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Different regions of the immunoglobulin heavy-chain locus are involved in chromosomal translocations in distinct pathogenetic forms of Burkitt lymphoma

(B lymphocyte/t(8;14) breakpoints/recombination/c-*myc* oncogene)

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ABSTRACT **We show that endemic (eBL), sporadic (sBL), and acquired immunodeficiency syndrome-associated (AIDS-BL) forms of Burkitt lymphoma (BL) carrying t(8;14) chromosomal translocations display different breakpoints within the immunoglobulin heavy-chain locus (*IGH*) on chromosome 14. In sBL (7 out of 11) and AIDS-BL (5 out of 6), the breakpoints occurred within or near the *IGH* μ switch (S_μ) region on chromosome 14 and within the c-*myc* locus (*MYC*) on chromosome 8. In most eBL (13 out of 16) the breakpoints were mapped within or 5′ to the *IGH* joining (J_H region on chromosome 14 and outside the *MYC* locus on chromosome 8. Cloning and sequencing of the t(8;14) chromosomal junctions from two eBL cell lines and one eBL biopsy sample show that the recombinations do not involve *IGH*-specific recombination signals on chromosome 14 or homologous sequences on chromosome 8, suggesting that these events are not likely to be mediated by the same mechanisms or enzymes as in *IGH* rearrangements. In general, these data have implications for the timing of occurrence of chromosomal translocations during B-cell differentiation in different BL types.**

Reciprocal chromosomal translocations involving the c-*myc* oncogene locus (*MYC*) on chromosome 8 and one of the chromosome segments bearing immunoglobulin genes on chromosome 2, 14, or 22 are found in Burkitt lymphoma (BL), other undifferentiated B-cell lymphomas, and L_3-type acute lymphoblastic leukemias (for reviews see refs. 1–3). These *MYC*/immunoglobulin gene juxtapositions seem to be characterized by remarkable heterogeneity, involving different chromosomal breakpoints in different tumors. In the more frequent t(8;14) translocation, breakpoints located 5′ (i.e., centromeric) to *MYC* lead to its translocation into the immunoglobulin heavy-chain locus (*IGH*) on chromosome 14, while in the variant t(2;8) and t(8;22) translocations an immunoglobulin light-chain locus is translocated 3′ (i.e., telomeric) to *MYC*, which remains on chromosome 8.

Further heterogeneity appears at the molecular level, with respect to the position of the chromosome 8 breakpoints in the t(8;14) translocations in the two forms of BL—i.e., the endemic, African-type BL (eBL) and the sporadic, American-type BL (sBL) (4). In eBL carrying the t(8;14) translocation, the chromosomal breakpoint is located at an undefined distance 5′ to the translocated *MYC* locus, whereas in sBL and in acquired immunodeficiency syndrome-associated BL (AIDS-BL) the translocation truncates *MYC* within its 5′ portion, in most cases within the first intron or within sequences flanking the first exon.

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We have now comprehensively studied the position of breakpoints on chromosome 14 in eBL, sBL, and AIDS-BL. In analogy with previous data available for sBL, we have analyzed a panel of eBL, including detailed molecular analysis of the breakpoint in three eBL cases.§ Our results indicate that different *IGH* regions are involved in chromosomal translocations in distinct forms of BL and provide insight into the mechanisms of the abnormal recombinations.

MATERIALS AND METHODS

Pathologic Samples, Cell Lines, and Diagnostic Criteria. All fresh eBL samples analyzed in this study originated from Ghana and were obtained through the National Cancer Institute's Burkitt Tumor Project. sBL samples originated from Europe and North America. AIDS-BL samples were collected at the New York University Medical Center. The BL cell lines have been described (5).

DNA Extraction and Southern Blot Analysis. DNA was prepared by cell lysis, digestion with proteinase K, extraction with phenol, and precipitation with ethanol (6). Southern blot analysis was performed by standard procedures (6).

Construction and Screening of Recombinant DNA Libraries. Libraries of genomic DNA from cell lines Ag876 and P3HR-1 and tumor biopsy sample IM-12 were constructed by partial digestion of DNA with *Mbo* I restriction endonuclease and ligation into EMBL3 phage DNA. Screening was performed by plaque hybridization (6).

DNA Probes. Both *MYC* (7) and *IGH* joining-region (J_H) (8) probes have been described (see Fig. 1*d*). Purified DNA fragments were ^{32}P-labeled by nick-translation (6).

DNA Sequencing. DNA sequencing was performed by "dideoxy" chain-termination analysis of fragments cloned in the pGEM-3 (Promega Biotec, Madison, WI) plasmid vector, which carries the bacteriophage SP6 and T7 promoters. Sequencing reactions were performed as described in the Promega Biotec sequencing manual.

Somatic Cell Hybrids. The lines used were obtained by fusing human lymphocytes to hypoxanthine phosphoribosyltransferase-negative Chinese hamster ovary cell lines YH-21 or RJK88 (9). Hybrid clones were examined for human

Abbreviations: BL, Burkitt lymphoma(s); eBL, endemic BL; sBL, sporadic BL; AIDS-BL, acquired immunodeficiency syndrome-associated BL; *C*, constant; *D*, diversity; *J*, joining; *S*, switch; *V*, variable.

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§Two of these breakpoint sequences are being deposited in the EMBL/GenBank data base (Bolt, Beranek, and Newman Laboratories, Cambridge, MA, and Eur. Mol. Biol. Lab., Heidelberg) [accession nos. J03272 (for eBL cell line Ag876) and J03273 (for eBL biopsy sample IM-12)].

chromosome content by cytogenetic characterization based on Q-banding and by electrophoretic isozyme analysis.

RESULTS

Different Location of Chromosome 14 Breakpoints in eBL vs. sBL. Positions of chromosomal breakpoints within the *IGH* locus can be preliminarily determined from linkage between *MYC* sequences and various *IGH* regions [namely, J_H and the μ-chain switch (S_μ) and constant (C_μ) regions] as shown by comigration of restriction fragments that hybridize to both *MYC* and *IGH* probes.

In 7 of 11 sBL and 5 of 6 AIDS-BL (Table 1), the chromosomal breakpoint was located within or in close proximity to the S_μ region (see Fig. 1*a* for one representative case). *Bam*HI digestion and subsequent hybridizations to C_μ and J_H probes (Fig. 1*d*), which allows the exploration of the entire J_H–S_μ–C_μ region, indicated two rearranged fragments: the first has C_μ and *MYC* but not J_H sequences and therefore spans the breakpoint on chromosome 14q+, whereas the second contains C_μ and J_H but not *MYC* sequences and must represent a rearranged *IGH* gene on normal chromosome 14. Hybridization of J_H probe to *Eco*RI digests showed two rearranged alleles, both lacking *MYC* coding sequences. Finally, the *Hin*dIII fragment normally containing S_μ and C_μ regions was found to be rearranged and to contain both the C_μ and the *MYC* sequences. These data indicate that the breakpoint is located within the 5′ *Hin*dIII–3′ *Eco*RI fragment containing S_μ sequences. The general validity of this approach is supported by cloning and sequence analysis of chromosomal breakpoints in one of the sBL cases studied here (ST486 cell line; ref. 10) and in several other cases (11–13). In one case the breakpoint was located within the J_H region; in the three remaining cases it could not be mapped by this approach (Table 1).

Generally different results were obtained in eBL (Table 1). In 13 of 16 cases hybridization of *Bam*HI digests with J_H and C_μ probes showed a linkage between J_H and C_μ regions (Fig. 1 *b* and *c*), suggesting a breakpoint located within the region hybridizing to the J_H probe or 5′ to this region. In a number of cases, the former possibility was strongly suggested by the presence of three rearranged bands detected by the J_H probe with at least one restriction enzyme (*Bam*HI, *Eco*RI, or *Hin*dIII), a pattern consistent with a physiologically rearranged *IGH* locus on chromosome 14 and a reciprocal translocation that places parts of the J_H region on both chromosomes 14q+ and 8q−. This interpretation is directly supported by the cloning of these genomic regions from three eBL cases (see below).

Table 1. Chromosome 14 breakpoint locations in eBL and sBL

BL type	No./no. tested				
	t(8;14)	*IGH* breakpoints*			*MYC* rearrangements†
		J_H	S_μ	UD	
sBL					
Cell lines	7/7	0/7	5/7	2/7	6/7‡
Biopsy samples	ND	1/4	2/4	1/4	4/4
eBL					
Cell lines	5/5	5/5	0/5	0/5	2/5
Biopsy samples	ND	8/11	1/11	2/11	1/11§
AIDS-BL					
Biopsy samples	ND	0/6	5/6	1/6	6/6

ND, not determined.

*Location of breakpoints within the *IGH* locus. See text for definition and limits of mapping criteria. UD, cases in which breakpoint location could not be determined (see text).

†Monoallelic rearrangement within *MYC*.

‡Cell line lacking *MYC* rearrangements is one of two with undetermined *IGH* breakpoint locations.

§Biopsy sample with *MYC* rearrangement is the one showing breakpoint location in S_μ region.

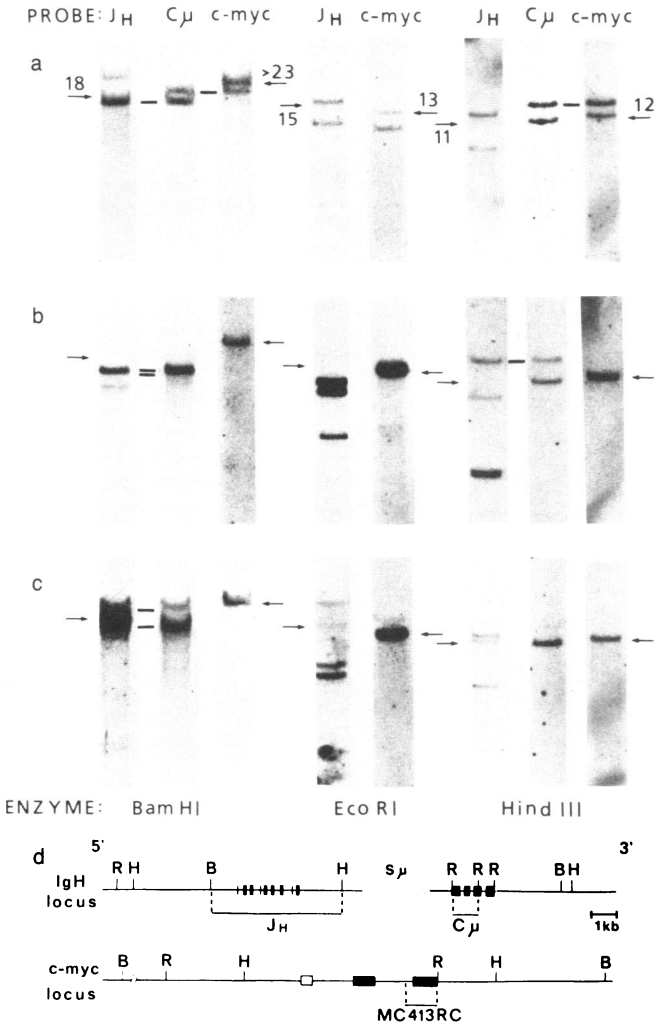

FIG. 1. Southern blot analysis of *IGH* and *MYC* organization. DNA from DK-179 sBL biopsy sample (*a*), Ag876 eBL cell line (*b*), and IM-12 eBL biopsy sample (*c*) was digested with the indicated restriction enzymes, size-separated by electrophoresis in 1% agarose gels, and transferred to nitrocellulose filters. Each filter was subsequently hybridized to the probes indicated. Comigrating fragments are indicated by dashes between lanes. Arrows indicate position of germ-line fragments from control DNAs run on the same gel; their sizes are indicated in kilobases (kb). The two germ-line *Hin*dIII fragments containing J_H and C_μ display a similar size under our experimental conditions. (*d*) Diagrams of the human *IGH* and *MYC* loci and the *IGH* and *MYC* probes. Restriction sites: R, *Eco*RI; B, *Bam*HI; H, *Hin*dIII.

The position of the breakpoints could not be determined in six BL cases (Table 1). These breakpoints may be (*i*) within restriction fragments that are too large to be transferred effectively in the Southern blot procedure; (*ii*) outside the J_H or S_μ region, possibly 5′ to J_H in eBL (14) and 3′ to C_μ [C_γ (15)] or C_α (16, 17) in sBL; or (*iii*) in variant t(2;8) or t(8;22) translocations, which are present in ≈15% of BL (18).

Cloning and Analysis of Chromosomal Breakpoints in eBL. Since several examples of the involvement of S_μ regions in sBL have been studied (10–13), we cloned and examined in detail the t(8;14) chromosomal junctions from two eBL cell lines (P3HR-1 and Ag876) and one eBL biopsy sample (IM-12). While this work was in progress, an analysis of the P3HR-1 junctions was reported (19). Therefore this part of the study will not be presented, although the results will be discussed.

To clone the chromosomal breakpoints from cell line Ag876, a library of Ag876 genomic DNA was constructed and screened with the J_H probe. We isolated three phages representative of a normally rearranged *IGH* locus on chromosome 14 and two distinct regions containing rearranged portions of *IGH* (Fig. 2*a*) linked to unidentified sequences

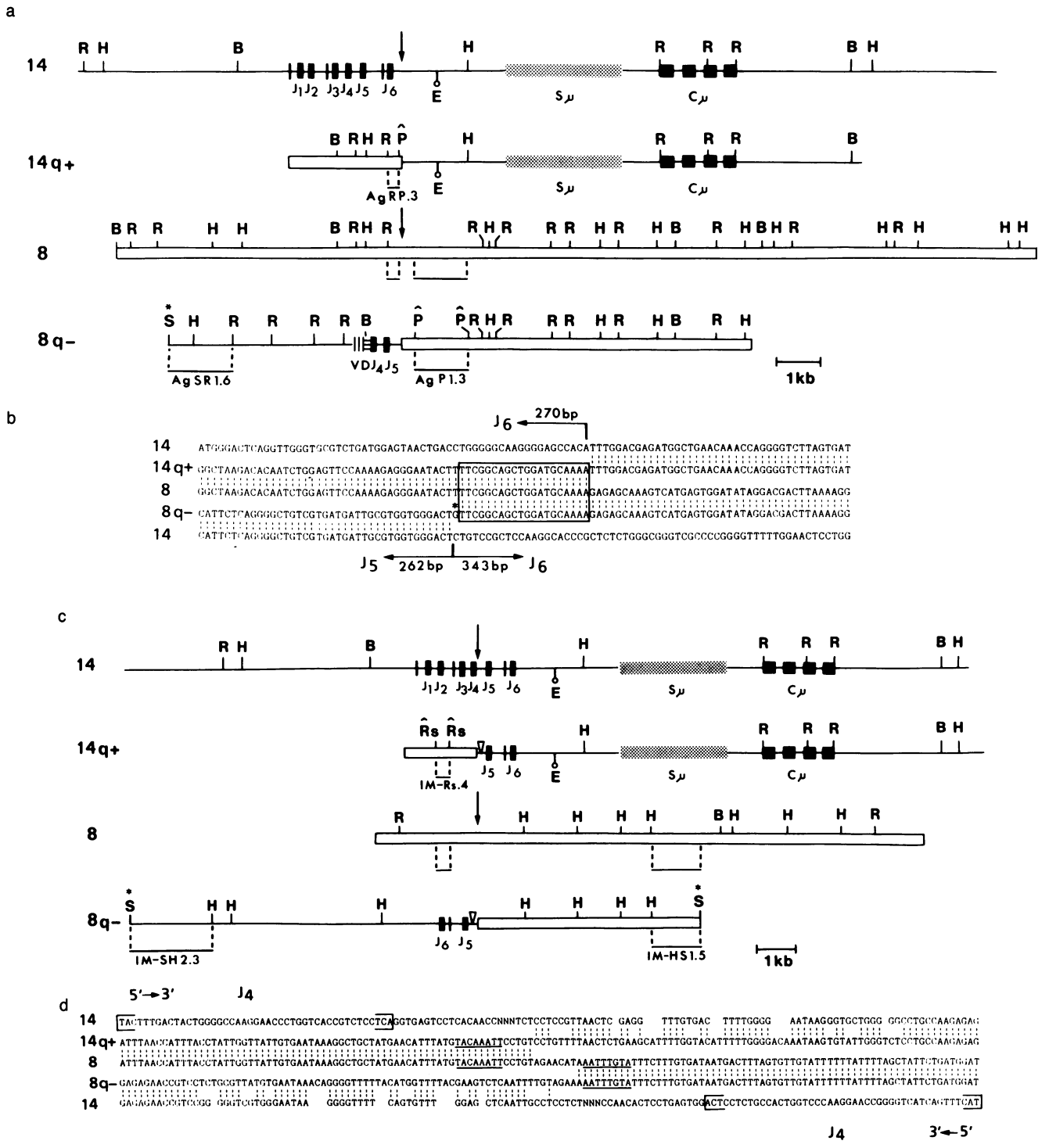

FIG. 2. Molecular cloning of chromosomal breakpoints from Ag876 and IM-12 DNA. (*a* and *c*) Schematic representations of the cloned reciprocal breakpoint regions (14q+ and 8q−) and their respective germ-line counterparts (14 and 8). Chromosome 14 sequences are indicated by a solid line with black or stippled boxes representing different *IGH* regions. Chromosome 8 regions are shown as open boxes. Vertical arrows show position of breakpoints. Below the 14q+ and 8q− maps are indicated the probes used for chromosomal mapping (Table 2). Restriction enzyme symbols: R, *Eco*RI; H, *Hin*dIII; B, *Bam*HI; P, *Pst* I; S, *Sal* I; Rs, *Rsa* I. For restriction enzymes marked by carets (^), only sites delineating probes are shown; the entire map is not given. Cloning sites are marked by asterisks. E, immunoglobulin transcriptional enhancer. Triangles in *c* indicate a 90-base-pair (bp) deletion in the region between J_4 and J_5 of the duplicated J_H fragment on both 14q+ and 8q−. (*b* and *d*) Nucleotide sequence analysis of breakpoint regions and their alignment to corresponding germ-line regions. Sequences were obtained by analysis of both DNA strands and are derived from at least 700 bp across the breakpoints. In *b*, boxed sequences indicate regions of chromosome 8 that are duplicated and present at both translocation sites (see text); distances from adjacent J_H elements are indicated; the base indicated by an asterisk is not present in either germ-line region. In *d*, the J_H element is bracketed, and gaps in the germ-line sequence of chromosome 14 have been introduced to maximize the sequence alignment; underlining indicates inverted repeats.

that, upon hybridization to a panel of hamster–human somatic cell hybrids containing either human chromosome 8 or 14, were identified as deriving from chromosome 8 (Table 2). Based on the presence of either C_μ or *IGH* variable-region (V_H) sequences, these two regions were identified as containing the t(8;14) junctions on chromosome 14q+ or 8−, respectively (Fig. 2*a*). Comparison of the nucleotide sequences of J_H-containing fragments for both region 14q+ and region 8q− with the sequences of the corresponding germ-line regions from chromosomes 14 (8) and 8 (isolated from a normal human DNA library screened with the AgP1.3 probe) shows that the chromosomal translocation represents an imprecise, reciprocal recombination involving a deletion of 613 bp containing J_H gene segment J_6 from chromosome 14 and a duplication of 20 bp from chromosome 8 at both the 14q+ and 8q− junctions (Fig. 2*b*). The breakpoint on chromosome 14 is located 270 bp from the 3′ border of J_6. Sequences similar to the J_H heptamer–nonamer recombination signals cannot be recognized in the proximity of the breakpoint sites on either chromosome 14 or chromosome 8. The structure of the chromosomal junctions, and in particular the presence of duplicated sequences from chromosome 8, suggests the occurrence of staggered double-strand DNA breaks followed by "filling-in" of the protruding strand and interchromosomal ligation. A similar staggered break, along with nucleolytic digestion of the single strands, can account for the deletion of sequences from chromosome 14, although other models are also consistent with these data. Finally, we note that 5′ to the breakpoint on chromosome 14 is a normally rearranged V_H–D_H–J_H region (where D_H represents the diversity gene segment) as determined by hybridization and nucleotide sequence analysis (data not shown); whether this rearrangement preceded or occurred after translocation cannot be determined.

The same strategy was adopted to isolate and characterize the chromosome 14, 14q+, and 8q− regions from the IM-12 eBL biopsy sample (Fig. 2*c*). Comparative analysis of recombined and germ-line regions indicated a complex, reciprocal, yet largely imprecise recombination involving (*i*) on chromosome 14, a breakpoint between J_4 and J_5 accompanied by duplication and inversion of a 1.4-kb segment containing J_5 and J_6, which is found on both chromosomes 14q+ and 8q−; (*ii*) on chromosome 8, a loss of 7 bp accompanied by the addition of 4 bp, which could represent an "*N*" segment at the 8q− junction (Fig. 2*d*). The breakpoint on chromosome 8 lies between two 8-bp inverted repeats, a feature previously noted in several analogous translocations in mouse plasmacytomas (20). As for Ag876, no J_H-specific recombination signals were recognizable at both junctions. In addition, heavily mutated chromosome 14 sequences flank the chromosomal junctions (Fig. 2*d*). 5′ to the breakpoint, the J_H region on chromosome 8q− appears to be joined to sequences from chromosome 14 (Table 2), which, however, do not contain known D_H or V_H sequences (data not shown) and remain of unknown origin. As for Ag876, the temporal relationship between this rearrangement and the translocation cannot be determined.

Table 2. Chromosomal assignment of various genomic regions involved in translocation in eBL cases Ag876 and IM-12

	Hybridization with probe†			
	Chromosome 8		Chromosome 14	
Probe*	Hy.36.1	Hy.46BF	Hy.95A1	Hy.95B
C_μ	−	−	+	+
MC413RC	+	+	−	−
AgRP.3	+	+	−	−
AgP1.3	+	+	−	−
AgSR1.6	−	−	+	+
IM-Rs.4	+	+	−	−
IM-HS1.5	+	+	−	−
IM-SH2.3	−	−	+	+

*See Fig. 1*d* (C_μ and MC413RC), Fig. 2*a* (Ag876 probes), and Fig. 2*d* (IM-12 probes) for schematic representation of the probes.

†Clones containing either human chromosome 8 (chr. 8) or human chromosome 14 were chosen among a complete panel (9). Complete human chromosome content of each clone is as follows. Hy.36.1: X,8,11,19. Hy.46BF: X,3,6,8,13. Hy.95.1: X,3,5,10,-11,14. Hy:95B: X,4,6,7,14,18,22.

Lack of Clustering of Chromosome 8 Breakpoints in eBL. To determine whether any of these breakpoints on chromosome 8 were involved in the translocation in other eBL cases, we hybridized probes from each of the three germ-line regions to restriction digests of 11 eBL DNAs. None of the probes recognized rearranged fragments in any of the eBL samples (Fig. 3), with the exception of the P3-B2.5 probe, which detected rearrangements in Daudi DNA (Fig. 3*a*), as previously reported (19). We conclude that the breakpoints are not clustered in eBL. Since none of the three probes detects an amplified fragment in HL-60 DNA (Fig. 3, lanes 1), the breakpoint region must reside outside the 90-kb region containing the *MYC* amplification unit in the HL-60 genome (21). Finally, several probes derived from each of the three breakpoint regions failed to detect transcripts in blot hybridization of electrophoretically fractionated RNAs from several BL and other hematopoietic cell lines (data not shown), suggesting the absence of transcribed genes in the proximity of the breakpoints.

DISCUSSION

Correlation Between Types of Translocation and Stages of Differentiation in eBL and sBL. The results extend those reported for the breakpoints on chromosome 8 (4), indicating that two types of t(8;14) translocation can be distinguished at the molecular level. One type, found in most sBL and AIDS-BL, involves sequences within or immediately 5′ to *MYC* on chromosome 8 and sequences within or near the *IGH S* regions on chromosome 14. The second type, found in most eBL, involves sequences on chromosome 8 at an unidentified distance upstream from *MYC* and sequences within or near the J_H region on chromosome 14.

The location of breakpoints in regions that normally mediate differentiation-stage-specific immunoglobulin gene rearrangements supports the hypothesis that the position of the breakpoints may correlate with the stage of differentiation of the involved cells. In fact, sBL appear to derive from cells more advanced along the B-cell differentiation pathway than eBL, since sBL but not eBL cell lines secrete IgM (5). As previously suggested (19), chromosomal translocations involving J_H may occur at the time of V_H–D_H–J_H joining in the more immature eBL cells, whereas translocations involving *S* sequences may occur at the time of class switching, leading to the more differentiated sBL. However, translocations can involve already-rearranged V_H–D_H–J_H alleles (see Ag876), and most eBL (including biopsy specimens) carry clonally rearranged immunoglobulin light-chain genes (A.N. and R.D.-F., unpublished data). Thus, in eBL, the translocations may occur after V_H–D_H–J_H joining and immunoglobulin light-chain gene rearrangement. Alternatively, the eBL translocations may occur at the time of V_H–D_H–J_H joining, but additional genetic changes affecting a more differentiated subclone are necessary for full expression of the malignant phenotype.

Implications for the Mechanism of Translocation. The translocations could represent mistakes of normal immunoglobulin gene rearrangement mechanisms—i.e., that specific recombinases may mistakenly recognize homologous J_H or *S* signal sequences (8) in two different chromosomes instead of those on the same chromosome. This has been proposed

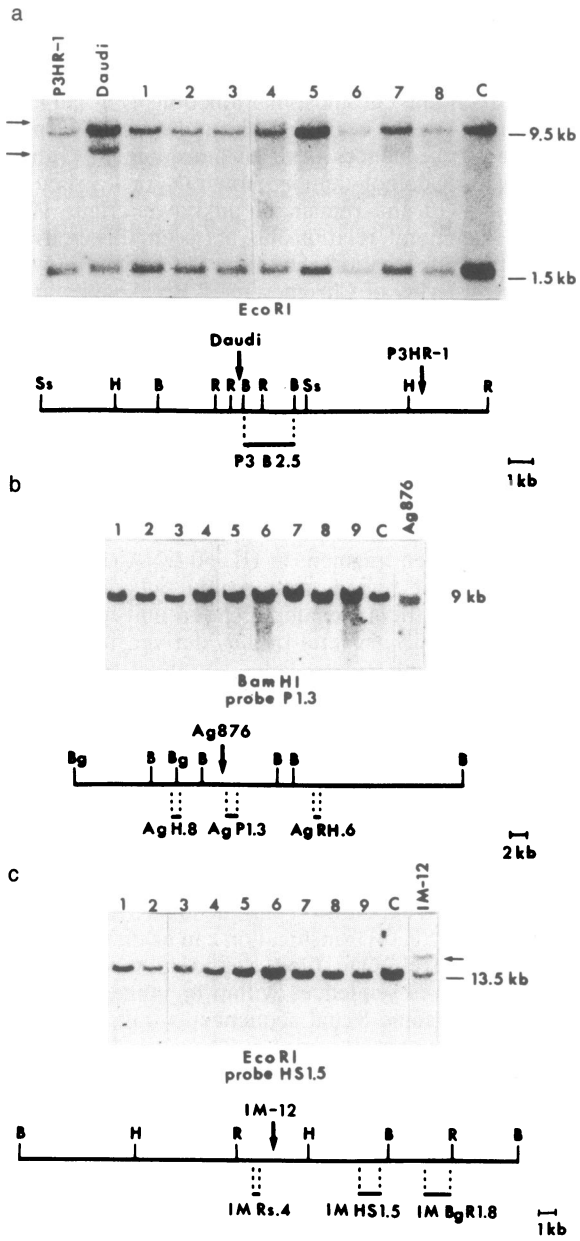

FIG. 3. Screening for breakpoint clusters on chromosomes 8 in eBL. Probes for the normal counterparts of the regions containing chromosome 8 breakpoints from eBL P3HR-1 (*a*), Ag876 (*b*), and IM-12 (*c*) were used to screen for rearrangements in eBL and control DNA. Lanes 1, HL-60 (promyelocytic leukemia) DNA; lanes 2–9, eBL biopsy samples; lanes *c*, human fibroblasts. Each probe shown (below maps) has been hybridized to DNA digests using all the indicated restriction sites; only representative data are shown. Restriction enzyme sites: R, *Eco*RI; B, *Bam*HI; H, *Hin*dIII; Ss, *Sst* I; Bg, *Bgl* II. Dashes indicate the germ-line fragments. Horizontal arrows indicate rearranged fragments. Vertical arrows indicate breakpoint sites. Daudi is an eBL cell line (5).

for the t(11;14) and t(14;18) translocations found in other B-cell malignancies (22, 23), as well as for the t(8;14) translocation in eBL based on the analysis of a single case (P3HR-1, ref. 19). However, results obtained for other sBL cases as well as the three eBL cases analyzed here argue against this model. First, in sBL the breakpoint is not always precisely within S_μ (24). Accordingly, in eBL the consistent location of the breakpoint between J_H regions is not compatible with the pattern of a physiologic D_H–J_H joining. Second, no region of consistent and evident homology with S_μ sequences or with D_H–J_H joining signals is found at the breakpoint site on chromosome 8 for either sBL and eBL. The suggestion that pseudosignals and a pseudo-*J* element are recognizable at the breakpoints of the P3HR-1 line (19) is based on weak, possibly insignificant sequence homologies that are not recognizable in the two new eBL cases analyzed here. Third, deletions and duplications are frequently found at the chromosomal junctions, and these events are typical of repair of the randomly occurring staggered double-strand DNA breaks. In this respect, our findings generally support the models proposed by Gerondakis *et al.* (25) for translocations involving *S* regions in mouse plasmacytomas and by Bakhshi *et al.* (26) for a t(14;18) translocation involving J_H in a human follicular lymphoma.

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