Korean J. Medicinal Crop Sci. 14(2) : 96 – 100 (2006)

Candidate Tumor-Suppressor Gene Regions Responsible for Radiation Lymphomagenesis in F1 Mice with Different p53 Status

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ABSTRACT : Regions of allelic loss on chromosomes in many tumors of human and some experimental animals are generally considered to harbor tumor-suppressor genes involved in tumorigenesis. Allelotype analyses have greatly improved our understanding of the molecular mechanism of radiation lymphomagenesis. Previously, we and others found frequent loss of heterozygosity (LOH) on chromosomes 4, 11, 12, 16 and 19 in radiation-induced lymphomas from several F_1 hybrid mice. To examine possible contributions of individual tumor-suppressor genes to tumorigenesis in *p53* heterozygous deficiency, we investigated the genome-wide distribution and status of LOH in radiation-induced lymphomas from F_1 mice with different *p53* status. In this study, we found frequent LOH (more than 20%) on chromosomes 4 and 12 and on chromosomes 11, 12, 16 and 19 in radiation-induced lymphomas from (STS/A×MSM/Ms)F_1 mice and (STS/A×MSM/Ms)F_1-*p53*$^{KO/+}$ mice, respectively. Low incidences of LOH (10-20%) were also observed on chromosomes 11 in mice with wild-type *p53*, and chromosomes 1, 2, 9, 17 and X in *p53* heterozygous-deficient mice. The frequency of LOH on chromosomes 9 and 11 increased in the (STS/A× MSM/Ms)F_1-*p53*$^{KO/+}$ mice. Preferential losses of the STS-derived allele on chromosome 9 and wild-type *p53* allele on chromosome 11 were also found in the *p53* heterozygous-deficient mice. Thus, the putative tumor-suppressor gene regions responsible for lymphomagenesis might considerably differ due to the *p53* status.

Key words **:** *p53*, chromosome, lymphomaganesis, tumorigenesis, heterozygosity

INTRODUCTION

The Loss of Heterozygosity LOH regions often harbor tumor-suppressor genes in numerous malignancies in both human and experimental animals (Weinberg, 1991; Levine, 1993) Therefore, the search for the tumor-suppressor genes responsible for tumorigenesis has centered on LOH studies to demonstrate the molecular genetic mechanism underlying the tumorigenesis. Analyses of allelotype in radiation-induced tumors from F_1 hybrid mice of inbred strains have been performed by several groups, because they are very simple and all tumors are uniformly informative at a number of loci as to the location of the tumor-suppressor gene regions.

Extensive allelotype analyses have been performed for understanding of the molecular mechanism of radiation lymphomagenesis. Santos *et al.* (1996) suggested the existence of two tumor-suppressor gene regions, TLSR (*Thymic lymphoma suppressor region*) 1 and the more distal TLSR2, third region (TLSR3) centered at the marker *D4Mit54*, each homologous to the human chromosomal regions 9p21-22 and 1p32-36, respectively, in radiation-induced lymphomas of (C57BL/6J×RF/J) F_1 mice (Santos *et al.*, 1996). Also they found two additional tumor-suppressor gene loci, defined by the markers *D4Mit116* (TLSR4) and *D4Mit21* (TLSR5).

An extremely high frequency (more than 60%) of allelic loss closed to *D12Mit233* (Park *et al.* 2000) on distal chromosome 12 was observed in radiation-induced lymphomas from (BALB/cHeA×MSM/Ms)F_1 [(C×M)F_1] mice (Okumoto *et al.*, 1998; Matsumoto *et al.* 1998). Interestingly, this region is syntenic homologous to human chromosome 14q32-33, which region has been reported in a variety of tumors (Suzuki *et al.*, 1989; Young *et al.* 1993; Chang *et al.*, 1995; Cliby *et al* 1993; Bandera *et al.* 1997; Fujino *et al.*, 1994; Kovacs, 1993). Also the *Ikaros* gene on centromeric chromosome 11 has been suggested to be an important tumor-suppressor gene in those of mouse thymic lymphomas (Shimada *et al.*, 2000; Okano *et al.* 1999). Okumoto *et al.* also found frequent LOH on chromosome 19 with syntenic homology to human chromosomes 10q

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Received February 21, 2006 / Accepted April 20, 2006

and 11p in addition to the LOH on chromosomes 4 and 12 in the lymphomas from (BALB/cHeA×STS/A)F_1 [(C×S)F_1] mice (1999).

In this study, we performed an allelotype analysis in thymic lymphomas from (STS/A×MSM/Ms)F_1 [(S×M) F_1] and (STS/A×MSM/Ms)F_1-*p53*$^{KO/+}$ [(S×M) F_1 -*p53* $^{KO/+}$] hybrid mice. From these we investigated the frequent LOH regions and examined the effects of the *p53* status and genetic background of these mice group upon genome-wide features of LOH.

MATERIALS AND METHODS

Mice

STS/A-p53 KO/+mice were generated by back-crossing 129 p53-deficient mice with STS/A mice ten times. STS/A-p53 KO/+ mice were crossed with MSM/Ms mice to generate (S×M) F1 and (S×M) F1-p53 KO/+ offspring. The conditions for breeding were described previously (Okumoto *et al.*, 1998).

Induction of thymic lymphomas

Mice were exposed four times to X-rays of 1.7Gy (0.5Gy/min) with weekly intervals starting at 4 weeks of age, and the moribund mice were examined as previously described (Okumoto *et al.* 1990).

DNA isolation and LOH analysis

Developed lymphomas and normal tissues were removed. The isolation of DNA, PCR of microsatellite markers, electrophoresis of PCR products and assessment of allelic losses were performed according to a procedure described previously (Okumoto *et al.*, 1990). Oligonucleotide primers corresponding to microsatellite loci were purchased from Research Genetics, Inc. (Huntsville, AL). The chromosomal locations of the microsatellite markers and several loci were based on the 2000 Chromosome Committee Reports in the Mouse Genome Database (Mouse Genome Informatics; Jackson Laboratory, Bar Harbor, ME). Representative profiles for polyacrylamide gel electrophoresis of PCR products at microsatellite loci of DNA from normal and tumor tissues are shown in Fig. 1.

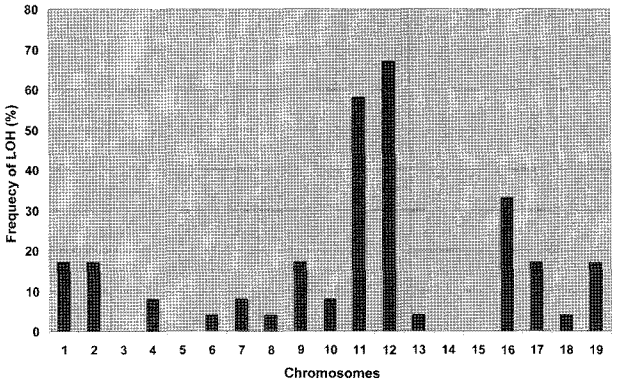

Fig. 1. Representative profiles for polyacrylamide gel electrophoresis of PCR products at microsatellite loci of DNA from normal and tumor tissues. Allelotypes at microsatellite loci *D13Mit14, D19Mit80* and *D19Mit71* are shown. Lanes marked STS and MSM contain normal liver DNA; Normal liver DNA (N174) and tumor DNA (T173) were obtained from the same mouse. T169 and T175 to T208, tumor DNA.

RESULTS

Genome-wide search for LOH in thymic lymphomas from (S×M) F1-p53 KO/+ mice

Mice at 81 polymorphic microsatellite loci Table 1 gives the frequency of LOH at each locus as shown in Table 1. Highly

Table 1. Allelotype analysis of the LOH regions in lymphomas from (S×M) F1-p53KO/+ mice and (S×M) F1-p53+/+ mice.

		p53KO/+				p53+/+			
		Number of	Number with	STS/A	MSM/Ms	Number of	Number with	STS/A	MSM/Ms
Chrs	Loci (cM)	tumors tested	LOH (%)	allele loss	allele loss	tumors tested	LOH (%)	allele loss	allele loss
4	D4Mit54 (66)	24	2 (8)	2	0	20	5 (25)	5	0
9	D9Mit10 (49)	87	14 (16)*	13***	1	24	0 (0)	0	0
11	D11Mit1 (0.25)	24	14 (58)**	0	14****	20	3 (15)	1	2
12	D12Mit233 (52)	45	34 (76)	15	19	20	12 (60)	8	4
16	D16Mit4 (27.3)	24	8 (33)	1	7	20	2 (10)	2	0
19	D19Mit80 (22)	123	29 (24)	17	12	24	2 (8)	1	1

Statistical comparison of the incidence of LOH or allele loss was carried out by x^2 analysis or Fishers exact probability test.
* P< 0.05 compared to the incidence of LOH (%) on chromosome 9 in mice with $p53^{+/+}$.
** P< 0.005 compared to the incidence of LOH (%) on chromosome 11 in mice with $p53^{+/+}$.
*** P< 0.002 compared to MSM/Ms allele loss in Lymphomas from (STS/A X MSM/Ms) F1-$p53^{KO/+}$ mice.
**** P< 0.001 compared to STS/A allele loss in Lymphomas from (STS/A X MSM/Ms) F1-$p53^{KO/+}$ mice.

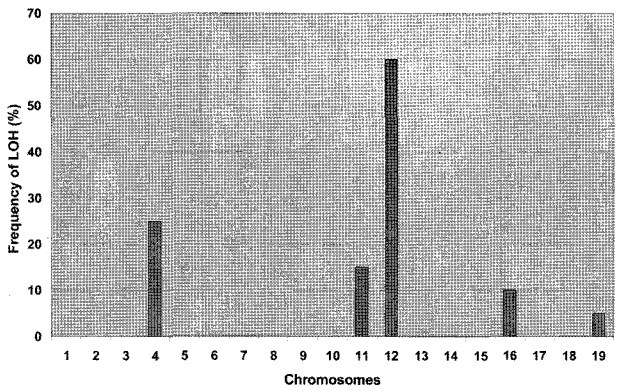

Fig. 2. Genome-wide search for LOH in 24 radiation-induced thymic lymphomas from (STS/A×MSM/Ms) F1-p53 KO/+ mice. The maximum frequency obtained on each chromosome is shown. The loci at which the frequency is shown are as follows: *D1Mit1* (8 centimorgans from the centromere: 8.7 cM), *D2Mit208* (76.7 cM), *D3Mit11* (49 cM), *D4Mit54* (66 cM), *D5Mit9* (54 cM), *D6Mit11* (49.4 cM), *D7Mit16* (40.00 cM), *D8Mit80* (41 cM), *D9Mit24* (56 cM), *D10Mit15* (35 cM), *D11Mit1* (0.25 cM), *D12Mit233* (52 cM), *D13Mit14* (10 cM), *D14Mit31* (28 cM), *D15Mit123* (30.6 cM), *D16Mit4* (27.3 cM), *D17Mit1* (56.7 cM), *D18Mit49* (49 cM), *D19Mit63* (35 cM).

frequent peaks were found at *D12Mit233* (52 cM from centromere) to *D12Mit263* (58 cM), *D11Mit1* (0.25 cM) near *Znfn1a1* (*Ikaros*), *D11Mit4* (37 cM) near *p53* and *D16Mit74* (9.7 cM) to *D16Mit4* (27.3 cM); the frequencies of LOH at these regions or loci were 67, 58, 50 and 33%, respectively. LOH with a lower incidence was also observed in several regions; four lymphomas out of 24 had LOH at *D1Mit1* (8.7 cM), *D2Mit208* (76.7 cM), *D9Mit12* (55 cM) to *D9Mit17* (62 cM), *D17Mit18* (4 cM), *D17Mit1* (56.7 cM), *D19Mit80* (22 cM) to *D19Mit71* (54 cM) and *DXNds1* (17 cM) to *DXMit1* (29.01 cM) (Fig. 1).

Genome-wide search for LOH in thymic lymphomas from (S×M) F1-p53 +/+ mice

Allelic losses were examined for 20 thymic lymphomas from (S×M) F1 mice bearing wild-type *p53* at 26 microsatellite loci covering the LOH regions observed in (S×M) F1-*p53 KO*/+ mouse lymphomas (Fig. 2).

Allelotype analysis of the LOH regions in lymphomas from (S×M) F1-p53KO/+ mice and (S×M) F1-p53+/+ mice

We compared the frequencies of the loss of the alleles derived from each parent in tumors. Preferential losses of STS-derived alleles on chromosome 9 and MSM-derived wild-type *p53* alleles on chromosome 11 were found in (S×M) F1-*p53 KO*/+ mice. LOH on chromosome 9 was significantly more frequent in the *p53* heterozygous-deficient mice in addition to the LOH on chromosome 11 mentioned above. Of 87 lymphomas, 14 (16%) showed LOH at *D9Mit10* (49 cM) on chromosome 9 in the *p53*-deficient mice, while none of 24 lymphomas had allelic loss in wild-type mice (Table 1).

DISCUSSION

Malignant lymphomas are considered to develop through a multi-step genetic process (Kim *et al.*, 2002; Chung *et al.*, 1999; Moon and Zee 1999) and to be efficiently induced by genetic events brought about by irradiation. In an epidemiological study, few events are supposed to be directly involved in the leukemogenesis compared with those which occur in solid tumors (Armutage and Doll, 1954). To identify the genes involved in the development of leukemia/lymphoma, we studied radiation-induced lymphomas in mice. Also, to detect tumor-suppressor genes involved in the lymphomagenesis, we analyzed allelotypes in the tumors from F_1 hybrid mice.

The two hybrids, (S×M) F_1-*p53* $^{KO/+}$ and (S×M) F_1-*p53* $^{+/+}$, used in this study, differed considerably in the latent period of lymphoma development. X-irradiated female (S×M) F_1-$p53^{+/+}$ mice first developed thymic lymphomas about 4 months after the last irradiation, and thereafter the lymphomas were induced frequently from 6 to 10 months after the last irradiation (data not shown). The mean latent period of lymphoma development was 252 ± 36 days (95% confidence interval by *t* test). Incidences of the tumors reached 33% (20/60) at 1 year after the last irradiation. On the other hand, in irradiated female (S×M) F_1-$p53^{KO/+}$ mice, the lymphomas were first observed after about 3 months, and were induced most frequently from 3.5 to 7 months after the last irradiation (data not shown). The mean latent period was 147 ± 12 days. The incidences of the tumors reached 32% (19/59) 1 year after the last irradiation. The $p53^{+/+}$ mice developed lymphomas about 3.5 months later than $p53^{KO/+}$ mice. Thus, *p53* heterozygous deficiency shortened the latent period of tumor development. The shortening of this period in (S×M)F_1-$p53^{KO/+}$ mice might be mainly due to the highly frequent and preferential loss of MSM-derived wild-type *p53*alleles (Table 1) as well as an increased incidence of LOH in several other regions (Fig. 2).

The frequency of LOH at *D9Mit10* (49 cM) on chromosome 9 was significantly increased in the (S×M)F_1-*p53* $^{KO/+}$ mice, and a preferential loss of STS/A-derived alleles at this locus was found. The STS/A mouse is extremely resistant to radiation lymphomagenesis (Okumoto *et al.*, 1989). We previously found STS/A-specific preferential allelic loss on chromosome 4 in (CXS) F_1 where the lymphoma resistance locus has been suggested to exist by analyzing CXS recombinant inbred strains (Okumoto *et al.* 1999). A susceptibility locus for

the lymphomagenesis was recently reported using the same BALB/cHeA and STS/A mice (Mori *et al.* 2000). An analysis of the underlying genes for susceptibility to ionizing radiation is relevant for radiation oncology (Tauchi, 2000). The region lost around *D9Mit10* might also contain gene (s) that modify the resistance to radiation lymphomagenesis. *Pml* (promyelocytic leukemia) and *Mlh1* (*mutL* homolog 1) have been mapped near this region on chromosome 9. The fact that LOH on chromosome 9 increased in *p53* heterozygous-deficient mice suggests that the loss of function of the putative tumor-suppressor gene on chromosome 9 cooperates with *p53* deficiency for lymphomagenesis.

Although LOH at *D16Mit4* (27.3 cM) on chromosome 16 was also more common in the (S×M)F_1-*p53*$^{KO/+}$ mice, no bias in the loss of alleles was found at this locus. In (C×M)F_1-*p53*$^{KO/+}$ mice, frequent allelic loss in the centromeric region around (D16Mit122/D16Mit162) of chromosome 16 has been found, and the frequency is raised by the existence of *p53*-deficient allele (Matsumoto *et al.*, 1998). LOH is reported around *D9Mit355* (53 cM) and *D16Mit57* (21.5 cM)in islet cell carcinomas arising in transgenic mice and referred to as *Loh1* and *Loh2*, respectively (Parangi *et al.*, 1995). It is also suggested that *Loh1*contributes to the progression from the angiogenic stage to a solid tumor and that *Loh2* contains an angiogenic suppressor. It is unclear whether *Loh1* and *Loh2* contain identical tumor-suppressor genes to our LOH regions.

The most frequent LOH on chromosome 12 occurred in all crosses tested, and has syntenic homology to human chromosome 14q32-33. LOH of 14q has been observed in a variety of human tumors such as neuroblastomas (Suzuki *et al.*, 1989), advanced colorectal carcinomas (Young *et al.*, 1993), bladder cancers (Chang *et al.*, 1995), ovarian carcinomas (Cliby *et al.*, 1993), renal cell tumors (Kovacs, 1993) and endometrial carcinomas (Fujino *et al.*, 1994). Recently, Kominami reported *Rit1*coding a transcription factor, as a novel candidate for a tumor-suppressor gene at the common allelic loss region on the distal chromosome 12 of mice (Kominami, 2000). However, sequence information on the gene has not yet been released.

Twenty-nine (24%) of 123 lymphomas exhibited LOH at *D19Mit80* (22 cM) on chromosome 19 in (S×M)F_1-*p53*$^{KO/+}$ mice (Table 1). The region was observed to encompass *D19Mit80* (22 cM) to *D19Mit71* (54 cM) (Fig. 1). This wide area may contain more than one tumor-suppressor gene. Chromosome 19 is homologous to human chromosomes 10q23-q26, 9 and 11q11-q13. Human chromosome 10q23-q26 contains putative tumor-suppressor genes, such as *PTEN / MMAC1* (Li *et al.* 1997; Derr *et al.*, 1998; Steck *et al.* 1997) and *MXI-1* (Tamura *et al.* 1998). *PTEN*, a protein tyrosine phosphatase gene, of human chromosome 10q23.3, is mutated at a considerable frequency in brain, breast, and prostate cancer (Li *et al.*, 1997; Tamura *et al.*, 1998). Mutations and deletions of *MMAC1* at chromosome 10q23.3 were observed in multiple advanced cancers, such as glioma, prostate, kidney and breast cancers (Steck *et al.*, 1997). Mice lacking *Mxi1 (Mad)* (10q24-q25) exhibit increased susceptibility to tumorigenesis either following a carcinogen treatment, or when also missing *Ink4a* (Schreiber *et al.* 1998). Human chromosome 11q13 contains the multiple endocrine neoplasia type-1 (*MEN1*) gene, which is frequently mutated in familial MEN1 tumors and some sporadic endocrine tumors (Chandrasekharappa *et al.*, 1997).

Acknowledgment

This work ws supported by the Ministry od Science Technology through the Bio Food and Drug Research Center at Konkuk University and BioGreen 21 Program the rural development administration, Korea. The author deeply appreciate these support

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