

# T Lymphomagenesis Is Determined by a Dominant Host Gene *Thymic Lymphoma Susceptible Mouse-1 (TLSM-1)* in Mouse Models

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## Summary

Susceptibility to T lymphomas in mice is determined by a number of viral and host genetic factors. We analyzed the types and latent period of lymphomas spontaneously occurring in crosses between AKR/Ms, a T lymphoma-prone mouse strain, and SL/Kh, a pre-B lymphoma-prone strain. The incidence of T lymphomas in the F<sub>1</sub> hybrids backcross to SL/Kh as well as F<sub>2</sub> generation mice indicated that a dominant host gene *thymic lymphoma susceptible mouse-1 (Tlsm-1)* of AKR/Ms determined the type of lymphomas to be thymic. Linkage analysis with microsatellite markers assigned *Tlsm-1* to the map position 61 cM from centromere of the chromosome 7. Close scrutiny of this region of AKXD recombinant inbred strains for spontaneous T lymphomas revealed the presence of *Tlsm-1*-like gene most likely between *D7MIT71* (map position 62) and *D7MIT13* (map position 70). On the other hand, a SL/Kh-derived recessive allele at a major histocompatibility complex (MHC)-linked locus accelerated development of both T and B lymphomas.

The tremendous recent increase in genetic markers has remarkably accelerated the search for genes involved in multifactorial diseases (1, 2). Considering extensive syntenic conservation of chromosomal segments across species, it becomes realistic to analyze animal disease models genetically to understand human diseases. Spontaneous thymic lymphomagenesis in mice is a multistep event involving complicated interactions between endogenous retroviruses and many host genes. This type of tumor occurs spontaneously in several laboratory strains of mice, most typically in AKR mice, and are readily induced by virus, chemical carcinogens, hormonal treatment, and X-rays. In this study, we asked the genetic basis of determination of types of spontaneous tumors to T lymphomas in mouse models.

AKR/Ms mice are highly susceptible to spontaneous T lymphomas; 80–90% of the individuals of this inbred strain succumb to this disease by 7–12 mo of age. Rowe et al. (3) found that endogenous ecotropic proviral loci, *Emv-11(Akv-1)* and *Emv-12(Akv-2)*, are etiologically essential. AKR endogenous ecotropic viruses, however, are only weakly lymphomagenic by themselves and the type of lymphoma seems not to be determined by virus alone, because *Emv-11* or *-12* congenic NIH-Swiss strain mice develop follicular center cell lymphomas (mature B lineage lymphoma) rather than T lymphomas (4). Thymotropic and leukemogenic virus in AKR is not encoded in germline: it is generated by successive recom-

binational events among three endogenous parental viruses (5, 6). First, an endogenous ecotropic virus, for example *Emv-11*, *-12*, or *-14*, acquires an *env* segment from a noncrotropic parent, and thus obtains a broader host range. Subsequently, this virus acquires an U3 long terminal repeat segment from xenotropic parent *Bxv-1* on chromosome 1 (Chr)<sup>1</sup>, generating thymotropic and lymphomagenic mink cell focus-forming (MCF) virus. Somatic integration of the MCF virus in several hot spots in host chromosome (7) is the most plausible explanation for T lymphocyte transformation. Resistance to this virus is conferred by a gene *Rmcf* (8), which is a truncated MCF-like *env* sequence, and probably competes for the viral receptor on the host cell surface (9).

On the other hand, the SL/Kh strain established in our laboratory as a subline of SL mice features an extremely early and high rate of spontaneous pre-B lymphomas, e.g., at almost 100% by 6 mo of age (10, 11). Out of six endogenous ecotropic proviral loci in SL/Kh, two are expressed, one of which seems to be identical to *Emv-11* (12). Expression of either of them is essential for lymphomagenesis. Despite high expression of both eco- and xenotropic viruses, however, MCF

<sup>1</sup> Abbreviations used in this paper: Chr, chromosome; d.f., degree of freedom; ICAM-1, intercellular adhesion molecule 1; LD, linkage disequilibrium; MCF, mink cell focus-forming; RI, recombinant inbred; *Tlsm-1*, *thymic lymphoma susceptible mouse-1*.

virus is not readily detected. Analysis of the backcross to NFS/N with microsatellite markers (12) revealed that a dominant gene *Esl-1* linked with SL/Kh MHC is required for acute pre-B lymphomas to develop and the homozygosity of a recessive gene *foc-1* on Chr 4 from NFS/N is required for follicular center cell lymphomas by ecotropic viruses.

The fact that AKR/Ms and SL/Kh mice share at least one ecotropic provirus *Emv-11* (12) and host genes affecting horizontal spread of ecotropic virus such as *Fv-1<sup>n</sup>* and *Fv-4<sup>s</sup>* (Hiai, H., unpublished data) may provide a simpler combination to analyze the genetic principle that determines types of disease. In a preliminary study, F<sub>1</sub> hybrids between AKR/Ms and SL/Kh preferentially developed T lymphomas. We analyzed the apparently dominant determinants of T lymphomas in backcross and F<sub>2</sub> generation and found an AKR-derived dominant gene on Chr 7 was the major determinant. The same genes seems to play the major role in several murine T lymphoma models including AKXD recombinant inbred (RI) strains.

## Materials and Methods

**Mice.** SL/Kh was an inbred strain of mice established in this laboratory (10). AKR/Ms, originally derived from AKR/J, was maintained in Saitama Cancer Center Research Institute (Saitama, Japan) by sister-brother mating over 100 generations. Reciprocal F<sub>1</sub> hybrids and backcrosses to SL/Kh were produced by appropriate matings. As no significant difference in incidence and types of spontaneous lymphomas was observed between reciprocal F<sub>1</sub> hybrids or among any of the four combinations of backcrosses to SL/Kh, data for reciprocal F<sub>1</sub> and those for all backcrosses were pooled. All in vivo experiments were done by H. Shisa at Saitama Cancer Center Research Institute in a specific pathogen free animal facility. All the mice were individually identified and carefully observed twice a week until 15 mo of age. Germline DNAs of AKXD recombinant inbred strains were obtained from The Jackson Laboratory (Bar Harbor, ME) and in part provided by Dr. H. Yonekawa (Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan).

**Type of Lymphomas.** The surface phenotype of lymphomas was analyzed by flow cytometry as described previously (11, 13). SL/Kh and AKR/Ms shared Thy1.1, a T cell differentiation antigen (10). The most reliable marker for T lymphomas was the expression of Thy1.1 and those for B lymphomas were B220, BP-1, and surface immunoglobulin expression.

**Microsatellite Analysis.** All primers for microsatellite analysis were purchased from Research Genetics (Huntsville, AL). DNA extracted from kidneys was used for genetic analysis. PCR and agarose gel electrophoresis of PCR products were described previously (12).

**Statistical Analysis.** The association of lymphoma susceptibility with alleles of the markers were evaluated by a chi-square test of independence (degree of freedom [d.f.] = 1) (14) of frequencies of heterozygous (AKR/SL) and homozygous (SL/SL) in T and B lymphoma-bearing mice. Associations were considered significant when  $\chi^2$  values exceeded 11.7 (a value significant to a 95% probability of linkage in mouse backcross). Gene order was determined by minimizing the number of recombination events among the allele distribution patterns of markers across the chromosome using GENE-LINK (15) and MAPMAKER (16). Three-point linkage analysis was performed in order to determine the most likely position of *thymic lymphoma susceptible mouse-1* (*Tlsm-1*) in backcross study as described in (17).

## Results

**Spontaneous Lymphomas in Crosses between AKR/Ms and SL/Kh.** In this study, we defined T lymphomas as those tumors expressing either Thy1.1, CD3, CD4, or CD8, and the B lymphomas as those having either cell surface immunoglobulin (sIg), B220, or BP-1 antigen. As shown in Table 1, among 84 lymphomas out of 91 (AKR/Ms  $\times$  SL/Kh)F<sub>1</sub> mice (overall incidence, 92.3%), 75 (89.3% of all tumors) were T lymphomas. Among 74 lymphomas out of 75 backcross mice to SL/Kh (incidence, 98.7%), 35 (47.3%) were T lymphomas, 34 (45.9%) were B lymphomas, and 5 (6.8%) mixed T and B lymphomas. Furthermore, among 144 lymphomas in F<sub>2</sub> mice (incidence, 90.0%), 96 (66.7%) were T, 38 (26.4%) were B, and 10 (6.8%) were mixed T and B lymphomas. The mode of segregation of individuals with T lymphomas, therefore, seemed best explained by assuming that a dominant gene of AKR/Ms strain determines T lymphomagenesis in backcross ( $\chi^2 = 0.35$ , d.f. = 1) and F<sub>2</sub> intercrosses ( $\chi^2 = 0.2$ , d.f. = 1) ( $p > 0.05$ ). We named this gene *Tlsm-1*. Development of a few B lymphomas in F<sub>1</sub> (9.9%) indicates that the penetrance of *Tlsm-1* is not complete. Both T and B lymphomas exhibited variable combinations of differentiation phenotypes as seen in FACS<sup>®</sup> analysis (Becton Dickinson & Co., Mountain View, CA) (Table 1).

**Microsatellite Analysis of Lymphoma Bearing Backcross Mice.** To identify and map *Tlsm-1*, we studied microsatellite markers in genomic DNA from 31 T lymphoma-bearing backcross mice and 28 B lymphomas. Any tumors without surface phenotype data or of mixed lineage origin were excluded from this mapping study. Out of some 250 microsatellite markers examined, 45 were polymorphic between AKR/Ms and SL/Kh. For screening, two to three markers were selected for each chromosome that covered ~56% of the total chromosomal region. As seen in Table 2 and Fig. 1, significant linkage disequilibrium (LD) was observed at 4 loci on Chr 7 (*D7MIT32*, *D7MIT40*, *D7MIT8*, and *D7MIT13*). In particular, at *D7MIT8* (map position 54), there was only one discordance among 31 T lymphoma-bearing backcross mice. Three-point analysis with *D7MIT32*, *D7MIT8*, and *D7MIT13* indicated that *Tlsm-1* is localized between *D7MIT8* and *D7MIT13*, maximum lod score at 7 cM distal on *D7MIT8*, e.g., 61 cM from centromere. The chromosomal region of one lod unit lower (1:10 likelihood) spanned from map position 57 to 64 (Fig. 2).

It was reported that a locus at centromere of Chr 3 had weak linkage with frequency of MCF-virus positive lymphomas in AKXD RI strains (19). In the present backcross, two loci on Chr 3, *D3MIT46* and *D3MIT21*, showed weak LD, however, statistically they were not significant ( $p = 0.0015$  and 0.025 respectively), when one took  $p = 0.0006$  as a limit of significance.

**Effect of MHC-linked Loci on Types of Lymphomas and Latent Period.** Our previous study showed that genetic predisposition to acute pre-B lymphomas in SL/Kh is associated with a dominant MHC-linked locus (12). In (AKR  $\times$  SL/Kh)F<sub>1</sub>  $\times$  SL/Kh, however, no statistically significant LD was observed for lymphoma types at the microsatellite marker *D17MIT21* linked to the D end of MHC (Table 2). The

**Table 1.** Phenotypes of Lymphomas in Crosses between SL/Kh and AKR/Ms Mice

Type of lymphomas	No. of mice (percentage tumors)		
	F <sub>1</sub>	Backcross	F <sub>2</sub>
<b>T lineage:</b>			
All T tumors	75 (89.3)	35 (47.3)	96 (66.7)
CD4 <sup>-</sup> CD8 <sup>-</sup>	3 (3.3)	10 (13.5)	12 (7.5)
CD4 <sup>+</sup> CD8 <sup>+</sup>	7 (7.7)	14 (18.9)	41 (25.6)
CD4 <sup>+</sup> CD8 <sup>-</sup>	11 (12.1)	2 (2.7)	13 (8.1)
CD4 <sup>-</sup> CD8 <sup>+</sup>	11 (12.1)	5 (6.8)	18 (11.3)
Probably T*	43 (47.3)	4 (5.4)	12 (7.5)
<b>B lineage:</b>			
All B tumors	9 (9.9)	34 (45.9)	38 (26.4)
sIg <sup>+</sup>	3 (3.3)	2 (2.7)	8 (5.0)
BP-1 <sup>+</sup> B220 <sup>+</sup>	0 (0)	26 (35.1)	16 (10.0)
Nonthymic <sup>†</sup>	6 (6.6)	6 (8.1)	14 (8.8)
Mixed B and T lineage	0 (0)	5 (6.8)	10 (6.3)
No tumor	7	1	16
All tumors/mice	84/91	74/75	144/160

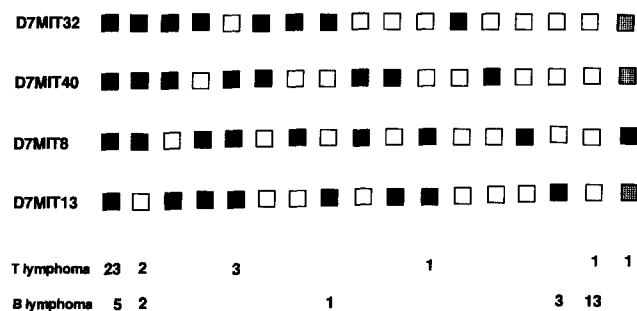
\* Diagnosis was made on the basis of macroscopically enlarged thymus or positive expression of Thy1.1, but further details of phenotype and/or DNA samples were not available. These cases were not included in the mapping study. In an earlier stage of this study, surface markers of F<sub>1</sub> tumors were not analyzed.

† Macroscopically identified as nonthymic lymphomas, but detailed phenotype data and/or DNA samples were not available.

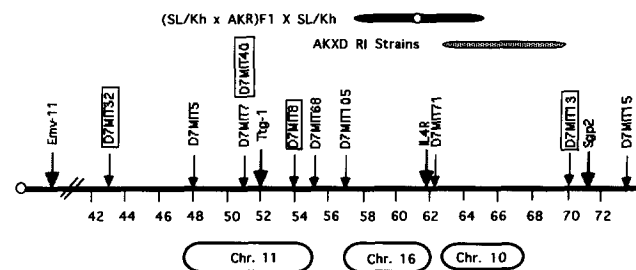
majority of B lymphomas in the backcross were acute pre-B lymphomas as seen in the parental SL/Kh strain. On the other hand, the length of the latent period of both T and B lymphomas was significantly shorter in the homozygotes of the SL/Kh-derived allele than in heterozygotes at this locus (Table 3). Therefore, a recessive MHC-linked gene of SL/Kh favored earlier occurrence of lymphomas irrespective of their types. All 16 F<sub>2</sub> mice and a backcross mouse that failed to develop any lymphoma by 18 mo of age were either heterozygotes or AKR-derived allele-homozygotes at *D17MIT21*. The latter observation also seems consistent to the concept of a MHC-linked recessive lymphoma accelerating gene in SL/Kh.

**Analysis of AKXD Recombinant Inbred Strains.** The AKXD strains are a set of RI strains between AKR/J and DBA/2J. Many AKXD RI strains developed a high incidence of spon-

aneous lymphomas of various pathological forms, depending on combinations of host and viral genomes contributed by either parental strain. We examined whether or not loci on Chr. 7 were involved in the lymphoma type determination. In Table 4, 20 AKXD RI strains are arranged in a descending order of T lymphoma incidence reported by Copeland et al. (19). Data on H-2 haplotype, *Rmcf* and percentage of tumors with somatically acquired MCF virus are also cited from their data (19). As seen in Table 4, at *D7MIT71* (map position, 62) most T lymphoma-prone AKXD RI strains (AKXD-



**Figure 1.** Haplotype analysis of loci near *Tlsm-1* locus in 55 lymphoma-bearing backcross mice. ■, Heterozygote; □, homozygote; and ▨, genotype not determined.



**Figure 2.** Multipoint linkage map of *Tlsm-1* and Chr 7 markers. Three-point linkage analysis was based on the linkage map (18) with the following order and genetic distance: *D7MIT32*- (11 cM)-*D7MIT8*- (16 cM)-*D7MIT13*. This analysis gave the maximum LOD score 10.9 at a map position 7 cM distal from *D7MIT8*. The LOD-1 confidence interval between *D7MIT8* and *D7MIT13* was shown by a solid bar. The hatched bar indicates the position of *Tlsm-1* estimated from AKXD RI strains. Shaded arrows indicate the position of *Emv-11*, *Tlg-1*, *IL4R*, and *Sgp2* (see text). Markers in square were those polymorphic between SL/Kh and AKR/Ms. Human chromosomes syntenic to mouse Chr 7 were shown by open rods.

**Table 2.** *Microsatellite Analysis of (AKR/Ms × SL/Kh) × SL/Kh Backcross Mice Bearing T or B Lymphomas*

Locus	Chromosome (map position in cM*)	Tumors with AKR/Ms-derived allele		$\chi^2$
		T lymphoma	B lymphoma	
D1MIT7	1 (35.0)	16/28	11/24	
D1Nds2	1 (46.0)	12/24	9/23	
D2MIT6	2 (11.0)	13/29	7/23	
D2MIT48	2 (66.0)	13/26	8/20	
D3MIT46	3 (37.0)	20/26	7/22	9.9
D3MIT21	3 (39.0)	19/26	8/20	5.1
D3MIT19	3 (100.0)	21/30	12/24	
D4MIT17	4 (31.0)	16/27	16/24	
D4MIT11	4 (53.0)	12/25	11/20	
D5MIT1	5 (9.0)	9/24	7/22	
D5MIT24	5 (52.0)	12/25	9/22	
D5MIT32	5 (77.0)	15/29	7/20	
D6MIT23	6 (53.0)	11/25	14/23	
D6MIT15	6 (74.0)	16/28	16/24	
D7MIT32	7 (43.0)	25/30	8/24	14.0
D7MIT40	7 (51.0)	28/30	7/24	24.1
D7MIT8	7 (54.0)	30/31	7/24	28.1
D7MIT13	7 (70.0)	27/30	9/24	16.5
D8MIT42	8 (59.0)	14/26	9/22	
D9MIT21	9 (35.0)	12/27	12/23	
D10MIT2	10 (13.0)	14/26	12/22	
D10MIT12	10 (60.0)	14/24	11/24	
D11MIT21	11 (24.0)	12/29	13/24	
D11MIT8	11 (45.0)	15/27	13/24	
D12MIT18	12 (64.0)	10/20	9/15	
D13MIT1	13 (17.0)	19/29	13/19	
D13MIT8	13 (48.0)	15/27	8/21	
D14Nds1	14 (3.0)	9/26	11/24	
D14MIT5	14 (15.0)	10/26	13/23	
D15Nds1	15 (19.0)	10/28	12/18	
D15MIT24	15 (22.0)	14/28	17/24	
D16Nds2	16 (30.0)	9/22	6/18	
D17MIT28	17 (17.0)	15/29	6/23	
D17MIT21	17 (19.0)	16/31	6/23	
D18MIT10	18 (28.0)	13/26	10/22	
D19MIT6	19 (42.0)	13/27	8/22	
DXMIT19	X (41.0)	11/28	7/22	

\* Map position in cM from centromere is cited from (18).

† Chi-square test (d.f. = 1). Only  $\chi^2$  values above 4 are shown.

21, 6, 26, 24, 22) except AKXD-12 had the AKR-derived gene, which extended to AKXD-18, 7, and 9. In the AKXD-12 RI strain with moderately high T lymphomas, a recombination was observed between *D7MIT71* (map position 62) and *D7MIT13* (map position 70). Allelic difference at a locus in this segment seemed strongly associated with the frequency

of T lymphomas. It is possible that RI strains with intermediate or lower incidence of T lymphomas (AKXD-18, 7, and 9) have AKR-derived allele at this locus and the lower incidence might be explained by assortment of other resistant genotypes at *H-2* and *Rmcf*, or less frequent acquisition of MCF virus. As shown in Fig. 2, the map position was

**Table 3.** Acceleration of Lymphoma Development by a SL/Kh Derived Allele of a MHC-linked Locus

Mice	Type of lymphomas	Average latency in days $\pm$ SD (No. of cases)			<i>p</i> *
		D17MIT21 <sup>AKR/AKR</sup>	D17MIT21 <sup>AKR/SL</sup>	D17MIT21 <sup>SL/SL</sup>	
AKR/Ms	T	257.2 $\pm$ 47.1 (40)	–	–	
SL/Kh	Pre-B	–	–	148.1 $\pm$ 31.6 (79)	
(SL $\times$ AKR) <sub>F</sub> <sub>1</sub>	T	–	246.7 $\pm$ 51.0 (74)	–	
F <sub>1</sub> $\times$ SL/Kh	T	–	257.3 $\pm$ 44.3 (16)	195.3 $\pm$ 49.8 (15)	<0.01
	Pre-B	–	241.0 $\pm$ 43.4 (6)	197.8 $\pm$ 38.1 (26)	<0.05

\* Significant in a *t* test.

in good consensus with that of *Tlsm-1* determined in the backcross study. Supposing that the gene responsible for T lymphoma in AKXD and *Tlsm-1* are identical, *Tlsm-1* is mapped in close vicinity of the *D7MIT71*. As far as we know, no MCF-related sequence has been reported in this region.

### Discussion

The type of spontaneous lymphoma in crosses between AKR/Ms and SL/Kh was demonstrated to be determined principally by the AKR/Ms-derived dominant gene *Tlsm-1* at the approximate map position 61 on Chr 7. Analysis of AKXD RI strains provided evidence supporting this conclusion.

A number of determinants of lymphomagenesis have been related to viral genome or its replication. An ecotropic virus, provirus *Emv-11*, is mapped at the proximal end of Chr 7 (Fig. 2). Judging from the map position as well as the size of the restriction fragment containing viral genome (12), SL/Kh mice are most likely to share *Emv-11* with AKR/Ms. Moreover, as seen in Table 1, the linkage to T lymphomas waned as markers were closer to the Chr 7 centromere, which means that *Emv-11* was unlikely to be a major determinant in this cross. In this region, as far as we know, no MCF-like sequence has been described. *Bxv-1*, a xenotropic parent yielding long terminal repeat segment to MCF virus, is mapped on Chr 1 (20). *Rmcf*, a resistant gene to MCF virus, is on Chr 5 (8). Therefore, these genes also seemed irrelevant.

The role of MCF virus in T lymphomagenesis had been studied in detail with RI mouse strains (7, 19, 21). In these strains, somatic integration of MCF virus favors occurrence of T lymphomas but is apparently not a sole determinant of whether the lymphoma is type T or type B. Alleles at *Rmcf* locus correlated with the length of the latency period but not with types of lymphomas (19). Examining 226 polymorphic loci in the AKXD RI strains, Copeland et al. (19) found that allelic differences at *Pmv-25* on Chr 4 and *Mtv-6* on Chr 16 are associated with frequent development of T lymphomas. However, association of T lymphomas with a host gene on Chr 7 has not been noted. In the present backcross study, we could not detect LD with Chr 4 and 16 markers (Table 2).

From the map position of *Tlsm-1*, we can mention genes for IL-4R (22, 23), LFA-1 (CD11a) (23), and leukosialin

(CD43) (24) as possible candidates. IL-4R, LFA-1 (CD11a), and leukosialin (CD43) are all involved in T cell activation. IL-4R is a 140-kD molecule composed of 785 amino acids. IL-4R has tyrosine kinase activity and binding of IL-4 triggers the phosphorylation of tyrosine residue of its cytoplasmic domain and support the proliferation of T cells. In AKXD RI strains, the IL-4R gene is mapped most likely between D7MIT105 and D7MIT71 (Table 4). LFA-1 (CD11a) is an integrin  $\alpha$  chain that is expressed as a heterodimer noncovalently associated with CD18 (integrin  $\beta$ 2). CD11a/CD18 binds to the NH<sub>2</sub>-terminal domain of intercellular adhesion molecule 1 (ICAM-1) (CD54) and to ICAM-2, and mediates cell–cell adhesion which is important in a wide range of leukocyte function including T and B cell proliferation. There are discrepancies on relative map position of IL-4R and CD11a genes (18, 23). Analysis with AKXL and BXC RI strains (23) indicates that CD11a gene is distal to IL-4R gene. CD43 is the major sialoglycoprotein of thymocytes and mature T cells. Its extracellular domain has been shown to interact with ICAM-1 (CD54), and CD43 enhances antigen-specific T cell activation. Based on consistent isolation of cellular complexes of lymphoma cells and thymic epithelial cells from primary lymphomatous thymuses and stroma-dependent growth of these lymphoma cells, we have proposed a hypothesis that cell interaction between developing lymphoma cells and thymic microenvironments is an essential step in thymic lymphomagenesis (25, 26). All of these candidate genes may well be involved in cell attachment in such complexes or in signaling to support growth of early T lymphoma cells, and therefore merit for further investigation. Another possible candidate is *Sgp2* (27), a gene encoding the lipopolysaccharide-induced serum glycoprotein, mapped at 71 cM (18). However, its map position is much distal from the position of *Tlsm-1* estimated either by backcross or RI strains.

In this particular region, host genes related to T lymphomagenesis have been described in several other experimental models. F344 strain rats develop a high incidence of T lymphomas when they are given the carcinogen propylnitrosourea (28), whereas most other strains develop erythroleukemias. Analysis of crosses between F344 and LE strain rats revealed that a single dominant gene *Tls-1* in F344 rats determine susceptibility to T lymphomas. In this cross, T lymphomas are associated with coat color genes albino (*c*) and pink-eyed di-

Table 4. Association of T lymphomas with Chr 7 Microsatellite Markers in AKXD Recombinant Inbred Strains\*

Recombinant inbred strain	Major type of lymphomas (percent fraction of T, B, M tumors)	H-2	R <sub>mcf</sub>	MCF	Emv-11	D7MIT53	D7MIT7	D7MIT8	D7MIT68	D7MIT105	IL-4R	D7MIT71	D7MIT13	D7MIT15
AKXD 21	T (100, 0, 0)	k	s	100	A	D	D	D	D	D	D	A	A	A
AKXD 6	T (85, 15, 0)	k	s	85	A	D	A	A	A	A	A	A	A	D
AKXD 26	T (82, 12, 0)	k	s	94	D	A	A	A	A	A	A	A	A	A
AKXD 24	T (69, 15, 0)	d	s	77	A	A	A	A	A	A	A	A	D	A
AKXD 12	T (67, 33, 0)	d	s	75	A	D	D	D	D	D	D	D	A	A
AKXD 22	T (57, 43, 0)	d	r	14	A	A	A	A	A	A	A	A	A	A
AKXD 18	(45, 55, 0)	d	r	55	A	A	A	A	A	A	A	A	A	A
AKXD 7	(40, 50, 0)	k	r	30	D	A	A	A	A	A	A	A	A	A
AKXD 9	(38, 54, 8)	d	r	38	D	D	D	D	D	D	D	A	A	A
AKXD 8	(38, 50, 0)	d	s	88	A	D	D	D	D	D	D	D	D	A
AKXD 3	(33, 40, 0)	k	r	0	A	D	A	A	D	D	D	D	D	D
AKXD 15	(33, 56, 11)	k	r	0	A	A	A	A	A	A	A	A	A	A
AKXD 27	B (23, 77, 0)	k	s	23	D	D	D	D	D	D	D	A	A	A
AKXD 10	B (20, 73, 0)	k	s	20	A	A	D	D	D	D	D	D	A	D
AKXD 16	B (13, 69, 0)	d	s	31	A	A	A	A	A	A	A	D	D	D
AKXD 13	B (13, 69, 0)	d	r	13	D	D	D	D	D	D	D	D	D	D
AKXD 23	M (10, 10, 70)	d	s	10	A	A	A	A	A	A	A	A	D	D
AKXD 2	B (9, 91, 0)	d	r	0	D	D	D	D	D	D	D	D	A	A
AKXD 14	B (8, 83, 0)	d	s	0	A	D	D	D	D	D	D	D	A	A
AKXD 11	B (0, 89, 0)	k	s	22	D	D	D	D	D	D	D	D	D	A

\* Data on lymphoma incidence, alleles of H-2 as well as R<sub>mcf</sub> and percent incidence MCF virus detection in AKXD RI strains are cited from Gilbert et al. (18). Tumor types: T, T lymphomas; B, B lymphomas; and M, myeloid leukemias. Data for IL-4R are from Suzuki et al (23). One of T lymphoma-prone RI strains AKXD 17 had been extinct and its DNA was no longer available. A, indicates AKR-derived allele, and D, DBA/2-derived allele.

lution (*p*) on Chr 1 and *Tls-1* is  $27.9 \pm 3.6$  cM distal to *p*. This segment gene is syntenic to the segment of mouse chromosome 7 (29), where we mapped *Tlsm-1*. Studying genetic determination of thymus size in spontaneous thymoma-prone BUF/Mna rats, Matsuyama et al. (30) recently mapped thymus enlargement-1 (*Ten-1*) in this region. Interestingly, in this rat system, another dominant gene *Tls-2*, independently assorted to *Tls-1*, determine the length of the latent period (28). Our recent study indicates that *Tls-2* is on rat Chr 20 bearing *RT-1* (rat MHC) (Shisa, H. and L. M. Lu, unpublished observations). In this study we identified a SL/Kh-derived recessive gene linked with MHC shortened latent period. It remained obscure, however, whether this gene was allelic to the mouse homologue of *Tls-2*. On the other hand, in the same chromosomal segment of the mouse, Angel et al. (31) mapped a dominant gene determining resistance to T lymphomas induced by methylnitrosourea. At present the map position of genes in other models is rather crude, so that it remains obscure whether genes with related functions cluster in a distal segment of Chr 7 or *Tlsm-1* is conserved across species and executes its function irrespective of its viral or chemical etiology. In the nearby segment of Chr 7, a T cell oncogene rhombotin (*Ttg-1*) has been mapped. *Ttg-1* is originally identified as a transcriptionally activated gene at the breakpoint region in t(11;14) (p15;q11) translocations of T cell acute lymphoblastic leukemias (32). Transgenic mice with an active *Ttg-1* transgene develop T lymphomas at a high incidence (33, 34). However, the *Ttg-1* is located 1.5 cM distal to *Hbb* locus (35), which is approxi-

mately 51.5 cM from the centromere. The most probable map position of *Tlsm-1* as shown in SL/Kh  $\times$  AKR/Ms crosses as well as in AKXD was 61 cM from centromere, which was  $\sim 10$  cM distal from *Ttg-1*. From a mouse-human comparative map, *Tlsm-1* human homologue could be assigned to human chromosome 16p11-13 or 10q. In 16p13, a frequent break point in M4 acute myelomonocytic leukemia is reported (36).

In (SL/Kh  $\times$  NFS/N) $F_1$   $\times$  NFS/N (12), we have shown that pre-B lymphomas are determined by a dominant MHC-linked gene of SL/Kh. In the backcross to AKR/Ms, pre-B lymphomas were slightly more frequent in homozygotes of SL/Kh allele at a MHC-associated locus than heterozygotes, although not statistically significant. However, the MHC-linked recessive gene significantly shortened the length of the latent period irrespective of the type of tumors. Our preliminary data indicate that the SL/Kh has a defect in the class II molecule (Ogawa, M., unpublished observations). The role of defects in immune response to virus or virus-infected cells has been well documented in experimental leukemias (37).

Until now it had been our belief that the type of spontaneous lymphomas in mice was determined by tissue tropism of murine leukemia virus. In this study, we showed that a host gene plays a major role in determination of types of lymphomas, although the role of virus as an initiating agent is by no means excluded. Supposing that the function of *Tlsm-1* is conserved across species, there is good reason to extend the study as an approach to genetic predisposition to T cell dyscrasias in humans.

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