

## Molecular cloning of the breakpoint junction of a human chromosomal 8;14 translocation involving the T-cell receptor $\alpha$ -chain gene and sequences on the 3' side of *MYC*

(gene mapping/lymphoid neoplasia/malignant transformation/protooncogene)

TIMOTHY W. McKEITHAN<sup>\*†</sup>, ELIZABETH A. SHIMA<sup>\*</sup>, MICHELLE M. LE BEAU<sup>\*</sup>, JUN MINOWADA<sup>‡§</sup>, JANET D. ROWLEY<sup>\*</sup>, AND MANUEL O. DIAZ<sup>\*</sup>

<sup>\*</sup>Joint Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL 60637; and <sup>‡</sup>Loyola University Stritch School of Medicine, Maywood, IL 60153, and <sup>§</sup>Hines Veteran's Administration Medical Center, Hines, IL 60141

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**ABSTRACT** The MOLT-16 cell line, which was established from the malignant cells of a patient with T-cell acute lymphoblastic leukemia, is characterized by a translocation involving chromosome 8 (band q24) and chromosome 14 (band q11) [t(8;14)(q24;q11)]. To determine the position of the gene encoding the  $\alpha$  chain of the T-cell receptor and of the protooncogene *MYC* (formerly *c-myc*) in relation to the breakpoint junction and to evaluate their possible role in the pathogenesis of T-cell neoplasia, we applied the techniques of *in situ* chromosomal hybridization, Southern blot analysis, and molecular cloning to MOLT-16 cells. Our results indicate that the breakpoint on chromosome 14 at band q11 occurs close to a joining sequence of the gene encoding the  $\alpha$  chain of the T-cell receptor. The constant region and part of the joining region of this gene are translocated to the 3' side of the *MYC* exons. The breakpoints on chromosomes 8 and 14 are close to, but distinct from, those found in SKW-3, another T-cell leukemia cell line, which has a t(8;14). The identification of a breakpoint to the 3' side of *MYC* suggests that this recurring translocation is analogous to the variant t(2;8) and t(8;22) translocations observed in the B-cell malignancies.

Nonrandom chromosomal abnormalities are present in the cells of most human tumors (1, 2). In particular, B-cell lymphocytic neoplasms are often associated with specific cytogenetic abnormalities that correlate with the histological and immunological phenotypes (3). Moreover, experimental evidence obtained during the past few years indicates that the genes located at the breakpoints of the recurring chromosomal translocations in B-cell neoplasms are integrally involved in the pathogenesis of the corresponding tumors. The best understood example is the alteration of the *MYC* (formerly *c-myc*) protooncogene in Burkitt lymphoma, in which one invariably finds one of three translocations [t(8;14), t(2;8), or t(8;22)] involving *MYC* and the immunoglobulin loci. The expression of *MYC* is altered as a result of these rearrangements (4, 5).

Although fewer tumors of T-cell origin have been studied, a distinct pattern of nonrandom karyotypic abnormalities is emerging. Similar to B-cell neoplasms, in which rearrangements frequently involve the chromosomal bands containing the immunoglobulin loci, T-cell neoplasms frequently show rearrangements involving the proximal band of chromosome 14 (14q11), the site of the T-cell receptor  $\alpha$ -chain (*TCRA*) gene (6, 7) and, less often, two regions of chromosome 7 (7q35-q36 and 7p15) to which the  $\beta$  (*TCRB*) (8) and  $\gamma$  (*TCRG*) (9) genes, respectively, have been localized. Band 14q11, the site of *TCRA*, is associated with at least three recurring

abnormalities—inv(14)(q11q32) (10–12), t(11;14)(p13;q11) (13), and t(8;14)(q24;q11). In light of the nonrandom involvement of chromosome 14 in T-cell malignancies, it is likely that the *TCRA* gene plays a role in the pathogenesis of human T-cell neoplasia analogous to that of the immunoglobulin genes in B-cell lymphomas and leukemia.

We have reported an analysis of a translocation 8;14 in the SKW-3 cell line, derived from the malignant cells of a patient with T-cell chronic lymphocytic leukemia (14). In this cell line, the break in chromosome 8 occurs on the 3' side of the *MYC* coding sequences, and the break in chromosome 14 is found within the joining region of the *TCRA* gene (*J $\alpha$* ).

We have now analyzed a second cell line, MOLT-16, which also contains a translocation 8;14. By applying the techniques of *in situ* chromosomal hybridization and Southern blot analysis to MOLT-16, we found that the breaks in chromosomes 8 and 14 occur at sites close to, but distinct from, those found in SKW-3. This analysis has been confirmed by molecular cloning and mapping of the breakpoint junction fragment in MOLT-16.

### MATERIALS AND METHODS

**Cells.** MOLT-16 is a lymphoid cell line that expresses the T-cell-specific surface markers T3, T11, Leu-1, and 3A1; T4, T6, and T8 are each expressed on  $\approx 10\%$  of the cells. This line was established from a patient with T-cell acute lymphoblastic leukemia.

**Cytogenetic Analysis.** For cytogenetic analysis, MOLT-16 cells in logarithmic-phase growth were processed using routine techniques. Chromosomal abnormalities are described according to the International System for Human Cytogenetic Nomenclature (1978) (15).

**DNA Probes.** pMC41 3RC is a 1.4-kilobase (kb) *Cl*<sub>1</sub>*A* I-EcoRI genomic subclone that contains the third *MYC* exon (16). pCA1.7S is a 1.7-kb *Sst* I genomic fragment in pUC19 from a region approximately 800 base pairs (bp) on the 3' side of exon 3. pPA1.3SB is a 1.3-kb *Sst* I-BamHI genomic clone from a region  $\approx 20$  kb on the 3' side of exon 3. pY14, our *TCRA* probe, is a 1.1-kb insert containing a variable (*V $\alpha$* ), *J $\alpha$* , and the constant (*C $\alpha$* ) sequence of *TCRA* (17). pH $\alpha$ T1, our *C $\alpha$*  probe, is a 900-bp cDNA clone for part of the *C $\alpha$*  region (6). The *V $\alpha$*  probe was prepared by cutting a 1.4-kb *Sca* I fragment (0.5-kb insert, 0.9-kb vector) from the pY14 clone. *J $\alpha$ A*, *J $\alpha$ B*, *J $\alpha$ C*, and *J $\alpha$ D* are probes for the *J $\alpha$*  region (18). *J $\alpha$ D* [previously

Abbreviations: *MYC*, cellular homolog of the transforming gene of avian myelocytomatosis virus, formerly *c-myc*; *TCRA*,  $\alpha$  chain of the T-cell receptor; *V $\alpha$* , *C $\alpha$* , *J $\alpha$* , variable, constant, and joining regions, respectively, of the *TCRA* gene; bp, base pair(s); kb, kilobase(s).  
<sup>†</sup>To whom reprint requests should be addressed.

<sup>§</sup>Present address: Fujisaki Cell Center, 675-1, Fujisaki, Okayama, 702 Japan.

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called 5b-12 [14]) is a 2.9-kb *Eco*RI insert specific for a region  $\approx 30$  kb on the 5' side of the  $C_\alpha$  gene segment.

**In Situ Chromosomal Hybridization.** *In situ* chromosomal hybridization was performed as described (19). Radiolabeled probes were prepared by nick-translation with all four of the  $^3\text{H}$ -labeled deoxynucleoside triphosphates (Amersham) to specific activities of  $1.6 \times 10^8$  dpm/ $\mu\text{g}$  (TCRA, pCA1.7S probes),  $2.5 \times 10^8$  dpm/ $\mu\text{g}$  ( $C_\alpha$  and  $V_\alpha$  probes),  $2.1 \times 10^8$  dpm/ $\mu\text{g}$  (pPA1.3SB probe), and  $5.5 \times 10^7$  dpm/ $\mu\text{g}$  (pMC41 3RC probe). Metaphase cells were hybridized at 2.0 and 4.0 (TCRA,  $C_\alpha$ ,  $V_\alpha$ , pCA1.7S, pPA1.3SB probes) or 4.0 and 20.0 (pMC41 3RC probe) ng per ml of hybridization mixture. Autoradiographs were exposed for 11 days at  $4^\circ\text{C}$ .

**Gel Electrophoresis, Southern Transfer, and Hybridization of DNA.** These methods were performed as described (14).

**Molecular Cloning.** MOLT-16 DNA was digested to completion with *Eco*RI and ligated to arms of the  $\lambda$  bacteriophage vector EMBL4 (20), which had been prepared by differential precipitation following double digestion with *Eco*RI and *Bam*HI. The ligated DNA was packaged into bacteriophage with the Gigapack system (Vector Cloning Systems, San Diego, CA) and screened using Colony/Plaque Screen hybridization filters (New England Nuclear) following the procedure suggested by the manufacturer.

## RESULTS

**Cytogenetic Analysis.** Cytogenetic analysis revealed that MOLT-16 consists of two chromosomally abnormal cell lines. Each of 30 metaphase cells analyzed was hypodiploid and contained multiple structural rearrangements. These included a reciprocal translocation involving the long arm (q) of chromosome 3 and the short arm (p) of chromosome 11, a reciprocal translocation between the long arms of chromosome 8 and 14[t(8;14)(q24;q11), Fig. 1], a dicentric translocation of chromosomes 9 and 15, a nonreciprocal translocation involving the short arms of both chromosome 9 homologs, and an unbalanced translocation involving the short arm of chromosome 7. Seventy percent of metaphase cells examined contained these rearrangements; the remaining 30% contained a deletion of the long arm of chromosome 6, in addition to the above abnormalities. Thus, the karyotype of the

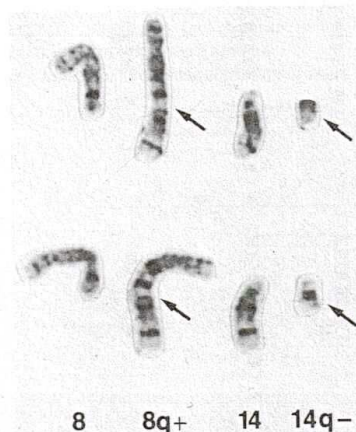


Fig. 1. Partial karyotype of a trypsin-Giemsa-banded metaphase cell of the MOLT-16 cell line illustrating the normal chromosome 8 and 14 homologs and the rearranged chromosomes, 8q+ and 14q-, resulting from the t(8;14)(q24;q11). The rearranged chromosomes are located on the right of each pair of homologs; the chromosomal breakpoints are identified with arrows.

MOLT-16 cell line is 45,XX,-7,-9,t(3;11)(q26;p14),t(8;14)(q24;q11),dic(9;15)(p11;p11),+der(7)t(7;7)(7qter→7p15::7q11→7qter),+der(9)t(9;9)(p24;p11) (70%)/45,XX,same,del(6)(q11q14) (30%).

**In Situ Chromosomal Hybridizations.** The results of *in situ* hybridizations to metaphase cells from the MOLT-16 cell line using probes specific for TCRA and for MYC are listed in Table 1 and illustrated in Figs. 2 and 3.

**TCRA Probe.** To determine whether the TCRA gene was relocated to chromosome 8 as a result of the t(8;14), we hybridized the TCRA probe to metaphase cells from the MOLT-16 cell line. This resulted in specific labeling of the rearranged chromosomes 8 (8q+) and 14 (14q-) as well as the normal 14, but not of the normal chromosome 8 (Fig. 2A, Table 1). Thus, the breakpoint at 14q11 occurs within the TCRA gene, and a portion of this gene is translocated to chromosome 8 as a result of the t(8;14).

**$C_\alpha$  and  $V_\alpha$  Probes.** To determine the position of the break in the TCRA gene relative to the variable and constant region sequences, we hybridized the specific probes for these regions to metaphase cells from the MOLT-16 cell line. In the hybridizations with the  $C_\alpha$  probe, we observed labeling on the 8q+ chromosome, but not on the 14q- chromosome (Fig. 2B, Table 1), whereas the  $V_\alpha$  probe hybridized to the 14q- chromosome only (Fig. 2C, Table 1). These results suggest that the breakpoint on chromosome 14 occurred between the  $V_\alpha$  and  $C_\alpha$  sequences.

**MYC Probes.** To determine whether MYC, which is normally located at 8q24, was moved to chromosome 14 following the t(8;14), we analyzed cells that were hybridized with a MYC-specific probe, pMC41 3RC (Fig. 3A, Table 1). This probe contains the third exon of MYC as well as 565 bp of the 3' sequences (see Fig. 5A). In this analysis, we observed labeling on the normal chromosome 8 at band q24 and on the 8q+ chromosome at the translocation breakpoint junction. The normal chromosome 14 homolog and the 14q- chromosome were not specifically labeled. These results suggest that all or most of the MYC gene remains on chromosome 8 following the translocation.

To determine whether probes derived from sequences on the 3' side of the MYC gene were translocated to chromosome 8, we hybridized two probes, pCA1.7S and pPA1.3SB, to metaphase cells from the MOLT-16 cell line. Hybridization of the pCA1.7S probe, which contains sequences 0.8–2.5 kb from the 3' side of MYC, resulted in labeling of both the normal 8 homolog and the 8q+ chromosome, but not of the 14q- chromosome (Fig. 3B, Table 1). Thus, these results indicate that the breakpoint on 8q is on the 3' side of the sequences encompassed by the pCA1.7S probe and, therefore, is at least 2.5 kb from the 3' side of the MYC gene.

We also hybridized the pPA1.3SB clone, a probe that contains sequences approximately 20 kb from the 3' side of MYC, to MOLT-16 metaphase cells. This resulted in labeling of the normal chromosome 8 only, but not of the rearranged chromosomes 8 or 14 (Fig. 3C, Table 1), indicating that the DNA sequences encompassed by this probe were not translocated to chromosome 14 as a result of the t(8;14) and suggesting that most or all of these sequences were deleted in the 8q+ chromosome.

**Southern Blot Analysis.** To determine whether the MYC and TCRA gene loci were rearranged as a consequence of the translocation, we hybridized Southern blots of MOLT-16 DNA digested with various restriction enzymes to probes specific for the different regions of these genes.

**MYC Probes.** A restriction map of the human MYC gene locus on chromosome 8 (modified from ref. 21) showing the genomic probes used in Southern blot analysis is illustrated in Fig. 5A. The pMC41 3RC probe hybridized only to a germ-line-sized *Eco*RI restriction fragment (data not shown). The pCA1.7S probe, however, hybridized to three *Eco*RI



Table 1. *In situ* chromosomal hybridization of MOLT-16 cells

Probes	Metaphase cells analyzed/ total labeled sites, no./no.	Labeled sites, no. (percent)							
		Chromosome 8				Chromosome 14			
		Normal 8	Bands q23-24	8q+	8q+ breakpoint junction†	Normal 14	Bands q11-13	14q-	14q- breakpoint junction‡
TCRA	100/196	5 (2.6%)	2 (1.0%)	20 (10.2%)*	14 (7.1%)	27 (13.8%)*	21 (10.7%)	13 (6.6%)*	13 (6.6%)
C <sub>α</sub>	100/188	4 (2.1%)	1 (0.5%)	29 (15.4%)*	20 (10.6%)	25 (13.3%)*	22 (11.7%)	2 (1.1%)	2 (1.1%)
V <sub>α</sub>	111/180	6 (3.3%)	1 (0.6%)	11 (6.1%)	3 (1.7%)	28 (15.6%)*	22 (12.2%)	18 (10.0%)*	18 (10.0%)
pMC41 3RC	100/167	15 (9.0%)*	13 (7.8%)	17 (10.2%)*	10 (6.0%)	5 (3.0%)	0	3 (1.8%)	2 (1.2%)
pCA1.7S	100/185	18 (9.7%)*	18 (9.7%)	29 (15.7%)*	17 (9.2%)	6 (3.2%)	2 (1.1%)	3 (1.6%)	2 (1.1%)
pPA1.3SB	100/141	16 (11.4%)*	13 (9.2%)	9 (6.4%)	4 (2.8%)	4 (2.8%)	0	2 (1.4%)	1 (0.7%)

\* $\chi^2$  value corresponds to  $P < 0.0005$ .

†Breakpoint junction consists of bands 8q23 to q24 and bands 14q11 to q13.

‡Breakpoint junction consists of the long arm of the 14q- chromosome (centromere and band q11 of chromosome 14 and band 8q24).

fragments; one fragment was of germ-line size, and the remaining two were fragments found only in MOLT-16 (Fig. 4A, lane 2). One of the fragments was 11 kb. The other

abnormal fragment was 22.8 kb and probably was a partial digestion product. Southern blots performed after digestion with the restriction enzymes *Bgl* II, *Hind* III, and *Xba* I did not show rearranged bands after hybridization to the pCA1.7S probe, but after *Kpn* I digestion, a germ-line-sized (17 kb) and a slightly smaller rearranged band hybridized to this probe (Fig. 4A, lane 4). After hybridization to the pPA1.3SB probe, Southern transfer analysis revealed only germ-line bands following digestion with *Eco* RI and *Bam* HI; digestion with *Kpn* I resulted in only a single band that differed from the placental control. The band most likely resulted from a

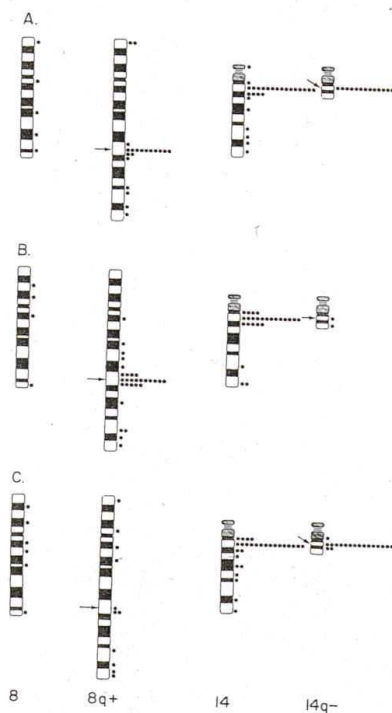


FIG. 2. Distribution of labeled sites on chromosome 8 and 14 homologs in metaphase cells from the MOLT-16 cell line after hybridization with the TCRA (A), C<sub>α</sub> (B), or V<sub>α</sub> (C) probe. The rearranged chromosomes 8 and 14 (8q+ and 14q-) resulting from the t(8;14) are illustrated on the right of each pair of homologs; the arrows identify the translocation breakpoint junctions. Each dot indicates one labeled site observed in the corresponding band. We used the  $\chi^2$  test for goodness of fit to determine whether these chromosomes were specifically labeled; such an analysis tests the hypothesis that labeling is random over the entire genome. According to this test, both the 8q+ and 14q- chromosomes were specifically labeled in the hybridization with the TCRA probe ( $P < 0.0005$ ), whereas only the 8q+ chromosome was labeled in the hybridization of the C<sub>α</sub> probe ( $P < 0.0005$ ), and the 14q- chromosome alone was labeled in the hybridization of the V<sub>α</sub> probe ( $P < 0.0005$ ).

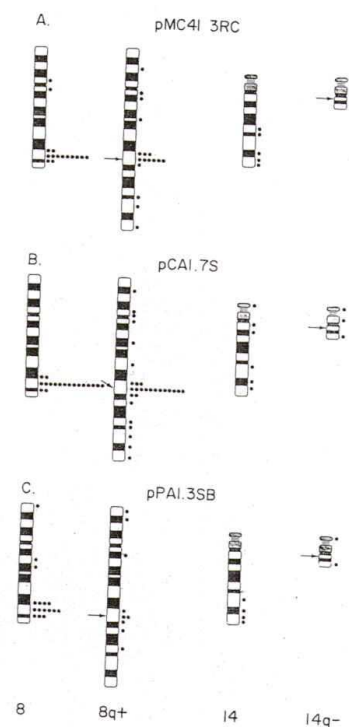


FIG. 3. Distribution of labeled sites on the chromosome 8 and 14 homologs in metaphase cells that were hybridized with the MYC pMC41 3RC (A), pCA1.7S (B), or pPA1.3SB (C) probes. Specific labeling was observed on the normal 8 and the 8q+ chromosomes in the hybridization of the pMC41 3RC and pCA1.7S probes, but only on the normal 8 in the hybridization of the pPA1.3SB probe.

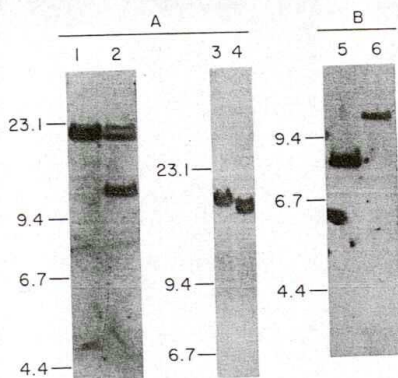


FIG. 4. Hybridization of DNA from the MOLT-16 cell line to MYC probe pCA1.7S (A) and to TCRA J region probe J $\alpha$ D (B). DNA was digested with *Eco*RI (lanes 1, 2, 5, and 6) or *Kpn* I (lanes 3 and 4) and electrophoresed on a 0.8% gel (lanes 1, 2, 5, and 6) or on a 0.6% gel (lanes 3 and 4). The pCA1.7S probe (A) detected an 11-kb rearranged band in the *Eco*RI digest of MOLT-16 DNA that was identical in size to the rearranged band observed after hybridization to the J $\alpha$ D probe (B). (Lanes 1, 3, and 5) Normal human placental DNA used as control. (Lanes 2, 4, and 6) MOLT-16 DNA. Molecular size standards are in kb.

restriction fragment length polymorphism. The results suggest that there was deletion of the sequences homologous to pPA1.3SB from the chromosome 8 involved in the translocation.

**TCRA and J $\alpha$  Probes.** The TCRA probe hybridized to a number of bands in different restriction digests of MOLT-16 DNA. All of these bands correspond to germ-line-sized fragments (data not shown). Four probes homologous to various portions of the J $\alpha$  region were used in Southern transfer analysis. Three of these, J $\alpha$ A, J $\alpha$ B, and J $\alpha$ C, failed to show a rearrangement. A fourth probe, J $\alpha$ D, showed a rearranged band in MOLT-16 DNA digested with *Eco*RI (Fig. 4B) with a size (11 kb) identical to that of the rearranged band seen with the pCA1.7S probe; these results suggested that this 11-kb *Eco*RI fragment contained the translocation breakpoint junction. No unrearranged band was detected with the J $\alpha$ D probe, suggesting that these sequences had been deleted from the normal chromosome 14.

**Molecular Cloning of the Breakpoint Junction.** A library of

*Eco*RI restriction fragments was constructed using the bacteriophage  $\lambda$  vector EMBL4 (20). Approximately 800,000 plaques from a nonamplified library were simultaneously screened using the pCA1.7S and the pPA1.3SB probes. Southern blot analysis suggested that the breakpoint junction fragment from the 8q+ chromosome should contain sequences immediately on the 3' side of MYC (hybridizing to pCA1.7S) but should lack sequences located further away from MYC (hybridizing to pPA1.3SB); the corresponding unrearranged *Eco*RI fragment should hybridize to both probes. A single clone was obtained that hybridized to pCA1.7S but failed to hybridize to pPA1.3SB. As expected, this clone contained an 11-kb *Eco*RI fragment, corresponding to the rearranged fragment seen on Southern blot analysis of MOLT-16 DNA.

Using standard techniques, a restriction map of this clone was prepared and compared to a restriction map of the region 3' of MYC (Fig. 5). A map of the normal region on the 3' side of MYC (Fig. 5A) also illustrates the probes used in these experiments. A map of the t(8;14) junction fragment (Fig. 5B) illustrates the position of the J $\alpha$ D probe. The map limits the possible position of the breakpoint junction to a region of  $\approx$ 850 bp between the *Hind*III and *Bam*HI restriction sites (Fig. 5B, arrows) that lie 6.2–7.0 kb on the 3' side of the MYC coding region. The restriction map was identical for a second clone isolated by simultaneously screening  $\approx$ 400,000 plaques with the J $\alpha$ D and pCA1.7S probes; this result eliminates the possibility of errors due to rearrangements during the cloning process.

## DISCUSSION

The results of *in situ* chromosomal hybridization studies of the MOLT-16 cell line show that the TCRA gene is split by the break in chromosome 14 at band q11. The constant region of this gene is translocated to the 8q+ chromosome distal to MYC, whereas all the variable region sequences detectable by our probe remain on the 14q- chromosome. As shown by Southern transfer analysis, additional bands are seen in digests of MOLT-16 using probes close to the 3' end of the MYC gene. Because new bands were found when two different restriction enzymes were used, it did not appear likely that they resulted from restriction fragment length polymorphisms, but instead were due to a DNA rearrangement and contain the breakpoint junction of the 8;14 translocation. This possibility was strongly supported by the finding that a J $\alpha$  probe and a probe containing sequences on

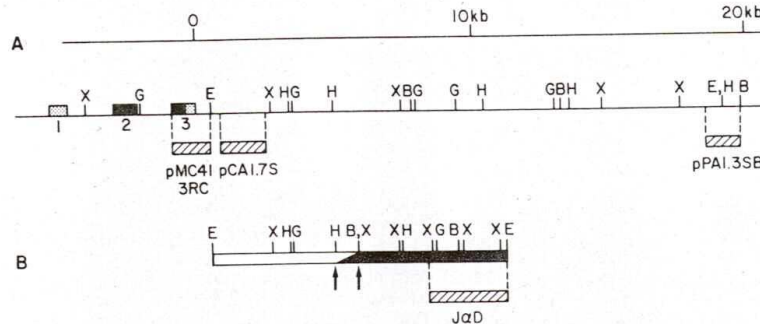


FIG. 5. (A) Restriction map of the human MYC gene locus, including 22 kb of the 3'-flanking region [modified from ref. 21 using data derived from the unrearranged MYC locus of the SKW-3 cell line (14)]. The schematic diagram illustrates the three MYC probes used in these studies. Rectangles represent the three MYC exons; the solid regions are the coding portions of the exons; 5'- and 3'-noncoding regions are stippled. Abbreviations: B, *Bam*HI; G, *Bgl*II; E, *Eco*RI; H, *Hind*III; X, *Xba*I. (B) Restriction map of the 11-kb *Eco*RI restriction fragment containing the chromosomal breakpoint junction of the t(8;14) in MOLT-16. Arrows indicate the limits of the possible location of the breakpoint junction between chromosome 8 sequences (open box) and chromosome 14 sequences (filled box). Also indicated is the region homologous to the J $\alpha$ D probe.



the 3' side of *MYC* hybridized to rearranged bands of identical size following digestion with *EcoRI*, suggesting that *MYC* 3' sequences and *J<sub>α</sub>* sequences are present on the same *EcoRI* fragment as a result of the translocation.

This possibility was confirmed by cloning the 11-kb *EcoRI* fragment and showing that it hybridizes to both probes. The break on chromosome 8 lies 6.2–7.0 kb on the 3' side of *MYC*, while the break on chromosome 14 occurs about 2.6–3.4 kb from the 5' side of the *J<sub>αD</sub>* sequences, the *J<sub>α</sub>* probe that showed rearrangements on Southern blots. The *J* region of the *TCRA* locus is much larger than the *J* regions of the immunoglobulin genes and of *TCRB* and *TCRG* and extends for over 50 kb (18). The *J<sub>αD</sub>* probe is from approximately the middle of this region.

We have reported the analysis of the t(8;14) present in SKW-3, another T-cell leukemia cell line (14). As with MOLT-16, the break in chromosome 8 occurs on the 3' side of *MYC*. The break in SKW-3 is closer to *MYC* and lies 1.4–3.0 kb on the 5' side of the break in MOLT-16. In SKW-3, the break in chromosome 14 occurs almost immediately on the 5' side of the *J<sub>αD</sub>* sequences, at a site 2.5–3.3 kb on the 3' side of the break in MOLT-16.

Rearrangements within the *J* region of the immunoglobulin heavy chain locus occur in some cases of the t(8;14)(q24;q32) of Burkitt lymphoma and in most cases of t(14;18) and t(11;14) of follicular lymphoma and chronic lymphocytic leukemia, respectively. There is considerable evidence that these rearrangements result from errors in the normal mechanisms of *VDJ* joining in this locus (D, diversity) (22–24). We anticipate that the break in chromosome 14 may involve a similar mechanism in *TCRA*. If this proves to be true, a *J* coding sequence may be found immediately adjacent to the breakpoint junction. The region in which the chromosome 14 breakpoint in MOLT-16 occurs is known to contain *J* sequences; however, the precise location of each of these *J* sequences is not yet available.

The translocation t(8;14)(q24;q11) is a nonrandom chromosome abnormality associated with human T-cell neoplasia. This specific translocation has been described in T-cell malignancies and in cell lines established from leukemia cells of patients with T-cell acute lymphoblastic leukemia or chronic lymphocytic leukemia (13, 25, 26). In one study, Caubet *et al.* (26) found that a t(8;14)(q24;q11) resulted in a rearrangement of restriction enzyme sites downstream of the *MYC* gene, consistent with a break in chromosome 8 at a site close to the breakpoint in SKW-3. The gene at the 14q11 breakpoint, however, remains unidentified. Since it is frequently rearranged in other T-cell neoplasms (27), it is likely also to be in the *J* region of *TCRA*. A study of another cell line from a T-cell leukemia patient also showed rearrangement on the 3' side of *MYC*, with a breakpoint within 500 bp of the third *MYC* exon; however, in this case, the origin of the material translocated adjacent to *MYC* was not identified (28). No t(8;14) was seen in this cell line.

The movement of elements of the *TCRA* gene adjacent to *MYC* in the t(8;14)(q24;q11) of T-cell leukemia is reminiscent of the translocations associated with Burkitt lymphoma and other B-cell neoplasms—t(2;8), t(8;14)(q24;q32), and t(8;22)—in which *MYC* and one of the immunoglobulin loci are juxtaposed. However, unlike these translocations, the t(8;14)(q24;q11) does not yet appear to be strongly associated with any characteristic morphologic form of T-cell leukemia or lymphoma.

Selection for cells that contain the translocations associated with Burkitt lymphoma appears to derive from the abnormal *MYC* expression that follows the juxtaposition of an immunoglobulin locus adjacent to this gene. The importance of this translocation in the pathogenesis of the tumors

has been confirmed by the very frequent occurrence of clonal B-cell tumors in transgenic mice carrying, in their germ line, sequences from a breakpoint junction from such a translocation (29). Abnormal regulation of the expression of *MYC* due to its juxtaposition to elements of the *TCRA* is likely to have an equal pathogenetic importance in T-cell neoplasms that contain a t(8;14)(q24;q11).

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