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Centromeric interval of chromosome 4 derived from C57BL/6 mice accelerates type 1 diabetes in NOD.CD72^{b} congenic mice

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ABSTRACT

The nonobese diabetic (NOD) mouse is a useful model of autoimmune type 1 diabetes exhibiting many similarities to human type 1 diabetes patients including the presence of auto-reactive T cells and pancreas-specific autoantiboies. Multiple *Idd* loci control the development of diabetes in NOD mice. CD72, a B cell membrane-bound glycoprotein carrying a C-type lectin-like domain, is an inhibitory co-receptor of the B cell antigen receptor (BCR) that negatively regulates BCR signaling. Among four known haplotypes of mouse CD72, NOD mice carry the CD72^{c} haplotype, whereas most of the other inbred strains of mice carry either CD72^{a} or CD72^{b}. In this study, we generated congenic NOD.CD72^{b} mice that carry C57BL/6 (B6) mouse-derived centromeric chromosome 4 interval (24–45 cM) surrounding the CD72^{b} locus. Unexpectedly, NOD.CD72^{b} mice were not protected from diabetes, but rather exhibited accelerated development of both insulitis and diabetes. Our result defines novel locus or loci in the vicinity of CD72 gene that negatively control diabetes, indicating that NOD disease is under complex genetic controls of not only *Idd* genes but also disease-resistant genes.

The nonobese diabetic (NOD) mouse is an important model of autoimmune type1 diabetes. This mouse strain develops spontaneous autoimmune diabetes with many similarities to type1 diabetes in human, including appearance of autoreactive T cells, pancreas-specific autoantiboies, destruction of pancreatic islet β-cells and a genetic predisposition [1]. In both humans and NOD mice, a crucial susceptibility locus is mapped to the major histocompatibility complex (MHC) locus [2], but many other loci termed *Idd* (insulin dependent diabetes) also contribute to disease development in NOD mice. To date, around 20 *Idd* loci have been identified on different chromosomes based on studies using crosses of NOD mice with various diabetes-resistant strains. Some of them have fine-mapped to small intervals in congenic mice [3,4].

CD72, a 45 kDa type II membrane protein containing a C-type lectin-like domain, is expressed as a homodimer in B cells of most developmental stages except for plasma cells. CD72 is an inhibitory co-receptor of the B cell antigen receptor (BCR) that negatively regulates BCR signaling [5]. CD72 polymorphism is associated with both SLE and ITP in humans [6,7]. In mice, four haplotypes of CD72, i.e., CD72^{a}, CD72^{b}, CD72^{c}, CD72^{d}, have been identified. cDNA sequence comparisons among CD72^{a}, CD72^{b}, and CD72^{c} exhibit a high degree of conservation in their transmembrane and cytoplasmic regions but show a polymorphism involving amino acid substitutions, deletions and insertions in their extracellular regions. Among these alterations, CD72^{c} exhibits a deletion of seven amino acids due to alternation in splicing in the extracellular region [8]. CD72^{c} is a rare haplotype expressed in AKR, MRL/Mp, SJL, and NOD strains, whereas most of the other strains express either CD72^{a} or CD72^{b} [9]. In MRL/lpr mice that spontaneously develop lupus-like autoimmune disease, the CD72^{c} locus has been identified as a susceptibility locus for the autoimmune disease including vasculitis and nephritis [10]. In this study, we generated NOD.CD72^{b} congenic mice carrying a C57BL/6 (B6)-derived centromeric interval (24–45 cM) including B6-type CD72^{b} allele on chromosome 4. Unexpectedly, NOD.CD72^{b} congenic mice were not protected from diabetes but rather exhibited acceleration of the disease compared to NOD mice. Our finding suggests that the centromeric chromosome 4 region of NOD mice includes a novel gene or cluster of genes that negatively regulates the development of diabetes.

Abbreviations: NOD, nonobese diabetic; B6, C57BL/6; BCR, B cell antigen receptor; PLN, pancreatic lymph node; MZ, marginal zone.

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Materials and methods

Mice. B6 and NOD mice were purchased from CLEA Japan (Tokyo) and Sankyo Labo Service (Tokyo), respectively. B6, NOD and NOD.CD72^b congenic mice were maintained under a specific pathogen-free condition at Tokyo Medical and Dental University. All experiments were performed in accordance with our institutional guidelines. Blood glucose levels were measured by using a blood glucose monitor (ACCU-CHEK Aviva).

Genotyping. DNA was extracted from mice tail. Genotyping for microsatellite markers and CD72 haplotype was done by PCR. Microsatellite primers (*D4Mit193, D4Mit196, D4Mit268, D4Mit17, D4Mit9, D4Mit308,* and *D4Mit203*, located at 7.5, 12.1, 17.9, 31.4, 44.5, 57.4, and 60.0 cM distal from the centromere on chromosome 4, respectively) were synthesized according to mouse Genome Database (Mouse Genome Informatics, The Jackson Laboratory). The CD72^b and CD72^c genes were specifically amplified using the following primers sets: CD72^b: 5′-ACATATTACCAGAAGTGGGA-3′, 5′-GGTTAAGGATGTAGGTCACAAGGTCTT-3′; CD72^c: 5′-ATATATAAC AAGAAGTGGGC-3′, 5′-GGTTAAGGATGTAGGTCACAAGGTCTT-3′.

Flow cytometry analysis. Cells were stained with the following reagents: PE-conjugated anti-CD25 mAb (Biolegend), APC-conjugated anti-CD4 mAb (BD Pharmingen), FITC-conjugated anti-Foxp3 mAb (eBioscience), FITC-conjugated anti-CD3 mAb (eBioscience), Cy5-labeled B220 mAb (eBioscience), FITC-conjugated anti-CD21 mAb (BD Pharmingen), and PE-conjugated anti-CD23 mAb (eBioscience). 4, 6-Diamino-2-phenylindole (Sigma–Aldrich) was used for exclusion of dead cells. Cells were analyzed using an LSR with the CELLQuest software (BD Biosciences).

Cytokine production. Pancreatic lymph node (PLN) cells (1×10^6/well) were cultured in RPMI 1640 medium supplemented with 10% FCS, 50 μM 2-mercaptoethanol, and 1 mM glutamine for 72 h using 96-well flat-bottom plates pre-coated with 10 μg/ml anti-CD3 (145-2C11) and anti-CD28 (37.51) mAbs. Amounts of IL-4, IFN-γ (BD Pharmingen) and IL-17 (eBioscience) in the culture supernatants were measured using standard sandwich ELISA using cytokine ELISAset.

Histopathology analysis. Pancreata were removed, fixed with 10% buffered formalin and processed for paraffin embedding. Tissue sections (5 μm) were stained with hematoxylin and eosin and microscopically evaluated for the presence of mononuclear infiltrates. Insulitis scores were determined by the following scale: 0, normal islet; 1, peri-insulitis or infiltration of less than 25% of the islet surface area; 2, infiltration of 25–50% of the islet surface area; 3, infiltration of more than 50% of the islet surface area.

Quantitative RT-PCR analysis of Pax5 and Munc13-2 transcripts. Total RNA was isolated from pancreas and spleen of NOD and NOD.CD72^b congenic mice using ISOGEN (Nippon Gene). First-strand cDNA was synthesized using an oligo (dT) primer and cDNA fragments were amplified using 5′ and 3′ primers (for *Pax5*: 5′-CCA TCAGGACAGGACATGGAG-3′, 5′-GGCAAGTTCCACTATCCTTTGG-3′, for *Munc13-2*: 5′-GTGCCTTGCGCCTGTGACGTCAG-3′, 5′-TGCTTAAT CAAGAGGATCAGGT-3′). Quantitative RT-PCR was performed using GeneAmp 5700 system (ABI).

Statistics. Statistical analysis was performed using the Student's *t* test. A value of $P < 0.05$ was considered to have a statistical significance.

Results

Establishment of congenic NOD.CD72^b mice

We established NOD congenic strain homozygous for the CD72^b haplotype (NOD.CD72^b) by selective backcrossing of F1 hybrid between NOD (CD72^c) and B6 (CD72^b) to NOD mice for eight generations and by subsequent brother–sister mating. Genotyping of CD72 haplotype was done by PCR at each generation. Genotyping of B6-derived chromosome 4 interval introduced into established NOD.CD72^b congenic strain was examined using the microsatellite markers, as shown in Fig. 1. The result showed that an interval between *D4Mit193* (7.5 cM from centromere) and *D4Mit17* (31.4 cM from centromere) is derived from B6 mice (Fig. 1).

Augmented development of both insulitis and diabetes in congenic NOD.CD72^b mice

We compared blood glucose levels between NOD (9 males and 8 females) and NOD.CD72^b (10 males and 13 females) mice up to 24 weeks of age. NOD and NOD.CD72^b congenic mice were housed at the same specific pathogen-free facility. When mice showing more than 250 mg/dl blood glucose were diagnosed as diabetic as described previously [21], NOD mice did not develop diabetes up to 20 weeks of age, and only two out of 17 mice (12%) were diabetic at 24 weeks of age (Fig. 2A). Surprisingly, the onset of diabetes began at 16 weeks of age in NOD.CD72^b mice and the incidence of diabetes was significantly higher than that in NOD mice ($P < 0.05$). The accelerated development of diabetes was especially evident in female NOD.CD72^b mice (Fig. 2B).

Because of the higher incidence of diabetes in female NOD.CD72^b mice, we histopathologically examined pancreas for development of insulitis in female NOD ($n = 9$) and NOD.CD72^b ($n = 12$) mice. Neither of these mice developed insulitis at 6 weeks of age (data not shown). At 10 to 12 weeks of age, 92% and 56% of NOD.CD72^b and NOD females, respectively, developed insulitis. When 5–10 islets in each pancreatic section were examined, NOD.CD72^b mice showed a significantly higher percentage of islets containing cellular infiltration than NOD mice (Fig. 3A). Moreover, NOD.CD72^b mice showed more extensive cellular infiltration in affected islets than NOD mice (Fig. 3B and C). Taken together, the B6-derived chromosomal region containing CD72^b may play a role in acceleration of both insulitis and diabetes in NOD.CD72^b mice.

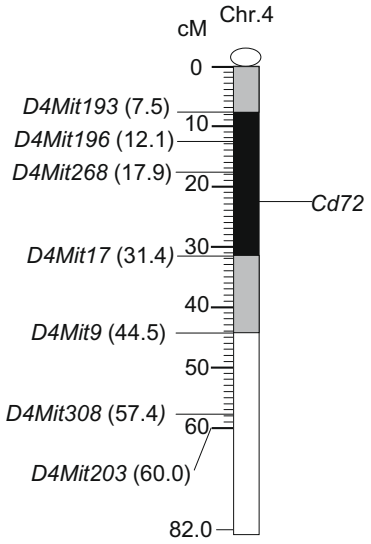

Fig. 1. Genetic map of the centromeric region on chromosome 4 in NOD.CD72^b congenic strain. The gene segment from *D4Mit193* (7.5 cM from the centromere) to *D4Mit17* (31.4 cM from the centromere) derived from B6 strain (black bar) was introduced into NOD strain (white bar). The microsatellite markers used to delineate the boundaries of the B6 intervals are indicated. Positions in cM from the centromere are shown in parentheses. Gray bars represent the area of recombination between NOD and B6 strains.

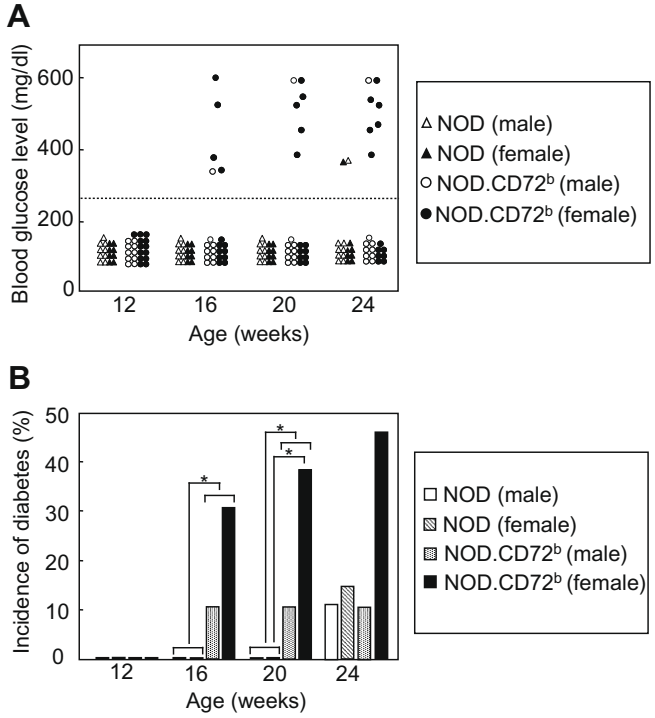

Fig. 2. Accelerated development of diabetes in NOD.CD72^b mice. (A) Blood glucose levels of NOD (triangle) (open, male; closed, female) and NOD.CD72^b (circle) (open, male; closed, female) mice at indicated age. Diabetes was diagnosed when the blood glucose level was greater than 250 mg/ml. Each symbol represents data of each mouse. (B) Comparison of the incidence of diabetes between NOD and NOD.CD72^b mice. The difference was statistically significant ($P < 0.05$).

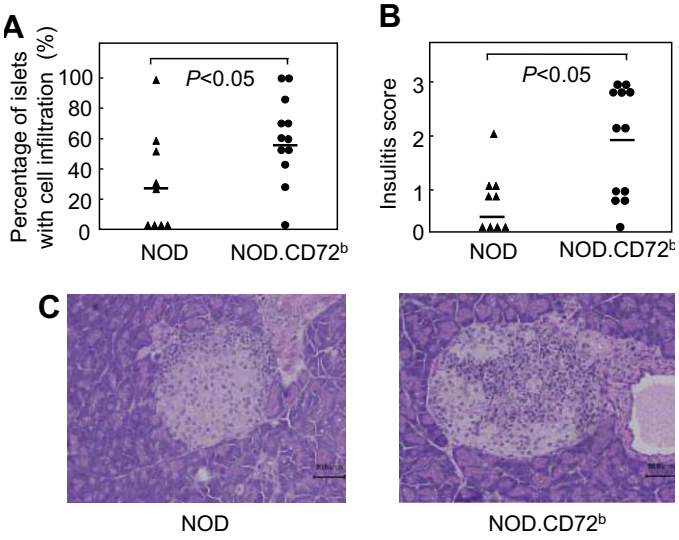

Fig. 3. Accelerated development of insulitis in NOD.CD72^b mice. Pancreas sections from 10 to 12 week-old female NOD ($n = 9$) and female NOD.CD72^b mice ($n = 12$) were stained with hematoxylin and eosin. (A) Comparison of the percentage of islets with cell infiltration between NOD and NOD.CD72^b mice. Each symbol and horizontal bar represents data of each mouse and the mean of total mice examined, respectively. The difference was statistically significant ($P < 0.05$). (B) Comparison of the severity of insulitis between NOD and NOD.CD72^b mice. Severity was scored as described in Materials and methods. Each symbol and horizontal bar represents the mean score in 5–10 islets examined in each mouse and the mean of total mice examined, respectively. The difference was statistically significant ($P < 0.05$). (C) Representative histopathological findings of insulitis in NOD and NOD.CD72^b mice.

Frequency of Treg cells or cytokine-producing potentials of T cells in NOD.CD72^b mice are not different from those in NOD mice

To address whether severe disease in NOD.CD72^b mice correlates with lymphocyte function, we first analyzed spleen and PLN cells in female NOD and NOD.CD72^b mice at 8–12 weeks of age using flow cytometry. The results revealed that the percentages of CD3$^+$ T cells and B220$^+$ B cells were similar in both spleen and PLN in these two strains (Table 1). The percentages of CD69$^+$ activated B cells and T cells, B220$^+$CD21^{high}CD23$^-$ marginal zone B cells and B220$^+$CD21^{low}CD23^{high} follicular B cells in spleen, and CD4$^+$ T cells and CD8$^+$ T cells in PLN were also similar in both strains. In addition, there was no significant difference in the percentage of CD4$^+$CD25$^+$Foxp3$^+$ Treg cells in PLN between NOD and NOD.CD72^b mice.

We next compared cytokine-producing potential of PLN T cells between female NOD and NOD.CD72^b mice after stimulation with anti-CD3 and anti-CD28 mAbs. The *in vitro* IL-4- and IL-17-producing potentials of NOD.CD72^b T cells tended to be lower as compared to that of NOD T cells; however, the difference was not statistically significant. Unexpectedly, IFN-γ producing potential was significantly lower in NOD.CD72^b T cells than that in NOD T cells (Fig. 4).

Quantitative RT-PCR analysis of Pax5 and Muc13-2

Since *Pax5* and *Munc13-2* are located in the B6-derived interval in NOD.CD72^b mice, and are involved in B cell development and secretion in islets, respectively, these genes are also the possible candidate genes besides *Cd72* that accelerate diabetes in NOD.CD72^b mice. When we examined the expression of *Pax5* and *Munc13-2* in spleen and pancreas by quantitative RT-PCR, no significant difference in the expression levels of these transcripts was detected between NOD and NOD.CD72^b mice (Table 2). Thus, the expression levels of *Pax5* and *Munc13-2* do not appear to be responsible for the accelerated disease in NOD.CD72^b mice.

Discussion

In this study, we generated NOD.CD72^b congenic mice that carry a B6-derived centromeric interval (24–45 cM) containing the CD72^b locus on chromosome 4 (Fig. 1). Development of both insulitis and diabetes was accelerated in NOD.CD72^b mice especially in females as compared with NOD mice with CD72^c haplotype. Since the broad interval was substituted, it is impossible to clarify whether CD72^b haplotype *per se* is responsible for this disease acceleration at present. However, current study suggests that the centromeric interval of NOD chromosome 4 contains a novel gene or cluster of genes that negatively controls both insulitis and diabetes.

Among the reported *Idd* genes, *Idd9* and *Idd11* loci are mapped on chromosome 4. *Idd9* was mapped to the distal portion between *D4Mit27* (42.5 cM from the centromere) and *D4Mit180* (81.0 cM from the centromere) on chromosome 4 by analyzing the NOD mice backcrossed to B10 strain, and NOD.B10*Idd9* congenic mice displayed profound resistance to diabetes even though nearly all developed insulitis [12]. Possible candidate genes of *Idd9* were shown to be *Cd30*, *Tnfr2* and *Cd137* [12]. *Idd11* was initially identified by analysis of backcross mice using NOD and B6 strains. Diabetes was protected in NOD congenic mice carrying B6-derived interval between *D4Mit31* (50.3 cM from the centromere) and *D4Mit204* (61.2 cM from the centromere), suggesting that *Idd11* was located in this interval [13]. It remains to be determined whether *Idd9* and *Idd11* is the same gene or not. In contrast to the above congenic NOD mice, our NOD.CD72^b congenic mice

Table 1
Flow cytometric analysis of spleen and pancreatic lymph node cells.

Tissue	Cell population	NOD	NOD.CD72^b
Spleen	B220$^+$CD3$^-$	40.5 ± 2.4	39.2 ± 1.9
	B220$^+$CD69$^+$	1.6 ± 0.1	1.9 ± 0.01
	CD3$^+$B220$^-$	50.6 ± 2.8	50.4 ± 1.7
	CD3$^+$CD69$^+$	1.1 ± 0.05	1.2 ± 0.05
	B220$^+$CD21$^+$CD23$^+$	32.6 ± 2.0	28.4 ± 1.8
	B220$^+$CD21$^+$CD23$^-$	1.3 ± 0.2	1.6 ± 0.2
PLN	B220$^+$CD3$^-$	13.3 ± 2.5	13.2 ± 3.9
	CD3$^+$B220$^-$	80.5 ± 2.6	79.2 ± 4.9
	CD3$^+$CD4$^+$	66.4 ± 3.2	69.8 ± 4.5
	CD3$^+$CD8$^+$	17.5 ± 1.3	14.1 ± 1.0
	CD4$^+$CD25$^+$Foxp3$^+$	11.0 ± 0.9	8.8 ± 0.9

Numbers represent the percentage of lymphocytes expressing the indicated surface makers in total lymphocytes of spleen and PLN cells. Values are represent means ± SEM of 3–11 mice at 8–12 weeks age.

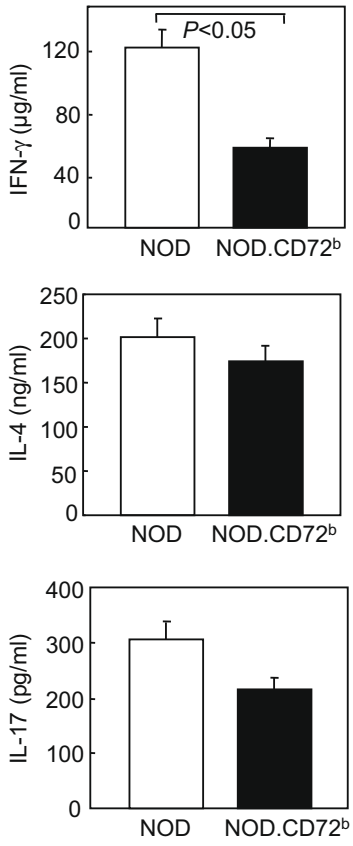

Fig. 4. Comparisons of cytokine-producing potential of PLN T cells between NOD and NOD.CD72^b mice. PLN cells from 12 week-old female NOD and NOD.CD72^b mice (n = 5–8) were stimulated with anti-CD3 and anti-CD28 mAbs for 3 days and the amounts of IL-4, IFN-γ, and IL-17 in culture supernatants were measured by ELISA. Mean and SEM are shown. The difference in an amount of IFN-γ was statistically significant (P < 0.05).

Table 2
Quantitative RT-PCR analysis of *Pax5* and *Munc13-2* transcripts.

Tissue	Candidate gene	NOD	NOD.CD72b
Pancreas	*Pax5*	0.16 ± 0.1	0.17 ± 0.04
	Munc13-2	0.7 ± 0.3	0.6 ± 0.2
Spleen	*Pax5*	1.4 ± 0.5	1.5 ± 0.6
	Munc13-2	1.2 ± 0.4	1.0 ± 0.4

Means ± SEM of the relative value (relative to GAPDH) of expression levels of *Pax5* and *Munc13-2* transcripts in pancreas and spleen of 10-week-old NOD (n = 3) and NOD.CD72b (n = 3) mice.

showed accelerated insulitis and diabetes, indicating that the centromeric interval of NOD chromosome 4 contain disease-resistant gene(s) and that NOD disease is under the complex genetic control by genes with both positive and negative effects.

Identification of possible candidate gene(s) located in this centromeric interval on chromosome 4 is the important issue for better understanding of the pathogenesis of type 1 diabetes. Besides *Cd72*, the B6-derived substituted interval in NOD.CD72^b mice contains plausible candidate genes, such as *Pax 5* and *Munc13-2*. *Pax5* is involved in development and proliferation of B cells [14,15]. *Munc13-2* is one of three highly homologous *Munc13* members (*Munc13-1, Munc13-2, Munc13-3*), which are genes for essential secretory vesicle priming proteins. It has been shown that at least *Munc13-1* is expressed in pancreatic islet beta cells and overexpression of *Munc13-1* in insulin secreting cells leads to an increased insulin secretion [16], indicating that *Munc13* members may act as a priming protein in insulin granule exocytosis. Thus, these genetic loci might control diabetes by regulating B cells or insulin secretion, although the expression levels of these genes were not different between NOD and NOD.CD72. NOD.CD72^b mice. To identify the candidate genes, it is essential to shorten the interval by further backcrossing, and this work is under way in our laboratory.

Because transfer of NOD T cells induces diabetes in host mice, it is widely believed that autoimmune diabetes in NOD mice is mediated primarily by T cells [17], and that Th1 cytokines play a crucial role [18,19]. Furthermore, increasing body of evidence suggests that Th17 cells are crucial for inflammatory diseases and autoimmune diseases [20]. However, PLN T cells from NOD.CD72^b mice did not exhibit increased production of IFN-γ or IL-17, representative cytokines from Th1 and Th17 cells, respectively, suggesting that enhanced disease in these mice is not simply explained by augmented activation of Th1 or Th17 cells.

In addition to the role of T cells, B cells appear to play a role in NOD diabetes, since B cell deficient μMT NOD mice do not develop diabetes [21]. Furthermore, a recent study demonstrated that diabetes is prevented in NOD mice by B cell depletion using anti-CD20 mAb [11]. These findings strongly suggested that, while the exact mechanism is not known, B cells play a pivotal role in development of diabetes in NOD mice. Because CD72 regulates B cell signaling, it may control development of diabetes by regulating B cell function. Further studies on immunopathology of disease acceleration in NOD.CD72^b mice as well as identification of candidate genes may shed light on pathogenesis of diabetes in NOD mice. These studies may help to provide clues to establish new strategies for preventive and therapeutic clinical approaches for type 1 diabetes.

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