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*J Immunol* 1998; 160:1472-1478; ;
http://www.jimmunol.org/content/160/3/1472

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Subcongenic Analysis of the *Idd13* Locus in NOD/Lt Mice: Evidence for Several Susceptibility Genes Including a Possible Diabetogenic Role for β₂-Microglobulin\(^1\)

David V. Serreze,\(^2\) Margot Bridgett, Harold D. Chapman, Emmie Chen, Scott D. Richard, and Edward H. Leiter

Although they share ~88% of their genome with NOD mice including the *H2*\(^{\text{g7}}\) haplotype, NOR mice remain free of T cell-mediated autoimmune diabetes (IDDM), due to non-MHC genes of C57BLKS/J (BKS) origin. NOR IDDM resistance was previously found to be largely controlled by the *Idd13* locus within an ~24 cM segment on Chromosome 2 encompassing BKS-derived alleles for *H3a*, *B2m*, *III*, and *Pen*. NOD stocks carrying subcongenic intervals of NOR Chromosome 2 were utilized to more finely map and determine possible functions of *Idd13*. NOR-derived *H3a-III* (~6.0 cM) and *III-Pen* (~1.2 cM) intervals both contribute components of IDDM resistance. Hence, the *Idd13* locus is more complex than originally thought, since it consists of at least two genes. *B2m* variants within the *H3a-III* interval may represent one of these. Monoclonal Ab binding demonstrated that dimerizing with the *β₂m\(^{\text{null}}\)* (NOD type) vs *β₂m\(^{\text{m}}\)* isomorph (NOR type) alters the structural conformation, but not total expression levels of *H2*\(^{\text{g7}}\) class I molecules (e.g. *K\(^d\)*, *D\(^b\)*). *β₂m*-induced alterations in *H2*\(^{\text{g7}}\) class I conformation may partially explain findings from bone marrow chimera analyses that *Idd13* modulates IDDM development at the level of non-hematopoietically derived cell types controlling selection of diabetogenic T cells and/or pancreatic β cells targeted by these effectors. Since *trans*-interactions between relatively common and functionally normal allelic variants may contribute to IDDM in NOD mice, the search for *Idd* genes in humans should not be limited to functionally defective variants.

\(^1\) This work was supported by National Institutes of Health Grants DK46266, DK51090, and AI41469 (D.V.S.), DK36175 and DK27722 (E.H.L.), as well as by grants from the Juvenile Diabetes Foundation International, and Cancer Center Support (CORE) CA34196.

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Received for publication July 29, 1997. Accepted for publication October 9, 1997.

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but contains genetic material of C57BLKS/J (BKS) origin on regions of chromosomes (Chr.) 1, 2, 4, 5, 7, 11, 12, and 18 (17, 18). The BKS strain itself represents a recombinant congenic strain, carrying defined genomic contributions primarily from a C57BL/6 (B6) donor, but also from a “DBA/2-like” donor (19). Constitutive levels of MHC class I expression in NOD and NOR mice are equivalent to that of the BKS control strain (20). However, the ability of macrophages from NOD and NOR mice to mount up-regulate expression of H2βγδ MHC class I molecules in response to stimulation with IFN-γ is differentially controlled by genes within chromosomal regions distinguishing these two strains. IFN-γ fails to up-regulate H2βγδ MHC class I expression in macrophages from NOD mice, but does so normally in NOR macrophages (20). The failure of NOD macrophages to up-regulate MHC class I expression in response to IFN-γ could diminish the capacity of these APC to activate tolerogenic mechanisms that normally delete or inactivate diabetogenic CD8+ T cells. Autoreactive CD8+ T cells that are generated as a result of such tolerogenic defects in NOD mice could then be efficiently targeted to the pancreatic β cells, since these cells regulate H2βγδ MHC class I expression in a normal fashion. (NODxNOR)F₂ segregation analysis demonstrated that the major genetic component contributing to IDDM resistance in NOD is the Idd13 locus on Chromosome 2 in linkage with BKS-derived genes for β₂m, both isofoms of IL-1 (Illa and Il hb), and proliferating cell nuclear Ag (Pcen)(18). Existence of the Idd13 locus was confirmed by the induction of IDDM resistance in a stock of NOD mice congenic for an ~24 cM segment of NOR Chromosome 2 that contains these linkage markers flanked by the H3a minor histocompatibility and adenosine deaminase (Ada) genes (18, 21). However, it is unknown which gene(s) within this segment of Chromosome 2 contributes to IDDM susceptibility in NOD and resistance in NOR mice, and if this effect is mediated through a modulation of H2βγδ MHC class I expression or function. The present study was conducted to gain insight to these questions through an analysis of IDDM development and H2βγδ MHC class I expression and function in NOD stocks carrying variable truncations of the originally defined congenic segment of NOR Chromosome 2 found to confer Idd13-mediated resistance.

Materials and Methods

Mice

NOD/Lt and NOD/Lt mice (both H2βγδ = K4, Aβγδ, E(mll), Dp) have been maintained at The Jackson Laboratory by brother-sister mating. Currently, IDDM develops in 90% of female and 65% of male NOD/Lt mice by one year of age, whereas both sexes of NOR/Lt mice are IDDM resistant. A stock of NOD mice carrying a previously defined congenic segment of NOR Chromosome 2 conferring Idd13-mediated IDDM resistance was initially utilized at the N12 backcross generation (18, 21). To further refine the localization of genes contributing to IDDM resistance within the NOR-derived Idd13 locus, the Chromosome 2 congenic segment present in this N12 stock was variably truncated by further backcrossing to the NOD parental strain. Backcross mice were screened for further recombination events on Chromosome 2 using the genotyping methodologies described below. At the 20th backcross (N21) generation, the indicated NOR-derived Chromosome 2 congenic segments were fixed to homozygosity on the NOD background by brother-sister matings. C57BLKS/J (H2βδ) mice were supplied by the Animal Resources Unit of The Jackson Laboratory. All mice were maintained under specific pathogen-free (SPF) conditions and allowed free access to autoclaved Chow diet (diet 96WA, Emory Morse, Guilford, CT.) and acidified drinking water.

Assessment of diabetes and insulitis development

Mice from each of the indicated strains were simultaneously monitored at weekly intervals for the development of glycosuria with Ames Diastix (kindly supplied by Miles Diagnostics, Elkhart, IN). Glycosuric values of ≥3 were considered diagnostic of diabetes onset. Development of stable glycosuria was confirmed by weekly urinalysis for 2 weeks after the initial diagnosis. A subset of non-diabetic mice were necropsied for pancreatic histology at 1 year of age. Pancreata were stained with aldehyde fuchsin to detected granulated β cells and then counterstained with hematoxylin and eosin.

Genotyping methodologies

DNA samples used for genotypic analyzes were extracted from tail clips. Most polymorphic markers were typed either by PCR or Southern blotting as previously described (18, 22). Allelic variations at the H2α minor histocompatibility gene were typed as previously described (21) by assessing the sensitivity of splenic leukocytes from the various congenic stocks to lysis by cloned lines of gene product-specific cytotoxic T-lymphocytes (CTL).

Effect of B. m polymorphisms on the conformation of MHC class I molecules expressed by splenic leukocytes

Spleen leukocytes from the indicated strains were prepared as previously described (23), and resuspended at 2 x 10^7/mL in FACS buffer (PBS containing 0.1% sodium azide with 2% FBS). Aliquots of 1 x 10^6 cells (50 µl) were incubated for 30 min at 4°C with FITC-conjugated mAbs specific for the alallelicly variable regions of the H2Kβ (SF1-1.1) or H2Dβ (28-14-4) MHC class I molecules, or an epitope within the MHC class I constant region that undergoes dimerization with β₂m (M11/42) and is shared by all alleles. The cells were washed in FACS buffer after staining. Data for the extent of MHC class I Ab binding are presented as mean channel of log fluorescence (MF) ± SEM, as determined by FACScan (Becton Dickinson, San Jose, CA.) using the Cell Quest 3.0 data reduction program.

Regulation of MHC class I expression by IFN-γ in peritoneal macrophage cultures

Thiglycollate-elicited peritoneal macrophages were isolated from the indicated male mice using our previously described protocols (20). Macrophages were suspended at 2.0 x 10^7/mL in the previously described culture medium (23) in the presence and absence of 50 U/ml rat recombinant IFN-γ (kindly supplied by P. van de Meide, Rijswijk, Netherlands) and then incubated for 6 days at 37°C. At this time macrophages were harvested by washing with calcium- and magnesium-free HBSS and subsequent treatment with enzyme-free cell dissociation buffer (Life Technologies, Gaithersburg, MD). To assess IFN-γ-regulated levels of cell surface MHC class I expression, the macrophages were stained with the FITC-conjugated mAb 31–3–4S that recognizes the Kd MHC class I molecule shared by all of the strains used for these experiments. Levels of total Kd MHC class I expression in IFN-γ-treated and untreated macrophages are presented as MFI as determined by FACScan analysis.

Production of bone marrow chimeras

Females from the indicated strains were lethally irradiated (1200r from a 137Cs source) at 4 wk of age, and then reconstituted as previously described (24) with 5 x 10^6 bone marrow cells isolated from the indicated 8-wk-old female donors. Bone marrow chimeras were then reconstituted through a 21-wk postreconstitution for the development of IDDM as described above. Upon the onset of IDDM or at 21 wk of postreconstitution, chimerization was assessed by genotyping splenic DNA for donor or recipient type B2m polymorphisms by Southern blot analysis of a BglII restriction fragment length variant (B2m* = 801 bp fragment; B2m* = 575 and 226 bp fragments). A B2m-specific probe was generated by PCR amplification of C57BL/10J genomic DNA with the primer set 5’-CAAGCCACCCAC CGGAGAATG-3’ and 5’-GATGCTGTACACATGTCCTGC-3’.

Results

IDDM development in NOD mice congenic for various intervals of NOR Chromosome 2 carrying Idd13 resistance alleles

As shown in Table I, three congenic intervals derived from NOR Chromosome 2 were fixed to homozygosity on the NOD inbred background at the 20th backcross generation. The first of these congenic stocks carries the largest segment of NOR Chromosome 2 spanning a ~31.5 cM interval encompassing the link markers D2Mit490 through D2Mit144 (designated NOD.D2Mit490-Mit144NOB). This large congenic segment contains all markers previously found to be linked to Idd13-mediated IDDM resistance in NOR mice (18). This segment of NOR-derived Chromosome 2 is originally derived from the B6 strain contribution to the BKS genome (18) such that the H2α and B2mα alleles, as well as the
Table I. Comparative lengths of NOR-derived Chromosome 2 congenic segments crossed to the NOD genetic background

<table>
<thead>
<tr>
<th>Marker</th>
<th>Interval Between Markers (cM)*</th>
<th>NOD.D2Mit490-Mit144&lt;sub&gt;NOR&lt;/sub&gt;</th>
<th>NOD.H3a-Il1&lt;sub&gt;NOR&lt;/sub&gt;</th>
<th>NOD.II1-Pcna&lt;sub&gt;NOR&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actc</td>
<td>0.5</td>
<td>NOD</td>
<td>NOD</td>
<td>ND</td>
</tr>
<tr>
<td>D2Mit490</td>
<td>2.5</td>
<td>NOR</td>
<td>NOD</td>
<td>ND</td>
</tr>
<tr>
<td>H3a</td>
<td>2.0</td>
<td>NOR</td>
<td>NOR</td>
<td>NOD</td>
</tr>
<tr>
<td>β2m</td>
<td>4.0</td>
<td>NOD</td>
<td>NOD</td>
<td>NOD</td>
</tr>
<tr>
<td>Il1a</td>
<td>1.2</td>
<td>NOD</td>
<td>NOD</td>
<td>NOD</td>
</tr>
<tr>
<td>Pcna</td>
<td>4.3</td>
<td>NOR</td>
<td>NOD</td>
<td>NOR</td>
</tr>
<tr>
<td>D2Mit166</td>
<td>3.5</td>
<td>NOR</td>
<td>NOD</td>
<td>NOD</td>
</tr>
<tr>
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<td>3.5</td>
<td>NOD</td>
<td>NOD</td>
<td>NOD</td>
</tr>
<tr>
<td>Ada</td>
<td>3.0</td>
<td>NOD</td>
<td>ND</td>
<td>NOD</td>
</tr>
<tr>
<td>D2Mit144</td>
<td>4.0</td>
<td>NOD</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>D2Mit229</td>
<td>2.0</td>
<td>NOD</td>
<td>ND</td>
<td>ND</td>
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</tbody>
</table>

* Intervals between markers based on map positions obtained from The Jackson Laboratory’s Mouse Genome Database.

Microsatellite-based markers are the same as found in the B6 genome. The present analysis extends the proximal boundary of this NOR-derived Chromosome 2 congenic segment by ~4 cM to the D2Mit490 rather than the H3a marker, and the distal boundary by ~3 cM to D2Mit144 rather than Ada. Smaller intervals derived from this large segment of NOR Chromosome 2 through selection of recombinants have been fixed to homozygosity in two other NOD congenic stocks. One of these carries an ~6.0 cM congenic interval of NOR Chromosome 2 spanning the linkage markers H3a through Il1a (designated NOD.H3a-II1<sub>NOR</sub>). The other carries an ~1.2 cM segment of NOR Chromosome 2 spanning the interval delineated by Il1a and Pcna (designated NOD.II1-Pcna<sub>NOR</sub>).

As shown in Figure 1, by 30 wk of age the female incidence of IDDM in the NOD.D2Mit490-Mit144<sub>NOR</sub> congenic stock (16%) was significantly less than in standard NOD mice (100%). By 52 wk, IDDM incidence in these congenic females had increased to only 26% (5 of 19), and no diabetes was observed in a group of 18 NOD.D2Mit490-Mit144<sub>NOR</sub> congenic males (compared with 50% incidence in a group of 18 standard NOD/Lt males). Histologic analysis of insulitis in pancreata from three of these non-diabetic congenic mice of each sex necropsied at a year of age showed widespread perivascular/periductular leukocytic infiltrates. When associated with islets, these were primarily peri-insular, with granulated β cell mass largely preserved in >80% of the islets. This histopathology was similar to that observed in year-old NOR/Lt mice of both sexes. This confirmed the results originally obtained at an earlier backcross generation (18) that Iddd13-mediated IDDM resistance in NOR mice did not prevent the pancreatic T-lymphoaccumulation characteristic of NOD mice, but rather retarded activation of autoimmune effector functions. In this regard, the pancreatic histopathology in non-diabetic NOD.D2Mit490-Mit144<sub>NOR</sub> congenic mice was very reminiscent of that observed in a NOD stock made IDDM resistant through the elimination of B-lymphocyte development by congenic transfer of a null mutation in the Ig<sub>μ</sub> heavy chain locus (25).

Evidence that the Iddd13 locus is genetically more complex than initially reported was provided by the finding that the strong IDDM resistance conferred by an ~31.5 cM region of NOR Chromosome 2 spanning D2Mit490 through D2Mit144 was partially attenuated upon differential truncation of this interval in two subcongenic stocks of NOD mice (Fig. 1). By 30 wk of age, the female incidence of IDDM in both the NOD.H3a-II1<sub>NOR</sub> (56%) and NOD.II1-Pcna<sub>NOR</sub> (62%) congenic stocks was significantly lower than in standard NOD mice, but significantly higher than in the NOD.D2Mit490-Mit144<sub>NOR</sub> congenic stock. Similarly, the male incidence of IDDM in these two subcongenic stocks was significantly less than that observed in standard NOD mice. By a year of age, the cumulative incidence of IDDM in the NOD.H3a-II1<sub>NOR</sub> stock reached 62% (10 of 16) in females and 25% (4 of 16) in males. In the NOD.II1-Pcna<sub>NOR</sub> stock, IDDM developed in 75% (9 of 12) of females and 12% (2 of 17) of males by 46 wk of age. Thus, the H3a-II1 and/or II1-Pcna intervals on Chromosome 2 carry at least one, but not the complete set of polymorphic genes contributing to Iddd13 locus-mediated IDDM susceptibility in NOD and resistance in NOR mice.

Contribution of the Iddd13 locus to differential regulation of H2<sup>β</sup> MHC class I expression in IFN-γ-stimulated macrophages from NOD and NOR mice

While no defects in constitutive expression were observed, our previous studies demonstrated that IFN-γ stimulation fails to further up-regulate H2<sup>β</sup> MHC class I levels in NOD macrophages (20). Such a defect could conceivably reduce the ability of these APC in NOD mice to activate tolerogenic mechanisms that normally delete or inactivate diabetogenic CD8<sup>+</sup> T cells. We hypothesized that this possible APC tolerogenic defect might be controlled by a gene(s) within the Iddd13 locus since H2<sup>β</sup> MHC class I expression is up-regulated normally in IFN-γ-stimulated macrophages from IDDM-resistant NOR mice. To test this hypothesis, we compared the pattern of IFN-γ-regulated MHC class I expression in macrophages from the
The studies described above demonstrated that dimerization with different isoforms of \( \beta_m \) may alter the structural conformation of H2\( ^{g7} \) MHC class I molecules expressed on cell types regulating the original selection of diabetogenic T cells (thymic epithelium and hematopoietically derived APC) and/or on the pancreatic \( \beta \) cells targeted by these autoreactive effector cells. Such a mechanism may mediate the selection and targeting of diabetogenic T cells in the gut epithelium, which may play a role in the development of autoimmune diabetes.

### Contributions of the Idd13 locus to the selection and targeting of diabetogenic T cells

The studies described above demonstrated that dimerization with different isoforms of \( \beta_m \) may alter the structural conformation of H2\(^{g7} \) MHC class I molecules expressed on cell types regulating the original selection of diabetogenic T cells (thymic epithelium and hematopoietically derived APC) and/or on the pancreatic \( \beta \) cells targeted by these autoreactive effector cells. Such a mechanism may mediate the selection and targeting of diabetogenic T cells in the gut epithelium, which may play a role in the development of autoimmune diabetes.
reconstitution with NOR marrow elicited a significantly higher incidence of IDDM in NOD (55.5%) than in syngeneic NOR female recipients (0%). Thus, some portion of the Idd susceptibility or resistance variants distinguishing NOD from NOR mice control functions in non-hematopoietically derived cell types that regulate the development and/or functional activation of the diabetogenic T cells that normally differentiate from NOD bone marrow. Providing support that Idd13 variants are at least partial contributors to this process was the finding that reconstitution with NOD bone marrow resulted in a significantly lower incidence of IDDM in NOD.2Mit490-Mit144\^NOR recipients (37.5%) than in syngeneic NOD female recipients (75%). Furthermore, IDDM developed in 77.8% of standard NOD female recipients reconstituted with NOD2Mit490-Mit144\^NOR marrow. This was significantly greater than the IDDM incidence in NOD2Mit490-Mit144\^NOR recipients of syngeneic marrow (26.7%), but did not differ from that of NOD recipients reconstituted with syngeneic marrow.

**Discussion**

We have previously demonstrated that the major genetic component contributing to T cell-mediated autoimmune IDDM susceptibility in NOD mice vs resistance in the H2\^\*
identical NOR strain is the Idd13 locus on Chromosome 2 (18). The present study demonstrates that multiple polymorphic genes within the originally defined Idd13 locus contribute to IDDM susceptibility or resistance. Our data demonstrates that the Idd13 locus does not contribute to autoimmune IDDM by controlling the previously described phenotype of defective vs normal trans-regulation of IFN-\gamma-stimulated H2\^\* MHC class I expression in hematopoietically derived macrophages from NOD and NOR mice (20). Indeed, the present studies indicate that at least some portion of the multiple genes contributing to Idd13-mediated IDDM susceptibility or resistance exert their effects in non-hematopoietically derived cell types. These could include thymic epithelial cells contributing to the original selection of the T cell repertoire, and/or the pancreatic \(\beta\) cells targeted by autoreactive T cells in IDDM. Along these lines it should be noted that Idd13 represents the first locus we have identified that does not exert a pathogenic or protective effect at the level of hematopoietically derived cell types (30).

The H3a-II1 and II1-Pcna intervals on Chromosome 2 carry at least one, but not the complete set, of polymorphic genes contributing to Idd13-mediated IDDM susceptibility in NOD and resistance in NOR mice. Since the H3a-II1 and II1-Pcna intervals overlap, it is possible that they share a gene contributing to IDDM susceptibility or resistance. One seemingly good candidate would be the structural genes for both isoforms of IL-1 that are contained within both of these intervals. Their candidacy is based on the findings that NOD macrophages are poorer producers of IL-1 (23, 31), and that IDDM is inhibited in NOD mice treated with IL-1 in vivo (31). However, arguing against the candidacy of NOD-derived II1 alleles as contributors to IDDM is that despite the presence of BKS-derived II1 variants, macrophages from NOR mice are also defective in IL-1 production (17). The unlikely contribution of II1 variants to IDDM susceptibility or resistance supports the possibility that H3a-II1 and II1-Pcna intervals carry separate components of Idd13. However, regardless of whether the H3a-II1 and II1-Pcna intervals are characterized by shared or different Idd genes, it remains possible that additional polymorphic genes outside of these regions, but within the larger segment flanked by D2Mit490 and D2Mit144, also contribute to Idd13-mediated IDDM susceptibility or resistance. Subcongenic analysis of the Idd10 region on Chromosome 3 (32) and the Idd2 region on Chromosome 9 (this laboratory, unpublished) are similarly providing evidence that Idd loci initially inferred to be composed of single genes in fact represent contributions from multiple genes.

Within the H3a-II1 interval, allelic variants of B2m represent an excellent candidate for representing one component of Idd13-mediated IDDM susceptibility in NOD and resistance in NOR mice. The \(\beta_2\)m\(^b\) (NOD type) and \(\beta_2\)m\(^b\) (NOR type) isoforms exert trans-acting effects that alter the structural conformation, but not the total expression levels, of H2\^\* MHC class I molecules shared by NOD and NOR mice. Such alterations in the structural conformation of H2\^\* MHC class I molecules elicited by dimerization with different isoforms of \(\beta_2\)m may skew their ability to bind and present certain Ags, and hence contribute to IDDM susceptibility or resistance by effecting the selection and/or targeting of \(\beta\) cell autoreactive CD8\(^+\) T cells. Support for this possibility is provided by previous reports that dimerization with different \(\beta_2\)m isoforms may alter the structural conformation of MHC class I molecules (26–28), which may in turn skew the array of antigenic peptides they bind and present to CD8\(^+\) T cells (29). Our bone marrow chimera studies indicate that any such effects are manifest at the level of non-hematopoietically derived thymic epithelial cells contributing to the original selection of the T cell repertoire, or at the level of pancreatic \(\beta\) cells targeted by autoreactive T cells in IDDM. Supporting this hypothesis is that in retrospect, all nominally resistant mouse stocks that developed IDDM following reconstitution with NOD marrow have been at least heterozygous for the B2m\(^b\) allele (24, 33–37). Further evidence that heterozygous expression of the B2m\(^b\) allele may be sufficient to support IDDM development is provided by our previous finding that the NOR-derived Idd13 locus (containing B2m\(^b\)) can only inhibit disease when in the homozygous state (18). It should also be noted that neither the B2m\(^b\) nor B2m\(^b\) variant can be considered to represent a deleterious mutant allele since the gene products encoded by both function normally in terms of mediating the transport to and stable expression of MHC class I molecules on cell surfaces. Thus, if future studies ultimately demonstrate that B2m variants represent actual Idd susceptibility and resistance alleles, it would strongly support the previously proposed hypothesis (8) that autoimmune IDDM is not produced by rare
mutations, but rather a set of common genetic variants that have coalesced in a dysfunctional array.

The present findings in no way support previous assertions by a single laboratory (38–40) that NOD splenic leukocytes are characterized by aberrantly low constitutive levels of MHC class I molecules as a consequence of defects in expression of the intron-MHC Tαp1 gene. None of the findings from this aforementioned laboratory have been replicated by other investigators (10–11, 20, 41–45). The erroneous conclusion that constitutive MHC class I expression was decreased can be explained by the fact that T lymphocyte numbers, which normally express lower levels of class I than other leukocyte populations, are proportionally increased in NOD lymphoid organs relative to that observed in diabetes-resistant strains (42, 44). A polymorphism in an intron of the NOD Tαp1 gene was shown by others not to affect loading of Ag to MHC class I molecules or their presentation to CTLs (21, 46). The conclusion that mice lacking a functional B2m gene developed spontaneous autoimmune diabetes (38) has also not been replicated (9–12). As emphasized above, NOD and NOR mice are H2g7-identical, and thus share the same Tαp genes. Neither strain is β2m deficient; the allelic polymorphism distinguishing NOD from NOR entails a single amino acid difference at position 85 (47). Dimerization with these subtly different isoforms of β2m may affect the structural conformation of the H2g7 MHC class molecules, but not their overall (normal) level of expression.

In conclusion, our studies have demonstrated that multiple polymorphic genes within the originally defined Idd13 locus on Chromosome 2 contribute to IDDM susceptibility in NOD mice and resistance in the H2g7 identical NOR strain. It is possible that normal allelic variants of B2m represent one component of Idd13 through an ability to differentially alter the structural conformation of the relatively common H2g7 MHC class I molecules and hence promote or inhibit their ability to select and/or target diabetogenic T cells. If correct, this would indicate that some of the processes that underlie the development of autoimmune IDDM in NOD mice are controlled by trans-interactions between relatively common and functionally normal allelic variants. That trans-interactions between relatively common and functionally normal allelic variants may contribute to autoimmune IDDM in NOD mice indicates that the search for Idd genes in humans should not be limited to functionally defective variants.

References


