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Genetics

Cellular homologs of the avian erythroblastosis virus *erb*-A and *erb*-B genes are syntenic in mouse but asyntenic in man

(viral oncogenes/gene mapping/microcell hybrids/conserved linkage group)

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ABSTRACT **Avian erythroblastosis virus, a retrovirus that causes erythroblastosis and sarcomas in infected birds, possesses two host cell-derived genes [viral (v) *erb*-A and *erb*-B]. Although v-*erb*-B seems to be responsible for oncogenic transformation, v-*erb*-A might have an enhancing effect on transformation. In chickens, the natural host for avian erythroblastosis virus, cellular (c) *erb*-A and *erb*-B genes appear to be unlinked, but their chromosomal locations in other species are unknown. To ascertain the chromosomal location of c-*erb* genes in man and mouse, we analyzed interspecies somatic cell and microcell hybrids by Southern filter hybridization techniques using specific v-*erb*-A and v-*erb*-B probes. We found c-*erb*-A sequences on human chromosome 17 (17p11 → qter) and located c-*erb*-B on human chromosome 7 (7pter → q22). In contrast, both c-*erb*-A and c-*erb*-B reside on mouse chromosome 11.**

Avian erythroblastosis virus (AEV) is a rapidly transforming retrovirus that induces erythroid leukemias and sarcomas in infected birds and transforms erythroblasts and fibroblasts *in vitro* (1). AEV requires a helper virus for replication, as portions of its genome have been substituted with two genetic loci [viral (v) *erb*-A and *erb*-B] that have been derived from the chicken genome and are responsible for viral oncogenesis (2). Transformation by AEV appears to arrest the development of erythroid precursor cells, and it has been suggested that the chicken cellular (c) *erb*-A and *erb*-B genes might function normally in the control of hematopoietic cell differentiation (3). An involvement of chicken c-*erb*-B in avian leukosis virus-induced erythroblastosis has been found in the form of activation of the proto-oncogene by avian leukosis virus promoter insertion (4). Although recent studies using *in vitro* mutagenesis techniques apparently indicate that the ability of AEV to transform both fibroblasts and erythroblasts resides solely in the v-*erb*-B locus, a role for v-*erb*-A in leukemogenesis has not been rigorously excluded (5). The v-*erb*-A gene may, in fact, have an enhancing effect on transformation in these cell systems (6).

Inasmuch as AEV is composed of two independent cell-derived sequences, it has been of interest to determine the molecular and chromosomal organization of the chicken c-*erb*-A and c-*erb*-B genes. The chicken c-*erb*-A and c-*erb*-B genes are carried on cellular DNA fragments that must be separated by a distance of at least 12 kilobase pairs (kbp), and the genes might be unlinked altogether (2).

Recently, isolation of c-*erb*-A and c-*erb*-B genes in man and their characterization in man and mouse have been described (7). To analyze the chromosomal organization of c-*erb* genes in man and mouse, we have used molecular probes specific for the v-*erb*-A and v-*erb*-B genes and filter hybridization of DNAs isolated from interspecies somatic cell and microcell hybrids. Although we found human c-*erb*-A and c-*erb*-B genes asyntenic on chromosomes 17 and 7, respectively, both mouse c-*erb* homologs were assigned to chromosome 11. Thus, in the mouse, c-*erb* genes are physically linked. Moreover, in humans, c-*erb* genes reside on chromosomes whose structural or numerical abnormalities are often associated with hematopoietic disorders (8).

MATERIALS AND METHODS

Somatic Cell Hybrids. The human–mouse somatic cell hybrids were constructed by the fusion of human fibroblasts or leukocytes (with normal karyotype or containing translocation chromosomes) with rodent cell lines (LMTK$^-$, RAG, or A9). The construction and characterization of these hybrid cell lines (WIL, REW, NSL, TSL, DUA, JSR, ATR, XER, XTR, JWR) have been described extensively elsewhere (9). In addition, hybrid cell lines containing single human chromosomes were used: DUA1CSAZF and DUA1CSAZH (chromosome 7), IT22xWeRi (chromosome 17; originally obtained from A. Bernstein).

The mouse–Chinese hamster somatic cell hybrids (EBS) were derived from the fusion of BALB/c mouse spleen cells with Chinese hamster V79 lung fibroblasts (clone E36) (10, 11). Their chromosome content has been described elsewhere (12). Additional hybrids (PBH) were constructed by the fusion of mouse spleen cells (F_1 of Peru–B10129) with Dona3 Chinese hamster cells lacking thymidine kinase activity (unpublished observations). By selecting PBH hybrids for retention of mouse thymidine kinase (*Tk*), portions of chromosome 11 encoding *Tk* were retained. The mouse microcell rat cell hybrid F(11)F constructed by microcell fusion (13) contained an intact mouse chromosome 11. Counterselection of F(11)F with BrdUrd yielded F(11)FR, which lacked both detectable *Tk* activity and mouse chromosome 11.

v-*erb*-A and v-*erb*-B Probes. Different domains from the region of AEV-11 encompassing v-*erb*-A and v-*erb*-B were used (2). Plasmid pAEPst contains a 0.5-kbp *Pst* I fragment originating from the v-*erb*-A locus, whereas plasmid pAE-BamRI contains a 0.5-kbp fragment from the 3′ region of the v-*erb*-B locus. Both recombinant plasmids were gifts of J. M. Bishop and colleagues.

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Abbreviations: AEV, avian erythroblastosis virus; kbp, kilobase pair(s).

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The 0.5-kbp v-*erb*-A probe was prepared by *Pst* I digestion of pAEPst. A *Bam*HI–*Pvu* II digestion of pAEBamRI yielded a 0.4-kbp v-*erb*-B probe without sequences of the flanking viral envelope region. Both inserts were purified by electroelution from agarose, followed by chromatography on NACS-52 resin (Bethesda Research Laboratories). The ^{32}P-labeled probes used for filter hybridization were prepared by nick-translation as described (14).

Filter Hybridization. Human and mouse c-*erb*-A and c-*erb*-B sequences were detected by filter hybridization methods (15) using cell hybrid DNA isolated at the same cell passage used for karyotyping and marker enzyme analysis (12). DNA isolation, restriction enzyme digestion, and agarose electrophoresis were performed as reported (12). Filters were hybridized with probe in a buffer containing 50% formamide, 0.75 M sodium chloride/75 mM sodium citrate, 1× concentrated Denhardt's solution [0.02% (each) polyvinyl pyrollidone, bovine serum albumin, and Ficoll 400], 20 mM sodium phosphate (pH 6.5), 10% sodium dextran sulfate, 0.1% NaDodSO$_4$, and 200 μg of sonicated, denatured salmon sperm DNA per ml for 48 hr at 30°C. Filters were rinsed briefly at 25°C in 0.3 M sodium chloride/0.03 M sodium citrate/0.1% NaDodSO$_4$ and then in 15 mM sodium chloride/1.5 mM sodium citrate/0.1% NaDodSO$_4$ for 30 min at 50°C. Filters were then exposed to Kodak XAR film at −70°C with Dupont Cronex intensifying screens.

RESULTS

Hybridization of Cellular DNAs to v-*erb*-A and v-*erb*-B Probes. The specificity of the v-*erb*-A and v-*erb*-B oncogene probes was examined by comparing the hybridization patterns obtained with mouse and human DNAs with DNA from chicken, whose c-*erb* genes have been characterized (2). The chicken *Eco*RI DNA fragments hybridizing with v-*erb*-A (20 and 5.5 kbp) and v-*erb*-B (12, 5.5, 3, 2, 1.3, and 0.5 kbp) (Fig. 1 *A* and *B*) are generally consistent with those reported by others (2, 16). The 20-kbp chicken DNA fragment hybridizing with v-*erb*-A has been observed in chicken DNA (2) but the minor 5.5-kbp fragment has not. Although the origin of hybridizing chicken DNA fragments not previously reported (2) is not clear, variations in c-*erb* hybridizing fragments have been observed in different chicken lines and even in individual members of a single chicken line (see ref. 4 and discussions therein). The v-*erb*-A probe hybridized strongly to a 10-kbp *Eco*RI fragment of human DNA and weakly to a 2-kbp fragment. Several minor human DNA fragments (≈3–4 kbp) that were poorly resolved and inconsistently detected with the v-*erb*-A probe probably result from the low-stringency hybridization conditions used (see *Materials and Methods*). Mouse DNA yielded hybridizing fragments of 23, 4.2, and 3.6 kbp (Fig. 1*A*). The v-*erb*-B probe hybridized principally to 7- and 6-kbp *Eco*RI fragments in human DNA and to a 2.4-kbp fragment of mouse DNA (Fig. 1*B*). Thus, human *Eco*RI fragments of unique mobilities could be used to identify c-*erb*-A and c-*erb*-B sequences in interspecies somatic cell hybrids.

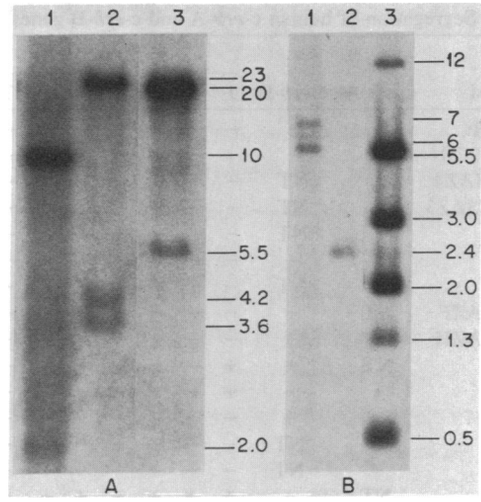

FIG. 1. Hybridization of v-*erb*-A and v-*erb*-B to *Eco*RI-cleaved cellular DNAs. Lanes 1–3 in *A* and *B* contain human, mouse, and chicken DNA (from White Leghorn chicken erythrocytes), respectively. (*A*) DNAs hybridized with v-*erb*-A. Major hybridizing fragments are 10 kbp in human and 23, 4.2, and 3.6 kbp in mouse. Chicken DNAs yield 20-kbp and 5.5-kbp hybridizing fragments. (*B*) DNAs (same as those in *A*) hybridized with v-*erb*-B. Hybridizing fragment sizes are 7 and 6 kbp (human, lane 1), 2.4 kbp (mouse, lane 2), and 12, 5.5, 3.0, 2.0, 1.3, and 0.5 kbp (chicken, lane 3).

Chromosome Assignment and Regional Localization of Human c-*erb*-A and c-*erb*-B Genes. The DNAs from 15 human–mouse somatic cell hybrids were cleaved with *Eco*RI and hybridized with the v-*erb*-A probe (Fig. 2*A*). The 10-kbp *Eco*RI human c-*erb*-A fragment was coordinately present or absent together only with human chromosome 17 in these enzyme- and chromosome-correlated cell hybrids, without

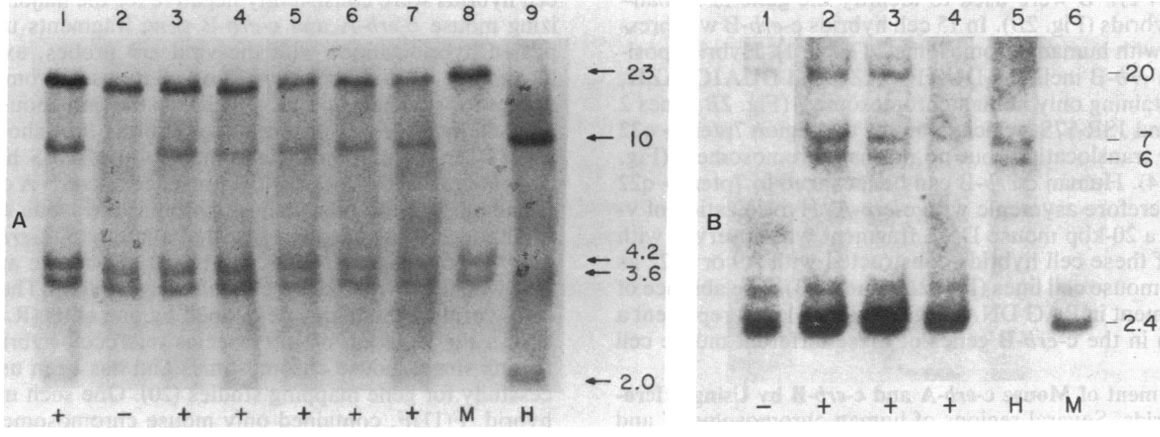

FIG. 2. Filter hybridization of v-*erb*-A (*A*) and v-*erb*-B (*B*) probes to cell hybrid DNAs cleaved with *Eco*RI. (*A*) The major hybridizing fragment in human DNA (lane 9) is 10 kbp, whereas mouse DNA (lane 8) yields hybridizing fragments of 23, 4.2, and 3.6 kbp. Lanes 1–7 contain DNAs from a set of human–mouse somatic cell hybrids (IT22xWeRi, XER-7, TSL-2, NSL-5, WIL-14, REW-10, and REW-12, respectively) either positive (+) or negative (−) for the 10-kbp *Eco*RI human c-*erb*-A1 fragment. (*B*) The v-*erb*-B probe hybridized to two major human *Eco*RI DNA fragments of 7 and 6 kbp (lane 5) and to a 2.4-kbp mouse (RAG) *Eco*RI DNA fragment (lane 6). The three cell hybrids positive for human c-*erb*-B (lanes 2–4) are DUA1CSAZF, DUA1CSAZH, and JSR-17S. Cell hybrid IT22xWeRi in lane 1 is negative for c-*erb*-B.

Table 1. Segregation of human c-*erb*-A and c-*erb*-B genes in human–mouse somatic cell hybrids

Cell hybrid	c-*erb*-A	c-*erb*-B	Chromosome composition																						Translocation chromosomes
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X	
IT22xWeRi	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	
MH21 15-2-20	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	
REW8ICSAZ4	+	NT	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	+	−	−	
REW8DCSAZ3	−	NT	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	
TSL-2	+	NT	−	+	−	−	+	+	−	−	−	+	−	+	−	−	−	−	−*	+	−	+	+	−	+	17/3
NSL-5	+	−	−	−	−	−	−	−	−	−	−	+	−	+	−	+	+	+	−*	+	−	+	−	−	−	17/9, 12q$^+$
NSL-16	+	NT	−	−	+	+	+	−	+	−	−	−	−	+	−	−	+	−	+	+	−	+	+	−	−	17/9, 9/17
DUA1CSAZF	NT	+	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
DUA1CSAZH	NT	+	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
JSR-17S	NT	+	+	−	+	−	+	−	−*	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	7q$^-$
REW-10	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	−	+	−	+	
REW-11	−	+	−	−	−	+	−	−	+	−	−	−	+	−	+	−	−	+	−	−	−	+	+	−	+	
REW-12	+	NT	−	+	+	+	−	−	−	+	−	+	+	−	+	+	+	+	+	+	−	+	+	−	+	
REW-13	+	NT	−	+	+	−	−	+	−	−	−	+	+	−	−	+	−	−	+	+	−	−	+	−	+	
REW-15	NT	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+	−	−	+	
WIL-14	+	−	−	−	+	−	−	−	−	+	−	+	−	−	−	+	−	−	+	−	−	−	−	−	+	
ATR-13	+	+	+	+	+	+	−	+	+	+	−	+	−	+	−	+	+	−	+	+	−	−	−	−	−	5/X
XER-7	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	−	+	+	−	−	+	+	11/X
XTR-22	−	−	−	+	−	+	+	+	−	+	−	+	+	−	−	−	−	−	−	+	+	+	+	+	−	X/3
JWR-22H	NT	−	−	−	−	−	+	−	−	−	−	+	+	−	−	+	−	−	+	+	−	+	+	−	−	2/1
JWR-26C	NT	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	−	+	+	−	+	+	1/2
% discordancy																										
With c-*erb*-A			60	53	27	60	53	53	60	53	60	33	60	40	60	33	40	60	0	33	73	53	53	87	40	
With c-*erb*-B			20	27	27	27	33	33	0	40	40	47	40	27	27	40	27	47	47	47	40	53	60	47	27	

The chromosome composition of each cell hybrid (indicated by a "+" or "−") is the consensus of enzyme assays of cell homogenates and karyotyping. Translocation chromosomes present in some cell hybrids are derived from human parental cells used for cell fusion and have been described (9). Hybrid JSR-17S contains the translocation chromosome 7pter → 7q22::9p24 → 9pter but no normal chromosome 7. The hybrid is positive for c-*erb*-B. Hybrid TSL-2 contains the translocation chromosome 17qter → 17p13::3p21 → 3pter, and hybrid NSL-5 contains the translocation chromosome 17qter → 17p11::9q12 → 9qter, but neither cell hybrid contains a normal chromosome 17. Both cell hybrids are positive for c-*erb*-A. The % discordancy between the presence in cell hybrids of a given chromosome and c-*erb*-A or c-*erb*-B is summarized at the bottom of the table. NT, not tested.
*See translocation chromosomes.

discordancy (Table 1). The hybrid ITT22xWeRi contained only human chromosome 17 (ref. 17; 2*A*, lane 1) and was positive for c-*erb*-A. Hybrid NSL-5 contained the region 17p11 → qter in a 17/9 translocation, but no normal chromosome 17, and was also positive for c-*erb*-A (Fig. 2*A*, lane 4). The hybridization intensity of the 2.0-kbp *Eco*RI human DNA fragment was too weak in cell hybrids to assess its segregation.

The 7- and 6-kbp human *Eco*RI DNA fragments hybridizing with v-*erb*-B were used to identify the gene in human–mouse hybrids (Fig. 2*B*). In 15 cell hybrids c-*erb*-B was present only with human chromosome 7 (Table 1). Hybrids positive for c-*erb*-B included DUA1CSAZF and DUA1CSAZH, both containing only human chromosome 7 (Fig. 2*B*, lanes 2 and 3), and JSR-17S, which contains the region 7pter → q22 (in a 7/9 translocation) but no normal chromosome 7 (Fig. 2*B*, lane 4). Human c-*erb*-B can be localized to 7pter → q22 and is therefore asyntenic with c-*erb*-A. Hybridization of v-*erb*-B to a 20-kbp mouse DNA fragment was observed with DNAs of these cell hybrids constructed with A9 or IT22 as parental mouse cell lines (Fig. 2*B*, lanes 1–3). The absence of this fragment in RAG DNA (Fig. 2*B*, lane 6) may represent a variation in the c-*erb*-B genes of these different mouse cell lines.

Assignment of Mouse c-*erb*-A and c-*erb*-B by Using Microcell Hybrids. Several regions of human chromosomes 7 and 17 encode genes whose mouse homologs appear to be syntenic. For example, genes for β-glucuronidase, malate dehydrogenase-2, argininosuccinate lyase, and phosphoserine phosphatase on human chromosome 7 have homologs located on mouse chromosome 5 (18). Genes for thymidine kinase (*TK*, human; *Tk*, mouse) and galactokinase (*GALK*, human; *Glk*, mouse) are located on human chromosome 17 and mouse chromosome 11 (18). We have described conserved linkage groups in man and mouse that include several proto-oncogenes (19) and were interested in determining if such a relationship existed for mouse c-*erb*-A and c-*erb*-B genes. Assignment of mouse c-*erb*-A and c-*erb*-B was attempted by using 15 well-characterized mouse–Chinese hamster EBS cell hybrids, previously used to assign five other cellular homologs of retroviral oncogenes (12, 19). The DNAs of these cell hybrids were consistently negative for the major hybridizing mouse c-*erb*-A and c-*erb*-B gene fragments upon repeated hybridizations with the viral *erb* probes, excluding location of c-*erb*-A and c-*erb*-B on all mouse chromosomes except for chromosome 11, which was the only mouse chromosome not present in this set of hybrids (not shown; see ref. 12 for the chromosome composition of EBS hybrids). The rate of discordancy for the presence of c-*erb*-A or c-*erb*-B and each of the other mouse chromosomes was ≥27%.

Although these results suggested synteny of c-*erb*-A and c-*erb*-B on mouse chromosome 11, an alternative approach that would provide positive results was sought. The microcell hybrid methodology developed by one of us (R.E.K.F.) allows the isolation of interspecies microcell hybrids containing single mouse chromosomes and has been used successfully for gene mapping studies (20). One such microcell hybrid, F(11)F, contained only mouse chromosome 11, encoding *Tk* whereas F(11)FR, counterselected with BrdUrd, lacked mouse chromosome 11.

DNAs of F(11)F and F(11)FR were cleaved with *Hin*dIII (Fig. 3*A*) or *Xba* I (Fig. 3*B*) and hybridized with v-*erb*-A and v-*erb*-B probes, respectively. The 13-kbp mouse *Hin*dIII c-*erb*-A fragment and the 9-kbp *Xba* I c-*erb*-B fragment were

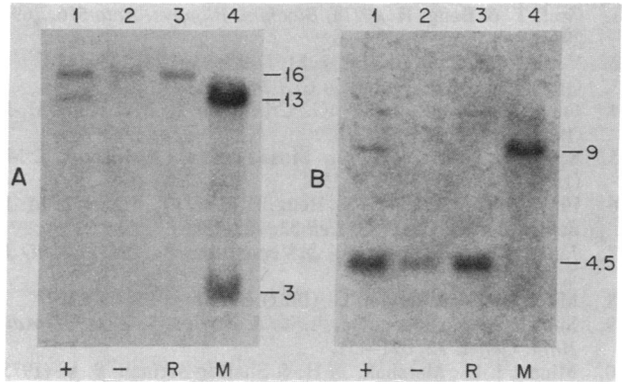

FIG. 3. Hybridization of rat–mouse microcell hybrid DNA to v-*erb*-A (*A*) and v-*erb*-B (*B*). Cellular DNAs in *A* (cleaved with *Hin*dIII) and *B* (cleaved with *Xba* I) are: lane 1, rat–mouse microcell line F(11)F containing only mouse chromosome 11; lane 2, hybrid F(11)FR, derived from F(11)F by counterselection using BrdUrd; lane 3, rat; lane 4, mouse. (*A*) The v-*erb*-A probe hybridizes strongly to a 13-kbp mouse *Hin*dIII DNA fragment and less intensely with a 3-kbp fragment (lane 4). A 16-kbp fragment is detected in rat DNA (lane 3). The 13-kbp mouse DNA fragment was coordinately present or absent with mouse chromosome 11 (lanes 1 and 2). (*B*) The v-*erb*-B probe hybridizes with a 9-kbp *Xba* I mouse DNA fragment (lane 4) and with a 4.5-kbp *Xba* I fragment of rat DNA (lane 3). The 9-kbp mouse c-*erb*-B DNA fragment was present or absent together with mouse chromosome 11 (lanes 1 and 2).

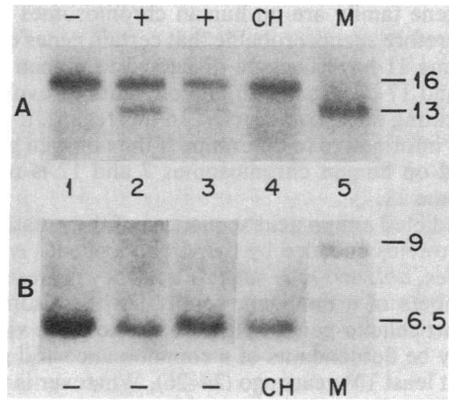

FIG. 4. Cellular DNAs from mouse–Chinese hamster hybrids (PBH) cleaved with *Hin*dIII (*A*) or *Xba* I (*B*) and hybridized to v-*erb*-A (*A*) and v-*erb*-B (*B*). The PBH hybrids contain fragments of mouse chromosome 11 and were also tested for mouse chromosome 11 markers thymidine kinase (*Tk*) and galactokinase (*Glk*). The results of the filter hybridization and enzyme analyses for three of the six PBH hybrids shown are as follows: lane 1, PBH-1 (Tk^+, Glk^-, c-*erb*-A^-, c-*erb*-B^-); lane 2, PBH-5 (Tk^+, Glk^-, c-*erb*-A^+, c-*erb*-B^-); lane 3, PBH-15 (Tk^+, Glk^-, c-*erb*-A^+, c-*erb*-B^-). Lanes 4 and 5 contain Chinese hamster DNA and mouse DNA, respectively.

both present in F(11)F and coordinately absent in F(11)FR (Fig. 3 *A* and *B*). These results established the localization of mouse c-*erb*-A and c-*erb*-B genes to chromosome 11. The 3-kbp *Hin*dIII fragment that hybridized less strongly than the 13-kbp fragment to v-*erb*-A (Fig. 3*A*, lane 4) was not observed in F(11)F even after prolonged exposure of filters to x-ray film. Elucidation of the relationship of the 3-kbp *Hin*dIII fragment to the 13-kbp *Hin*dIII c-*erb*-A fragment will require isolation of the mouse c-*erb*-A genes.

Another set of mouse–Chinese hamster cell hybrids (PBH) was examined to obtain additional data concerning the proximity of mouse c-*erb*-A and c-*erb*-B genes to two other mouse chromosome 11 markers, *Tk* and *Glk*. During passage in culture PBH hybrids had apparently suffered deletions in mouse chromosome 11 (unpublished observations). Whereas all PBH clones examined retained *Tk*, only some were Glk^+, indicating that chromosome breakage had separated these two syntenic markers. DNAs of PBH hybrids were hybridized to the v-*erb*-A and v-*erb*-B probes (Fig. 4 *A* and *B*). The results of filter hybridization and *Tk* and *Glk* assays of PBH hybrids were as follows: PBH-1 and -2, Tk^+, Glk^+, c-*erb*-A^-, c-*erb*-B^-; PBH-4 and -8, Tk^+, Glk^-, c-*erb*-A^-, c-*erb*-B^-; PBH-5 and -15, Tk^+, Glk^-, c-*erb*-A^+, c-*erb*-B^-. Thus, two of the six PBH hybrids (PBH-5 and -15) were positive for mouse c-*erb*-A, whereas all six were negative for mouse c-*erb*-B. The fact that mouse c-*erb*-A and *Glk* were present independently of each other suggests that they might reside on opposite sides of the *Tk* locus. However, since we have not presently excluded multiple breakage events in PBH hybrids, the topographical relationship of these four genes on mouse chromosome 11 remains to be established.

DISCUSSION

Several avian retroviruses have now been shown to possess two host cell-derived genes. These include AEV, MH2, and E26 isolates (21–24). In the case of AEV, the v-*erb*-A and v-*erb*-B genes are both assumed to function in inducing erythroblastosis and sarcomas in infected birds (3). In chickens, the natural host for AEV, c-*erb*-A and c-*erb*-B genes are separated by at least 12 kbp of DNA in the genome and might be unlinked entirely (2). Attempts to map the two genes to chromosomes have given contrasting results: both c-*erb* loci were located on chromosomes of intermediate size (using fractionation of chromosomes by rate-zonal centrifugation) or on the microchromosomes 10–12 (by *in situ* hybridization methods) (see ref. 24).

DNA sequences homologous to v-*erb*-A and v-*erb*-B, recently isolated from a human genomic DNA library by Jansson *et al.* (7), suggest the existence of at least two distantly related c-*erb*-A genes (c-*erb*-A1 and c-*erb*-A2) in human and mouse. The c-*erb*-A1 locus shares the greatest homology with v-*erb*-A and appears to be the gene assigned in the present study to human chromosome 17 and mouse chromosome 11. The fragments detected by Jansson *et al.* (7) with their human c-*erb*-A1 probe in *Eco*RI-cleaved human DNA and *Hin*dIII-digested mouse DNA were similar in size to those detected in our study (10 kbp and 13 kbp, respectively). In addition, the v-*erb*-A probe hybridized weakly to a 2.0-kbp *Eco*RI human DNA fragment (Fig. 1) most likely representing c-*erb*-A2-related sequences, detected by Jansson *et al.* (7) using their human c-*erb*-A2 probe. Hybridization to the 2.0-kbp human band was too weak to analyze its segregation in human–mouse hybrids, and we therefore do not know if c-*erb*-A2 is linked to c-*erb*-A1.

We used a v-*erb*-B probe to map c-*erb*-B in human–mouse hybrids by following the segregation of two major hybridizing bands (7- and 6-kbp fragments of human DNA cut with *Eco*RI) and localized c-*erb*-B on human chromosome 7 (7pter → q22). In mouse we localized c-*erb*-B to chromosome 11, thus clearly establishing physical linkage of c-*erb*-A and c-*erb*-B. Although linked, the physical distance between c-*erb*-A and c-*erb*-B in mouse must be significant, however, as the two PBH hybrid cell lines with a portion of mouse chromosome 11 that were positive for c-*erb*-A were negative for c-*erb*-B.

We anticipated the location of c-*erb*-A on mouse chromosome 11 as several other human chromosome 17 markers (*TK*, *GALK*, and sarcomeric myosin heavy chain genes *MYHSA1*, *MYHSA2*, and *MYHSE1*) reside on mouse chromosome 11 (17, 18). Some other data indicate a possible relationship of genes on human chromosomes 7 and 17. Although *MYHSA1*, *MYHSA2*, and *MYHSE1* are on chromosome 17, another cluster of myosin heavy chain genes, *MYH4*, was localized on chromosome 7 (18); members of the

collagen gene family are on human chromosomes 7 and 17 (18). It therefore seems probable that certain genes on mouse chromosome 11 have become dispersed to human chromosomes 7 and 17 during the 80 million years of evolutionary time separating these two species. In this regard, it would be especially informative to determine if the collagen gene family located on human chromosomes 7 and 17 is on mouse chromosome 11.

The predicted amino acid sequences of the putative transforming proteins encoded by the viral oncogenes *erb*-B, *src*, *yes*, *fps*, *fes*, *abl*, and *mos* suggest that they represent divergent members of a multigene family. At least some of the counterpart cellular genes that gave rise to these viral oncogenes may be descendants of a common ancestral gene that evolved at least 10^8 years ago (24–26). Whatever is the exact kinship of these cellular genes, they have become, by and large, dispersed in the genomes of man and mouse during evolution [c-*src*, human chromosome 20, mouse chromosome 2 (19, 27); c-*fes*, human 15, mouse 7 (28, 29); c-*abl*, human 9, mouse 2 (28, 30); c-*mos*, human 8, mouse 4 (31, 32)].

Although v-*erb*-A may enhance transformation by v-*erb*-B (3), it is unknown whether the normal c-*erb*-A and c-*erb*-B gene products might interact in the cell. This possibility can only be explored when the c-*erb*-A- and c-*erb*-B-encoded products are identified. Nevertheless, the chromosomal localization of c-*erb*-A and c-*erb*-B in humans could prove useful in analyzing possible rearrangements of these genes in malignancies with aberrations of chromosomes 7 and 17 (see ref. 33). Marker chromosomes $7q^-$ (with different long arm breakpoints) have been observed in myeloproliferative disorders and malignant lymphomas (8). In childhood preleukemia partial or total loss of chromosome 7 appears to be the most frequent change (34). Chromosome 17 is also frequently involved in secondary chromosome changes in tumor development (isochromosome 17q translocation involving chromosome 17 or extra chromosome 17), changes that might potentiate the malignant process by providing certain cell clones with a proliferative advantage (35). A consistent aberration involving chromosome 17 is observed in acute promyelocytic leukemia: a translocation between chromosomes 15 and 17 (36), t(15;17)(q22;q21) (18). In one case of acute promyelocytic leukemia that was examined, the c-*erb*-A gene was not rearranged (not shown; the acute promyelocytic leukemia cells were kindly provided by J. Rowley). In the mouse, to our knowledge, chromosome 11 has not been prominently involved in hematopoietic malignancies. However, murine cancers have not been extensively characterized karyotypically as have similar human cancers.

The predicted amino acid sequence of the putative transforming protein of v-*erb*-B was recently shown to bear homology with a portion of the human epidermal growth factor receptor (37). Based upon this homology, it seems possible that an epidermal growth factor receptor-like gene might reside on mouse chromosome 11. Assignment of c-*erb*-A and c-*erb*-B to human chromosomes 17 and 7, respectively, has now been reported independently (38).

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