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Genetics

Translocation of immunoglobulin V_H genes in Burkitt lymphoma

(mouse-human B cell hybrids/chromosome segregation/specific chromosome rearrangements/genetics of malignancy)

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ABSTRACT We have produced cell hybrids between mouse myeloma cells, which do not produce immunoglobulin chains, and Burkitt lymphoma cells (Daudi), which express surface IgM. Daudi cells carry a reciprocal chromosome translocation between chromosomes 8 and 14, described as t(8;14)(q24;q32). The hybrids were studied for the expression of human immunoglobulin chains and human isozyme markers, for the presence of human chromosomes, and for the presence of the human genes for heavy chain variable regions (V_H) and μ and γ chain constant (C) regions. The results indicate that the expressed μ chain gene is on normal chromosome 14 in Daudi cells. We have also determined that the chromosome 14 involved in the translocation (14q+) carries the gene for C_μ and $C_{\gamma 1-4}$ and probably several genes for the variable region (V). Certain hybrids had lost both the chromosomes 14 but had retained the abnormal chromosome 8 (8q−) that carries the terminal end of the long arm of chromosome 14. These hybrids were studied for the presence of human V_H, C_μ, and C_γ DNA sequences, and the results indicated that the hybrid cells with the 8q− chromosome contained V_H genes but not *C* genes. Therefore, we conclude that, in the Daudi Burkitt lymphoma, the break in chromosome 14 occurred within the chromosome segment containing *V* region genes. As a result of the translocation some of these V_H genes became associated with chromosome 8. It is possible that the expression of malignancy in Burkitt lymphoma is caused by immunoglobulin *V* region gene translocation resulting in activation of a gene on the long arm of human chromosome 8.

Manolov and Manolova have shown that Burkitt lymphoma cells carry a specific chromosome rearrangement, a reciprocal translocation between chromosome 8 and chromosome 14 (1). The breakpoint on chromosome 8 is in band q24 and the breakpoint on chromosome 14 is near the terminal end of the long arm (band q32) (1, 2). As a result of the translocation two rearranged chromosomes are formed: a 14q+ chromosome that carries the region q24-qter of chromosome 8, and an 8q− chromosome that carries the terminal end of the long arm of human chromosome 14 (1, 2). Very recently, two variant translocations have been described in both African and non-African cases of Burkitt lymphoma involving chromosome 8 and either chromosome 2 or chromosome 22, the breakpoint on chromosome 8 also being in band q24 (3–5). By studying somatic cell hybrids between mouse myeloma cells and different human B cells for the expression of human heavy chains we have determined that the human heavy chain gene cluster is located on human chromosome 14 (6, 7). These results were confirmed in different laboratories (8, 9). More recently, the heavy chain gene cluster has been localized to band 14q32 (10). By using somatic cell hybridization procedures, we and others have also been able to map the genes for human λ and κ light chains to human chromosomes 22 (11, 12) and 2 (12, 13), respectively. Thus one of the two chromosomes involved in the specific reciprocal chromosome translocations observed in Burkitt lymphoma is always one of the chromosomes carrying immunoglobulin genes. In view of these observations, we and others speculated that there might be a relationship between chromosome translocations, human immunoglobulin genes, and the expression of lymphoma (11, 14, 15). Therefore, we have produced somatic cell hybrids between mouse myeloma cells, which do not produce immunoglobulins, and Daudi Burkitt lymphoma cells, which express surface IgM, in order to obtain clones in which the human chromosomes involved in the (8;14) translocation in Burkitt lymphoma segregate (16). These segregants have been studied for the expression of human immunoglobulin chains and for the presence of human immunoglobulin gene sequences in an effort to establish whether the chromosome rearrangements observed in Burkitt lymphoma involve chromosomal regions carrying immunoglobulin gene sequences.

MATERIALS AND METHODS

Cells. Daudi Burkitt lymphoma cells were hybridized with NP3 nonproducer mouse myeloma cells in the presence of polyethylene glycol 1000 according to established procedures (16, 17). The hybrids were selected in the presence of hypoxanthine/aminopterin/thymidine medium (18) containing 10 μM ouabain (19). Each of the hybrid clones described in Table 1 derived from an independent fusion event, with the exception of 3E5 Cl 1 and 3E5 Cl 3, which are two subclones of an additional clone (3E5).

Chromosome Analysis. Air-dried chromosome preparations were trypsin-Giemsa banded by standard methods (20). At least 25 metaphases were examined from each hybrid, and they were scored only when there was adequate banding of human chromosomes. Selected metaphases were destained and restained by the G-11 technique (21), as modified by H. Morse (personal communication), to confirm the human origin of relevant chromosomes.

Isozyme Analysis. Hybrid and parental cells were studied for the expression of human glutathione reductase, which is coded for by a gene that is located on the short arm of chromosome 8, and of nucleoside phosphorylase, which is coded for by a gene located on the proximal half of the long arm of human chromosome 14 (22). We have also studied the hybrids for the expression of esterase D and mannosephosphate isomerase, which are markers for human chromosomes 13 and 15, respectively (22).

Expression of Immunoglobulin Chains. Parent and hybrid cells were grown for 5–8 hr in leucine-deficient medium or methionine-deficient media containing 5% dialyzed fetal calf serum and [^{3}H]leucine (70 Ci/mmol) at 100 μCi/ml or

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Abbreviations: kb, kilobase(s); V_H, heavy chain variable region; J, joining region; C, constant region; SV40, simian virus 40.

[^{35}S]methionine (400 Ci/mmol) at 100 μCi/ml (1 Ci = 3.7 × 10^{10} becquerels). The expression of human μ chain was determined by immunoprecipitation of culture fluids or of cytoplasmic extracts of the hybrid and parental cells by using rabbit antibodies specific for human μ, γ, and α chains, followed by the addition of 50 μl of a 10% suspension of fixed *Staphylococcus aureus* as described (6, 7, 16). Labeled immunoglobulin chains were then separated by $NaDodSO_4$/polyacrylamide gel electrophoresis (23).

DNA Gel Electrophoresis and Southern Transfer. Agarose gel (0.7% or 1%) electrophoresis was carried out in 40 mm Tris·HCl/5 mM NaOAc/2.0 mM EDTA, pH 8.0. *Hin*dIII-digested λ phage DNA molecular weight markers (0.75 μg per lane) (Bethesda Research Laboratories) were included on every gel. Cellular DNA samples were digested with *Bam*HI, *Eco*RI, *Hin*dIII, or *Xba* I and then subjected to electrophoresis in a horizontal agarose (Sigma) slab gel (10 μg of DNA per lane). Gels were stained for 10 min with ethidium bromide (1 μg/ml) and photographed under UV light. Transfer of DNA from gel to nitrocellulose sheet (Millipore) was performed essentially as described by Southern (24, 25).

Preparation of Labeled Probe DNAs. The V_{HIII} probe (M1326-8) for the heavy chain variable region is a 1.9-kilobase (kb) *Eco*RI fragment of a V_{HIII} gene that has been cloned in the M13 phage vector (8, 26). This probe was a generous gift of Terry Rabbitts (Medical Research Council Laboratory of Molecular Biology, Cambridge, England). Rabbitts and his coworkers have used this probe to demonstrate the synteny of the V_H genes and the genes for heavy chains (8). The probe specific for the constant region of human μ chain is a 655-base pair μ cDNA that contains enough sequences to code for amino acids glycine (residue 421) through the terminal tyrosine (residue 576) of the human μ chain as well as the entire 3′ noncoding sequence (27). The human γ-specific probe was a kind gift of Joel Bauxbaum (New York University). This probe is a 1.0-kb fragment that was inserted at the *Pst* I site of the plasmid pBR322 (POMM-B). It cross-hybridizes with all four γ chain genes (28). We have obtained the human J region by subcloning a 3.3-kb fragment of the human genomic μ DNA clone (H18 Cl 10). This fragment contains 2.2 kb of the human joining (*J*) region DNA (29) and 1.1 kb of flanking sequences at the 3′ end. The γ chain, μ chain, and J chain-specific inserts were isolated from the pBR322 vectors and labeled by the nick-translation procedure (30). The V_{HIII} probe was nick-translated in its M13 phage vector isolated in its replicative form. DNA polymerase I was purchased from Boehringer Mannheim and [α-^{32}P]NTPs were from Amersham. V_H, μ, γ, and *J* region probes labeled with ^{32}P and with specific activities of 0.5–5 × 10^8 cpm/μg of DNA were used in the experiments described in this paper.

Hybridization. DNA on nitrocellulose sheets was hybridized to ^{32}P-labeled probe DNA (V_{HIII}, J_H region, μ cDNA, γ cDNA) in a hybridization solution containing 50% (vol/vol) formamide (25). After hybridization, the filters were washed, air dried, and exposed to Kodak XRP-5 film for various periods. Prior to rehybridization, filters were washed two times at 65°C with H_2O for 15 min (31).

RESULTS

Chromosome and Isozyme Analysis of Hybrid Clones. The karyotype of Daudi parental cells is shown in Fig. 1*a*, demonstrating the reciprocal translocation between chromosomes 8 and 14, (q24;q32), that is observed in most cases of African Burkitt lymphoma (1, 2). The only other consistent abnormalities in the Daudi karyotype were a small interstitial deletion in the proximal portion of the long arm of one chromosome 15 and trisomy for chromosome 7 in a minority of the cells, both previously described (32).

Six hybrid clones were included in this study, four of which were independent. The other two (3E5 Cl 1 and 3E5 Cl 3) were subclones of an additional independent clone (3E5). These hybrids were studied for the presence of human chromosomes by trypsin-Giemsa and G11 banding and for the expression of human isozyme markers. The cells of the different hybrid clones contained 70–100 chromosomes, with 10–20 of human origin. Table 1 summarizes the results concerning human chromosomes 8 and 14, demonstrating a consistent correlation between

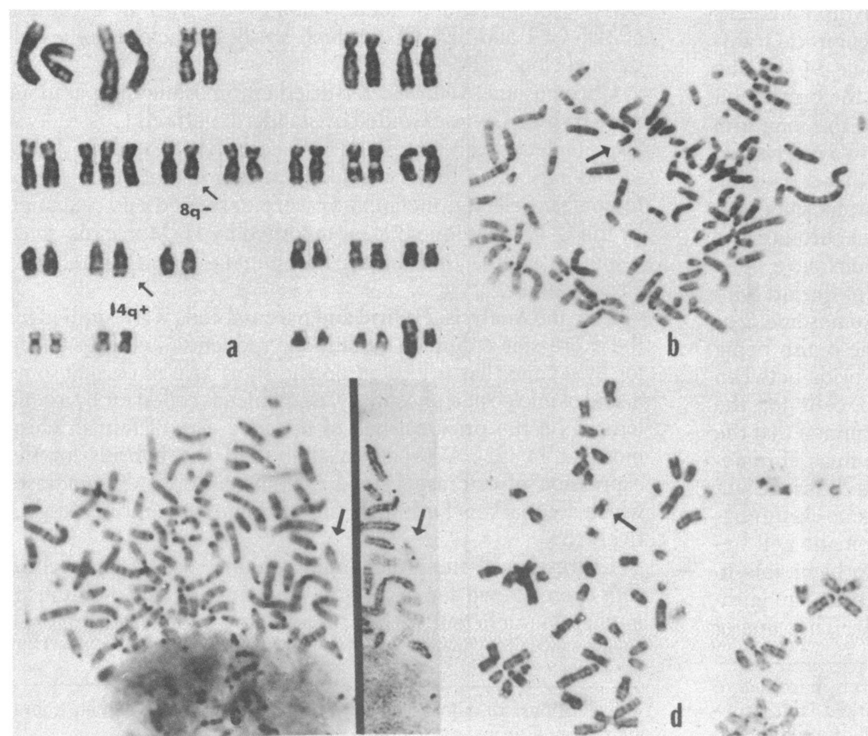

FIG. 1. (*a*) Karyotype of parental Daudi cell line with t8;14 (q24;q32) (arrows) and small interstitial deletion in 15q. Trisomy 7 was present in a minority of the cells. (*b*) Trypsin-Giemsa banded metaphase from hybrid 3E5 Cl 3 containing normal 14 (arrow) and no 14q+. (*c*) Trypsin-Giemsa banded metaphase from hybrid 3F2 with 14q+ (arrow) and no normal 14. G-11 staining of the same metaphase (*Inset*) indicates the human origin of 14q+. (*d*) Trypsin-Giemsa banded metaphase from hybrid 1E8 Cl 2 containing human 8q− (arrow) and no 14 or 14q+.

Table 1. Human immunoglobulin genes in NP3–Daudi cell hybrids

Cell line	Human chromosomes*				Human isozymes†		Expression of human μ chains	Human immunoglobulin genes		
	8	8q−	14	14q+	Glutathione reductase	Nucleoside phosphorylase		V_H	C_μ	C_γ
Daudi	++	++	++	++	+	+	+	+	+	+
NP3	−	−	−	−	−	−	−	−	−	−
3E5 Cl 1	+	−	+	+	+	+	+	+	+	+
3E5 Cl 3	+	+	++	−	+	+	+	+	+	+
3F2	++	++	−	+	+	+	−	+	+	+
1D8	++	−	−	+	+	+	−	+	+	+
1E8 Cl 2	++	+	−	−	+	−	−	+	−	−
2B8 Cl 22	++	±	−	−	+	−	−	±	−	−

* Frequency of metaphases with relevant chromosome: − = none; ± = <10%; + = 10–30%; and ++ = >30%.

† Glutathione reductase is a marker for human chromosome 8; nucleoside phosphorylase is a marker for human chromosome 14.

the cytogenetic and the isozyme data. Because clone 3E5 Cl 3 contained the normal chromosome 14 but not the 14q+, and clones 3F2 and 1D8 were the reverse (Fig. 1 *b* and *c*), it was felt that analysis of these clones for the expression of μ chains should indicate whether they were the product of the normal chromosome 14 or, alternatively, of the 14q+ chromosome. In addition, because two hybrid clones (1E8 Cl 2 and 2B8 Cl 22) had lost both the normal and the translocated chromosome 14 but had retained the 8q− chromosome (Fig. 1*d*) that carries a terminal segment of the long arm of chromosome 14 (q32→qter), these clones were examined to determine whether the small segment of chromosome 14 translocated to chromosome 8 carried human immunoglobulin heavy chain DNA sequences.

Expression of μ Chains. Human Daudi cells express surface IgM (33, 34) but do not secrete immunoglobulins (16). We previously showed that hybrids between Daudi cells and mouse myeloma cells secrete human IgM when the chromosomes carrying the active genes for light and heavy chains are present in the hybrids (16). We screened the hybrids described in Table 1 for the expression of secreted and cytoplasmic μ chains and found that hybrids 3E5 Cl 1 and 3E5 Cl 3 had human cytoplasmic μ chains (Fig. 2). They did not secrete IgM because they did not produce light chains. Hybrid 3E5 Cl 3 produced μ chains and did not have the 14q+ chromosome, whereas hybrid clones 3F2 and 1D8 did not express human μ chains and had lost the normal chromosome 14 but retained the 14q+ chromosome. This strongly suggests that the normal human chromosome 14 in these hybrids carries the expressed μ chain gene and that the 14q+ chromosome carries the unexpressed μ allele.

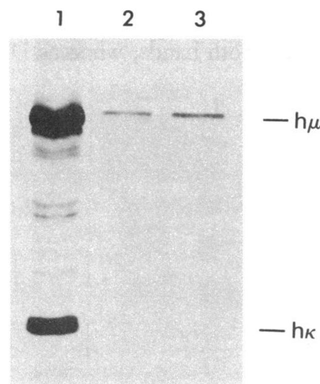

FIG. 2. NaDodSO$_4$/polyacrylamide gel electrophoresis of human immunoglobulins immunoprecipitated from cytoplasmic extracts prepared from a human lymphoblastoid line, GM607 (6) (lane 1), that secretes κ-containing IgM and two Daudi–NP3 cell hybrids, 3E5 Cl 1 (lane 2) and 3E5 Cl 3 (lane 3), that produce only μ heavy chains. These clones do not secrete immunoglobulin (data not shown).

Southern Transfer Analysis of Hybrid Cell DNA. We analyzed the DNA derived from the parental Daudi and NP3 cells and from the hybrid cells for the presence of the genes for the variable region (V_{HIII}) of human heavy chains and for the μ and γ constant (C) regions by Southern blotting procedures (24). As shown in Table 1, we detected the human μ and γ constant region genes in all hybrids containing either the normal chromosome 14 or the 14q+ (Fig. 3 *Lower* and Table 1). Hybrids that did not contain either chromosome 14 but retained the 8q− chromosome had lost the genes for the μ and γ constant regions (Fig. 3 *Lower* and Table 1).

We rehybridized the filters that were hybridized with the constant region probes (μ and γ) with a probe specific for a human variable region gene, V_{HIII}. This human chromosome 14-specific probe has been used to demonstrate the synteny of the V_H and C_H genes in man by Rabbitts and his associates (8, 26). As shown in Fig. 3 *Upper* and Table 1, the two hybrids (1E8 Cl 2 and 2B8 Cl 22) that contained human chromosome 8q−

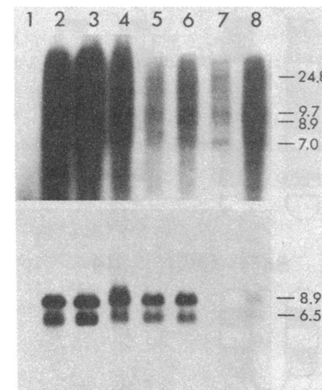

FIG. 3. Hybridization of *Hin*dIII-digested cellular DNA with the V_{HIII} probe (*Upper*) and the same filter rehybridized with the γ cDNA probe (*Lower*). In lane 1 is DNA from the mouse myeloma parent NP3, which shows no hybridization to either probe. Lane 2 is Daudi DNA, which hybridizes to both probes, as does DNA from 6M54VA, a simian virus 40 (SV40)-transformed human cell line, in lane 3. In lane 4 is the hybrid clone 3E5, which produces human μ chain. Lanes 5 and 6 are DNAs from two clones that are nucleoside phosphorylase positive. Lane 7 is DNA from the 1E8 Cl 2 clone, which is nucleoside phosphorylase negative and has the 8q− chromosome. This DNA hybridizes to the variable region probe (*Upper*) but not the (γ) constant region probe. In lane 8 is DNA from the 1D8 clone, which has the 14q+ chromosome but not the 8q− chromosome. DNA from this clone hybridizes to both probes. Here and in later figures the lengths of the fragments are indicated in kb.

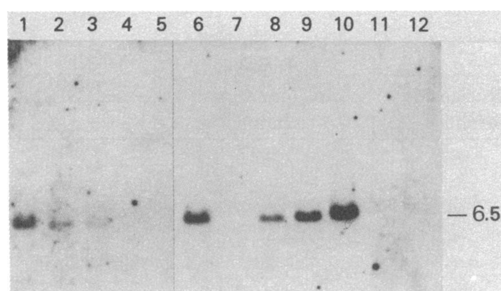

FIG. 4. Hybridization of *Xba* I-digested cellular DNA with the μ cDNA probe, demonstrating the presence or absence of μ gene sequences in Daudi hybrids. Lanes 1 and 2 (clones 3E5 and 3A9) are DNAs from hybrid clones that produce μ chain. In lane 3 is DNA from clone 3F2, which is nucleoside phosphorylase positive. In lanes 4 and 5 are DNAs from two nucleoside phosphorylase-negative clones. In lanes 6–10 are human DNAs: lane 6 is Daudi; lane 7 is an IgA-expressing lymphoblastoid line; lane 8 is an IgM-expressing lymphoblastoid line; and lanes 9 and 10 are two SV40-transformed human cell lines (19) (GM54VA and GM637). In lane 11 is DNA from NP3 and in lane 12 is DNA from a SV40-transformed mouse cell line, neither of which hybridizes to the human μ cDNA probe.

and had lost both the normal chromosome 14 and the 14q+ chromosome contained human V_{HIII} gene sequences. This result indicates that in the Daudi cells some of the variable region genes are translocated to chromosome 8. Because the 14q+ chromosome in clone 1D8, which is lacking the 8q− and the normal 14, seems to have retained V_{HIII} gene sequences (Fig. 3, Table 1), we can further conclude that the breakpoint in Daudi cells occurs in a region of chromosome 14 containing V_H genes.

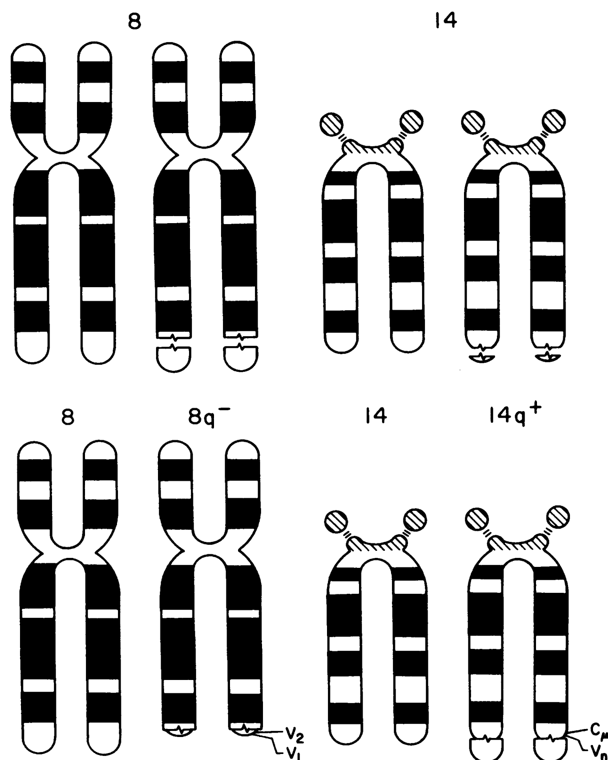

FIG. 5. Diagram of the (8;14) chromosome translocation in Daudi cells. (*Upper*) The breakpoint on chromosome 8 and 14; (*Lower*) the t(8;14) reciprocal translocation. The figure also shows the postulated position of the genes for variable regions ($V_1 \rightarrow V_n$) and constant regions of immunoglobulin heavy chains on the involved chromosomes as indicated by our data.

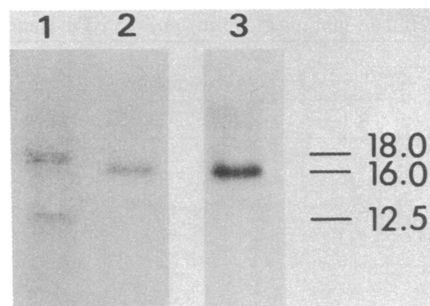

FIG. 6. Hybridization of *Bam*HI-digested cellular DNA with the μ-specific cDNA probe. In lane 1 is Daudi DNA with two bands. In lane 2 is DNA from an adenovirus-transformed human cell line (F6 Cl 3), and in lane 3 is GM54VA, a SV40-transformed fibroblastic human cell line (18); both show a single band that does not comigrate with either of the Daudi bands.

Because the genes for the μ and γ constant regions were all present in the hybrids 1D8 and 3F2, which contained the 14q+, and were not present in the hybrids containing only the 8q− (1E8 Cl 2 and 2B 8 Cl 22) (Figs. 3 and 4 and Table 1), we also conclude that these heavy chain genes are proximal to the breakpoint observed in Daudi cells, and that the variable region genes are distal to the constant region genes on human chromosome 14 (Fig. 5).

We also cleaved the cellular DNA with *Bam*HI and, after agarose gel electrophoresis and Southern transfer, we hybridized the nitrocellulose filters with the μ-specific cDNA. As shown in Fig. 6, Daudi cells appear to have the μ genes on both no. 14 chromosomes rearranged. The results from the hybrids, in conjunction with the data in Table 1, indicate that the 14q+ chromosome in these cells contains the larger *Bam*HI μ chain-specific fragment (18.0 kb), whereas the normal chromosome 14 carries the smaller fragment (12.5 kb). Germ-line DNA gives a single band at 16.0 kb. Thus, it appears that in Daudi cells both μ chain genes have undergone rearrangement, but that only the rearranged gene on the normal chromosome 14 is expressed.

We also cleaved the DNA derived from parental Daudi cells and from hybrids containing either the normal chromosome 14 or the 14q+ chromosome with *Eco*RI, and, after agarose gel electrophoresis and Southern transfer, we hybridized the filter with a J_H-specific probe. This J_H region probe hybridizes to a single 13.8-kb DNA fragment from germ-line cellular DNA. With parental Daudi DNA, it hybridized to a 12.2-kb and an 8.9-kb fragment (Fig. 7). DNA from a hybrid clone that expressed μ chains had both bands, whereas DNA from hybrid

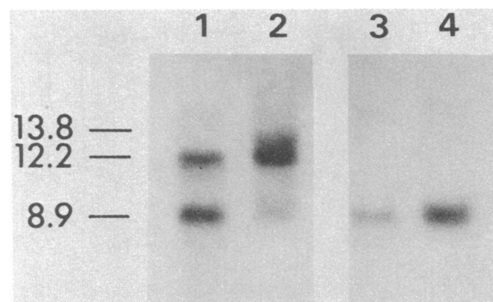

FIG. 7. Hybridization of *Eco*RI-digested cellular DNA with J region probe. In lane 1 is Daudi DNA. In lane 2 is DNA from 3E5, which expresses μ chains. In lanes 3 and 4 are DNAs from two hybrid clones that are nucleoside phosphorylase positive and do not express μ chains. DNA from a cell whose immunoglobulin genes are not rearranged gives a 13.8-kb band (data not shown).

clones with only the 14q+ chromosome had only the 8.9-kb band. Thus, the results of this experiment provided additional evidence for immunoglobulin gene rearrangements on both number 14 chromosomes.

DISCUSSION

Somatic cell hybridization of mouse myeloma cells with Burkitt lymphoma cells has yielded hybrids in which the chromosomes involved in the 8;14 translocation have segregated and enabled us to study the organization of the human immunoglobulin genes in these chromosomes. Lenoir and his associates have previously described a specific correlation between expression of κ or λ light chains in Burkitt tumor lines and translocations involving chromosome 8 and chromosome 2 (which carries the κ chain genes) or 22 (which carries the λ chain genes) (15). Our observation in hybrids from the Daudi line, that the expressed μ chain was carried on the normal chromosome 14, indicates that the expression of μ chains in the Burkitt tumor is not necessarily related to the chromosome translocation.

We have also demonstrated that the 14q+ chromosome in the Daudi cell line carries the genes for μ and γ heavy chain constant regions, indicating that these genes are proximal to the breakpoint in chromosome 14 (q32). The analysis of the hybrids containing the 8q− chromosome and no chromosome 14 or 14q+ confirms this finding, because no μ- and γ-specific DNA sequences were detectable in these hybrids. We did detect, however, the presence of V_{HIII} sequences in these clones, suggesting that the small segment of chromosome 14 that is translocated to the 8q− carries V_H genes. Because we also detected the presence of V_H sequences in a hybrid (1D8) that contained the 14q+ and neither the 8q− nor the normal 14, it seems likely that the break occurred within the chromosomal segment carrying V_H region genes. It will be of interest to determine whether a similar phenomenon occurs in other cases of Burkitt lymphoma, including those with the rare (2;8) and (8;22) translocations.

The fact that the small segment of chromosome 14 translocated to the 8q− chromosome in the Daudi line appears to carry V_H genes raises the possibility that the expression of malignancy in these cells results from activation of a gene located on the long arm of chromosome 8, by recombination with either a V_H region or a V_H promoter. We cannot exclude, however, an alternative suggestion that a gene located on the translocated segment of chromosome 8 becomes activated by association with a DNA sequence proximal to the breakpoint on chromosome 14 (14, 15).

If the hypothesis that malignancy in Burkitt lymphoma can result from recombination of a V_H gene or promoter with a sequence proximal to the breakpoint on chromosome 8 leading to the formation of an active oncogene is correct, it seems likely that similar immunoglobulin variable region gene translocations will be demonstrable in other lymphomas and leukemias. The availability of hybrids containing either the 8q− chromosome or the 14q+ chromosome should also make it possible to clone the DNA sequences immediately proximal and distal to the breakpoint on chromosome 8. The availability of these cloned DNA sequences will permit further exploration of specific molecular events involved in the relevant neoplasms.

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