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Genetics

# Transcriptional activation of the translocated c-*myc* oncogene in Burkitt lymphoma

(chromosome translocations/oncogene activation/human B cell neoplasia)

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ABSTRACT **We have previously demonstrated that translocations of $V_H$ genes from chromosome 14 to chromosome 8 and of the c-*myc* oncogene from chromosome 8 to chromosome 14 occur in Burkitt lymphomas with the t(8;14) chromosome translocation. An association of the c-*myc* gene with the $C_\mu$ immunoglobulin gene has been observed in some but not all Burkitt lymphomas studied previously. In the present study, we have investigated the organization of the human heavy chain locus and of the c-*myc* gene in the P3HR-1 Burkitt lymphoma cell line. Because mouse/P3HR-1 somatic cell hybrids that retain only the 14q+ chromosome and no other human chromosome contain the human $C_\mu$ and $C_\gamma$ genes but not $V_H$ genes, we have concluded that the breakpoint on chromosome 14 in P3HR-1 cells is distal to $C_\mu$ and between $C_\mu$ and $V_H$. Thus, the breakpoint of human chromosome 14 differs in different Burkitt lymphoma cell lines. We also found that the human c-*myc* oncogene translocated to chromosome 14 in the P3HR-1 cell line is not recombined with the $C_\mu$ gene. The breakpoint on human chromosome 8 may therefore also differ in different Burkitt lymphoma cell lines, because we have observed DNA rearrangement of the c-*myc* gene with the $C_\mu$ gene in only some of the Burkitt lymphoma cell lines studied elsewhere. Interestingly, high levels of transcripts of the c-*myc* oncogene were observed in Burkitt lymphomas with translocated c-*myc* oncogenes both rearranged and unrearranged. Therefore, the translocation of a c-*myc* oncogene to the heavy chain locus on human chromosome 14 is apparently sufficient for its transcriptional activation and may be an essential step in the pathway leading to neoplasia.**

Burkitt lymphoma cells carry specific chromosome translocations between chromosome 8 and chromosome 14 (1, 2), chromosome 2, or chromosome 22 (3–5). By the somatic cell genetic approach, we and others have mapped the human Ig heavy (H) chain locus to chromosome 14 (6–8), the λ chain locus to chromosome 22 (9, 10), and the κ chain locus to chromosome 2 (10, 11). In most Burkitt lymphomas, the region q24→qter of chromosome 8 is apparently translocated to one of the chromosomes containing human Ig chain genes. By using somatic cell hybrids between mouse myeloma cells and Burkitt lymphoma cells of the Daudi cell line, we have previously demonstrated that the breakpoint on human chromosome 14 in Daudi cells is distal to the H chain constant region genes $C_\mu$ and $C_\gamma$ and that the variable region $V_H$ genes are distal to the $C_H$ gene on chromosome 14 (12). We also demonstrated translocation of $V_H$ genes to the involved chromosome 8 (8q−) in Daudi cells (12).

Using the same approach, we also demonstrated that the human homologue of the myelocytomatosis virus (MC29) oncogene, named c-*myc*, is located on human chromosome 8 and is translocated to chromosome 14 in Burkitt lymphoma cell lines with the t(8;14) chromosome translocation (13). We observed head-to-head rearrangements of the c-*myc onc* gene with the $C_\mu$ gene in some, but not all, of the Burkitt cell lines studied (13–15). Taub *et al.* (16) have also observed translocation of c-*myc* into immunoglobulin genes in some, but not all, Burkitt lines studied.

In addition, we have investigated the rearrangements of the mouse c-*myc* homologue in murine plasmacytomas with a t(12;15) chromosome translocation and demonstrated rearrangements of the c-*myc onc* gene with $C_H$ Ig sequences in some, but not all, plasmacytomas analyzed (14). Interestingly, we observed high levels of transcription of the mouse c-*myc onc* gene, which is normally located on mouse chromosome 15 (17), in murine plasmacytomas carrying the t(12;15) chromosome translocation. The heavy chain locus of the mouse has been mapped to mouse chromosome 12 (18). Thus, the consistent chromosome translocation observed in mouse plasmacytomas (19), as in the Burkitt tumor, involves chromosomes containing Ig genes and the c-*myc onc* gene (14, 17).

In the present study we have investigated the location of the breakpoint on chromosomes 14 and 8 in the Burkitt lymphoma cell line P3HR-1 and also the level of transcription of the c-*myc* gene in these cells and in other Burkitt lymphoma cell lines, using Epstein–Barr virus-transformed human lymphoblastoid cell lines as controls. The results indicate that translocation of the c-*myc onc* gene to an Ig locus leads to its transcriptional activation, perhaps an essential step in the pathway leading to neoplasia.

## MATERIALS AND METHODS

**Cells.** P3HR-1, Daudi, Ag876, and CA46 Burkitt lymphoma cells carry the t(8;14) chromosome translocation (12, 20). The JI and LY91 Burkitt lymphoma cell lines have the t(2;8) chromosomal translocation (21). The LY67 and BL2 lines carry the t(8;22) chromosome translocation (21). P3HR-1 Burkitt lymphoma cells were hybridized with either NP3 nonproducer mouse myeloma cells deficient in hypoxanthine phosphoribosyltransferase (12) or with Cl 1D mouse fibroblasts deficient in thymidine kinase (22) according to established procedures (12). The hybrids were selected in hypoxanthine/aminopterin/thymidine (HAT) medium (23) containing 0.1 mM ouabain (24). Clones M44C12S5 and M44C122 are hybrids between Cl-1D and P3HR-1 cells. Clones JE8D5aF8 and JE4D6 are hybrids between NP3 and P3HR-1 cells.

The GM607, GM2247, GM2669, and GM2294 lymphoblastoid cell lines used in this study were obtained from the Human Cell Repository (Institute for Medical Research, Camden, NJ). PAF cells are simian virus 40-transformed human fibroblasts.

**Chromosome Analysis.** Parental and hybrid cell chromosomes were studied by the trypsin/Giemsa banding method as

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Abbreviation: kb, kilobase(s).

described (12, 25). At least 20 metaphases were examined from each hybrid, and they were scored only if there was adequate banding of human chromosomes. Selected metaphases were destained and restained by the G-11 technique to confirm the human origin of relevant chromosomes (12, 26).

**Isozyme Analysis.** Hybrid and parental cells were studied for the expression of human glutathione reductase coded for by a gene located on the short arm of chromosome 8 (27), and for nucleoside phosphorylase coded for by a gene on the proximal half of the long arm of human chromosome 14 (27).

**Expression of Immunoglobulin Chains.** Parental and hybrid cells were grown in leucine-deficient medium or methionine-deficient medium containing 5% dialyzed fetal calf serum and [$^3$H]leucine (70 Ci/mmol) at 100 $\mu$Ci/ml or [$^{35}$S]methionine (400 Ci/mmol) at 100 $\mu$Ci/ml for 5–8 hr (1 Ci = $3.7 \times 10^{10}$ Bq). The expression of human Ig chains was determined by immunoprecipitation of culture fluids or cytoplasmic extracts of the hybrid and parental cells using rabbit anti-human $\mu$, $\kappa$, $\lambda$, $\gamma$, and $\alpha$ chain-specific antibodies followed by the addition of 50 $\mu$l of a 10% suspension of fixed *Staphylococcus aureus* as described (11, 12, 26). Labeled Ig chains were then separated by $NaDodSO_4$/polyacrylamide gel electrophoresis (6, 12, 28).

**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 phage $\lambda$ DNA (0.75 $\mu$g per lane) (Bethesda Research Laboratories) molecular weight markers were included on every gel. Cellular DNA samples were digested with *Bam*HI, *Eco*RI, *Sst* I, or *Hin*dIII restriction endonuclease and then subjected to electrophoresis in a horizontal agarose (Sigma) slab gel (10 $\mu$g of DNA per lane). Gels were stained for 10 min with ethidium bromide (1 $\mu$g/ml) and photographed under UV light. Transfer of DNA from gel to nitrocellulose sheet (Millipore) was performed essentially as described by Southern (29).

**RNA Transfer.** Cytoplasmic RNA was extracted by the cesium chloride method as described (30). RNA was denatured in 1 M glyoxal in 10 mM $NaPO_4$, pH 6.5, at 50°C for 1 hr, electrophoresed in 1% agarose gel, transferred to nitrocellulose, prehybridized, and hybridized to 0.2 $\mu$g of the *myc* probe (about $4 \times 10^7$ cpm) according to the method of Thomas (31). Twenty micrograms of RNA was loaded in each lane. Prehybridizations and hybridizations were performed as reported (32). Twenty micrograms of cytoplasmic RNA was added to each lane. Molecular weight markers were electrophoresed in each gel.

**Preparation of Labeled Probe DNAs.** The $V_{HIII}$ probe (M1326-8) is an *Eco*RI 1.9-kilobase (kb) fragment of a $V_{HIII}$ gene that has been cloned in the phage M13 vector. This probe was a generous gift of T. Rabbitts (Medical Research Council Laboratory of Molecular Biology, Cambridge, U.K.) (7). Rabbitts and his co-workers have used this probe to demonstrate the synteny of the $V_H$ genes and the genes for heavy chains (7). The probes specific for the constant region of human $\mu$ chain were a 655-base-pair cDNA that contains enough sequences to code for amino acids glycine (residue 421) through the terminal tyrosine (residue 576) of the human $\mu$ chain as well as the entire 3′ noncoding sequence (33), and a 1.2-kb *Eco*RI genomic probe that includes the first, the second, and part of the third exon of the human $C_\mu$ gene (unpublished data). The human $\gamma$-specific probe was a kind gift of Joel Bauxbaum (New York University) (34). 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 $\gamma$ chain genes (34). We obtained the human $J_H$ (joining) region probe by subcloning a 3.3-kb fragment of the human $\mu$ genomic DNA clone (H18 Cl 10) (unpublished data). This fragment contains 2.2 kb of the human $J_H$ region DNA and 1.1 kb of flanking sequences at the 3′ end. The $\mu$ chain, $\gamma$ chain, and $J_H$-specific inserts were isolated from the pBR322 vectors and labeled by the nick-translation procedure (35). The $V_{HIII}$ probe was nick-translated in its M13 phage vector isolated in its replicative form (12). The human c-*myc* probe is a 1.2-kb cDNA clone in the plasmid pBR322 that contains the entire 3′ exon and 60% of the 5′ exon of the c-*myc* gene (Ryc 7.4) (14). DNA polymerase I was purchased from Boehringer Mannheim; [$\alpha$-$^{32}$P]NTPs were from Amersham. $V_H$, $\mu$, $\gamma$, and $J_H$ region probes labeled with $^{32}$P and with specific activities of 0.3–5 $\times 10^8$ cpm/1 $\mu$g of DNA were used in the experiments described in this paper.

**Hybridization.** DNA on nitrocellulose sheets was hybridized to $^{32}$P-labeled probe DNA in a hybridization solution containing 50% (vol/vol) formamide. After hybridization, the filters were washed, air dried, and exposed to Kodak XAR-5 film for various periods. Prior to rehybridization, filters were washed two times at 65°C in water for 15 min.

## RESULTS

**Chromosome Localization of the Ig DNA Sequences.** Table 1 summarizes the results of chromosome analysis of the hybrid clones from the P3HR-1 Burkitt lymphoma that we have used in this study. As shown in Table 1, and previously reported (2), a hybrid clone derived from the Cl 1D mouse fibroblast line, M44 Cl 2S5, has the human 14q+ chromosome from P3HR-1 and no other intact human chromosome (Fig. 1*B*). Southern blotting analysis of DNA from this clone, using the human-specific probes, allowed determination of whether the human Ig genes were present or absent. This hybrid had retained the human $C_\mu$ gene (Table 1) and $C_\gamma$ genes (Fig. 2*B*), but had lost all the human $V_{HIII}$ genes (Fig. 2*A*), indicating that the breakpoint in chromosome 14 in P3HR-1 is between the $C_\mu$ and the

Table 1. Immunoglobulin genes in P3HR-1 hybrids

| | Human chromosomes* | | | | Human isozymes† | | 63-kilodalton heavy chain | Human Ig genes | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Cell line | 8 | 8q− | 14 | 14q+ | GSR | NP | | $V_H$ | $C_\mu$ | $C_\gamma$ |
| P3HR-1 | ++ | ++ | ++ | ++ | + | + | + | + | + | + |
| NP3 | − | − | − | − | − | − | − | − | − | − |
| Cl 1D | − | − | − | − | − | − | − | − | − | − |
| M44 Cl 2S5 | − | − | − | ++ | − | + | (−)‡ | − | + | + |
| JE8D5 aF8 | + | ++ | − | + | + | + | − | + | + | + |
| JE4D6 | + | − | ++ | ++ | + | + | + | + | + | + |

* Frequency of metaphases with relevant chromosome: −, none; +, 10–30%; ++, >30%.

† GSR, glutathione reductase (marker for human chromosome 8); NP, nucleoside phosphorylase (marker for human chromosome 14).

‡ Hybridized with mouse fibroblasts (Cl 1D).

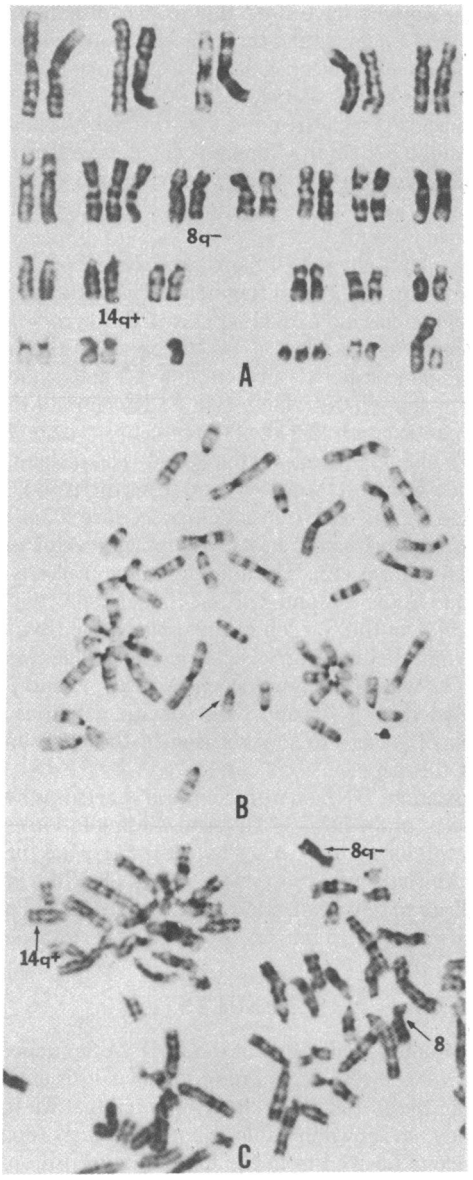


FIG. 1. (*A*) Karyotype of parental P3HR-1 cell line with t(8;14)(q24;q32), trisomy 7 and 21, and an unidentified marker. (*B*) Trypsin/Giemsa-banded metaphase from hybrid M44Cl2S5 containing 14q+ as the only human chromosome (arrow). (*C*) Portion of a trypsin/Giemsa-banded metaphase from hybrid JE8D5aF8 that retained human 14q+ and 8q− chromosomes and a normal 8, but no normal 14.

$V_H$ genes. Because a rearranged $J_H$ segment is present in hybrid M44Cl2S5 (data not shown), it seems likely that the rearrangement of the $\mu$ gene occurred within this segment.

Analysis of an NP3-derived clone (JE8D5aF8) that had lost the normal 14 but retained the 8q− and the 14q+ chromosomes (Fig. 1*C*) demonstrated retention of $V_H$ genes (Table 1). The results from this clone are consistent with the conclusion that the $V_H$ genes missing from the 14q+ chromosome in this Burkitt tumor line have been translocated to the 8q− chromosome.

**Expression of Heavy Chains in P3HR-1 Cells and in NP3/P3HR-1 Hybrids.** Southern blotting analysis of DNA from P3HR-1 cells indicates that they contain only one rearranged $C_\mu$ gene, 18 kb in size (Fig. 3*A*, lane 5), and that it is located on the 14q+ chromosome (Table 1). The germ-line $C_\mu$ gene is 16 kb in size (Fig. 3*A*, lane 6). Blotting data from the parental line and relevant hybrids demonstrated that the $C_\mu$ gene on the normal chromosome 14 has been deleted (data not shown).

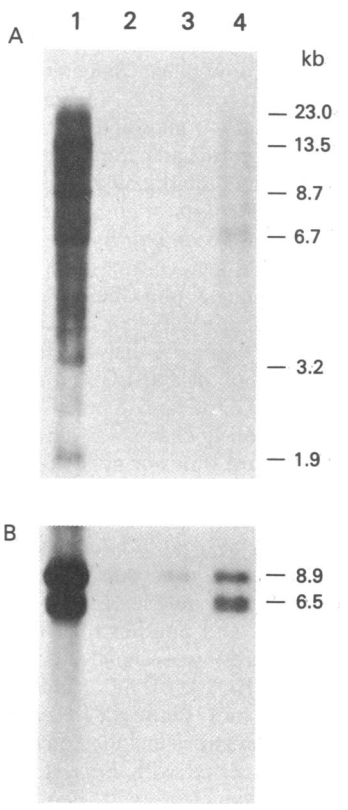


FIG. 2. Southern blotting analysis of *Hin*dIII-cut DNA derived from P3HR-1 (lane 1), hybrid M44Cl22 (lane 2), hybrid M44Cl2S5 (lane 3), and Namalwa, an additional Burkitt lymphoma cell line (lane 4). (*A*) The filter was hybridized with the $V_{HIII}$ probe. The same filter was rehybridized with the $\gamma$ cDNA probe. (*B*) The pattern difference in lanes 1 and 4 reflects differences in $V_H$ contents in different B cell lines.

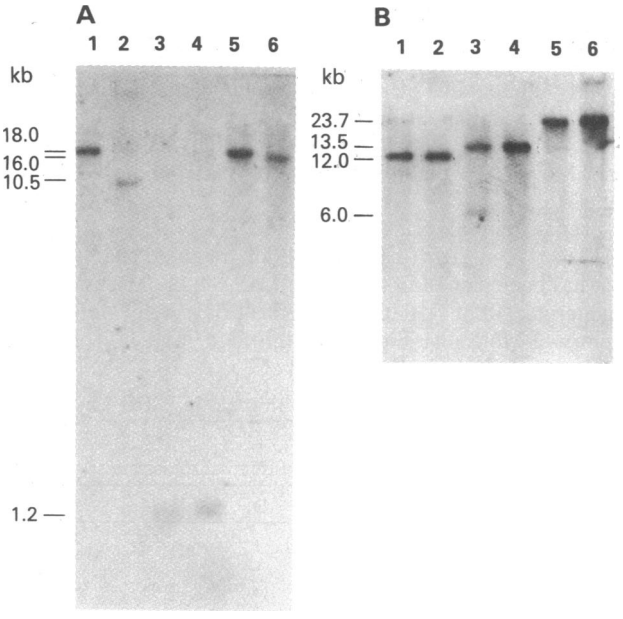


FIG. 3. Southern blotting analysis of P3HR-1 cell DNA. (*A*) The nitrocellulose filter was hybridized with the $\mu$ 1.2-kb genomic probe. (*B*) A separate filter was hybridized with a human *myc* cDNA probe (Ryc 7.4) (14). Lanes 1 and 2, P3HR-1 and PAF DNA, respectively, cleaved with *Hin*dIII; lanes 3 and 4, P3HR-1 and PAF DNA, respectively, cleaved with *Eco*RI; lanes 5 and 6, P3HR-1 and PAF DNA, respectively, cleaved with *Bam*HI.

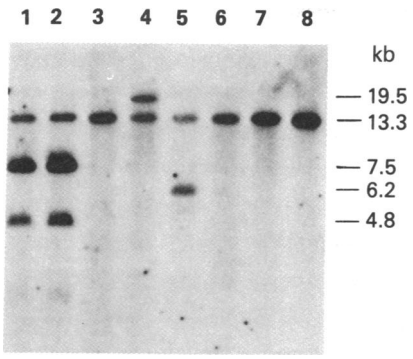


FIG. 4. Southern blotting of *Eco*RI-cut Burkitt lymphoma DNA. Lane 1, LY 91 DNA; lane 2, JI DNA; lanes 3–6, Ag876, CA46, P3HR-1, and Daudi DNA, respectively; lane 7, GM607 DNA; and lane 8, PAF human DNA. The DNA on the nitrocellulose filter was hybridized with the human *myc* cDNA probe (Ryc 7.4) (14).

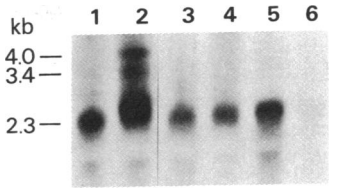


FIG. 5. Blotting analyses of Burkitt lymphoma cell RNA hybridized to the *myc* probe (Ryc 7.4). Lane 1, Daudi; lane 2, P3HR-1; lane 3, JI; lane 4, LY 67; lane 5, BL2; and lane 6, GM2669. The results obtained with the RNA of the other two lymphoblastoid cell lines (GM2247 and GM2294) were identical to the result obtained with the GM2669 RNA (data not shown).

Analysis of the parental and NP3-derived hybrid cells for the expression of heavy chains indicates that P3HR-1 cells and a hybrid (JE4D6) with the normal chromosome 14 express a 63-kd heavy chain (Table 1) different from $\mu$ (data not shown) but the hybrids with the 14q+ and no normal 14 do not express Ig (Table 1). Thus we can conclude that in P3HR-1 cells, as in Daudi Burkitt lymphoma cells, the expressed heavy chain is coded for by the normal chromosome 14.

**Organization of the Human c-*myc* Oncogene in P3HR-1 Cells.** We have previously shown that the c-*myc* oncogene, normally located on chromosome 8 (13), translocates to chromosome 14 in Burkitt lymphomas (13). We have also shown that the c-*myc* oncogene rearranges with the $C_\mu$ gene in the Burkitt lymphoma cell lines CA46 and JD38-IV (13, 14). Therefore, we have investigated whether the human c-*myc* oncogene is also rearranged in P3HR-1 cells. As shown in Figs. 3*B* and 4, we observed rearrangements of the c-*myc* gene in this cell line. While we do not detect rearrangement after digestion with *Bam*HI (Fig. 3*B*, lane 5), cleavage with *Eco*RI, which also cuts the DNA outside the c-*myc* gene (14), results in two c-*myc* bands (13.5 and 6.2 kb) (Fig. 3*B*, lane 3, and Fig. 4, lane 5). The 13.5-kb band represents the normal c-*myc* allele, whereas the 6.2-kb band represents a rearranged allele (Fig. 3*B*, lane 3, and Fig. 4, lane 5). However, we do not detect rearrangement of the c-*myc* gene in P3HR-1 DNA after digestion with *Hind*III that also cuts outside the c-*myc* gene (Fig. 3*B*, lane 1) (36).

**Transcription of the c-*myc* Oncogene in P3HR-1 Cells.** Blotting analysis was done with cytoplasmic RNA derived from three human lymphoblastoid cell lines, used as controls, and from five Burkitt lymphoma cell lines, with the t(8;14), t(2;8), or t(8;22) chromosome translocation. The results show high levels of c-*myc* RNA transcripts that are 2.3 kb in size in Burkitt lymphoma cells (estimated at 5- to 10-fold higher than in Epstein–Barr virus-transformed B lymphocytes) (Fig. 5), with either a rearranged (P3HR-1, JI, LY67, and BL2) or an unrearranged (Daudi) c-*myc* gene (Fig. 4). Epstein–Barr virus-transformed human B cell lines seem to be the proper control for this experiment because they belong to the same cell lineage, are nontumorigenic, and do not carry the specific chromosome translocations. The size of the *myc* RNA transcripts in Burkitt lymphoma is approximately the same as that of the *myc* RNA transcripts observed in mouse spleen, liver, and some plasmacytomas (14). A more heterogeneous profile of transcripts is observed in the P3HR-1 cells than in the other Burkitt lymphoma cell lines (Fig. 4). On the contrary, we observed shorter mouse c-*myc* transcripts in BALB/c mouse plasmacytomas with t(12;15) chromosome translocation (14).

## DISCUSSION

We have examined the organization of the human Ig heavy chain genes and of the c-*myc* oncogene in the Burkitt lymphoma

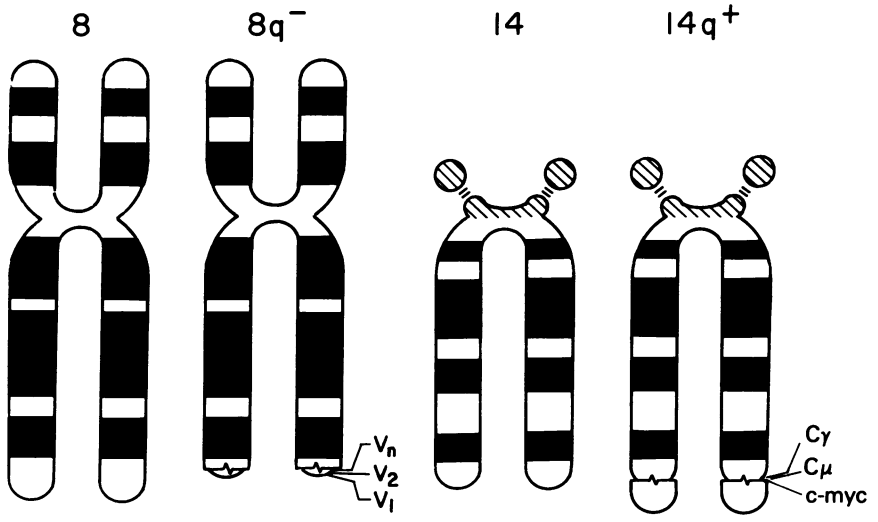


FIG. 6. Diagrams of the t(8;14) chromosome translocation in P3HR-1 cells. The $C_\mu$ and $C_\gamma$ genes are proximal to the breakpoint on chromosome 14, while the $V_H$ gene translocates to the 8q− chromosome. The human c-*myc* gene on the broken chromosome 8 translocates to the heavy chain locus. Whereas in the Burkitt lymphoma cell lines, CA46 and JD38-IV, the c-*myc* gene is in the same 22-kb *Bam*HI fragment with the $C_\mu$ gene (13, 14), the c-*myc* gene is not joined to the $C_\mu$ gene in P3HR-1 cells.

P3HR-1 cell line that carries the t(8;14) chromosome translocation. We find that in this cell line the breakpoint on human chromosome 14 is between $C_\mu$ and $V_H$. Concomitant with the translocation of the c-*myc* oncogene to chromosome 14, we observe a translocation of the $V_H$ genes to chromosome 8. The diagrams in Fig. 6 indicate in detail these translocations in P3HR-1 cells.

Previously we have studied the organization of the human heavy chain genes in the Burkitt lymphoma cell line Daudi (12). In this cell line we found that the $C_\mu$ and $C_\gamma$ genes are located on the 14q+ chromosome and that some $V_{HIII}$ genes have translocated to the 8q− chromosome but some have remained on the 14q+ chromosome (12). In both the P3HR-1 and Daudi cell lines, the c-*myc* oncogene has translocated to chromosome 14 (13) but is not closely associated with the $C_\mu$ gene (this study and ref. 15). On the contrary, lines CA46 and JD38 IV, which also carry a t(8;14) chromosome translocation, contain a c-*myc* gene rearranged with a $C_\mu$ gene (14). In these two cell lines, the c-*myc* and $C_\mu$ genes are located in the same 22-kb *Bam*HI restriction fragment (33). Thus, breakpoint heterogeneity on both chromosomes 8 and 14 occurs in Burkitt lymphoma.

Interestingly, we observe high levels of c-*myc* transcripts in Burkitt lymphoma lines with different genetic rearrangements and with different chromosome translocations. Therefore, we conclude that the translocation of either a rearranged or unarranged c-*myc* oncogene can result in a considerable increase in its transcriptional activity and a postulated role in B cell neoplasia.

Preliminary attempts to transfect mouse 3T3 cells with the recombinant c-*myc* sequences from murine plasmacytomas suggest that the rearranged translocated oncogene in this system is not able to transform these cells (14). It will be of considerable interest to determine whether transfection of normal human B cells and of Epstein–Barr virus-transformed human B cell lines with human (and murine) c-*myc* sequences results in malignant transformation. This experiment may also indicate whether active B cell proliferation and translocation of the c-*myc* gene to an Ig locus are necessary steps in converting normal B lymphocytes to lymphoma cells.

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