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Burkitt Lymphoma Cell Line Carrying a Variant Translocation Creates New DNA at the Breakpoint and Violates the Hierarchy of Immunoglobulin Gene Rearrangement

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The Burkitt lymphoma cell line KK124, which contains a reciprocal t(8;22) translocation, was shown to have rearranged in a region 3′ to the c-*myc* proto-oncogene on chromosome 8 and 5′ to the lambda constant region on chromosome 22. The breakpoint was cloned and sequenced, revealing that c-*myc* and a portion of its 3′ region abutted a complete lambda variable gene that had undergone V-J recombination. Since this cell line expresses kappa light chain, this lambda rearrangement violates the previously proposed hierarchy of immunoglobulin gene rearrangement. A novel duplication of normal chromosome 8 sequences was also found at the breakpoint. The first exon of c-*myc* and its flanking sequence from the translocated allele was sequenced and compared with a normal counterpart. Extensive mutation was found within the first exon in contrast to its 3′ and 5′ flanking regions. S1 nuclease analysis revealed that it was the translocated c-*myc* being expressed and that there was a promoter shift from P2 to P1. The detailed structural analysis of this cell line provides clues concerning mechanisms of chromosomal translocation and c-*myc* deregulation in Burkitt lymphomas.

The association between specific chromosomal aberrations and specific diseases is now firmly established (29, 42). However, the major questions concerning the mechanism and the molecular consequences of chromosomal aberrations remain unanswered. The data presented here, drawn from our analysis of a particularly revealing chromosomal translocation found in a Burkitt lymphoma cell line, provide new clues for answering these questions.

Burkitt lymphoma (and the murine plasmacytoma analog) is the best analyzed of the tumors in which a specific disease-associated chromosomal aberration occurs (21, 26). Approximately 80% of tumors from patients with Burkitt lymphoma carry a reciprocal translocation between chromosome 8 and 14, t(8;14). These exchanges involve the chromosomal regions on which the c-*myc* oncogene (8q24.1) (37) and the heavy-chain immunoglobulin gene (14q32) (15) reside. It has been demonstrated by us and many others that these exchanges of genetic material often occur within the transcriptional units of these genes (18). Recently, we have turned from our analyses of the more common t(8;14) lymphomas to the less common translocations which are present in the remaining 20% Burkitt lymphomas. These variant translocations involve reciprocal exchanges between chromosome 8, in the region of the c-*myc* gene, and either chromosome 2 t(2;8) or 22 t(8;22) (19), in the chromosomal regions in which the kappa (2p11) (20) or lambda (22q11) (9, 24) chain immunoglobulin genes reside. Our hope has been that by analyzing these more exceptional cases and comparing them to the more frequent variety, the necessary, sufficient, and consistent features of all translocations seen in Burkitt lymphoma would become apparent. This article reports the detailed study of one such Burkitt lymphoma line, KK124, which carries a variant translocation, t(8;22) (q24.1;q11) (10; C. T. Denny, G. F. Hollis, I. T. Magrath, J. Whang-Peng, and I. R. Kirsch, UCLA Symp. Mol. Cell. Biol., in press). Our results support a new model of chromosomal breakage and rejoining in which new DNA sequences are created at the junction point of the translocation. The results also demonstrate a series of specifically targeted molecular changes in the transformed cell most probably related to events surrounding the occurrence of the translocation.

Because of the location of the breakpoint in KK124 we were also able to provide new information on the structure of the human lambda immunoglobulin genes. We report the nucleotide sequence of a human immunoglobulin lambda light chain joining sequence (J) and a lambda variable region (V) J sequence site-specific recombination event: regions of the lambda gene which have not been previously sequenced. We have also demonstrated that the immunoglobulin gene rearrangements observed in this tumor cell line appear to have occurred in violation of a previously postulated ordered hierarchy of immunoglobulin gene rearrangement in B lymphocytes (16).

Our data are compared with previous analyses of Burkitt lymphoma cell lines from our own and other laboratories in an attempt to dissect out the essential factors involved in the development of such translocations and the malignant transformation of the B lymphocytes in which such translocations occur.

MATERIALS AND METHODS

Cell line. KK124 is an Epstein-Barr viral DNA-positive cell line derived from a patient with Burkitt lymphoma. Previous karyotypic analysis revealed the presence of a reciprocal translocation between chromosomes 8 and 22 (10; Denny et al., in press). The cell line was passaged in RPMI 1640 plus 15% fetal calf serum to achieve a final cell number of 2×10^9, and DNA and RNA were harvested.

Preparation of DNA and RNA. High-molecular-weight DNA was prepared by the method of Hieter et al. (12). Intact

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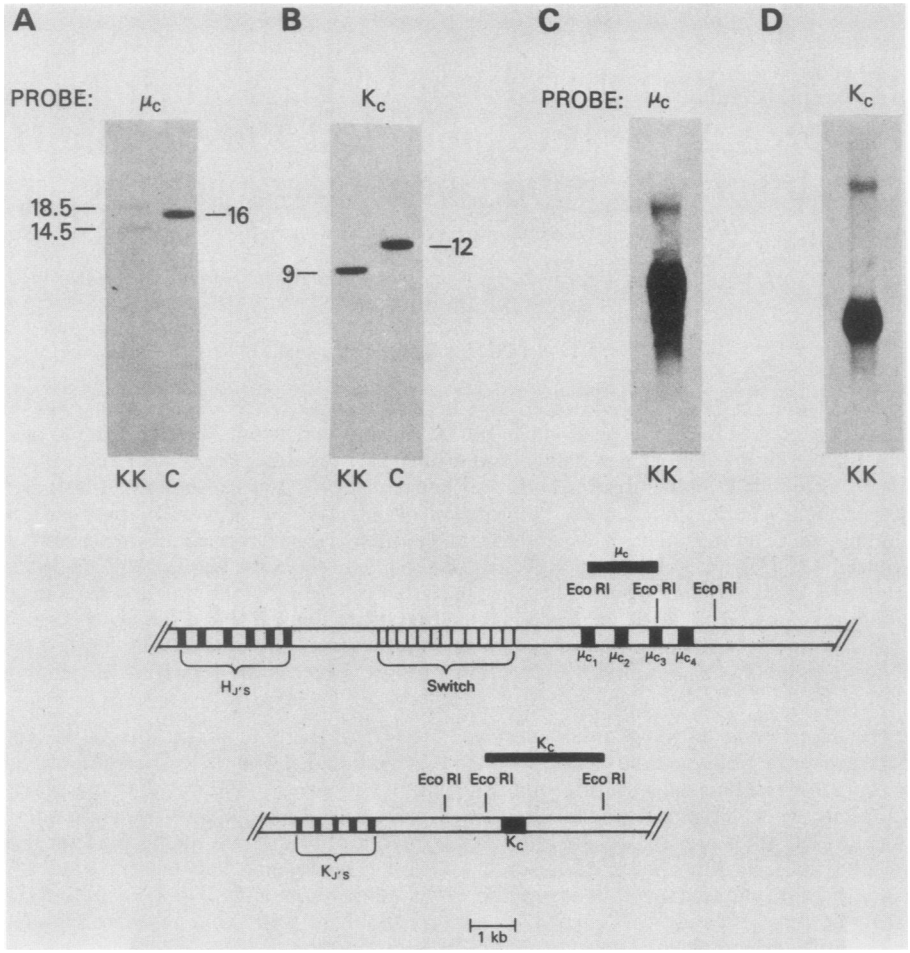

FIG. 1. Rearrangement and expression of mu and kappa immunoglobulin loci. Shown are Southern blots of *Eco*RI-digested genomic RNA probed with the fragments from the mu and kappa loci (A and B, respectively) illustrated in the schematic. The results indicate that both alleles from both loci were rearranged. One of the rearranged kappa alleles has deleted its kappa constant region. Northern blot analyses with these same probes reveal abundant expression of mu and kappa (C and D, respectively).

cellular nuclei were isolated from 10^9 washed cells by Dounce homogenization and subsequent centrifugation through a sucrose cushion. The nuclei were then incubated overnight in proteinase K and sodium dodecyl sulfate. DNA was purified from the resultant solution by phenol-chloroform extraction, precipitated in ethanol, and suspended in deionized water.

Total cellular RNA was prepared by the method of Chirgwin et al.(4) by suspending 10^9 washed and pelleted cells in 4 M guanidine thiocyanate–25 mM NaCl–100 mM 2-mercaptoethanol. The solution was layered over 5.7 M aqueous CsCl and spun in a Beckman SW41 rotor overnight at 32,000 rpm and 25°C. The resultant pellet was washed in cold ethanol and suspended in deionized water.

Restriction enzyme digestion and Southern analyses. All restriction endonucleases were obtained from either Bethesda Research Laboratories, Gaithersburg, Md., or New England Biolabs, Beverly, Mass. Digestions were performed under conditions suggested by the manufacturers. Hybridization analyses were performed with genomic DNA cut by restriction endonucleases, separated into different-sized fragments on 0.8% agarose gels (Sea Kem ME; FMC Corp., Rockland, Maine) and blotted onto nitrocellulose filters as described by Southern (34). Filters were then hybridized to ^{32}P-labeled (Amersham Corp., Arlington Heights, Ill.) probes overnight at 42°C in a Tris-buffered solution containing 10% dextran, 5× SSC (1× SSC is 0.15 M NaCl plus 0.015 M sodium citrate), and 40% formamide. After hybridization, filters were washed with 2× SSC–0.1% sodium dodecyl sulfate three times at room temperature and with 0.1× SSC–0.1% sodium dodecyl sulfate twice at 52°C before autoradiography was performed.

Northern analyses. Total cellular RNA (10 μg per lane) was dissolved in an aqueous solution containing 45% formamide and 16% formaldehyde, heated to 70°C for 3 min, and then chilled briefly on ice. Samples were loaded on a 1% agarose–0.2% formaldehyde gel which had been made in a buffer system of 20 mM MOPS (morpholinepropanesulfonic acid)–5 mM sodium acetate–1 mM EDTA. A voltage of 180 V was applied for 3 h. RNAs were then transferred directly to nitrocellulose and hybridized under the same conditions as those of the Southern analyses.

Cloning procedure. Genomic library construction was performed in the following fashion. High-molecular-weight DNA was partially digested with *Mbo*I and size fractionated by ultracentrifugation through sucrose gradients. The fractions containing DNA fragments in the range of 12 to 23 kilobases (kb) were pooled, ligated into the lambda phage

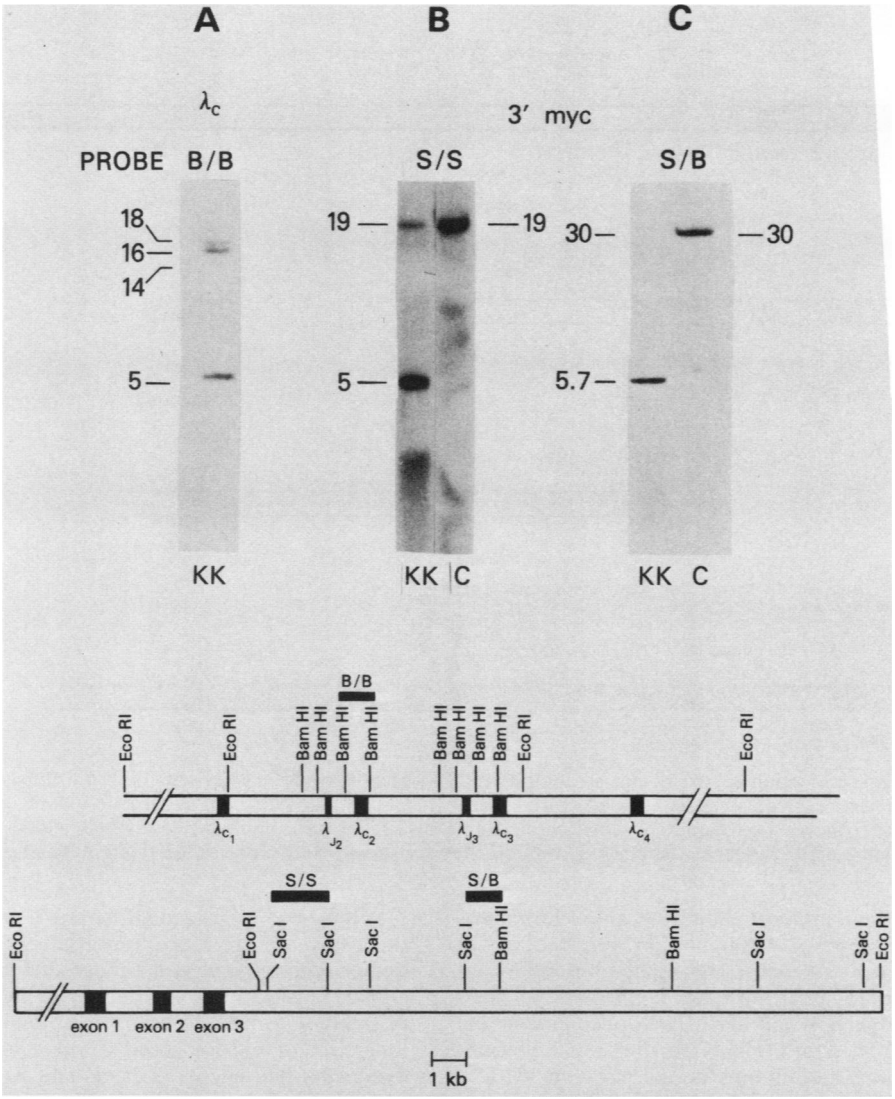

FIG. 2. Identification of translocation partners with lambda and c-*myc* probes. (A) A 5-kb recombinant band is found on the Southern blot of *Eco*RI-digested genomic DNA probed with the lambda constant region fragment B/B shown on the schematic. (B) This same band is seen again when under the same conditions, a Southern blot is probed with the 3′ of c-*myc* fragment S/S. (C) The reciprocal partner is identified as a 5.7-kb recombinant band seen on a Southern blot of *Bam*HI-digested DNA probed with the fragment S/B 3′ of c-*myc*.

vector EMBL-3 (Promega, Madison, Wis.) (11), and packaged with Packagene extract (Promega). Recombinant phage were then plated onto an *Escherichia coli* P2 lysogen to give a final unamplified base of 8×10^5 PFU.

Screening of the library was performed as described by Benton and Davis (3). Selected phage-cloned DNAs were mapped, and areas of particular interest were subcloned into the plasmid pBr327.

Nucleotide sequence procedure. Dideoxy sequencing (30) was performed by reagents and instructions prepared by Bethesda Research Laboratories.

S1 nuclease assay. S1 nuclease strategies and reaction conditions followed closely those of Taub et al. (38). S1 probes were prepared by [^{32}P]dATP incorporation into primer-extended M13 clones. Labeled probes were isolated by preparative urea-acrylamide gel electrophoresis and hybridized to 30 μg of total RNA overnight at 54 to 55°C. The hybridization mixture was then digested with S1 nuclease, and fragments were fractionated by size on 0.4-mm urea-acrylamide gels. Gels were dried, and autoradiography was performed.

RESULTS

Immunoglobulin gene status in the cell line KK124 t(8;22). To determine the state of the immunoglobulin genes in this B-lymphocyte tumor cell line, Southern and Northern blot analyses were performed (Fig. 1). The Southern blots reveal the anticipated DNA rearrangements within the mu and kappa transcriptional units. These rearrangements reflect the V-D (diversity)-J and V-J recombinations which are prerequisites to the formation of active immunoglobulin genes. The Northern analysis clearly indicates that these cells express abundant mu and kappa mRNA, but we were unable to detect lambda message. Serologic screening for surface and cytoplasmic immunoglobulin was performed by using affinity

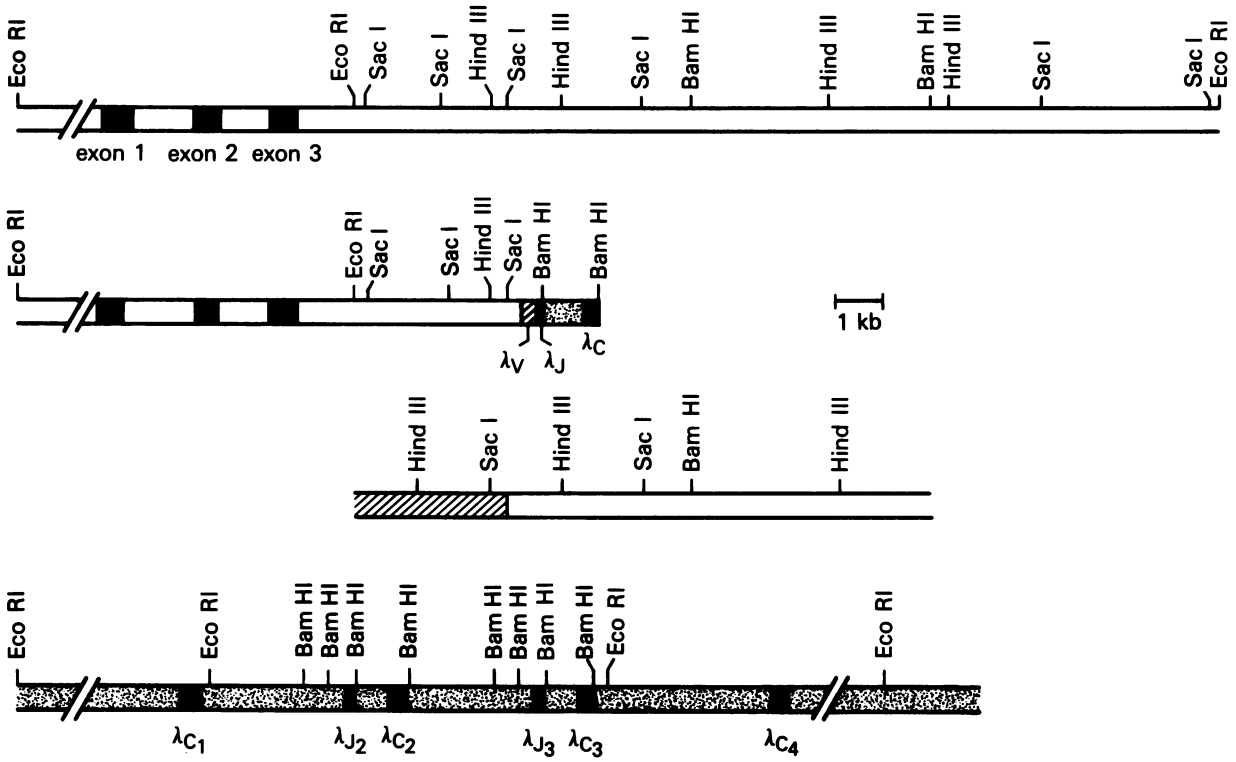

FIG. 3. Schematic representation of normal chromosomes 8 and 22 with both translocated partners. Der 8 consists of c-*myc* and a portion of its 3′ flanking region (clear regions) abutting a lambda variable gene (hatched regions) that has undergone V-J recombination into the lambda constant locus (stippled regions). The reciprocal der 22 chromosome has sequences from the lambda variable locus upstream in conjunction with further downstream c-*myc* sequences. Selected restriction sites are shown; all exons are indicated in black.

purified goat anti-human immunoglobulin (Cappel Laboratories, Cochranville, Pa.) at a 1:4,000 dilution. It was detected by an avidin-biotin system incorporating alkaline phosphatase and an appropriate substrate. This confirmed the presence of mu and kappa polypeptides. The specificity of the antibodies was confirmed with highly purified human immunoglobulin (Cappel). This finding is inconsistent with a previous report of a correlation between t(2;8) and kappa production and t(8;22) and lambda production (19). It is, in fact, the second discrepant line that we have analyzed (13). In view of this and the small number of cell lines on which the initial correlation was established, the biological significance and, indeed, the validity of the apparent correlation must be open to question.

Molecular characterization of the t(8;22). Despite the fact that no lambda transcript was observed, Southern blot analysis of KK124 DNA revealed a lambda constant gene rearrangement resulting in the generation of a new fragment of approximately 5 kb on an *Eco*RI digest (Fig. 2). A rearranged band of approximately the same size was also identified in an *Eco*RI digest by a probe taken from a region 3′ of a normal c-*myc* oncogene (see the map in Fig. 2). The comigration of the rearranged bands identified by the lambda constant probe from chromosome 22 and a 3′ c-*myc* probe from chromosome 8 suggested that a single *Eco*RI fragment contained both lambda and c-*myc* sequences and, therefore, a translocation breakpoint. Given previous information on the orientation of the c-*myc* and lambda loci on their respective chromosomes (2, 12; unpublished data) we were able to identify one of the partners of this reciprocal translocation, the derivative 8 (der 8) chromosome. The reciprocally rearranged fragment on the derivative 22 (der 22) chromosome was identified by using a probe further 3′ of the c-*myc* oncogene, beyond the region where the breakage and rejoining event had occurred (Fig. 2C). Thus, chromosomal translocation resulted in an exchange between the end of the long arm of chromosome 8 and a large portion of the long arm of chromosome 22 in a breakage and rejoining event that had occurred 3′ of the c-*myc* oncogene and 5′ of an immunoglobulin lambda gene such that these formerly distinct gene regions were now contiguous.

Molecular cloning of the translocation partners. V-J rearrangement of the immunoglobulin lambda gene. By using appropriate probes as described in the figure legends, clones of the translocated partners were obtained, analyzed, and compared to their corresponding nontranslocated alleles. From this information, we derived a scheme of the translocation that had taken place in the cell line KK124 (Fig. 3). Surprisingly, this analysis revealed an apparent insertion of 420 base pairs (bp) on the der 8 chromosome between the point at which the 3′ c-*myc* region from chromosome 8 ended and the point at which the lambda J region from chromosome 22 began. The location of the insertion, immediately 5′ of the J sequence, suggested to us that immunoglobulin gene rearrangement, as it occurs normally during V-J joining, might account for this finding. Sequence analysis of the insertion confirmed this possibility. The insertion encoded an intact lambda variable region that had undergone V-J recombination (Fig. 4). As is often seen, this appears to be an example of an aberrant V-J recombinational event (23) that resulted in a frameshift mutation in hypervariable region III. This recombinational event apparently violates the proposed hierarchy of immunoglobulin gene rearrangement proposed for B lymphocytes, in which lambda genes remain in a germline

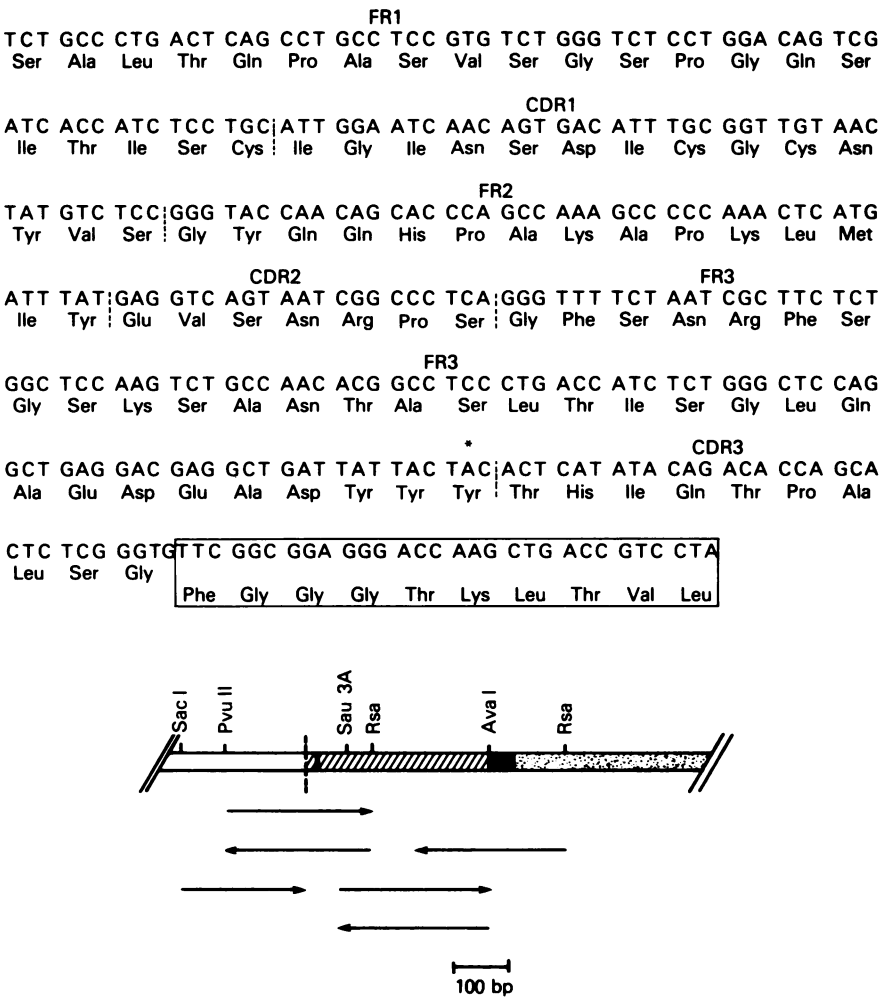

FIG. 4. Sequence of der 8, showing variable gene and V-J joining. The complete lambda variable gene sequence and its amino acid translation, consisting of three framework (FR) and hypervariable (CDR) regions, are shown. The lambda J segment and its translation are boxed. It is near here that a frameshift occurs, possibly caused by an aberrant V-J join. The last codon in FR3 (asterisk) codes for tyrosine instead of a structural cysteine seen on all other lambda variable sequences and may represent a further mutational event. Sequencing strategy with partial restriction map is schematically shown below. Chromosome 8 3′ of c-*myc* (clear region), lambda variable (hatched region), lambda J exon (black region), and intervening sequences (stippled region) are represented. The breakpoint is shown as a vertical dotted line, and the start of the lambda variable gene is shown as a vertical solid line.

configuration in kappa light-chain producers (16). Our analysis has not allowed us to determine whether this V-J recombinational event took place before or after the translocation event.

The regions encompassing the breakpoints on chromosomes 8 and 22 (3′ of the c-*myc* oncogene and 5′ of the lambda variable region) were subcloned and sequenced. These sequences were compared with the analogous region from the normal untranslocated chromosome 8. With the exception of a six-bp deletion, all chromosome 8 sequences could be accounted for in either der 8 or der 22. Interestingly, a 39-bp sequence present on the normal chromosome 8 was found at the breakpoint on both derivative chromosomes (Fig. 5). On the der 22, one complete copy of this 39-bp sequence was found, identical but for an internal 8-bp duplication. On the der 8 chromosome, one identical copy of the 39-bp sequence was found, separated by a five-nucleotide A-T rich region from a second copy of nucleotides 14 through 39 of the 39-bp sequence.

A closely related unrearranged lambda V region was cloned by using probes from the coding and 5′ flanking sequence of the variable region abutting the der 8 and der 22 breakpoints. A 550-bp segment which hybridized to both probes was identified and sequenced. There was over 80% nucleotide sequence homology continuously throughout the flanking and coding sequence between this closely related gene and its translocated counterpart. No evidence of the 39-bp sequence seen at the translocation junction was found in this closely related germline lambda V segment. Because the homology between this germline V and its closely related translocated counterpart was high, a comparable site of chromosomal breakage in the germline sequence could be pinpointed. On the germline V region clone, a 32-bp sequence was detected which has no counterpart on either the der 8 or der 22 chromosome and is not related to the 39-bp sequence found on both these derivative chromosomes at the junction site. Thus, this 32-bp sequence must have been deleted as a consequence of the translocation. In summary, the translocation event appears to have occurred via a mechanism which resulted in the duplication of a 39-bp

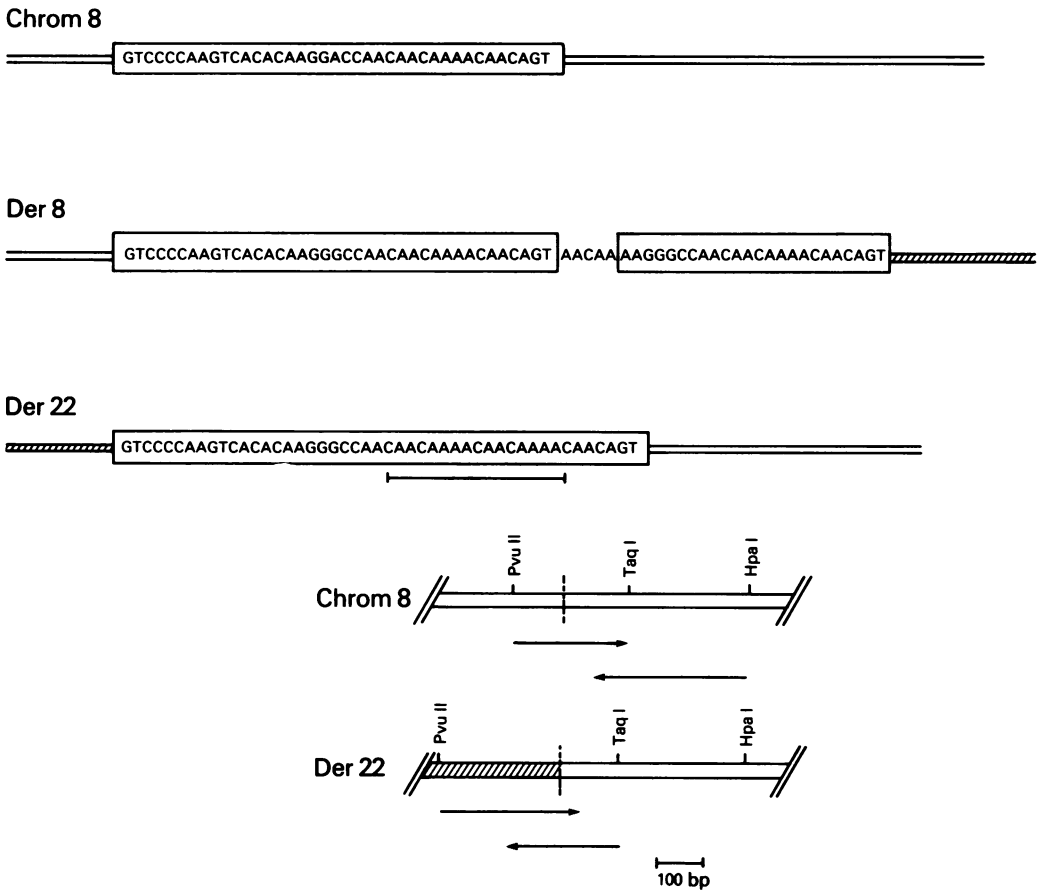

FIG. 5. Der 8 and der 22 breakpoints. The 39-mer sequence in normal chromosome 8 is boxed and shown to span the breakpoints in der 8 and der 22. In der 8, a complete copy is present, followed by a second incomplete copy (boxed area). Der 22 has only one complete copy, which has an internal duplication (underlined area). The adenine residue found in position 20 of the normal chromosome 8 differs from the guanine residue found in the same position in both der 8 and der 22 and may represent a single-nucleotide polymorphism. Below are schematics representing sequence strategies for normal chromosome 8 and der 22. Breakpoints are indicated by vertical dotted lines. In both sequences and schematics, clear areas denote regions 3′ of c-*myc*, and hatched areas denote lambda variable regions.

sequence from chromosome 8 and the deletion of a 32-bp sequence from chromosome 22.

Changes in the first exon of the translocated c-*myc*. The first exon of the c-*myc* oncogene is not translated into protein, but is highly conserved among higher eucaryotes and is therefore believed to play a regulatory role in c-*myc* expression (2, 18). The c-*myc* first exon and parts of its 5′ and 3′ flanking sequences from the der 8 chromosome of KK124 were sequenced and compared to an untranslocated gene. Within the first exon, an 8-bp direct repeat at the site of the second c-*myc* promoter (P2) and a 23-bp deletion were seen (Fig. 6). Additional single- and double-bp deletions were noted throughout the first exon. The portions of the intervening sequences both 5′ and 3′ of the first exon showed only scattered single-point variations from the nontranslocated gene. On the basis of this study, it appeared that a mutational event had actively targeted changes to the first exon as opposed to the flanking sequences of the translocated c-*myc* gene in this tumor.

S1 nuclease assay of the expressed c-*myc* gene. A probe that includes the altered first exon of the KK124 translocated c-*myc* gene and extends into its 5′ flanking region (see Fig. 7) was annealed to intact total RNA from the KK124 cell line. After this, S1 nuclease was added to the hybrid mixture to digest away all single-stranded nucleic acid. Because we had sequenced the probe and identified the two promoter segments, we could predict the size of fragments in the altered first exon protected from S1 nuclease digestion by formation of the DNA-mRNA hybrid molecules. These predicted fragments were precisely those seen when the reaction mixture was analyzed (Fig. 7). Transcripts of a c-*myc* gene with a sequence even subtly different from the probe used here would have led to the generation of other sizes of protected fragments. Because no other protected fragments were observed, all the c-*myc* transcripts in the KK124 cell line appear to be transcribed from the translocated oncogene. The major proportion of RNA transcription is initiated from the most 5′ of the two potential c-*myc* promoters, as is indicated by the relative intensity of the protected fragments.

DISCUSSION

Three constant features emerge from all analyses of human Burkitt lymphomas and mouse plasmacytomas. First, a genomic rearrangement brings a c-*myc* oncogene and some recognizable part of an immunoglobulin gene from disparate locations into the same chromosomal context (6, 8, 18). The c-*myc* and immunoglobulin elements are not always directly linked, but their presence in the same chromosomal region has, so far, always been demonstrable. Secondly, the first

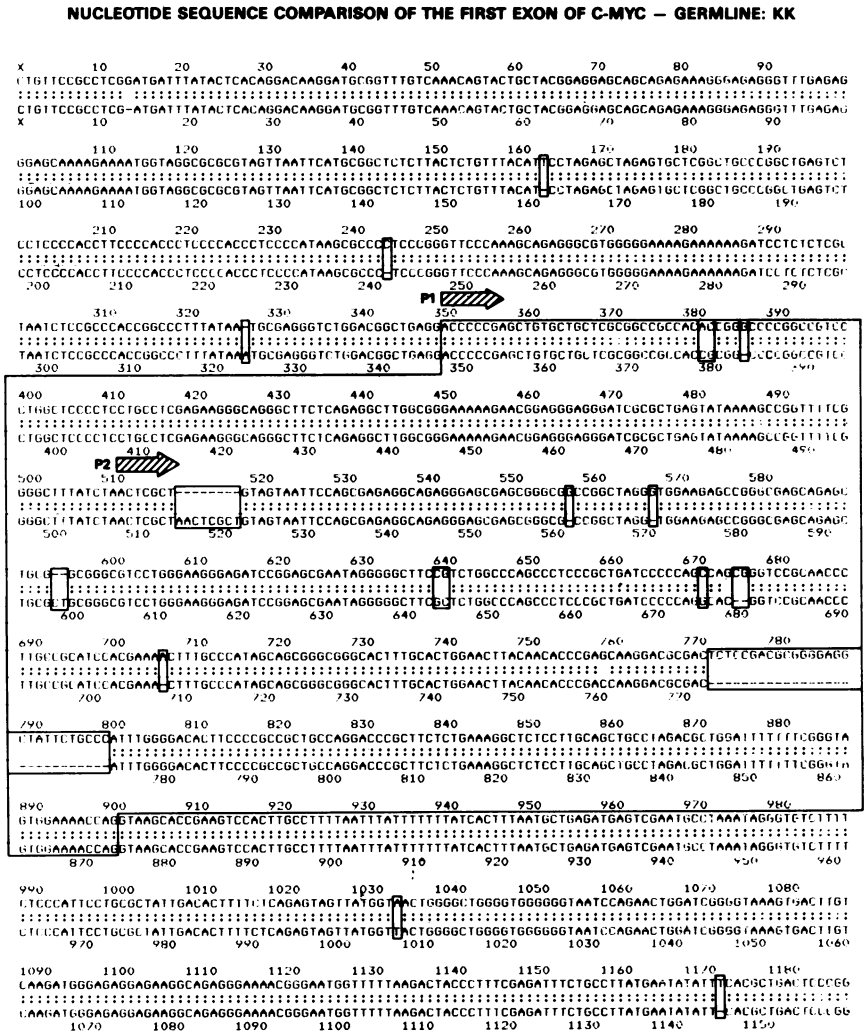

FIG. 6. Comparison of KK124 *myc* first exon with normal counterpart. Normal (upper line) and KK124 (lower line) *myc* first exon and flanking region sequences are compared. Boundaries of first exon are shown in the large box, and promoters P1 and P2 are indicated by arrows. Differences are highlighted by smaller boxes.

exon of c-*myc* or sequences immediately upstream appear to undergo somatic mutation on the translocated allele (1, 28, 33, 36, 40). Thirdly, either as a result of this alteration, or in concert with other, as yet unidentified, cellular alterations, it is always the translocated c-*myc* oncogene that is expressed in the tumor cells (7, 39). The only exceptions to this third point have arisen in certain derivatives of widely dispersed and continuously passaged cell lines (e.g., Raji CA46) where changes have also been detected in the coding sequence of the translocated c-*myc* (27, 32).

It is important to consider these three features in the context of this analysis of the translocation occurring in the KK124 cell line. Here the *myc*-immunoglobulin gene relationship is a very obvious one with direct physical linkage between the translocated c-*myc* and the immunoglobulin lambda locus. Often, in Burkitt lymphomas or mouse plasmacytomas, breakpoints occur within the immunoglobulin switch recombination region (25; P. D. Fahrlander, J. Sumegi, J. Yang, F. Weiner, K. Marcu, and G. Klein, Proc. Natl. Acad. Sci. USA, in press). Occasionally, in rare Burkitt lymphomas or in translocations seen in other B-lymphocyte tumors, t(14;18) (38) translocations involving immunoglobulin J sequences have been postulated. The KK124 line shows that translocation can occur without the obvious involvement of switch or V-J signal sequences. One need not invoke an extant immunoglobulin recombination system (i.e., recombinases) to explain the translocation process seen here. Such a system may not be necessary for the translocation to occur, although its presence may predispose certain sites (e.g., switch sites) to a chromosomal breakage and rejoining event.

The KK124 cell line produces immunoglobulin mu and kappa, but the translocation of c-*myc* has occurred within the lambda locus. No lambda transcripts are detected. Elsewhere, we have postulated that chromosomal translocations occur preferentially in regions of genomic activity in differentiated cells (14, 15; Denny et al., in press). This activity may be directly evidenced by transcription or may be reflected by some special attribute (e.g., hypomethylation) or by openness of the chromatin structure in these regions. In a B lymphocyte, the immunoglobulin gene encoding regions demonstrate this change in chromatin structure, as shown by transcriptional or microdeletional activity or both before actual V-J or switch recombination (35, 41).

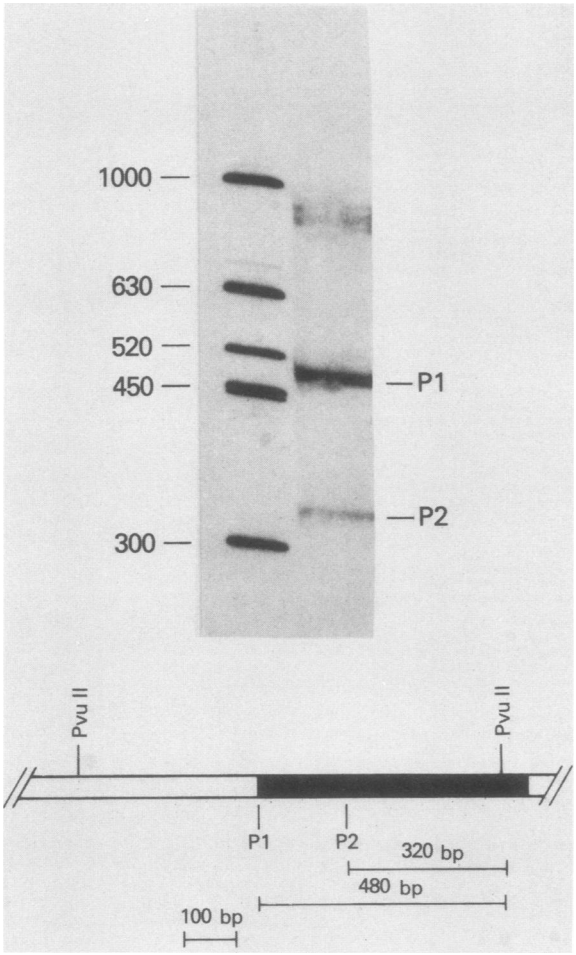

FIG. 7. S1 nuclease analysis of KK124 c-*myc* first exon. An S1 probe was constructed from the first exon of c-*myc* from der 8 by using a *Pvu*II-*Pvu*II fragment shown on the schematic below. When annealed to total RNA, protection from S1 nuclease digestion was afforded to two fragments. These fragments correspond to those predicted for mRNAs initiating at promoters P1 and P2 from this particular first exon. No other signs of probe-mRNA mismatch are evident.

The observation of a V-J recombinational event on the der 8 chromosome is consistent with the notion of regional genomic activity as a necessary, if not sufficient, factor in the generation of chromosomal aberration.

As previously stated, in every Burkitt lymphoma or mouse plasmacytoma analyzed, with one exception, the first exon of the c-*myc* oncogene appears to have undergone somatic mutation. In the one exceptional case, a murine plasmacytoma showed somatic mutation in the presumptive regulatory regions 5′ of the first exon (5). The targeted nature of the first exon changes in the KK124 cell line implies either a specific mechanism for recognizing the first exon and inducing a mutation or a strong selection bias during neoplastic progression for more extensive (more than just single point mutations) changes in this exon. But it is difficult to imagine why, if these gross changes were being selected for, they would be limited to the first exon, as appears to be the case in KK124. Thus, at the present time, we feel that a specifically targeted mutational mechanism is more likely. We realize though, that sequences further 5′ than our analysis have been implicated in c-*myc* regulation (33), and significant mutation in these areas cannot be ruled out.

Earlier reports have described a shift in promoter utilization of the translocated c-*myc* in which the level of transcript from P1 rises until it is equivalent to or greater than that from P2 (38). The KK124 cell line provides a particularly dramatic example of this shift with at least fourfold more P1 transcript than P2. The significance of this shift in promoter utilization is still obscure. The fact that frequently the entire first exon and, therefore, both promoters are split away from the c-*myc* coding sequence by the translocation makes it difficult to implicate changes in promoter utilization as a general requirement for neoplastic progression in Burkitt lymphomas.

Very few tumor cell lines have been analyzed in sufficient detail to allow definitive statements about the involved chromosomal regions before and after the translocation events. The process appears to be relatively conservative in nature. In the KK124 cell line, about 32 bp are deleted from chromosome 22 on each derivative chromosome by the duplication of a sequence present on the normal and, therefore, presumptively original chromosome 8. Because the region of chromosome 22 does not contain any sequence similar to this duplication unit, homologous recombination is ruled out as a mechanism mediating the translocation event. KK124 is the only Burkitt tumor so far analyzed in which a duplication of DNA at the junction of the translocation has been observed. Deletions from the immunoglobulin side of the translocation are often seen. In mouse plasmacytomas and Burkitt lymphomas with t(8;14), the deletions often occur within the switch region, an area frequently observed in normal circumstances to undergo internal deletion (22, 31). A recent study of a t(8;14) (25) revealed a 3,000-bp deletion from the mu switch and a 16-bp deletion from the *myc* region. A variant t(8;22) translocation that we have previously analyzed showed a 21-bp deletion at the site of translocation within the lambda locus but no deletion from the *myc* side (13). The kind of breakage and rejoining event seen in these tumors does not exactly mimic any previously described recombinational event but seems to have elements of switch and staggered nick and repair recombination models.

Inappropriate expression of c-*myc* has been shown to act in concert with other genes to cause malignant transformation of cells in vitro (17). The chromosomal translocations seen in Burkitt lymphomas result in inappropriate expression of the translocated c-*myc* (6, 18). The analysis of the KK124 variant translocation Burkitt lymphoma cell line has provided clues for our eventual understanding of the mechanism of translocation as well as the consequences of that translocation at the molecular level.

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