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Gene encoding the α chain of the T-cell receptor is moved immediately downstream of c-*myc* in a chromosomal 8;14 translocation in a cell line from a human T-cell leukemia

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

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ABSTRACT **The SKW-3 cell line, which was established from the malignant cells of a patient with T-cell chronic lymphocytic 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 α chain of the T-cell receptor and of the human protooncogene *myc* (c-*myc*) in relation to the breakpoint junctions and to evaluate their possible role in the pathogenesis of T-cell neoplasia, we applied the techniques of *in situ* chromosomal hybridization and Southern blot analysis to SKW-3 cells. Our results indicate that the breakpoint on chromosome 14 at band q11 occurs close to a joining sequence of the gene encoding the α chain of the T-cell receptor. Additional rearrangements within the α-chain locus appear to split the variable region cluster. As a result of the rearrangements, the constant region of this gene, as well as some variable region segments, are translocated to chromosome 8, to the 3′ side of the c-*myc*-coding exons. The identification of a breakpoint to the 3′ side of c-*myc* suggests that this translocation is analogous to the variant t(2;8) and t(8;22) translocations observed in the B-cell malignancies.**

It is now well established that the cells in most human tumors are characterized by nonrandom chromosomal abnormalities (1, 2). In the hematologic malignant diseases, lymphoid neoplasms of B-cell origin are associated with specific abnormalities that correlate with distinct 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. Perhaps the best example is that of Burkitt lymphoma, in which one of three translocations [t(8;14), t(2;8), t(8;22)] involving the immunoglobulin loci and c-*myc* is invariably observed. As a result of these rearrangements, the transcriptional regulation of c-*myc* is altered (4, 5).

Although fewer tumors of T-cell origin have been studied, a distinct pattern of nonrandom karyotypic abnormalities is emerging. Rearrangements involving the proximal bands of chromosome 14 (14q11–q13) and two regions of chromosome 7 (7q35–q36 and 7p15) that correlate with the positions of the genes encoding the α chain (*TCR-α*) (6, 7), β-chain (8), and γ chain (9), respectively, of the T-cell receptor appear to be particularly frequent in T-cell malignancies but have also been observed in nonmalignant T-cell disorders. Moreover, structural abnormalities involving these regions of chromosomes 14 and 7 are very rare in other malignant diseases (10, 11). One recurring rearrangement in T-cell neoplasia is a paracentric inversion of chromosome 14 with a proximal breakpoint at q11 and a distal breakpoint at q32 (11–13). A closely related rearrangement, t(14;14)(q11;q32), is seen in T-cell neoplasia (14, 15) and in phytohemagglutinin-stimulated lymphocytes from patients with ataxia-telangiectasia as well as in the leukemic cells of those patients in whom this disease evolved (13). Also, Williams *et al.* (16) have described a t(11;14)(p13;q13) in the leukemic cells of 4 of 16 patients with T-cell acute lymphoblastic leukemia.

Thus, in some of these T-cell diseases, breaks occur in either 14q11 or 14q32, or in both bands in the same patient; in B-cell disorders, however, breaks occur essentially only in 14q32, and they rarely involve 14q11 (11). In 1985, the gene coding for TCR-α was localized to chromosome 14 at band q11–q12 (6, 7). In light of the nonrandom involvement of chromosome 14 in T-cell malignancies, it seems likely that, in the pathogenesis of human T-cell neoplasia, the *TCR-α* gene plays a role analogous to that of the immunoglobulin genes in B-cell lymphomas and leukemias.

In this study we have characterized the chromosomal abnormalities in an established cell line, SKW-3, derived from the malignant cells of a patient with T-cell chronic lymphocytic leukemia. We found that the SKW-3 cell line contains a t(8;14) with breakpoints in chromosome 8 at band q24 and in chromosome 14 at band q11. By using *in situ* chromosomal hybridization and Southern blot analysis, we found that a joining sequence of the *TCR-α* gene has been translocated close to the 3′ end of the c-*myc* gene on the 8q+ chromosome. Unexpectedly, additional rearrangements have resulted in translocation of some variable region segments to the 8q+ chromosome.

MATERIALS AND METHODS

Cells. SKW-3 is a lymphoid cell line that expresses the T-cell specific surface markers T1, T4, T8, T9, T10, and T11 (17). This line was established from a patient with T-cell chronic lymphocytic leukemia.

Cytogenetic Analysis. For cytogenetic analysis, SKW-3 cells in logarithmic-phase growth were processed by using

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Abbreviations: kb, kilobase(s); TCR-α, α chain of the T-cell receptor; *VTα, CTα, JTα*, variable, constant, and joining regions, respectively, of the *TCR-α* gene; bp, base pair(s).

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routine techniques. Chromosomal abnormalities are described according to the International System for Human Cytogenetic Nomenclature, 1978 (18).

DNA Probes. pRyc7.4 (*myc* B) is a 1092-base-pair (bp) cDNA insert into the *Pst* I site of pBR322 (4); it codes for the third c-*myc* exon plus 200 bp of the second c-*myc* exon. pMC41 3RC is a 1.4-kilobase (kb) *Cla* I–*Eco*RI genomic subclone that contains the third c-*myc* exon (19). pCA1.7S is a 1.7-kb *Sst* I genomic fragment in PUC19 from a region approximately 800 bp to the 3′ side of exon 3. pY14, our TCR-α probe, contains a variable (V), a joining (J), and the constant (C) sequence of the human *TCR-α* gene; this probe is a 1.1-kb cDNA insert (20). pHαT1 is a 900-bp cDNA clone for part of the *CTα* region (6). The probe for the variable region of the *TCR-α* gene (*VTα*) is a 1.4-kb *Sca* I fragment from the pY14 clone. 5b-12 (J_αD) is a 2.9-kb *Eco*RI insert containing joining segments from a specific region at least 40 kb to the 5′ side of the *CTα* gene (21).

***In Situ* Chromosomal Hybridization.** *In situ* chromosomal hybridization was performed as described (22). Radiolabeled probes were prepared by nick-translation with all four of the ^{3}H-labeled deoxynucleoside triphosphates (Amersham) to specific activities of 1.6×10^8 dpm/μg (TCR-α probe), 1.8×10^8 dpm/μg (CTα and VTα probes), and 4.3×10^7 dpm/μg (c-*myc* probe). Metaphase cells were hybridized at 2.0 and 4.0 (TCR-α, CTα, and VTα probes) or 20.0 and 40.0 (c-*myc* probe) ng of probe per ml of hybridization mixture. Autoradiographs were exposed for 11 days at 4°C.

Preparation of DNA and Gel Electrophoresis. High-molecular-weight DNA fragments were isolated from SKW-3 cells and from normal human placental tissue by a modification of the method of Blin and Stafford (23). Aliquots of 8 or 12 μg were digested to completion at 37°C with restriction endonucleases (2 units/μg of DNA) and separated by agarose gel electrophoresis.

Southern Transfer and Hybridization of DNA. DNA was transferred to GeneScreen *Plus* membranes (New England Nuclear) and hybridized according to the manufacturer's suggested protocol and the method of Southern (24). Radiolabeled probes were prepared by nick-translation (25) with [α-^{32}P]deoxycytidine and [α-^{32}P]thymidine triphosphates (Amersham). The specific activity of the probes was 1–3 $\times 10^8$ dpm/μg of DNA. Following hybridization for 12–18 hr at 42°C in 50% (vol/vol) formamide, the membranes were routinely washed in 0.1× NaCl/Cit/1% $NaDodSO_4$, at 65°C, for 1 hr; low-stringency washes were carried out in 1× NaCl/Cit/1% $NaDodSO_4$. (1× NaCl/Cit = 0.15 M NaCl, 0.015 M sodium citrate, pH 7.0.) Autoradiographs were exposed for 3–5 days at −70°C.

RESULTS

Cytogenetic Analysis. Cytogenetic analysis showed that SKW-3 consists of a single chromosomally abnormal cell line. Each of 20 metaphase cells analyzed had a pseudodiploid karyotype that was characterized by structural and numerical abnormalities (Fig. 1). Both chromosome 3 homologs were rearranged as a result of a reciprocal translocation involving the long arms (q) of these chromosomes. Similarly, both chromosome 8 homologs were rearranged as a result of two translocations. One chromosome 8 homolog (8p+) was involved in a reciprocal translocation with chromosome 11, whereas the other chromosome 8 (8q+) had undergone a reciprocal exchange of material with the long arm of chromosome 14, t(8;14)(q24;q11), and was present in two copies; however, only one 14q− chromosome was observed. Moreover, in each cell, the normal chromosome 14 homolog was absent. A rearranged chromosome 12 was also noted. Thus, the karyotype of the SKW-3 cell line is 46,XY,−14,t(3;3)(q21;q29),t(8;11)(p11;p11),t(8;14)(q24;q11),+der(8)t(8;14)(q24;q11),inv ins(12) (q24.3p13.31p12.2)(100%).

***In Situ* Chromosomal Hybridizations.** The results of *in situ* hybridizations with the T-cell receptor-specific and c-*myc* probes to metaphase cells from the SKW-3 cell line are listed in Table 1 and are illustrated in Figs. 2 and 3.

TCR-α probe. To confirm the localization of the gene encoding the TCR-α to chromosome 14, we hybridized the TCR-α probe to normal metaphase chromosomes prepared from phytohemagglutinin-stimulated peripheral blood lymphocytes. This hybridization resulted in specific labeling of a single chromosome, chromosome 14 (data not illustrated). Of 100 metaphase cells examined, 21 (21%) were labeled on bands q11 to q21, of one or both chromosomes 14 ($P < 0.0005$). A total of 25 grains were observed on this chromosome; of these, 23 (92%) were clustered at bands q11 to q21 and represented 15.4% (23/149) of all labeled sites. This localization of the *TCR-α* gene to 14q11 to q21 is consistent with that reported (6, 7).

To determine whether the *TCR-α* gene was relocated to chromosome 8 as a result of the t(8;14), we hybridized the TCR-α probe to metaphase cells from the SKW-3 cell line. This resulted in specific labeling of the 8q+ chromosomes (Fig. 2*A*). Of 100 metaphase cells analyzed from this hybridization, 22 (22%) were labeled on one or both of the two 8q+

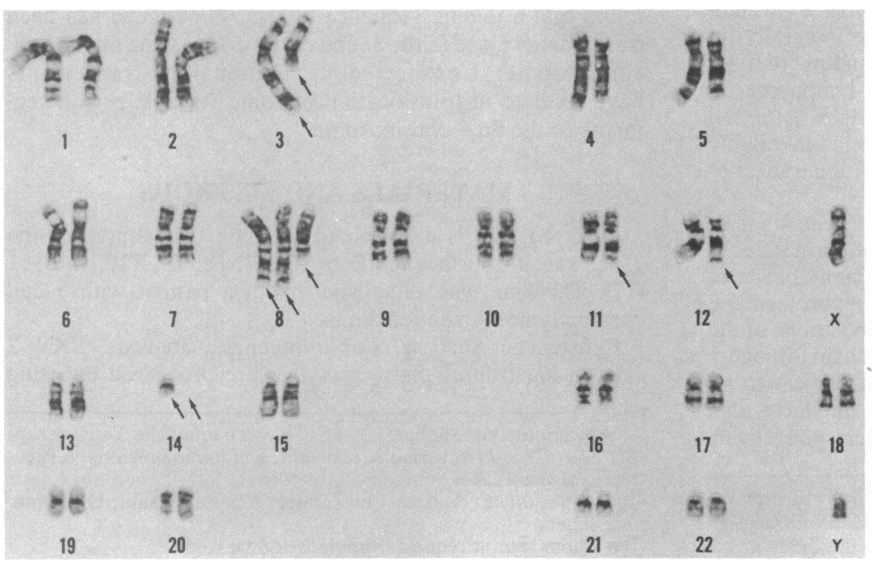

FIG. 1. Karyotype of a trypsin/Giemsa-banded metaphase cell of the SKW-3 cell line. The rearranged and missing chromosomes are identified with arrows. The 8q+ chromosomes resulting from the t(8;14) are located to the left of the chromosome 8 homologs. The 14q− chromosome is marked by an arrow; the normal chromosome 14 homolog has been lost in this cell line. The homologous chromosome 8 (8p+) is also involved in a reciprocal translocation involving chromosome 11; the derivative chromosomes 8 and 11 resulting from this rearrangement [t(8;11)(p11;p11)] are located on the right of each pair of homologs.

Table 1. *In situ* hybridizations of SKW-3 metaphase cells

Probe	Metaphase cells analyzed, no.	Total labeled sites, no.	Labeled sites, no. (%)			χ^2 value		
			8p+	8q+	14q−	8p+	8q+	14q−
TCR-α	100	140	2 (1.4)	27 (19.3)	1 (0.7)	0.5	30.2*	0.07
CTα	100	184	3 (1.6)	32 (17.4)	2 (1.1)	0.6	28.4*	0.97
VTα	150	210	5 (2.4)	34 (16.2)	10 (4.8)	0	25.3*	67.4*
c-myc	100	145	16 (11)	23 (16)	2 (1.4)	45.3*	16.3*	1.8

*χ^2 value corresponds to $P < 0.00050$.

chromosomes that are present in each cell of the SKW-3 cell line. The labeled sites on this chromosome were clustered at the translocation breakpoint junction (bands 8q23 to q24 and bands 14q11 to q13); this cluster of grains represented 14.3% (20/140) of all labeled sites. The 14q− chromosome had only a single grain ($P > 0.7$), and the 8p+ chromosome had two labeled sites ($P > 0.40$). Thus, all or most of the *TCR-α* gene, as detected by this probe, appeared to be translocated to chromosome 8 as a result of the t(8;14).

CTα and VTα probes. To determine whether the breakpoint on chromosome 14 occurs within the *TCR-α* gene, we hybridized the specific probes for the *VTα* and *CTα* genes to metaphase cells from the SKW-3 cell line. In hybridizations with the CTα probe, we observed specific labeling on the 8q+ chromosomes, whereas the VTα probe hybridized to both the 8q+ and the 14q− chromosomes. These results suggest that the breakpoint on chromosome 14 occurred within the *VTα* sequences.

We analyzed 100 metaphase cells from the hybridization of the CTα probe (Fig. 2*B*); of these, 19 cells had a labeled site on one or both of the 8q+ chromosomes at the translocation breakpoint junction (8q23 to q24 and 14 q11 to q13). These sites represented 13% (24/184) of all labeled sites. Only two labeled sites were noted on the long arm of the 14q− chromosome (2/184, 1.1%, $P > 0.3$). The 8p+ chromosome contained three labeled sites (3/184, $P > 0.4$). In contrast, analysis of 150 metaphase cells that were hybridized to the VTα probe resulted in specific labeling of both the 8q+ and 14q− chromosomes (Fig. 2*C*). A labeled site was observed on one or both 8q+ chromosomes in 21 metaphase cells (14%),

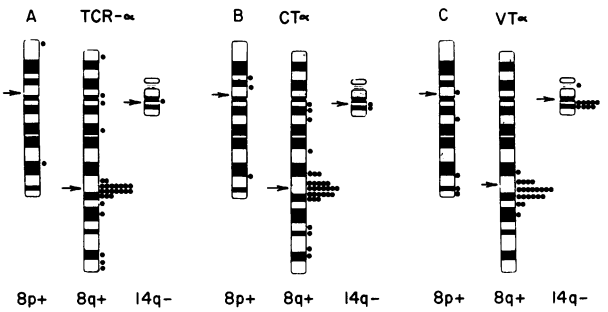

FIG. 2. Distribution of labeled sites on chromosome 8 and 14 homologs in metaphase cells prepared from the SKW-3 cell line after hybridization with the TCR-α (*A*), CTα (*B*), or VTα (*C*) probe. The 8p+ chromosome resulting from the reciprocal translocation involving chromosome 11, t(8;11)(p11;p11), and the rearranged chromosomes 8 and 14 (8q+ and 14q−) resulting from the t(8;14) are illustrated. The arrows identify the translocation breakpoint junctions. Each dot indicates one labeled site observed in the corresponding band. We used the χ^2 test for 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, only the 8q+ chromosome was specifically labeled in the hybridizations with the TCR-α and CTα probes ($P < 0.0005$), whereas both the 8q+ and 14q− chromosomes were specifically labeled in the hybridization with the VTα probe ($P < 0.0005$).

and these sites were clustered at the translocation breakpoint junction. This cluster of grains represented 10% (21/210) of all labeled sites. The 8p+ chromosome that has an intact long arm was not specifically labeled (5/210, $P > 0.9$). In this hybridization, significant labeling was also observed on the 14q− chromosome. Nine grains were noted on the q arm of this chromosome at the translocation breakpoint junction, and these represented 4.3% of all labeled sites ($P < 0.0005$).

c-myc probes. To identify whether c-*myc*, which is normally located at 8q24, was moved to chromosome 14 following the t(8;14), we analyzed 100 metaphase cells that were hybridized with a c-*myc*-specific probe (Figs. 3 and 4). In this analysis, we observed labeling on the 8p+ chromosome at band q24 in 12 metaphase cells and on one or both of the 8q+ chromosomes at the translocation breakpoint junction (8q23 to q24 and 14q11 to q13) in 16 metaphase cells. These sites represented 8.3% (12/145) and 13% (19/145) of all labeled sites, respectively. Thus, both the 8p+ and the 8q+ chromosomes were specifically labeled ($P < 0.0005$). This was not the case for the 14q− chromosome; only two grains were noted on this chromosome ($P > 0.10$). These results suggest that all or most of the c-*myc* gene remains on chromosome 8 following this translocation.

Southern Blot Analysis. To determine whether the c-*myc* and *TCR-α* gene loci were rearranged as a consequence of the translocation, we hybridized Southern blots of SKW-3 DNA digested with various restriction enzymes to probes specific for the different regions of these genes.

c-myc probes. A restriction map of the human c-*myc* gene locus on chromosome 8 (modified from ref. 26) showing the two genomic probes used in Southern blot analysis is illustrated in Fig. 4. The pMC41 3RC (data not shown) and pCA1.7S (Fig. 5*A*) probes hybridized to a rearranged *Hin*dIII restriction fragment of 11.8 kb. In addition, the pCA1.7S probe hybridized to two *Eco*RI fragments; one band was of germ-line size, and the other was a 5.3-kb fragment that was unique to SKW-3 (Fig. 5*A*). Southern blots performed after digestion with the restriction enzyme *Xba* I did not show

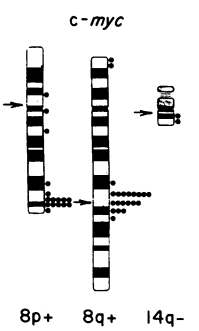

FIG. 3. Distribution of labeled sites on the 8p+, 8q+, and 14q− chromosomes from SKW-3 cells that were hybridized with the c-myc probe. The arrows identify the translocation breakpoint junctions. Specific labeling was observed on both the 8p+ and the 8q+ chromosomes (χ^2 test, $P < 0.0005$).

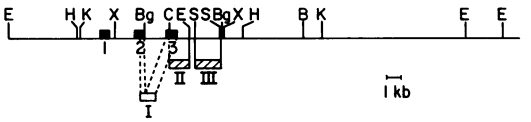

FIG. 4. Simplified restriction map of the human c-*myc* gene locus, including 22 kb of the 3'-flanking region (modified from ref. 26). The schematic diagram illustrates (I) the cDNA probe pRyc7.4 (4), which was used for *in situ* chromosomal hybridization, and the two genomic probes (II) pMC41 3RC (19) and (III) pCA1.7S, which were used for Southern blot analyses. Solid rectangles represent the three c-*myc* exons. Abbreviations: B, *Bam*HI; Bg, *Bgl* II; C, *Cla* I; E, *Eco*RI; H, *Hin*dIII; K, *Kpn* I, S, *Sst* I; X, *Xba* I.

rearranged bands after hybridization to the pCA1.7S probe, but rearrangements were detected in SKW-3 DNA digested with *Bam*HI and *Kpn* I (not shown).

JTα and VTα probes. The JTα probe detected a rearranged *Eco*RI restriction fragment of 5.3 kb (Fig. 5*B*) that was identical in size to the rearranged band observed after hybridization to the pCA1.7S probe (Fig. 5*A*). The VTα probe hybridized to a number of bands in placenta DNA (Fig. 5*C*). Analysis of SKW-3 DNA using *Hin*dIII, *Eco*RI, *Kpn* I, or *Xba* I showed deletion of one or more of these bands.

DISCUSSION

The results of *in situ* chromosomal hybridization studies of the SKW-3 cell line show that the *TCR-α* gene is split by the break in chromosome 14 at band q11. The constant region of this gene, as well as some of the variable region sequences, are translocated to the 8q+ chromosome distal to the c-*myc* gene. As shown by Southern transfer analysis, additional bands are seen in digests of SKW-3 DNA using probes close to the 3' end of the c-*myc* gene. Because new bands were found when four different restriction enzymes were used, it is likely that they do not result from restriction length polymorphisms, but instead are due to a DNA rearrangement and contain the breakpoint junction of the 8;14 translocation. This possibility is strongly supported by the finding that a JTα probe and a probe containing sequences on the 3' side of

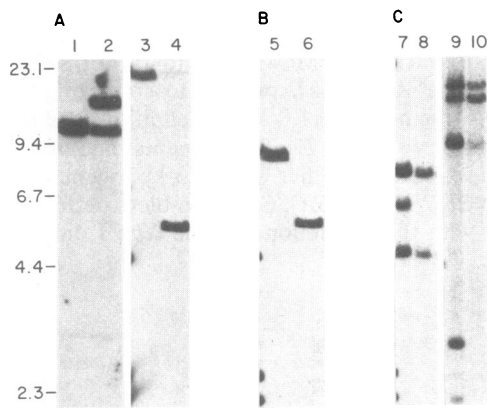

FIG. 5. Hybridization of DNA from the SKW-3 cell line to c-*myc* 3' probe pCA1.7S (*A*), JTα probe 5b-12 (*B*) (21), and VTα probe (*C*). DNA was digested with *Hin*dIII (lanes 1, 2, 7, and 8) or *Eco*RI (lanes 3, 4, 5, 6, 9, and 10) and electrophoresed on a 0.8% agarose gel. The pCA1.7S probe (*A*) detected a 5.3-kb rearranged band in the *Eco*RI digest of SKW-3 DNA that was identical in size to the rearranged band observed after hybridization to the JTα probe (*B*). The 20.5-kb germ-line-sized band in lane 4 is weak due to its presence in only a single copy per cell in the SKW-3 genome and because of poor transfer of high-molecular-weight DNA. Deletion of one or more germ-line VTα bands was observed in SKW-3 (*C*). (Odd-numbered lanes) Normal human placental DNA used as control. (Even-numbered lanes) SKW-3 DNA. Molecular size standards are in kbp.

c-*myc* hybridize to rearranged bands of identical size following digestion with *Eco*RI, suggesting that c-*myc* 3' segments and JTα sequences are present on the same *Eco*RI fragment as a result of the translocation. We have confirmed this possibility by cloning this 5.3-kb *Eco*RI fragment and showing that it hybridizes to both probes (E.A.S., T.W.McK., and M.O.D., unpublished results). The *Xba* I restriction site that is not rearranged in SKW-3 DNA lies 3.3 kb downstream of the c-*myc* coding sequences, whereas the rearranged *Hin*dIII site normally lies 4.4 kb on the 3' side of c-*myc*; thus, the breakpoint on chromosome 8 lies 3.3–4.4 kb downstream of the c-*myc* coding sequences.

The translocation t(8;14)(q24;q11) appears to be 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 leukemic cells of patients with T-cell acute lymphoblastic leukemia (16, 27, 28). In one study, Caubet *et al.* (28) found that a t(8;14)(q24;q11) resulted in a rearrangement of restriction enzyme sites downstream of the c-*myc* gene. The gene at the 14q11 breakpoint, however, remained unidentified. Our data suggest that the t(8;14) in the T-cell line SKW-3 is analogous to the variant translocations [t(2;8), (8;22)] observed in Burkitt lymphoma and in B-cell acute lymphoblastic leukemia (L3) (29–35), where a breakpoint also occurs to the 3' side of c-*myc*, but here it involves the gene for TCR-α rather than the immunoglobulin light chain genes.

Two earlier reports also demonstrate a breakpoint within the *TCR-α* gene as a result of a chromosomal translocation. Erikson *et al.* (36) and Lewis *et al.* (37) reported that, in cells from T-cell acute leukemias that contain a t(11;14)(p13;q11 or q13), the *TCR-α* gene is split between VTα sequences and CTα by the breakpoint in chromosome 14. (Therefore, although the breakpoint in chromosome 14 was originally identified as band q13, these results indicate that the breakpoint is actually in band q11.) These reports and many of our findings are consistent with the following orientation of the *TCR-α* gene on chromosome 14: centromere, 5' end, 3' end, telomere.

Given this order, if the break in chromosome 14 occurred within the JTα region, all VTα segments would be expected to remain on chromosome 14. Contrary to this expectation, however, we found that some VTα sequences have moved to the 8q+ chromosome while some VTα sequences remain on the 14q− chromosome in SKW-3. In the *in situ* chromosomal hybridization experiments performed with the complete TCR-α cDNA clone, we did not see significant labeling of the 14q− chromosome; however, when the VTα probe was used, a small, but highly significant, signal was observed on this rearranged chromosome. We attribute this to an increased efficiency of hybridization arising from the use of a higher effective concentration of variable region sequences. Southern blot analysis showed deletion of at least one member of the Jurkat VTα family. This result, in addition to the splitting of the family by the chromosomal rearrangement, suggests that this VTα family may be directly involved in one of the breakpoints of this complex rearrangement.

If there is an invariant orientation of VTα segments, JTα segments, and the constant region within the *TCR-α* gene, the translocation of VTα sequences to the 8q+ chromosome in SKW-3 is not compatible with a simple reciprocal translocation involving a single break within the J region of a *TCR-α* gene. These results, however, can be explained if we assume that there are VTα segments interspersed among JTα sequences or downstream of CTα. With regard to the latter possibility, a variable region segment has been described on the 3' side of the mouse TCR-β constant region (38); however, it is very unlikely that the VTα sequences homologous to the Jurkat cDNA are on the 3' side of CTα since they

remain on chromosome 14 in other reciprocal translocations in which CTα has been translocated (36, 37). We favor an alternative explanation of our results; namely, that an inversion within the *TCR-α* gene simultaneous with, or previous to, the translocation resulted in splitting and inversion of part of the VTα cluster so that some *VTα* genes are on the 3′ side of the translocated J region and thus are located on the 8q+ chromosome. Inversions resulting from rearrangements in the heavy chain (39) and kappa light chain (40) immunoglobulin loci have been identified in mouse plasmacytomas. It is possible that a VTα or a JTα sequence with an orientation opposite to the overall orientation of the *TCR-α* gene may be responsible for such an inversion.

Identification of the precise nature of the chromosome junctions in these translocations may provide important information about the location of regulatory regions within the *TCR-α* gene. It may also explain the possible involvement of mechanisms of somatic gene rearrangement, normally operating during T-cell differentiation, in the generation of abnormal chromosome rearrangements.

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