Molecular Pathways: Targeting the microenvironment in chronic lymphocytic leukemia—focus on the B-cell receptor

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Running title: B-cell receptor targeting in CLL

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Abstract

Interactions between malignant B lymphocytes and the tissue microenvironment play a major role in the pathogenesis of chronic lymphocytic leukemia (CLL) and other B cell malignancies. The coexistence and coevolution of CLL cells with their tissue neighbors provided the basis for discovery of critical cellular and molecular drivers of the disease and identification of new therapeutic targets. Bone marrow stromal cells, monocyte-derived nurselike cells, and T cells are key players in the CLL microenvironment, which activate and protect CLL cells within the tissues. CLL surface molecules, such as the B cell antigen receptor (BCR), chemokine receptors, adhesion molecules, and TNF receptor superfamily members (e.g. CD40, BCMA, BAFF-R) engage in cross talk with respective tissue ligands. This cross talk results in survival and expansion of the CLL clone, and protects CLL cells from conventional cytotoxic drugs. Inhibiting these pathways represents an alternative therapeutic strategy to more conventional chemo-immunotherapy. Here, we review central components of the CLL microenvironment, with a particular emphasis on BCR signaling, and we summarize the most relevant clinical advances with inhibitors that target the BCR-associated kinases SYK (fostamatinib), BTK (ibrutinib), and PI3Kδ (idelalisib).
Background

**Anatomy of the CLL microenvironment**

CLL cells recirculate between peripheral blood and tissue compartments, (i.e. the bone marrow and secondary lymphatic organs), where they proliferate in distinct tissue areas termed “proliferation centers” or “pseudofollicles”. Proliferation in these pseudofollicles accounts for a daily birth rate of approximately 1 - 2 % of the entire clone, as determined by deuterated water labeling (1). Studying the cross talk between CLL and tissue stromal cells led to the discovery of key mechanisms involved in CLL homing, proliferation, and survival, providing a rationale for therapeutic targeting of the CLL - stroma crosstalk (Figure 1 and Table 1).

Tissue stromal cells, such as stromal cells and monocyte-derived nurselike cells are critical elements of the tissue microenvironment in CLL, and the latter share lineage and function with lymphoma-associated macrophages described in other B cell malignancies. Mesenchymal stromal cells, such as bone marrow stromal cells, provide “feeder” layers for hematopoietic progenitor cells and are part of hematopoietic stem-cell niches in the normal bone marrow. They protect CLL cells from spontaneous and drug-induced apoptosis in a contact-dependent fashion (2, 3). These interactions not only take place in the marrow, mesenchymal stromal cells also are commonly found in secondary lymphatic tissues in CLL patients (4), where they can provide survival and migration signals to CLL cells. In contrast, nurselike cells spontaneously develop in vitro from monocytes in CLL peripheral blood mononuclear cell cultures (5), where they
form feeder layers and maintain CLL cell viability by activating numerous surface receptors and signaling pathways. Nurselike cells can be found in lymphoid organs from CLL patients (6, 7), and gene expression profiles of CLL cells after co-culture with nurselike cells (8) are highly similar to those of CLL cells isolated from CLL lymph nodes (9), suggesting that nurselike cells are a highly relevant model system for studying the microenvironment.

Stromal cells constitutively secrete chemokines which organize CLL cell trafficking and tissue homing (10) and provide additional signals that support survival and growth and protect CLL cells from drug-induced apoptosis. Not only CLL cells benefit from bone marrow stroma contact, the stromal cells in turn also become activated by the CLL cells, with induction of protein kinase C (PKC)-βII expression and subsequent NF-κB pathway activation (11). In vivo, nurselike cells are found in lymphoid organs from CLL patients (6) and activate pro-survival signaling pathways in CLL cells (8). Nurselike cells attract and protect leukemic CLL cells through secretion of chemokines (CXCL12 (5) and CXCL13 (7)), support their survival via expression of the TNF family members BAFF and APRIL (12), and promote CLL disease progression, as demonstrated in recent CLL animal models (13, 14). The similarity between nurselike cells -induced gene expression profiles (GEP) in CLL cells (8) and GEP of CLL cells isolated from lymphatic tissues (9) suggests that nurselike cells are a valid and probably the best model system to imitate the in vivo microenvironment.

**T and NK cells**
CLL cells influence T-cell and NK-cell composition and function in the microenvironment to escape from immune-mediated cytotoxicity (15) (see Table 1). Contact between T cells (either T helper CD4+ or cytotoxic CD8+ lymphocytes) and CLL cells prevents appropriate immune synapse formation by inducing changes in cytoskeletal gene transcription (16) and defective actin polymerization and T cell motility (17, 18), which can be restored by revlimide (16, 17). Increased expression of inhibitory receptors (e.g. PD-1) on T cells from CLL patients and high numbers of CD4+CD25high T regulatory cells in the CLL microenvironment may contribute to increased evasion from antitumor immunity (15). CD8+ cytotoxic T cells have an exhausted phenotype and fail to establish cytotoxic immune synapses, with impaired granzyme B packaging and impaired degranulation (18). NK-cell mediated antitumor activity is also limited, as NK cells from CLL patients express low levels of the activating receptor NKp30 (19, 20) and show reduced cytotoxicity in response to soluble BAG6 ligand produced by CLL cells (19). Taken together, it is evident that CLL cells actively shape an immune-protected environment, where the leukemia cells can escape immune-mediated destruction.

**CLL tissue homing: role of chemokines and adhesion molecules**

CLL cells traffic between peripheral blood and tissues is organized by chemokines that are secreted by tissue stromal cells, attracting CLL cells via corresponding chemokine receptors. CXCR4 is the receptor for the chemokine CXCL12 (previously called stromal cell-derived factor-1 or SDF-1), which is
constitutively secreted by bone marrow stromal cells. CXCL12 regulates CXCR4 surface expression through receptor endocytosis (21), resulting in low CXCR4 surface expression in the presence of high CXCL12 tissue levels. CXCR4 activation causes actin polymerization, CLL cell chemotaxis, transendothelial migration and tissue homing (21). High CXCR4 expression on CLL cells is associated with a higher degree of lymphoid organ infiltration (22). Furthermore, CLL cells expressing high levels of the intracellular adaptor ZAP-70 (23), CD38 (24) or VLA-4 integrins (25) display higher migratory potential towards CXCL12. VLA-4 integrins cooperate with chemokine receptors and CD38 (26) in CLL cell adhesion to stromal cells (27). In addition, high CD38 (28) and VLA-4 (29) expression are also predictors of an inferior clinical outcome, supporting the notion that disease aggressiveness is linked to tissue homing and adhesion of CLL cells. Another layer of complexity is added by chemokines secreted by CLL cells in response to activation. BCR triggering and nurselike cell-contact induces secretion of CCL3 and CCL4 (8), and co-stimulation through CD40 ligand engagement by CD40+ T cells induces CCL17 (30) and CCL22 (30, 31). Increased CCL3 plasma levels correlate with poor outcome and are an independent prognostic marker in CLL (32), demonstrating the relevance of CLL-produced chemokines. CCL17 and CCL22 induce transendothelial migration of activated T cells (30), but the function of these chemokines in CLL pathogenesis remains ill defined. The function of CCL3 and CCL4 is better defined; these chemokines attract CD4+ T cells and monocytes to activated B cells (33), contributing to normal B or CLL cells support at tissue sites (34).
**B-cell receptor signaling in CLL**

There is accumulating evidence to support that B cell antigen receptor (BCR) signaling plays a key role in CLL pathogenesis (35-37). The BCR (Figure 2) is composed of the antigen-specific surface membrane immunoglobulin (smIg), and Ig-α/Ig-β hetero-dimers (CD79A, CD79B). Antigen binding to the smIg induces phosphorylation of ITAMs in the cytoplasmatic tails of CD79A and CD79B by LYN. This, in turn, activates SYK, BTK, and PI3Kδ kinases and downstream pathways, including calcium mobilization, activation of phospholipase C gamma 2 (PLC-γ2), PKCβ, NF-κB signaling, MAP kinases and nuclear transcription. The precise mechanism triggering BCR activation, for example the importance of ligand (antigen)-dependent and –independent (autonomous) signaling remains controversial, but indirect and some more direct evidence points towards the central role of the BCR. First, the prognostic importance of the mutational status of immunoglobulin heavy-chain variable (IGHV) genes indicates that CLL BCRs encounter antigens, which ultimately promote a certain degree of somatic hypermutations, which in turn influences the clinical behavior of the disease. Secondly, the expression of quasi-identical (“stereotyped”) BCRs among different CLL patients suggests that a set of common antigens contributed to the stereotypy of the BCR in individual patients. Thirdly, GEP studies demonstrated that BCR signaling is the key regulatory pathway activated in CLL cells in lymph nodes, the sites of CLL cell proliferation (9).
Naïve B cells develop in the bone marrow and are characterized by the presence of a functional surface immunoglobulin of the M isotype (sIgM). Further maturation takes place in secondary lymphoid organs, where naïve B cells undergo further maturation, including expression of immunoglobulins of the D isotype (sIgD) (38). As CLL cells show features of mature B cells, most of them express surface immunoglobulins of both M (sIgM) and D isotypes (39, 40). Previous studies suggested a dominant role of sIgM signaling (39, 40) and differential responsiveness to IgM stimulation was demonstrated for CLL cases carrying unmutated immunoglobulin heavy chain (IGHV) genes (U-CLL) versus mutated IGHV (M-CLL). U-CLL cases typically are more responsive to BCR triggering, with activation of robust intracellular signaling, whereas cells from M-CLL patients generally are less responsive to BCR cross-linking (39). Prolonged ERK kinase activation after sIgM triggering supports expression of the proto-oncogene MYC (40), suggesting that IgM signaling promotes cell cycle entry and CLL cell growth. The role of sIgD signaling is less defined. The majority of CLL clones appear to respond to IgD triggering (39, 40), and anti-IgD responsiveness was described to impact prognosis (41). Given that both IgM and IgD BCRs have the same antigen specificity, we currently assume that both, sIgM- and sIgD-derived signals govern overall BCR pathway activation. The caveat with interpreting these in vitro data, however, remains that they are based on somewhat artificial modes of BCR activation, relaying on generally high concentrations of soluble or immobilized BCR ligands used for CLL cell stimulation, which likely differs from in vivo BCR ligation.
In addition, the BCR signaling is modulated by receptor endocytosis, signaling of positive (e.g. CD19) and negative (e.g. CD5, CD22) regulatory co-receptors, intracellular kinases (e.g. SYK, BTK and PI3K) and phosphatases, (e.g. FcβRIIIb, SHIP, SHP-1 and PTPN22 (42)), which fine-tune the functional outcome of BCR signaling (35) (Figure 2).

Regarding potential antigens responsible for BCR stimulation in CLL, several studies suggested that ligand-dependent BCR signaling is a main mechanism. Generally, BCRs from U-CLL cells have low-affinity binding to a broader range of self-antigens, whereas affinity-matured BCRs from M-CLL cases have high-affinity binding to restricted, more specific antigens (43-45). Recently, defined epitopes within the BCR third complementarity-determining region of the heavy chain (HCDR3) have been described as targets of BCR (self-)recognition in CLL, representing an alternative form of auto-antigen (46, 47). This form of autonomous BCR signaling likely contributes to CLL growth and survival, in concert with extrinsic BCR ligands. In contrast to ABC subtype diffuse large B-cell lymphoma, CLL cells have no activating mutations within BCR signaling components. The variability and complexity of BCR signaling in CLL is mirrored by variable levels of activation of BCR downstream signaling molecules, including LYN (48), the cytoskeletal protein HS1 (48, 49) and ERK kinase (50).

Clinical-translational advances

The current standard of care for younger patients with CLL is chemo-immunotherapy, and one of the most commonly used regimens is FCR
(fludarabine, cyclophosphamide, rituximab). The inferior outcomes in subsets of patients, especially those with high-risk cytogenetics (i.e. del17p) and poor tolerability of chemo-immunotherapy in patients over the age of 70 (which is the majority of CLL patients) has promoted the introduction of additional agents including ofatumumab, alemtuzumab, or bendamustine, and prompted the development of alternative therapeutics that target interactions between CLL cells and the microenvironment, including lenalidomide, inhibitors of BCR signaling, and chemokine receptors.

**Targeting BCR-associated kinases BTK, PI3Kδ, and SYK**

BTK, PI3Kδ, and SYK kinases are rapidly activated following BCR triggering, but also involved in other pathways, such as chemokine and integrin signaling, they promote signal transduction to downstream partners, and regulate actin polymerization, cell-cell and cell-matrix adhesion and chemokine secretion (CCL3, CCL4). BTK, PI3Kδ, and SYK knock-out mouse models show deficiencies in B cell development and function, supporting the development of specific inhibitors that target these kinases (51). Several orally bioavailable inhibitors are currently tested in clinical trials in CLL patients, generating excitement because of promising responses and benign side effect profiles (52, 53).

BTK is a non-receptor tyrosine kinase of the Tec family, and is rapidly activated by both LYN and SYK kinases upon BCR engagement, resulting in the activation of NF-κB signaling, B-cell proliferation and differentiation. In addition,
BTK is also involved in regulation of migration and adhesion via CXCR4/CXCR5 and integrin signaling (54). Ibrutinib, previously called PCI-32765, is an irreversible BTK inhibitor that blocks BTK kinase phosphorylation and activity. Ibrutinib alone induces only modest CLL cell apoptosis in vitro, but it is capable of overcoming pro-survival signals derived from nurselike cell-contact, CD40 ligation, BAFF, fibronectin, IL-6, IL-4, TNFα (55) and BCR stimulation (56). Ibrutinib inhibits CLL cell proliferation (56), chemotaxis towards CXCL12 and CXCL13 (56, 57), integrin-mediated adhesion (57) and CLL cells release of CCL3 and CCL4, in vitro and in CLL patients receiving therapy with ibrutinib (56). Ibrutinib also reduces tumor burden in mouse models of human CLL (56, 58). The results of a phase 1b-2 multicenter study conducted on 85 patients have recently been published and show high rates of durable remissions in patients with relapsed or refractory CLL, including patients with high-risk genetic lesions (52). Early lymphocytosis and organomegaly reduction was observed, followed by lymphocyte count normalization, which occurred more frequently and more rapidly in patients carrying unmutated IGHV genes. The estimated progression-free survival rate was 75% at 26 months, with an overall survival rate of 83%. Ibrutinib is currently explored in combination with either chemotherapy or monoclonal antibodies to shorten lymphocytosis and to increase complete remission rates (59). Whether higher response rates translate into longer progression-free survival will be critical for further development of combination strategies.

PI3Ks are divided into 3 classes (I through III) and class I is further
composed by four different isoforms (α, β, γ, δ). PI3Ks regulate several cellular functions, including survival, migration and cell growth after BCR, chemokine receptor and integrin signaling activation. The predominant form expressed by hematopoietic cells is PI3Kδ, which plays a critical role in B-cell homeostasis and function. Idelalisib, previously called GS-1101 or CAL-101, is a reversible, highly selective PI3Kδ inhibitor (60). Similar to BTK inhibition, PI3Kδ inhibition is not very effective in causing high levels of apoptosis in unstimulated CLL cells (55), but it effectively thwarts survival signals from microenvironmental triggers, such as nurselike cell- contact (61), CD40 ligation, TNFα, fibronectin and BCR stimulation (55, 60), and reduction of CLL cell chemotaxis towards CXCL12 and CXCL13 (61). In addition, CCL3/4 release by CLL cells was reduced by idelalisib in vitro and in patients receiving idelalisib therapy (61). Similar to patients receiving ibrutinib therapy (52, 62), patients receiving idelalisib show early lymphocytosis after treatment start, due to CLL cell redistribution from tissues into the blood. Reduced CLL cell adhesion to stromal cells may promote their mobilization to the peripheral blood early after treatment start; once in the peripheral circulation, reduced responsiveness to CXCL12 and CXCL13 may interfere with CLL-cell tissue homing. Subsequently, the lack of pro-survival signals in the peripheral blood ultimately sensitizes CLL cells to apoptosis.

SYK belongs to the SYK/ZAP70 family of nonreceptor kinases, and activates signaling pathways downstream of the BCR, chemokine and integrin receptor, suggesting that SYK participates in tissue homing and retention of activated B cells. Fostamatinib (FosD, R788) is an orally available inhibitor of
SYK and rapidly converts in vivo into the bioactive form called R406 (63). R406 inhibits CLL cell migration, chemokine secretion and BCR signaling (64) and inhibits tumor growth in a CLL mouse model (65). On the clinical side, partial responses in a number of relapsed CLL patients were reported in phase I/II study (66), but further development of this drug focused on rheumatoid arthritis (67). Additional SYK-specific inhibitors are under development and preclinical testing, showing effective inhibition of CLL cell survival and response to microenvironmental cues (68).

**Targeting the CXCR4-CXCL12 axis**

The CXCR4-CXCL12 axis is an attractive therapeutic target, based on the importance of CXCR4 signaling for tissue homing, adhesion and survival of CLL cells (12, 21, 69). Several classes of CXCR4 inhibitors have been developed, including small molecule CXCR4 antagonists (Plerixafor; T140 analogs), small molecule CXCL12 antagonists (NOX-A12) and antibodies to CXCR4 (MDX-1338/BMS 93656). CXCR4 antagonists inhibit CXCL12-induced signaling, chemotaxis, and stromal-cell mediated drug resistance (70). One of the early concerns in clinical development of these inhibitors was their capacity to mobilize normal hematopoietic stem cells (71), which may result in increased toxicity if cytotoxic drugs are used in combination. However, no major hematotoxicity of plerixafor in combination with chemotherapy was observed in patients with relapsed acute myelogenous leukemia (72). In a recent Phase I clinical trial in relapsed CLL patients, patients were treated with rituximab in combination with
plerixafor, and a plerixafor dose-dependent mobilization of CLL cells from the tissues into the blood was reported (73). Given the robust and sustained mobilizing effects of BCR kinase inhibitors (BTK, PI3Kδ, SYK inhibitors) (52, 62) it is unclear in which setting the more specific CXCR4 or CXCL12 antagonists may have advantages.

Conclusions and perspective

A plethora of cellular and molecular players in the CLL microenvironment promote the survival and evolution of CLL leukemic cells. Over the past few years, the clinical success of kinase inhibitors targeting BCR-associated kinases put the spotlight on the CLL microenvironment. The rapid translational development of these agents, along with basic discoveries, identified BCR signaling as a central patho-mechanism, and BCR-related novel biomarkers that predict disease progression and response to therapy with these novel agents. The BTK inhibitor ibrutinib and the PI3Kδ inhibitor idelalisib induce highly encouraging responses in CLL and will change the landscape of CLL therapy, and already have changed our view of CLL disease biology. The redistribution of CLL cells from tissue sanctuaries into the peripheral blood represents a peculiar clinical activity of these new drugs and provides a rationale for combination treatment with B cell-directed antibodies that generally have limited activity in tissue sites. That notwithstanding, as some patients may become refractory to treatment and eventually relapse after initial response to these novel agents, a
more complete understanding of the *in vivo* mechanisms of action of these drugs and of the relationships between CLL cells and the immune microenvironment is needed, in order to identify additional survival pathways responsible for drug resistance and treatment failure.
References
12. Nishio M, Endo T, Tsukada N, Ohata J, Kitada S, Reed JC, et al. Nurselike cells express BAFF and APRIL, which can promote survival of


Figure 1. The CLL microenvironment. A) In the CLL microenvironment, CLL cells interact with bone marrow stromal cells (BMSC) and nurselike cells (NLC) through adhesion molecules and chemokine receptors, expressed on CLL cells. These interactions, in addition to B-cell receptor engagement, promote CLL survival, proliferation and B cell homing to tissues. B) CD4+ T cells are recruited into the tissue microenvironment by CLL cell-derived chemokines, including CCL3 and CCL4, to support CLL cell survival and proliferation. Inhibitory receptors expressed by CLL cells induce defective immune synapse formation between CLL and normal T cells. Cytotoxic granule secretion by CD8+ T cell also is defective and production of soluble factors by CLL cells suppresses NK cell cytotoxicity, favoring immune-evasion of CLL cells.

Figure 2. B-cell receptor signaling pathway. Schematic representation of the B-cell receptor (BCR) signaling pathway and small-molecule kinase inhibitors utilized to interfere with BCR signaling.
Table 1. Cellular components of the CLL microenvironment.

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<th>Function in normal immune responses</th>
<th>Function in CLL microenvironment</th>
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<td><strong>Bone Marrow Stromal cells (BMSC)</strong></td>
<td>Formation of hematopoietic stem-cell niches and regulation of hematopoiesis; constitutive secretion of CXCL12 and various other hematopoietic chemokines.</td>
<td>Tissue retention of CLL cells [2]; CLL cells drug resistance [2] and protection from apoptosis [2]; PKC-βII activation in BMSCs induced by CLL cells [4]</td>
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<tr>
<td><strong>Nurselike cells (NLC)</strong></td>
<td>Not applicable</td>
<td>Tissue retention of CLL cells [3]; CLL cells drug resistance [3] and protection from apoptosis [3]; CLL cell attraction by CXCL12 and CXCL13 production [3]; BAFF and APRIL expression [11]; activation of BCR and NF-kB pathway genes in CLL cells [8]; disease progression in vivo [6,7]; interaction with CD38-expressing cells via CD31 [14].</td>
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<tr>
<td><strong>CD4+ T cells/ T helper cells</strong></td>
<td>Adaptive immune responses; antigen recognition; T-APC immune synapse formation; APC activation via CD40/CD40L interaction.</td>
<td>CLL engraftment in vivo [24]; defective immune synapse formation upon contact with CLL cells [26,28]; CD40L+ CD4+ T cells induce CLL cells to produce CCL17 and CCL22 [20,21]; increased expression of inhibitory receptors (e.g. PD-1) [27]</td>
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<tr>
<td><strong>CD4+CD25high T regulatory cells/ Treg</strong></td>
<td>Inhibition of proliferation and cytokine release by CD4+ T cells; inhibition of antitumor immunity.</td>
<td>High proportion of CD4+CD25high regulatory T cells may contribute to CLL immune-evasion [25]</td>
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<tr>
<td><strong>CD8+ T cells/ cytotoxic T cells</strong></td>
<td>Adaptive immune responses; antigen recognition when presented on MHC class I molecules by target cells (e.g. cancer cells, virally infected cells); apoptosis induction of target cells.</td>
<td>Defective immune synapse formation upon contact with CLL cells [26,28]; exhausted phenotype and impaired cytotoxicity [27]</td>
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<tr>
<td><strong>Natural Killer cells/ NK cells</strong></td>
<td>Innate immune responses; antigen recognition when presented on MHC class I molecules by target cells (e.g. cancer cells, virally infected cells); apoptosis induction of target cells.</td>
<td>Reduced cytotoxicity [28]; low expression of NKP30 activating receptor [29]</td>
</tr>
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Figure 1AB:

A

B

NKp30

PBMC

CD40L

CD40

CCL3/4

CCL17/22

Inhibitory receptors

Defective synapse formation

Soluble BAG6

CD4+ T cells

CD8+ T cells

Defective cytotoxicity

Survival proliferation

Inhibitory receptors

Defective synapse formation

NK cells

CD107a

Cytotoxic granules

BMSC

VCAM-1

FN

VLA-4

PKC-βII

NFκB

CFX12

CXCR4

BCMA

TACI

BAFF-R

CD31

BAFF APRIL

CD38

BTK

Syk

P13K

BCR

Tissue homing

survival

proliferation

CLL cell

TACI

NLC

CLL cell

NK cells

CD8+

CD4+

T cells

CD40L

CCL3/4

CCL17/22

Inhibitory receptors
Figure 2:

[Diagram showing cellular signaling pathways involving proteins such as BCR, PI3K, PKC, and transcription factors.]
# Clinical Cancer Research

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