studied, integrin $\alpha_5\beta_1$ or VLA-5 (very late antigen-5) also binds to VCAM-1 and mediates chemotherapy resistance (14) (Table 3). Both VLA-4 and VLA-5 have been reported to bind fibronectin, and the data indicate such interactions might be important in cell survival in many hematological malignancies (Table 4). AS101, a nontoxic tellurium compound that targets thiol residues in the exofacial domain of the VLA-4 molecule required for fibronectin ligation, chemosensitized AML cells by triggering intracellular cytoskeletal changes and decreasing PI3K/Akt/Bcl-2 signaling (22) (5). This compound is currently in phase 2 clinical trials to treat AML and myelodysplastic syndrome patients (Table 5).

VLA-4 also binds to other ECM components such as osteopontin, a glycoprotein secreted by osteoblasts. VLA-4 ligation to osteopontin induces dormancy in B-ALL cells by forcing cell cycle exit (23). Since a majority of cytotoxic drugs are thought to target actively proliferating cells, induction of dormancy in ALL cells may result in protection from cytotoxic chemotherapy agents such as cytarabine.

Integrin $\alpha_L\beta_2$ or LFA-1 (leukocyte function-associated antigen-1) is another key heterodimer expressed on the surface of T-ALL cells that confers chemotherapy resistance (24) (Table 3). Multiple myeloma cells co-cultured with bone stromal cells were successfully sensitized to chemotherapy treatments via the use of monoclonal antibodies or an LFA-1 inhibitor (LFA703) (25) (Table 5).

Cadherins

Cadherins are type-1 transmembrane proteins that mediate Ca^{2+} ion dependent homophilic cell adhesion, such that adhesion is mediated by cadherin molecules located on contacting cells. The extracellular domains are responsible for mediating tight cell-cell contacts, while the intracellular domains interact with a wide variety of adaptor and signaling proteins (26) to mediate diverse functions such as leukocyte extravasation, HSC maintenance and actin dynamics (Table 6). Like integrins, cadherins such as VE-cadherin (CD144), N-cadherin (CD325) and Fat1 cadherin have been implicated in mediating resistance to chemotherapy in hematological cancers (Table 7).

Selectins

Selectins are single chain glycoproteins that contain an N-terminal calcium-dependent lectin domain. The selectin family comprises E- (endothelial), P- (platelet) and L- (leukocyte) selectins named CD62E, CD62P, and CD62L respectively (27). Their role in leukocyte homing and recruitment to inflammatory sites is well characterized (Table 8). Recent reports have identified the role of selectins in chemoresistance in a number of hematological malignancies (Table 9). Although there are no studies on the role of selectins in ALL chemoresistance, it is possible that P-selectin glycoprotein ligand 1 (PSGL-1) plays a similar role in ALL because PSGL-1 transcript levels are increased in B-ALL and T-ALL cells compared to normal lymphoblasts (28–30). The pan-selectin inhibitor GMI-1070 was tested in pre-clinical studies for the treatment of multiple myeloma (31). GMI-1271, an E-selectin antagonist selectively sensitized leukemia cells to chemotherapy while avoiding HSC mobilization (32), and is in phase 1/2 clinical trial for treatment of AML (Table 5).

Immunoglobulin superfamily

Members of the immunoglobulin superfamily (IgSF) are transmembrane glycoproteins possessing a structural immunoglobulin domain which perform multiple functions (33) (Table 10). IgSF family members CD28, CD147 (or EMMPRIN – extracellular matrix metalloproteinase inducer) and CD47 have been implicated in inducing chemoresistance in solid tumors or other hematological malignancies (Table 11). These proteins are also highly expressed in ALL, suggesting that further investigation is warranted to determine the role of IgSF family members in chemoresistance in ALL. Targeting CD47 by antibody reduced leukemic burden (34–37). Humanized anti-CD47 antibodies are currently in clinical trial for AML (38) (Table 5).

Other CAMs

Certain other CAMs, that do not belong to the four CAM families describe above also mediate chemoresistance (Table 12). CXCR4 is the most prominent CAM in this group. Plerixafor, a CXCR4 antagonist, is currently in clinical trials for the treatment of hematological malignancies including AML, CLL, multiple myeloma, and relapsed ALL (Table 5). Plerixafor (or AMD3100) treatment in combination with cytotoxic chemotherapy improved overall survival in pre-clinical studies (39–42) as well as in phase 1/2 clinical trials in acute leukemia (43,44). New drugs that also target CXCR4 are at various stages of development. POL5551, a novel CXCR4 antagonist, was found to be more effective than

plerixafor in pre-clinical models of high-risk ALL (45). Ulocuplumab (MDX-1338) is a humanized anti-CXCR4 antibody, which was efficacious as monotherapy in mouse xenografts and is currently in phase 1 trials for treatment of relapsed AML, CLL, non-Hodgkin lymphoma and multiple myeloma (46). GMI-1359, a dual CXCR4/E-selectin inhibitor, showed a 50% increase in survival in combination with cytarabine in pre-clinical mouse models of AML (47). Thus, reverting cell adhesion-mediated drug resistance by targeting CXCR4 has proven to be beneficial and is actively pursued in the clinic (Table 5).

Human anti-ICAM1 antibody (BI-505) bestowed enhanced survival to multiple myeloma bearing mice (48). A phase 1 dose-escalation study with BI-505 is completed, and it is ready for entering the next phase of clinical trials (49) (Table 5). Thalidomide and its analogue lenalidomide are immunomodulators that function as anti-TNFα agents, via the regulation of cell surface expression of key adhesion molecules like ICAM-1, VCAM-1, E-selectin and L-selectin thereby decreasing cell-cell interaction between T-ALL cells and umbilical vein endothelial cells (50,51). Lenalidomide is being used in clinical trials for the treatment of refractory and relapsed AML (52) (Table 5).

Ectoenzymes

Ectoenzymes are transmembrane proteins bearing their catalytically active sites on the extracellular cell surface (53). However, these proteins are known to have multiple functions including cell adhesion (Table 13). Further studies are warranted to distinguish the contribution of the enzymatic activities and cell adhesion properties of ectoenzymes in imparting chemoresistance.

Co-operation between different CAMs enhances chemoresistance

Association between different CAMs can constitute alternate mechanisms of chemoresistance. Chemokine receptor CXCR4 described above, complexes with integrin β_1 (CD29) and enhances adhesion and engraftment of ALL cells in the bone marrow (54). This complex formation also leads to the recruitment of an hERG1 channels in ALL cells co-cultured with mesenchymal stem cells resulting in downstream activation of PI3K/Akt pro-survival pathways and chemotherapy resistance (11). N-cadherin clustering on the cell membrane mediated by tetraspanin CD82 enhanced bone marrow trafficking of AML cells (55). Interaction between VLA-4 and CD44 in AML cells adhering to the stroma regulates chemotherapy efflux via ABC transporters, providing another cell-adhesion mediated drug resistance mechanism (56). Thus, collaboration between CAMs on the leukemic cell surface further strengthens the chemoprotective effect provided by the bone marrow microenvironment.

Soluble factors involved in chemoresistance

Soluble factors within the bone marrow microenvironment which contribute to chemotherapy resistance are listed in brief in the following section because the major focus of this review is CAMs and the intercellular interactions with other CAMs or the ECM components. Stromal cells are known to secrete soluble factors such as galectin-3, which are involved in imparting chemoresistance in hematological cancers (57–59) (Table 14). An example by which a secretory factor from ALL cells influences the bone marrow

microenvironment and modulates it to suit its benefit is connective tissue growth factor (CTGF). CTGF interacts with ECM and integrins, and promotes adhesion of B-ALL cells to stromal cells as well as stimulates proliferation of stromal cells and aids in chemoresistance (60). CTGF expression is high in pediatric and adult BALL (61,62) and higher CTGF expression corresponded with reduced overall survival (63).

Conclusion

Resistance to chemotherapeutics still remains a major cause of ALL relapse and poor prognosis. The importance of CAMs in conferring chemotherapy resistance in ALL is slowly becoming evident while the role of cell adhesion as an important mediator of disease pathology is unraveled. Although there are no ongoing clinical trials evaluating CAMs as therapeutic targets for ALL, this approach is being tested in clinical trials in other hematological disorders (Table 5). Activation of pro-survival and quiescence pathways initiated by the binding of CAMs on the leukemia cell surface to targets in the bone marrow microenvironment can be routes for cells to evade chemotherapy. Modulation or blocking of these adhesive interactions provides an opportunity for the design of novel targeted therapies in ALL. Although the majority of CAMs discussed here are also present on HSCs, there are a few CAMs whose expression is restricted to leukemic cells or which can have a greater effect on leukemic cells compared to normal HSCs. Targeting these specific CAMs should retain HSC function, while attacking leukemic cells. Further investigation on novel interactions will furnish opportunities for development of targeted therapy with minimal side effects.

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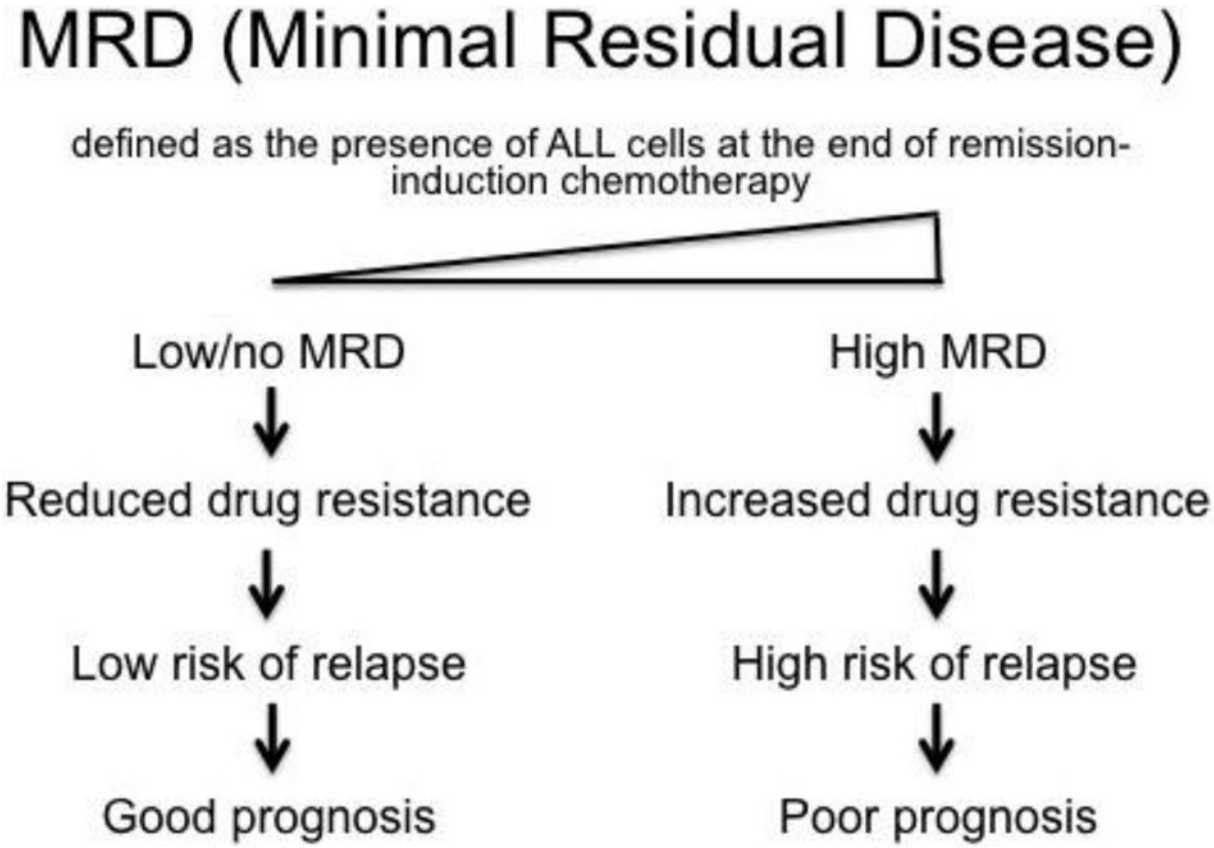

Fig. 1.
A schematic showing the significance of minimal residual disease in determining prognosis in ALL.

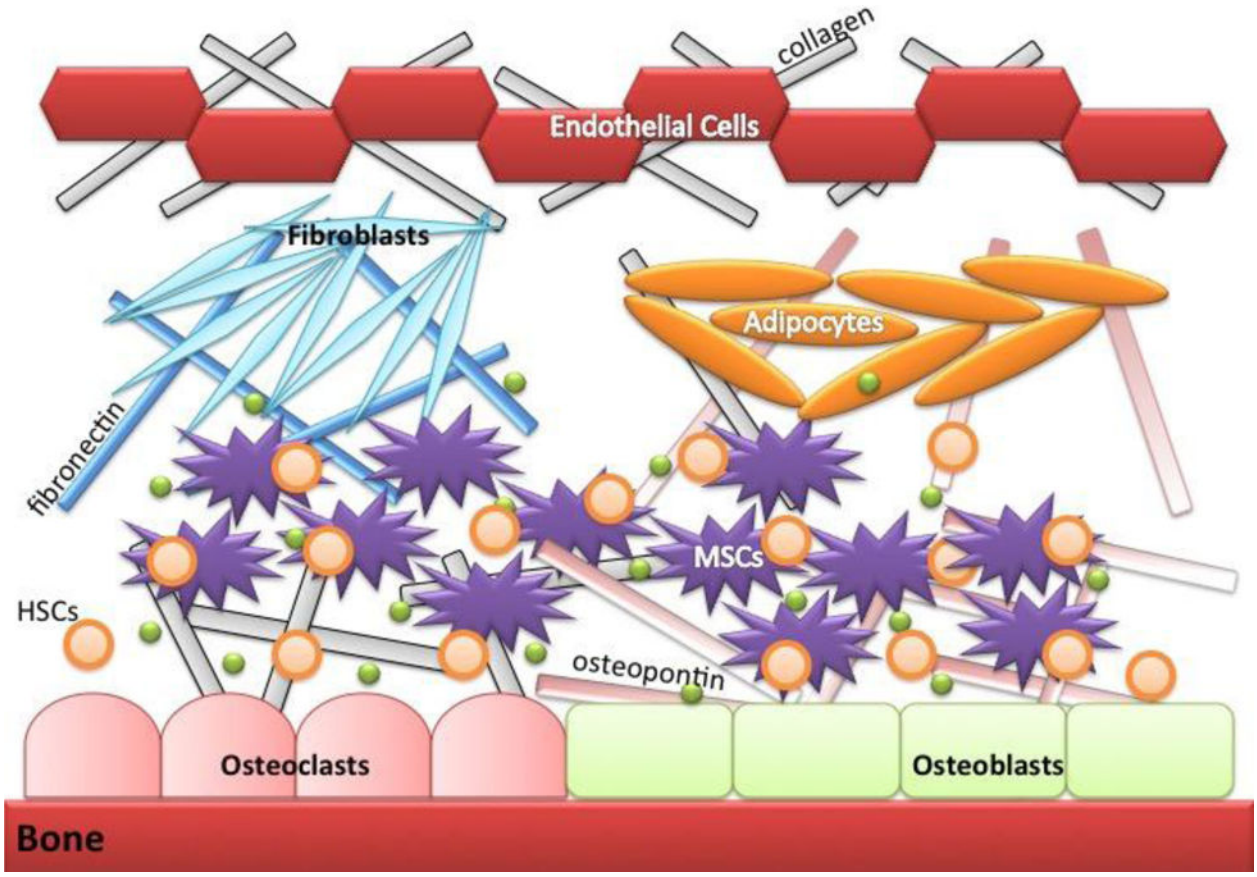

Fig. 2.

Pictorial representation of elements in the normal bone marrow microenvironment. The bone marrow microenvironment (BM) contains multiple cell types such as osteoblasts, osteoclasts, endothelial cells, mesenchymal stromal cells, fibroblasts and adipocytes that can interact with normal hematopoietic stem cells (HSCs) and control hematopoiesis and quiescence. ECM proteins, specifically fibronectin and osteopontin, and soluble factors such as SDF-1 and galectins (green spheres).

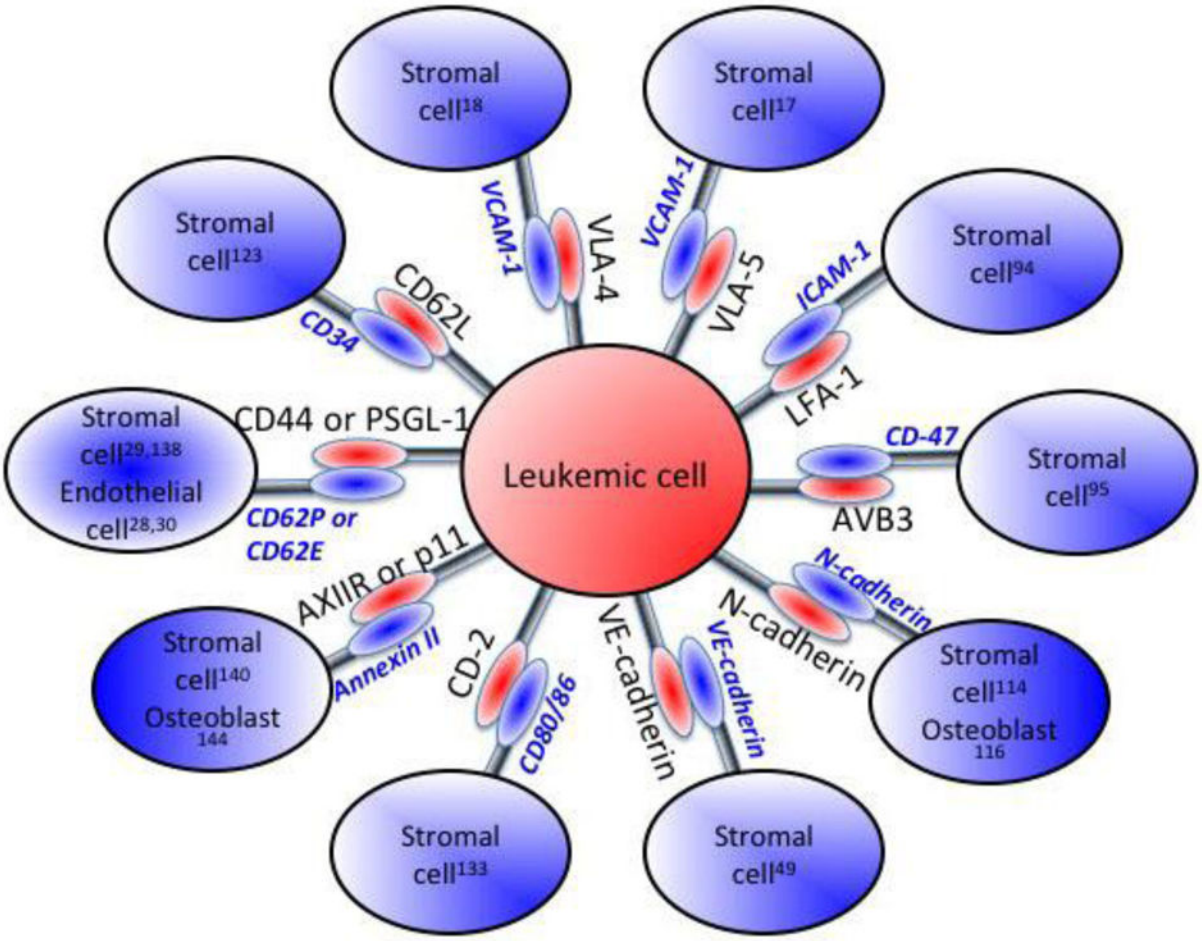

Fig. 3.

Pictorial representation of CAMs on leukemic cells and their cognate interacting partners on cells within the bone marrow microenvironment. The numbers in superscript correspond to the citation describing the particular interaction.

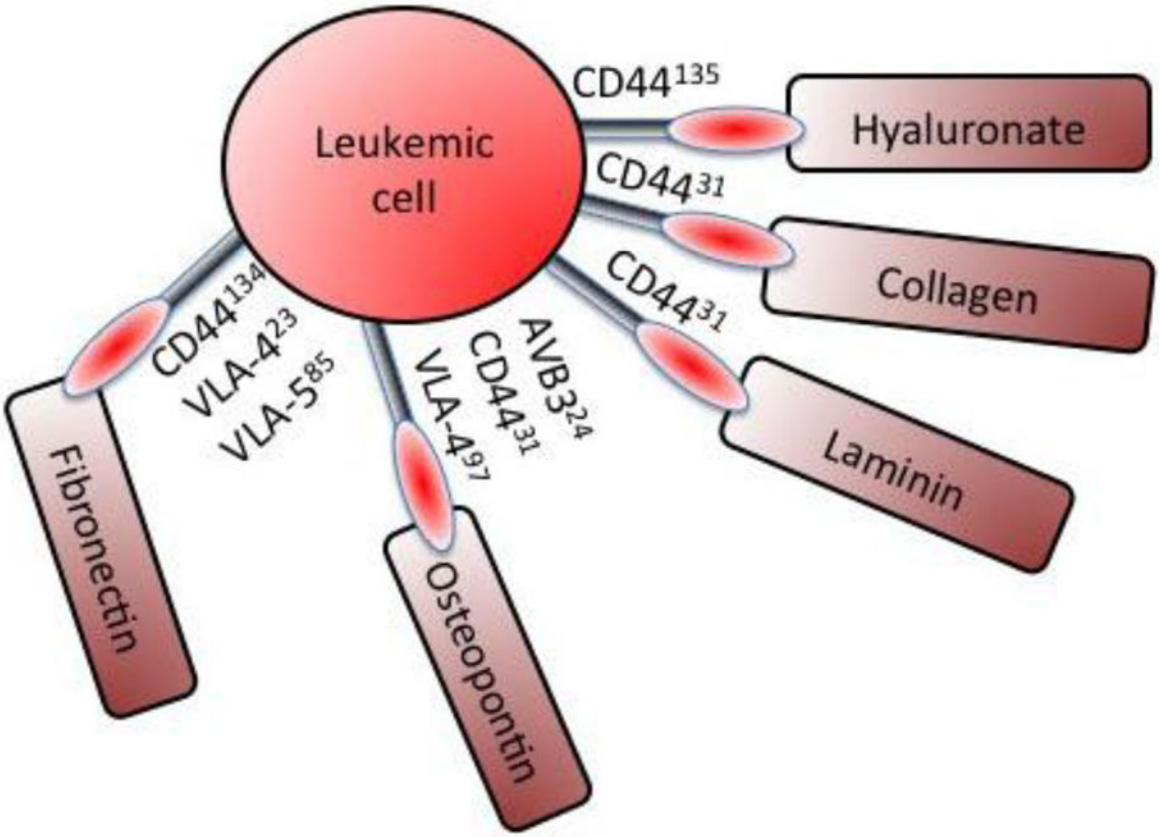

Fig. 4.

Representation of CAMs mediating ALL cell adhesion to different ECM proteins. The numbers in superscript correspond to the citation describing the particular interaction.

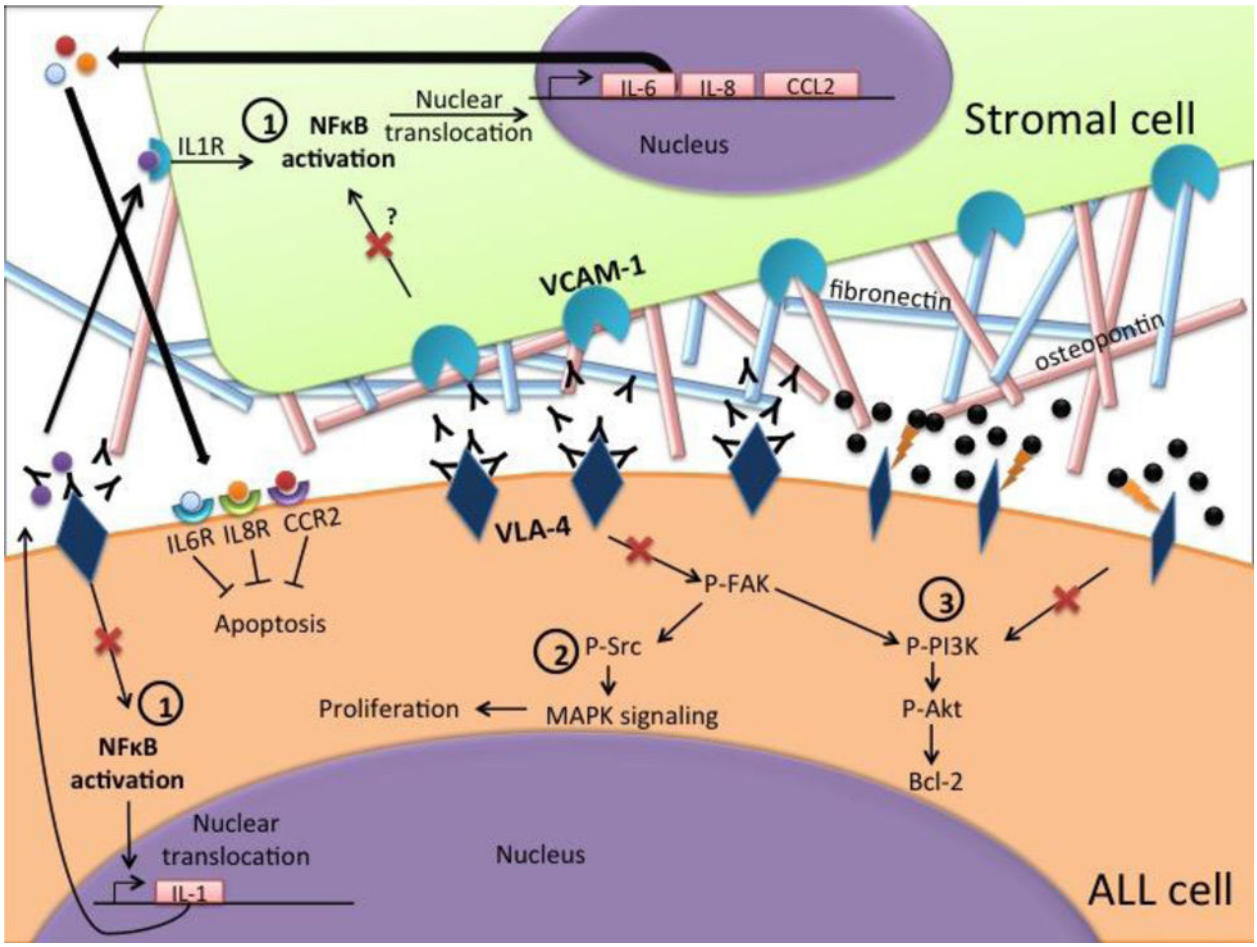

Fig. 5.

Pictorial representation of the mechanisms of drugs targeting VLA-4. VLA-4 binds to its target VCAM-1 on bone marrow stromal cells or to ECM proteins such as osteopontin and fibronectin. This interaction activates pro-survival signaling pathways such as 1) NF-κb, 2) Src/MAPK and 3) PI3K/Akt. Disruption of these interactions by Natalizumab (Black Ys), a monoclonal antibody that targets VLA-4, or AS101 (black spheres), which oxidizes adjacent thiol residues in the exofacial domain of VLA-4 molecules. This prevents target binding and causes cytoskeletal and conformational changes in the VLA-4 molecule, results in inhibition of these pathways (shown by red crosses).

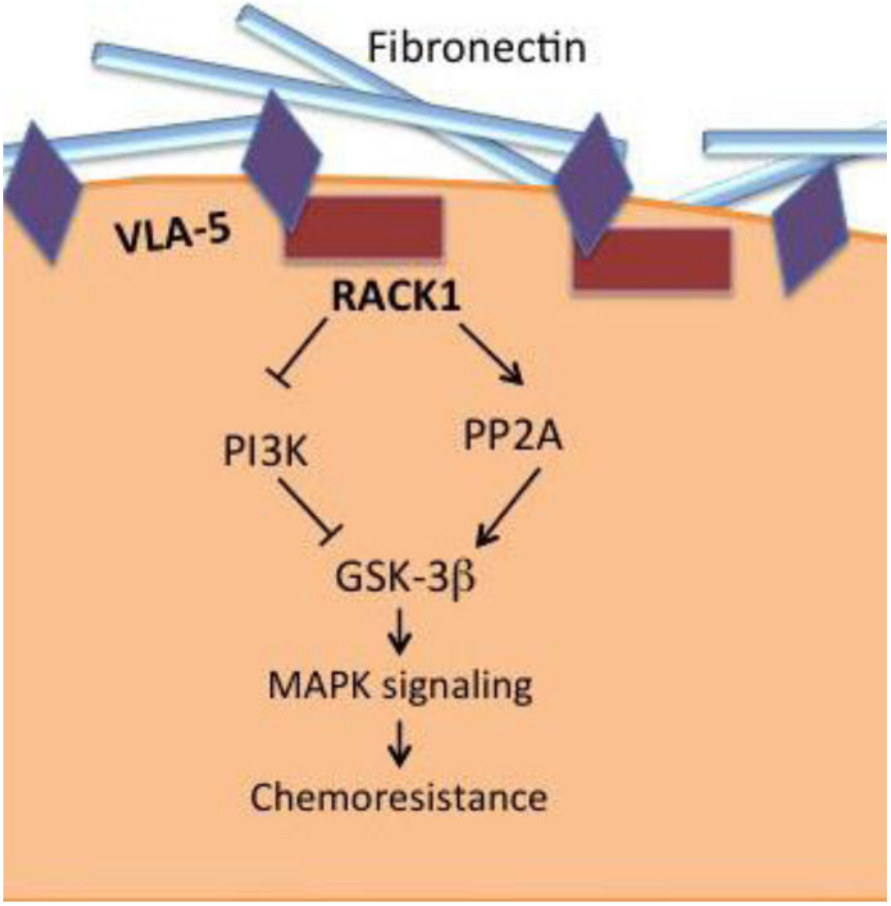

Fig. 6.

Pictorial representation of the signaling pathway activated by VLA-5 binding to fibronectin. This interaction mediates the binding of scaffolding protein RACK1 to VLA-5 which recruits protein phosphatase PP2A. PP2A dephosphorylates GSK-3β on Ser 9 resulting in its activation. Activated GSK-3β signals via MAPK pathway to induce chemoresistance.

Table 1

Mechanisms of drug resistance in leukemia

Chemoresistance mechanism	Example protein/pathway	Mode of action and drugs affected	Reference/s
Drug receptor downregulation or inactivation	Glucocorticoid receptor	Reduced expression, decreased activity, internalization or receptor mutations prevents drug activity and induction of apoptosis	(64,65)
Drug efflux	ATP-binding cassette (ABC) superfamily of transporters e.g. MRP3 in ALL	Transporters mediate active efflux of a broad spectrum of cytotoxic compounds thereby reducing intracellular drug accumulation and toxicity	(5,66–69)
Intracellular drug degradation	*NT5C2* cytosolic 5′ Nucleotidase II	Enzyme metabolizes and inactivates nucleoside analogs which constitute chemotherapeutic agents	(70,71)
Gene deletion/mutation	DCK/FPGS	Genetic deletions of DCK and FPGS prevent drug activation and lead to resistance against cytarabine and methotrexate respectively	(72)
Targeted protein modification	BCR/ABL	BCR/ABL kinase domain mutations confer resistance to imatinib treatments	(73)
Upregulation of proliferative proteins	A20	Overexpression of A20 leads to increased proliferation and anti-apoptotic effects in conjunction with MAPK signaling and p53 to confer chemoresistance	(74)
Cellular quiescence	Exit to G_0	Intracellular signaling causes an exit from cell cycle to G_0 and resistance to multiple drugs that are effective only on proliferating cells	(75)
Overexpression of negative regulators of apoptosis	GSTM1	Overexpression prevents the activity of apoptotic regulators like Bim	(76)
Ion flux	hERG1	hERG1 channel activity increased pro-survival signaling and conferred multidrug resistance	(11)
Redox adaptation	Antioxidant production and MCL-1	Increased mitochondrial calcium influx increases levels of reactive oxygen species, leading to an adaptation process that increases antioxidant and MCL-1 levels to induce multidrug resistance	(77)
Abnormal glucose metabolism	GLUT1	Increase in transporter expression increases glucose uptake and prevents cells from undergoing metabolic stress and defends against chemotherapy	(78)
Unfolded protein response	XBP1	Expression of XBP1 protects cells from ER stress and leads to chemoresistance	(79)
Increased protein expression of DNA repair proteins	Alt-NHEJ pathway	Increased activity of DNA repair pathway allows cells to repair more readily and protect against chemotherapy	(80)
Protein stabilization	p73	p73 stabilization by Kpm/Lats2 phosphorylation of YAP2 protected cells from DNA damaging chemotherapeutics	(81)
MicroRNA aberrations	miR125b/100/99a	Dysregulation of miRNAs can alter expression patterns of key proteins and lead to resistance against chemotherapy drugs like vincristine	(82)
Cell adhesion mediated drug resistance	Cell-cell/matrix adhesion	Binding of cellular adhesion molecules on the surface of ALL cells to other cells or the ECM in the BM stimulate a chemoprotective effect	(83,84)

Table 2

Physiological role of integrins with as putative role in chemoresistance

Integrin	Function in normal cells	Reference/s
Integrin $\alpha_4\beta_1$ or VLA-4 (very late antigen-4)	Leukocyte attachment, rolling and trans-endothelial migration at sites of inflammation	(85)
Integrin $\alpha_5\beta_1$ or VLA-5 (very late antigen-5)	HSC homing and adhesion	(86)
Integrin $\alpha_L\beta_2$ or LFA-1 (leukocyte function-associated antigen-1)	Leukocyte adhesion and recruitment to sites of infection. Promotes interaction between naïve T-cell and antigen-presenting cell for effective T-cell activation	(87) (88)

Table 3

Integrins implicated in chemoresistance in ALL

Integrin	Target Expression	Function in malignant cells	Reference/s
Integrin $\alpha_4\beta_1$ or VLA-4 (very late antigen-4)	Binds to VCAM-1 (vascular cell adhesion molecule-1) expressed on bone marrow stromal cells and osteoblasts	• VLA-4/VCAM-1 interactions required for engraftment of human B-ALL in immunocompromised mice • VLA-4/VCAM-1 interaction protected B-ALL cells from apoptotic cell death induced by variety of chemotherapy agents • These interactions activate pro-survival pathways such as PI3K/Akt • VLA-4/VCAM-1 interaction activated reciprocal NF-κb signaling in contacting ALL/AML cells and stromal cells • VLA4/VCAM-1 mediated adhesion to bone marrow stromal cells induced resistance to vincristine in lymphoma cells • VLA-4 played a critical role in CAM-DR in multiple myeloma cells	• (85,89) • (13,19–21,90) • (19) • (90) • (91) • (92)
Integrin $\alpha_5\beta_1$ or VLA-5 (very late antigen-5)	Also binds to VCAM-1 (vascular cell adhesion molecule-1)	• Bcr/Abl tyrosine kinase expressed by patients presenting with the Philadelphia chromosome stimulates VLA-5 function. • VLA-5 mediated adhesion to bone marrow stromal cells protected Ph+ ALL cells from imatinib-induced apoptosis • VLA-4/VCAM-1 interactions required for engraftment of Ph+ ALL in immunocompromised mice	• (93) • (94) • (94)
Integrin $\alpha_L\beta_2$ or LFA-1 (leukocyte function-associated antigen-1)	Binds to ICAM-1 (intercellular cell adhesion molecule-1) on bone marrow stromal cells	• LFA-1/ICAM-1 interaction enhanced the survival of T-ALL cells by decreasing the rate of apoptosis	• (95)

Table 4

Consequences of VLA4/5 Binding to fibronectin in normal and malignant cells

Cell type	Consequences	Reference/s
Normal cells	• Embryogenesis • Maturation of bone marrow progenitor cells • Maturation of thymocytes • Localization of sensitized T lymphocytes to antigenic sites	
B-cell ALL	• B-ALL cell adherence to fibronectin mediated by VLA-4 and VLA- 5 enhanced survival via Src/mitogen activated protein kinase pathway • Inhibition of VLA-5/fibronectin interaction in Ph+ B-ALL cells suppressed growth in combination with nilotinib	• (96) • (94)
T-cell ALL	• T-ALL cell adherence to fibronectin via VLA-4 or VLA-5 induced Akt activation and chemoresistance to doxorubicin-induced apoptosis	• (97)
Multiple Myeloma	• VLA-4 binding to fibronectin prevented drug-induced apoptosis induced by doxorubicin and melphalan	• (98)
CLL	• VLA-4 binding to fibronectin prevented fludarabine-induced apoptosis accompanied by increased Bcl-xL protein	• (99)
AML	• VLA-4 binding to fibronectin activated PI3K/Akt/Bcl2 signaling and prevented drug-induced apoptosis. • Impairing interaction of VLA-4 to fibronectin with FNIII14, a fibronectin-derived peptide, sensitized AML cells to cytarabine and reduced leukemic burden in mice • VLA-5 binding to fibronectin promoted resistance to tumor necrosis alpha induced apoptosis by activation of glycogen synthase kinase-3beta	• (100) • (101) • (102)
CML	• VLA-5 binding to fibronectin prevented apoptosis induced by BCR/ABL inhibitors, DNA damaging agents and gamma-irradiation	• (103)
T-cell ALL, AML, CML, Lymphoma	• Potentiated and sustained binding of VLA-4 to fibronectin induces apoptosis by inactivating ERK1/2 and Akt	• (104)

Table 5

Summary of clinical trials using compounds to modulate the expression of different CAMs.

Drug	Target	Disease	Mechanism	ClinicalTrials.gov Identifier	Reference
Natalizumab	VLA-4	Multiple myeloma	Monoclonal antibody	NCT00675428	
Natalizumab	VLA-4	B-ALL	Monoclonal antibody	Pre-clinical	(20)
AS101	VLA-4	Adult AML	Redox inactivation	NCT01010373	(22)
FNIII14	VLA-4	AML	Antagonism	Pre-clinical	(101)
TBC3486	VLA-4	B-ALL	Ligand-mimetic	Pre-clinical	(21)
LFA703	LFA-1	Multiple myeloma	Antagonism	Pre-clinical	(25)
GMI-1271	E-selectin	AML	Antagonism	NCT02306291	(32)
GMI-1359	CXCR4, E- selectin	AML	Antagonism	Pre-clinical	(47)
Hu5F9-G4	CD47	AML	Antagonism	NCT02216409	(38)
BI-505	ICAM-1	Multiple myeloma	Monoclonal antibody	NCT01025206	(49)
Plerixafor	CXCR4	AML	Antagonism	NCT00906945	(43)
Plerixafor	CXCR4	Acute leukemia	Antagonism	NCT01068301	(44)
MDX-1338	CXCR4	AML	Monoclonal antibody	NCT01120457	(46)
POL5551	CXCR4	High-risk ALL	Antagonism	Pre-clinical	(45)
Lenalidomide	ICAM-1, VCAM-1	Multiple myeloma	Downregulation of TNFα	NCT00772915	(105)
Lenalidomide	ICAM-1, VCAM-1	Acute AML	Downregulation of TNFα	NCT01615042	(52)

Table 6

Physiological role of cadherins involved in chemoresistance in hematological malignancies

Cell type/cadherin	Consequences	Reference/s
Endothelial cells/VE-cadherin (CD144)	• VE-cadherin regulates endothelial junction permeability and leukocyte extravasation.	• (106)
HSC/N-cadherin (CD325)	• N-cadherin may be involved in HSC maintenance and adhesion to osteoblasts.	• (107–109)
Epithelial cells/Fat1-cadherin	• Fat1 cadherin, the largest cadherin in the cadherin family, regulates actin dynamics at cell-cell contacts and leading edge	• (110)

Table 7

Role of cadherins in mediating chemoresistance in hematologic malignancies

Cell type/cadherin	Consequences	Reference/s
B-cell ALL/VE Cadherin (CD144)	• VE-cadherin expressed in Ph+ leukemia cells mediates chemotherapy resistance by increasing expression of β-catenin and in turn resulting in nuclear localization and activation of β –catenin • β-catenin/Wnt signaling pathway is essential for Ph+ leukemia stem cell survival, and has been identified as a contributor to chemoresistance in ALL	• (111–113) • (114–116)
B-cell ALL/N- Cadherin (CD325)	• N-cadherin is involved in adhesion of E2A-PBX1 positive B-ALL cells to stromal cells. • N-cadherin expression is increased in the population of Bcr/Abl transformed ALL cells that survive treatment with farnesyltransferase inhibitor in co-culture with fibroblasts • N-cadherin expression sufficient to induce chemoresistance in the population of Bcr/Abl transformed lymphoblastic leukemia cells • Gene expression profiling analyses have shown N-cadherin overexpression in B-ALL cells compared to normal lymphoblasts; N-cadherin could be exploited to specifically target ALL cells	• (117) • (118) • (118) • (28–30)
T-cell ALL/N- Cadherin (CD325)	• Gene expression profiling analyses has shown N-cadherin overexpression in T-ALL cells compared to normal lymphoblasts; N-cadherin could be exploited to specifically target ALL cells	• (28–30)
AML/N-cadherin (CD325)	• In AML patients, N-cadherin expressing leukemia stem cells were resistant to chemotherapy and greatly enriched following induction therapy • N-cadherin expressing AML stem cells engraft faster in NOD/SCID mice	• (119) • (120)
CML/N-cadherin (CD325)	• N-cadherin mediated adhesion in CML cells co-cultured with stromal cells protects CML cells from apoptotic cell death induced by treatment with tyrosine kinase inhibitors	• (121)
Multiple Myeloma/N-cadherin (CD325)	• N-cadherin blocking peptide, which completely disrupted interactions between N-cadherin on neoplastic cells with N-cadherin on stromal cells, induces widespread cell death in multiple myeloma cells	• (122)
B-cell ALL/Fat1 cadherin	• Overexpression of Fat1 cadherin in pediatric and adult B-ALL • High FAT1 mRNA expression associated with shorter relapse-free survival in pediatric B-ALL; Similar results were not observed in adult B-ALL or T-ALL • FAT1 is considered MRD marker since it is absent in hematopoietic progenitors • Mutations in *FAT1* gene have been identified in different cancers including ALL. • Some *FAT1* mutations in solid tumors prevented Fat1 cadherin binding to β-catenin resulting in deregulated	• (123–126) • (123,124) • (124,125) • (124,126,127) • (128)

Cell type/cadherin	Consequences	Reference/s
	activation of Wnt signaling pathway; the effect of these mutations in ALL is not characterized.	
T-cell ALL/Fat1 cadherin	• Overexpression of Fat1 cadherin in pediatric and adult T-ALL.	• (123–126)
CLL/Fat1 cadherin	• Fat1 cadherin mutated in fludarabine-resistant CLL samples	• (129)

Table 8

Physiological role of selectins

Cell type/selectin	Consequences	Reference
Endothelial cells/E-selectin and P-selectin	• B-cell extravasation into lymphoid tissue and inflammatory sites	(130)
T-cell/L-selectin	• Lymphocyte homing	(27)
HSC/E-selectin	• E-selectin expressed on bone marrow endothelial cells promotes HSC proliferation and imparts chemosensitivity	(131)

Table 9

Role of selectins in mediating chemoresistance in hematologic malignancies

Cell type/selectin	Consequences	Reference/s
AML/E-selectin	• E-selectin expressed on bone marrow endothelial cells induces quiescence and chemoresistance in AML cells	(132)
CLL/L-selectin	• L-selectin on CLL cells induces chemoresistance by mediating binding of CLL cells with bone marrow stromal cells	(133)
CML/L-selectin	• L-selectin and PSGL-1 are essential for homing and engraftment of Bcr/Abl+ chronic myeloid leukemia (CML) cells in the bone marrow niche	(134)
Multiple myeloma/P-selectin	• P-selectin on bone marrow stromal cells, endothelial cells and macrophages interacts with P-selectin glycoprotein ligand-1 (PSGL-1) on multiple myeloma cells to mediate homing, engraftment and chemoresistance	(31,135)

Table 10

Physiological role of immunoglobulin superfamily (IgSF) proteins

Cell type/IgSF	Consequences	Reference
HSCs/CD47	• CD47 binds to signal-regulatory protein-α on macrophages to prevent HSC phagocytosis	(136)
Leukocyte CD47	• CD47 also called integrin-associated protein (IAP) as it complexes with integrins and regulates leukocyte adhesion and migration to endothelial cells	(137)
T-cell/CD28	• T-cell activation	(138)

Table 11

Role of immunoglobulin superfamily (IgSF) members in mediating chemoresistance in hematologic malignancies

Cell type/IgSF	Consequences	Reference/s
T-ALL/CD28	• Functions as a T-cell co-stimulatory molecule with demonstrated role in T-cell proliferation, survival and differentiation • CD28 expression increased in Jurkat cells cultured in direct contact with stromal cells • CD28 is a target of Notch signaling known to play major role in microenvironment-induced drug resistance in TALL	• (138) • (139) • (140)
Multiple myeloma/CD28	• CD28 ligation to CD80/86 on bone marrow stromal cells activates PI3K/Akt signaling pathway leading to increased survival and protection from chemotherapy	• (141)
CLL/CD47	• CD47 promotes drug resistance in solid and hematological cancers	• (142,143)
ALL, AML/CD47	• CD47 is overexpressed in leukemia and is considered an indicator of poor prognosis • CD47 on AML cells allows AML cells to escape phagocytosis	• (34,35) • (34)
B-ALL/CD147	• CD147 is overexpressed in B-ALL samples collected at diagnosis from patients who suffered relapse • CD147 expression is further elevated in samples collected at relapse and also in B-ALL cells invading central nervous system • CD147 has numerous binding partners – CD147 itself, E-selectin, CD44, cyclophilins and integrins. • CD147 is also expressed on stromal cells	• (144) • (145) • (146,147) • (148)
Lymphoma/CD147	• CD147 plays an important role in drug resistance in other hematological malignancies such as murine lymphoma	• (149–151)

Table 12

Role of other CAMs in mediating chemoresistance

Cell type/CAM	Consequences	Reference/s
B-ALL/CD9	• CD9 is overexpressed in B-ALL • It is a key mediator of ALL cell dissemination via C-X-C chemokine receptor type 4 (CXCR4)/Rac1 mediated migration and plays a significant role in homing and engraftment of B-ALL cells to the bone marrow and the testes • CD9+ cells had increased tumorigenic potential, self-renewal capacity, and drug resistance in B-ALL	• (28,30) • (152) • (153)
Lung cancer, small cell/CD9	• CD9 mediates chemoresistance by modulating avidity of integrin β_1 leading to increased cell adhesion; whether CD9 behaves similarly in ALL remains to be determined	• (154)
HSC/CD44	• CD44 or homing cell adhesion receptor is involved in HSC adhesion	• (155)
Lymphocytes/CD44	• CD44 binds to endothelial cells and ECM components such as fibronectin to mediate lymphocyte recruitment to lymphoid organs	• (156,157)
B-ALL and AML/CD44	• CD44 expression is strongly augmented in ALL and is directly correlated with higher rates of relapse, suggesting its role in chemoresistance	• (158–160)
Multiple myeloma/CD44	• CD44 variant 9 splice isoform binds to stromal cells and is correlated with unfavorable prognosis	• (161)
ALL/CXCR4	• CXCR4 binds to stromal-derived factor 1 (SDF1) secreted by bone marrow stromal cells and induces calcium influx, integrin-mediated adhesion, chemotaxis and migration, and homing and engraftment in the bone marrow • CXCR4/SDF1 axis triggers multiple signaling cascades such as JAK/STAT, PI3K/Akt, Src, Ras/Raf/MEK/ERK providing defense against chemotherapy • CXCR4 is required for leukemia initiating activity and T-ALL cell migration • A small molecule competitive antagonist of CXCR4 – plerixafor acts as a chemosensitizing agent by mobilizing neoplastic cells from the bone marrow sanctuary	• (162) • (162,163) • (163,164) • (165)
Multiple myeloma/ICAM1	• ICAM1 binding to CD18 activated Src, ERK1/2 and c- myc pathways resulting in macrophage mediated drug resistance	• (135)
HSC/Annexin II	• Annexin II is a peripheral membrane protein expressed on stromal cells, osteoblasts and endothelial cells in bone marrow involved in HSC homing and engraftment	• (166)
Multiple myeloma/Annexin II	• Annexin II binding to annexin II receptor increases cell adhesion and promotes growth in the bone marrow	• (167)
B-ALL/Annexin II	• Annexin II interaction with p11 is required for ALL cell homing and engraftment and induces chemoresistance	• (168)

Table 13

Role of ectoenzymes in mediating physiological functions and chemoresistance

Cell type/ectoenzyme	Consequences	Reference/s
B-ALL/CD10, neutral endopeptidase	• CD10 is overexpressed in nearly half of B-ALL cases with sustained expression during relapse. • CD10 inhibits focal adhesion kinase and prevents the turnover of cell-matrix contacts • CD10 expression in ALL cells is positively correlated with the presence of an ion channel hERG1 (human ether-a-go-go related gene 1), which is associated with chemotherapy resistance	• (169) • (170) • (11)
Head and neck squamous cell carcinoma/ CD10	• CD10 has also been identified as a marker for therapeutic resistance and as a cancer stem cell marker	• (171)
CML/CD26, dipeptidyl peptidase 4	• CD26 identified as a cancer stem cell marker in several cancer types including CML	• (172)
Lymphoma/CD26	• CD26 regulates adhesion by modulation of integrinβ_1 phosphorylation via p38 MAPK	• (173)
T-ALL/CD26	• CD26 expression restricted to aggressive pathological entities such as T-ALL; however its role in ALL is not well studied	• (174)
T-ALL/CD73, ecto-5′- nucleotidase	• CD73 generates extracellular adenosine, interacts with death receptor, inhibits TRAIL-induced apoptosis and induces multi-drug resistance • CD73 is highly expressed in ALL and used for MRD monitoring	• (175) • (176)
CLL/CD73	• CD73 activity reduced drug-induced apoptosis	• (177)

Table 14

Role of soluble factors secreted by stromal cells in mediating chemoresistance

Cell type/soluble factor	Consequence	Reference/s
Galectin-3, galactose-binding lectin	Galectin-3 implicated in the development of chemoresistance in several solid as well as hematological cancers	(59)
B-ALL/Galectin-3	Galectin-3 protects ALL cells by auto-induction of galectin-3 mRNA and activation of the NFκB pathway and Wnt/β-catenin signaling pathway	(178,179)
Ph+ B-ALL/Galectin-3	Galectin-3 transcript levels upregulated in Ph+ B-ALL cells that had developed resistance to tyrosine kinase inhibitor nilotinib	(180)
CML/Galectin-3	Galectin-3 induced multi-drug resistance by activation of Akt and ERK and preventing apoptosis	(181)
Multiple myeloma/Galectin-3	Galectin-3 implicated in chemoresistance mechanisms	
Chemoprotective factor/ALL	This soluble factor induces an increase in calcium influx into mitochondria, which leads to an increase in reactive oxidation species (ROS) in ALL cells. Cells respond by undergoing a redox adaptation to decrease ROS, thereby reducing ALL sensitivity to drug treatment	(77)
Chemoprotective factor/AML	This soluble factor promotes chemoresistance by blocking the activity of equilibrative nucleoside transporter (ET1) which regulates cytarabine incorporation inside the cell	(182)