Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 5039–5043, July 1989
Genetics

Involvement of the *TCL5* gene on human chromosome 1 in T-cell leukemia and melanoma

(human T-cell leukemia/human melanoma/oncogene activation/genetics of malignancy)

LAWRENCE R. FINGER*, JACOB KAGAN*, GEORGE CHRISTOPHER*, JOANNE KURTZBERG†, MICHAEL S. HERSHFIELD†, PETER C. NOWELL‡, AND CARLO M. CROCE*

*The Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine, 3420 North Broad Street, Philadelphia, PA 19140; ‡Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA 19104; and †Departments of Pediatrics and Medicine, Duke University Medical Center, Durham, NC 27710

Contributed by Peter C. Nowell, April 7, 1989

ABSTRACT **We analyzed a t(1;14)(p32;q11) chromosomal translocation in a human lymphohemopoietic stem cell line derived from a patient with acute T-lymphoblastic leukemia. The chromosomal joining on the 1p+ chromosome occurred at the T-cell receptor δ diversity ($D\delta_2$) segment, and the reciprocal chromosomal joining on the 14q– chromosome occurred at the T-cell δ diversity segment $D\delta_1$. The involvement of δ diversity segments at the translocation junctions suggests that the translocation occurred during an attempt at $D\delta_1$–$D\delta_2$ joining in a stem cell. The segment of chromosome 1 at band p32, adjacent to the chromosomal breakpoint, encodes a transcriptional unit designated *TCL5* (T-cell leukemia/lymphoma 5). The differential expression of the *TCL5* RNA transcripts in this lymphohemopoietic stem cell line relative to several other T- and B-cell lines suggests that *TCL5* gene expression is an integral event in the pathogenesis of the T-cell leukemia. Rearrangement of the *TCL5* locus in a human melanoma cell line carrying a del(1p32) further implies that the *TCL5* gene may play a role in malignant transformation.**

The finding of consistent chromosomal translocations directly involving the *MYC* and *ABL* oncogenes in, respectively, Burkitt lymphoma and chronic myeloid leukemia (1, 2) led to the now central dogma that chromosomal aberrations that alter the expression of specific genes are involved in the pathogenesis of human leukemias and lymphomas. In T-cell tumors, the majority of chromosomal abnormalities involve the T-cell receptor (TCR) α/δ locus on chromosome 14 at band q11 (3, 4). To identify a possible activated oncogene adjacent to the breakpoint on chromosome 1, and to elucidate mechanisms of such chromosomal translocations, we have cloned and analyzed the junctions of the t(1;14)(p32;q11) translocation in a T-lymphoblastic leukemia involving the TCR α/δ locus.

Human chromosome 1 band p32 aberrations have been detected in acute T-cell leukemia (5, 6), human cutaneous malignant melanomas (7), and human neuroblastomas (8). Definition of the molecular basis of 1p32 abnormalities in human malignancy was approached by characterizing the t(1;14)(p32;q11) translocation observed in two cell lines, DU.528 and 730-3, derived from a 16-year-old boy with acute T-lymphoblastic leukemia (9).

MATERIALS AND METHODS

Molecular Analyses. Procedures for molecular cloning, Southern blot analysis, RNA isolation, and Northern blot analysis were performed as described (10).

DNA Sequencing. After fine genomic mapping of regions of interest, DNA fragments were subcloned in M13mp18 or M13mp19 phage and their sequences were determined by using the Sanger dideoxy method (11) with Sequenase (United States Biochemical).

Cells. Parental cells and somatic cell hybrids used in this study have been described (3, 12, 13). M44c12S5 hybrid retains the 14q+ chromosome from the t(8;14)(q24;q32) translocation. GL5 hybrid retains chromosomes 4, 13, 14, 18, 20, 21, and X and partial chromosomes 17 and 22. 401AD5EF3 hybrid retains partial chromosomes 8 and 22 and chromosomes 19, 21, and X. 52-63c17-17 hybrid retains the 14q+ chromosome from the translocation t(X;14)(q32;q13). PB5 hybrid retains partial chromosomes 1, 2, 3, 5, and 17. GM7299 hybrid retains chromosomes 1, 6, and X. GM7299 hybrid was obtained from the National Institute of General Medical Sciences Human Genetic Mutant Cell Repository (Camden, NJ).

RESULTS

Identification of the t(1;14) Chromosomal Translocation Breakpoint. The t(1;14) chromosomal translocation has been described in the leukemic cells of a 16-year-old boy with acute T-lymphoblastic leukemia (14). Two cell lines, DU.528 (9) and 730-3 (J. Kurtzberg, unpublished results), derived from the leukemic cells prior to and after chemotherapy, respectively, showed an apparently identical karyotype. Our description of the 730-3 karyotype is 47,XY,+17,t(1;13)(p32;q34),t(1;14)(p32;q11). This interpretation, with translocations involving the p32 region of both number 1 chromosomes, differs somewhat from the initial report (9).

On chromosome 14 at band q11 the TCR constant δ chain gene lies within the TCR α locus approximately 85 kilobases (kb) upstream of the constant α locus (15, 16). Direct involvement of the TCR δ locus in the t(1;14) translocation was suggested by the results of the hybridization of the TCR δ pJK3.0S probe to a Southern filter with bound DU.528 and 730-3 DNAs (Fig. 1*A*). Since the pJK3.0S insert has an internal *Hin*dIII site, the probe detects two germ-line restriction fragments, 3.4 and 6.2 kb, in *Hin*dIII-digested placental DNA (Fig. 1*A*, lane 4). In contrast to the expected germ-line *Hin*dIII pattern, pJK3.0S detects a 3.4-kb germ-line restriction fragment and a 9.8-kb rearranged restriction fragment in *Hin*dIII-digested DNAs of DU.528 and 730-3 cells (Fig. 1*A*, lanes 5 and 6). Thus, we concluded that the t(1;14) breakpoint probably occurred within the 9.8-kb *Hin*dIII fragment detected by the pJK3.0S probe. The lack of pJK3.0S hybridization to both a 19-kb *Bam*HI germ-line fragment and a 6.2-kb *Hin*dIII germ-line fragment originating from the DU.528 (and 730-3) nontranslocated chromosome 14 may be

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: TCR, T-cell receptor; V, D, and J, variable, diversity, and joining segments.

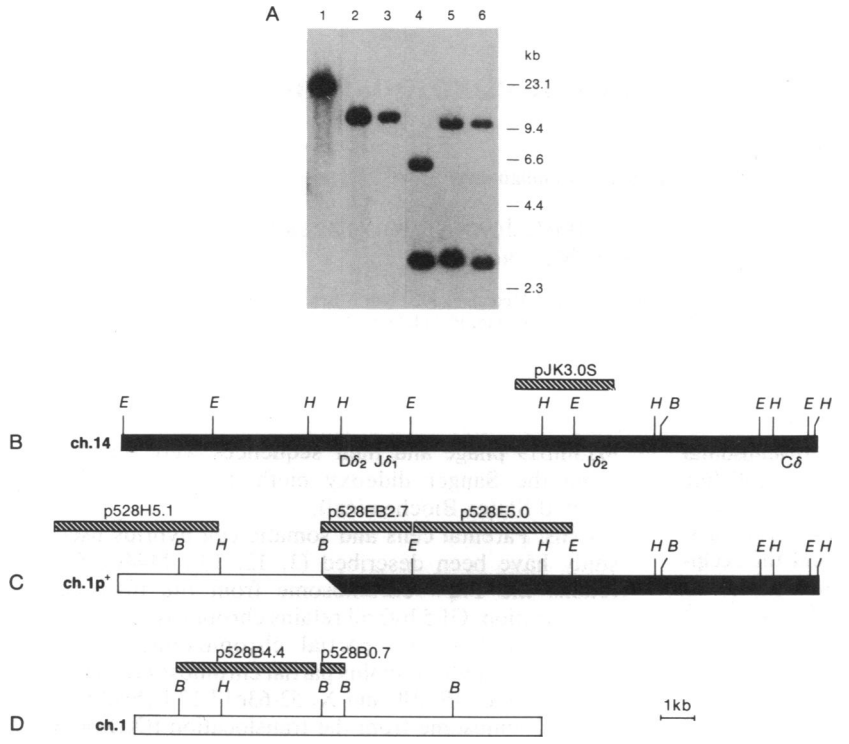

FIG. 1. The t(1;14) chromosomal breakpoint on the 1p+ chromosome. (*A*) Hybridization of DNA from the t(1;14) cell line with the TCR δ pJK3.0S probe. DNA (10 μg) isolated from cells of placenta (lanes 1 and 4), 730-3 (lanes 2 and 5), and DU.528 (lanes 3 and 6) was digested with *Bam*HI (lanes 1–3) or *Hin*dIII (lanes 4–6). (*B–D*) Restriction maps of regions surrounding the 1p+ chromosomal breakpoint in DU.528: (*B*) The normal configuration of the TCR δ locus on chromosome 14. (*C*) The rearranged *TCL5* locus on the 1p+ chromosome. (*D*) The complementary germ-line *TCL5* locus on chromosome 1. Black bar, chromosome 14 DNA sequences; white bar, chromosome 1 sequences. Probes are shown as hatched boxes. Restriction sites: E, *Eco*RI; B, *Bam*HI; H, *Hin*dIII. D, J, and C, diversity, joining, and constant segments.

due to the deletion of this δ allele after functional Vα–Jα rearrangement (V, variable segment).

We have cloned the t(1;14) chromosomal breakpoint from a DU.528 genomic library constructed in the λ phage vector EMBL3A. One class of rearranged clones from the phage library of DU.528 was obtained and a representative map of the overlapping phage clones is shown in Fig. 1*C*. The sizes of the rearranged DU.528 fragments (Fig. 1*A*) are in agreement with the calculated values for the appropriate restriction fragments in the rearranged clone (Fig. 1*C*). To determine the point of divergence from the TCR δ sequences in the rearranged clone, the chromosome 14 p528E5.0 probe, containing a 5.0-kb *Eco*RI fragment as illustrated in Fig. 1*C*, was used to isolate and map the complementary germ-line TCR δ locus from a human placental library (Fig. 1*B*). A repeat-free 5.1-kb *Hin*dIII fragment located close to the breakpoint, where the restriction enzyme sites had diverged from the normal δ locus restriction sites (Fig. 1*C*), was cloned in pUC19 (p528H5.1) to be used in determining its chromosomal origin. Probe p528H5.1 was hybridized to a Southern filter with bound DNA from rodent–human hybrid cells containing either human chromosome 1 or human chromosome 14. The presence in the hybrids of the 5.1-kb *Hin*dIII fragment correlates only with the presence of human chromosome 1 (data not shown), demonstrating that we have cloned the t(1;14) breakpoint on the DU.528 1p+ chromosome (1qter→1p32::14q11→14qter). The p528H5.1 probe was also used to screen a human placental library to clone the normal chromosome 1 counterpart of the breakpoint region (Fig. 1*D*).

Isolation of the Reciprocal Chromosomal Translocation. To complete analysis of the structural aspects of the t(1;14) translocation, we wanted to analyze the joining segment between chromosomes 1 and 14 on the derivative 14q− chromosome (14pter→14q11::1p32→1pter). The p528B0.7 probe contains a germ-line 0.7-kb *Bam*HI insert from chromosome 1 that includes the DU.528 1p+ translocation breakpoint (as illustrated in Fig. 1*D*). Upon hybridization with the p528B0.7 probe, an *Eco*RI digest of DU.528 DNA showed a germ-line fragment of 17.5 kb and rearranged fragments of 8 and 14 kb (Fig. 2*A*, lane 3). The 17.5-kb *Eco*RI fragment (Fig. 2*A*, lanes 2 and 3) corresponds to the germ-line chromosome 1 fragment detected in both the DU.528 and human control DNAs. The 14-kb *Eco*RI rearranged fragment (Fig. 2*A*, lane 3) corresponds to the *Eco*RI segment encompassing the breakpoint on the DU.528 chromosome 1p+.

The 8-kb rearranged *Eco*RI fragment (Fig. 2*A*, lane 3) could correspond to the translocation junction on the derivative

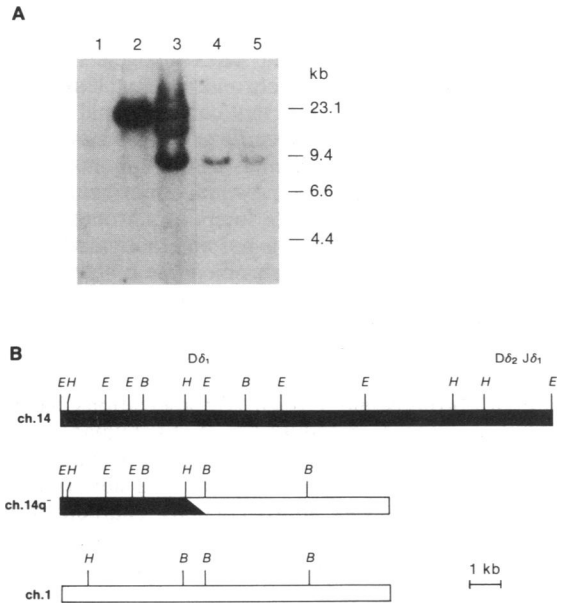

FIG. 2. The 14q− chromosomal reciprocal breakpoint. (*A*) Southern filter hybridized with the p528B0.7 probe, which contains a germ-line chromosome 1 insert encompassing the t(1;14) breakpoint. DNA (10 μg per lane) from mouse cell line (lane 1), human placenta (lane 2), DU.528 cell line (lane 3), hybrid 726c122 (lane 4), and hybrid 726c124 (lane 5) was digested with *Eco*RI, electrophoresed, and transferred to a nitrocellulose filter. (*B*) Restriction maps of the chromosome 14 TCR δ locus (black bar) and the chromosome 1 *TCL5* locus (white bar) that recombined to form the 14q− chromosome of the t(1;14) translocation (black and white bar). E, *Eco*RI; B, *Bam*HI; H, *Hin*dIII.

chromosome 14q− in DU.528. We therefore rescreened the DU.528 genomic library with the p528B0.7 probe, our objective being to obtain clones corresponding to the 14q− chromosome. A comparison of the restriction map representing one class of the above isolated clones with the restriction maps representing the chromosome 1 and chromosome 14 normal counterparts presented in Fig. 2*B* clearly demonstrates that we have also cloned the chromosome 14q− reciprocal breakpoint of the t(1;14) translocation in DU.528.

By subcloning mouse–human hybrids isolated after fusion of mouse and 730-3 cells, we obtained hybrid lines 726c122 and 726c124, which retained the 8-kb rearranged *Eco*RI fragment corresponding to the 14q− (14pter→14q11::1p32→1pter) chromosomal junction region (Fig. 2*A*, lanes 4 and 5). The two hybrids also retained the *L-MYC* locus, which has been mapped to chromosome region 1p32 (17), but did not retain the nerve growth factor β locus, which has been assigned to chromosome region 1p22 or 1p13 (18, 19) (data not shown). Thus, analysis of the somatic cell hybrids is consistent with the *TCL5* locus residing on the short arm of chromosome 1 centromeric to the *L-MYC* locus and telomeric to the nerve growth factor β locus.

Chromosomal Translocation Involves the Dδ Locus. The nucleotide sequences of the translocation junction sites and the normal counterparts are presented in Fig. 3. Except for the loss of one nucleotide at the breakpoint, the chromosome 1 sequences at the junction on the 1p+ chromosome and the 14q− chromosome are continuous in relation to the germ-line chromosome 1, thus demonstrating the reciprocity of the translocation in relation to chromosome 1. Examination of the sequence from chromosome 14 at the translocation junction identified features which may have influenced the translocation process. The joining on the 1p+ chromosome occurred at the $D\delta_2$ segment (Fig. 3*A*). An unrearranged $D\delta_2$ segment normally possesses the 3′ and 5′ heptamer and nonamer recombination signal sequences used during D segment rearrangements (16). Strikingly, the t(1;14) breakpoint on the 1p+ chromosome occurred in $D\delta_2$ precisely at a site where normal D segment rearrangement occurs—i.e., at the site immediately 3′ to the 5′ signal sequences, such that these sequences are lost during the recombination process (20).

The chromosome 14 sequences from the reciprocal chromosome 14q− side of the breakpoint demonstrate that the junction site is at the $D\delta_1$ segment of the TCR δ locus (Fig. 3*B*). Analogous to normal D segment rearrangement (20), the reciprocal breakpoint has occurred precisely 5′ to the 3′ $D\delta_1$ signal sequences. Extra nucleotides present at both the junction sites on chromosomes 1p+ and 14q− are highlighted by the stippled rectangles in Fig. 3 and are not derived from the normal germ-line sequences. Such additional nucleotides at breakpoints in B- and T-cell translocations may represent N regions, stretches of extra nucleotides that are presumably added by the enzyme terminal transferase at the pre-B- and pre-T-cell stage of differentiation.

Identification of the *TCL5* Gene. Frequently, chromosomal loci aberrantly juxtaposed to immunoglobulin superfamily loci by chromosomal rearrangements are inappropriately transcriptionally active, a feature which is thought to reflect the transcription of a gene contributing directly to the malignant process (1). We therefore sought evidence for the presence of a gene located in the region of chromosome 1 adjacent to the t(1;14) translocation breakpoint by performing Northern blot analysis using purified insert from the p5028B0.7 probe (528B0.7), a fragment from normal chromosome 1 which overlaps the breakpoint. Total cellular RNAs used for Northern blot analyses were from 730-3, an acute lymphoblastic leukemia T-cell line (TALL-101), a γ/δ-producing T-cell line (Peer), an α/β-producing T-cell line (Jurkat), and a pre-B-cell leukemia cell line (697). Hybridization of a filter retaining these RNAs to a ribosomal probe indicates that there are similar amounts of 28S ribosomal RNA in sample lanes (Fig. 4*B*). The same RNA preparations on a duplicate filter show various sizes and amounts of transcripts hybridizing to the chromosome 1 probe, 528B0.7 (Fig. 4*A*). The 528B0.7 probe detects a 5.4-kb RNA transcript and possibly a low level of 2.2- and 2.6-kb RNA transcripts in the T-cell lines Jurkat and TALL-101. The gene represented by these transcripts, located at the translocation junction on chromosome 1, is designated *TCL5* (T-cell leukemia/lymphoma 5). A barely detectable level of a 5.4-kb *TCL5* RNA transcript in the 730-3 and Peer T-cell lines and the 697 pre-B-cell line may be due either to low expression of *TCL5* or to nonspecific cross-hybridization to 28S ribosomal RNA. In the 730-3 cell line, however, the 528B0.7 probe detects a high expression of the 2.2- and 2.6-kb *TCL5* RNA transcripts, suggesting that an alteration of *TCL5* gene expression in 730-3 cells is directly involved in the neoplastic process in this human T-cell leukemia.

Alteration of *TCL5* Locus in a Melanoma Cell Line with a 1p32 Chromosomal Abnormality. A number of human cutaneous malignant melanomas (CMM) have been shown to carry nonrandom chromosome 1p deletions or rearrangements which often appear to involve the proximal segment 1p12→1p22 (7). Approximately 8–12% of all CMMs occur in individuals with a family history of the disease (26). Genetic studies of familial CMM kindreds indicate a highly penetrant, autosomal, dominant mode of inheritance for a dysplastic nevus syndrome/CMM susceptibility gene with provisional linkage to the Rh blood locus on chromosome region 1p34–36 (27).

We have examined the possible involvement of the *TCL5* locus in chromosome 1 aberrations in several melanoma cell lines. The p528B4.4 probe, which contains a 4.4-kb *Bam*HI

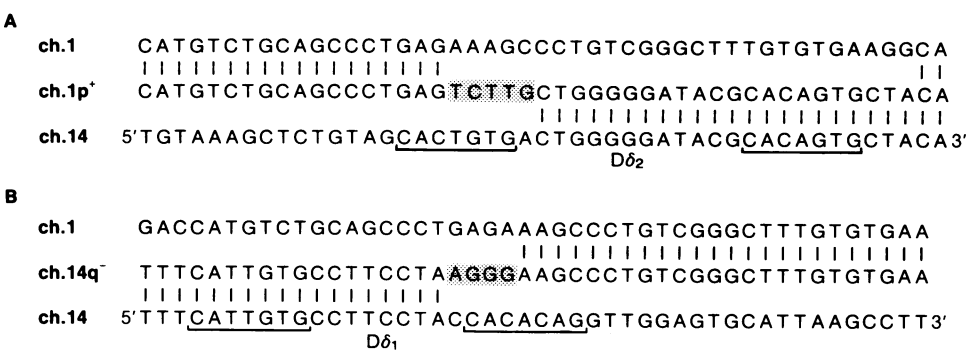

FIG. 3. Comparative nucleotide sequence at the t(1;14) translocation junctions and alignment to the corresponding germ-line sequence. Vertical lines indicate identities. (*A*) The 1p+ chromosomal breakpoint sequence. (*B*) The 14q− chromosomal reciprocal breakpoint sequence. Germ-line chromosome 14 $D\delta_1$ and $D\delta_2$ sequences are shown as previously published (16). Brackets indicate heptamer signal sequences of the Dδ segments. The shaded sequences are thought to represent N regions.

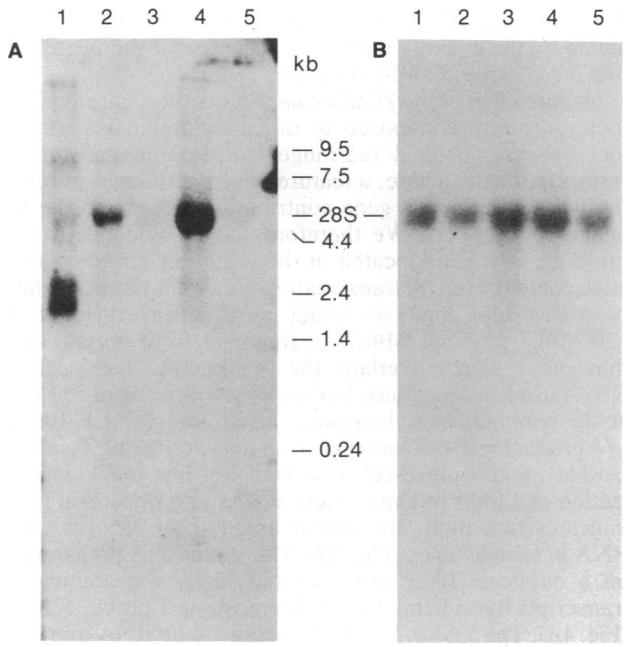

FIG. 4. Expression of a *TCL5* transcript. Samples (10 μg) of total cellular RNA from five cell lines were electrophoresed in 1% agarose containing 2.2 M formaldehyde and then transferred to nitrocellulose. Duplicate filters were prepared and hybridized with the *TCL5* 528B0.7 probe (*A*) or with the human ribosomal pA probe (*B*) (21). Filters were washed with 15 mM NaCl/1 mM sodium phosphate, pH 7.4/0.1 mM EDTA/0.1% $NaDodSO_4$ at 42°C prior to autoradiography. Lane 1, 730-3; lane 2, TALL-101 (22); lane 3, Peer (23); lane 4, Jurkat (24); lane 5, 697 (25).

fragment derived from chromosome 1 adjacent to the breakpoint on the 1p+ chromosome as illustrated in Fig. 1*D*, detected a genomic rearrangement in DNA from the primary melanoma cell line WM8. Two DNA preparations from the WM8 cell line yielded identical results (Fig. 5, lanes B and C). The WM8 cell line carries a del(1)(p32) and numerous other chromosomal aberrations (M. Herlyn and P.C.N., unpublished results). Genomic rearrangements detected in WM8 DNA compared to human control DNA by using several different restriction enzymes allowed us to exclude restriction fragment length polymorphisms as an explanation of the

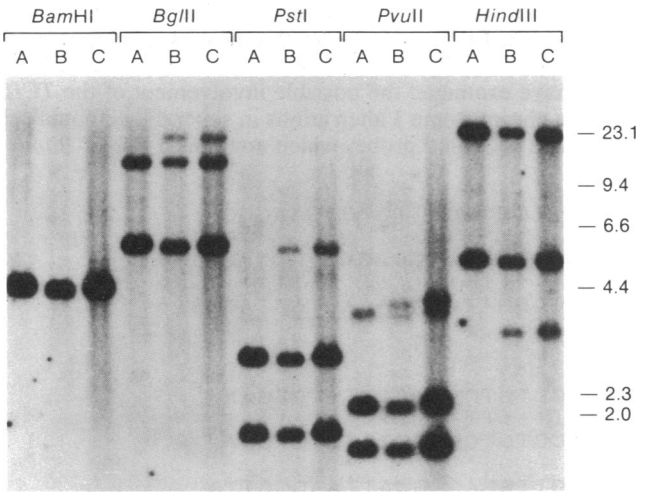

FIG. 5. Rearrangement of the *TCL5* locus in WM8 melanoma DNA. Samples (10 μg) of GM607 DNA used as a germ-line control (lanes A) or WM8 DNA (lanes B and C) were digested with the enzymes indicated, fractionated, and hybridized with the p528B4.4 probe.

new rearranged fragments. The lower intensity of the rearranged restriction fragments relative to the germ-line restriction fragments may be due to a low copy number of the del(1)(p32) chromosome relative to the other chromosomes 1 observed in WM8, which is a hypotetraploid cell line. Thus, we have presented evidence for the involvement of the *TCL5* locus in two different tumor cell types with chromosome 1 aberrations.

DISCUSSION

At the molecular level, the t(1;14) breakpoint that we have analyzed is reminiscent of a physiologically recombining TCR gene segment. The DU.528 1p+ chromosomal breakpoint occurred 5′ of the $D\delta_2$ segment, precisely where one would expect to find breakage mediated by the recombinase. Our analysis of the DU.528 14q− chromosomal breakpoint sequence indicates that the reciprocal breakpoint site is immediately 3′ of the $D\delta_1$ segment, again precisely where one would expect to find breakage mediated by the recombinase. A rule that applies to recombinase-mediated V–D–J joining is that recombination can occur only between heptamer and nonamer signals separated on one side of the potential join by 23 base pairs and on the other side by 12 base pairs (20). Without violating this rule, $D\delta_1$–$D\delta_2$ somatic recombination can occur early in development of a T cell. The model that emerges, therefore, from the t(1;14) translocation is that the stem cell precursor of the tumor cell was undergoing rearrangement of TCR δ; as $D\delta_1$–$D\delta_2$ joining was in the process of occurring, the recombinase had made a sequence-specific cut at $D\delta_1$ and at $D\delta_2$, but instead of completing the $D\delta_1$–$D\delta_2$ fusion, the inadvertent breakage of chromosome 1 resulted in the interchromosomal reciprocal joining of the chromosome 1 sequences at the $D\delta_1$ and $D\delta_2$ breakage sites on chromosome 14 (Fig. 6*A*). From a mechanistic view these results imply that the translocation event occurred specifically during TCR gene assembly mediated by the recombinase enzyme system. This view of the mode of chromosomal translocation is supported by sequence analysis in B-cell tumors of the t(14;18)(q32;q21) chromosomal junctions of follicular lymphomas and the t(11;14)(q13;q32) chromosomal junctions of chronic lymphocytic leukemias (CLL) (28). While the 14q+ chromosome in the follicular lymphomas and CLLs involved a J heavy chain segment, the reciprocal joining sites on the 18q− and the 11q− chromosomes involved a D heavy chain segment, indicating that these translocations may also have occurred during attempts at physiological recombination of

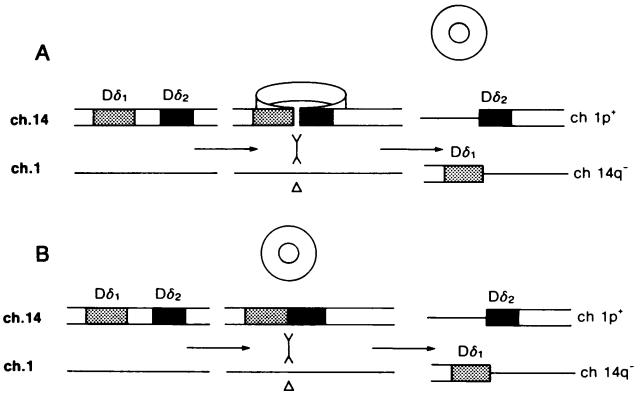

FIG. 6. Models of the t(1:14) translocation. $D\delta_1$ and $D\delta_2$ segments are shown by the stippled and black boxes, respectively. Chromosomes 1 and 14 are shown by a single and a double line, respectively. (*A*) The translocation and $D\delta_1$–$D\delta_2$ attempted joining occur simultaneously. (*B*) The $D\delta_1$–$D\delta_2$ joining precedes the translocation. The triangle represents the breakpoint site on chromosome 1.

gene segments into a mature gene of the immunoglobulin superfamily.

Another possibility in the present instance is that a $D\delta_1$–$D\delta_2$ rearrangement occurred before the chromosome 1 sequences translocated into this rearranged $D\delta$ locus (Fig. 6*B*). In this model, the recombinase-signal-like sequences would have been deleted prior to the translocation, and consequently the translocation process would not necessitate the usage of the recombinase enzyme system. However, DNA sequence analysis of a number of T-cell chromosomal translocation junctions supports the view that the recombinase enzyme system makes at least one sequence-specific cut at the chromosomal breakpoint (4).

Evidence is accumulating that chromosomal aberrations may result in the deregulation of expression of a protooncogene juxtaposed to the chromosomal breakpoint. This is true of the *MYC* protooncogene in Burkitt lymphoma (1). Analogously, chromosome 1 in the present circumstance may be contributing a "growth regulatory" gene, designated *TCL5*, whose expression is disturbed by its new location within the TCR α/δ locus. *TCL5* RNA transcripts of 5.4 kb were detected in several T-cell lines, but only the 730-3 cell line had high expression of the 2.2- and 2.6-kb *TCL5* RNA transcripts. High expression of the 2.2- and 2.6-kb *TCL5* transcripts may be relevant to tumor pathogenesis. Interestingly, no significant expression of a 5.4-kb *TCL5* RNA was detected in 730-3 cells. Assuming that the 5.4-kb transcript derives from its uninvolved *TCL5* allele, *TCL5* gene expression from the translocated allele may escape normal transcriptional control, while the *TCL5* allele on the uninvolved chromosome 1 in 730-3 cells remains subject to regulation. This interpretation is compatible with the previous finding that the translocated *MYC* gene is expressed and the normal *MYC* gene on the uninvolved chromosome 8 is not expressed in Burkitt lymphoma (29, 30). Alternatively, since the other chromosome 1 in 730-3 cells is involved in a t(1;13)(p32;q34) translocation, normal *TCL5* gene expression from this allele may be shut off by this rearrangement. Thus far, however, we have not detected genomic DNA rearrangements related to the t(1;13) translocation in these cells.

We have also shown *TCL5* gene rearrangement in a different tumor type, a human melanoma cell line, carrying a del(1p32). This observation strengthens the proposition that the *TCL5* gene may become involved in tumor pathogenesis as a result of chromosomal aberration. The challenge now will be to determine how widely this gene is involved in tumor development and its role in both normal and abnormal cellular growth.

Note Added in Proof. Since the submission of this manuscript, Begley *et al.* (31) have published their molecular analysis of the t(1;14) translocation observed in DU.528 cells. Our findings differ in two aspects: (*i*) we feel the DU.528 karyotype is best described as 47,XY,+17,t(1;13)(p32;q34), t(1;14)(p32;q11) and (*ii*) since our data indicate that the t(1;14) chromosomal breakpoint is proximal to the *L-MYC* gene, the putative new oncogene (*TCL5*, *SCL*) appears to be located at chromosome band 1p32 rather than band 1p33. We have also presented data demonstrating that two leukemic T-cell lines without the t(1;14) translocation express a *TCL5* RNA transcript that is larger than the predominant *TCL5* RNA transcripts in DU.528 cells illustrated in both papers.

We thank Dr. K. Huebner for making available a number of the hybrid DNAs and critically reading the manuscript; Dr. M. Herlyn for the use of the WM8 cell line; Drs. J. Minna, M. Isobe, and R. Harvey for providing probes; J. Finan and E. DeJesus for excellent technical assistance; and C. Long for manuscript preparation. This work was supported in part by National Institutes of Health Grants CA 09485, CA 39860, and CA 25875 and American Cancer Society Grant CH-378 (all to C.M.C.) and by National Institutes of Health Grant CA-42232 (to P.C.N.).

1. Croce, C. M. & Nowell, P. C. (1985) *Blood* **65**, 1–7.
2. Kurzrock, R., Gutterman, J. U. & Talpaz, M. (1988) *N. Engl. J. Med.* **319**, 990–998.
3. Croce, C. M., Isobe, M., Palumbo, A., Puck, J., Ming, J., Tweardy, D., Erikson, J., Davis, M. & Rovera, G. (1985) *Science* **227**, 1044–1047.
4. Rabbitts, T. H., Boehm, T. & Mengle-Gaw, L. (1988) *Trends Genet.* **4**, 300–304.
5. Mathieu-Mahul, D., Bernheim, A., Sigaux, F., Daniel, M. T., Larsen, C. J. & Berger, R. (1986) *C. R. Acad. Sci. (Paris)* **302**, 525–528.
6. Raimondi, S. C., Pui, C. H., Behm, F. G. & Williams, D. L. (1987) *Blood* **69**, 131–134.
7. Balaban, G. B., Herlyn, M., Clark, W. M., Jr., & Nowell, P. C. (1986) *Cancer Genet. Cytogenet.* **19**, 113–122.
8. Gilbert, F., Balaban, G., Moorhead, P., Bianchi, D. & Schlesinger, H. (1982) *Cancer Genet. Cytogenet.* **7**, 33–42.
9. Kurtzberg, J., Bigner, S. H. & Hershfield, M. S. (1985) *J. Exp. Med.* **162**, 1561–1578.
10. Finger, L. R., Huebner, K., Cannizzaro, L. A., McLeod, K., Nowell, P. C. & Croce, C. M. (1988) *Proc. Natl. Acad. Sci. USA* **85**, 9158–9162.
11. Sanger, F., Nicklen, S. & Coulson, A. R. (1977) *Proc. Natl. Acad. Sci. USA* **74**, 5463–5467.
12. Dürst, M., Croce, C. M., Gissmann, L., Schwarz, E. & Huebner, K. (1987) *Proc. Natl. Acad. Sci. USA* **84**, 1070–1074.
13. Haluska, F. G., Huebner, K., Isobe, M., Nishimura, T., Croce, C. M. & Vogt, P. K. (1988) *Proc. Natl. Acad. Sci. USA* **85**, 2215–2218.
14. Herschfield, M. S., Kurtzberg, J., Harden, E., Moore, J. O., Whang-Peng, J. & Haynes, B. F. (1984) *Proc. Natl. Acad. Sci. USA* **81**, 253–257.
15. Isobe, M., Russo, G., Haluska, F. G. & Croce, C. M. (1988) *Proc. Natl. Acad. Sci. USA* **85**, 3933–3937.
16. Takihara, Y., Tkachuk, D., Michalopoulos, E., Champagne, E., Reimann, J., Minden, M. & Mak, T. W. (1988) *Proc. Natl. Acad. Sci. USA* **85**, 6097–6101.
17. Nau, M. M., Brooks, B. J., Battey, J., Sausville, E., Gazdar, A. F., Kirsch, I. R., McBride, O. W., Bertness, V., Hollis, G. F. & Minna, J. D. (1985) *Nature (London)* **318**, 69–73.
18. Münke, M., Lindgren, V., de Martinville, B. & Francke, U. (1984) *Somatic Cell. Genet.* **10**, 589–599.
19. Garson, J. A., van den Berghe, J. A. & Kemshead, J. T. (1987) *Nucleic Acids Res.* **15**, 4761–4770.
20. Sakano, H., Kurosawa, Y., Weigert, M. & Tonegawa, S. (1981) *Nature (London)* **290**, 562–565.
21. Erickson, J. M., Dorney, D. J., Wilson, G. N. & Schmickel, R. D. (1981) *Gene* **16**, 1–9.
22. Valtieri, M., Santoli, D., Caracciolo, D., Kreider, B. L., Altmann, S. W., Tweardy, D. J., Gemperlein, I., Mavilio, F., Lange, B. & Rovera, G. (1987) *J. Immunol.* **138**, 4042–4050.
23. Hata, S., Brenner, M. B. & Krangel, M. S. (1987) *Science* **238**, 678–681.
24. Sangster, R. N., Minoada, J., Suciu-Foca, N., Minden, M. & Mak, T. W. (1986) *J. Exp. Med.* **163**, 1491–1508.
25. Findley, H. W., Jr., Cooper, M. D., Kim, T. H., Alvarado, C. & Ragab, A. H. (1982) *Blood* **60**, 1305–1309.
26. Greene, M. H. & Fraumeni, J. F. (1979) in *Human Malignant Melanoma*, eds. Clark, W. H., Jr., Goldman, L. I. & Mastrangelo, M. J. (Grune and Stratton, New York), pp. 139–166.
27. Greene, M. H., Goldin, L. R., Clark, W. H., Jr., Lovrien, E., Kraemer, K. H., Tucker, M. A., Elder, D. E., Fraser, M. C. & Rowe, S. (1983) *Proc. Natl. Acad. Sci. USA* **80**, 6071–6075.
28. Tsujimoto, Y., Louie, E., Bashir, M. M. & Croce, C. M. (1988) *Oncogene* **2**, 347–351.
29. ar-Rushdi, A., Nishikura, K., Erikson, J., Watt, R., Rovera, G. & Croce, C. M. (1983) *Science* **222**, 390–393.
30. Nishikura, K., ar-Rushdi, A., Erikson, J., Watt, R., Rovera, G. & Croce, C. M. (1983) *Proc. Natl. Acad. Sci. USA* **80**, 4822–4826.
31. Begley, C. G., Aplan, P. D., Davey, M. P., Nakahara, K., Tchorz, K., Kurtzberg, J., Hershfield, M. S., Haynes, B. F., Cohen, D. I., Waldmann, T. A. & Kirsch, I. R. (1989) *Proc. Natl. Acad. Sci. USA* **86**, 2031–2035.