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c-*myc* and immunoglobulin κ light chain constant genes are on the 8q+ chromosome of three Burkitt lymphoma lines with t(2;8) translocations

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We have determined the localization of c-*myc* and the immunoglobulin κ light chain genes on the 8q+/2p− chromosomes of the three Burkitt lymphoma lines BL21, LY66 and LY91 with t(2;8) translocation by *in situ* hybridization. BL21 is characterized by a complex translocation in which a piece of chromosome 9 appears to be located between the fragments of chromosome 8 and 2 on the 8q+ chromosome. Our data indicate that in all three cell lines the c-*myc* gene is located on the 8q+ chromosome proximal to the breakpoint in band 8q24. In all cell lines examined the cluster of κ variable genes has remained on the 2p− chromosome. In LY91 cells the major part of the joining region remained on 2p−, while the joining region has moved to 8q+ in the cell lines BL21 and LY66. In all three cell lines the constant κ light chain gene was found on the 8q+ chromosome. The fact that an essentially identical pattern was found in the cell line BL21, with the complex translocation, suggests that the insertion of the piece of chromosome 9 into the 8q+ chromosome might be a secondary event. Our present data fit into the concept that in all Burkitt lymphoma lines investiged so far, including cases with t(8;14) and the variant translocations t(2;8) and t(8;22), the c-*myc* gene becomes situated at the 5′ side of an immunoglobulin constant gene. This may have implications for the generation of somatic mutations in the coding and non-coding part of the c-*myc* gene.

Key words: Burkitt lymphoma/chromosomal translocation/immunoglobulin genes/c-*myc*

Introduction

Chromosomal translocations always involving the long arm of chromosome 8 are a consistent feature of Burkitt's lymphoma. In ~75% of the cases, reciprocal translocations between the distal parts of the long arms of chromosome 8 and 14 are observed (Manolov and Manolova, 1972; Zech *et al.*, 1976; Manolova *et al.*, 1979), whereas in ~25% so-called variant translocations, either the short arm of chromosome 2 or the long arm of chromosome 22 is participating in the reciprocal exchange with the distal piece of the long arm of chromosome 8 (Bernheim *et al.*, 1981). The assignment of the c-*myc* oncogene onto chromosome 8q24 (Taub *et al.*, 1982; Neel *et al.*, 1982; Dalla Favera *et al.*, 1982) and of the immunoglobulin genes onto chromosome 14q32 (heavy chain locus) (Croce *et al.*, 1979; Hobart *et al.*, 1981; Kirsch *et al.*, 1982), chromosome 2p12 (κ light chain locus) (Malcolm *et al.*, 1982; McBride *et al.*, 1982) and onto chromosome 22q11 (λ light chain locus) (Erikson *et al.*, 1981; McBride *et al.*, 1982) opened up the possibility of studying the events induced by the specific chromosomal translocations on a molecular level.

The c-*myc* oncogene consists of one non-coding and two coding exons separated by two introns (Hamelyn and Rabbitts, 1983; Watt *et al.*, 1983; Saito *et al.* 1983; Battey *et al.*, 1983; Bernard *et al.*, 1983). In the majority of cases with t(8;14) translocation the breakpoint is located in the direct vicinity of the c-*myc* gene 5′ to the coding region (Taub *et al.*, 1982; Dalla-Favera *et al.*, 1983; Adams *et al.*, 1983). In different cases the position of the breakpoint varies, lying either in the first intron, the first exon or 5′ to the first exon (Bernard *et al.*, 1983; ar-Rushdi *et al.*, 1983; Taub *et al.*, 1984a). In most cases with variant translocations the breakpoints are more distantly located from the c-*myc* gene. Only in one case with a t(8;22) translocation (BL37) was the c-*myc* gene found to be fused at its very 3′ end to one of the constant genes of the λ light chain locus (Hollis *et al.*, 1984). In other cases studied the breakpoint is not within the 29-kb *Bam*HI fragment carrying the c-*myc* gene (Taub *et al.*, 1982; Adams *et al.*, 1983; Erikson *et al.*, 1983; Croce *et al.*, 1983). In four more cases with variant translocations [three with t(2;8) and one with t(8;22)] the position of the breakpoints has been determined relative to the c-*myc* gene by *in situ* hybridization (Davis *et al.*, 1984; Taub *et al.*, 1984b) and the use of somatic cell hybrids (Croce *et al.*, 1983; Erikson *et al.*, 1983). In all these cases the breakpoints were found to be located at the 3′ side of the c-*myc* gene leaving c-*myc* on the derivative chromosome 8. Whether this is a consistent feature of all variant translocations is not yet clear.

With respect to the light chain locus, the position of the breakpoint was studied in two cases with t(2;8) and in two cases with t(8;22) translocation. The break was reported to lie within the cluster of variable genes (V_k) in one cell line (Erikson *et al.*, 1983; Emanuel *et al.*, 1984) and 5′ to the κ joining region in the other (Taub *et al.*, 1984b). In the two cases with t(8;22) translocation part of the λ constant genes was found on the 8q+ chromosome (de la Chapelle *et al.*, 1983).

We have attempted to shed more light on the localization of the breakpoints relative to c-*myc* and to the κ light chain genes using three different cell lines (BL21, LY66, LY91) with t(2;8) translocations. It was particularly interesting to study a cell line with a complex translocation (BL21) in which, as defined by the banding pattern, a piece of chromosome 9 is located between the long arm of chromosome 8 and the translocated short arm of chromosome 2 on the 8q+ marker chromosome (Philip *et al.*, 1981). Thus, only on the 2p− chromosome was material from chromosomes 2 and 8 assumed to be directly attached to each other.

A similar case of a complex t(8;14) translocation has also been reported by Rowley (1982). Assuming that the juxta-

position of sequences from chromosome 8 and the Ig locus is of great importance in the development of Burkitt's lymphoma, such complex translocations suggest that the critical event has occurred on both derivative chromosomes where chromosome 8 and the Ig locus became directly fused to each other (Philip *et al.*, 1981; Rowley, 1982; Klein, 1983).

Results

The c-myc gene is located on the 8q$^+$ chromosomes

Hybridization of a ^{32}P-labeled c-*myc* probe to nitrocellulose filters containing separated *Eco*RI and *Bam*HI fragments visualized only the germline bands of 12.5-kb (*Eco*RI) and 29-kb (*Bam*HI) in DNA of the cell lines LY66, LY91 and BL21 (Figure 1). This indicates that the breakpoint of the chromosomal translocation is not within these fragments in these cell lines. To decide whether the c-*myc* gene is located on the 8q$^+$ or the 2p$^-$ chromosome, we hybridized a ^{3}H-labeled c-*myc* probe to denatured metaphase chromosomes. In addition to LY66, LY91 and BL21, the *in situ* hybridization with the c-*myc* probe was extended to chromosomes of a fourth cell line with a t(2;8) translocation, the Burkitt lymphoma line J1, in which the c-*myc* gene is also unrearranged (Erikson *et al.*, 1983). The 8q$^+$ and 2p$^-$ marker chromosomes and chromosomes 2 of the four cell lines used in this study are shown in Figure 2. The results of the hybridization of the c-*myc* probe to metaphase chromosomes of BL21, LY66, LY91 and J1 are shown in Figure 3. In all four lines the c-*myc* gene has remained on the 8q$^+$ chromosome.

Table I gives a survey of different *in situ* hybridization experiments with the c-*myc* probe. In all experiments the number of silver grains on the specific segment of 8q$^+$ exceeded the number of grains expected at random at the 99% confidence level, which indicated a statistically highly significant binding site.

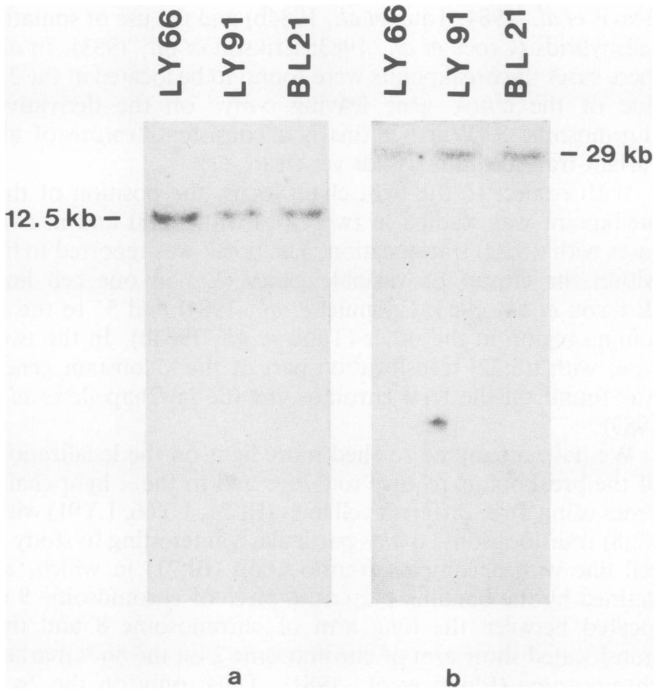

Fig. 1. Hybridization of a ^{32}P-labeled c-*myc* probe to separated *Eco*RI (**a**) and *Bam*HI fragments (**b**) of the Burkitt lymphoma cell lines BL21, LY66 and LY91 with t(2;8) translocations. Fragments were separated in 0.6% agarose before being transferred to nitrocellulose.

Localisation of the variable κ light chain genes

Using a cloned V_k subgroup 1 probe (HK101/80), we have localized the cluster of variable genes in the cell lines BL21, LY66 and LY91 relative to the breakpoints of the chromosomal translocations. In all three cases the highest number of grains was found on the 2p$^-$ chromosome (see Table I). An example is given in Figure 4 for BL21, showing the highest binding efficiency to the 2p$^-$ chromosome, where 34.8% of all grains are situated at the centromeric region of chromosome 2.

Localisation of the κ light chain joining and constant regions

The localisation of the V_k genes on the 2p$^-$ chromosome of

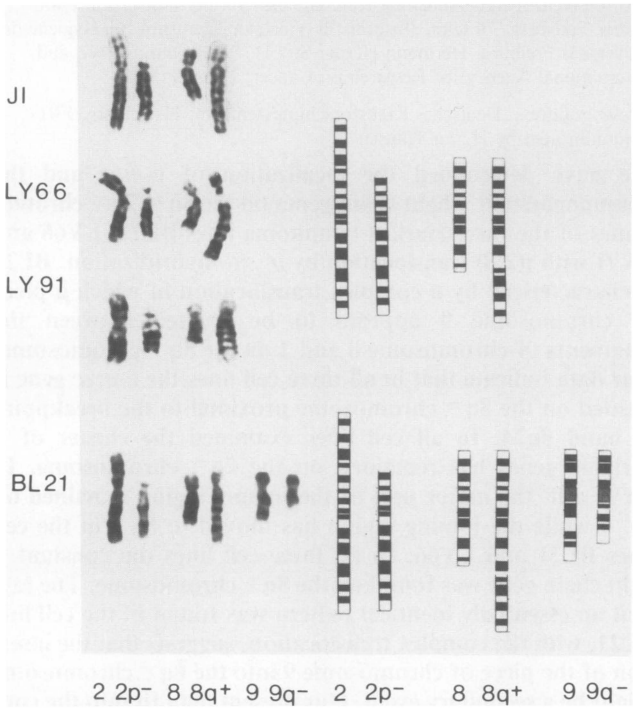

Fig. 2. GTG-banding of the translocation chromosomes 2p$^-$, 8q$^+$ 9q$^-$ and their normal homologues. A schematic drawing is given to the right.

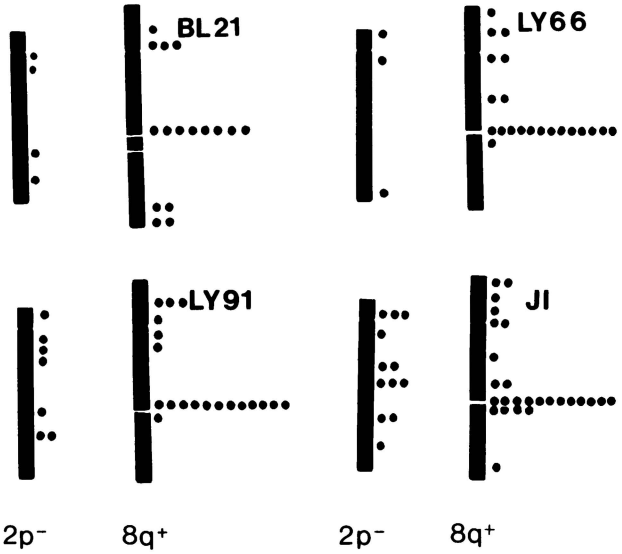

Fig. 3. *In situ* hybridization of the c-*myc* probe to metaphase chromosomes of BL21, LY66, LY91 and J1. Only the two translocation chromosomes 2p$^-$ and 8q$^+$ were evaluated.

the three cell lines suggested that the breakpoints are located downstream of the variable gene cluster. Therefore we have hybridized ^{3}H-labeled cloned probes specific for the joining and the constant region, respectively, to metaphase spreads of BL21, LY66 and LY91. The localisation of J_k and C_k in the three cell lines is shown in Figures 5 and 6. In LY91 cells the J_k probe hybridized mainly to the $2p^-$ chromosome (Figure 5) and the C_k probe to the $8q^+$ chromosome (Figure 6) indicating that the break has occurred between the joining and the constant coding regions. By Southern blot hybridization, with probes spanning over the whole region, it could be shown that the breakpoint is located within the 1.8-kb *Sac*I fragment carrying the joining region (B. Henglein and G.W. Bornkamm, unpublished observation).

In BL21 and LY66 cells, both probes J_k and C_k, were assigned only to the $8q^+$ and not to the $2p^-$ chromosomes. In BL21 cells a bimodal distribution of grains was observed on the $8q^+$ chromosome after hybridization with the J_k probe. Their binding sites are likely to be situated proximal and distal to the inserted piece of chromosome 9, within the long arm of $8q^+$, although the assignment of silver grains to specific chromosomal bands is tentative in the absence of chromosome banding. With regard to the bimodal distribution of J_k, the grains observed after hybridization with C_k and c-*myc* appeared to be at the more proximal of both sites on the $8q^+$ chromosome.

Table I.

Probe	Cell line	No. of metaphase spreads	Total no. of grains	No. of grains on specific segment of chromosome[a] 2, $2p^-$, $8q^+$	% of specific grains
c-*myc*	BL21	20	166	1, 8	4.8
C_k	BL21	118	330	13, 2, 17	9.1
J_k	BL21	87	475	36, 3, 40	16.0
V_k	BL21	35	258	35, 55, 1	34.8
c-*myc*	LY91	18	66	1, 1	18.2
C_k	LY91	72	333	16, 7, 21	11.1
J_k	LY91	81	339	11, 12, 3	7.7
V_k	LY91	22	106	4, 8, 1	11.3
c-*myc*	LY66	46	157	1, 14	8.9
C_k	LY66	69	200	8, 1, 19	13.5
J_k	LY66	76	355	11, 1, 11	6.2
V_k	LY66	23	149	8, 5, 0	8.7
c-*myc*	J1	23	217	3, 14	6.4

[a]All grains on chromosome $2p^-$ which were located at the short arm including the centromeric region were considered to be specific. In the case of the normal chromosome 2 a region of the same size was evaluated for specific grains. Similarly, grains located on the $8q^+$ chromosome in a segment of the same size at the breakpoint were regarded as specific.

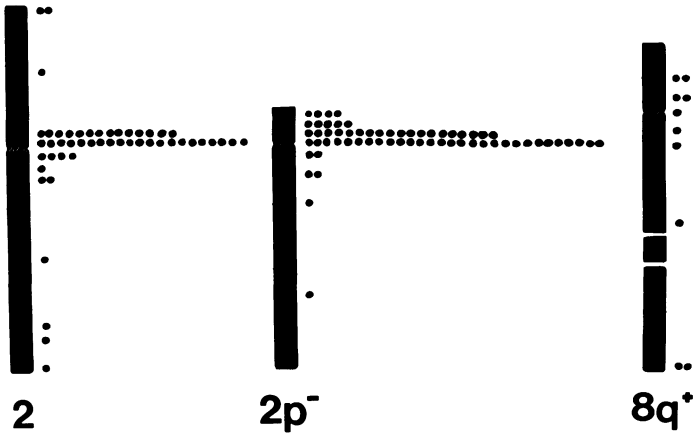

Fig. 4. *In situ* hybridization of the V_k probe to the chromosomes 2, $2p^-$ and $8q^+$ of the cell line BL21.

Discussion

We have mapped the c-*myc* gene and different parts of the κ light chain locus relative to the breakpoints of the chromosomal translocations in cell lines with t(2;8) translocations. In all cell lines examined the c-*myc* gene was found on the $8q^+$ chromosome proximal to the breakpoint. The distance from the c-*myc* gene to the breakpoint is not known in the cells which we have studied. From Southern blot analysis we know, however, that the breakpoints of the different cell lines are at least 8 kb downstream from the 3′ end of the c-*myc* gene which is the distance from the 3′ end to the nearest *Bam*HI site. In all three cell lines tested the cluster of κ variable genes had remained on the $2p^-$ chromosomes. In one line (LY91) the breakpoint could be assigned to the joining region. In the second cell line (LY66) J_k hybridized only to the $8q^+$ chromosome, indicating that the translocation has

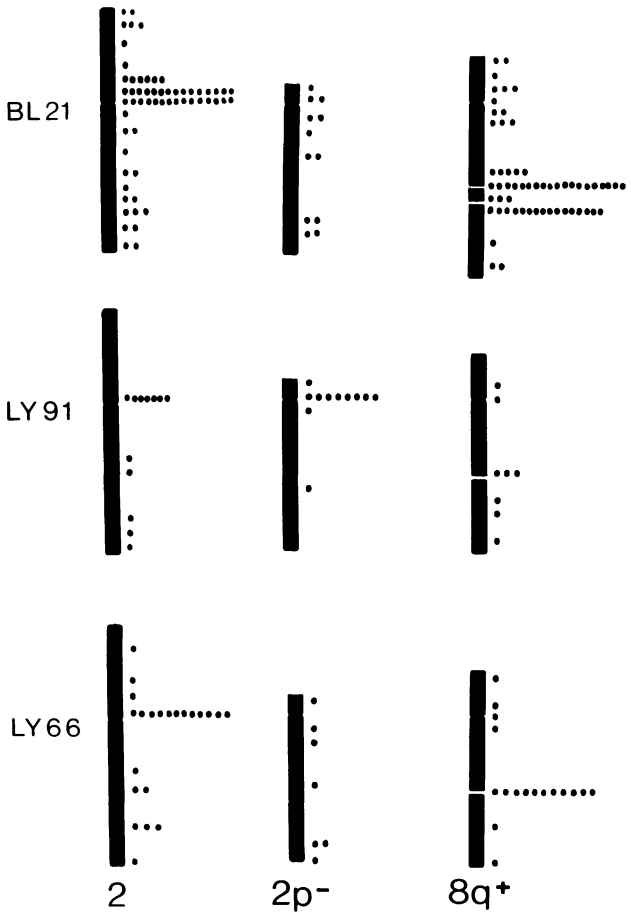

Fig. 5. *In situ* hybridization of the J_k probe to chromosomes 2, $2p^-$ and $8q^+$ of BL21, LY91 and LY66. Note the biphasic distribution of grains on the $8q^+$ chromosome of BL21.

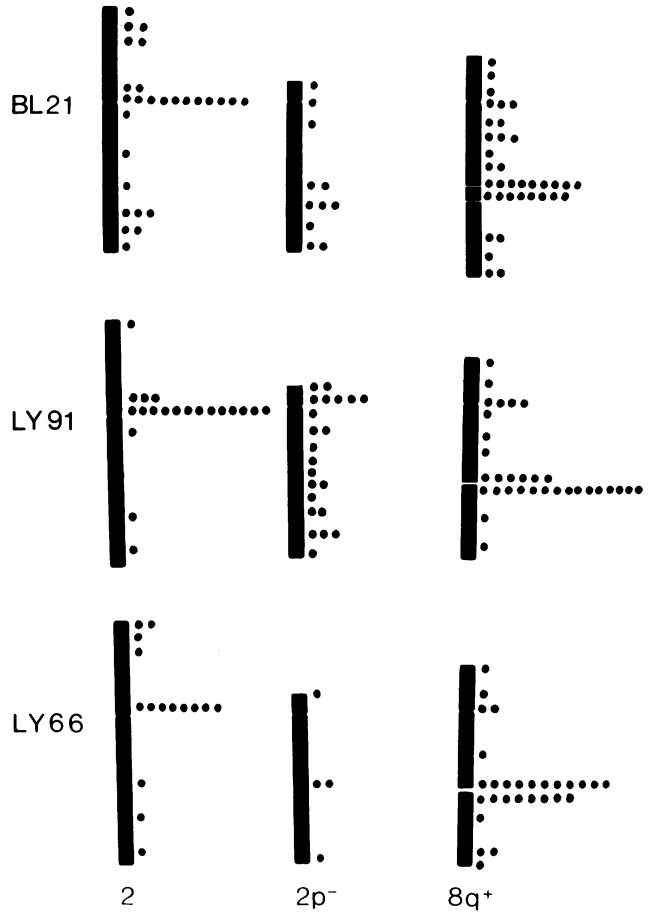

Fig. 6. *In situ* hybridization of the C_k probe to chromosomes 2, $2p^-$ and $8q^+$ of BL21, LY91 and LY66.

occurred between the variable genes and the joining region, or alternatively, which is not excluded from our experiments, in the distal part of the variable genes. Consistent with the hybridization of the J_k probe, C_k hybridized only to the $8q^+$ chromosome in both cell lines.

In the third cell line (BL21) with the complex translocation we found in principal the same pattern as in LY66 cells with c-*myc*, J_k and C_k on the $8q^+$ chromosome. The only difference between LY66 and BL21 was that a bimodal distribution of grains was observed in BL21 cells after hybridization with a J_k probe. These two sites might represent the regions proximal and distal to the band inserted from chromosome 9. c-*myc* and C_k were localized to the more proximal of both sites. The fact that c-*myc*, J_k and C_k were assigned to the same site on the $8q^+$ chromosome by *in situ* hybridization, disproved the assumption made previously and based on cytogenetic data only (Philip *et al.*, 1981) that the segment of chromosome 9 would link the fragments of chromosome 8 and 2 on the $8q^+$ chromosome of BL21 cells. It rather suggests that the insertion of a piece from chromosome 9 into the $8q^+$ chromosome represents a secondary event after the t(2;8) translocation has taken place. No simple model can account for the bimodal distribution of grains after hybridization with the J_k probe. Only by cloning of the respective fragments carrying J_k sequences will it be possible to elucidate the events which led to the complex translocation. Regardless, however, which sequence of events has led to the complex translocation, the important point is that in BL21 cells the situation is very similar to other cases with variant translocations.

Taking into account the reports from the literature and the results presented here, a considerable amount of information is now available about the localization of the chromosomal breakpoints with respect to c-*myc* and immunoglobulin genes in cell lines with t(8;14), t(2;8) and t(8;22) translocations. So far, no exception has been found from the rule that the breakpoints are located 5′ to the coding region of c-*myc* in cases with t(8;14) translocations and 3′ to c-*myc* in cases with variant translocations. Considering the different orientation of the heavy chain (telomeric towards centromeric) and light chain genes (centromeric towards telomeric), the only common denominator among all cases is that the c-*myc* gene is always located 5′ to a coding region of an immunoglobulin constant gene. Since somatic mutation is a well established phenomenon for generation of antibody diversity (for review, see Tonegawa, 1983) and since mutations have been observed in the coding (Rabbitts *et al.*, 1983, 1984) and non-coding region of the c-*myc* gene (Taub *et al.*, 1984a; Rabbitts *et al.*, 1984), this raises the question whether a mutational process is operating unidirectionally upstream of the immunoglobulin constant genes in Burkitt lymphoma cells. Such a process would apparently have to operate over a large distance, since the c-*myc* gene and the immunoglobulin loci are far away from each other in most cases with variant translocations, as well as in some cases with t(8;14) translocation (e.g., Daudi). Mutations and other alterations of the c-*myc* gene (Taub *et al.*, 1984b) would, apparently, be selected for by the strong selective advantage associated with cell proliferation. It remains to be proven that somatic mutations in the c-*myc* gene are general features of variant translocations.

Materials and methods

Cell lines

All cell lines were grown in RPMI 1640 medium (Gibco), supplemented with 10% fetal calf serum. BL21 and LY66 were derived from male patients, and LY91 and JI from females (Philip *et al.*, 1981; Bernheim *et al.*, 1981; Bornkamm *et al.*, 1980). In addition to the $2p^-$ and $8q^+$ chromosomes, LY66 is characterized by an $1q^+$ marker chromosome.

Cloned probes

The 1.3-kb *ClaI-Eco*RI fragment carrying almost the complete 3′ exon of the c-*myc* gene was subcloned from an intact c-*myc* gene into pBR327 and used as a c-*myc* probe. The original clone represents the germline allele of the Burkitt lymphoma line Raji cloned as a 12.5-kb *Eco*RI fragment into phage λ. The V_k probe was kindly provided by T. Rabbitts and contains a 558-bp *Pst*I fragment coding for a V_k subgroup 1 gene (HK101/80, Bentley and Rabbitts, 1981).

The J_k and C_k specific probes were subcloned from a phage, kindly provided by P. Leder, carrying J_k and C_k in germline configuration (Hieter *et al.*, 1980). J_k was sublconed as a 1.8-kb *Sac*I fragment into pCK19 (a pBR322 derivative with the *Hind*III site converted into a *Sac*I site, kindly provided by G. Klobeck). C_k was subcloned as a 2.5-kb *Eco*RI fragment into pACYC 184.

DNAs were prepared from cleared lysates (Clewell and Helinski, 1969) followed by two consecutive runs in CsCl-ethidium bromide gradients.

Blot hybridization

DNA was isolated from the cells as described (Polack *et al.*, 1984). After digestion with *Eco*RI and *Bam*HI, respectively, the fragments were separated on a 0.6% agarose gel and denatured and transferred to nitrocellullose according to Southern (1975) using the modifications introduced by Wahl *et al.* (1979). The c-*myc* probe was labeled with [^{32}P]dCTP (400 Ci/mmol, Amersham) to a specific activity of 10^8 c.p.m./μg by nick-translation (Rigby *et al.*, 1977). The conditions of hybridization and washing were as described (Bornkamm *et al.*, 1982).

Preparation of metaphase chromosomes and in situ hybridization

Mitotic cells were arrested by colcemid (0.1 μg/ml), treated by hypotonic shock (0.075 M KCl; 20–30 min), fixed in methanol/acetic acid (3:1) and spread on slides precoated with Denhardt's solution (Gerhard *et al.*, 1981). *In situ* hybridization was carried out as described in detail by Rappold *et al.*

(1984). Briefly, denaturation of chromosomal DNA was performed with 70% formamide/30% 2 x SSC (v/v) (1 x SSC is 0.15 M sodium chloride, 0.015 M sodium citrate) at 70°C for 2 min. The [^{3}H]DNA probes used for cytologic hybridization experiments averaged 2 – 5 x 10^7 d.p.m./μg. Hybridization was carried out for 16 h at 40°C. After extensive washings in 2 x SSC at 65°C and 0.1 x SSC at room temperature, slides were dehydrated in ethanol and air dried. Autoradiography was performed using Ilford L4 emulsion. Slides were exposed for 14 – 25 days. Autoradiographs were stained with Giemsa. In all evaluated metaphase spreads the marker chromosomes $8q^+$, $2p^-$ could be identified by their characteristic size, differing from all other chromosomes.

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