Proc. Natl. Acad. Sci. USA
Vol. 79, pp. 7837–7841, December 1982
Genetics

Translocation of the c-*myc* gene into the immunoglobulin heavy chain locus in human Burkitt lymphoma and murine plasmacytoma cells

(recombination/chromosome/cancer/DNA)

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Contributed by Philip Leder, October 12, 1982

ABSTRACT **The consistent appearance of specific chromosomal translocations in human Burkitt lymphomas and murine plasmacytomas has suggested that these translocations might play a role in malignant transformation. Here we show that transformation of these cells is frequently accompanied by the somatic rearrangement of a cellular analogue of an avian retrovirus transforming gene, c-*myc*. Moreover, we map c-*myc* to human chromosome 8 band q24, the chromosomal segment involved in the reciprocal Burkitt translocations [t(8;14), t(8;22), and t(2;8)]. In two t(8;14) human Burkitt cell lines, c-*myc* appears to have been translocated directly into a DNA restriction fragment that also encodes the immunoglobulin μ chain gene. In the case of a specific cloned fragment of DNA derived from a mouse plasmacytoma, we demonstrate directly that c-*myc* has been translocated into the immunoglobulin α switch region. Our data provide a molecular basis for considering the role that specific translocations might play in malignant transformation.**

Certain chromosomal translocations are so characteristic of specific human and murine leukemias and lymphomas that their occurrence is thought to be critical to the malignant transformation of these cells (see refs. 1 and 2 for reviews). In human Burkitt lymphoma (3–12) and murine plasmacytoma cells (13, 14), these translocations involve chromosomes upon which the immunoglobulin genes are located (13). In fact, in man, these translocations involve precisely those chromosomal segments that encode the immunoglobulin genes—i.e., in Burkitt lymphoma, reciprocal translocations involve 8q24 and 14q32 [IgH (15)], 2p12 [κ (16)], or 22q11 [λ (unpublished data)]. In considering how translocation and transformation might be related, Klein (1) and later Rowley (2) suggested that translocations alter the expression of a cellular transforming gene (c-*onc*) by bringing it under the control of a new promoter (17). In any case, the role of these specific translocations might be elucidated if it were possible to isolate and determine the structure and products of the fused chromosomal segments.

In what follows, we identify a segment of mouse DNA that appears to contain the breakpoint of just such a translocation. We find that this fragment, isolated several years ago as a somatically rearranged segment of DNA from the mouse myeloma S107 (18), encodes the murine cellular analogue of the avian MC-29 viral transforming gene, c-*myc*. Furthermore, it is joined to a segment of DNA encoding the immunoglobulin α constant region and switch sequences. We use this segment of DNA, the mouse c-*myc* sequence, to show that human c-*myc* is located at band q24 on chromosome 8, the breakpoint for the characteristic Burkitt translocations. We then show that a DNA fragment containing c-*myc* is frequently rearranged in Burkitt cell lines and, using two different restriction enzymes, we show that in two such lines the c-*myc* and immunoglobulin μ region sequences comigrate, suggesting that they are on the same DNA restriction fragment.

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METHODS

Cloned DNA Fragments. Details regarding the cloned DNA fragments used as probes are given in the maps and in the legends that accompany various figures. In particular, the murine c-*myc* probe was obtained from an aberrantly rearranged fragment cloned from the murine myeloma S107 (18). The chicken c-*myc* plasmid was the generous gift of George vande Woude and was derived from a clone originally isolated by Robins *et al.* (19, 20). The human c-*myc* clone was derived (unpublished data) from a random human embryonic liver library screened with the avian v-*myc* gene [2.8-kilobase (kb) *Bam*HI fragment]. A 1.5-kb *Sst* I fragment was subcloned and, as shown by appropriate restriction enzyme digestion, blot hybridization, and heteroduplex mapping, was free of *Alu* sequences and primarily homologous to the 5′ sequence of v-*myc*.

Burkitt and Murine Cell Lines. The Burkitt cell lines, identified in the relevant figures, were obtained from the International Agency for Research on Cancer in Lyon, France, and have been described, together with their karyotype and immunoglobulin product, by Lenoir *et al.* (21). The murine cell line S107 (22) has been described, as has the arrangement of its immunoglobulin genes (18).

***In Situ* Chromosomal Hybridization and Gene Mapping.** Details of the chromosomal mapping technique involving the use of ^{3}H-labeled DNA probes and quinacrine mustard staining has been described by Kirsch *et al.* (15). The method is a modification of that described by Harper and Saunders (23).

DNA Blot Hybridization. Genomic DNAs were prepared as described (24), digested with restriction endonucleases, electrophoresed in 0.8% agarose gels, and transferred to nitrocellulose filters essentially as described by Southern (25). Hybridized nitrocellulose filters were washed at 52°C in 15 mM NaCl/1.5 mM sodium citrate, pH 7.0, containing 0.1% $NaDodSO_4$.

RESULTS

An Aberrantly Rearranged Murine Plasmacytoma DNA Fragment Contains Both Immunoglobulin and c-*myc* Sequences. Several years ago, an aberrantly rearranged segment

Abbreviation: kb, kilobase(s).

of DNA that had been joined to the immunoglobulin α switch region in the IgA-producing mouse plasmacytoma, S107, was identified (18). Studies at that time established that one of the two allelic copies of this sequence (shown below to carry mouse c-*myc*) was rearranged in five of six different mouse plasmacytomas and that it did not carry immunoglobulin sequences. In addition, it was shown that the aberrantly rearranged fragment of DNA did not originate from within the region bordered by the heavy chain joining and constant region sequences. Similar rearrangements of this fragment have recently been observed in a large number of murine B-cell tumors by the research groups of Marcu (26), Adams and Cory (27), and Hood (referred to in ref. 26). Our preliminary chromosomal mapping studies of this DNA fragment, involving the use of a mouse–Chinese hamster ovary hybrid cell line that contained only mouse chromosome 12, indicated that it was not normally on mouse chromosome 12, the location of immunoglobulin heavy chain genes. This raised the possibility that the new fragment might represent a sequence from chromosome 15, the chromosome involved in the characteristic translocation to chromosome 12 in mouse plasmacytomas (13). In light of the translocation hypothesis referred to above (1, 2), we were anxious to map this fragment in greater detail and to assess its ability to hybridize to various c-*onc* sequences. In this connection we were especially interested in analogues of c-*myc*, a gene activated during transformation of avian B cells by avian leukosis virus (28).

Fig. 1 shows the result of a blot hybridization experiment in which a 5.5-kb *Bam*HI fragment derived from the aberrantly rearranged DNA fragment cloned from mouse plasmacytoma S107 was used to hybridize with cloned segments containing the chicken and human c-*myc* gene sequences. The murine probe hybridized to a 3.5-kb *Sst* fragment containing the chicken c-*myc* gene. More specifically, it hybridized strongly to a 0.5-kb *Sst–Sal* fragment containing the 5′ portion of the chicken c-*myc* gene and weakly to a 3-kb fragment containing the 3′ segment of the chicken c-*myc* gene (19). The murine fragment also hybridized to a 1.5-kb *Sst* fragment containing the 5′ portion of the human c-*myc* gene. In addition, the mouse probe was hybridized to an *Sst* I digest of human genomic DNA (Fig. 1, last lane) and detected two fragments that corresponded in length to the *Sst* I fragments that have been found to contain both the 3′ and 5′ human c-*myc* sequences (2.8 and 1.5 kb, respectively) (ref. 29; unpublished data). We conclude from this and previous data (18) that the aberrantly rearranged fragment contains mouse c-*myc* sequences that have been joined to the immunoglobulin heavy chain locus in mouse plasmacytoma S107. We refer to the rearranged fragment as "mouse c-*myc*."

Establishment of the Chromosomal Localization of the Human c-*myc* Sequence. The mouse c-*myc* fragment was then used to localize the analogous human c-*myc* sequence on metaphase chromosome spreads derived from phytohemagglutinin-stimulated normal human lymphocytes. The degree of homology between the human and mouse sequences was sufficient to allow significant hybridization (refs. 29 and 30; see Figs. 1 and 3). The results are shown in Fig. 2. The murine c-*myc* probe detected a single band located at chromosome 8 band q24, the segment that is involved in the 8;14, 2;8, and 8;22 reciprocal translocations of Burkitt lymphoma. Preliminary results of analogous experiments using a human c-*myc* probe are consistent with this conclusion.

The Human c-*myc* Gene Is Frequently Rearranged in Burkitt Lymphoma Cells. The frequent rearrangement of what we now recognize to be the murine c-*myc* gene in mouse plasmacytomas and the location of human c-*myc* sequences on chromosome 8 band q24 suggested that c-*myc* might also be rearranged in Burkitt lymphoma cell lines. The results of an experiment designed to test this possibility are shown in Fig. 3. *Eco*RI digests of DNA derived from various Burkitt cell lines are shown hybridized to the human c-*myc* probe. In each case, we detected a 12.5-kb *Eco*RI fragment; this has been shown to be the size of the authentic, nonrearranged, human c-*myc* gene fragment (31, 32). Rearrangements of the other allelic copy of this gene were seen in 5 of the 10 lines examined with this enzyme (BL22, BL31, Raji, Ly65, and JBL2). The human c-*myc* probe also hybridized to homologous fragments from mouse liver and mouse plasmacytoma S107 as shown in the last two lanes of the first set in Fig. 3. The human probe detected two *Eco*RI fragments in mouse liver DNA; one of these was rear-

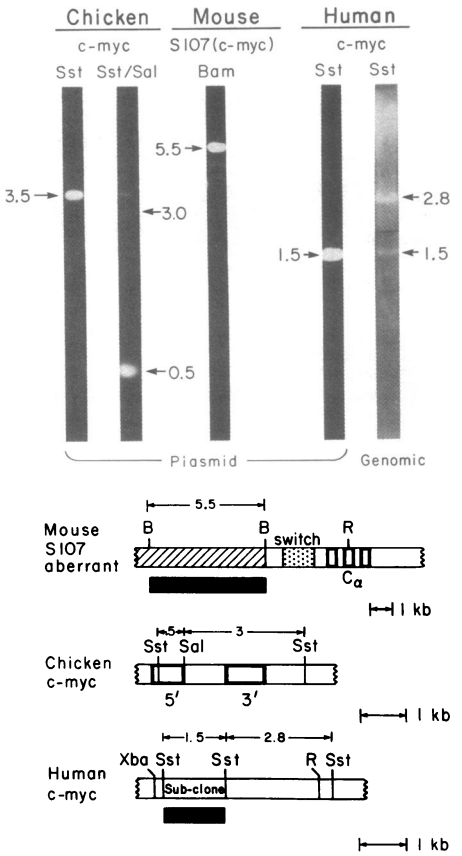

FIG. 1. Hybridization between a somatically rearranged mouse DNA fragment cloned from a mouse myeloma and chicken and human c-*myc* sequences. The mouse S107 aberrant map was established by Kirsch *et al.* (18); the chicken c-*myc* map was established by Robins *et al.* (19), and the human c-*myc* map, by us as indicated below. Southern (25) transfers of restriction endonuclease-digested DNA from pBR322 subclones of chicken c-*myc*, mouse S107 (c-*myc*), human c-*myc*, and normal human lymphocytes were hybridized to a ^{32}P-labeled 5.5-kb *Bam*HI fragment prepared from the mouse S107 *Bam*HI subclone (solid box under mouse S107 aberrant map). The chicken c-*myc* pBR322 subclone which contains an 11-kb *Bam*HI insert with the entire c-*myc* gene as well as flanking DNA (19) was digested with *Sst* I and *Sal* I/*Sst* I to isolate the c-*myc* gene portion to separate the 5′ and 3′ exons (in chicken c-*myc* map). The human c-*myc* subclone which contains a 1.5-kb *Sst* I fragment representing the 5′ portion of the c-*myc* gene [as determined by probe homology to the 5′ portion of the MC29 v-*myc* gene; (unpublished data)] was digested with *Sst* I, separating the 1.5-kb insert from plasmid sequences. This fragment, indicated by a solid box, was used as the human c-*myc* probe in subsequent experiments. Arrows point to the strongly hybridizing fragments in the gels. Note that there is a weakly hybridizing band at ≈3 kb in the chicken *Sst/Sal* lane, just under the partially digested 3.5-kb fragment. This indicates that the mouse probe weakly hybridizes to a segment in the 3′ portion of the chicken c-*myc* sequence.

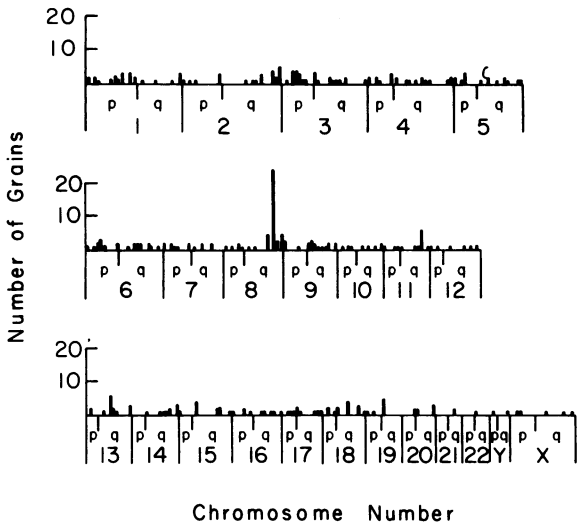

FIG. 2. Chromosomal localization of human c-*myc* sequences. The histogram illustrates the distribution of silver grains (54 cells analyzed; total of 326 grains counted) over metaphase chromosome spreads when a ^{3}H-labeled plasmid containing the 5.5-kb *Bam*HI mouse S107 (c-*myc*) fragment was hybridized to normal human male chromosomes. As determined by Poisson distribution analysis (15), the grain accumulation noted at band 8q24 is highly significant ($P << 10^{-20}$).

ranged in the S107 plasmacytoma. Similarly, the murine c-*myc* probe detected rearrangements and homologous fragments in human cell lines (see last three lanes in the second set in Fig. 3). The Burkitt lymphoma rearrangements were confirmed by *Bam*HI digestions of DNA from cell lines Raji, BL22, and Ly65. By using this enzyme, additional rearrangements were detected in cell lines Seraphina and BL42 (data not shown). In all, DNA from 12 Burkitt cell lines (2 in addition to those shown in Fig. 3) were tested with two enzymes. Eight showed rearranged c-*myc* fragments.

The Human c-*myc* Sequence and the Immunoglobulin Heavy Chain Locus μ Are on Restriction Fragments of the Same Size in at Least Two Burkitt Cell Lines. The possibility that the human c-*myc* sequence and the immunoglobulin heavy chain region are joined on a single fragment of DNA from Burkitt lymphoma cells carrying the 8;14 translocation could be tested in the following way. Formation of an active immunoglobulin μ chain gene involves the joining of V, D, and J region segments (map, Fig. 4). In μ-producing cells, each somatic recombinant retains a portion of the J region, a switch region, and a μ constant region sequence. Because the Burkitt lines used in the experiment shown in Fig. 4 both produce a μ chain, we expect that each will have at least one normally rearranged immunoglobulin μ gene. Alternatively, if the joining of the human c-*myc* sequence is analogous to that observed in the murine plasmacytoma S107 (see Fig. 1), we would expect that c-*myc* would be joined close to the switch region, possibly deleting the J region segment from the segment containing the μ and the μ switch. Furthermore, we would expect that, in some restriction digests, the human c-*myc* probe might appear on the same segment of DNA that encodes the μ switch region or the μ constant region sequence.

The Burkitt lymphoma lines that contain obviously rearranged human c-*myc* sequences (BL22, BL31, Raji, Ly65, JBL2) were analyzed in greater detail. In two of these, BL22 and BL31, c-*myc* appears to have been joined to the immunoglobulin region (Fig. 4). As shown in the *Eco*RI digest of BL22, the c-*myc* probe detected a 12.5-kb fragment of DNA which corresponds to the nonrearranged allelic copy of c-*myc* (31, 32). It was slightly smaller than a rearranged DNA fragment in BL22 that hybridized to the switch and J region probes. The latter fragment is likely to be a normally rearranged μ gene. On the other hand, the rearranged human c-*myc* fragment (9 kb) comigrated with a fragment that contained the μ switch region but lacked a J segment. Similarly, in the *Bam*HI digest there were two germ-line *Bam*HI c-*myc* fragments of 25 and 6.6 kb, and in BL22 there was a rearranged 18-kb human c-*myc* segment that comigrated with a fragment that contained μ constant region sequences and also lacked J_H sequences. This fragment appears to contain both c-*myc* and μ region sequences. Taken together with the *Eco*RI result, this is consistent with c-*myc* having recombined with a region near the μ switch. The c-*myc*–μ recombinant is represented diagrammatically at the bottom of Fig. 4 (c-*myc* Rearrangement). Note that there is an additional 16-kb *Eco*RI fragment that hybridized to the J_H probe which may represent the reciprocal product of the recombination event.

Analysis of cell line BL31 gave results similar to that of BL22.

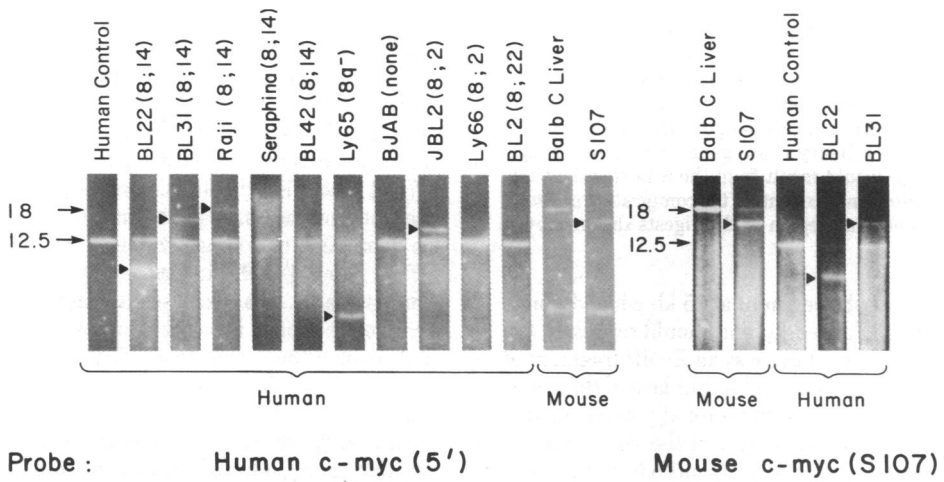

FIG. 3. Arrangement and rearrangement of c-*myc* sequences in Burkitt lymphoma cell lines. Southern transfers of *Eco*RI-digested DNAs prepared from human Burkitt lymphoma lines, normal human lines, BALB/c mouse liver, and mouse S107 plasmacytoma and hybridized to ^{32}P-labeled human c-*myc* and murine c-*myc* (S107) probes. The probes used are indicated by the solid boxes under the gene maps in Fig. 1. The designation in parenthesis after the name of each Burkitt cell line indicates the chromosome translocation observed in that cell line (21). The solid triangles beside the lanes indicate rearranged fragments.

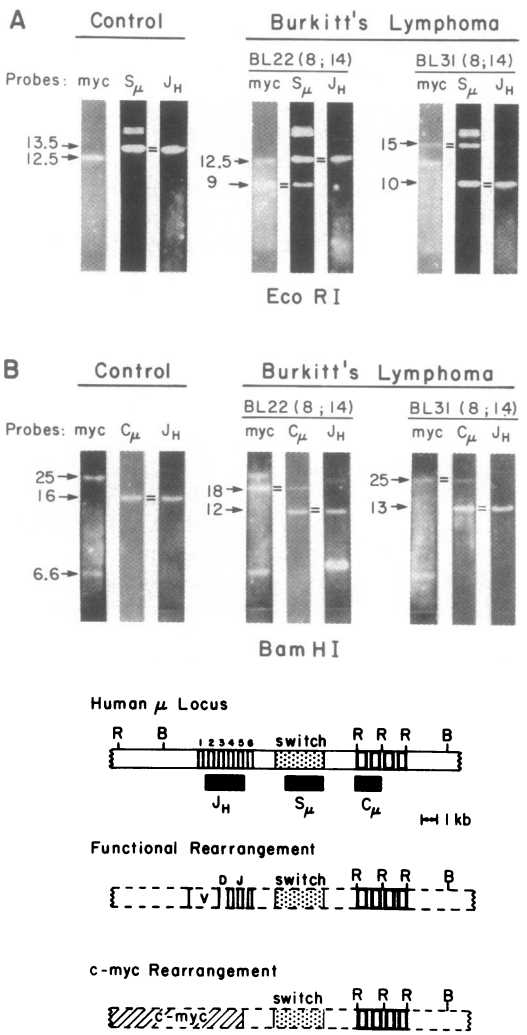

FIG. 4. Comigration of restriction fragments containing c-*myc* and immunoglobulin gene sequences in Burkitt lymphoma cell lines. Southern transfers from *Eco*RI-digested (*A*) and *Bam*HI-digested (*B*) genomic DNAs prepared from a normal human control and two Burkitt lymphoma lines (BL22 and BL31) were hybridized to various ^{32}P-labeled probes as indicated at the top of each lane. The location of the probes from the human μ locus is shown in the diagram of this region. "J_H," from the J region of the heavy chain locus; "S_μ," from the μ switch region; and "C_μ," from the μ constant region (32). The 1.5-kb *Sst* human c-*myc* (5′) fragment was the "myc" probe used (see Fig. 1). The equal signs indicate comigrating fragments in each lane. Below the human μ locus diagram is a model which would account for the observed genomic rearrangements. "Functional Rearrangement" would result in the production of a normal μ heavy chain gene. "c-myc Rearrangement" (in BL22 and BL31) would result from the 8;14 translocation, bring c-*myc* into the μ region, and account for the comigration of c-*myc*, the μ switch, and the μ encoding region in the digests shown above.

There was a rearranged *Eco*RI segment at 15 kb which hybridized to c-*myc* and μ switch, lacked J_H, and should represent the c-*myc*–μ region recombinant. There was an *Eco*RI fragment at 10 kb which hybridized to μ switch and J_H but lacked the c-*myc* sequence, as would be expected of the normally rearranged μ chain gene. Similarly, the *Bam*HI digest of the BL31 line revealed germ-line *Bam*HI fragments of 25 and 6.6 kb that contain c-*myc* sequences. One of these comigrated with a rearranged Cμ fragment, consistent with a rearrangement that has occurred in such a way as to produce a new c-*myc*-containing fragment joined to the μ region that is the same size as the germline c-*myc* fragment. Therefore, it does not appear in this c-*myc*-probed digest as a rearranged gene; its rearrangement is only demonstrated by *Eco*RI digestion (Fig. 4*A*). The data from BL22 and BL31 obtained by using both enzymes lead us to conclude that c-*myc* has been joined to the μ region in these tumors and that these fragments also contain the crossover points from the 8;14 translocation. Analysis of the remaining 8;14 lines in which c-*myc* is rearranged does not permit us to place c-*myc* and the μ region on the same fragment. Their crossover point may be elsewhere in or beyond the IgH locus. We have also analyzed the lines that show chromosome 2 and 22 translocations (see Fig. 3) but thus far have not seen rearranged c-*myc* fragments that comigrate with κ or λ region sequences (data not shown).

DISCUSSION

Immunoglobulin Heavy Chain Genes and c-*myc* Are Linked at the Molecular Level. Two lines of evidence indicate that immunoglobulin and c-*myc* genes are joined in at least some murine plasmacytomas and human Burkitt lymphoma cell lines. Direct evidence comes from the hybridization experiments in which c-*myc* sequences and mouse IgA sequences are joined within the α switch region on a single cloned fragment of DNA derived from the murine plasmacytoma S107 (Fig. 1). We have also shown that the human c-*myc* is located on chromosome 8 (Fig. 2), precisely at the band that is involved in the characteristic Burkitt 8;14, 2;8, and 8;22 translocations. Separate restriction enzyme analyses show that this segment of DNA containing the human c-*myc* sequence is rearranged in 8 of 12 Burkitt lines (10 shown in Fig. 3), and more detailed analyses (Fig. 4) show that in 2 of these lines the human c-*myc* sequence and the immunoglobulin μ chain sequences are on the same size restriction fragment. We believe that this segment of DNA includes the crossover point for the 8;14 translocation. The possibility that these rearrangements are actually polymorphisms is unlikely because we have not observed *Eco*RI polymorphisms in DNA prepared from leukocytes of 18 normal individuals. Furthermore, we see different c-*myc* rearrangements in each Burkitt cell line, and each of these is accompanied by an allelic *Eco*RI fragment that is identical to the fragment seen in normal cells. The question of polymorphism does not arise in the mouse plasmacytoma system in which tumors are derived from inbred strains and direct evidence in the form of cloned DNA fragments is available (Fig. 1; ref. 18).

Is the *myc* Translocation Necessary or Sufficient for Transformation? Although the most interesting feature of our study has been the recognition that the c-*myc* gene undergoes a somatic rearrangement in many Burkitt lymphoma cells, it is also noteworthy that we did not see this rearrangement in 4 of the 12 cell lines we have examined. The analogous rearrangement in mouse B cells and plasmacytomas is also inconstant (18, 26, 27). It is possible that the crossover point in these lines is quite distant from the c-*myc* gene which is nevertheless altered either in expression or coding sequence. The blot hybridization data (Figs. 3 and 4) indicate that in any case the crossover point is quite variable. It is also possible that the transformation of these cell lines has been brought about by some mechanism that does not involve the c-*myc* gene. The further possibility that rearrangement of the c-*myc* gene is sufficient to cause transformation cannot be assessed from our data.

Quantitative Versus Qualitative Alterations in the c-*myc* Product as a Cause of Transformation. Obviously, one of the attractive ideas put forward by Klein (1) and Rowley (2) to explain the potential role of translocation in inducing transformation is that this brings about a quantitative alteration in the amount of an oncogene product synthesized. The possibility that these translocation events may bring about a qualitative

change in the nature of the c-*myc* gene product—for example, by virtue of the formation of a fusion protein—must also be considered (34). The availability of probes that will allow the cloning and eventual sequence determination of *myc* genes from rearranged and germ-line genomes will allow us to distinguish between these possibilities.

Potential Mechanisms of Chromosomal Joining and Other Nonrandom Translocations. The mechanism that joins a c-*myc* sequence to a switch-like segment in the heavy chain locus immediately suggests that mechanisms similar to those involved in normal immunoglobulin gene switching or V/J recombination might play a role in the Burkitt translocation process as well. We have already speculated on this point and only wish to note that switch-like segments scattered through the mouse and human genome (ref. 18; unpublished data) might facilitate such translocations. It is also clear that other chromosomal translocations associated with transformed cells may involve the interchromosomal rearrangement of specific c-*onc* genes. The Burkitt lymphoma and mouse plasmacytoma precedent suggests an obvious experimental approach to this question.

Note Added in Proof. Recent studies by Dalla-Favera *et al.* (35) localized the c-*myc* gene to the region (q24→qter) of human chromosome 8.

We are grateful to George vande Woude for his generous gift of the avian c-*myc* clone. We are also grateful to Ms. Terri Broderick for her expert assistance in the preparation of this manuscript. We wish also to acknowledge the support of grants from the American Business Cancer Research Foundation and I. E. du Pont de Nemours and Co. for portions of this work. R.T. is supported in part by a fellowship from the Damon Runyon–Walter Winchell Cancer Foundation.

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