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A deletion mutation of the protein tyrosine phosphatase kappa (*Ptprk*) gene is responsible for T-helper immunodeficiency (*thid*) in the LEC rat

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Abstract Bone marrow (BM)-derived T-cell progenitors differentiate into CD4 or CD8 single-positive (SP) cells in the thymus. We have previously reported that a single autosomal mutation, *thid*, causes a defect in the maturation of CD4 SP thymocytes and an abnormality of peripheral helper T cells in the LEC rat. In this study we attempted to identify a gene responsible for the *thid* mutation. We first performed genetic linkage analysis and mapped the *thid* locus between *Myb* and *D1Rat392* on Chr 1. In this region we found an approximately 380-kb deletion from intron 3 of the *Ptprk* gene, which encodes a receptor-like protein tyrosine phosphatase type κ (RPTPκ) to intron 1 of the *RGD1560849* predicted gene in the LEC rat genome. Reconstitution with syngenic BM cells transduced *Ptprk* but not the *RGD1560849* predicted gene rescued development of CD4 SP cells in the LEC rat thymus. It is confirmed by this result that the *Ptprk* gene is responsible for the *thid* mutation in the LEC rat. Our results further suggest that RPTPκ plays a critical role in the development of CD4 SP cells in the thymus.

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Introduction

The thymus is a major site of development of T lymphocytes. Bone marrow (BM)-derived T-cell progenitors enter the thymus and differentiate into mature T cells through sequential stages defined by expression of T-cell receptors (TCRs), expression of accessory molecules on the cell surface, and antigen-induced selection (Singer and Bosselut 2004). The most immature T cells in the thymus express neither the TCRs nor the coreceptors CD4 and CD8 (double negative, or DN). The DN thymocytes are found in the subcapsular zone and the outer cortical region of the thymus and migrate to the inner cortex (Lind et al. 2001; Porritt et al. 2003). During this step, DN thymocytes differentiate into CD4 and CD8 double-positive (DP) cells. The DP cells are selected by the extent of signaling, depending on the interactions between TCRs and self-peptide-bound major histocompatibility complex (MHC) molecules, leading to either deletion (negative selection) or development of MHC-restricted CD4 or CD8 single-positive (SP) cells (positive selection) (Ladi et al. 2006). The self MHC on the cortical thymus epithelial cells mediates positive selection (Bousso et al. 2002; Witt et al. 2005). The CD4/CD8 lineage commitment is regulated by the strength or duration of TCR-MHC binding, and the activities of the signaling pathway control the expression of CD4/CD8 molecules (He et al. 2005; Laky et al. 2006; Liu and Bosselut 2004; Sun et al. 2005). SP cells move to the medulla and are negatively selected for removal of thymocytes bearing TCRs reactive to self-antigens (Siggs et al. 2006). Negative selection is supported by the medullary thymic epithelial cells that present tissue-specific antigens on MHC molecules (Gallegos and Bevan 2004).

We have previously reported that a mutant strain of rats, LEC, exhibits a defect in T-cell maturation from DP to CD4 SP but not to CD8 SP cells in the thymus (Agui et al. 1990, 1991b). Although the thymocytes from LEC rats contain less than 1% of CD4 SP cells, some $CD4^+$ T cells appear in the peripheral lymphoid organs. However, these peripheral $CD4^+$ cells are not functional as helper T cells, i.e., the secretion of IL-2 after treatment with mitogenic lectin is impaired (Sakai et al. 1993). Moreover, LEC rats do not produce antibodies against T-cell-dependent antigen sheep red blood cells (Agui et al. 1990). These defects in the LEC rat are caused by a single autosomal recessive locus designated as *thid* (T-helper immunodeficiency) (Yamada et al. 1991). In this study we attempted to identify a gene responsible for the *thid* mutation by positional cloning and succeeded to show that a deletion mutation of the *Ptprk* gene, encoding a receptor-type protein tyrosine phosphatase type κ (RPTPκ), is responsible for the *thid* in the LEC rat.

Materials and methods

Animals

LEC/Ncu, BN/SsN, and (BN × LEC)F_1 × LEC backcrossed progenies were maintained at animal breeding rooms in the Center for Experimental Animal Science, Graduate School of Medical Sciences, Nagoya City University, and the Graduate School of Veterinary Medicine, Hokkaido University. Animal breeding rooms were kept at 23 ± 2°C and 50 ± 10% relative humidity with a 12-h light-dark cycle. Research was conducted according to the Guidelines for the Care and Use of Laboratory Animals of both the Graduate School of Medical Sciences, Nagoya City University and the Graduate School of Veterinary Medicine, Hokkaido University. The experimental protocols were approved by the Institutional Animal Care and Use Committee of both the Graduate School of Medical Sciences, Nagoya City University and the Graduate School of Veterinary Medicine, Hokkaido University.

Genome mapping

A total of 197 (BN × LEC)F_1 × LEC backcrossed progenies were used for PCR-based single sequence length polymorphism (SSLP) analysis. The sequences of all microsatellite primers were based on the Rat Genome Database <http://www.rgd.mcw.edu/> (RGSC 3.4, Dec 2004). We found a 12-bp-long polymorphism in the coding region of the *Myb* gene between the LEC and BN rats (data not shown). The sequences of the primers for detecting this polymorphism are given in Table 1. The *thid* genotype was estimated from the phenotype determined by the ratio of $CD4^+$ T cells in mesenteric lymph node cells with flow cytometry as described previously (Jung et al. 2001). Briefly, backcrossed progenies showing the normal ratio (40–50%) of $CD4^+$ cells in mesenteric lymph node cells were classified as *thid*/+ genotype, whereas backcrossed progenies showing the small ratio (10–20%) of $CD4^+$ cells were classified as *thid*/*thid* genotype. Backcrossed progenies were clearly segregated into two groups with 1:1 ratio as reported previously (Jung et al. 2001; Wei et al. 1997; Yamada et al. 1991). Linkage analysis was performed by MapManager QTXb20 software (Manly et al. 2001).

Identification of gene responsible for *thid* and sequencing of genomic DNA

The sequence around the *Ptprk* gene in the rat genome was searched in the rat genome browser of Ensembl (release 43, February 2007) (http://www.ensembl.org/index.html) and NCBI (http://www.ncbi.nlm.nih.gov/) by BLAST software (ver. 2.2.15, October 2006) with the sequence of mouse genome based on the information of the homologous synteny. The sequence obtained was used for the construction of PCR primers for genes located in the *thid* region. The sequences of PCR primers are given in Table 1. Sequencing of PCR products was performed with an ABI 377 genetic analyzer (Applied Biosystems, Foster City, CA).

Flow cytometry

Mesenteric lymph node cells and thymocytes (10^6 cells) stained with fluorescein isothiocyanate (FITC)-conjugated anti-rat CD4 (Calbiochem, San Diego, CA) and phycoerythrin (PE)-conjugated anti-rat CD8 (Calbiochem) were analyzed with an EPICS XL ADC flow cytometer (Beckman Coulter, Fullerton, CA).

Lentiviral transduction

The rat *Ptprk* gene and the *RGD1560849* predicted gene cDNAs were amplified by RT-PCR with primers given in Table 1 using total RNA from the BN rat thymus as template. The amplified cDNAs were sequenced (GenBank accession Nos. AB297790 and XR_008922 for *Ptprk* and *RGD1560849* predicted gene, respectively) and cloned downstream of the cytomegalovirus (CMV) promoter of pLenti6/V5 lentiviral vector (Invitrogen,

Table 1 Primers used for PCR

Genes	Primers	Length of PCR products (bp)
RT-PCR		
Ptprk	F: 5′-ACAAATGTCAGCCTCAAGATGAT-3′	429
	R: 5′-ATCAACGCCTTCATAGTCAGGTA-3′	
RGD1560849	F: 5′-GTAAGGAATCAACAGAGCCA-3′	724
	R: 5′-TCTCGGAATGATGCACTAGA-3′	
Aldh8a1	F: 5′-AGCACATTTTGGAGAAAGAATCA-3′	344
	R: 5′-CTCCCTCTCTTCCTATTCCAGAG-3′	
Arhgap18	F: 5′-AGAACAAATGAAAACGAAGACCA-3′	324
	R: 5′-ATATAGGGCAGTGAGTTCGATCA-3′	
Hbs1l	F: 5′-TTACCTTCTGAGGAAAATGGACA-3′	450
	R: 5′-AACATCCATTGTTACTCCCCTTT-3′	
L3mbtl3	F: 5′-GAATTCGGAGCTTTGGAAGTTAT-3′	438
	R: 5′-CTTGGAGTCAGCCTTCAGAGATA-3′	
Lama2	F: 5′-ACTGATAGAAGTATCGCGTCTGC-3′	438
	R: 5′-AGGTATGGAAGGTTGTCCAAAAT-3′	
RGD1560695	F: 5′-CGTACTTCTACCTGGGTTGTG AA-3′	419
	R: 5′-AATGACCTTTATGGTGGATTGTG-3′	
Ptprk (full length)	F: 5′-GCTGGCTGTCGGATTTCGCCGCGAT-3′	4,464
	R: 5′-GGAACAGGTGCAACAGCTGCTGGCT-3′	
RGD1560849 (full length)	F: 5′-CGGTCGACAATTGACATCTGGAAGC-3′	1,996
	R: 5′-AGAGTTCTGTAGGCACATCAGTGCT-3′	
Genomic PCR		
Myb	F: 5′-TGCTATCAAGAACCACTGGA-3′	186 (BN)
	R: 5′-GGATATTCGCCGTTGACTGA-3′	174 (LEC)
Region A	F: 5′-AGCTCCTGCTGACCTGAAGA-3′	258
	R: 5′-GCAGAAATCAGATGGTCCCA-3′	
Region B	F: 5′-TAGCAATGCATCCTGCAGAT-3′	388
	R: 5′-GCTTATTGACATGCAGCCCT-3′	
Region C	F: 5′-ACCTCAGAGAGAACAGTTCC-3′	297
	R: 5′-CTGTGACTTTGGCTGAGAGC-3′	
Region D	F: 5′-TGGCCACAGTATAGGGTCAT-3′	406
	R: 5′-CGACTGTGACCAGAGCAACT-3′	

Carlsbad, CA). Recombinant lentivirus was generated by using the ViraPower lentivirus expression system (Invitrogen).

Generation of BM-reconstituted rats

Recipient female LEC rats at 6–8 weeks of age were treated with 6 Gy X-irradiation, which is a lethal dose for LEC rats (Hayashi et al. 1994). BM cells (10^6 cells) from donor male LEC rats (8 weeks old) were infected with recombinant lentivirus and transplanted to recipient LEC rats through the tail vein on the next day. At 5–6 weeks after BM reconstitution, thymocytes were examined with flow cytometry.

Results

Genetic linkage analysis of the *thid* locus

It has been reported that the *thid* locus is mapped between markers *D1Mgh17* and *D1Mgh3* on Chr 1 (Wei et al. 1997). To identify the precise position of the *thid* locus, we performed genetic linkage analysis using markers closer to the *thid* locus than the previous markers. We produced 197 (BN × LEC)F_1 × LEC backcrossed progenies. The ratio of peripheral $CD4^+$ T cells in the mesenteric lymph nodes was examined by flow cytometry in all progenies to classify *thid*/*thid* or *thid*/+ phenotype (Fig. 1A). Genotyping with markers on Chr 1 was also performed in all progenies (Fig. 1B) and a linkage panel was generated (Fig. 1C). We

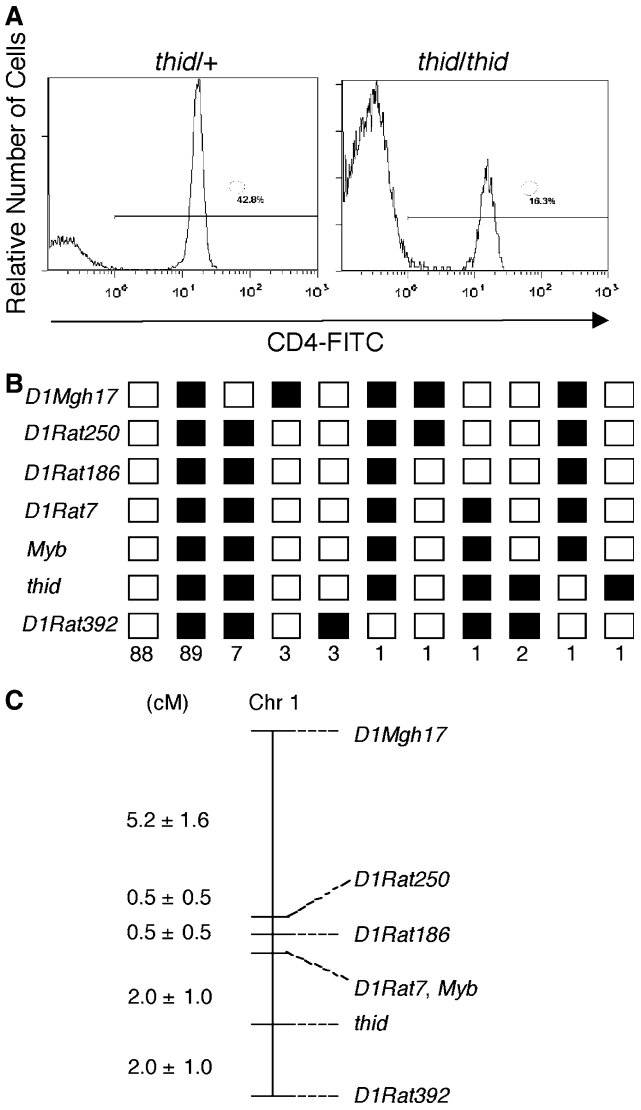

Fig. 1 Genetic mapping of the *thid* locus. A FACS analysis of mesenteric lymph node cells. Backcrossed progenies possessing normal ratio of $CD4^+$ cells (40–50%) were classified as *thid*/+ genotype, while those with a smaller ratio of $CD4^+$ cells (10–20%) were classified as *thid/thid* genotype. Figure is representative of each genotype. **B** Genotyping panel generated from 197 (BN × LEC)F_1 × LEC backcrossed progenies. Open and filled squares indicate BN/LEC heterozygous and LEC/LEC homozygous genotypes, respectively. The values under the squares indicate the numbers of progenies. **C** Linkage map generated from the data of genotyping panel. The values indicate the genetic distance (cM) ± standard error between the two loci

found that the *thid* locus locates between markers *Myb* and *D1Rat392* at the interval of 2 cM. The rat genomic sequence data (RGSC 3.4, December 2004) between *Myb* and *D1Rat392* and the homologous region of the mouse genome in terms of the synteny indicated that there are six genes and two predicted genes in the *thid* locus. These genes were positioned as follows: *Myb* (16.5 Mb)-*Hbs1l* (16.7 Mb)-*LOC683474* (*Aldh8a1*) (16.75

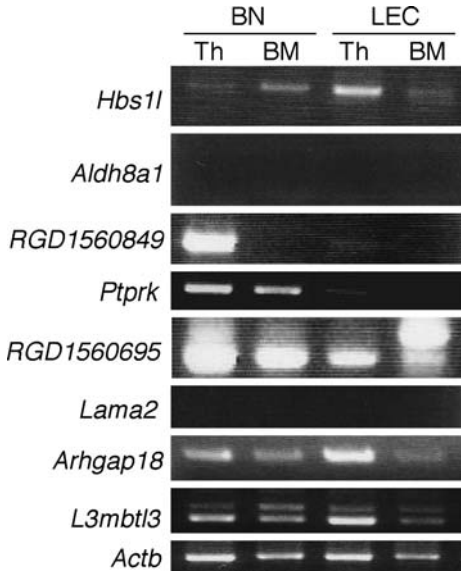

Fig. 2 Expression of genes located in the *thid* locus. RT-PCR was performed with cDNAs prepared from the thymus and BM tissues of BN and LEC rats. Primers for each gene are given in Table 1

Mb)-*RGD1560849*-predicted (17.2 Mb)-*Ptprk* (17.8 Mb)-*RGD1560695*-predicted (18.1 Mb)-*Lama2* (18.4 Mb)-*Arhgap18* (19.0 Mb)-*L3mbtl3* (19.5 Mb)-*D1Rat392* (19.6 Mb).

Identification of the *thid* mutation

We examined the expressions of all genes located in the *thid* region in the BM and thymus and compared them between BN control and LEC rats (Fig. 2). Among genes located in the critical region, the *Ptprk* gene and the *RGD1560849* predicted gene were found to be expressed differently in BN and LEC rats. The *Ptprk* gene was expressed in both BM and thymus of BN rats but not in those of LEC rats, while the *RGD1560849* predicted gene was expressed in the thymus of BN rats but not in that of LEC rats. Therefore, we next analyzed the genomic structure of *Ptprk* and *RGD1560849* predicted gene in the LEC rat. Because complete sequence data of the region around the rat *Ptprk* gene was not registered in the rat genome database, we searched sequence data in the trace archive of the rat genome by comparing it with the sequence of the mouse genome using BLAST. Using these sequence data, we designed several PCR primers and performed genomic PCR. Among them, the data for A, B, C, and D shown in Fig. 3A were informative. Both A and B sites are located approximately 3 kb downstream from the donor site of exon 1 of the *RGD1560849* predicted gene, which is located downstream of the *Ptprk* gene. Sites C and D are located approximately 17 kb downstream from the donor site of exon 3 of the *Ptprk* gene (Fig. 3A). Sites A and D could be amplified when genomic DNA of LEC rats was

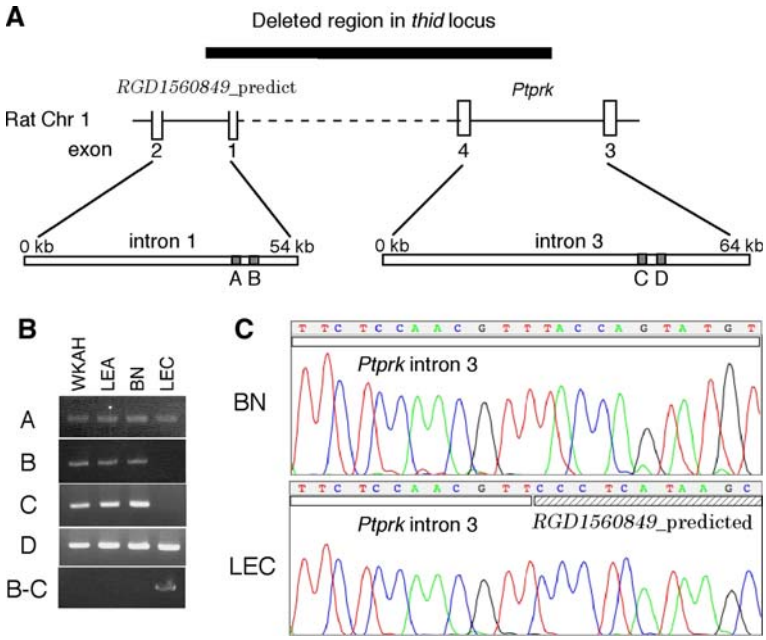

Fig. 3 Identification of the *thid* mutation. **A** Genomic structure around the *thid* locus on rat Chr 1. A deleted region between region A in intron 1 of the *RGD1560849* predicted gene and region D in intron 3 of the *Ptprk* gene is indicated as a filled column. **B** PCR amplification of regions A through D indicated in panel **A**. Genomic DNAs from WKAH, LEA, BN, and LEC rats were used to amplify regions A through D. B–C indicates the PCR products of the region between B and C. **C** DNA sequencing of PCR products. The sequence of the BN rat was derived from the PCR product of region C in panel **B**. The sequence of the LEC rat was derived from the PCR product of region B–C in panel **B**

used as a template as well as BN control rats. We used LEA and WKAH rats as additional controls because the LEA rat has been established from the Long-Evans closed colony simultaneously with the LEC rat and is the most genetically closed strain to the LEC rat. The WKAH rat was used as a nonrelevant control because we and others have been used it as a control strain for the LEC rat in previous reports (Agui et al. 1990; Hayashi et al. 1994; Sakai et al. 1993; Wei et al. 1997; Yamada et al. 1991). In contrast, sites B and C could not be amplified in the LEC rat only (Fig. 3B). These results suggest that the region expanding from the intron 3 of the *Ptprk* gene to the intron 1 of the *RGD1560849* predicted gene is largely deleted in the LEC rat genome. Because the genomic region between B and C could be amplified using the forward primer of B and the reverse primer of C in the LEC rat, we sequenced the PCR product to confirm the breakpoint of the *thid* mutation. The PCR product of the LEC rat contained the sequence of parts of both the *Ptprk* intron 3 and the *RGD1560849* predicted intron 1, as expected (Fig. 3C). Because the *Ptprk* gene and the *RGD1560849* predicted gene are not completely assembled in the rat genome database at present, the precise size of the deleted region in the *thid* locus is unknown. However, the size is estimated to be approximately 380 kb, considering the homologous region of the mouse genome.

Ptprk expression rescues T-helper immunodeficiency phenotype in LEC rats

Our results indicate that two genes, *Ptprk* and *RGD1560849* predicted, are defective in the LEC rat. *Ptprk* encodes a receptor protein tyrosine phosphatase κ (Jiang et al. 1993), and *RGD1560849* predicted gene encodes a hypothetical protein similar to *E430004N04Rik* of the mouse and whose function is unknown. We performed BM reconstitution with syngenic BM cells transduced with *Ptprk* or *RGD1560849* predicted gene using the lentiviral gene expression system in X-irradiated recipient LEC rats, since it has been reported that BM cells but not thymic epithelial cells are defective due to the *thid* mutation (Agui et al. 1990a). When *Ptprk* or *RGD1560849* predicted gene was transduced into LEC-derived BM cells, BM cells sufficiently expressed each gene (Fig. 4A). Next, these BM cells were reconstituted into X-irradiated recipient LEC rats. After 5–6 weeks, recipient rats were sacrificed and expression of these genes in the thymus and spleen was examined. As shown in Fig. 4B, each gene was sufficiently expressed, indicating that the reconstitution with exogenous gene-transduced BM cells succeeded. Thymocyte subsets were then examined by flow cytmetry (Fig. 4C). When *RGD1560849* predicted gene-transduced donor BM cells were reconstituted, CD4 SP cells in the thymus were as few as that in LEC rats. In contrast, when *Ptprk*-transduced donor BM cells were reconstituted, CD4 SP cells apparently appeared as consisting of 3.7% of the total thymocytes, which corresponds to half of normal rat CD4 SP cells. These results indicate that *Ptprk* is a gene responsible for the defect in the development of CD4 SP cells in the LEC rat thymus, and further suggest that *Ptprk* expression in BM cells is a prerequisite for the development of CD4 SP cell lineage in the thymus.

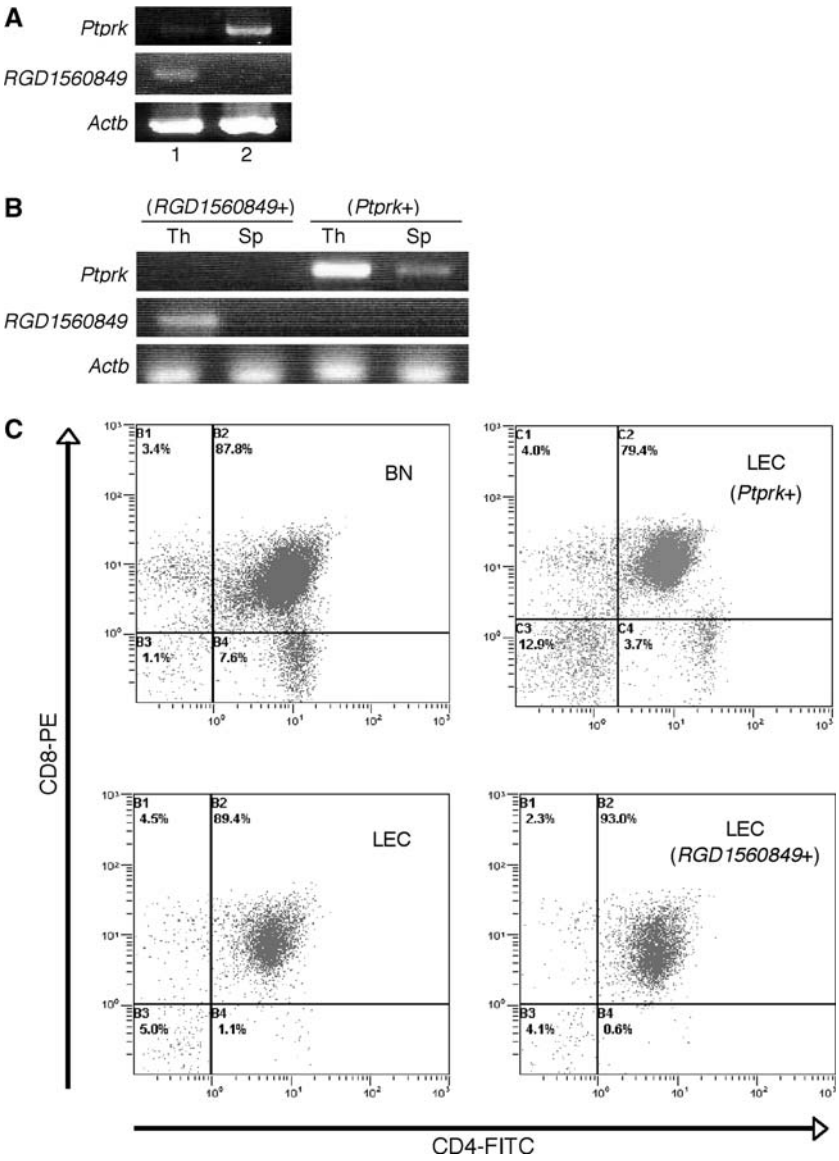

Fig. 4 Rescue experiment by transplantation of BM cells transduced with the *Ptprk* gene or the *RGD1560849* predicted gene. **A** Expression of *Ptprk* gene and *RGD1560849* predicted gene in LEC rat BM cells, which had been transduced by these genes using the lentiviral vector. Lane 1: *RGD1560849* predicted gene-transduced BM cells; lane 2: *Ptprk* gene-transduced BM cells. **B** Expression of *Ptprk* gene and *RGD1560849* predicted gene in the thymus and spleen of LEC rats transplanted with *Ptprk*- or *RGD1560849* predicted gene-transduced BM cells. *Ptprk*+ and *RGD1560849*+ indicate the data from recipient LEC rats transplanted with BM cells, which had been transduced by the respective genes. Note that the *Ptprk* gene was expressed in both thymus and spleen, whereas the *RGD1560849* predicted gene was expressed in the thymus but not in the spleen. **C** Flow cytometry of thymocytes from LEC rats transplanted with *Ptprk*- or *RGD1560849* predicted gene-transduced BM cells. BN and LEC indicate the data from untreated rats

Discussion

In the present study we have identified a deletion mutation of the *Ptprk* gene and the *RGD1560849* predicted gene in the *thid* locus of the LEC rat. Reconstitution with *Ptprk*-transduced but not *RGD1560849* predicted gene-transduced BM cells rescued development of CD4 SP cells in the thymus. Therefore, we conclude that a deletion mutation of the *Ptprk* gene is responsible for T-helper immunodeficiency in the LEC rat.

The *Ptprk* gene encodes a receptor-like protein tyrosine phosphatase type κ (RPTPκ) protein. RPTPκ contains a meprin/A5 antigen/RPTPμ (MAM) domain, an immunoglobulin-like (Ig) domain, and four fibronectin type III (FN) repeats in the extracellular region, and two protein tyrosine phosphatase domains in the cytoplasmic region (Jiang et al. 1993). The *Ptprk* gene in the LEC rat loses exons 4–31. It is unknown whether the truncated mRNA or protein of *Ptprk* is produced. However, it seems unlikely since the *Ptprk* mRNA is anticipated not to possess the polyadenylation signal. Furthermore, even if we assume that the truncated mRNA or protein would be present, it loses important domains such as Ig, FN, and tyrosine phosphatase. Thus, the LEC rat is considered to possess a null mutation of the *Ptprk* gene.

The extracellular region of RPTPκ plays a critical role in homophilic binding, which leads to cell-cell adhesion mediated by RPTPκ (Sap et al. 1994; Zondag et al. 1995). RPTPκ is upregulated by transforming growth factor (TGF)-β, associated with epidermal growth factor (EGF) receptor, and reduces phosphorylation of EGF receptor in a mammary epithelial cell line, MCF10A. Consequently, cell proliferation is reduced when RPTPκ is activated (Wang et al. 2005). In contrast, downregulation of RPTPκ

modulates Src and FAK phosphorylation and prevents TGF-β-mediated cell adhesion and migration (Wang et al. 2005). In addition, it is suggested that RPTPκ plays a role in tumor suppression. Previous reports indicate that human Chr 6q, which contains the *PTPRK* gene, has been deleted frequently in various tumors (Cooney et al. 1996, Theile et al. 1996). Indeed, loss of heterozygosity of 6q22-23, in which *PTPRK* is located, was found in primary central nervous system lymphomas (Nakamura et al. 2003). Moreover, *PTPRK* mRNA was downregulated in some melanoma cells (McArdle et al. 2001). It is reported that *PTPRK* mRNA is expressed in various tissues such as spleen, prostate, ovary, brain, kidney, liver, and epithelial cell line (Jiang et al. 1993; Shen et al. 1999; Yang et al. 1997). In contrast, a low expression of *PTPRK* mRNA was observed in human thymus and was not seen in peripheral blood leukocytes (Yang et al. 1997). To date, the expression and the biological function of RPTPκ in the immune cells is unknown. The present study is the first report describing the function of RPTPκ in the immune system. RPTPκ may play a role in the regulation of adhesion, proliferation, and migration of T-precursor cells in the thymus.

Ptprk-deficient mice were generated by gene trap (Shen et al. 1999; Skarnes et al. 1995). However, they were viable, fertile, and absent of overt phenotypes. Abnormality of the immune system was not examined. There are four homologous proteins, RPTPκ, RPTPλ, RPTPμ and RPTPρ in the protein tyrosine phosphatase family that contain MAM, Ig, and FN extracellular domains in humans and rodents (Alonso et al. 2004). Therefore, it is suggested that other members compensate the biological functions when one is deficient. Indeed, homozygous mice in which *Ptprm* is gene-trapped are viable and appear to be normal like *Ptprk*-disrupted mice (Koop et al. 2003). However, our results indicate for the first time that a deficiency of a member of the protein tyrosine phosphatase family, *Ptprk*, is not compensated by the other three homologs, showing a deficient phenotype with respect to the development of CD4 SP cells in the thymus.

After we submitted this article, a similar report was published elsewhere (Kose et al. 2007). Although they reached the conclusion that the *Ptprk* gene is responsible for the *thid* mutation, their report is incomplete. Thus, they did not show the deleted region in the LEC rat genome nor verify their result by the rescue experiment.

In summary, we show that the T-helper immunodeficiency mutation in the LEC rat is attributed to a deletion mutation of the *Ptprk* gene, which encodes a receptor-like protein tyrosine phosphatase type κ. It was verified by the data that BM reconstitution with *Ptprk*-transduced BM cells could rescue the T-helper immunodeficiency phenotype in LEC rats. Thus, the present study proposes a crucial role for the RPTPκ in the positive selection and/or maintenance of CD4 SP cells in the thymus.

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