**REVIEW ARTICLE**

**B-Cell Chronic Lymphocytic Leukemia:**

* A Bird of a Different Feather

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**Purpose:** To review the recent major advances in the molecular and cell biology of B-cell chronic lymphocytic leukemia (B-CLL).

**Methods:** We analyzed the nature of malignant B-CLL B cells and their interactions with the microenvironment.

**Results:** B-CLL is a malignancy of a mantle zone-based subpopulation of anergic, self-reactive, activated CD5⁺ B cells devoted to the production of polyreactive natural autoantibodies. It is the quintessential example of a human malignancy that primarily involves defects in the induction of programmed cell death. An abnormal karyotype is observed in about 50% of patients with B-CLL. Patients with 13q14 abnormalities show heavy somatic mutation and have a benign disease. Trisomy 12 is associated with unmutated VH genes, atypical cellular morphology, and progressive disease. Extended cell survival is further shielded by a kinetic refractoriness likely promoted by abnormalities of the B-cell antigen receptor complex and favored by some cytokines that highlight a reciprocal dialog between malignant B and T cells. Because the tumor cells act as the major accessory cells, the accumulating malignant B-cell population per se is a hurdle to the production of normal antibodies and leads to a progressive and severe hypogammaglobulinemia. Conceivably, in the presence of certain immunoglobulin genes and when the T-cell control becomes deficient, activated malignant B cells may become able to present self-antigens and drive residual normal B cells to produce polyclonal autoantibodies restricted to self-antigens expressed only by blood cells and cause autoimmune cytopenias.

**Conclusion:** The distinctiveness of B-CLL B cells explains why B-CLL is different from other B-cell tumors and accounts for the development of immune deficiency and autoimmunity.

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B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA (B-CLL) is characterized by the relentless accumulation of monoclonal B cells that have the appearance of small mature lymphocytes, disrupt easily during preparation of blood smears, and have a typical immunophenotype. Because B-CLL is the most common leukemia in the Western world and because patients frequently survive for many years, the leukemic cells are readily available for study. As a result, B-CLL has become the prototypical chronic B-cell malignancy and its cellular properties have been used extensively to explain the cellular properties of normal B cells. However, by all analyses, B-CLL is clearly different from other B-cell tumors, and its cells are so distinctive that it is an inappropriate model for normal B cells.

THE DISTINCTIVENESS OF B-CLL

Three major lines of evidence provided by epidemiology, molecular and cellular biology, and clinical investigation underscore the distinctiveness of B-CLL. First, B-CLL is the only blood malignancy whose frequency was not increased in atomic bomb survivors and that is not associated with exposure to toxic drugs and chemicals.¹ In addition, there is evidence for a genetic susceptibility. It is very rare in the Far East and in Japanese immigrants to the United States.¹ There are also families in which siblings have the disease and it appears in succeeding generations at an ever earlier age.¹ Second, B-CLL is the quintessential example of a human malignancy that primarily involves defects in the induction of programmed cell death. Cellular and molecular studies have demonstrated that the gene setting of B-CLL cells is optimally organized to avoid apoptosis. The extended cell survival is further shielded by a kinetic refractoriness to exogenous stimuli.

Third, patients with B-CLL have an unusually high prevalence of autoimmune phenomena. In most cases, polyclonal autoantibodies (autoAbs) restricted to self-antigens (self-Ags) expressed only by blood cells² cause autoimmune cytopenias. Paradoxically, patients also develop progressive hypogammaglobulinemia, which deteriorates with advancing disease and may achieve a severity not seen in other chronic lymphoid malignancies.³

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THE NATURE OF MALIGNANT B CELLS IN B-CLL

Immunophenotype

Although B-CLL cells express aberrant markers not found on normal equivalent cells as most leukemia cells do, the immunophenotype of B-CLL cells most closely resembles that of lymphocytes detectable on the mantle zone of secondary lymphoid follicles. They express most of the membrane antigens present on mature B cells, but their distinctive characteristic is the coexpression of CD5 with faint to virtually undetectable amounts of monoclonal surface immunoglobulins (sIgs). These sIgs are usually sIgM and only rarely sIgG or sIgA. The monoclonal Igs detectable on the cell membrane often have polyreactive autoAb activity and frequently behave as a rheumatoid factor. There is evidence of a skewed usage of V1–59 (51p1), the heavy chain variable region gene that codes for monoclonal rheumatoid factor. This gene is usually in a germline configuration, which indicates that these cells have not undergone the process of somatic hypermutation that occurs in the germinal centers of secondary follicles.

The faint sIg/CD5 coexpression serves two purposes. First, it distinguishes B-CLL from the small-cell lymphomas in leukemic phase that mimic B-CLL. Second, it provides a clue as to the cell of origin in B-CLL. Such low levels of sIgM are seen only in normal B lymphocytes that have been anergized by interaction with self-Ag. Furthermore, normal CD5+ B cells, which are found at the edge of germinal centers in the mantle zone of lymphoid follicles, often produce polyreactive, low-affinity, natural autoAbs. These autoAbs are encoded by the same repertoire of unmutated Ig V genes that operate in many cases of B-CLL and share the same cross-reactive idiotypes, ie, the 51p1-encoded idio-
type, represented most frequently on the surface of malignant B-CLL cells.

Kinetic Hyporesponsiveness

More than 99% of circulating B-CLL lymphocytes are in the G_0 phase of the cell cycle. It is not clear which of the cell characteristics are directly implicated in the kinetic hyporesponsiveness and which are epiphenomena. A prominent role must be played by abnormalities of the B-cell antigen receptor complex (BCR) (Fig 1), because the mitogenic signals that induce the proliferation of normal B cells are weak stimuli for B-CLL cells.
The BCR is a multimeric complex formed by the slg and the Igα/Igβ (CD79a/CD79b) heterodimer that translates the Ig engagement into the biochemical signals that drive the B-cell response. The extracellular domain of CD79b that is normally present on the malignant cell surface in B-cell lymphomas is absent in most B-CLL patients. Recently it has been claimed that the diminished display of BCR on the membrane of B-CLL cells is because of the occurrence of somatic mutations predicted to affect CD79b expression. An alternative explanation is offered by the detection of a truncated form of CD79b that arises by alternative splicing of the CD79b gene and lacks exon 3, which encodes the extracellular Ig-like domain in a variety of human B cells and B-cell lines. This alternatively spliced variant has been detected in all B-CLL cases analyzed, thereby suggesting a role for the alternative splicing of the CD79b gene in causing the reduced expression of BCR on the surface of B-CLL cells. No matter what mechanism is responsible, the low levels of BCR on the membrane of B-CLL cells may account for the defective signal transduction via the BCR, which correlates with a reduced induction of protein tyrosine kinase activity similar to that seen in anergic normal B cells. A defective Ca²⁺ response coupled with an altered pattern of protein tyrosine phosphorylation has also been observed in several cases.

Other membrane molecules amplify signaling via the BCR and have an accessory role in the signal transduction of B cells. An example is CD22, which when stimulated potentiates the proliferation induced by anti-Ig. Although CD22 is present in the cytoplasm of B-CLL cells, it is absent from or only weakly expressed on their surface. Other B-cell malignancies express CD22 both on the cell surface and within the cytoplasm. Another example is CD21, which is also the receptor for the Epstein-Barr virus (EBV). B-CLL cells express the EBV receptor and have no defect in EBV receptor binding activity nor in EBV uptake. Despite this, it is almost impossible to immortalize B-CLL cells with EBV. In contrast, workers have used EBV to readily immortalize normal CD5⁺ and CD5⁻ B cells in order to study more effectively their Ig gene repertoire and antibody production.

B-CLL cells also have a marked reduction of functional Na⁺/H⁺ antiporter units. Na⁺/H⁺ antiporter units are necessary for lipopolysaccharide-induced proliferation of normal human B cells and represent a relevant step in the signal transduction of many growth factors and mitogens.

Cytokines

For such an apparently anergic cell, it is surprising that the B-CLL cell produces (or at least displays the mRNA for) virtually all cytokines investigated. Interleukin (IL) 1 alpha, IL-1β, IL-6, IL-7, IL-8, IL-10, IL-13, interferon-gamma (IFN-γ), tumor necrosis factor (TNF), granulocyte-macrophage colony-stimulating factor, and transforming growth factor beta1 (TGF-β1) have all been detected. Their role in the natural history of B-CLL is still unclear, even if some are responsible for negative autocrine circuits. Although a role for IL-10 has been advocated, there are still conflicting data on its precise role. TGF-β and IFN-γ are frequently detectable at high levels in patients’ serum. As a potent inhibitor of lymphocyte proliferation, TGF-β has been proposed as an endogenous growth inhibitor that might account for the slow progression of malignant growth. TGF-β can also induce apoptosis in several cell systems, including human B cells. Interestingly, CLL B cells are resistant to the apoptotic effects of TGF-β in vitro. Data document that the addition of TGF-β variably inhibits CLL B-cell proliferation without affecting apoptosis. IFN-γ promotes the survival of leukemic cells by preventing apoptosis. Other cytokines, including TNF-α, soluble CD23, and IL-8 have been proposed as autocrine growth-promoting candidates. However, no cytokine is individually able, unequivocally and consistently, to force the G0 blockade of B-CLL cells.

Cytokines may also derive from and participate in a reciprocal dialog between B-CLL cells and the interacting T cells (Fig 2). Chronic lymphocytic leukemia cells are influenced in vitro by a number of exogenously added cytokines that include IL-2, IL-4, IL-10, IL-13, IL-15, TNF-α, TGF-β, IFN-α, and IFN-γ. IL-4 inhibits proliferation and spontaneous cytokine release by CLL cells and shows noticeable antiapoptotic activity, which is also exerted by IFN-α. The activity of IL-4 may be related to the increased expression of IL-4 receptors by CLL B cells as compared with normal B cells.

The B-CLL/T-cell discussion is highlighted by the observation that B-CLL cells and T cells share a number of functionally relevant molecules and their counterreceptors. CD5 is associated with the BCR and is coexpressed with its natural ligand CD72 and is also present on the membrane of T cells. Likewise, the T cell-associated molecule CD27, a member of the TNF receptor family, is coexpressed with its natural ligand CD70 on the membrane of malignant B-CLL cells.

Cytogenetics and Molecular Abnormalities

B-CLL is the cytogenetic Cinderella of blood malignancies for two reasons: first, the spontaneous mitotic rate of B-CLL cells is extremely low, and second, the standard mitogen used in the 1960s and 1970s was phytohemagglutinin, a T-cell but not a B-cell stimulator. The use of B-cell activators, such as lipopolysaccharide, EBV, and especially...
12-O-tetradecanoylphorbol-13-acetate, has improved the cytogenetic definition of B-CLL.62,63 Fluorescence in situ hybridization and molecular studies progressively facilitate the detection of genetic abnormalities and even recognize microdeletions in morphologically normal chromosomes.64 Gradually, information is accumulating on the molecular effects of the chromosomal abnormalities.

An abnormal karyotype is observed in approximately 50% of patients.65 When a normal karyotype is present, metaphases may derive from either T cells or the clonal B-cell population itself. The most frequent abnormalities are deletions or translocations of chromosome arm 13q14,66 trisomy 12,67 and deletions at chromosome arms 11q2368 and 6q.69 Approximately half the patients with an abnormal karyotype have a single chromosomal abnormality, one quarter have two abnormalities, and the remainder have a complex pattern.65

Deletions or translocations at 13q are the most common abnormalities in CLL. The suggestion that the BRCA2 deletion at 13q12 is involved70 has not been confirmed by other workers.71 However, a detailed molecular delineation of a region of 13q14.3 telomeric to RB-1, which is frequently deleted, has now been published.72 With the help of molecular tools, a minimally deleted region of no more than 10 kilobases has been recognized, and from within this region, two candidate tumor suppressor genes, Leu1 and Leu2, have been cloned.73 These genes show little sequence homology to any previously published genes.

Patients with 13q14 abnormalities characteristically have a benign disease74 that usually manifests as an isolated, stable or only slowly progressive lymphocytosis. The disease is monoclonal but bears none of the other hallmarks of a malignancy. In particular, these patients survive as long as their age- and sex-matched controls.75

In contrast, trisomy 12 is associated with progressive disease76,77 and atypical cellular morphology.78 The biological importance of trisomy 12 is still poorly understood, although it has been suggested that one or more genes may have been duplicated to lead to a more malignant phenotype. A case with amplification of 12q13–22 found during a clinically aggressive relapse has been investigated molecularly.79 A smaller region, 12q13–15, which contains the murine double minute 2 (MDM-2) gene was implicated. Fluorescence in situ hybridization studies have also demonstrated partial duplication of this region in other cases of CLL.80 The MDM-2 oncoprotein exists in an autoregulatory feedback loop with the tumor suppressor protein p53. Amplification of the MDM-2 gene leads to overexpression of the protein that inactivates p53. Overexpression of MDM-2 RNA has been detected,81 and more recently several MDM-2 proteins (p57, p59, P67, and p90) were found to be overexpressed in various combinations in CLL.82

A surprising difference between CLLs with trisomy 12 and those with 13q14 deletions is the finding that trisomy 12 is predominantly associated with unmutated VH genes, whereas CLLs with 13q14 deletions show heavy somatic mutation.83 It is unclear whether this points to two different diseases, one deriving from a pregerminal and the other from a postgerminal center cell, or to a cell so disordered by genetic damage as to be unable to differentiate further.

Deletions and translocations at 11q fall into two distinct types. Although some cases of apparent CLL with translocations at 11q13 involving the Bcl-1 gene have been reported,84 most workers believe these to be a variant of mantle cell lymphoma.85 Deletions at 11q23 are found in up to 10% of CLLs. Patients with these deletions are reported to
have B-CLL with extensive lymph node involvement and require an aggressive clinical course.86

Mutations or deletions of p53 at 17p13.3 have been reported in up to 15% of patients with CLL. p53 aberrations are particularly associated with atypical cellular morphology, characteristically with more than 10% prolymphocytes, advanced disease, a high proliferation rate, and shortened survival.87 They are also associated with Richter’s transformation, ie, the development of a high-grade lymphoma from within the clone.88

In contrast to follicular lymphoma, the t(14;18) translocation is exceedingly rare.89 Nevertheless, the Bcl-2 gene product is consistently overexpressed in B-CLL.90,91 The mechanism involved in this overexpression is unclear, but it may depend on hypomethylation of the gene, which would lead to increased transcription,92 or it may be under the influence of apoptosis-protecting cytokines. In vitro data indicate that IL-4,55,56 IFN-α,88 and IFN-γ inhibition of CLL cell apoptosis is accompanied by preservation or even up-regulation of the Bcl-2 protein.

Bcl-2 belongs to a rapidly expanding family of genes that have an interrelated role in the control of apoptosis.93 Bax codes for a protein that is the partner for the Bcl-2 protein94 and counters its repression of apoptosis; Bcl-xl synergizes with Bcl-2, whereas Bcl-xS inhibits Bcl-2 function.95 B-CLL cells express high levels of Bcl-2, Bcl-xl, and Bax, whereas Bcl-xS is present in low to trace amounts in a smaller proportion of cases.96 Thus the pattern of expression of Bcl-2 family genes in B-CLL cells favors the suppression of apoptosis (Fig 1). In the same vein, B-CLL cells do not express the proapoptotic surface molecule Fas,97 nor do they express c-myc, a potent inducer of apoptosis.98

Bcl-3 translocations, t(14;19)(q32.3;q13.2), are even rarer than Bcl-2 translocations. In 50% of cases, they are found in association with trisomy 12. Patients are frequently younger than 40 years old and the disease is often rapidly progressive. The Bcl-3 gene encodes an I kappa B-like protein that modulates the activity of NF-kappa B transcription factors.99

**MALIGNANT B-CELL MICROENVIRONMENT INTERACTIONS**

Several observations indicate that the microenvironment might influence the natural history of B-CLL. In vitro data demonstrate that cytokines produced by B-CLL cells modulate the environment in which they accumulate.20,51 A striking predominance of CD4+ helper T cells is observed in involved bone marrow (BM) and lymph nodes and reflects a redistribution of T-cell subsets reminiscent of that seen in immunoregulatory disorders such as rheumatoid arthritis and sarcoidosis.100 In vitro data indicate that the behavior of B-CLL cells is influenced by T cell-produced cytokines (see above). The CD4+ T cells are intrinsically normal, but their pattern of cytokine secretion is modulated by accessory cells101: the tumor cells themselves act as the major accessory cells in B-CLL.101 The coexpression of CD27 and CD70 on malignant B cells may modify their accessory cell function and influence their ability to activate T cells.61 Finally, it is reasonable to maintain that binding of B-CLL cells to stromal cells and extracellular matrices may account for the in vivo patterns of lymphoid infiltration and thus influences the clinical presentation.

The migration and traffic pattern of lymphocytes is determined by the presence on the cell surface of adhesion molecules, among which a central role is played by the transmembrane heterodimers known as integrins. Integrins bind to specific ligands and have a cytoplasmic domain connected with the microfilament bundles of the cytoskeleton.102 B-CLL cells have an unusual cytoskeletal organization that, among lymphohemopoietic cells, is shared only by cells of the monocyte-macrophage lineage.103 They consistently express the β1 (CD29) and β2 (CD18) integrins together with variable amounts of α3 (CD49c), α4 (CD49d), and α5 (CD49e); leukocyte function-associated antigen 1 (CD11a/CD18) and α4/α7 are variably expressed.104 The leukocyte function-associated antigen 1 ligands, intercellular adhesion molecule (ICAM)-1 (CD54), ICAM-2 (CD102) and ICAM-3 (CD50), are also present on the surface of CLL cells.105 Interleukin 4 enhances homotypic adhesion of activated CLL cells by selectively up-regulating ICAM-1.106 The L-selectin (CD62L) and the “homing receptor” CD44 have been detected in a high proportion of cases.107 Chronic lymphocytic leukemia cells bind weakly to the surface of nonstimulated endothelium.104 However, the stimulation of endothelium markedly increases the expression of vascular cell adhesion molecule (VCAM) 1. In this setting, the endothelial binding of CLL cells that express the VCAM-1 ligand, α4/β1, is enhanced.104 The expression of α4/β1 may also allow the interaction of CLL cells with VCAM-1–expressing sites in the BM and secondary lymphoid organs.108

The pattern of adhesion molecule expression has been used to define distinct subsets of patients.109 More specifically, the expression of β2 integrins has been related to the presence of a higher number of leukemic cells in patients with more advanced disease.107

In vitro, malignant CLL cells have been shown to interact with BM stromal cells via β1 and β2 integrins.110 This binding rescues CLL cells from apoptosis100,111 and extends their life span. These data suggest a potential mechanism to explain the in vivo accumulation and survival of malignant cells in the BM and also account for the discrepant behavior of cells that in vivo have a prolonged half-life but in vitro die...
rapidly of apoptosis. It should also be noted that in the early nodular phase of BM involvement, B-CLL cells are closely associated with follicular dendritic cells, which are absent from normal BM. The relationship between B-CLL and follicular dendritic cells warrants further exploration.

**Immune Incompetence and Autoimmunity**

Immune incompetence is a cardinal feature of B-CLL. It is characterized by a progressive profound hypogammaglobulinemia that eventually develops in all patients and by an impaired cell-mediated immunity to recall antigens. B-cell chronic lymphocytic leukemia cells secrete TGF-β, which is a potent inhibitor of B-cell proliferation, and release high levels of circulating IL-2 receptor, which might act as a sponge for endogenous IL-2 and thus down-regulate the T helper function. Furthermore, B-CLL cells (as do anergic normal B cells) fail to present soluble antigen and alloantigen, whereas normal, activated B cells are very effective antigen-presenting cells (APCs). The inability of B-CLL cells (and of anergic normal B cells) to properly act as APCs is explained, at least in part, by the low levels of sIg and the suboptimal expression of the costimulatory molecules CD80 and CD86. The defective expression of CD79b may be an additional element. It should also be considered that CLL CD4+ T cells express CD40 ligand (CD154) mRNA but fail to express the molecule on the cell surface after CD3 ligation. In a disease characterized by an excess of CD40+ leukemic cells, such a receptor-mediated down-modulation of CD154 could interfere with antigen-specific cognate interaction. The conclusion to be drawn from all these data is that the accumulating malignant B-cell population per se is a hurdle obstructing the production of normal antibody and may lead to progressive immunoincompetence (Fig 3).

Any explanation of the immunodeficiency has to be consistent with the fact that up to 25% of patients develop either autoimmune hemolytic anemia, autoimmune thrombocytopenia, or, more rarely, autoimmune neutropenia or pure red cell aplasia. In the vast majority of cases, the autoAbs are polyclonal and, by definition, not produced by the malignant clone. The production of polyclonal, monoreactive, high-affinity, pathogenic autoAbs of IgG class in the context of a malignancy characterized by the accumulation of anergic B cells that produce monoclonal, polyreactive, low-affinity autoreactive IgM antibodies is an obvious paradox. Two other facts need to be accommodated by any global theory. First, autoimmunity in B-CLL is almost entirely confined to an attack on the formed elements of the blood. Second, autoimmunity is much more common in patients treated with fludarabine, a drug known to induce profound suppression of circulating CD4+ T cells. It is not unreasonable to suppose that immune incompetence and autoimmunity are two sides of the same coin. A common explanation of these immune defects may lie in aberrations of the immunoregulatory circuits that involve the malignant B cells as well as the T cells and residual normal B cells (Fig 3). One of these abnormalities may well be the role of B-CLL cells as APCs. In vitro experiments have shown that stimulation of CD40 on the membrane of B-CLL cells (as well as on anergic normal B cells) by the T cell-expressed CD154 may up-regulate the surface expression of CD80 and CD86 molecules and thus transform
anergic CD80\(^{-}\)CD86\(^{-}\) cells into efficient CD80\(^{+}\)CD86\(^{+}\) APCs.\(^{115,120}\) The role of malignant B cells as APCs is underscored by experiments with severe combined immunodeficiency mice: when reconstituted with peripheral blood lymphocytes from CLL patients,\(^{121}\) they frequently develop polyclonal human IgG autoAbs to human red blood cells even though the CLL itself does not proliferate within the mouse. Further complexity is added to the system by the recent report that CLL malignant B cells can express CD154 and may demonstrate a T cell-type costimulatory capacity that provides inappropriate B-cell “help.”\(^{122}\)

Another eccentricity may lie in the Ig gene usage of the CLL cells. In patients with autoimmune hemolytic anemia, it has been suggested that a particular CDR3 region is used by the leukemic cells.\(^{123}\) This implies that the antibody used may be involved in the pathogenesis of the hemolytic anemia, perhaps by promoting an increased clearance of senescent erythrocytes.

Finally, T-cell numbers are increased in B-CLL patients\(^{124}\) and have profound abnormalities of their antigen receptor (TCR) repertoire.\(^{125}\) If we assume that certain T-cell subsets are unable to prevent the development of autoreactive B cells, it follows that when these T-cell subsets are absent, eg, after treatment with purine analogs, autoreactive B-cell clones may easily emerge and expand.

Although the extent to which in vitro experiments reproduce what occurs in vivo remains to be established, we favor the use of these observations to interpret the concurrence of immune incompetence and blood cell-specific autoimmunity (Fig 3). B-CLL cells may become activated by T helper cells (perhaps via CD154 if an adequate T cell to malignant B cell ratio is maintained) in an environment such as the spleen, where senescent anucleate blood cells are removed. Such activated malignant B cells may then become able to present red cell and/or platelet membrane degradation products (self-Ag) and drive residual normal B cells to produce target-restricted pathogenic autoAbs.\(^{18}\) This process would be facilitated if the B-CLL cells used certain Ig genes and might become clinically evident when the control exerted by T cells becomes deficient.

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