Chromosomal Location of the Regulator of Mouse α-Fetoprotein, *Afr-1*

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ABSTRACT

Afr-1 is a gene whose product contributes to the adult regulation of mouse α-fetoprotein (AFP). In *Afr-1*$^{b/b}$ homozygotes, the adult serum levels of AFP are 10- to 20-fold higher than in *Afr-1*$^{a/a}$ or *Afr-1*$^{a/b}$ mice. The studies reported here were performed to map the *Afr-1* gene. Our results show that *Afr-1* resides on mouse chromosome 15, approximately 25 cM from *Gdc-1*. *Afr-1* appears to be located in close proximity to the mouse c-*myc* oncogene. These results are discussed with respect to the susceptibility or resistance of different BALB/c sublines (which are either *Afr-1*^{a} or *Afr-1*^{b}, respectively) to pristane-induced plasmacytomas.

ALPHA (α)-FETOPROTEIN (AFP) is the major serum protein of fetal animals. AFP is closely related to serum albumin, both evolutionarily and structurally (RUOSLAHTI and TERRY 1976; MORINAGA *et al.* 1983) and presumably in its function as well. AFP is replaced in the serum of neonatal mice by albumin over a period of a few months following birth. The normal mouse adult serum AFP levels are on the order of a few hundred nanograms per milliliter (OLSSON, LINDAHL and RUOSLAHTI 1977; BLANKENHORN *et al.* 1985).

The down-regulation of AFP synthesis in the neonate is developmentally controlled by genetic elements which are linked to the AFP structural gene on chromosome *5* (TILGHMAN and BELAYEW 1982). However, a second genetic element also controls adult serum levels of AFP in mice (OLSSON, LINDAHL and RUOSLAHTI 1977). This regulator of AFP (originally named *Raf-1*, and now designated as *Afr-1*) has two known alleles: a recessive allele named *Afr-1*^{b}, found in BALB/cJ mice, and *Afr-1*^{a}, found in all other strains tested, including all other sublines of BALB/c (OLSSON, LINDAHL and RUOSLAHTI 1977; BLANKENHORN *et al.* 1985). Linkage of *Afr-1* to other mouse chromosomal markers has remained elusive. We report here our results which indicate that *Afr-1* is on mouse chromosome *15*, in linkage with the genetic loci encoding glycerol-3-phosphate dehydrogenase (GPDH; EC 1.1.1.8) and the protooncogene, c-*myc*.

MATERIALS AND METHODS

Animals: Mice were bred and maintained in a closed, conventional mouse colony at Hazleton Laboratories, Rockville, MD, under NCI contract NO1 CB 25584. The mice were fed Purina Mouse Chow pellets and acidified tap water *ad libitum*. Mice in this colony occasionally have serum antibodies to Sendai and mouse hepatitis virus. Such mice are excluded from further analysis. The use of closed colony mice allows for confidence in the measurement of serum levels of AFP, as the mice are not stressed by displacement or other environmental influences.

Mice from three F_2 populations were analyzed: the first group was derived by mating (C57BL/6N × BALB/cJ) F_1 animals, abbreviated B6CJF2; the second F_2 mating was from (BALB/cJ × DBA2/n) F_1 mice, abbreviated CJD2F2; and the third mating from (BALB/cJ × CLA) F_1 mice (denoted CJCLF2). CIA is an inbred *Mus musculus domesticus* strain of mice recently derived from the wild (D'HOOSTELAERE and POTTER 1986). BALB/cJ has the genotype *Afr-1*$^{b/b}$, *Gdc-1*$^{c/c}$; DBA2/n, C57B1/6N, and CLA mice are *Afr-1*$^{a/a}$ and *Gdc-1*$^{b/b}$. CLA mice also carry a unique allele of the c-*myc* locus (provisionally designated *Myc-1* to distinguish it from other *myc*-related loci) which is not found in any other inbred mouse strain tested (HUPPI, DUNCAN and POTTER 1988).

Typing: The *Afr-1*^{b} allele is defined by the presence of high levels of AFP in adult mouse serum (OLSSON, LINDAHL and RUOSLAHTI 1977). AFP levels in sera from 10–15-week-old F_2 mice were determined by a solid phase radioimmunoassay (BLANKENHORN *et al.* 1985). The mean AFP level for *Afr-1*$^{a/-}$ mice was 200 ng/ml, with a range of 50–750 ng/ml; for *Afr-1*$^{b/b}$ mice, 4,000 ng/ml (range 1,200–11,000) ng/ml. *Afr-1* segregated in accordance with the predicted inheritance of single locus with one dominant and one recessive allele (Table 1). F_2 mice with the *Afr-1*$^{b/b}$ genotype were studied further for their inheritance of alleles of *Gdc-1* and, in (BALB/cJ × CLA) F_2 mice only, *Myc-1*. The likelihood of linkage between *Afr-1*, *Gdc-1*, and *Myc-1* was evaluated by χ^2 analysis.

Gdc-1 and *Myc-1* genotypes were determined by Southern blot analysis of kidney or liver DNAs from the *Afr-1*$^{b/b}$ homozygotes. *Gdc-1* displays a restriction fragment length polymorphism (RFLP), where the two alleles *Gdc-1*^{b} and *Gdc-1*^{c} are associated with *Pst*I restriction fragments of approximately 3.5 kB and 3.3 kB, respectively. The RFLP alleles for *Myc-1*^{a} found in BALB/cJ mice and *Myc-1*^{b} in CLA mice are associated with *Taq*I restriction fragments of 2.3 kB and 3.3 kB, respectively. High molecular weight DNAs were digested with the restriction enzymes according to the manufacturer's directions. Southern blots were performed using standard procedures, and the nitrocellulose filters were hybridized with a nicktranslated plasmid containing coding sequences of GPDH (KOZAK and BIRKEN-

TABLE 1

Typing

Parental genotypes:			
BALB/cJ	*Afr-1*^{b}	*Myc-1*^{a}	*Gdc-1*^{c}
C57B1/6	*Afr-1*^{a}	*Myc-1*^{a}	*Gdc-1*^{b}
DBA/2	*Afr-1*^{a}	*Myc-1*^{a}	*Gdc-1*^{b}
CLA	*Afr-1*^{a}	*Myc-1*^{b}	*Gdc-1*^{b}
Segregation of *Afr-1* in progeny:			
	Afr-1$^{b/b}$	*Afr-1*$^{a/-}$	*Ratio* ($a/-$: b/b)
B6CJF2[a]	40	139	3.5:1
CJD2F2[a]	47	141	3.0:1
CJCLF2[b]	21	75	3.6:1

[a] Results taken from Blankenhorn *et al.* (1985). Twenty-eight mice from the B6CJF2 and 24 mice from the CJD2F2 *Afr-1*$^{b/b}$ progeny were chosen at random for the present study.

[b] Results of (BALB/cJ × CLA)F_2 male progeny.

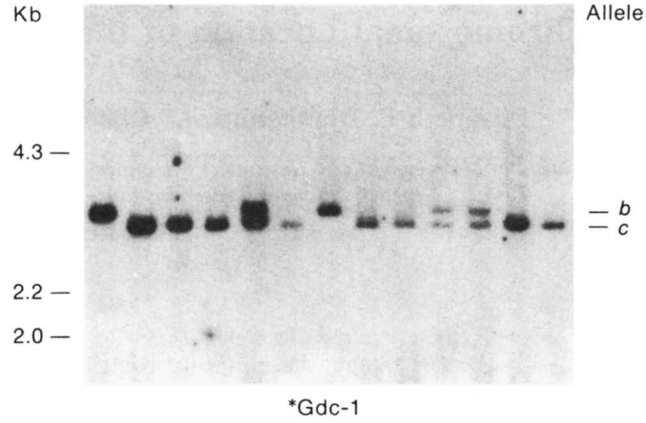

FIGURE 1.—Analysis of the segregation of *Gdc-1*. Autoradiogram of a Southern blot of *Pst*I-digested F_2 mouse DNA, after hybridization with the ^{32}P-labeled Gdc-1 probe. The samples shown here were chosen at random; the genotype *Gdc-1*$^{b/b}$ is represented in lane 1, and the genotype *Gdc-1*$^{c/c}$ is represented by the restriction fragment in lane 13.

MEIER 1983) for *Gdc-1* typing, and a *Bam*HI-*Pst*I fragment of p-c-*myc* 54 (STANTON, WATT and MARCU 1983) for typing alleles at the *Myc-1* locus. These plasmids were generously provided to us by L. P. KOZAK and K. MARCU.

RESULTS

We originally chose the *Gdc-1* marker to study its possible linkage to *Afr-1* because BALB/cJ differs from other BALB/c sublines in the expression of GPDH, the product of the *Gdc-1* locus, in brown adipose tissue (KOZAK 1985). Two regulatory loci (*Gdcr-1, Gdcr-2*) have been postulated to control the expression of *Gdc-1*, and we entertained the possibility that one of these might be located near the *Gdc-1* structural gene. Furthermore, it is an attractive hypothesis that at least some of the few differences known to exist between the BALB/c sublines might be clustered.

In a previous study (BLANKENHORN *et al.* 1985), 367 mice of two F_2 groups (B6CJF_2 and CJD2F_2) were scored for the inheritance of high or low adult levels of AFP. Because the *Afr-1*^{b} allele responsible for high adult serum levels of AFP is recessive, only the homozygous *Afr-1*$^{b/b}$ segregants were further analyzed. No genetic association was found between *Afr-1* and a variety of other markers typed in the CJD2F2-*Afr-1*$^{b/b}$ mice: *Pep-3* (chromosome *1*), *Idh-1* (*1*), agouti (*2*), *Pgm-1* (*5*), color (*7*), dilute (*9*) or *Es-3* and *Hba* (*11*) (BLANKENHORN *et al.* 1985). Liver DNAs were prepared from 28 B6CJF_2 mice and from 24 CJD2F_2 mice. The DNAs were digested with *Pst*I and subjected to Southern blot analysis. Filters were hybridized to the radiolabeled plasmid containing the structural gene for *Gdc-1* (Figure 1).

The results from the *Afr-1*$^{b/b}$-selected populations are given in Table 2. Because both parental alleles can be determined by the RFLP in F_2 mice scored for *Gdc-1*, the results can be expressed as recombination events/gamete. The B6CJF2 mice represented 18 recombinant gametes of 56 scored, providing an estimate of linkage distance of 32 cM. The CJD2F2 progeny exhibited 12 recombinant chromosomes of the 48 scored, for a map distance of 25 cM. The CJCLF2 progeny were also typed for both *Afr-1* and *Gdc-1*, and this cross also revealed a 24% recombination between the two markers (Table 2).

The combined results indicate a loose genetic linkage of 27 ± 4 cM between *Gdc-1* and *Afr-1* ($\chi^2 = 24$, $P < 0.001$). Because these markers are quite far apart, there is a likelihood that double crossover segregants are scored as parental combinations in this F_2 cross, thus 27 cM may be an underestimate of the distance between the two loci. Furthermore, because F_2 mice were used for this study, linkage analysis of selected *Afr-1*$^{b/b}$ progeny relies on the assumption that *Gdc-1* is segregating in a normal fashion in these animals, an assumption which is likely but was not tested in this work.

The CJCLF_2 cross was scored for a variety of marker loci: as expected, no genetic linkage was detected between *Afr-1* and genes on chromosomes *1, 3, 4, 5, 7,* or *11* (E. P. BLANKENHORN and R. DUNCAN, unpublished data; R. DUNCAN, R. MATTHAI, K. HUPPI, T. RODERICK and M. POTTER, unpublished data). Because CLA carries several polymorphic genes on chromosome *15* that distinguish CLA from BALB/cJ, we had the opportunity to screen these progeny for markers which are monomorphic in other inbred strains of mice. Of special interest was the polymorphism of the *Myc-1* protooncogene found on chromosome *15*. The recombination of this marker with *Afr-1* in the (CLA × BALB/cJ) F_2 progeny was 2.4%, indicating a very close linkage between the two genes (Table 3).

TABLE 2

Recombination of markers

Cross and class of gamete	No. of progeny	No. of gametes in class	No. expected[a]	χ^2 [b]
B6CJF$_2$-*Afr-1*$^{b/b}$				
Parental class: *Gdc-1*$^{c/c}$	14	38	28	7.1
Recombinant classes:		18	28	
Gdc-1$^{b/c}$	10			
Gdc-1$^{b/b}$	4			
CJD2F$_2$-*Afr-1*$^{b/b}$				
Parental class: *Gdc-1*$^{c/c}$	12	36	24	12.0
Recombinant classes:		12	24	
Gdc-1$^{b/c}$	12			
Gdc-1$^{b/b}$	0			
CJCLF$_2$-*Afr-1*$^{b/b}$				
Parental class: *Gdc-1*$^{c/c}$	13	32	21	11.8
Recombinant classes:		10	21	
Gdc-1$^{b/c}$	6			
Gdc-1$^{b/b}$	2			
Total:				
Parental type gametes		106	73	29.8
Recombinant gametes		40	73	($P < 0.001$)
Percent recombination = 27 ± 3.7%				

[a] Expected number of gametes in each class if *Afr-1* and *Gdc-1* were unlinked.
[b] χ^2 for gamete distribution with an expected 1:1 segregation if the two loci were unlinked.

DISCUSSION

Our interest in identifying and mapping genes that distinguish BALB/cJ from BALB/cAn relates in part to the difference between these two sublines in developing plasmacytomas. BALB/cAn and most other BALB/c sublines are highly susceptible to developing plasmacytomas (mean incidence ~60%) after the intraperitoneal injection of pristane (2,6,10,14-tetramethylpentadecane), while BALB/cJ mice are relatively resistant (mean incidence ~10%) (POTTER and WAX 1981). This relative resistance is a unique feature of the BALB/cJ subline and may be controlled by one of the few polymorphic genes which are known to distinguish BALB/cJ from the other BALB/c sublines.

The genetic difference between BALB/c sublines examined in the present study is *Afr-1*. BALB/cJ is unique among all inbred strains of mice by carrying *Afr-1*^{b}, an allele which greatly elevates the adult level of serum AFP. The physiological importance of the 10–20-fold increase in serum AFP levels in apparently healthy adult BALB/cJ mice is unknown. AFP itself is an oncofetoprotein, appearing normally during embryonic and fetal stages, and virtually disappearing in mice (other than BALB/cJ) during adult life. Abnormally high levels of serum AFP in mice are also found in association with the presence of hepatocellular carcinomas (ABELEV 1974) and during the regeneration of liver following trauma (PIHKO and RUOSLAHTI 1974), although this latter elevation is due to another, independent regulatory locus now known as *Afr-2* (BELAYEW and TILGHMAN 1982). Our results show that the *Afr-1* gene is located on mouse chromosome *15*.

TABLE 3

Gamete distribution

Cross: CJCLF2-*Afr-1*$^{b/b}$ Class of gamete	No. of progeny	No. of gametes	No. expected[a]	χ^2 [b]
Parental: *Myc-1*$^{a/a}$	20	41	21	38.1
Recombinant:		1	21	
Myc-1$^{a/b}$	1[c]			
Myc-1$^{b/b}$	0			
Percent recombination = 2.4%				

[a] Expected number of gametes in each class if *Afr-1* and *Myc-1* were unlinked.
[b] χ^2 value for gamete distribution, with an expected 1:1 segregation if the two loci were unlinked.
[c] Recombinant: *Afr-1*$^{b/b}$ . . . cross-over . . . *Myc-1*$^{b/a}$ . . . *Gdc-1*$^{b/c}$. All other recombinants in this cross were outside the *Afr-1–Myc-1* interval [see also HUPPI, DUNCAN and POTTER (1988)].

Other genetic differences between BALB/cJ and other BALB/c sublines have been reported. BALB/c sublines differ in their expression of *Qa-2*, an *H-2*-linked gene on chromosome *17* (ROGERS *et al.* 1985). Most of the other distinctions involve quantitative differences in the expression of a variety of enzymes. These include: three enzymes in the catecholamine synthetic pathway (CIARANELLO *et al.* (1974); two inducible enzymes involved in gluconeogenesis (COLEMAN 1980); and induced brown fat levels of GPDH

(Cook et al. 1986; Kozak 1985), which are *all* higher in BALB/cJ mice than in BALB/cAn-related sublines. In addition, we have found a difference in the pattern of mouse major urinary protein (MUP) excretion in the urine of BALB/cJ *vs.* BALB/CAnPt (Roderick, Langley and Leiter 1985; R. Duncan, R. Matthai, K. Huppi, T. Roderick and M. Potter, unpublished data).

The regulation of these tightly controlled enzymatic activities could be multigenic in nature, or could result from a single gene having multiple, transacting effects, or from a cascade effect in which a single gene deregulation triggers multiple secondary changes. Genetic mapping experiments to pinpoint the location of regulatory genes for the catecholamine synthesis and for gluconeogenesis would be helpful to distinguish these possibilities.

The proximity of *Afr-1* to c-*myc* is intriguing, and presents a possible explanation of how this mutation might "convert" a plasmacytoma-susceptible mouse strain (BALB/c An) to a resistant one (BALB/cJ). Over 95% of the tumors induced by pristane in BALB/cAn mice have chromosomal translocations involving regions in or near the *Myc-1* locus: about 70% are reciprocal translocations between chromosome *12* and *15* (rcpt *12;15*) and about 25% are rcpt *6;15* (Potter 1984). These translocations occur within the c-*myc* locus in the rcpt *12;15* tumors. In the case of rcpt *6;15* tumors, the region physically involved in the translocation is designated *pvt-1*, a locus that is located at least 90 kb downstream (3′) of c-*myc* (Cory *et al.* 1985).

Both types of translocation effect c-*myc* transcription (Cory *et al.* 1985). To date, no gene product from the *pvt-1* locus has been identified, although homologues of the *pvt-1* gene are found in the genomes of both rats (Villeneuve *et al.* 1986) and humans (Graham and Adams 1986; Mengle-Gaw and Rabbitts 1987). In humans, the *pvt-1*-like gene is 300 kb 3′ of the third exon of c-*myc*, and DNA fragments isolated from human tumors with amplified *myc* genes (amplicons) contain both c-*myc* and *pvt-1*-like sequences (Mengle-Gaw and Rabbitts 1987). This suggests that the continuity of DNA between c-*myc* and *pvt-1* is important for at least one step in the tumorigenic pathway. It is interesting to speculate that the mutation responsible for $Afr\text{-}1^{b}$ might modify this region in such a way that it decreases the probability of rcpt *12;15* or rcpt *6;15* translocations occurring.

In related studies, we have crossed BALB/cAnPt × BALB/cJ, and have developed a breeding stock designated BALB/cAn.J $Afr\text{-}1^{b/b}$. BALB/cAn.J $Afr\text{-}1^{b/b}$ mice, like BALB/cJ, are relatively resistant to plasmacytoma induction by pristane (Potter, Wax and Blankenhorn 1985, and unpublished observations), further indicating the importance of a gene or genes on mouse chromosome *15* in genetic resistance to plasmacytoma induction.

Linkage analysis of F_2 mice is more cumbersome than a similar study would be using backcross mice. The fact that three independent F_2 crosses (established with the aim of collecting information about other genes for which a BALB/cJ backcross was not particularly useful) gave the same result lends confidence to the map assignment. Preliminary studies of our F_2 progeny using probes diagnostic of other chromosome *15* markers [*Ly-6* and *sis* (Meruelo *et al.* 1987)] indicate a map order consistent with other published chromosome 15 maps (Blankenhorn *et al.* 1988).

It is very likely, based on our genetic mapping data and on the resistance profile of *Afr-1* congenic mice, that the *Afr-1* regulatory locus may provide a clue to these questions about the chromosomal events which precede malignant transformation of plasma cells. In this regard, the precise location of *Afr-1* in BALB/cJ mice, with respect to c-*myc*, *pvt-1*, and plasmacytoma resistance, is currently being studied in our laboratories. Furthermore, a precise map location would be the first step in a path leading to the identification of this unusual, *trans*-acting regulator of serum AFP levels.

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