Functional Up-regulation of HERG K⁺ Channels in Neoplastic Hematopoietic Cells*

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Kv1.3 channels regulate proliferation of normal lymphocytes, but the role of voltage-gated potassium channels in transformed hematopoietic cells is not known. We examined transcripts for KvL3, h-erg, e-ag, and BEC1 genes in primary lymphocytes and leukemias and in several hematopoietic cell lines. Surprisingly, BEC1, formerly thought to be brain-specific, was present in all the primary leukemias examined, in resting peripheral blood lymphocytes, and in proliferating activated tonsillar cells, lymphocytes from Sjögren’s patients, and Epstein-Barr virus-transformed B-cells. Only h-erg mRNA was up-regulated in the cancer cells, but this was not due to proliferation per se, because it was not elevated in any of the proliferating noncancerous lymphocyte types examined. Nor did h-erg transcript levels correlate with the B-cell subset, because it was elevated in immature neoplastic B-CLL cells (CD5⁺) and in a CD5⁻ Burkitt’s lymphoma cell line (Raji) but not in Sjögren’s syndrome cells (enriched in CD5⁻ B-cells) or Epstein-Barr virus-transformed B-cells, which are mature CD5⁻ B-cells. The protein and whole cell current levels roughly corresponded with the amount of mRNA expressed in three hematopoietic cell lines: CEM (an acute lymphoblastic leukemic line), K562 (a chronic myelogenous leukemic line), and U937 (an acute promyelocytic leukemic line). The selective HERG channel blocker, E-4031, reduced proliferation of CEM, U937, and K562 cells, and this appears to be the first direct evidence of a functional role for the HERG current in cancer cells. Selective up-regulation of h-erg appears to occur in neoplastic hematopoietic cells, thus providing a marker and potential therapeutic target.

Voltage-gated potassium (Kv) channels are key determinants of normal cellular activity but can contribute to disease and, consequently, are increasingly recognized as potential therapeutic targets (for reviews, see Refs. 1–3). Changes in the properties of Kv channels and even the types expressed have been linked to several cardiac and neurological diseases (4, 5). In immune cells, Kv channels play roles in proliferation (6, 7), cytotoxicity (8), volume regulation (9, 10), and the respiratory burst (11); however, with a few notable exceptions, the particular Kv channel has not been identified. There are many channels in the Kv superfamily, which is divided into Shaker (Kv1–Kv4) and ether-a-go-go (eag) families. In normal T lymphocytes, Kv1.3 channels have been clearly demonstrated as important for proliferation and volume regulation (for reviews, see Refs. 7, 9, and 12). Because pharmacological blockade of Kv1.3 dramatically inhibits activation of naive T-cells, this channel has become a therapeutic target for controlling T-cell-mediated inflammation (13, 14). The commonly proposed role of Kv channels in proliferation is to maintain the driving force for calcium influx, thereby affecting calcium-dependent cell cycle control proteins.

In contrast to normal lymphocytes, the role of Kv channels in the proliferation of transformed immune cells (i.e. leukemias and lymphomas) is not known. For instance, in the human myeloid leukemia cell line, ML-1, the nonselective Kv channel blocker 4-aminopyridine reduced proliferation and induced differentiation (15–17). The specific Kv channel or mechanism of involvement was not identified. In direct contrast to these findings, it was proposed that the absence of a delayed rectifier (Kv) current contributed to the malignant state of megakaryocytes from myelogenous leukemia patients and in a human erythroleukemia cell line (18).

Ablerrant expression of Kv channels has been detected in some cancers of nonhematopoietic origin. The most compelling evidence for a role in cell transformation, and thus a therapeutic potential, exists for the eag family. eag transcripts and protein are present in numerous primary human cancers, such as endometroid adenocarcinomas, and in several human and murine cell lines (19–21). Evidence for their oncogenic potential is that overexpression of eag in CHO or NIH3T3 cells induced several features characteristic of malignant transformation (faster growth, loss of growth factor and substrate dependence, and loss of contact inhibition), and antisense reduction of eag mRNA expression decreased the proliferation of several tumor cell lines (20).

Another member of the eag channel family, the human eag-related gene (h-erg), appears to be aberrantly expressed in some cancer cells of epithelial, muscle, and neuronal origin (19, 21, 22) and in the human preosteoclastic cell line, FLG 29.1 (19, 23, 24), but its role in oncogenesis is unknown. There is broad interest in HERG in normal cells because its naturally occurring mutations in cardiac muscle cause type II heart arrhythmias (25–27). More recently, h-erg has been identified in some neuronal cells and cell lines, where it may contribute to the
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resting membrane potential (28, 29), spike frequency adaptation (30), seizure-like activity (31), and hormone secretion (32–35).

In the present study we examined expression of Kv1.3 and two eag family members, h-erg and the recently cloned BEC1, in a broad range of human hematopoietic cell lines, in cells from several chronic lymphocytic leukemia patients, and in peripheral blood lymphocytes from several normal individuals. h-erg was expressed in all of the hematopoietic cell types examined, except Epstein-Barr virus (EBV)-transformed B-cells. h-erg expression (but not BEC1 or Kv1.3) was consistently higher in all the cancer cells than in the noncancer cells. We detected macroscopic HERG currents in three human leukemic cell lines: the T-cell lymphoblastic leukemia, CEM, the chronic myelogenous leukemia, K562, and the histiocytic leukemia, U937, and the average current amplitude correlated with the amount of protein detected by Western blot analysis. Using the specific HERG blocker E-4031, we show that the HERG current plays a role in proliferation of these leukemic cell lines.

**EXPERIMENTAL PROCEDURES**

**Cells—**Normal peripheral blood lymphocytes (PBL) and EBV-transformed B-lymphocytes were generated in the F. Tsui laboratory. Primary cells from patients with Sjögren’s syndrome and B-cell chronic lymphocytic leukemia (B-CLL) were obtained from Dr. A. Bookman (Toronto Western Hospital) and Dr. J. Scott (Toronto General Hospital). Permanent human cell lines representing Burkitt’s lymphoma (Raji), chronic myelogenous leukemia (K562), acute lymphoblastic leukemia (CEM), and acute promyelocytic leukemia (U937 and HL-60) were obtained from ATCC (Manassas, VA). Primary tonsillar lymphocytes were activated by a 72-h incubation in 1% (v/v) of the mitogen, phytohemagglutinin (Sigma). All cells were cultured in endothin-free a-minimal essential medium that was supplemented with 26 mM NaHCO3, 100 mg/ml streptomycin, and 10% fetal bovine serum. The cultures were grown in a humidified incubator at 37 °C, 5% CO2. The cells were counted each day with a hemacytometer using 0.4% trypan blue and then passed every 2 days to maintain them in the exponential growth phase (i.e. maintained at 1–2 × 105 cells/ml). All of the cell culture reagents were purchased from Invitrogen.

**Reverse Transcription-Polymerase Chain Reaction—**For all primary cells and cell lines the total mRNA was extracted using the TriZol® method (Invitrogen). Total mRNA (0.5 μg) reverse transcribed at 37 °C for 30 min in 1× RT buffer (50 mM KCl, 10 mM Tris, pH 8.3, 1.5 mM MgCl2, 0.1% gelatin) with 1 mM dNTP, 5 mM MgCl2, 15 units/μl RNasin, 100 μg/ml oligo(dT), and 50 units SuperScript II reverse transcriptase. After first-strand cDNA synthesis, the PCR amplifications were conducted using the GeneAmp PCR 9600 system (PerkinElmer Life Sciences) with the following primers. For h-erg the forward primer was 5′-ACTTCCTGGGCTGTTTCT-3′ and the reverse primer was 5′-CAGAAATGTCGGCAAGACTC-3′ (product size, 567 bp). For Kv1.3, the forward primer was 5′-TCGAGACCGGACCTGGAAGC-3′ and the reverse primer was 5′-GGTGACTGGAAGAGCGACAC-3′ (product size, ~350 bp). For h-eag, the forward primer was 5′-CGCATGACCTACCTGAAGG-3′ and the reverse primer was 5′-TGTGGACTGGGCGCATTTTC-3′ (data not shown). For BEC1, the forward primer was 5′-CAGCTGTCTGCTGCCTG-3′ and the reverse primer was 5′-TGTCCACCTCTGGCAAGACTC-3′ (product size, 366 bp). The PCR mixture was incubated for 1 min at 95 °C, and then 5 units of TaqDNA polymerase (PerkinElmer Life Sciences) was added. The mixture was subjected to 30 cycles of 95 °C for 1 min, a 15-s denaturing phase at 94 °C, a 15-s annealing phase (at 62 °C for h-erg, 60 °C for Kv1.3, and 64 °C for BEC1), and a 15-s extension phase at 72 °C, with a final extension phase of 6 min at 72 °C. The resulting DNA products were resolved in 2% agarose gels labeled with 0.5 mg/ml ethidium bromide, and their fluorescence intensities were measured with a fluorescence reader (Bio-Rad Fluor-S MultiImager). The identities of the RT-PCR-amplified products were confirmed by sequencing (ACGT, Toronto, Canada).

**Western Analysis—**The cells were lysed in RIPA buffer containing 50 mM Tris, pH 8.0, 1% Nonidet P-40, 150 mM NaCl, 1 mM EDTA, 2 mM Na3VO4, 1 mM NaF, and the protease inhibitors phenylmethylsulfonyl fluoride (1 μM), aprotinin (1 μg/ml), and leupeptin (1 μg/ml), and one protease inhibitor mixture tablet (Roche Molecular Biochemicals). The protein content of the supernatant was measured with the Bradford protein assay (Bio-Rad). Aliquots of 20–50 μg of each lysate were boiled for 3 min in 3× sample buffer (Bio-Rad) and then separated by 10% SDS-PAGE. The proteins were transferred to a nitrocellulose membrane, blocked with 5% nonfat milk in TBS containing 0.1% Tween 20 (TBST), and then incubated with anti-HERG antibody (Alomone Laboratories, Jerusalem, Israel; APC-062, residues 1106–1159 of HERG) overnight at 4 °C. After two washes with TBST, two washes with TBS, the membranes were incubated (for 1 h at room temperature) with horseradish peroxidase-conjugated secondary antibody (1:3000; Cedarlane Labs, Hornby, Canada). Following another two washes with TBST and two washes with TBS, labeled proteins were visualized using ECL on high performance chemiluminescence film (Hypermill®, Amersham Biosciences).

**Electrophysiology—**Whole cell patch-clamp recordings were obtained from CEM, K562, U937, Raji, and HL-60 cells using an Axopatch 200 or 200A amplifier (Axon Instruments, Union City, CA), using 5-KHz filtering and on-line compensation for series resistance and capacitance. All of the signals were analyzed using pCLAMP 6.0 or 8.0 software (Axon Instruments). The data were stored on a computer and displayed using the Origin program (version 6.1; Origin Labs, Northampton, MA). Pipettes with resistances of 3–5 MΩ were made from thin walled borosilicate glass capillaries (WPI, Sarasota). While HERG currents were being recorded, the cells were superfused with an extracellular solution containing 130 mM potassium aspartate, 1 mM CaCl2, 1 mM MgCl2, 5 mM g-glucose, 10 mM HEPES, pH 7.4, adjusted to 300 mOsm with sucrose. The pipette solution contained 130 mM potassium aspartate, 2 mM CaCl2, 1 mM MgCl2, 10 mM EGTA, 2 mM KATP, 5 mM HEPES, titrated with KOH to pH 7.2, and adjusted to 290 mOsm with sucrose. Aspartate was used as the major anion to reduce potential contamination by Cl− currents. All of the recordings were made at 20–23 °C. At normal [K+]o, outward HERG K+ currents are difficult to detect because of rapid inactivation of the channels at depolarized potentials (36–40). However, the currents can be amplified and inward currents can be measured at hyperpolarized potentials by using high extracellular K+ concentrations; we used 130 mM (Nernst potential, −0.4 mV), and hyperpolarizing steps from a holding potential of +20 mV. Stock solutions of CsCl (50 mM) and BaCl2 (1 mM) were made in distilled water and kept at room temperature. The selective HERG channel blocker, E-4031 (13), was prepared as a 1 mM stock solution in distilled water, stored at −20 °C, and then diluted in bath solution to the final concentration.

**Cell Proliferation—**The CyQUANT® cell proliferation assay kit (Molecular Probes, Eugene, OR) (41, 42) was used in conjunction with an HTS7000 BioAssay Reader (PerkinElmer Life Sciences) to assess the effect of the HERG channel blocker, E-4031, on the proliferation of the primary leukemic cells and leukemic cell lines: the T-cell lymphoblastic leukemia, CEM, the chronic myelogenous leukemia, K562, the histiocytic leukemia, U937, and the primary leukemic cells and leukemic cell lines was compared with the starting number of cells (indicated as a percentage of the starting number of cells) indicates an increase in cell proliferation.

**RESULTS**

**Expression of h-erg mRNA and Protein—**RT-PCR was used to detect transcripts for HERG, Kv1.3, and BEC1 channels (h-erg, Kv1.3, BEC1), and β-actin in cells from leukemia patients, several leukemic cell lines, and normal human lymphocytes (Fig. 1). To compare expression between different cells types (Table 1), the fluorescence intensity of each ethidium bromide-labeled product was first normalized to the β-actin signal from the same sample. Then the mRNA expression in the primary leukemic cells and leukemic cell lines was compared with expression in normal (i.e. unstimulated) mature PBL. All nine patients with B-cell chronic lymphocytic leukemia had substantially higher h-erg transcript levels (9–15-fold...
higher in the immature neoplastic B-CLL cells (95% CD5/H11001 hyperplasia and neoplasia, but the highly proliferative mature
primary leukemias and lymphocytes examined but was not
detected in the cell lines, except for CEM and MOLT-4. As a
further indication that h-erg was selectively up-regulated
among the Kv channels expressed, transcripts for the related
channel, h-erg, were not detected in any primary leukemic cells
or nontransformed lymphocytes examined and only at low levels
in K562 and the acute lymphoblastic leukemia cell line,
MOLT-4 (data not shown).

The presence of HERG protein was assessed in CEM, K562,
U937, and HL-60 cells using a polyclonal anti-HERG antibody
and Western blot analysis. We detected immunoreactive dou-
bles at ~130 and 140 kDa, with the highest level in K562 cells,
followed by CEM and then U937 cells, and with very low levels
in HL-60 cells (Fig. 2). A doublet with similarly sized bands has
been previously reported for both endogenous and heterolo-
gously expressed HERG (24, 43–47).

**Patch-Clamp Analysis of HERG Current**—An important fea-
ture of the HERG current is its unusual gating kinetics, that is,
the channels are opened by depolarization but inactivate
extremely quickly (36–40, 48). Inactivation is rapidly removed
by hyperpolarization, allowing the inward current to flow, and
then the channels close (deactivate) slowly. Thus, instead of
producing outward potassium currents like other Kv channels,
the HERG current is mainly inward. HERG is most easily
studied as an inward “tail” current during steps to very nega-
tive potentials after a depolarization to open the channels and
when using a high external potassium concentration to in-
crease the driving force and current amplitude. We monitored
whole cell HERG currents in CEM, K562, and U937 cells by
using an extracellular K+ concentration of 130 mM (Nernst
potential, −0 mV). The channels were activated at the holding
potential of +20 mV, and the inward tail current was measured
during steps to a variety of negative potentials (Fig. 3). U937
cells also exhibited an outward Kv current when extracellular
K+ was low and the holding potential was very negative. This
current was blocked by the potent Kv1.3 blocker, agitoxin-2, or
inactivated by raising the holding potential. The presence of
a Kv1.3-like current is consistent with the robust expression of
Kv1.3 transcripts (Fig. 1) and an earlier report of a Kv1.3-like
current in U937 cells (8). CEM cells also had a small Kv1.3-like
current. In all subsequent experiments, we eliminated Kv1.3-like
currents by holding the membrane potential at +20 mV, a
potential at which steady-state inactivation is complete.
E-4031 was used to assess the amplitude of the HERG compo-
nent, i.e. the current remaining in the presence of 1 μM E-4031
was subtracted from the total current to yield the E-4031-
sensitive HERG current. For CEM cells, 10 of 14 cells had
measurable HERG currents, and the average peak inward
current was −82 ± 11 pA (at −140 mV). For the 8 of 13 K562
cells with detectable HERG current, the average value was
−97 ± 18 pA (at −120 mV). For U937 cells, 6 of 10 cells had
measurable HERG currents, with an average amplitude of
−52 ± 14 pA (at −120 mV). No HERG currents were detected
in Raji or HL-60 cells (data not shown).

Because the cell cycle regulates expression of rat ether-à-
go-go Kv channels heterologously expressed in Xenopus oocytes

### Table I

| Cell type | Cell line | h-erg | BEC1 | Kv1.3 |
|-----------|-----------|-------|------|-------|
| BL        | BL2       | 6     | "    | 1.1   |
| BL        | Raji      | 6     | "    | "    |
| BL        | Ramos     | 1     | "    | 1     |
| CML       | K562      | 19    | "    | "    |
| PML       | U937      | 10    | "    | "    |
| CML       | HL-60     | 1     | "    | 1     |
| ALL       | CEM       | 18    | 2.7  | "    |
| B-CLL     | 9–15      | 0.4–1.1 | 0.7–1.8 |
| EBV       | 1         | "    | "    |
| TON       | 1         | 0.7–2 | 0.7–1.2 |
| SS        | 1         | "    | "    |

* Levels less than those in normal PBL.
The number of K562 cells was significantly reduced by E-4031 at a concentration that fully blocked the HERG current compared with the 5,000 or 10,000 freshly plated cells (Fig. 5). The peak HERG current amplitudes for the cells shown are 171 pA at +140 mV (CEM, capacitance, 6 picofarad), −120 pA at −120 mV (K562, capacitance, 27 picofarad), and −31 pA (U937, capacitance, 18 picofarad). Note the change in the amplitude scale for K562 cells.

Discussion

Expression of K⁺ Channels—Because oncogenic transformation of cells by Ras (50), Src (51), Rous sarcoma virus (52), v-RMSs (53), or SV40 (54) increased K⁺ channel activity; K⁺ channel up-regulation might be a common feature of cancer cells. However, based on our results, the particular K⁺ channel that is up-regulated may be characteristic of the cancer type. We identified transcripts for four Kv channel types in leukemia cells and hematopoietic cell lines: Kv1.3, BEC1, h-eag, and h-erg. Kv1.3 mRNA was expressed in all of the cells at similar levels to unstimulated lymphocytes except in K562 cells, where it was undetectable. We previously reported that K562 cells do not express Kv1.3 currents (8). The lack of up-regulation of Kv1.3 in stimulated tonsillar cells, EBV-transformed B-cells, or cells from Sjögren’s patients is not surprising, because activation of normal peripheral T-cells is only accompanied by a very small increase in Kv1.3 mRNA (41). In normal lymphocytes Kv1.3 is a target for developing new anti-inflammatory drugs because it plays important roles in T-cell proliferation; thus it is interesting that it was not up-regulated in the cancerous cells. A small Kv1.3-like current was present in U937 and CEM cells, which had low levels of Kv1.3 mRNA, but not in K562 cells, in which transcripts were not detected.

BEC1 is a recently cloned channel gene that is related to eag, and Northern analysis only detected it in human brain, where it is enriched in the telencephalon (55). Surprisingly, we found BEC1 transcripts in all of the primary leukemias examined, as well as in resting PBL, activated tonsillar cells, lymphocytes from Sjögren’s patients, and EBV-transformed B-cells. This BEC1 expression in immune cells is a novel finding. The only paper we could find on BEC1 (55) failed to detect transcripts in thymus, spleen, or peripheral blood lymphocytes, perhaps because of the sensitivity of Northern analysis, which is lower than that of RT-PCR analysis. For the hematopoietic cell lines, we detected BEC1 only in CEM cells and at very low levels in MOLT-4 cells. We conclude that BEC1 is not a marker of the cancerous state because it was not elevated in cancer cells compared with normal lymphocytes.

Nor was expression of the other α-go-go gene, h-eag, up-regulated; it was detectable at low levels in only two cell lines (K562, MOLT-4). This is particularly notable because the Eag channel has been proposed as a link between oncogenic transformation and K⁺ channel expression. Although high h-eag expression is normally restricted to the adult brain, it has been found in several somatic cancer cell lines (e.g., breast and cervical carcinomas, neuroblastoma). Moreover, proliferation of these cells is inhibited by reducing eag expression (with specific antisense oligonucleotides) (20), and conversely, transfecting eag into mammalian cells conferred a transformed phenotype characterized by faster growth, loss of contact inhibition and growth factor and substrate dependence, and tumor progression when injected into SCID mice.
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In contrast with Kv1.3, BEC1, and h-eag, we observed dramatic up-regulation of h-erg in all the hematopoietic cell lines examined and, even more importantly, in all the primary leukemias tested. h-erg has also been detected in the human preosteoclastic cell line, FLG 29.1 (19, 23, 24). Our observation that h-erg was not up-regulated in proliferating noncancerous lymphocytes (activated tonsillar cells, EBV-transformed cells, cells from Sjögren’s Syndrome patients), indicates that it is not a marker of proliferation but is selectively up-regulated in leukemic cells. We are not suggesting that HERG is restricted to cancers of hematopoietic origin. It is also up-regulated in a cell line derived from the macrophase-like brain microglia (39, 47), is expressed more frequently in human endometrial cancer tissue compared with normal and hyperplastic endometrium (21) and is present in some cancer cells of epithelial, muscle, and neuronal origin (19, 21, 22). Nor is h-erg expression restricted to cancerous tissue; it is expressed in astrocytes (56) and, most notably, in cardiac muscle, where its mutations cause type II heart arrhythmias (25–27).

Roles of K⁺ Channels in Proliferation—Specific K⁺ channels are involved in activation and proliferation of normal lymphocytes. Kv1.3 activity is important during the early activation phase of naïve T lymphocytes (6, 57), whereas in activated T-cells the SK4 Ca²⁺/calmodulin-activated K⁺ channel is dramatically up-regulated, and not surprisingly, it then plays a greater role in the restimulation that underlies the secondary immune response (41). Different K⁺ channels may underlie the function of transformed lymphocytes. Activity of an unidentified K⁺ channel regulates some functions of human myeloblastic leukemia ML-1 cells and rat basophilic leukemia cells: the early responses to β-integrin-mediated adhesion that lead to cell spreading and the EGF-mediated signal-transduction that is required for initiating cell proliferation (17, 24, 58). Our findings may be of clinical interest. The widespread expression of h-erg transcripts in primary leukemic cells but not in proliferating nontransformed lymphocytes and the significant reduction in proliferation by blocking HERG channels in several hematopoietic cell lines may indicate a role for HERG in the progression of leukemias. The sensitivity of RT-PCR analysis, along with the relative ease of acquiring peripheral blood lymphocytes, may offer a further means of differentiating leukemias from other lymphoproliferative disorders. Because the HERG blocker did not fully inhibit proliferation, it may be that Kv currents modulate, rather than control, tumor cell proliferation. However, there may also be differences in their roles in primary cancer cells, e.g. even in the compelling study linking aberrant Kv channel expression to oncogenesis, reduction of h-erg expression with an antisense oligonucleotide decreased proliferation by only 17–40% in four tumor cell lines (20).

K⁺ channel expression may also be linked to specific phases of the cell cycle. During progression from the G₁ to S phase, many cells undergo changes in membrane potential, cell volume, cytoplasmic pH, and ion content (59, 60), that, in principle, could arise from differing K⁺ channel expression. A requirement for Kv1.3 channel activity was rigorously demonstrated for progression of T lymphocytes through the G₁
phase (13, 61). Other studies show that K⁺ channel expression correlates with the cell cycle and may play a role in progression through the G₁ phase (59, 62–64), but the specific channels were not identified. The currents did not resemble HERG and, based on their drug sensitivity, were most likely Kv1 family members. Expression of EAG current may also be cell cycle-dependent because activity of heterologously expressed EAG channels was suppressed during maturation of Xenopus oocytes (49, 65). We did not directly assess K⁺ channel expression during the cell cycle, but as an initial indication we examined current density as a function of cell size for three of the hematopoietic cell lines. Presumably the largest cells in each culture were just before cell division. There was no compelling relationship. That is, cells with no detectable HERG current were a wide range of sizes, and in cells expressing current there was a generally inverse correlation between cell size and current density. This would occur if the total number of active channels per cell were similar but distributed over a larger surface area in large cells.

We monitored cell numbers following proliferation, which is important to examine the role of specific K⁺ channels, including HERG, in leukemia cell death because leukemias result from aberrant survival, a balance of proliferation and apoptosis, of hematopoietic cells at different differentiation states. In North America, chronic lymphocytic leukemia is the most common form of adult leukemia, and the cells are about 95% of the B-cell phenotype: mostly auto-reactive, antibody-producing tumor cells (e.g. CD5−CD19+H11001+). In nontransformed human lymphocytes, Kᵥ channels main-
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J. Biol. Chem. 2002, 277:18528-18534.
doi: 10.1074/jbc.M200592200 originally published online March 13, 2002

Access the most updated version of this article at doi: 10.1074/jbc.M200592200

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