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NOTES

Genetic Mapping of the Mouse c-*fms* Proto-Oncogene to Chromosome 18

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Chinese hamster × mouse somatic cell hybrids were analyzed by Southern blot hybridization with a probe specific for the cellular c-*fms* proto-oncogene. Results demonstrate that *Fms*, the genetic locus containing this sequence, maps to mouse chromosome 18. Mouse *Fms* is thus not linked to the same set of genes involved in growth regulation that human FMS is linked to.

Cellular DNA contains proto-oncogene sequences (c-*onc* genes) which have been identified largely by their homology with the transforming genes carried by the acute retroviruses, by their ability to transform NIH 3T3 cells, or by their frequent disruption in tumors by nonacute retroviruses (1). Oncogenesis is often associated with enhanced expression of these cellular sequences or with expression of mutant oncogenes. Although the normal physiological functions of most of these cellular sequences are unknown, similarities have been reported among the products of several oncogenes and specific cellular growth factors or their receptors (7). One of these proto-oncogenes, c-*fms*, was originally identified by its homology to the transforming gene v-*fms* (3, 5) carried by the McDonough strain of feline sarcoma virus (13). McDonough feline sarcoma virus induces fibrosarcomas in cats and morphological transformation of cultured cell lines. The cellular homolog of the viral oncogene c-*fms* is present in the DNAs of various species, and the c-*fms* gene product has now been identified as the receptor for the macrophage colony stimulating factor (CSF) M-CSF-1 or CSF-1 (18). The human *FMS* gene was recently mapped to a region of chromosome 5 which also contains the genes for interleukin-3, the granulocyte-macrophage-stimulating factor, CSF-1, and multi-CSF (16; M. M. Le Beau, UCLA Symp. Mol. Cell. Biol., 1987, in press). Disruptions in this chromosome are associated with myeloid disorders. These observations prompted us to determine the chromosomal map location of the *Fms* gene in the mouse to help determine its role, if any, in specific murine neoplasms.

To map *Fms* in the mouse, we analyzed DNAs from 45 hamster × mouse somatic cell hybrids by Southern blot hybridization (8, 19). The cell hybrids were derived from the fusion of E36 Chinese hamster cells with cells of three different mouse strains, BALB/c, NFS.*Akv-2*, and A/HeJ, as described previously (10–12). The mouse chromosome content of 23 hybrids was determined by Giemsa-trypsin banding. A total of 22 additional hybrids were typed for the presence of specific isozyme markers on 14 mouse chromosomes or for specific DNA sequences on 19 mouse chromosomes.

A molecularly cloned segment of the feline retroviral v-*fms* gene was kindly provided by C. Sherr (St. Jude Children's Research Hospital, Memphis, Tenn.) for use as a hybridization probe (19). This clone, pSM7C, contains approximately 0.4 kilobase pairs of human c-*fms* cloned from a partial *Mbo*I digest of placental DNA. When *Bam*HI digests of hamster and mouse genomic DNA were analyzed by Southern blot hybridization, each produced one major *fms*-reactive DNA fragment (Fig. 1). Hamster and mouse *fms*-specific DNA fragments could also be distinguished after digestion with *Sac*I, *Eco*RI, and *Hin*dIII (not shown).

DNAs from the 45 cell hybrids were analyzed, and 19 of the hybrids contained the 3.2-kilobase-pair mouse c-*fms* fragment (Fig. 1). Correlations with the chromosome content of these lines was done by using a program written to run on a MicroSoft Disk Operating System personal computer. This analysis showed that all hybrids with chromosome 18 contained c-*fms* and all the lines lacking this chromosome also

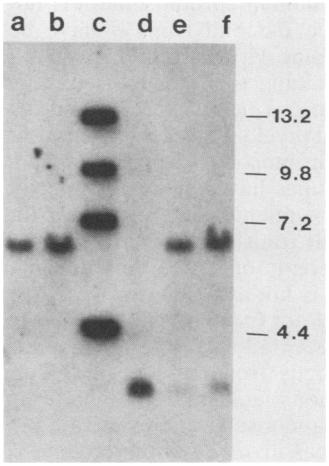

FIG. 1. Southern blot analysis of cell hybrid DNAs for *fms*-related sequences with pSM7C as hybridization probe. Lanes: a, hybrid HM31; b, Chinese hamster; c, markers; d, mouse; e, hybrid HM30; f, hybrid HM24. Sizes (in kilobase pairs) are indicated on the right.

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TABLE 1. Correlation among *Fms* and mouse chromosomes in 45 somatic cell hybrids

Mouse chromosome	No. of hybrid clones (*Fms* sequence/chromosome retention)				% Discordant
	+/+	−/−	+/−	−/+	
1	13	13	6	11	40
2	17	16	2	9	25
3	7	13	7	9	44
4	10	20	9	6	33
5	6	23	13	0	31
6	14	18	5	8	29
7	17	10	2	16	40
8	10	19	6	4	26
9	9	21	8	5	30
10	2	24	16	2	41
11	0	23	15	0	40
12	10	9	4	14	49
13	4	14	2	3	22
14	2	20	14	6	48
15	13	1	0	20	59
16	7	21	5	2	20
17	14	7	5	18	52
18	15	23	0	0	0
19	10	20	6	5	27
X	14	14	4	11	35

lacked the oncogene sequence (Table 1). Each of these DNAs was also typed by Southern blot analysis for the presence or absence of the mouse myelin basic protein from the shiverer locus (*shi*) on chromosome 18, kindly provided by L. Hudson and R. Lazzarini (National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, Md.) (14). There was a perfect correlation between presence or absence of this marker and *Fms*. Since no other chromosome showed any correlation with the *fms* sequence, the *Fms* oncogene locus can be assigned to mouse chromosome 18.

This genetic mapping confirms the partial homology which has been noted between mouse chromosome 18 and human chromosome 5. Both chromosomes are also known to contain *Fms*, as well as *Grl-1*, *Ii*, and *As-1* (2, 4, 15, 17); however, our data also indicate that the cluster of growth factor genes on human chromosome 5 is not maintained in the mouse, since *Il-3* and *Gm-Csf* have been mapped to mouse chromosome 11 (9). In humans, the region of chromosome 5 containing this cluster is frequently deleted in patients with various neoplastic myeloid diseases. Our results suggest that myeloid diseases in the mouse may involve sequences on chromosome 18 or chromosome 11.

Numerous studies have implicated specific oncogenes in the induction and maintenance of neoplastic disease in the mouse. Although translocations involving chromosome 18 are not characteristic of any murine malignancy, extensive karyotypic data is not available for many murine malignancies, particularly not for myeloid diseases. It has, however, recently been reported that insertional mutagenesis of the murine c-*fms* locus frequently occurs in Friend virus-induced myelogenous leukemia (6). Finally, our studies also located *Fms* on a mouse chromosome not previously shown to carry sequences involved in tumorigenesis in the mouse. This has practical implications, since it rules out the role of *Fms* as a *cis*-activated sequence in neoplastic diseases known to involve other chromosomes. It is hoped that knowledge of the chromosomal location of *Fms* will help focus additional studies on its possible involvement in malignant disease.

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