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Genetics

Differential expression of the normal and of the translocated human c-*myc* oncogenes in B cells

(chromosome translocations/translocated oncogene activation/untranslocated oncogene repression/gene regulation/B-cell neoplasia)

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ABSTRACT **We have investigated whether the translocated and the untranslocated human c-*myc* oncogenes of Burkitt lymphoma cells are equally or differentially expressed in host mouse B cells. The human c-*myc* mRNA levels in somatic cell hybrids between mouse plasmacytoma cells and Burkitt lymphoma cells with either the t(8;14) or the t(2;8) chromosome translocation were determined by using the nuclease S1 protection procedure. Although both the human parental lines and the hybrid cells carrying the translocated c-*myc* oncogene expressed high levels of human specific c-*myc* transcripts, the hybrid cells carrying the untranslocated c-*myc* gene on normal chromosome 8 did not contain human specific c-*myc* mRNA. These results suggest that the translocated human c-*myc* oncogene has escaped the normal transcriptional control to which the untranslocated c-*myc* gene remains subjected. This interpretation is also supported by the finding that the expression of the c-*myc* genes of lymphoblastoid cells and of HL-60 promyelocytic leukemia cells are repressed when they are transferred into a mouse plasmacytoma background. The ability of the translocated c-*myc* oncogene to escape the normal transcriptional control occurring in B cells may be important for the expression of B cell neoplasia in mouse and man. We have also transferred the Burkitt 14q+ chromosome carrying a translocated c-*myc* oncogene into mouse LM-TK$^-$ fibroblasts and studied the levels of the human c-*myc* transcripts in the hybrids. Because the levels of human c-*myc* transcripts in the fibroblast hybrids are dramatically decreased in comparison to the plasmacytoma hybrids, we conclude that the levels of transcripts of the translocated c-*myc* oncogene depend on the differentiated state of the cells harboring the translocated chromosome.**

Burkitt lymphoma cells carry a reciprocal translocation between chromosome 8 and either chromosome 14, 2, or 22 (1–5). Because we and others have shown that the genes for immunoglobulin heavy and λ and κ light chains are located on human chromosomes 14 (6), 22 (7, 8), and 2 (8, 9), respectively, we have speculated that the human immunoglobulin genes might be involved in the chromosome translocations occurring in Burkitt lymphoma (7). Therefore, we used somatic cell hybrids between mouse plasmacytoma cells and Burkitt lymphoma cells with the t(8;14) chromosome translocation to show that the V_H genes translocate to the deleted chromosome 8 (8q−) and the C_μ and C_γ genes remain on the 14q+ chromosome (10). Thus, we concluded that the chromosomal break observed in Burkitt lymphomas with the t(8;14) chromosomal translocation involves the heavy chain locus (10). Using DNA probes specific for the human homologues of viral oncogenes to determine their chromosomal location by Southern blotting analysis of hybrid cell DNAs (11–13), we have recently located the human c-*myc*, a homologue of the avian myelocytomatosis viral oncogene, v-*myc*, on the segment of chromosome 8 that translocates in Burkitt lymphomas (14). We and others have also demonstrated that in some cases of Burkitt lymphomas the c-*myc* oncogene is intact within a large *Bam*HI restriction fragment and in others the c-*myc* oncogene recombines head to head with the C_μ gene (14–17). Because high levels of c-*myc* transcripts are present in Burkitt lymphoma cells (18), in the present study we have investigated the levels of human and mouse c-*myc* transcripts in somatic cell hybrids between Burkitt lymphoma and mouse plasmacytoma cells to determine if there are differences in the levels of human c-*myc* mRNA transcribed from either the translocated or the untranslocated c-*myc* oncogene.

MATERIALS AND METHODS

Cells. *Human cell lines.* The Burkitt lymphoma cell lines used in this study are described in Table 1. GM607, GM2669, GM2294, and GM1056 are Epstein–Barr virus (EBV)-transformed human lymphoblastoid cell lines that were obtained from the Human Cell Repository (Institute of Medical Research, Camden, NJ). The human cell line HL-60, derived from a patient with promyelocytic leukemia (19), contains an amplified c-*myc* gene (20) in the form of an aberrantly banded region on one of the two chromosomes 8 (8q+) (21).

Mouse cell lines. The NP3 mouse plasmacytoma cell line is an immunoglobulin nonproducer cell variant (22) of the hypoxanthine phosphoribosyltransferase-deficient P3 × 63 Ag8 mouse plasmacytoma cell line originally derived from the MOPC21 myeloma (23). P3Bu4 mouse plasmacytoma cells are deficient in thymidine kinase (TK) and also derive from the MOPC21 mouse myeloma ($P_3$26BU4) (24). LM-TK$^-$ cells are TK-deficient mutants of mouse L cells (25).

Hybrids. Clone JE1D6, a hybrid between NP3 and P3HR-1 (18) cells, was subcloned by limiting dilution and four subclones (JE1D6-BB3, -AG5, -CC4, and -BC4) were characterized (Table 2). Clone 253 A-B3 is a hybrid between NP3 and JD38 non-Burkitt lymphoma cells. Clones JI 5-3 and JI 4-2 are hybrids between NP3 and JI (26) Burkitt lymphoma cells. Clone DSK1 B2A5 is a hybrid between NP3 and GM1056 cells. Clone M44 C12S5 is a hybrid between Burkitt P3HR-1 cells and LM-TK$^-$ fibroblasts (14). Clones 77B10 C129 and 77B10 C133 are hybrids between mouse plasmacytoma P3Bu4 cells and human HL-60 leukemia cells (21).

Chromosome Analysis. Metaphase spreads of parental and hybrid cells were stained by the trypsin Giemsa procedure according to established procedures (10, 27). Metaphases of hybrid cells were also restained by a modification of the G11 technique (10, 28).

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Abbreviations: EBV, Epstein–Barr virus; TK, thymidine kinase; bp, base pair(s).

Table 1. Human lymphoma cell lines used in this study

Cell line	Diagnosis*	Presence of EBV genome	Translocation	Origin
Daudi	BL	+	t(8;14)(q24;q32)	Africa
P3HR-1	BL	+	t(8;14)(q24;q32)	Africa
CA46	BL	−	t(8;14)(q24;q32)	South America
JD38	NBL	−	t(8;14)(q24;q32)	North America
JI	BL	+	t(2;8)(p12;q32)	Europe
LY91	BL	+	t(2;8)(p12;q32)	Africa
LY67	BL	+	t(8;22)(q24;q11)	Africa

*Histologic diagnosis (17): BL, Burkitt lymphoma; NBL, non-Burkitt lymphoma.

Isozyme Analysis. Hybrid clones were studied for the expression of human nucleoside phosphorylase (a marker of chromosome 14), glutathione reductase (a marker of chromosome 8p), malic dehydrogenase (a marker of chromosome 2p), and isocitrate dehydrogenase (a marker of chromosome 2q) according to established procedures (6, 7).

Southern Blotting Analysis of Hybrid Cells. Hybrids were studied for the presence of the human c-*mos* oncogene that is located on band q22 of chromosome 8 (29) and of the c-*myc* oncogene by Southern blotting analysis (30) after *Bam*HI digestion of the cellular DNAs and by using either a human c-*mos* genomic probe (PAB) (31) or a human *myc* cDNA probe (Ryc 7.4) (14). Results of the analysis of P3Bu4 × HL-60 hybrids are reported elsewhere (21). Hybrid 77B10 CL29 contained a single copy of the human c-*myc* gene per cell, whereas hybrid 77B10 CL33 contained 16 copies of the human c-*myc* oncogene per cell (21).

Nuclease S1 Analysis of Human and Mouse c-*myc* Transcripts in Hybrid Cells. Nuclease S1 analysis was carried out according to Sharp *et al.* (32) with modifications (33) by using 5′-end-labeled human (34) or mouse (35) c-*myc* cDNA clones. Cytoplasmic RNA was prepared by the cesium chloride method (18). The 5′-^{32}P-end-labeled DNA probes were heat denatured, hybridized in 80% deionized formamide to 20 μg of cytoplasmic RNA at 55°C for 10 hr, digested with 80 units of nuclease S1 (P–L Biochemicals), and analyzed by electrophoresis on a 7 M urea 4% polyacrylamide gel (36). The DNA probe was 5′-end-labeled by the method of Maxam and Gilbert (37). The relative amount of c-*myc* RNA in various cells was estimated by quantitative nuclease S1 mapping, followed by the scanning of suitably exposed autoradiograms.

RESULTS

Transcription of the c-*myc* Oncogene in Different Burkitt Lymphoma Cells and Human Lymphoblastoid Cell Lines. Fig. 1 describes the human (34) and the mouse (35) c-*myc* cDNA probes we have used for the nuclease S1 analysis of parental and mouse–human hybrid cells. As shown in Figs. 2 and 3*A* very high levels of c-*myc* transcripts were detected in three Burkitt lymphomas (Daudi, P3HR-1, and CA46) and one non-Burkitt lymphoma (JD 38IV) cell lines with the t(8;14) chromosome translocation. Amounts of c-*myc* RNAs in these cell lines were estimated about 10 times higher than in the three lymphoblastoid cell lines (GM607, 2669, and 2294) examined. Although Daudi and P3HR-1 cells contain a translocated unrearranged c-*myc* oncogene (17), CA46 and JD38 cells contain a translocated rearranged c-*myc* oncogene recombined with a C_μ gene (17). Two cell lines, JI and LY91, with the t(2;8) chromosome translocation, expressed levels of c-*myc* transcripts lower than the human lymphomas with the t(8;14) translocation and HL-60 cells, which contain an amplified c-*myc* gene, but higher than in the different lymphoblastoid cell lines we have examined (Fig. 2). The cell line LY67 expressed a lower level of c-*myc* transcripts. This level was still at least 2- to 3-fold higher than in the three lymphoblastoid cell lines we have examined (Fig. 2).

Transcription of the Human c-*myc* Oncogene in Mouse–Human Hybrids. Because the human and the mouse c-*myc* genes differ in their nucleotide sequence (34, 35, 38), we have investigated the expression of the human c-*myc* transcripts in mouse–human hybrids by the nuclease S1 procedure using a human cDNA probe. By this method we could detect the expression of the human c-*myc* transcripts in the hybrids without detecting the expression of the mouse c-*myc* gene (Figs. 3*A*

Table 2. Transcription of the mouse and human c-*myc* genes in mouse × human hybrids

Parental cells and hybrid clones	Human isozymes		Human chromosomes						Human oncogenes		Levels of c-*myc* transcripts	
	GSR	NP	8	8q−	14	14q+	2q−	8q+	c-*mos*	c-*myc*	Mouse	Human
P3HR-1 (BL)	+	+	+	+	+	+	−	−	+	+	−	+++
JE1D6 (NP3 × P3HR-1 hybrid)	+	+	+	−	−	+	−	−	+	+	+++	+++
BB3 (NP3 × P3HR-1 hybrid)	+	−	+	−	−	−	−	−	+	+	+++	−
AG5 (NP3 × P3HR-1 hybrid)	+	−	+	−	−	−	−	−	+	+	+++	−
CC4 (NP3 × P3HR-1 hybrid)	−	+	−	−	−	+	−	−	−	+	+++	+++
BC4 (NP3 × P3HR-1 hybrid)	−	+	−	−	−	+	−	−	−	+	+++	+++
NP3 (mouse plasmacytoma)	−	−	−	−	−	−	−	−	−	−	+++	−
JD38 (NBL)	+	+	+	+	+	+	−	−	+	+	−	+++
253 A-B3 (NP3 × JD38 hybrid)	+	−	+	−	+	−	−	−	+	+	+++	−
Daudi (BL)	+	+	+	+	+	+	−	−	+	+	−	+++
3E5 CL3 (NP3 × Daudi hybrid)	+	+	+	+	+	−	−	−	+	+	+++	−
JI (BL)	+	+	+	−	+	−	+	+	+	+	−	+++
JI 5-3 (NP3 × JI hybrid)	+	+	+	−	+	−	−	−	+	+	+++	−
JI 4-2 (NP3 × JI hybrid)	+	+	+	−	+	−	+	+	+	+	+++	+++
GM1056 (EBV transformed)	+	+	+	−	+	−	−	−	+	+	−	++
DSK 1B 2A5 (NP3 × GM1056 hybrid)	+	+	+	−	+	−	−	−	+	+	+++	−
LM-TK$^-$ (mouse fibroblast)	−	−	−	−	−	−	−	−	−	−	+++	−
M44 CL2S5 (LM-TK$^-$ × P3RH1 hybrid)	−	+	−	−	−	+	−	−	−	+	+++	±

See legend to Table 1. GSR, glutathione reductase; NP, nucleoside phosphorylase.

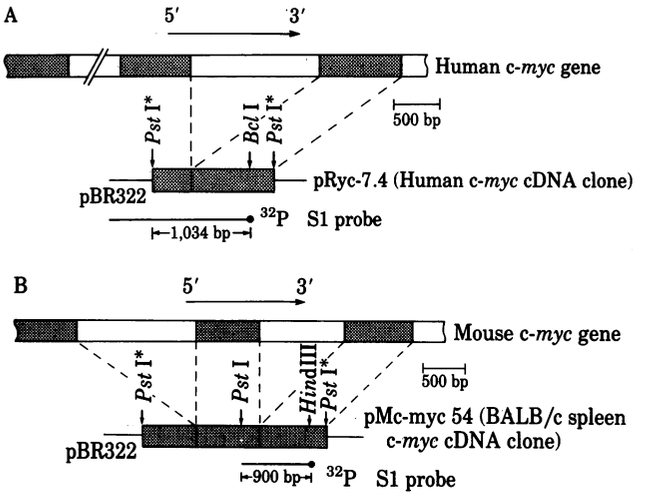

FIG. 1. Schematic representation of DNA probes used for nuclease S1 analysis. (*A*) Structure of the human c-*myc* cDNA clone pRyc-7.4 (16), which carries a human c-*myc* cDNA 1.2-kilobase insert in pBR322, and a part of human c-*myc* gene are schematically shown according to refs. 35–37. pRyc-7.4 plasmid DNA was digested by *Bcl* I, 5′-^{32}P-end-labeled, and used as a probe (human c-*myc* probe). The expected fragment protected by human c-*myc* mRNA (1,034 nucleotides) encompasses most of the protein coding sequences (34, 38). (*B*) Structure of the mouse c-*myc* cDNA clone pMC-myc 54 (35), which carries a mouse c-*myc* cDNA 2.2-kilobase insert in pBR322, and a part of mouse c-*myc* gene are schematically presented according to refs. 35 and 37. pMC-myc 54 plasmid was digested by *Hin*dIII, labeled with ^{32}P at the 5′ end, and cleaved with *Pst* I. The resulting *Pst* I–*Hin*dIII 900-base pair (bp) fragment was isolated and used as probe (mouse c-*myc* S1 probe). The fragment encompasses most of the protein coding sequences.

and 4*A*). Figs. 3*A* and 4*A* show the levels of the human c-*myc* transcripts in hybrids between human lymphoma cells with either the t(8;14) or the t(2;8) chromosome translocation and mouse plasmacytoma cells. As shown in Fig. 3*A*, lanes 2, 5, and 6, NP3 × P3HR-1 hybrids that have retained the 14q+ chromosome express very high levels of human c-*myc* transcripts (Table 2). On the contrary, we could not detect human c-*myc* transcripts in hybrids that retain the normal chromosome 8 carrying the untranslocated c-*myc* gene from three different Burkitt lymphoma cell lines with the t(8;14) translocation (Fig. 3*A*, lanes 3, 4, 8, and 10, and Table 2). We obtained similar findings in the case of hybrids between mouse plasmacytoma and JI Burkitt lymphoma cells with the t(2;8) chromosome translocation (Fig. 4*A*, lanes 2 and 3, and Table 2). The hybrid clone containing the two segments of chromosome 8 involved in the t(2;8) translocation and an unrearranged c-*myc* gene (unpublished data) expressed high levels of c-*myc* transcripts (Fig. 4*A*, lane 3, and Table 2). On the contrary, the hybrid JI 5-3 containing only the normal chromosome 8 of JI cells did not express detectable levels of human c-*myc* transcripts (Fig. 4*A*, lane 2, and Table 2). We could not detect human c-*myc* transcripts also in hybrids between mouse plasmacytoma cells and GM1056 human lymphoblastoid cells (Fig. 4, lane 6) that have retained the human chromosome 8 (Fig. 4*A*, lane 5). Very low levels of human *myc* transcripts were observed in a P3HR-1 × LM-TK$^-$ hybrid clone

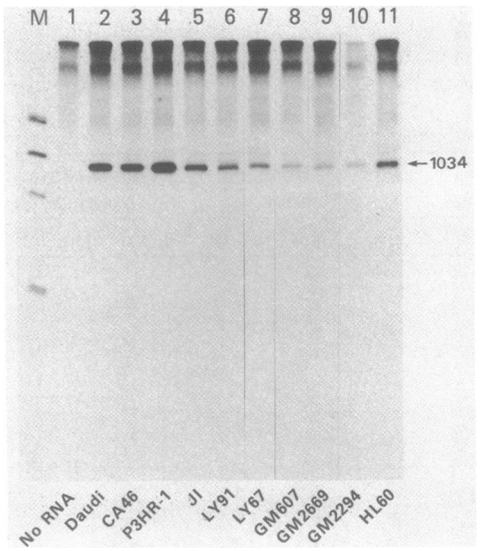

FIG. 2. Detection of the transcripts produced from the c-*myc* gene in various Burkitt lymphoma cells and human lymphoblastoid cell lines by nuclease S1 analysis. The probe, cleaved with *Bcl* I and 5′-^{32}P-end-labeled pRyc-7.4 plasmid, was heat denatured, hybridized in 80% formamide to 20 μg of cytoplasmic RNA at 55°C, digested with nuclease S1, and analyzed by electrophoresis on a 7 M urea 4% polyacrylamide gel (37). RNA was from Burkitt lymphoma cells. Lanes 2–7, Daudi, CA46, P3HR-1, JI, LY91, and LY67. RNA was from lymphoblastoid cell lines. Lanes 8–10, GM607, GM2669, and GM2294. Lane 11, RNA from promyelocytic leukemia cell line HL-60. Lane M, size marker: φX174 digested with *Hae* III and 5′-^{32}P-end-labeled.

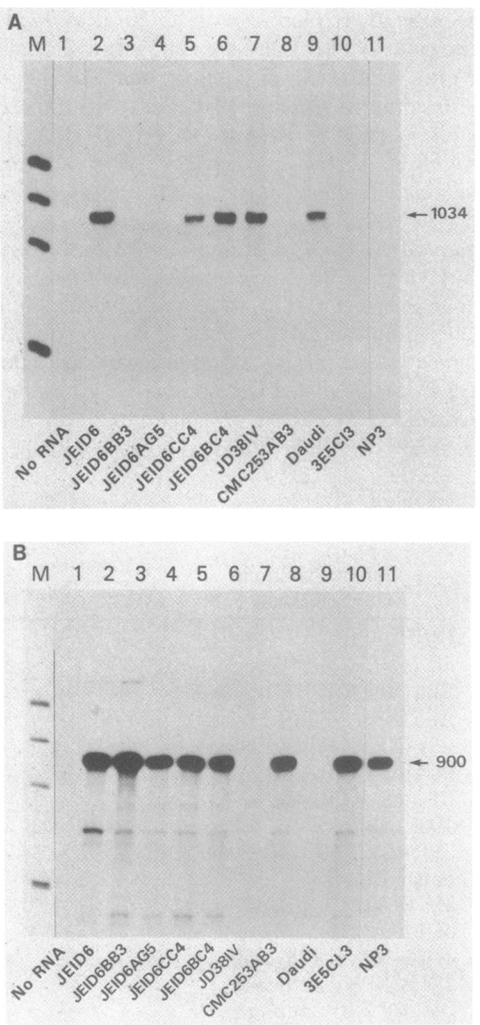

FIG. 3. Nuclease S1 analysis of c-*myc* RNAs in the hybrid cells between NP3 and Burkitt lymphoma cell lines with the t(8;14) chromosomal translocation. Cytoplasmic RNA (20 μg) was hybridized with human c-*myc* probe (*A*) or mouse c-*myc* S1 probe (*B*) described in the legend to Fig. 1. The parental NP3 used for hybrid preparation is a nonproducer mouse myeloma.

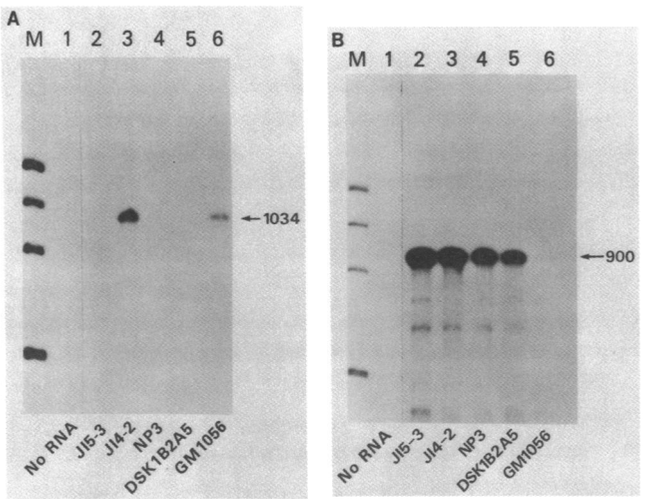

FIG. 4. Nuclease S1 analysis of c-*myc* RNAs in the hybrid cells between NP3 and Burkitt lymphoma cell line (JI) with the t(8;2) chromosomal translocation and between NP3 and a human lymphoblastoid cell line. Cytoplasmic RNAs were analyzed with human c-*myc* S1 probe (*A*) or mouse c-*myc* S1 probe (*B*) (Fig. 1).

that carries the 14q+ chromosome (Fig. 5*A*, lane 4).

Transcription of the Mouse c-*myc* Oncogene in Mouse × Human Hybrids. As shown in Fig. 3*B*, 4*B*, and 5*B*, all mouse plasmacytoma × human B cell hybrids expressed high levels of mouse c-*myc* transcripts. The P3HR-1 × LM-TK$^-$ fibroblast hybrid cells also expressed high levels of mouse c-*myc* transcripts (Fig. 5*B*, lane 4). LM-TK$^-$ tumor-derived parental fibroblasts, like many other tumor cell lines (16, 20, 39), express high levels of c-*myc* RNA (Fig. 5*B*, lane 5).

Transcription of the Human c-*myc* Oncogene in Hybrids Between Mouse Plasmacytoma Cells and HL-60 Human Promyelocytic Leukemia Cells. Because we did not detect the expression of the untranslocated human c-*myc* oncogene of GM1056 lymphoblastoid cells in a NP3 × GM1056 hybrid we decided to determine whether an amplified, unrearranged, untranslocated and active c-*myc* oncogene could be expressed on a mouse plasmacytoma background. Thus, we have tested two P3Bu4 mouse plasmacytoma × HL-60 hybrids, one with the normal human chromosome 8 and the other with the normal 8 and the 8q+ with an aberrantly banded region that carries the amplified c-*myc* oncogene, for the expression of the human c-*myc* gene. As shown in Fig. 5*A* and Table 3, the two hybrids 77 B10 Cl29 and 77 B10 C133 did not express human c-*myc* transcripts. On the contrary, they expressed high levels of mouse c-*myc* transcripts (Fig. 5*B* and Table 3).

DISCUSSION

Because mouse and human c-*myc* coding sequences are not identical (35, 36) we used the nuclease S1 mapping method to detect the levels of either the human or the mouse c-*myc* transcripts in somatic cell hybrids between mouse plasmacytoma and human Burkitt lymphoma cells. The results of this study indicate that the translocated human c-*myc* oncogene of Burkitt lymphoma cells, independently of being directly rearranged with either the C_μ immunoglobulin gene (14–17) or the κ locus, is transcriptionally highly active. Therefore, we can conclude that the enhancement of c-*myc* gene transcription occurs even if the translocated c-*myc* oncogene is unrearranged and located >20–30 kilobases away from either the C_μ locus or the C_κ locus in B cells. Although we found high levels of c-*myc* transcripts in hybrids containing the translocated c-*myc* gene, we were unable to detect human c-*myc* transcripts in hybrids containing the untranslocated human c-*myc* gene on the normal chromosome 8 of Burkitt lymphoma cells. This result indicates that the untranslocated c-*myc* oncogene on the normal chromosome 8 is repressed in plasmacytoma hybrid cells. To prove conclusively that the untranslocated c-*myc* gene is repressed in plasmacytoma hybrids, which express constitutively high levels

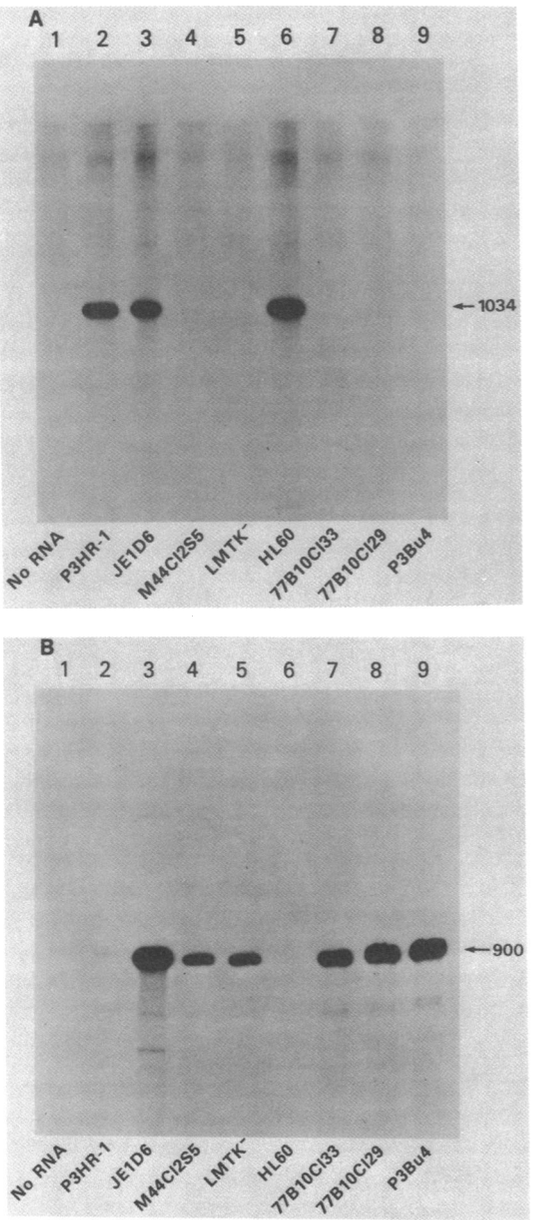

FIG. 5. Nuclease S1 analysis of c-*myc* RNAs in the hybrid cells with human c-*myc* S1 probe (*A*) or mouse c-*myc* S1 probe (*B*) (Fig. 1).

Table 3. Transcription of the mouse and human c-*myc* genes in P3Bu4 × HL-60 hybrids

Parental cells and hybrid clones	Human GSR	Human chromosomes 8	Human chromosomes 8q+	Human oncogenes c-*mos*	Human oncogenes c-*myc*	Levels of c-*myc* transcripts Mouse	Levels of c-*myc* transcripts Human
HL-60	+	+	+	+	+++	−	+++
Hybrid Cl29	+	+	−	+	+	+++	−
Hybrid Cl33	+	+	+	+	+++	+++	−
P3Bu4	−	−	−	−	−	+++	−

GSR, glutathione reductase.

of mouse c-*myc* transcripts (16), we have studied somatic cell hybrids between NP3 mouse plasmacytoma cells and GM1056 EBV-transformed human lymphoblastoid cells, which also express c-*myc* transcripts, and between P3Bu4 mouse plasmacytoma cells and HL-60 human promyelocytic leukemia cells in which the c-*myc* gene is amplified (20) and transcribed at high levels (39). Interestingly, we observed that the hybrids containing either the normal chromosome 8 or the chromosome 8 carrying the amplified c-*myc* oncogene do not express detectable levels of human c-*myc* transcripts. Therefore, we conclude that the normal untranslocated c-*myc* gene, which is transcribed in lymphoblastoid and HL-60 cells, is repressed on a mouse plasmacytoma background. It seems possible that such repression of the untranslocated c-*myc* gene could be mediated by the c-*myc* gene product itself because it is constitutively expressed at high levels in mouse plasmacytomas carrying the t(12;15) chromosome translocation and a mouse c-*myc* gene translocated to an immunoglobulin locus (16). Thus, high levels of either the mouse or the human c-*myc* product might be capable of turning off the untranslocated c-*myc* gene on the normal chromosome 8 but not the c-*myc* gene that has translocated to an immunoglobulin chain locus. Alternatively, it is also possible that a gene located 3′ of the mouse and of the human c-*myc* gene that regulates *myc* transcription might be activated by its proximity to an immunoglobulin locus in B cells. Activation of this putative regulatory gene might result in the repression of the untranslocated *myc* gene.

Interestingly, we have also observed a dramatic difference in levels of c-*myc* transcripts in hybrids containing the 14q+ chromosome on either a mouse plasmacytoma or a mouse LM-TK$^-$ fibroblast background. In fact, we have shown that the levels of the translocated human c-*myc* transcripts in the LM-TK$^-$ hybrids are much lower than the levels in the mouse plasmacytoma hybrids. Thus, we can conclude that mouse fibroblasts are not the appropriate recipients to assay for human genes that are involved in B cell neoplasia. In addition, this result indicates that the genetic elements capable of enhancing the translocated c-*myc* transcription in B cells are either inactive or ineffective in fibroblasts.

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1. Manolov, G. & Manolova, Y. (1972) *Nature (London)* **237,** 33–36.
2. Zech, L., Haglund, V., Nilsson, N. & Klein, G. (1976) *Int. J. Cancer* **17,** 47–56.
3. Van den Berghe, H., Parloir, C., Gosseye, S., Eglebienne, V., Cornu, G. & Sokal, G. (1979) *Cancer Genet. Cytogenet.* **1,** 9–14.
4. Miyoshi, I., Hiraki, S., Kimura, I., Miyamoto, K. & Sato, J. (1979) *Experientia* **35,** 742–743.
5. Bernheim, A., Berger, R. & Lenoir, G. (1981) *Cancer Genet. Cytogenet.* **3,** 307–316.
6. Croce, C. M., Shander, M., Martinis, J., Cicurel, L., D'Ancona, G. G., Dolby, T. W. & Koprowski, H. (1979) *Proc. Natl. Acad. Sci. USA* **76,** 3416–3419.
7. Erikson, J., Martinis, J. & Croce, C. M. (1982) *Nature (London)* **294,** 173–175.
8. McBride, O. W., Heiter, P. A., Hollis, G. F., Swan, D., Otey, M. C. & Leder, P. (1982) *J. Exp. Med.* **155,** 1680–1690.
9. Malcolm, S., Barton, P., Murphy, C., Fergusson-Smith, M. A., Bentley, D. L. & Rabbitts, T. H. (1982) *Proc. Natl. Acad. Sci. USA* **79,** 4957–4961.
10. Erikson, J., Finan, J., Nowell, P. C. & Croce, C. M. (1982) *Proc. Natl. Acad. Sci. USA* **79,** 5611–5615.
11. Dalla-Favera, R., Franchini, G., Martinotti, S., Wong-Staal, F., Gallo, R. C. & Croce, C. M. (1982) *Proc. Natl. Acad. Sci. USA* **79,** 4714–4717.
12. Swan, D. C., McBride, O. W., Robbins, K. C., Keithley, D. A., Reddy, E. P. & Aaronson, S. A. (1982) *Proc. Natl. Acad. Sci. USA* **79,** 4691–4695.
13. Dalla-Favera, R., Gallo, R. C., Giallongo, A. & Croce, C. M. (1982) *Science* **218,** 686–687.
14. Dalla-Favera, R., Bregni, M., Erikson, J., Patterson, D., Gallo, R. C. & Croce, C. M. (1982) *Proc. Natl. Acad. Sci. USA* **79,** 7824–7827.
15. Taub, R., Kirsch, I., Morton, C., Lenoir, G., Swan, D., Tronick, S., Aaronson, S. A. & Leder, P. (1982) *Proc. Natl. Acad. Sci. USA* **79,** 7837–7841.
16. Marcu, K. B., Harris, L. J., Stanton, L. W., Erikson, J., Watt, R. & Croce, C. M. (1983) *Proc. Natl. Acad. Sci. USA* **80,** 519–523.
17. Dalla-Favera, R., Martinotti, S., Gallo, R. C., Erikson, J. & Croce, C. M. (1983) *Science* **219,** 963–967.
18. Erikson, J., ar-Rushdi, A., Drwinga, H. L., Nowell, P. C. & Croce, C. M. (1983) *Proc. Natl. Acad. Sci. USA* **80,** 820–824.
19. Collins, S., Gallo, R. C. & Gallagher, R. (1977) *Nature (London)* **270,** 347–349.
20. Dalla-Favera, R., Wong-Staal, F. & Gallo, R. C. (1982) *Nature (London)* **299,** 61–63.
21. Nowell, P. C., Finan, J., Dalla-Favera, R., Gallo, R. C., ar-Rushdi, A., Romanczuk, H., Rovera, G. & Croce, C. M. (1983) *Nature (London)*, in press.
22. Erikson, J. & Croce, C. M. (1982) *Eur. J. Immunol.* **12,** 697–701.
23. Kohler, G. & Milstein, G. (1975) *Nature (London)* **256,** 495–497.
24. Margulies, D. H., Kuehl, W. M. & Scharff, M. D. (1976) *Cell* **8,** 405–415.
25. Dubbs, D. R. & Kit, S. (1964) *Exp. Cell Res.* **33,** 19–28.
26. Lenoir, G. M., Preud'homme, J. L., Bernheim, A. & Berger, R. (1982) *Nature (London)* **298,** 474–476.
27. Seabright, M. (1971) *Lancet* **ii,** 971–972.
28. Bobrow, M. & Cross, J. (1974) *Nature (London)* **251,** 74–79.
29. Neel, B. G., Jhanwar, S. C., Chaganti, R. S. K. & Hayward, W. S. (1982) *Proc. Natl. Acad. Sci. USA* **79,** 7843–7846.
30. Southern, E. M. (1975) *J. Mol. Biol.* **98,** 503–512.
31. Watson, R., Oskarsson, M. & Vande Woude, G. F. (1982) *Proc. Natl. Acad. Sci. USA* **79,** 4078–4082.
32. Sharp, P. A., Berk, A. J. & Berget, S. M. (1980) *Methods Enzymol.* **65,** 750–768.
33. Weaver, R. F. & Weissmann, C. (1979) *Nucleic Acids Res.* **7,** 1175–1193.
34. Watt, R., Stanton, L. W., Marcu, K. B., Gallo, R. C., Croce, C. M. & Rovera, G. (1983) *Nature (London)*, in press.
35. Stanton, L. W., Watt, R. & Marcu, K. B. (1983) *Nature (London)* **303,** 401–406.
36. Maniatis, T., Jeffrey, A. & van Sande, H. (1975) *Biochemistry* **14,** 3787–3794.
37. Maxam, A. M. & Gilbert, W. (1980) *Methods Enzymol.* **65,** 499–560.
38. Colby, W. W., Chen, E. E., Smith, D. H. & Levinson, A. D. (1983) *Nature (London)* **301,** 722–725.
39. Westin, E. H., Wong-Staal, F., Gelmann, E. P., Dalla-Favera, R., Papas, T. S., Lautenberger, J. A., Eva, A., Reddy, E. P., Tronick, S., Aaronson, S. A. & Gallo, R. C. (1981) *Proc. Natl. Acad. Sci. USA* **78,** 2490–2494.