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# Reports

## Translocation and Rearrangements of the c-*myc* Oncogene Locus in Human Undifferentiated B-Cell Lymphomas

Abstract. *The locus for the cellular* myc *(c-*myc*) oncogene in humans is located on the region of chromosome 8 that is translocated to chromosome 14 in cells from most undifferentiated B-cell lymphomas. It is shown in this study that the c-*myc *locus is rearranged in 5 out of 15 cell lines from patients with undifferentiated B-cell lymphomas, and that the rearrangement involves a region at the 5′ side of an apparently intact c-*myc *gene. In at least three patients, this rearranged region appears to contain immunoglobulin heavy chain* μ *sequences that are located on chromosome 14. The data indicate that this region contains the crossover point between chromosomes 8 and 14. The break point can occur at different positions on both chromosomes among individual cell lines.*

The cellular *myc* (c-*myc*) oncogene is the homolog of the transforming gene of avian myelocytomatosis virus [MC29] (*1, 2*). It belongs to a family of evolutionarily conserved cellular sequences from which viral *onc* genes are thought to originate (*1*). The fact that these normal cellular sequences are capable of inducing transformation upon recombination with a retroviral genome has led to the hypothesis that they play a role in the pathogenesis of cancer. The malignant phenotype may be the result of quantitative or qualitative changes in the product of a cellular *onc* gene.

Some of the mechanisms that may account for such changes in c-*myc* gene expression have been substantiated by studies of tumor tissues. In most B-cell lymphomas induced in chickens by the avian leukosis virus, oncogenesis is associated with the occasional chance integration of an avian leukemia provirus near to the c-*myc* gene (*3, 4*). As a result of this event a viral promoter apparently activates the cellular oncogene (*3, 4*). Although the precise molecular mechanism of activation is not known, neoplasia is thought to result from an increase in constitutive expression of the c-*myc* gene (*3, 4*). That the c-*myc* gene may be involved in cancer is also indicated by the recent finding that the human c-*myc* homolog (*5*) is amplified in a patient with promyelocytic leukemia (*6, 7*). In malignant cells from this patient, increased levels of *myc* messenger RNA (*8*) are correlated with the presence of 20 to 30 copies of the *myc* gene (*6, 7*). Thus in this patient too, increased *myc* expression, or the fact that normal gene regulation may be prevented in amplified genes, or both the events, may be responsible for malignant transformation.

Changes in the regulatory environment of a given *onc* gene may also occur as a consequence of chromosomal translocations or rearrangements. This possibility has important implications for human cancers since specific chromosomal abnormalities are associated with certain neoplasias, especially leukemias and lymphomas (*9, 10*). To study how translocations, oncogenes, and transformation might be related, we, and others, have investigated the chromosomal locations of several known cellular oncogenes (*11–14*) with a view to determining their location with respect to chromosome regions known to be involved in specific cytogenetic abnormalities. We found that the human c-*myc* gene is located in the region of chromosome 8 that is translocated in Burkitt's lymphoma cells (*14*). In virtually all patients with this neoplasia, a relatively small region of chromosome 8 (q24→qter) is translocated to chromosome 14 (in 90 percent of patients) or to chromosomes 2 or 22 (in 10 percent of patients) (*15, 16*). In these three chromosomes the segments that are involved in translocation also contain immunoglobulin genes (*17–18*). Since the c-*myc* locus is translocated in Burkitt's lymphoma, a B-cell malignancy, and since abnormal regulation of this gene occurs in an avian B-cell lymphoma (*3, 4*) we investigated whether the chromosomal translocation causes any alteration in the structure or expression of this *onc* gene in different human B-cell malignancies.

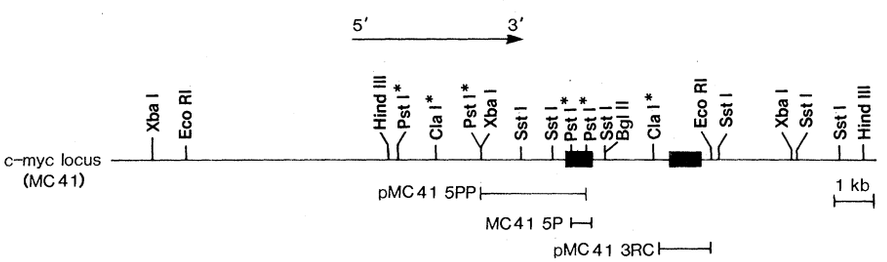


Fig. 1. Restriction enzyme map of the human c-*myc* locus and schematic representation of the *myc* specific probes used in this study. A complete map for the restriction enzymes Eco RI, Hind III, Sst I, and Xba I was constructed on clone λ-LMC41 (*5*). The 8.4-kb Hind III–Eco RI fragment containing c-*myc* sequences (black boxes) was subcloned into plasmid pBR322 [clone pMC41 (*5*)] and digested with Pst I, and the various fragments were ligated to plasmid pBR322. Clone pMC41 5PP is the fortuitous result of the ligation of two contiguous Pst I fragments into pBR322, probably as a result of a partial Pst I digestion. Probe MC41 5P was obtained by Pst I digestion of recombinant plasmid pMC415 PP and purification of the 0.4-kb Pst I fragment. The construction of recombinant plasmid pMC 413RC has been described (*7*). Asterisks on these sites indicate that they have been mapped only within the 8.4-kb Hind III–Eco RI fragment.

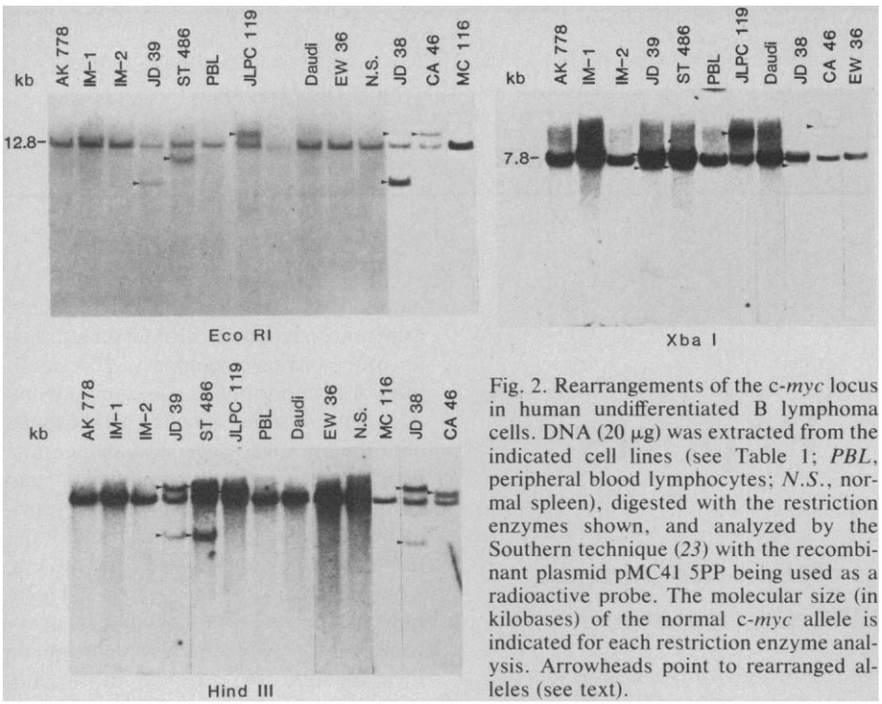


Fig. 2. Rearrangements of the c-*myc* locus in human undifferentiated B lymphoma cells. DNA (20 μg) was extracted from the indicated cell lines (see Table 1; *PBL*, peripheral blood lymphocytes; *N.S.*, normal spleen), digested with the restriction enzymes shown, and analyzed by the Southern technique (*23*) with the recombinant plasmid pMC41 5PP being used as a radioactive probe. The molecular size (in kilobases) of the normal c-*myc* allele is indicated for each restriction enzyme analysis. Arrowheads point to rearranged alleles (see text).

We now present evidence that the c-*myc* locus is frequently rearranged in cells from undifferentiated B-cell lymphomas of both the Burkitt's and non-Burkitt's type, and that the rearrangement involves a region at the 5′ end of the c-*myc* gene. In some patients, the c-*myc* gene and sequences from the immunoglobulin heavy chain μ ($IHC_\mu$) locus are contained in the same restriction enzyme fragments, indicating that the rearranged region at the 5′ end of the c-*myc* locus contains the joining segment between chromosomes 8 and 14.

*The* c-myc *locus is frequently rearranged in undifferentiated B-cell lymphomas*. The q24→qter translocation affecting chromosome 8 occurs in a group of patients with undifferentiated B-cell lymphomas that vary in their histology (Burkitt's and non-Burkitt's type), in the presence or absence of the Epstein-Barr virus (EBV) genome, in the type of chromosomal translocation [t(8:14), t(8:22), t(8:2)], and in the geographic origin of the patient. Cell lines established from these tumors maintain the original cytogenetic characteristics during prolonged cell culture (*19–22*). In the present study, we used the cell lines shown in Table 1. We also used, as controls, peripheral blood lymphocytes (PBL) from normal donors and two cell lines derived from B lymphocytes of patients with infectious mononucleosis (*21*); these cells have no chromosomal translocations.

To study the restriction enzyme pattern of the c-*myc* locus we used the blotting hybridization technique of Southern (*23*). We first used three restriction enzymes (Eco RI, Hind III, and Xba I) that would generate relatively large fragments containing the entire c-*myc* gene and 3′ and 5′ flanking sequences as shown on the restriction map of the cloned c-*myc* locus shown in Fig. 1 (*5*). As a probe, we used a clone (pMC41 5PP) containing the 5′ exon of the c-*myc* gene plus flanking sequences (see Fig. 1). Figure 2 shows representative results of these experiments. In all DNA samples tested, a 12.8-kb Eco RI fragment, a 11.6-kb Hind III fragment, and a 7.8-kb Xba I fragment hybridized to the c-*myc* probe, as expected (Fig. 1). These same three bands were detected in approximately 50 DNA samples from normal and neoplastic tissues of different individuals; this excluded the possibility that any of these restriction sites were polymorphic (data not shown). Samples of DNA from the lymphomas of 5 out of 15 patients displayed additional hybridization bands with the three restriction enzymes tested. The same five DNA samples showed the additional bands with all three enzymes, whereas no other extra bands were detected in samples of DNA from any other patients. These results indicate that a rearranged allele of the c-*myc* locus is present in these lymphoma cells.

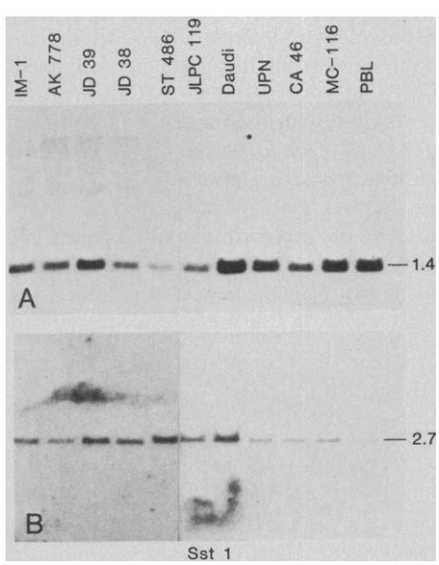


Fig. 3. Mapping of c-*myc* rearrangements outside the putative c-*myc* exons. Samples of DNA from the indicated cell lines were digested by the Sst I restriction enzyme and analyzed by the Southern blotting technique with (A) MC41 5P and (B) pMC41 3RC being used as probes. Molecular size is shown in kilobases. The differences in intensity of hybridization bands represent an artifact of DNA transfer in this particular experiment. The faint bands visible in (A) present hybridization to *myc*-related sequences or pseudogenes (*5*).

*Rearrangements occur in the 5′ flanking region of the* c-myc *gene*. To determine the approximate size and location of the genomic rearrangements detected in the DNA samples shown in Fig. 2, we used probes and restriction enzymes to define the 5′ and 3′ regions of the c-*myc* gene. A Pst I DNA fragment (MC41 5P) was derived from the recombinant plasmid pMC41 5PP (see Fig. 1). In combination with Sst I digestion this probe showed the intact 1.4-kb Sst I fragment which contains the 5′ c-*myc* exon in all the samples tested (Fig. 3A). Analogous results were obtained when the 3′ exon was explored by a probe (pMC41 3RC) that hybridized to a 2.7-kb Sst I fragment in all samples tested (Fig. 3B). Probe pMC41 3RC was also used in double digestions with Bgl II–Eco RI, Bgl II–Hind III, and Bgl II–Xba I, by means of which we explored the 3′ flanking sequences (data not shown) (see Fig. 1). Since no differences were detected by these experiments, we conclude that the allelic Eco RI, Hind III, and Xba I fragments shown in Fig. 2 are generated by a rearrangement occurring in the 5′ flanking sequence of the c-*myc* gene. Since Pst I, Bgl II, and Bam HI sites were also altered on one allele, in the same region and in the same DNA samples (data not shown), the results suggest that a different sequence is present at the 5′ side of the c-*myc* gene. In fact, the joining point between conserved and substituted sequences must be located in the ~ 2-kb region between the conserved Sst I site (5′ site of the unaltered 1.4-kb Sst I fragment) and the Xba I site at the 5′ side of the gene.

*Linkage of the* c-myc *gene and vari-*

*able parts of the IHCμ locus in the same restriction fragments.* The chromosome 14 break point of the reciprocal t(8:14) translocation (*15*) is located inside the heavy chain Ig gene locus on band (q32) (*24*). In the case of the Daudi (Burkitt's lymphoma) cell line this break point has been mapped within the chromosome fragment containing the Ig heavy chain variable region ($V_H$) genes (*24*). The precise break point on chromosome 8 is not known, but the translocation does involve the c-*myc* gene (*14*). Since we had found alterations in the 5′ end of the c-*myc* locus we thought this region might also contain the crossover point between chromosomes 8 and 14. If this were the case c-*myc* sequences and sequences coding for the constant region of the $IHC_\mu$ would be in sufficiently close proximity as to appear on the same restriction enzyme fragment. To test this hypothesis, we analyzed duplicate Bam HI digests of DNA from several B lymphoma cell lines using a c-*myc* probe (pMC41 3RC) and a $C_\mu$ probe that was derived from part of the μ chain gene region (*25*) as indicated in Fig. 4. Bam HI was chosen for this experiment because its cleavage sites are relatively distant from the sequences containing the c-*myc* locus (Fig. 1) and the $IHC_\mu$ locus (see Fig. 4), both of which participate in the translocation (*24*). Figure 5 shows that in three cell lines (JD 38, ST 486, and CA 46) the Bam HI fragment containing the rearranged *myc* allele comigrates with a fragment containing $C_\mu$ sequences. To exclude the possibility that coincidental comigration occurred, which might have been difficult to detect because of the poor resolution of the high molecular weight region of the gel, we analyzed these three cell lines further, using two additional restriction enzymes and two other probes specific for the adjacent switch (S) and joining (J) regions of the $IHC_\mu$ locus (*25*) (see Fig. 4). As shown in Fig. 6A, hybridization of the *myc* probe to normal human DNA digested with Eco RI yielded the expected 12.8-kb band containing the normal c-*myc* locus. Hybridization of the same, normal DNA to S+J and J probes yielded bands of higher molecular weight that contained the nonrearranged S and J regions of the germ line. Analysis of the B lymphoma cell lines showed the rearranged *myc* allele to be in the same fragment detected by the S+J probe. In DNA samples from ST 486 and JD 39, this fragment (10.5 kb and 9.2 kb, respectively) did not hybridize to the J probe, suggesting that the J region was no longer directly linked to the S region in these two cell lines. In both lines, the other allele retaining the S and J linkage was also present. In CA 46, a 13-kb fragment hybridized to the *myc*, S+J, and J probes, suggesting that at least part of the J region has been conserved in the same restriction fragment with S and *myc* sequences. Similar experiments in which the DNA was digested with Hind III confirmed the result (Fig. 6B). Although no linkage was observed in the control DNA, *myc* and S sequences appear to be contained in the same restriction fragments of DNA from ST 486 and JD 39 (approximately 16 kb in both cell lines). These fragments lacked J sequences. In the CA 46 DNA, the 12-kb Hind III fragment appeared to contain rearranged *myc*, S, and J sequences. In all three cell lines, additional bands representing the normal c-*myc* allele and rearranged S and J sequences were visible.

These data are consistent with the data obtained with Bam HI (Fig. 4) and indicate that the translocation of t(8:14) put the c-*myc* locus in close proximity to the

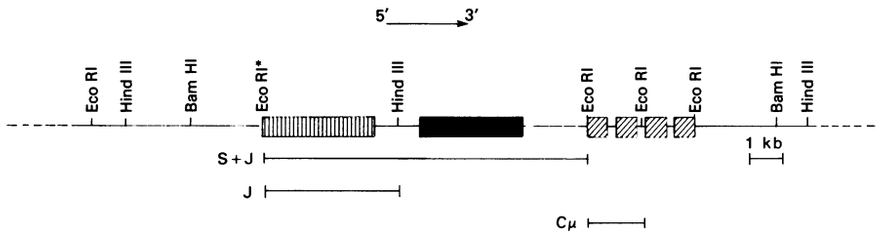


Fig. 4. Genomic organization of the human IHCμ locus and schematic representation of the probes used. This scheme was derived from several cloned fragments from this genomic region (*20*). Vertically hatched box, joining (*J*) genes; black box, switch region; diagonally hatched boxes, μ genes. The S+J, J, and $C_\mu$ probes were obtained by purification of the corresponding fragments. The Eco RI site marked by an asterisk is a result of the cloning procedure and is not present in the human genome.

Table 1. The cell lines used in this study.

| Cell line | Diagnosis* | Presence of EBV genome | Cytogenetic pattern | Origin |
|---|---|---|---|---|
| CA 46† | BL | − | t(8:14) | South America |
| MC 116† | BL | − | t(8:14) | North America |
| ST 486† | BL | − | t(8:14) | North America |
| EW 36† | NBL | − | t(8:14) | North America |
| JD 39† | NBL | − | t(8:14) | North America |
| JD 38† | NBL | − | t(8:14) | North America |
| JLPC 119† | NBL | − | t(8:14) | North America |
| Daudi† | BL | + | t(8:14) | Africa |
| AK 778† | BL | + | t(8:14) | Africa |
| P3HR-1† | BL | + | t(8:14) | Africa |
| AG876† | BL | + | t(8:14) | Africa |
| JI‡ | BL | + | t(2:8) | Europe |
| IARC/LY67‡ | BL | + | t(8:22) | Africa |
| IARC/LY91‡ | BL | + | t(2:8) | Africa |
| IM-1§ | IM | + | | North America |
| IM-2§ | IM | + | | North America |
| UPN‖ | BL | + | t(8:22) | Europe |

*Original histologic diagnosis: BL, Burkitt's lymphoma; NBL, non-Burkitt's type undifferentiated lymphoma; IM, infectious mononucleosis. †See Benjamin *et al.* (*19*). ‡See Lenoir *et al.* (*20*). §See Magrath (*21*). ‖See Magrath (*21*) and Wang-Peng (*22*).

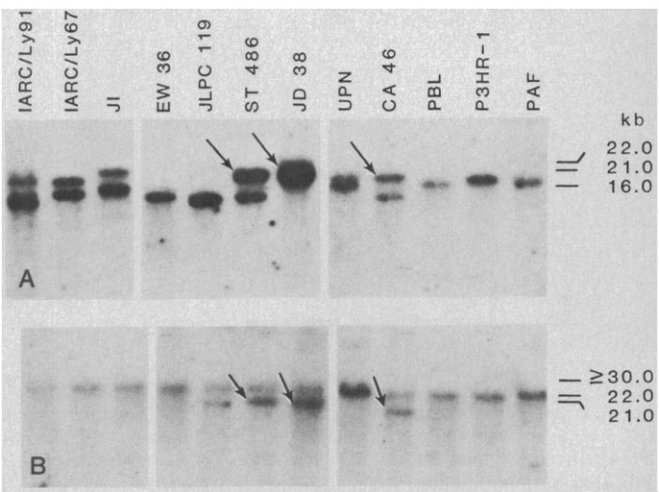


Fig. 5. Comigration of Bam HI restriction fragments containing *myc* and $C_\mu$ sequences in some undifferentiated B lymphoma cell lines. Duplicate samples of Bam HI–digested DNA were hybridized by the Southern technique (*23*) to (A) $C_\mu$ and (B) pMC41 3RC probes. Arrows point to the bands that display the same molecular weight in the two experiments.

$IHC_\mu$ locus. The Bam HI, Eco RI, and Hind III restriction fragments that contain the c-*myc* sequences $C_\mu$, S, and, in one case, also J, contain the crossover point between chromosomes 8 and 14. A tentative scheme of the new genomic rearrangement after chromosomal translocation is shown in Fig. 6C. Since both the c-*myc* locus and the immunoglobulin heavy chain locus appear to be rearranged at the 5′ side, recombination must result in the two loci being linked in a head-to-head fashion leading to opposite directions of transcription.

*Variability of the chromosomal breakpoints*. The differences in the juxtaposition of the *myc* and $IHC_\mu$ loci between cell lines S 486 and JD 39 and CA 46 suggested a variability in the break point on chromosome 14. Chromosome 14 seems to be interrupted at different points in the S-J fragment as judged by the absence of linked J sequences in two out of three cell lines tested (Fig. 6). By a different approach the Daudi cell line has also been reported to have conserved at least part of the J region (*24*). In the case of the JPLC 119 cell line, restriction enzyme analysis does not permit us to place the rearranged c-*myc* and the $IHC_\mu$ loci on the same fragment. The break point in this cell line may be elsewhere in or beyond the $IHC_\mu$ locus.

The variability of the break point on chromosome 8 is immediately suggested by the different sizes of the allelic c-*myc* fragments in the rearranged cell lines. Moreover, 10 out of 15 cell lines from undifferentiated B-cell lymphomas did not display any detectable c-*myc* rearrangement when analyzed by the Southern blot technique with four different restriction enzymes (Figs. 2 and 4). These cell lines included several with the t(8:14) translocation as well as some with either the t(8:22) or the t(2:8) translocation. We conclude that the chromosomal break point in these cell lines is located at a greater distance from the c-*myc* locus than can be detected by the restriction enzymes that we used for this analysis.

*Discussion*. Our main objective in this study was to explore the possibility that the c-*myc* locus is altered as a consequence of chromosomal translocation in cells from patients with B-cell lymphomas. In one-third of the cell lines examined we detected extensive sequence substitution at the 5′ end of the c-*myc* gene which otherwise appeared to be intact. These cases were all EBV negative; the significance of this correlation is unknown. Evidence for this substitution was based on the differences we found in the restriction sites for six different enzymes that showed no polymorphism in the normal population. By identifying two known genetic loci from the different chromosomes involved in the translocation, we were able to map, in three cell lines, the rearranged c-*myc* allele and variable parts of the $ICH_\mu$ locus in juxtaposition and thus locate the crossover point between chromosomes 8 and 14. We obtained this result by using three different restriction enzymes and three different probes derived from the Ig heavy chain locus. The probability of coincidental comigration in all these experiments is negligible. Moreover, data from our own work and that of others (*13, 26*) on different patients with human B-cell lymphomas indicate that the changes in the *myc* locus in human B-cell lymphomas are analogous to those that occur in mouse plasmacytomas, where a set of frequently rearranged sequences is translocated into $IHC_\mu$ genes (*27, 28*). These sequences have been identified as the mouse c-*myc* gene (*26, 29*).

The involvement of the c-*myc* oncogenic gene in translocations in different species suggests that this gene may have an essential role in malignancy. It has been suggested that chromosomal translocations may alter the expression of an *onc* gene by bringing it under the control of a new promoter (*9, 10*). In our three cell lines from undifferentiated B-cell lymphomas the c-*myc* gene is directly linked to the $IHC_\mu$ locus, and heavy chain promoters or enhancers may be responsible for *myc* activation in the 14q+ chromosome. In these three cell lines, *myc* and $IHC_\mu$ sequences appear to be arranged head-to-head in opposite directions of transcription. The same arrangement has been found in BALB/c mouse plasmacytomas (*29*). Although the effects of this arrangement on c-*myc* transcription are not known, an analogous situation has been reported for the virus-induced activation of the c-*myc* gene in rare cases of avian B-cell lymphoma (*4*).

That the $ICH_\mu$ locus may be involved in the mechanism of chromosomal translocation but not in the direct control of expression of the c-*myc* gene is suggested by the marked variability among patients in the chromosome 8 break point. This variability implies that the $IHC_\mu$ and *myc* loci may be more than 15 kb

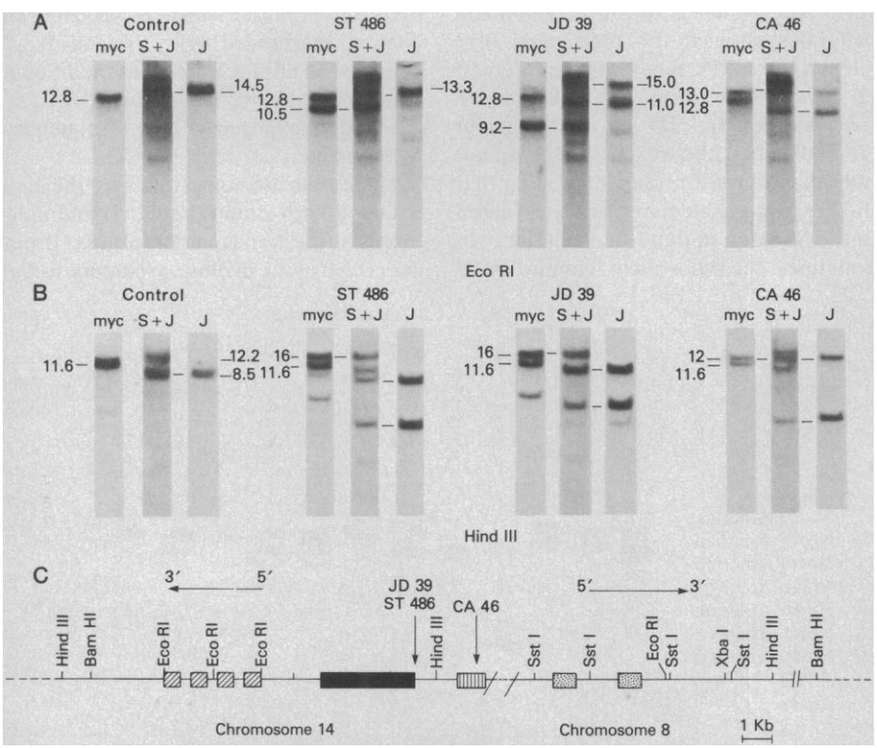


Fig. 6. Comigration of Hind III and Eco RI restriction fragments containing *myc* and different $IHC_\mu$ sequences. (A) Eco RI and (B) Hind III fragments of the control DNA's or B lymphoma DNA's (from cell lines ST 486, JD 39, and CA 46) were hybridized (*23*). Comigrating bands are indicated by joining bars. Molecular sizes are shown (in kilobases) for some representative bands. (C) The crossover region between chromosomes 8 and 14 as derived from the above experiments. The breakpoint sites for the different cell lines (indicated by arrows) as well the crossover point between the two chromosomes (indicated by the interrupted line) are arbitrarily located within the regions identified by the hybridization experiments. Diagonally hatched boxes, $C_\mu$ genes; black box, switch region; vertically hatched box, J genes; dotted boxes, c-*myc* sequences.

apart in those cell lines in which we did not detect any *myc* rearrangement by the Southern blot technique. Thus, other regulatory mechanisms (for example, nucleosome arrangement, DNA methylation, or distantly acting "enhancer" sequences) may be affected by the chromosomal translocation, leading to altered c-*myc* expression. It is also possible that the rearrangement in the *myc* locus activates new modes of splicing that generate a defective or fused (*30*) protein. Such a mechanism, which would generate new species of messenger RNA, has been proposed to occur in mouse plasmacytomas (*27–29*). However, a preliminary survey of cell lines from undifferentiated B-cell lymphomas displaying a rearranged or nonrearranged c-*myc* locus revealed no new messenger RNA species (*8, 31*) and indicated that *myc* RNA levels are variably increased (*8, 31*). The significance of this enhanced expression must be confirmed by the analysis of normal cells at the same stage of differentiation.

The frequent involvement of Ig genes in chromosomal translocations characteristic of B-lymphocyte tumors suggests that chromosomal abnormalities may be regarded as recombinational mistakes occurring in genomic regions characterized by high levels of physiologic recombination. These events may be relatively frequent, yet detectable only when they involve genes which, when activated, are able to confer a selective growth advantage to the cell in question. In most undifferentiated B-cell lymphomas the *myc* gene may be involved when the recombination event involves the region 8(q24→qter). However, in several follicular B-cell lymphomas carrying the 14q+ chromosome, one of chromosomes 18, 17, 11, or 12 is the donor chromosome (*32*). In all these lymphomas the break point on chromosome 14 was located at band q32, probably at the heavy chain locus (*27*). This supports the speculation that this locus of physiologic recombination may be active in other recombinational events. Other *onc* genes involved in these recombinations may be identified by exploiting their linkage to Ig loci.

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## Methane Synthesis on Nickel by a Solid-State Ionic Method

Abstract. *The feasibility of electrochemically synthesizing methane by a Fischer-Tropsch type reaction by use of a solid oxide electrolyte has been demonstrated. This solid-state ionic approach provides in situ control of the oxygen activity at the gas-catalyst interface by imposing a suitable voltage drop across an oxygen-conducting solid electrolyte from an external source. Methanation rates for hydrogen–carbon monoxide and hydrogen–carbon dioxide synthesis gas mixtures upon nickel electrodes showed substantial enhancement with the use of this technique, reaching values nearly two orders of magnitude higher than their intrinsic rates.*

The scarcity of liquid fossil fuels has created interest in abundant hydrogen-deficient materials, such as coal, as alternative energy sources and as chemical feedstocks. Hence, the Fischer-Tropsch and related processes have recently been receiving renewed attention.

The Fischer-Tropsch process consists of the catalytic conversion of $H_2$ and CO into a large variety of organic compounds. The product distribution is dictated primarily by the operating temperature and pressure, the choice of catalyst, and the $H_2$/CO ratio.

The kinetic aspects of the Fischer-Tropsch synthesis have been studied extensively (*1*). However, the nature of the critical reaction intermediate is still debated. Nevertheless, there seems to be reasonable agreement that the controlling feature of the overall rate of the $CH_4$ formation reaction is the decomposition of CO upon the gas-solid interface. Weakly bonded $H_2$ competes with the strongly chemisorbed CO for the active sites upon the catalyst surface. Recent spectrographic studies have also indicated that the rate-determining step in-