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REVIEW

CXCL12/CXCR4 axis in the pathogenesis of acute lymphoblastic leukemia (ALL): a possible therapeutic target

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Abstract Acute lymphoblastic leukemia (ALL) is the commonest childhood malignancy, accounting for approximately 80 % of leukemia in the pediatric group, and its etiology is unknown. This neoplasia is characterized by male predominance, high-risk features and poor outcome, mainly in recurrence patients and adults. In recent years, advances in the success of childhood ALL treatment were verified, and the rate of cure is over 80 % of individuals. However, there is a considerable scope for improving therapeutic outcome in this neoplasia. Improvements in ALL therapy might readily be achieved by developing additional biomarkers that can predict and refine prognosis in patients with ALL. In normal hematopoietic cells, cytokines provide the stimulus for proliferation, survival, self-renewal, differentiation and functional activation. Abnormalities of cytokines are characteristic in all forms of leukemia, including ALL. The stromal cell-derived factor-1 (SDF-1 or CXCL12) is a member of the CXC chemokine family that binds to CXC chemokine receptor 4 (CXCR4). The CXCL12/CXCR4 axis appears to play a role in dissemination of solid tumors and hematopoietic diseases. Understanding the mechanisms by which ALL cells are disseminated will provide additional information to expand therapeutic approach. Therefore, this review summarizes information relating to ALL cell biology, focusing specifically in a cytokine receptor important axis, CXCL12/CXCR4, that may have implications for novel treatment strategies to improve life expectancy of patients with this neoplasia.

Keywords Acute lymphoblastic leukemia · CXCL12 · CXCR4 · Therapeutic target

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Introduction

Acute lymphoblastic leukemia (ALL) is characterized by the monoclonal and/or oligoclonal proliferation of hematopoietic precursor cells of the lymphoid series within the bone marrow (BM) [61]. It occurs in approximately 6,000 individuals per year and results in approximately 1,400 deaths annually in the United States [73]. In Brazil, according to National Cancer Institute (INCA), leukemia represents between 25 and 35 % of all cancer types, and ALL is the most frequent in children aged from 0 to 14 years. Furthermore, INCA 2012 annual report estimates 5.050 new cases of leukemia in men and 4.320 in women [32].

Following lymphocyte profile, two subtypes of ALL malignant cells may be involved, T cell (T-ALL) and B cell (B-ALL) [57]. T-ALL accounts for 15 % of ALL, and it is identified by male predominance, high-risk features including high white blood cell (WBC) count, mediastinal enlargement, generalized lymphadenopathy, central nervous system involvement, and poor outcome [58, 62].

In T-ALL, T cell transformation is a multi-step process in which different genetic alterations cooperate to alter the normal mechanisms that control cell growth, proliferation,

survival, and differentiation during thymocyte development. Particularly, deletions of the *CDKN2A* locus in chromosome 9p21, which encompasses the *p16/INK4A* and *p14/ARF* suppressor genes, are present in more than 70 % of all T-ALL cases [22, 30]. Moreover, constitutive activation of NOTCH1 signaling comprises the core of the oncogenic program in the pathogenesis of T-ALL [87], cooperating with loss of *p16/INK4A* and *p14/ARF* in T cell transformation [82].

T-ALL is more aggressive than B-ALL, and limited therapeutic options are available for patients with primary resistant or relapsed disease, highlighting the urgency for treatment stratification protocols and identification of more effective antileukemic drugs [63]. This imperative was further supported by studies of the long-term effects of intensified chemotherapy in T-ALL survivors, which showed that improvements of leukemia-free survival have been achieved in parallel with significant increases in rates of acute and chronic life-threatening and debilitating toxicities [3].

B-ALL, especially B-cell precursor (BCP)-ALL, is the major form of the disease, accounting for approximately 85 % of all pediatric ALL [31]. Perturbation of B-cell differentiation in the BM must lead to B-ALL development, considering that its microenvironment provides a variety of cytokines, chemokines, growth factors and adhesion molecules that coordinately regulate B-cell development [35].

Most childhood cases of B-ALL may be subclassified by the presence of either gross or submicroscopic genetic alterations, such as aneuploidy or recurring gross chromosomal rearrangement, which are frequent in approximately 75 % of B-ALL cases [27, 63]. These rearrangements commonly perturb genes encoding regulators of hematopoiesis, tumor suppressors, oncogenes, or tyrosine kinases, but commonly it requires additional genetic hits to establish the full leukemic phenotype.

A number of chromosomal rearrangements are common in B-ALL and are critical events in leukemogenesis. Hyperdiploidy is one of the most frequent alterations in childhood ALL and is associated with favorable outcome [28]. At least five extra chromosomes are presently associated; however, the biologic basis of the acquisition of multiple chromosomal gains is poorly understood. Conversely, hypodiploidy, with fewer than 44 chromosomes, is associated with dismal prognosis [52].

Studies have identified new subtypes of ALL, and uncovered recurring submicroscopic genetic alterations in known ALL subtypes. These include loss-of-function mutations involving genes regulating lymphoid development that contribute to the arrest in maturation characteristic of B-ALL, mutations that inactivate tumor suppressor and cell cycle regulatory proteins, and mutations that drive cytokine receptor and/or kinase signaling. Concomitant lesions disrupting hematopoietic development and tumor suppression as well as driving signaling and proliferation are hallmarks of many ALL subtypes.

Importantly, several of these alterations are associated with specific subtypes of ALL defined by chromosomal alterations and different treatment outcome [51]. The translocations t(9; 22), expressing chimeric protein BCR-ABL, and t(4; 11), codifying MLL-AF4 protein, are related to poor prognosis. Patients with chromosomal alteration t(1; 19), related to E2A-PBX1 fusion protein, and t(12; 21), characterizing *TEL-AML1*, have a good treatment outcome [72, 75]. Contrariwise, T-ALL are derived from precursor T cells in the thymus, and infrequent but recurrent translocations lead to the overexpression of the transcription factors LYL1, HOX11, HOX11L2, and TAL1 [75]. Using gene expression profiling, Yeoh et al. [89] identified molecular markers to distinguish T-ALL subtypes with increased risk of relapse. In addition, they indicated that contemporary risk stratification fails to identify many patients who are at high risk of drug-induced toxicities or marrow relapse.

In the last years, advances of childhood ALL treatment have been achieved, with over 80 % of individuals cured [63]. This rate is supported by the accurate assignment of individual leukemia subtypes, in which genetic alterations figure primarily in most classification schemes [89]. However, a poor prognosis is still expected for a group of patients with various risk factors, such as central nervous system involvement, and those with ALL relapses. Einsiedel et al. [21] have demonstrated that more than one-third of patients may be cured from recurrent ALL with second complete remissions lasting more than 10 years. They also concluded that immunophenotype and time point of relapse are important prognostic factors that allow adapting more precisely treatment intensity to individual prognosis.

Despite the success in cure and survival rates, there is still scope for improvements, since ALL treatment is more likely to cause short- and long-term side effects, and some patients may experience relapse. Furthermore, studies about leukemic cells and niche correlation highlight the importance of therapeutically targeting the BM microenvironment [33].

In normal hematopoietic cells, cytokines provide the stimulus for proliferation, survival, self-renewal, differentiation and functional activation. Abnormalities of cytokine and growth factor signaling pathways are characteristic of all forms of leukemia: lymphoid and myeloid, acute and chronic. These pathways are usurped to sub serve critical parts of the malignant program in leukemic cells [81].

The stromal cell-derived factor-1 (SDF-1 or CXCL12) is a member of the CXC chemokine family that counteracts

with its cognate receptors CXC chemokine receptor 4 (CXCR4), widely expressed in numerous tissues, including immature osteoblasts and endothelial cells within BM, epithelial cells in many organs, central nervous system and hematopoietic cells, to stimulate physiological processes [13]. CXCL12/CXCR4 signaling is essential in maintaining the progenitor hematopoietic cell pool, and also regulates hematopoietic stem cells attachment within the bone marrow niche [80].

Ayala et al. [1] outlined that a high expression of CXCR4 by leukemic blasts and activation of the CXCL12/CXCR4 axis is involved in leukemia progression and disruption of normal hematopoiesis. Moreover, in this particular, leukemia-associated bone microenvironment markers could be used as prognostic or predictive indicators of ALL progression and/or treatment outcome.

Since chemokines and their receptors have been implicated in the pathogenesis of many diseases, including cancer risk and disease progression, this work reviewed the CXCL12/CXCR4 axis in the pathogenesis of ALL and its role as a possible therapeutic target.

Chemokine CXCL12 and its receptor CXCR4

CXCL12 monomer proteins are expressed in all human cells, except in blood cells. To date, at least six CXCL12 splicing variants were described named α, β, γ, δ, ε and ϕ, and the former is the most abundant and smallest, consisting of three exons instead of four, as others do. However, CXCL12β is twice as potent in the blood, exhibiting very similar activity to CXCL12α [34].

The proteolytical degradation process of both ends regulates CXCL12 constitutive expression [15]. Degradation of N-terminus occurs in the blood and the tissues, abolishing chemokine activity and reducing its affinity to the receptor. It is splicing variant-dependent and occurs slowly. Contrariwise, C-terminus proteolysis is rapid, splicing variant-dependent, and does not cease CXCL12, but reduces its activity, occurring specifically in the blood [34].

CXCL12 plays an important role in migration of progenitor and leukemic cells to the BM [66]. Its expression by endothelial cells along with endosteum regions of BM mediates not only homing and retention of progenitor cells, but is important for their trans-endothelium migration through the expression of E-selectin [54].

ALL arises from malignant transformation of lymphocytes, undoubtedly in a single BM site; however, the spread to essentially all BM cavities, resulting in extensive disease, may have occurred by the time of diagnosis. In addition, ALL cells also infiltrate the liver, spleen, lymph nodes, and central nervous system [14]. Chemokines and theirs receptors, in which CXCL12/CXCR4 axis is supposedly involved, tightly regulate this migration process. Indeed Tokoyoda et al. [79] demonstrated the B lymphocyte location and movement between specific niches within BM during development is maintained by CXCL12 interactions in that niche.

CXCL12 may contribute to leukemic marrow infiltration by increased CXCR4 expression and migratory response in BM-derived blasts compared with circulating cells [48]. In fact, CXCR4 is one of several chemokine receptors defined by their ability to induce cell migration toward a chemotactic cytokine gradient. This receptor has been investigated in breast cancer pathogenesis [20, 56], and several reports have addressed the expression and biological role of CXCR4 at different stages of B-cell development in normal and malignant hematopoiesis.

In immature B cells, CXCL12 stimulus induces activation of small GTP-binding protein (GTPases) such as Ras-related C3 botulinum toxin substrate 1 (Rac1) [59], leading to co-location of CXCR4 and small GTPase Rac1 into membrane lipid rafts, which is necessary for cell migration in response to a CXCL12 gradient [88]. Freret et al. [23] demonstrated that inactivation of Rac1 can interfere with the mechanisms involved in receptor internalization modulating the chemotactic response to CXCL12 by regulating internalization of CXCR4, and thus, it might play a role in B-ALL cell dissemination.

Shen et al. [70] and Spiegel et al. [74] have demonstrated that down regulation of CXCR4 following exposure to high doses of CXCL12 results in significant inhibition of ALL cell homing to the BM. However, stromal cells also secrete fibronectin, a component of the extracellular matrix that enhances CXCL12-induced migration of ALL cells without influencing CXCR4 expression [67].

The role for CXCL12/CXCR4 axis in the infiltration of extramedullary sites, which commonly expresses significant levels of CXCL12 [50] is supported by the association between high expression of CXCR4 by ALL cells and extramedullary organ invasiveness [14], and inhibition of extramedullary disease by treatment with CXCR4 antagonists [37]. So, binding of CXCL12/CXCR4 is one of the key interactions between human ALL cells and BM stroma, and high expression of the chemokine receptor CXCR4 is of predictive value for early relapse in ALL childhood [68].

Pediatric patients who had B-ALL and high CXCR4 expression had significantly more prominent liver or spleen infiltration compared with patients who had low CXCR4 expression [14]. Kato et al. [39] verified that hepatomegaly in ALL patients are not only due to random infiltration but rather, the result of CXCL12/CXCR4 axis-dependent migration and expansion of leukemic cells in the hepatic niche. These data indicate that this axis stimulates not only migration but in addition, proliferation of ALL leukemic

cells in vivo and in vitro, further, targeting the extramedullar microenvironment components to prevent recurrence from minimal residual disease.

Besides its crucial role in migration, there are reports indicating that CXCL12 may play a role in the pathogenesis of malignant tumors [17, 19], including leukemia [18, 55]. In this context, the primary role of CXCL12 seems to be facilitating metastasis or mobilizing tumor cell, and perhaps the establishment of cancer stem-like cell within the tumor microenvironment, where high levels of CXCL12 recruit a highly tumorigenic population of tumor cells, promoting cell survival, proliferation, angiogenesis, and metastasis.

Our research group have evaluated polymorphic mutations and gene expression of *CXCL12* and *CXCR4*, aiming to elucidate their roles in the pathogenesis of cancer, with a focus on hematological diseases. de Oliveira et al. [18] verified that *CXCL12* polymorphic alleles have implications in CML pathogenesis. de Oliveira et al. [19] studied the same SNP (rs1801157) in *CXCL12* gene, although in Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL), suggesting that this genetic variant may have important implications in this neoplasia subtype. de Oliveira Cavassin et al. [17] compared the same allelic variant between patients with lymphoid leukemias and lymphomas and indicated that Brazilian lymphoma patients are more likely to carry the polymorphic allele for *CXCL12* gene, indicating a differential role for this gene in subgroups of hematological diseases. Recently, de Lourdes Perim et al. [16] verified the positive association for *CXCL12* (rs1801157) and susceptibility to childhood ALL.

CXCL12/CXCR4 axis in ALL signaling

The molecular mechanism underlying CXCL12/CXCR4 signaling has been investigated extensively and revealed that multiple molecules are activated upon CXCL12 stimulation [74]. Firstly, the activation pathway of CXCL12/CXCR4 initiates after ligand CXCL12 sensitizing CXCR4, inducing receptor internalization and promoting an increase of cytoplasmic calcium store and mobilization levels.

The interaction with CXCR4 occurs between its 8 first amino acids residues in the N-terminus: the first two take part in receptor activation while further six are involved in the binding of the chemokine to the receptor. On the cell surface, CXCL12 binding to CXCR4 must be stabilized through the interaction with glycoseaminoglycans (GAGs), such as heparin sulfate, and this is responsible for leukocyte accumulation and prevention of CXCL12 proteolytic degradation [34]. Furthermore, association to GAGs can induce CXCL12 oligomerization, which in turn, promotes CXCR4 oligomerization, enhancing its activation function [10].

CXCR4 is a G-protein coupled receptor, which is composed by an intracellular heterotrimer of Gα, Gβ and Gγ subunits, bound to a guanine nucleotide GDP, in its basal state. CXCL12 ligand binding activates the receptor, and GDP is replaced by GTP, which in turn dissociates the βγ dimer. The Gα monomeric subunit can relay different GPCR signal, depending on the type of α monomer present and activated: $G\alpha_i$, $G\alpha_s$, $G\alpha_q$ and $G\alpha_{12}$ [77].

Chemokine receptors are typically coupled $G\alpha_i$ proteins which act inhibiting adenyl cyclase, whereas $G\alpha_s$ stimulates adenyl cyclase [25]. $G\alpha_i$ also stimulates kinase activity of the Src family tyrosine-protein kinase c-Src, binds to the catalytic domain, and changes the conformation of c-Src. In turn, c-Src phosphorylates the adaptor Shc, recruiting GRB2 and activating the H-Ras/c-Raf-1/MEK1-2/ERK1-2 pathway. This activated pathway increases the transactivation ability of transcription factor Elk1 and repressed STAT3 transcription factor [12, 43].

Contrariwise, activated CXCR4 enables the recruitment of STAT3 by the phosphorylation of Janus quinase 2 (JAK2), activating the downstream pathway of Stats, mitogen-activated protein kinase (MAPK) and phosphatidilynositol 3-kinase (PI3K)-Akt pathway [44]. In addition, its signal induces the activation of protein kinase C and phosphorylation of dual threonine and tyrosine recognition kinase (MEK), extracellular signal-regulated kinase (ERK) and components of focal adhesion complexes in many cell types, including B-cell precursors [6, 24, 85].

Moreover, calcium flux has been used to determine chemokine activity in cells. However, $G\alpha_i$ does not promote this flux, but $G\alpha_q$, suggesting that CXCR4 might hold other Gα proteins [65]. In addition, Gβγ subunit can trigger phospholipase C (PLC) activation and formation of diacylglycerol (DAG) and phosphatidilynositol 3 (IP3), resulting in Ca^{2+} mobilization from intracellular stores [46].

Chemokines and their receptors are involved in cell trafficking. Indeed, CXCL12-CXCR4 axis can mediate chemotaxis of multiple cell types, including lymphocytes, hematopoietic stem cells, endothelial and epithelial cells, and cancer cells [2, 76]. This process is mediated by the activation of PI3 kinase (PI3K) by both Gα and Gβγ subunits, leading to phosphorylation of considerable adhesion molecules, such as paxilin, focal adhesion kinase (FAK), proline-rich kinase-2 (Pyk-2), Crk substrate p130Cas, Crk, and Crk-L, Nck [85, 90].

Differences in the signaling mechanisms employed by ALL cells and normal hematopoietic stem cells (HSC) heightened the possibility of differential regulating traffic of ALL cells and thereby providing novel therapeutic applications. While both normal HSC and B cell

progenitors shared a dependence on PI3K signaling [41, 90], B-ALL leukemic cells demonstrated only a minor involvement of this pathway, with dominant signaling through mitogen-activated protein kinases (p38MAPK) [6, 38].

Zhang et al. [90] demonstrated that cytoplasmic tyrosine kinase, JAK2, is involved in CXCR4 receptor-mediated signaling through PI3K and seems to be required for CXCL12-induced migration of hematopoietic progenitor cells. These results suggest that JAK2 is required for the tyrosine phosphorylation of multiple focal adhesion proteins, and for cell migration in hematopoietic progenitor cells.

The expression of CXCL12 imposes a survival potential for hematopoietic cells due to activation of PI3K-AKT-NFκB and MAPK pathways [5, 85]. In addition, it has also been shown that signal transducer and activators (STATs) are activated upon binding of CXCL12 to CXCR4 [40, 83].

Signalling through PI3K is likely necessary for CXCL12-induced activation of very late antigen 4 (VLA-4) and increased adhesion of cells to vascular cell adhesion molecule 1 (VCAM-1) and fibronectin [70]. Moreover, it has been shown that VLA-4 function is essential for BM homing of B-ALL leukemic cells [70, 74].

The participation of MAPK pathway, through PKC or $G\alpha_i$, signaling to Erk1/2, Ras-activated signaling pathway, Src-related kinases (Src, Lyn, Fyn and Lck), T-cell activation molecule ZAP-70, and small GTPases have also been implicated in lymphocyte migration [6, 46, 77], suggesting that multiple signaling molecules might be accessed to support CXCL12/CXCR4 activation. However, the evidence of which of them are most important or which pathway is essential for inducing homing or migration in different ALL subtypes remains an unresolved issue.

Apparently, CXCL12/CXCR4 axis may not be directly involved in T-ALL leukemic cells signaling. Nonetheless, the analysis of the intracellular signaling profile of T-ALL patients has revealed that activation targets of CXCL12/CXCR4 signaling pathway, such as PI3K-Akt, MAPK and JAK-STAT, are implicated in oncogenic processes [11]. Thus, it is reasonable that some ALL subsets would benefit from strategic therapy concerning CXCL12/CXCR4 pathway and its derivatives.

The CXCL12/CXCR4 axis as a potential therapeutic target

The treatment of ALL is based on multidrug therapy with adjustment for risk of disease recurrence. The administered drugs include corticosteroids, metastasis inhibitors, asparaginase, antraciclics, alkylating agents, antimetabolites, and purine antagonist [4]. The remission induction therapy for ALL patients should include a glucocorticoid, vincristine, and asparaginase, not only because they are not myelosuppressive, but also because their antileukemic effects are different, and their mechanisms may act synergistically. Prednisone has been the most frequently used glucocorticoid treatment at this stage. However, dexamethasone has better results in patients with T-ALL, and appears to allow better control of the central nervous system invasion [64].

Lack of efficacy in the current treatment can be partly attributed to the fact that leukemia cells are protected by their microenvironment. Leukemic cells residing in BM niches are provided with favorable conditions for their growth and survival [8, 53] and thereby escape from chemotherapy-induced death [47]. In this context, several studies suggested that chemokine analogues or antagonists could be used in parallel with conventional therapies to improve ALL treatment. For example, Buonamici et al. [9] demonstrated that targeting the CCR7 receptor in T-ALL could block their CNS dissemination.

Additionally to the evidence that BM stromal niche can protect ALL cells against the cytotoxicity of chemotherapeutic agents, it is also a possible source of relapse. Since CXCL12/CXCR4 axis is a major determinant in the crosstalk between leukemic cells and BM stroma, the development of new drugs and approaches for the treatment of relapse remain an important goal to improve cure rates [60]. Kato et al. [39] showed that functions of the niche are maintained by CXCL12/CXCR4 axis, proposing a novel therapeutic approach targeting by inhibition of these molecules. It was demonstrated that liver dissemination of leukemia is not due to nonselective infiltration, but rather systematic invasion and proliferation of leukemic cells in hepatic niche. These findings formed the basis for therapeutic approaches that target extramedullary niche by inhibiting CXCL12/CXCR4 axis.

Mowafi et al. [49] demonstrated that the addition of recombinant CXCL12 increases proliferation of B-ALL cells in culture and induces a decreased internalization of CXCR4 receptor on the surface. However, this process does not interfere in cell proliferation. They believed that CXCL12 in childhood ALL deserves further study to clarify both the role of this chemokine in the pathogenesis of ALL and the possibility of modulating signaling directed by CXCL12.

The CXCR4 could be a potential therapeutic target, since it has been shown that this receptor neutralization enhances apoptosis and decreases proliferation in an experimental model of human non-Hodgkin's lymphoma (NHL) [7]. Konoplev et al. [42] concluded that the activated form of CXCR4 [26, 71] is directly related to metastasis progression and provides independent prognostic information in adult patients with ALL, independently

of other prognostic parameters. This observation is potentially important in both clinically and therapy as anti-CXCR4 has currently been evaluated and can be added into chemotherapy protocols designed for ALL patients. Hatse et al. [29] showed that a small-molecule CXCR4 antagonist, bicyclam or AMD3100, inhibited CXCR4 internalization, the calcium influx and chemotaxis of ALL cells. Kato et al. [39] developed a therapeutic model where AMD3100 prevented repopulation of extramedullary ALL cells after chemotherapy and dramatically improved overall survival in mice treated with AMD3100. They found that without AMD3100 administration, some leukemia cells remain in the portal region of liver after chemotherapy, contributing to leukemia relapse.

CXCR4 antagonists have been used in combination with chemotherapy in preclinical and clinical studies, which have demonstrated that blocking CXCR4 may be a novel promising approach. CXCR4 antagonists can theoretically be more effective in remission patients, as part of maintenance therapy, to destroy the residual leukemia stem cells. However, the biology of the residual leukemia stem cells after chemotherapy is different, and the targeting agents may be ineffective. Further studies that combine CXCR4 antagonists with chemotherapy in patients in complete remission are needed [77].

Some authors have proposed that CXCR4 could be a potential therapeutic target (Table 1). In this context Juarez et al. [36] demonstrated that polyphemusin II peptide analogues T140, T134 and TC14012, and AMD 3100 are potent inhibitors of CXCL12-mediated chemotaxis and BM stromal-dependent proliferation of precursor B-ALL cells. In other study, they examined the ability of CXCR4 antagonists to disrupt the interaction between precursor B-ALL cells and their supportive niche in vivo, and found that blocking CXCL12/CXCR4 interactions resulted in rapid mobilization of leukemic cells into the peripheral blood and in significant expansion reduction of precursor B-ALL, in a mice model [37].

Although higher levels of CXCR4 expression have been shown to correlate with poor patient survival, effective drugs affecting cell surface CXCR4 expression are still unknown. Matsumoto et al. [45] examined the effects of a synthetic retinoid Am80 on CXCR4 expression of cultured T-ALL cells. They observed that it inhibited surface CXCR4 expression and CXCL12-induced chemotaxis by the acceleration of CXCR4 internalization. Therefore, Am80 may be an effective drug to inhibit the extramedullary infiltration of T-ALL cells.

Disruption of ALL cell microenvironmental interaction could be used to enhance the effectiveness of chemotherapeutic agents due to loss of protection by the stroma. The treatment with AMD3100 causes maintenance of leukemic cells in peripheral blood for a longer time than normal hematopoietic progenitors, prolonging exposure to chemotherapeutic agents. Finally, AMD3100 increases the proportion of cells in the circulation that are actively cycling, a factor that is likely to increase sensitivity to cell cycle dependent agents commonly used for ALL treatment, such as vincristine [86].

Among other cytokines, IL-8 is highly expressed in T-ALL cells refractory to chemotherapy. The involvement of transcription factor NFκB is of particular interest as a key molecule in the establishment of T-ALL and, consequently, inhibiting agents are considered attractive candidates to T-ALL treatment. The IL-8 could be one NFκB target gene involved in the progression of T-ALL and the characterization of molecular mechanisms leading to IL-8 upregulation could be relevant to elucidate the development of T-ALL and design new therapeutic strategies [69]. It was demonstrated that NFκB and AP-1 transcription factors activity are central to induced IL-8 expression. [84].

Parameswaran et al. [60] demonstrated that the survival of mice bearing human and murine ALL cell lines could be extended by the combination of a CXCR4 antagonist AMD11070 and chemotherapy. It could represent an additional target to conventional chemotherapy treatments, without, however, replacing them. Within this context, CXCR4 has emerged as a promising therapeutic target, although further studies and consideration are required. In some way, it is plausible that inhibiting CXCR4 would result in mobilization of leukemic cells within circulation, which could cooperate to extramedullary invasion.

Understanding the mechanisms by which ALL cells disseminate may provide information to benefit developing

Table 1 Chemokine Receptor CXCR4 as a Target in ALL treatment

Drug	Model	Country	Year	References
AMD3100[a]	Human and murine	Belgium	2002	[29]
T140, T134, TC140012 and AMD3100[a]	Human and murine	Australia	2003	[36]
AMD3100[a] and TC140012	Human and murine	Australia	2007	[37]
Am80	Human	Japan	2010	[45]
AMD3100[a]	Murine	Japan	2011	[39]
AMD11070 (AMD070 or 070)	Murine	USA	2011	[60]
AMD 3100[a]	Murine	Australia	2013	[86]

[a] Plerixafor® or Mozobil™

therapeutic strategies based on targeting the ALL cell trafficking. Nevertheless, blocking CXCL12/CXCR4 axis could represent an important mechanism on managing therapeutic approaches in ALL.

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