*Proc. Natl. Acad. Sci. USA*
Vol. 86, pp. 8867–8871, November 1989
Genetics

# Activation of *MYC* in a masked t(8;17) translocation results in an aggressive B-cell leukemia

(*BCL3* gene/oncogene activation/tumor progression)

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ABSTRACT **We have analyzed the oncogene rearrangements involving *BCL2* and *MYC* in the leukemia cells of a patient with an aggressive prolymphocytic leukemia that had an abnormal karyotype including a t(14;18) translocation and a chromosome 17q+. Molecular analysis showed that *BCL2* was rearranged in the major breakpoint cluster region and had joined into the immunoglobulin heavy chain gene as in follicular lymphoma. Cloning and sequence analysis of the rearranged *MYC* gene revealed that *MYC* was truncated at the *Pvu* II site at the end of the first exon of *MYC* and had joined into the regulatory elements of a gene that we called *BCL3* (B-cell leukemia/lymphoma 3). The *BCL3* locus was mapped to chromosome 17 band q22. We found *BCL3* transcribed as a message of 1.7 kilobases in many hematopoietic cell lines representing all hematopoietic lineages. In the patient's leukemia cells, the truncated *MYC* gene was highly expressed under the influence of *BCL3* regulatory elements, leading to an aggressive B-cell leukemia that presumably had been derived from an indolent lymphoma carrying a rearranged *BCL2* gene.**

It is widely appreciated that the development of neoplasia is a clonal process that originates from a single altered tumor cell, while tumor progression is a multiple-step event involving several subsequently occurring cytogenetic changes (1). Evidence has now accumulated that genes are activated in these cytogenetic changes: protooncogenes turn into oncogenes by being placed into the proximity of an "activator" gene (2). Results of these molecular changes include alterations in growth characteristics that accompany the cellular transition from the normal to the neoplastic state.

The best-understood example of a cellular protooncogene placed in close proximity to an "activator" gene in a cytogenetic alteration is *MYC* (c-*myc*) in Burkitt lymphoma. In the t(8;14) translocation in Burkitt lymphoma the *MYC* gene from chromosome 8q24 moves into the neighborhood of the immunoglobulin heavy chain enhancer on chromosome 14q32. Under the influence of this enhancer element *MYC* is then deregulated, while the normal *MYC* allele is transcriptionally silent (3). A parallel situation exists for follicular lymphoma, characterized by a t(14;18) translocation (4, 5), where *BCL2* from chromosome 18q21 is placed in proximity to the immunoglobulin enhancer, again leading to deregulation of the translocated oncogene (4, 5). However, while the deregulation of the *BCL2* gene is associated with low-grade malignancy (6), the activation of *MYC* results in a high-grade malignancy.

More recently, we and others have shown that *MYC* activation also occurs during the progression from a low-grade B-cell lymphoma into a high grade B-cell malignancy, indicating that *MYC* also plays a crucial role during tumor progression (7–10). In addition, others described the occurrence of rearrangements involving chromosome 17 during the progression of hematologic malignancies and in those hematopoietic neoplasms with a very aggressive course of the disease, as well as in solid tumors (11, 12).

In the present study we have analyzed rearrangements of *BCL2* and *MYC* in the leukemia cells of a patient with a very aggressive acute prolymphocytic leukemia with a t(14;18) translocation and additional cytogenetic abnormalities, including 17q+. Cloning studies revealed that the 17q+ chromosome was due to a masked t(8;17) translocation in which *MYC* was placed into the regulatory region of a gene that we called *BCL3*. Although the disease appeared to implicate a single step, we assume that in this case the t(8;17) translocation is a subsequent event in the evolution of a B-cell malignancy that was characterized by a t(14;18) translocation as in follicular lymphoma.

## MATERIALS AND METHODS

**Southern Blotting, Hybridization Procedures, and DNA Probes.** For analysis of genomic DNA, 10-$\mu$g samples were digested with appropriate restriction enzymes, fractionated by electrophoresis, and blotted to nitrocellulose. For analysis of cloned DNA, 300- to 700-ng samples of DNA were used.

Hybridization was carried out in 4× SSC/50% (vol/vol) formamide at 37°C for 16 hr. For screening the genomic library, hybridization was in 5× SSC/1× Denhardt's solution at 65°C (1× SSC is 0.15 M NaCl/0.015 M sodium citrate, pH 7.0; Denhardt's solution is 0.02% Ficoll/0.02% polyvinylpyrrolidone/0.02% bovine serum albumin).

The probe for the joining region of the immunoglobulin heavy (H) chain locus ($J_H$) has been described by Erikson *et al.* (13); the *BCL2* probe is specific for the major breakpoint cluster region of the *BCL2* gene (14). Probes specific for exon 1 and for exon 2/3 of *MYC* and the diversity region of the immunoglobulin H chain locus ($D_H$) have been described (9, 15).

**Library Construction and Screening.** A complete genomic library was constructed in phage vector EMBL3 from partially *Sau*3A-digested DNA derived from the leukemia cells of a patient (designated ALL #217). One million clones were screened with the *BCL2* probe, the $J_H$ probe, and the exon 2/3 probe of *MYC*. The human placenta library was screened with probe p11A-1-1; 5.6 as described in *Results*.

**Subcloning.** DNA fragments were subcloned in pUC19, M13mp18, or M13mp19 vector, and competent *Escherichia coli* DH5 $\alpha$ cells (Bethesda Research Laboratories) were transformed. pUC19 colonies and white M13 phage plaques were analyzed for the presence of insert.

**DNA Sequences and Sequence Analysis.** DNA sequencing was performed by the dideoxynucleotide chain-termination method (16). Analyses of human nucleotides were performed with the University of Wisconsin Genetics Computer Group programs.

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Abbreviations: $J_H$ and $D_H$, joining and diversity regions of the immunoglobulin heavy chain locus.

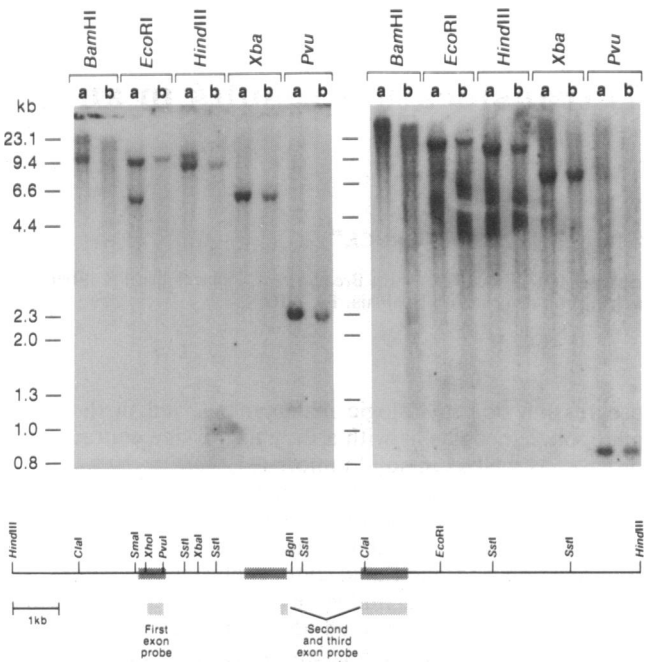


FIG. 1. Southern blot analysis of the patient's DNA (lanes a) and of human placenta DNA (lanes b) by hybridization to the exon 1 probe (*Right*) and exon 2/3 probe (*Left*) of the *MYC* gene. The exon 1 probe and the exon 2/3 probe are indicated in a simplified map of the human *MYC* gene at the bottom. kb, Kilobases.

**Northern Blots.** Total cellular RNA was extracted by using the guanidinium isothiocyanate method (17), analyzed on a 1% agarose gel containing formaldehyde, and transferred to nitrocellulose in 20× SSC.

***In Situ* Hybridization.** The techniques used for *in situ* hybridization were essentially as described (18). Metaphase chromosome spreads were prepared from normal human lymphocytes stimulated with phytohemagglutinin for 72 hr *in vitro*. Chromosome preparations were treated with RNase A (Sigma) at 100 $\mu g \cdot ml^{-1}$ in 2× SSC for 20 min to denature the chromosomal DNA. The preparations were then hybridized with $^3H$-labeled p11A-1-1;5.6 probe (specific activity $3 \times 10^7$ $cpm \cdot ml^{-1}$) in 50% formamide/2× SSC/sonicated salmon sperm DNA at 1 $mg \cdot ml^{-1}$/10% dextran sulfate (Pharmacia), pH 7.0, for 20 hr at 37°C, rinsed thoroughly in 50% formamide in 2× SSC at 39°C, and dehydrated in ethanol. Hybridized slides were coated with Kodak NTB2 emulsion (diluted 1:1 with water), exposed for 16 days, and developed with Kodak Dektol at 15°C. The chromosomes were then G-banded with a mixture of borate buffer (50 mM $Na_2SO_4$/2.5 mM $Na_2B_4O_7$, pH 9.2) and Wright's/Giemsa stain solution.

## RESULTS

**Rearrangements in Leukemia Cells.** When the patient's acute prolymphocytic leukemia (ALL #217) developed, an abnormal karyotype was found which showed a t(14;18) translocation and additional cytogenetic abnormalities, including 17q+, 12q+, and Xp+.

Genomic DNA from the patient's leukemia cells was analyzed for rearrangement of the *BCL2* gene and of the immunoglobulin H chain locus. Southern blots hybridized to the *BCL2* probe and to a $J_H$ probe revealed rearranged bands indicating a joining mistake of the *BCL2* gene from chromosome 18 into the immunoglobulin H chain locus on chromosome 14, as is characteristic for follicular lymphoma with a t(14;18) translocation (4, 5).

Because of the highly aggressive nature of the patient's B-cell disorder, we looked for rearrangement involving *MYC*. When Southern blots were hybridized to the exon 1 probe of *MYC* (Fig. 1 *Right*), no rearrangement was detected; but hybridization to the exon 2/3 probe (Fig. 1 *Left*) revealed rearrangement of the *MYC* gene, with a decapitation of the first exon of *MYC*, as occurs in sporadic Burkitt lymphoma.

To characterize this truncated *MYC* gene and *BCL2* involved in the t(14;18) translocation both rearranged onco-

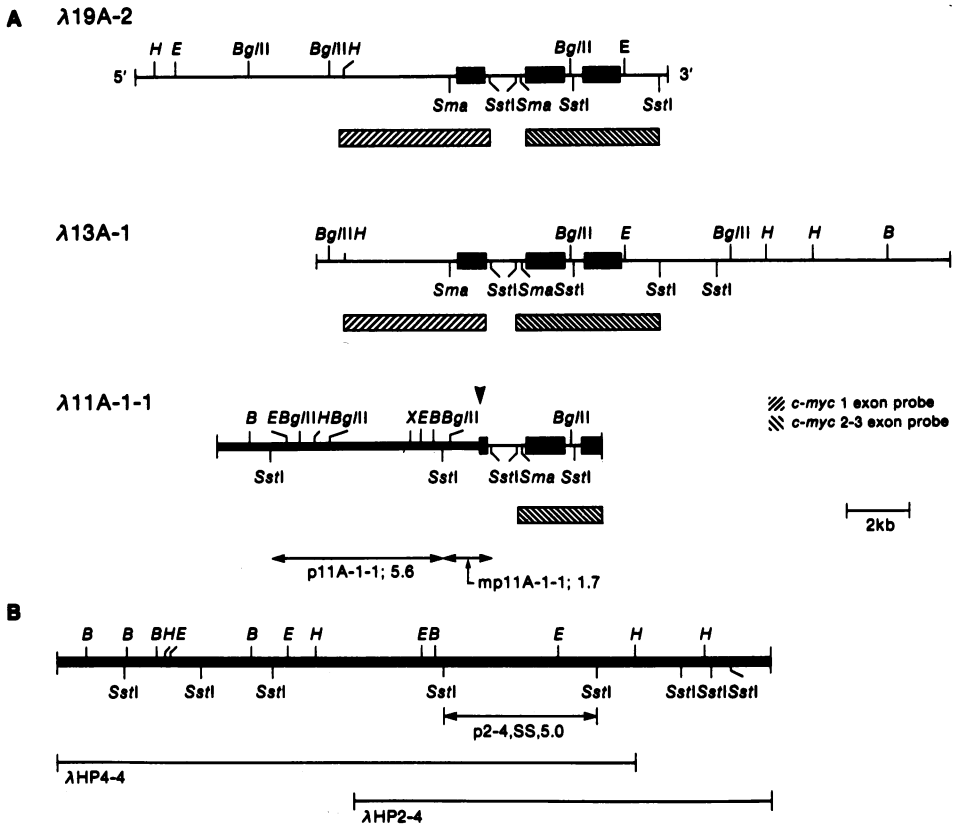


FIG. 2. Restriction map analysis of ALL #217 recombinant clones. (*A*) Restriction maps of three recombinant clones derived from the genomic library of the patient's DNA hybridizing to the exon 2/3 probe of *MYC*. Clones λ19A-2 and λ13A-1 represent the normal *MYC* gene. The bold line shows where the restriction map of λ11A-1-1 diverges from the normal chromosome 8. This portion of the clone is derived from chromosome 17. Triangle indicates the breakpoint. Scale bar = 2 kb. (*B*) Restriction map analysis of the recombinant clones λHP2-4 and λHP4-4 derived from a human placenta library. They represent the normal chromosome 17 and encompass the portion of the breakpoint. Cleavage sites of the restriction enzymes: B, *Bam*HI; E, *Eco*RI; H, *Hin*dIII; *Sma*, *Sma* I.

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1     ggagcaagtctgcgccatgctagtcaccgccgacaagcccagggcgcctctcgggggccctggcagggttgggggcct   77
78    taggaagccacaaggagggctgggggccttggagcaggagtcaggaggcctgggcagcctgaagagtacacgccgacggacagacagacagtgcagtcaccca   180
                                                  PvuII
181   taaagtagaaagcactactaacagcactggagggtgtagtgtttcctactttatggatgatgcttagacgctggatttttttcgggtagtggaaaaaccaggt   283
2842                                              TGCTTAGACGCTGGATTTTTTTCGGGTAGTGGAAAAACCAGGT   2883
                                                  △

284   aagcaccgaagtccacttgccttttaatttatttttttatcactttaatgctgagatgagtcgaatgcctaaataggggtgtcttttctcccattcctgcgcta   386
2884  AAGCACCGAAGTCCACTTGCCTTTTAATTTATTTTTTTATCACTTTAATGCTGAGATGAGTCGAATGCCTAAATAGGGTGTCTTTTCTCCCATTCCTGCGCTA   2986

387   ttgacacttttctcagagtagttatggtaactggggctggggtgggggtaatccagaactggatcggggtaaagtgacttgtcaagatgggagaggagaagg   489
2987  TTGACACTTTTCTCAGAGTAGTTATGGTAACTGGGGCTGGGGTGGGGGGTAATCCAGAACTGGATCGGGGTAAAGTGACTTGTCAAGATGGGAGAGGAGAAGG   3089

490   cagagggaaaacgggaatggtttttaagactacccctttcgagatttctgccttatgaatatattcacgctgactcccggccggtcggacattcctgctttatt   592
3090  CAGAGGGAAAACGGGAATGGTTTTTAAGACTACCCTTTCGAGATTTCTGCCTTATGAATATATTCACGCTGACTCCCGGCCGGTCGGACATTCCTGCTTTATT   3192

593   gtgttaattgctctctgggttttgggggggtgggggttgctttgcggtgggcagaaagccccttgcatcctgagctcggtaccagggtttggtgtag   690
3193  GTGTTAATTGCTCTCTGGGTTTTGGGGGGGTGGGGGTTGCTTTGCGGTGGGCAGAAAGCCCCTTGCATCCTGAGCTC.....TTGGAGTAG   3279
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FIG. 3. Nucleotide sequence across the breakpoint involving *MYC*. Our sequence, shown in lowercase letters in the upper line, is compared to the sequence of the normal *MYC* gene. The bracket indicates the 3′ end of the *MYC* exon 1. The triangle designates the breakpoint on exon 1. In the remaining sequence, promoter-like elements such as a CACCC box, a heptamer having similarity to the glucocorticoid response element, and an Sp1 binding site (CCGCCC) are indicated.

genes were cloned from a genomic library of the patient's leukemia cell DNA (not shown). One of the clones representing the rearranged *BCL2* gene contained fragments hybridizing to both the *BCL2* probe and to the probe specific for the $J_H$ segment. Thus, this clone contains the breakpoint of the t(14;18) translocation on chromosome 14q+. We also obtained a clone representing the reciprocal of the t(14;18) translocation on chromosome 18q−. Fragments of this clone hybridized to the *BCL2* probe and also to a probe specific for the $D_H$ region (9). The restriction map of the $D_H$ portion of this clone shows similarity to the $D_{H2}$ subunit of the germ-line $D_H$ gene (9), but there were some alterations. Thus, it appears that the reciprocal of *BCL2* on chromosome 18q− joins into a variant of the $D_{H2}$ segment.

Three clones were obtained representing the rearranged and unrearranged *MYC* alleles (Fig. 2*A*). Clones λ19A-2 and λ13A-1 show the normal *MYC* gene of chromosome 8, while clone λ11A-1-1 contains the rearranged *MYC* gene. Clone λ11A-1-1 hybridized to the exon 2/3 probe, but not to the exon 1 probe of *MYC*. To the 5′ side of an *Sst* I site in the first intron of *MYC* the restriction map of clone λ11A-1-1 diverges from that of the normal *MYC* gene. Thus, we can assume that a chromosomal break had occurred in the *MYC* gene close to the first intron (15).

Two subclones, designated p11A-1-1;5.6 and mp11A-1-1;1.7, were created. p11A-1-1;5.6 represents a 5.6-kb *Sst* I–*Sst* I fragment from the 5′ end of clone λ11A-1-1 subcloned in pUC19. mp11A-1-1;1.7 contains a 1.7-kb *Sst* I–*Sst* I fragment covering the rearrangement point in *MYC* subcloned in M13 (Fig. 2*A*). The sequence across this breakpoint revealed nucleotide sequence homology to *MYC* in the 3′ region up to the *Pvu* II site at the end of the first exon of *MYC* (Fig. 3), and then, exactly in the *Pvu* II site, the nucleotide sequence diverges. The nucleotide sequence 5′ of the breakpoint is remarkable for promoter-like sequences. Indicated in Fig. 3 are an Sp1 binding site (19), a CACCC box specific for the major β-globin promoter (20), and a heptamer with 86% identity to the glucocorticoid response element (21).

We used the p11A-1-1;5.6 probe to clone the normal genomic counterpart of the breakpoint region from a human placental library. Two clones, designated λHP2-4 and λHP4, were analyzed (Fig. 2*B*), and a 5.0-kb *Sst* I–*Sst* I fragment, p2-4,SS,5.0, was identified that covers the break and contains the promoter region, as revealed by hybridization studies.

**The *MYC* Joining Fragment Maps to the Long Arm of Chromosome 17.** The p11A-1-1;5.6 probe was also used for chromosomal localization of the fragment that joins into *MYC* (29). DNA from a panel of well-characterized rodent–human hybrids containing different overlapping subsets of human chromosomes (22) was tested for the presence of sequences homologous to p11A-1-1;5.6. Hybrid DNA digested with *Eco*RI was analyzed by Southern blotting and hybridized to probe p11A-1-1;5.6. The autoradiogram (not shown) revealed that the p11A-1-1;5.6 locus segregated with a region of the

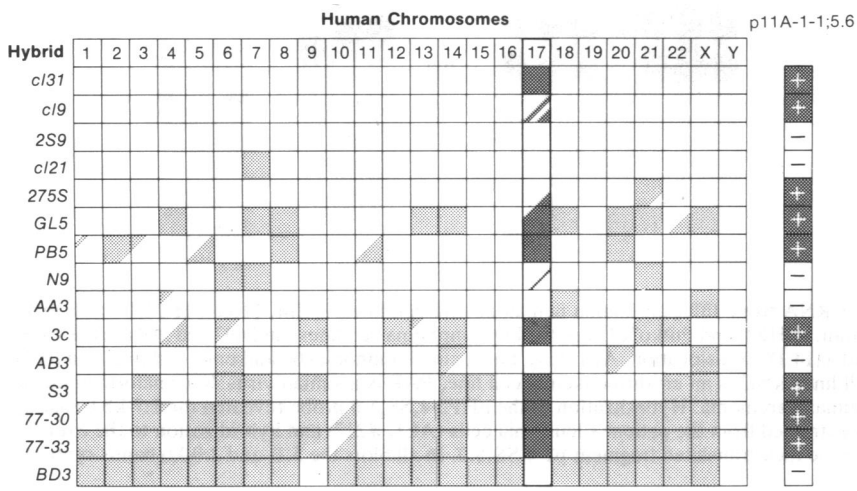


FIG. 4. Presence of the probe p11A-1-1;5.6 in a panel of 15 rodent–human hybrids; ■ indicates that the hybrid named in the left column contains the chromosome indicated in the upper row; ◪ indicates presence of the long arm (or part of the long arm, indicated by a smaller fraction of stippling) of the chromosome shown above the column; ◩ indicates presence of the short arm (or partial short arm) of the chromosome listed above the column; and □ indicates the absence of the chromosome listed above the column. The column for chromosome 17 is boldly outlined and stippled to highlight correlation of presence of this chromosome (or region of this chromosome) with the presence of the respective probe. The patterns of retention of the probe p11A-1-1;5.6 in the panel is shown in the column on the right, where presence of the probe in the hybrid is indicated by a stippled box with a plus sign and absence of the probe is indicated by an open box enclosing a minus sign.

Table 1. Regional localization of the p11A-1-1;5.6 probe on chromosome 17

| Cell line | Chromosome 17-linked DNA probes | | | | | | | Chromosome 17 region retained |
|---|---|---|---|---|---|---|---|---|
| | p53 (17p13) | *ERBB2* (17q11→q12) | *TOP2* (17q21) | *NGFR* (17q21→q22) | *HOX2* (17q21→q22) | p11A-1-1;5.6/ *BCL3* (17q22→q24) | *PKCA* (17q22→q24) | |
| GB31 | + | + | + | + | + | + | + | 17pter→17qter |
| cl9 | − | + | + | − | + | + | + | 17q11→q21, 17q21→qter |
| N9 | − | − | + | + | + | − | − | 17q21→17q22 |
| 275S | − | − | − | + | + | + | + | 17q21→17qter |

The region of chromosome 17 carried by hybrids GB31 and 275S has been defined cytogenetically and confirmed by using DNA probes for chromosome 17-linked genes (23, 24) as shown here and elsewhere. The region of chromosome 17 retained in hybrids N9 and cl9 has been defined by using the DNA markers listed in this table (25). The *BCL3* locus segregates with the *PKCA* locus and is thus distal to the chromosome 17 translocation breakpoint observed in the 275S hybrid, which is derived from an acute leukemia, and far distal to the characteristic acute promyelocytic leukemia breakpoint.

long arm of chromosome 17 (Fig. 4). Several hybrid cell lines retained subregions of chromosome 17 as defined in Table 1, which illustrates that only hybrids with chromosome region 17q22→17qter contain the locus for p11A-1-1;5.6. Since the p11A-1-1;5.6 locus segregates with the *PKCA* (protein kinase C, α polypeptide) locus at 17q22→17qter, our locus is distal to *HOX2* and distal to the breakpoint for acute promyelocytic leukemia (APL) (26).

The localization of the *MYC* joining fragment to chromosome 17 was confirmed by *in situ* hybridization of the $^{3}$H-labeled p11A-1-1;5.6 probe to metaphase chromosomes of human lymphocytes. After autoradiography, 15.8% of the labeling was found over the distal portion of the long arm of chromosome 17q21→17q23, with the peak of hybridization at 17q22 (not shown). Since the long arm of chromosome 17 includes approximately 2.2% of the haploid human genome, our finding is highly significant ($P < 0.005$).

***MYC* Joins a Gene That We have Called *BCL3*.** Since the DNA fragment that had joined into *MYC* revealed features of a promoter region, we hypothesized that this regulatory region might belong to a gene that had not been described before. Therefore, total cellular RNA was extracted from many different human hematopoietic cell lines representing T-cell, B-cell, and myeloid lineages and analyzed on Northern blots which were (Fig. 5) hybridized to the $^{32}$P-labeled nick-translated fragment p2-4,SS,5.0, which covers the break on chromosome 17 (Fig. 2*B*).

As Fig. 5*A* shows, we were able to detect transcripts that were 1.7 kb long, indicating that our gene, which we call *BCL3*, was highly expressed in all leukemia cell lines tested, but it was not expressed in the simian virus 40-transformed human kidney cell line PAF or in HeLa cells.

What might have happened in the masked t(8;17) translocation where the truncated *MYC* gene had joined into the regulatory region of *BCL3*? When total cellular RNA from the patient's leukemia cells was analyzed by Northern blotting, a highly expressed 2.0-kb truncated *MYC* transcript was detectable, while a 2.4-kb transcript was found for the PAF cell line when the exon 2/3 probe of *MYC* was used. ALL #217 did not express the normal *MYC* allele, similar to the case in Burkitt lymphoma, where only the translocated *MYC* is transcribed (3). The same filter was then rehybridized to the DNA fragment termed p2-4,SS,5.0, and the 1.7-kb band corresponding to *BCL3* was also found to be expressed in the patient's leukemia cells (Fig. 5*C*).

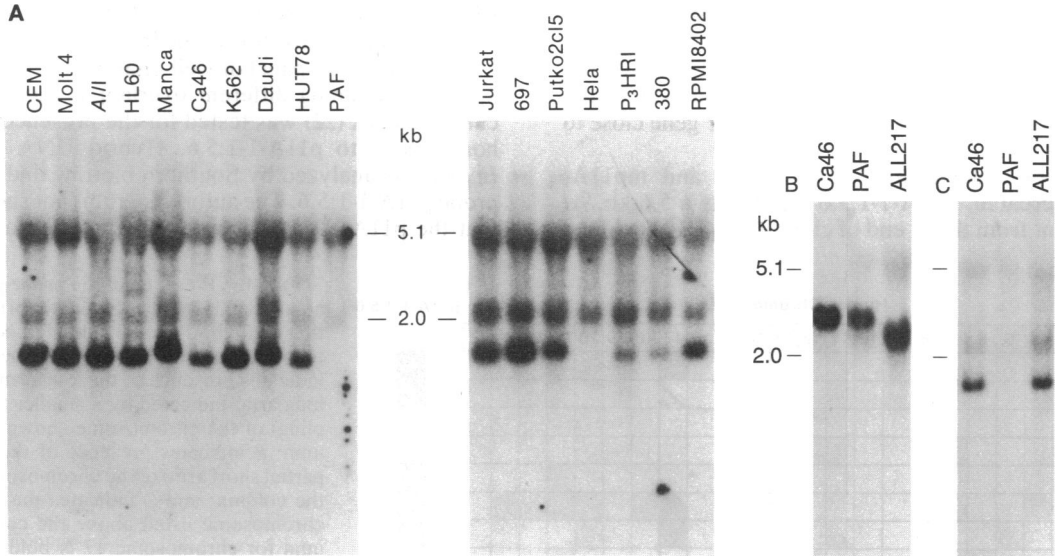


FIG. 5. (*A*) Northern blot analysis of total cellular RNA from different human hematopoietic cell lines. CEM, Molt4, HUT78, and Jurkat represent T-cell leukemia cell lines. Manca, Ca46, Daudi, P3HRI, and Putko2c15 are Burkitt lymphoma cell lines, and 697 and 380 are pre-B-cell lines; 697 carries a t(1;19), and 380 carries a t(8;14) and a (14;18) translocation. ALL I is a Ph+ acute lymphoblastic leukemia cell line, and RPMI 8402 is a B-cell line. HL60 is a myeloid leukemia cell line, K562 is an erythroleukemia cell line, PAF is a simian virus 40-transformed human kidney cell line, and HeLa cells are derived from a human carcinoma. Hybridization to the pHP2-4,SS,5.0 probe revealed the 1.7-kb transcript of the *BCL3* gene. (*B*) Analysis of total cellular RNA extracted from the patient's leukemia cells (ALL #217) and hybridization to the exon 2/3 probe of *MYC*. (*C*) The filter in *B* was rehybridized to the nick-translated fragment p2-4,SS,5.0. In all blots the 5.1- and 2.0-kb bands represent ribosomal RNA.

## DISCUSSION

We have cloned and characterized the oncogene rearrangements in a case of a very aggressive acute prolymphocytic leukemia with a karyotype that includes a t(14;18) translocation and additional cytogenetic abnormalities such as 12q+, 17q+, and Xp+. The finding that *BCL2* was rearranged in a manner characteristic of follicular lymphoma suggests that the patient's leukemia might have been derived from an indolent low-grade B-cell lymphoma (4, 5). The additional cytogenetic abnormalities might have contributed toward progression of the tumor. One of these abnormalities is a cytogenetically undetectable t(8;17) translocation in which *MYC* from chromosome 8 translocated into the regulatory region of *BCL3*, a previously undescribed gene we mapped to chromosome 17 at band q22. Under the influence of regulatory elements of *BCL3*, there is elevated expression of the translocated *MYC* gene while the normal *MYC* allele is transcriptionally silent, as seen in Burkitt lymphoma carrying a t(8;14) translocation (3). We also assume that the high activation of *MYC* might have contributed to the aggressive nature of the patient's leukemia.

The nucleotide sequence of the *BCL3* promoter region reveals the interesting features of an Sp1 binding site (19), G+C-rich repeat units, a glucocorticoid response element (21), and a CACCC box (20). Recent work has shown that the three regulatory elements as we found them in the *BCL3* regulatory region can act in concert and are able to initiate transcription at a high level (27). Interestingly, the long terminal repeat of the mouse mammary tumor virus (MMTV-LTR) containing a hormone response element has also been shown to be an effective activator for *MYC* expression in transgenic mice. In these studies, the *MYC* transgene was deregulated and contributed to an increased incidence of tumors of the testis and breast and of lymphocytic (B- and T-cell) and mast cell origin (28).

The obtained nucleotide sequence across the *MYC* breakpoint reveals information on how the t(8;17) translocation might have occurred. Interestingly, the break on chromosome 8 occurred in the *Pvu* II site at the end of the first exon of *MYC*, an area where point mutations occur often in endemic Burkitt lymphoma (23) or where chromosome breaks are seen in sporadic Burkitt lymphoma (2). The obtained sequence bears certain similarities to the normal *MYC* regulatory region, which also contains Sp1 binding sites and G+C-rich repeat units. Thus, it could be that after a chromosome break occurred in the *Pvu* II site the truncated *MYC* gene became accidentally hybridized into a fragment with a related nucleotide sequence.

The finding that *MYC* from chromosome 8 had joined band q22 of chromosome 17 is also of interest from the viewpoint that the distal portion on q21–q25 of the long arm of chromosome 17 is an area where chromosome rearrangements have been reported in treatment-resistant hematologic malignancies or during the course of their progression (11). The cellular oncogenes *ERBB2* and *ERBA1* are both proximal to *BCL3* and also proximal to the well-studied breakpoint in acute promyelocytic leukemia.

*BCL3* is transcribed as a message of 1.7 kb and is highly expressed in many human hematopoietic cell lines of the T-cell, B-cell, and myeloid types. This may indicate that *BCL3* is activated at an early stage of hematopoietic stem cell differentiation and that its activation during tumor progression is not restricted to B-cell malignancies but might also occur in T-cell and myeloid malignancies. This seems very likely, since *BCL3* is located on the distal portion of the long arm of chromosome 17, where chromosomal breaks occur during the evolution of T-cell, B-cell, and myeloid malignancies. However, further work needs to be done to determine how often the *BCL3* locus is involved in various types of leukemias and lymphomas.

We thank Dr. James Hoxie, from the Hospital of the University of Pennsylvania in Philadelphia, for providing the patient sample, Ms. Janet Finan for performing the karyotype analysis, and Ms. Charlotte Long for preparing the manuscript. This work was supported by National Institutes of Health Grant CA 01279 to C.E.G. and Outstanding Investigator Award CA 39860, American Cancer Society Grant CH398A, and a grant from the W. W. Smith Charitable Trust to C.M.C.

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