Human chronic lymphocytic leukemia modeled in mouse by targeted *TCL1* expression

Roberta Bichi*, Susan A. Shinton†, Eric S. Martin*, Anatoliy Koval*, George A. Calin*, Rossano Cesari*, Giandomenico Russo‡, Richard R. Hardy†, and Carlo M. Croce*§

*Kimmel Cancer Center, Jefferson Medical College, 233 South 10th Street, Philadelphia, PA 19107; †Institute for Cancer Research, Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111; and ‡Laboratory of Molecular Oncogenesis, Istituto Dermopatico dell'Immacolata, Via dei Monti di Creta 104, 00167 Rome, Italy

The *TCL1* gene at 14q32.1 is involved in chromosomal translocations and inversions in mature T cell leukemias. These leukemias are classified either as T prolymphocytic leukemias, which occur very late in life, or as T chronic lymphocytic leukemias, which often arise in patients with ataxia telangiectasia (AT) at a young age. In transgenic animals, the deregulated expression of *TCL1* leads to mature T cell leukemia, demonstrating the role of *TCL1* in the initiation of malignant transformation in T cell neoplasia. Expression of high levels of Tcl1 have also been found in a variety of human tumor-derived B cell lines ranging from pre-B cell to mature B cell. Here we describe the phenotype of transgenic mice, Eμ-*TCL1*, established with *TCL1* under the control of a V_H promoter-Ig_H-Eμ enhancer to target *TCL1* expression to immature and mature B cells. Flow cytometric analysis reveals a markedly expanded $CD5^+$ population in the peritoneal cavity of Eμ-*TCL1* mice starting at 2 mo of age that becomes evident in the spleen by 3–5 mo and in the bone marrow by 5–8 mo. Analysis of Ig gene rearrangements indicates monoclonality or oligoclonality in these populations, suggesting a preneoplastic expansion of $CD5^+$ B cell clones, with the elder mice eventually developing a chronic lymphocytic leukemia (CLL)-like disorder resembling human B-CLL. Our findings provide an animal model for CLL, the most common human leukemia, and demonstrate that deregulation of the Tcl1 pathway plays a crucial role in CLL pathogenesis.

B cell chronic lymphocytic leukemia (B-CLL) is the most common leukemia in the Western world, with as many as 10,000 new cases reported each year in the United States (1, 2). Characteristically, B-CLL is a disease of elderly people resulting from the progressive accumulation of a leukemic clone that may be derived from a normal $CD5^+$ B lymphocyte (3). B-CLL has a consistent association with CD5 expression (3), and, although there is still a debate on the role and significance of CD5 expression on B cells, it remains reasonable to consider $CD5^+$ B cells as the normal counterpart of B-CLL (4, 5).

Human hematopoietic malignancies are often caused by chromosome translocations involving either T cell receptor (TCR) or immunoglobulin loci (6). These chromosome breakpoints juxtapose enhancer elements of TCR and Ig loci to protooncogenes, leading to tumor initiation through oncogene deregulation (7, 8). We have previously identified the T cell leukemia-1 (*TCL1*) gene at chromosome 14q32.1 (9) that is commonly activated by inversions or translocations that juxtapose it to a T cell receptor locus at 14q11 or 7q35. *TCL1* has been found to be overexpressed in sporadic and ataxia telangiectasia-associated T prolymphocytic leukemia (T-PLL; refs. 10 and 11). We also provided evidence that *TCL1* is a bona fide oncogene, developing a transgenic mouse model where ectopic expression driven by the *lck* promoter in the T cell compartment results in the development of mature T cell leukemias after a long latency period, in a pattern closely resembling human mature T cell leukemia (12). In normal T cells, *TCL1* is expressed only at the very early $CD4^-/CD8^-$ double negative stage, whereas more mature T cells lack *TCL1* expression (9). In the B cell lineage, the product

of the *TCL1* gene, Tcl1, has been found in pre-B cells, surface IgM-expressing virgin B cells, mantle cells and germinal center B cells, whereas it is down-regulated at later stages of B cell differentiation, i.e., plasma cells (9). Interestingly, high levels of Tcl1 have been found in a broad variety of human tumor-derived B cell lines and in many cases of B cell neoplasias (13, 14). To elucidate the role of *TCL1* in B cell development and in B cell neoplasia, we generated transgenic mice under the control of a promoter and enhancer whose activity specifically targets expression of the transgene to the B cell compartment (15). Here, we show that Eμ-*TCL1* transgenic mice develop a disease resembling human CLL. The mice develop at first a preleukemic state evident in blood, spleen, bone marrow, peritoneal cavity, and peripheral lymphoid tissue, developing later a frank leukemia with all characteristics of CLL. These findings strongly indicate that *TCL1* and/or other gene(s) in the *TCL1* pathway are responsible for the initiation of human CLL.

Materials and Methods

Eμ-*TCL1* Transgenic Mice. A 350-bp fragment possessing the entire human *TCL1* coding region was generated by PCR and cloned into the *Eco*RV and *Sal*I sites of the pBSVE6BK (pEμ) plasmid containing a mouse V_H promoter (V186.2) and the Ig_H-μ enhancer along with the 3′ untranslated region and the poly(A) site of the human β-globin gene. The construct containing *TCL1* free from vector sequences was injected into fertilized oocytes from B6C3 animals. Mice were screened for the presence of the transgene by Southern blot analysis on tail DNAs digested with *Xho*I. Blots were hybridized with the same *Bss*HII DNA fragment used to inject the oocytes. Two founders were obtained (F3 and F10) and bred. Transgenic heterozygote mice issued from these founders were studied and compared with nontransgenic siblings raised in identical conditions. Genotyping was performed on tail DNAs by PCR.

Western Blot Analysis. Cell proteins were extracted with Nonidet P-40 lysis buffer, quantified by using the BCA kit (Pierce), size fractionated on 15% Tris-glycine SDS/PAGE gels, and electrotransferred onto nitrocellulose (Immobilon-P, Millipore). The membrane was blocked overnight in 10% nonfat dried milk in PBST (7.6 g/liter NaCl/0.7 g/liter Na_2PO_4/0.2 g/liter KPO_4/ 0.1% Tween 20). Expression was detected with the MoAb 27D6/20 for human Tcl1 protein (14) according to ECL protocol (Amersham Pharmacia). Ponceau-S staining was used to verify equivalent protein loading.

Cell Preparations. Bone marrow cells were isolated by flushing the cavities of the femur and tibia with ice cold staining medium

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(Deficient RPMI, Irvine Scientific) containing 10 mM Hepes, 0.1% NaN₃, and 3% FCS. Spleens were dissociated in staining medium between two frosted slides. Peritoneal cells were removed by injection of 10 ml of staining medium into the peritoneal cavity followed by withdrawal of the peritoneal exudates. Erythrocytes were lysed by brief treatment with 0.165 M ammonium chloride, and the cells then washed in staining medium.

WBC Preparation. Blood was collected from the cavernous sinus with a capillary tube in a tube coated with EDTA (Becton Dickinson). Smears were immediately prepared and stained with May-Grünwald-Giemsa. Full counts were made on a cell counter (Beckman). For immunofluorescence staining, cells were treated with 0.165 M ammonium chloride to eliminate red cells and washed in staining medium.

Immunofluorescence Analysis and Cell Sorting. Single cell suspensions of the indicated cell type were prepared and stained for surface expression as described previously (16). Cells were stained for surface expression of IgM and CD5, then fixed and permeabilized by using the Fix&Perm kit (Caltag, South San Francisco, CA) and stained for expression of Tcl1 by using a phycoerythrin-labeled anti-Tcl1 monoclonal antibody 27D6/20 (14). IgM/CD5 distributions were gated as indicated, and histograms of the Tcl1 staining were determined. Plots were done with FLOWJO software (Tree Star, San Carlos, CA). Exclusion of propidium iodide (PI) was used to eliminate dead cells, and samples shown were also gated by forward and right angle scatter to exclude non-lymphoid cells and debris. Flow cytometry and sorting were done on a dual-laser dye-laser FACStarPlus equipped with detectors for five color immunofluorescence. Samples were held on ice during sorting. Preparation of labeled reagents has been described previously (17).

Analysis of VH11 Sequences. Cells were stained for IgM/CD5 expression, and 1×10^5 IgM$^+$CD5$^+$ cells were sorted directly into lysis/denaturation buffer. RNA and cDNA were prepared as described previously (18), and a VH11-Cμ fragment was amplified by using a VH11 leader and Cμ primer using Pfu polymerase and PCR. The amplified material was cloned by using the TOPO TA cloning kit (Invitrogen) following the manufacturer's instruction. Colonies with insert were expanded, and plasmid DNA was isolated and sequenced by using an Applied Biosystems ABI 377 automated sequencer as described previously (19).

Cell Cycle. For PI staining, 10^5 cells were sorted directly into ice cold 95% ethanol, and nuclei were pelleted and then resuspended in PI-labeling solution (1 mg/ml RNase A/20 μg/ml PI in PBS containing 0.01% Nonidet P-40). After 30 min, cells were analyzed for PI fluorescence on a FACScan (Becton Dickinson) using doublet discrimination gating.

Cell Proliferation. Mice were injected i.p. with BrdUrd in PBS at a dose of 50 μg per gram of body weight daily for 4 days. Mice were killed, and cells were stained for expression of IgM and CD5, then sorted to obtain the indicated populations. Cells (5×10^5) were fixed and permeabilized, then treated with DNase in acid buffer and stained with an anti-BrdUrd monoclonal antibody labeled with FITC. Samples were analyzed on a FACScan for BrdUrd staining.

IgH Gene Rearrangement. Southern blots of DNA digested with *Eco*RI and *Stu*I were prepared following conventional methods and hybridized with a ^{32}P-labeled DNA probe PJ3 representing the J$_H$4 region of the IgH locus. The probe was synthesized by PCR amplification from mouse DNA with primers F2
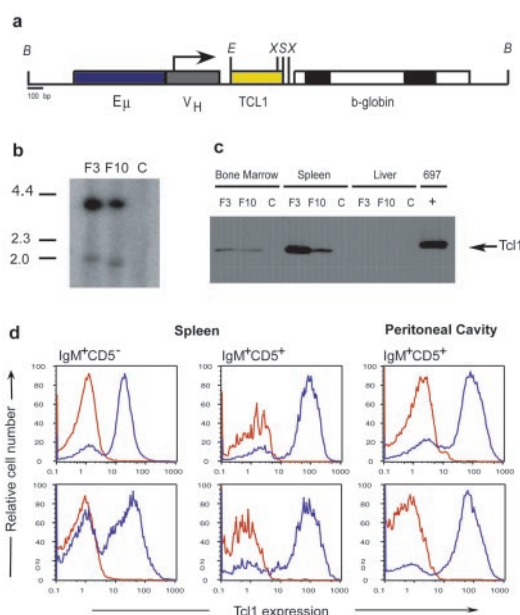
Fig. 1. Production of Eμ-*TCL1* transgenic (TG) mice. (*a*) Schematic representation of the construct used to generate the mice. Restriction sites: *X, Xho*I; *S, Sal*I; *E, Eco*RV; *B, Bss*HII. (*b*) Southern blot analysis of DNA isolated from the tails of the first TG progeny for both founders and non-TG control. (*c*) Immunoblot analysis on protein extracts from TG (F3 and F10) and non-TG (C = control) mouse tissues. 697 = pre-B leukemic cell line 697, which expresses high levels of Tcl1 protein (9). (*d*) *TCL1* expression on gate subsets of splenic B cells. (*Upper*) Refers to the F3 progeny. (*Lower*) F10 progeny (Blue = TG, Red = non-TG).

(5′-TGTGGTGACATTAGAACTGAAGTA-3′) and R1 (5′-CAAGATTAGTCTGCAATGCTCAGA-3′).

Long Distance Inverse PCR (LDI-PCR). High molecular weight DNA was digested with *Stu*I. LDI-PCR was performed as described (20). Primers designed within the mouse *JH* and *IGH* enhancer regions were used to amplify the purified DNA, and the gel-purified products were ligated into pCR 2.1-TOPO vector (Invitrogen). Plasmids containing the correct size insert were sequenced by using an ABI 377 automated sequencer and compared with the GenBank database by using the BLAST program (http://www.ncbi.nlm.nih.gov/BLAST/). The *VH*, *DH* and *JH* segments were identified by using the GenBank database.

Histopathology and Immunohistochemistry. Animals were autopsied, and tissues were fixed in 10% buffered formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin according to standard protocols and analyzed by mouse pathologists (University of Missouri, Research Animal Diagnostic Laboratory). Immunohistochemistry was performed on representative sections. For the dewaxing step, the sections were heated for 1 h at 55°C, followed by rehydration steps through a graded ethanol series and distilled water, immersed in PBS, and then treated with 0.1% trypsin solution in Tris buffer for 30 min at 37°C. Endogenous peroxidase was blocked with 10% normal serum. The 27D6/20 MoAb specific for recombinant human Tcl1 protein (14) was used as a primary antibody, and the immunohistochemical staining was performed by using streptavidin-biotin peroxidase labeling method according to the manufacturer's instructions (Histomouse-SP kit, Zymed).

Results and Discussion

Production and Characterization of Eμ-*TCL1* Transgenic Mice. We generated transgenic mice in which the expression of *TCL1* was under the control of a V$_H$ promoter-Ig$_H$-Eμ enhancer whose
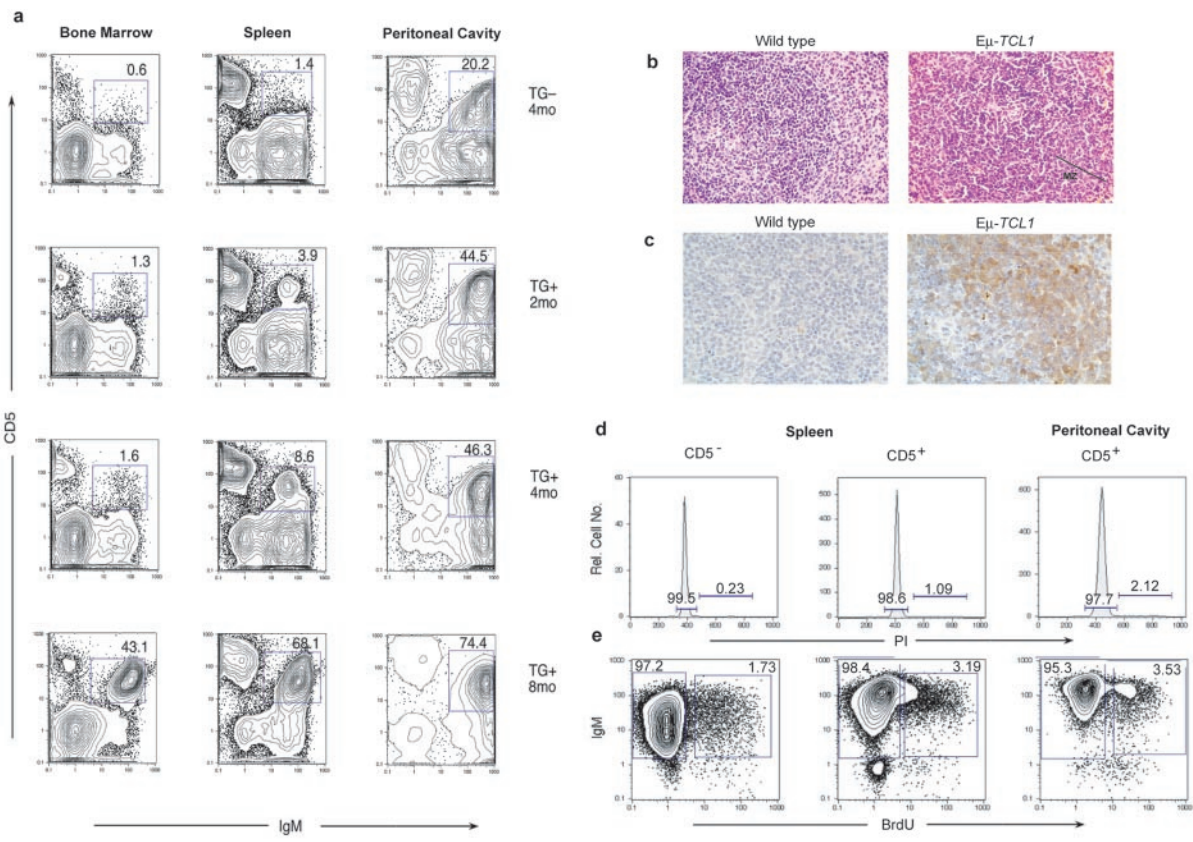
Fig. 2. Characterization of Eμ-*TCL1* mice. (*a*) Correlation between IgM and CD5 expression in single cell suspensions from bone marrow, spleen, and peritoneal cavity in TG animals and a non-TG littermate. (*b*) Hematoxylin and eosin-stained spleen of mouse showing an expanded MZ in Eμ-*TCL1* animals. (*c*) Immunodetection of Tcl1 protein in lymphoid cells of the MZ. (*d*) Cell cycle analysis on IgM and CD5 subsets of cells by PI-labeling. (*e*) Cell proliferation analysis by BrdUrd incorporation.

activity specifically targets expression of the transgene to immature and mature B cells (ref. 15; Fig. 1*a*). Two transgenic founders on a B6C3 background, designated F3 and F10, were generated and bred to establish two transgenic lines (Fig. 1*b*). The expression of the transgene in each was evaluated by Western blot of total protein extracted from spleen, bone marrow, and liver of 3-mo-old mice, by using a monoclonal antibody specific for human Tcl1 protein (14). The two transgenic lines expressed Tcl1 in spleen and bone marrow whereas no expression was detected in liver or in nontransgenic siblings (Fig. 1*c*). We also used fluorescence-activated cell sorting (FACS) to investigate the distribution of *TCL1* expression on gated subsets of B cells derived from spleen and peritoneal cavity of 3-mo-old mice, in both transgenic lines. The combination of cell surface markers with intracellular detection of Tcl1 revealed a high level of *TCL1* expression in normal resting B cells, with a 2.5-fold higher level in the CD5$^+$ cells (Fig. 1*d*).

The Immunophenotyping of Eμ-TCL1 Transgenic Mice Reveals an Expanded CD5$^+$/IgM$^+$ Population. We used flow cytometry to monitor the immunophenotypic profile of peripheral blood lymphocytes from mice of these two lines between 1 and 9 mo of age. The results revealed the presence of a B220low/IgM$^+$ population that was detected starting at 6 mo of age in 100% of the transgenic mice, but in the absence of any sign of disease. A normal distribution of B cell populations was found in the nontransgenic controls. T cell subsets were normal and identical between transgenic animals and their littermate controls. Eμ-*TCL1* transgenic mice were further characterized to identify the B cell subsets affected. The expanded B220low/IgM$^+$ population was found to coexpress CD5 and Mac-1/CD11b. This result suggested that the Eμ-*TCL1* transgenic mice had an expanded population of CD5$^+$/B1 cells in peripheral blood, where such cells are normally infrequent (21). In mice, CD5 is a pan-T cell surface marker that is also present on a subset of B lymphocytes

**Table 1. Analysis of V$_H$11 sequences in CD5$^+$ splenic B cells**

Seq. ID	V$_H$11	N	D$_H$	N	J$_H$	D$_H$	J$_H$
TCL1-4	TGTATGAGA	TA	TAGTAGC		TACTGGTACTTC	DFL16.1	J$_H$1
TCL1-11	TGTATGAGA		TATGGTAAC		TACTGGTACTTC	DSP2.8	J$_H$1
TCL1-17	TGTATGAGA		TACGGTAGT AGC		TACTGGTACTTC	DFL16.1	J$_H$1
TCL1-42	TGTATGAGA		TATGGTAAC		TACTGGTACTTC	DSP2.8	J$_H$1
TCL1-44	TGTATGAGA		TATGGTAACTAC		TACTGGTACTTC	DSP2.1	J$_H$1
TCL1-46	TGTATGAGA		TACGGTAGTAGC		TACTGGTACTTC	DFL16.1	J$_H$1
TCL1-47	TGTATGAGA		TATGATGGTTAC		TACTGGTACTTC	DSP2.9	J$_H$1
TCL1-52	TGTATGAGA		TATAGTAAC		TACTGGTACTTC	DSP2.X	J$_H$1

that appear during fetal/neonatal time, and whose development appears quite distinct from the majority of B cells (19, 22). CD5 is also frequently expressed on murine B cell lymphomas and leukemias (23, 24). We analyzed a group of animals at 2, 4, and 8 mo of age to assess the expansion of the $CD5^+/IgM^+$ population in bone marrow, spleen, and peritoneal cavity. FACS analysis revealed a phenotypically homogeneous population markedly expanded in the peritoneal cavity of the transgenic mice starting at 2 mo of age (44%) that became evident in spleen (8.6%) by 4 mo and bone marrow by 8 mo (43%; Fig. 2a).

Histological and Immunocytochemical Analysis of the Transgenic Mice. Eight-month-old transgenic mice presented a slightly enlarged spleen, 1.5-fold compared with littermate controls and moreover a very high cellularity in the peritoneal cavity, ranging between 50- to 100-fold increased. Histopathology of enlarged spleens of Eμ-TCL1 mice demonstrated a consistent increase in the size of the marginal zone (MZ; Fig. 2b). Immunostaining of lymphoid cells in the white pulp of the spleen showed Tcl1 staining more intensely in the MZ. As expected, no immunostaining was observed in the spleen of littermate controls (Fig. 2c). Interestingly, the anatomical localization of the expanded $CD5^+$ cells was in the MZ whereas they did not have the precise phenotype of typical MZ B cells, i.e., not CD21-high but rather CD21-low, like a normal $CD5^+$ B cell (25). The histological analysis of other tissues from the same animals—including thymus, liver, kidney, and intestine—did not reveal any pathologic alteration (not shown).

Analysis of V_H11 Sequences in the Expanded $CD5^+$ Population. The increased frequency of $CD5^+$ B cells in these transgenic mice could represent either the induction of CD5 expression on cells normally not $CD5^+$ or else the expansion of normally generated $CD5^+$ B cells. To distinguish between alternatives, we investigated V gene usage in the expanded cell population. Recurrent expression of certain V_HV_L combinations is a characteristic feature of normal and neoplastic $CD5^+$ B cells (19, 26). Using antibodies specific for variable regions, we found that one of these combinations, V_H11V_k9, was repeatedly represented at 5–10% in the expanded $CD5^+$ B cell population in all mice analyzed, similar to the frequency seen
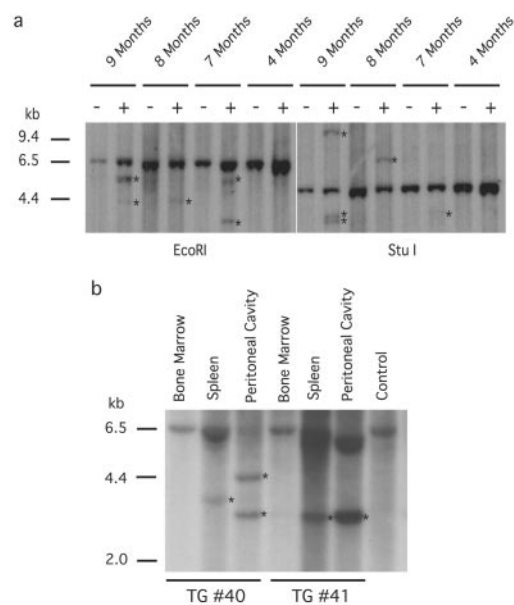

Fig. 3. Analysis of IgH gene configuration. (a) IgH gene rearrangements were analyzed by Southern blot on EcoRI and StuI-digested splenocyte DNAs. Transgenic mice (+) of 7, 8, and 9 mo show rearranged bands (asterisks). No predominant rearrangement is observed in the youngest mice. Controls (−) are non-TG mice with the genomic 6.5-kb EcoRI and 4.7-kb StuI fragments. (b) Southern blots on DNA isolated from bone marrow, spleen, and peritoneal cavity of TG mice (nos. 40 and 41) with the $CD5^+/IgM^+$ expanded population. IgH gene predominant rearrangements were detected in spleen and peritoneal cavity (asterisks). DNA from spleen of non-TG mouse was used as control.

in normal $CD5^+$ B cells (data not shown). Furthermore, analysis of V_H11 sequences from sorted $IgM^+/CD5^+$ cells from the spleen of a 3-mo-old transgenic mouse (Table 1) showed normal V_H11 rearrangements, with low levels of N-region addition, typical of $CD5^+$ B cells that are predominantly generated fetally/neonatally when levels of TdT are low (27).

Table 2. Results of VDJ rearrangements in selected cases of Eμ-TCL1 transgenic mice

Mouse	V_H	D_H	J_H	V_H	D_H	J_H
9 m	TACTGTGCCAG A	aATGGTTAC GA	CTATGCTATGGACTAC TGGGGTCAAGGAACCT CAGTCACCGTCTCCTC A	Vox-1	DSP2.6	J_H4
9 m	TACTGTGCCAG A	ACGGTAGTA GCcct	CTATGCTATGGACTAC TGGGGTCAAGGAACCT CAGTCACCGTCTCCTC A	Vox-1	DFL16.1	J_H4
8 m	GTCTATTACTG T	actccccACTAC GGTAGTAGC ct	CTGGTACTTCGATGTC TGGGGCACAGGGACC ACGGTCACCGTCTCCT CA	V130	DFL16.1	J_H1
No. 41 PerC	GCAGGAGACA GA	TATGGTTA	CTGGTACTTCGATGTC TGGGGCACAGGGACC ACGGTCACCGTCTCCT CA	NC1-A7	DSP2.6	J_H1
No. 41 Spleen	GCAGGAGACA GA	TATGGTTA	CTGGTACTTCGATGTC TGGGGCACAGGGACC ACGGTCACCGTCTCCT CA	NC1-A7	DSP2.6	J_H1

Variations from the germ-line sequence are underlined. N regions are in lowercase.
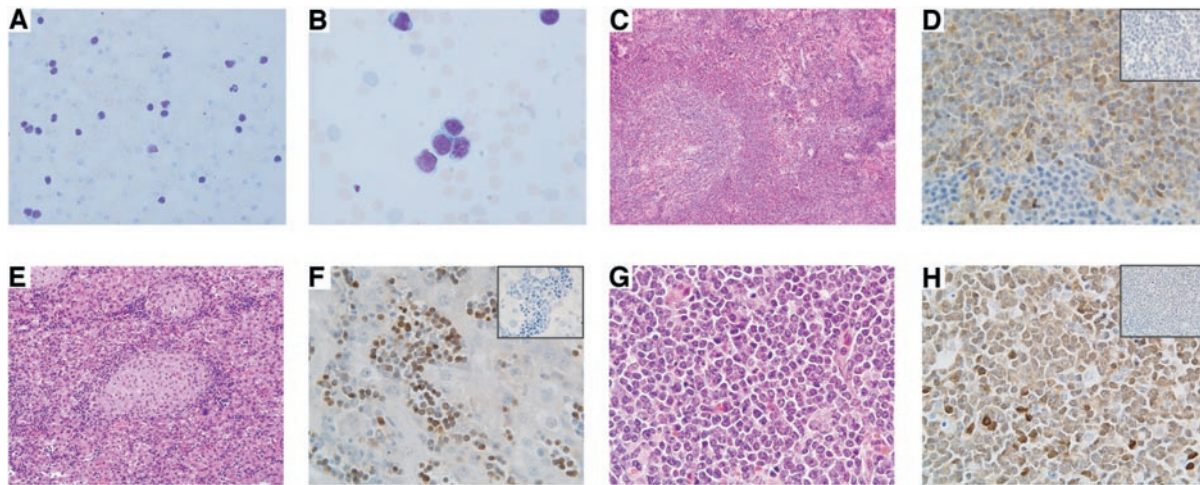
Fig. 4. Histopathological analysis of the Eμ-*TCL1* mice. (*A*) Blood smear stained with Wright Giemsa showing an increased number of circulating lymphocytes. (*B*) High magnification of the blood smear. (*C*) Histology of spleen, liver (*E*), and cervical lymph node (*G*) after hematoxylin-eosin staining. (*D*) Immunodetection of Tcl1 protein in spleen, liver (*F*), and cervical lymph node (*H*). (*Insets*) Negative control in which the primary antibody has been omitted.

IgM$^+$/CD5$^+$ Populations Are Arrested in the G$_0$/G$_1$ Phase of the Cell Cycle and Do Not Actively Divide. Chronic lymphocytic leukemia cells are characterized by a low proliferative activity and by the progressive accumulation of clonal B lymphocytes blocked in the early phases (G$_0$/G$_1$) of the cell cycle (28, 29). We investigated the cell cycle distribution and the rate of cell proliferation in spleen and peritoneal cavity of four transgenic mice and four littermate controls at 7 mo of age. Detection of DNA content in replicating cells by PI labeling and analysis of cell proliferation from the distribution of BrdUrd incorporation in IgM$^+$CD5$^+$ sorted populations revealed that most of these cells are not actively cycling in the transgenic mice (Fig. 2 *d* and *e*).

IgH Gene Configuration in Transgenic Mice with the Expanded CD5$^+$ Population. Analysis of Ig gene rearrangement revealed the presence of preleukemic or leukemic clones consistently in Eμ-*TCL1* mice over 7 mo of age. No clonality was observed in the youngest transgenics or in nontransgenic mice (Fig. 3*a*). The detection of clonal J$_H$ rearrangements indicated that there could be a clonal expansion without evidence of disease. Further analysis of Ig gene rearrangement in bone marrow, spleen, and peritoneal cavity from 8-mo-old mice with a markedly expanded CD5$^+$/IgM$^+$ population showed an identical size J$_H$ band detected in spleen and peritoneal cavity, but not bone marrow (Fig. 3*b*). The clonal J$_H$ band was not always shared between spleen and peritoneal cavity, as for example mouse no. 40 (Fig. 3*b*) with two independent clonal populations, suggesting multiple independent events in some cases. Clonal rearrangements were subsequently confirmed in some samples by cloning and sequencing the rearranged band by using LDI-PCR (20). Using this approach, the transgenic mice exhibited additional clonal rearrangements, compared with the littermate controls. Table 2 shows sequence data referring to the (+) samples marked as 9m and 8m in Fig. 3*a*, *Stu*I digested. Some sequences had a low level of N addition, whereas others had a higher level (Table 2), as has been noted in sequence analyses of normal CD5$^+$ B cells (30). The clonal population suggested by Southern blot for the transgenic no. 41 (Fig. 3*b*) in spleen and peritoneal cavity was also confirmed by LDI-PCR (Table 2).

Eμ-TCL1 Mice Developed Lymphocytic Leukemia on Aging. The onset of a frank leukemia in the elderly mice provided further evidence of the establishment of a murine model for B-CLL. All mice around the age of 13–18 mo became visibly ill and presented with enlarged spleens and livers associated with high WBC counts. The weight of the transgenic spleens was between 1.5 g and 2.3 g (normal splenic weight was 0.07 ± 0.01 g), and the mean of the WBC was 180.0×10^6 cells/ml (the mean WBC/ml blood for normal adult mice was 2.8×10^6 cells/ml). In addition, the mice also developed advanced lymphoadenopathy, a hallmark of human CLL. Cytological examination of blood smears showed an increase in circulating lymphocytes, with many of them displaying a clumped nuclear chromatin (Fig. 4 *A* and *B*). The predominant cell type was represented by large lymphoid cells, and smudged cells were also present. Histopathological examination demonstrated consistent infiltration of spleen, liver, and lymph nodes by small and large lymphocytes (Fig. 4 *C*, *E*, and *G*). Positive staining for Tcl1 protein was observed primarily in lymphocytes found in these tissues (Fig. 4 *D*, *F*, and *H*), and flow cytometric analysis confirmed the expansion of the CD5$^+$/IgM$^+$ population in all tissues (data not shown). Clonality was shown by Southern blot analysis of DNA isolated from leukemic splenocytes by using the PJ3 probe (Fig. 5). DNA from spleens of littermate controls showed the IgH gene in its germ-line configuration, whereas DNA from leukemic splenocytes presented extra-rearranged bands, indicating the presence of clonal B cell populations.
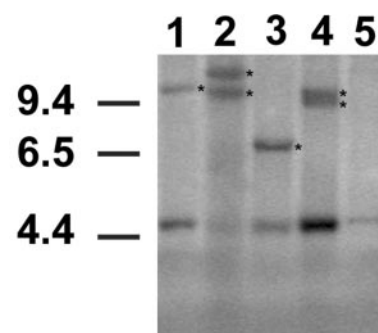
Fig. 5. Southern blot analysis of IgH gene rearrangements in leukemias from TG mice. DNAs from leukemic mice and a littermate control were digested with *Stu*I. The strong 4.7-kb bands represent the gene in its germ-line configuration. Clonal rearrangements are indicated by asterisks. Lanes 1 and 2, Leukemic mice from TG line F3; lanes 3 and 4, leukemic mice from TG line F10; lane 5, non-TG mouse.

Conclusions

B-CLL is the most common leukemia in humans, and its pathogenesis is still unknown. Transgenic mice in which we targeted the expression of *TCL1* in B cells develop a lymphoproliferative disease closely resembling human CLL. Our data strongly indicate that *TCL1* and/or other gene(s) in the *TCL1* pathway are responsible for the initiation of human B-CLL. The present findings provide an adequate animal model to investigate the mechanisms underlying the initiation and progression of human B-CLL, and we hope that ultimately this model may aid in the development and test of novel anti CLL therapeutics.

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