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A Major Histocompatibility Complex Class II Restriction for BioBreeding/Worcester Diabetes-inducing T Cells

By Karen E. Ellerman and Arthur A. Like

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Summary

Inbred diabetes-prone (DP) BioBreeding/Worcester (BB/Wor) (RT1u) rats develop spontaneous autoimmune diabetes, which, like human insulin-dependent diabetes mellitus, is mediated by autoreactive T lymphocytes. Breeding studies have shown an absolute requirement for at least one copy of the major histocompatibility complex (MHC) RT1u haplotype for spontaneous diabetes expression. Concanavalin A-activated spleen cells from acutely diabetic DP rats adoptively transfer diabetes only to recipients that express at least one RT1u haplotype. To investigate the basis for the MHC requirement in BB/Wor autoimmunity, diabetes-inducing T cell lines were derived from the spleens of acutely diabetic DP rats. Upon activation in vitro with islet cells, the T cell lines adaptively transfer insulitis and diabetes into young DP recipients and non-diabetes-prone RT1 congenic rat strains that are class II u. Recipients that are RT1a at only the class I A or C locus, but not at the class II B/D loci, do not develop diabetes after T cell transfer. The adoptive transfer of diabetes by Concanavalin A-activated diabetic DP spleen cells also requires that donor and recipient share class II B/Du gene products. Furthermore, the adoptive transfer of diabetes into MHC class IIu congenic rats is independent of the class I haplotype; i.e., it occurs in the presence of class I Aa Cu or Aa Cy gene products. BB/Wor T cells can be activated in vitro for the transfer of diabetes with islet cell antigens and class II-positive but not class II-negative antigen-presenting cells. The inductive phase of BB diabetes is therefore MHC class II restricted, and this appears to operate at the level of interaction between inducing T cells and class IIu antigen-presenting cells. These results may explain the well-documented, but not yet understood, MHC class II genetic contribution to insulin-dependent diabetes mellitus pathogenesis, and they may facilitate the development of protocols designed to prevent diabetes onset in susceptible individuals.

Diabetes-prone (DP)1 BioBreeding/Worcester (BB/Wor) rats develop spontaneous autoimmune diabetes, in which the frequency of insulin-dependent, ketosis-prone hyperglycemia is 80–95% in both sexes. BB diabetes is characterized morphologically by a β cell–specific mononuclear cell infiltrate (insulitis) within the pancreatic islets of Langerhans. The autoimmune attack selectively destroys the insulin-producing β cells, with sparing of glucagon-, somatostatin-, and pancreatic polypeptide–synthesizing islet cells (1). These clinical features of BB diabetes are identical to those of human insulin-dependent diabetes mellitus (IDDM) (2).

BB/Wor rat diabetes is T cell dependent; the development of hyperglycemia is prevented by neonatal thymectomy (3) and in vivo treatment with mAbs directed against CD5+ (pan T) or CD8+ (cytotoxic) T cells (4). Spontaneous BB diabetes is an MHC-linked disease. Breeding studies have shown an absolute requirement for at least one copy of the MHC RT1u haplotype for the appearance of spontaneous diabetes in crosses between BB and non-BB strains of rat (5–7). Genetic susceptibility, however, has not been previously assigned to single genes of the MHC, nor have the immune effector mechanisms leading to β cell destruction been identified as being class I– or class II–restricted events.

BB/Wor diabetes can be adoptively transferred with acutely diabetic DP spleen cells that have been activated in vitro with Con A, a polyclonal mitogen (8), or staphylococcal enterotoxin E (SEE; Toxin Technology, Sarasota, FL) (9), a T cell receptor Vβ family-specific stimulus (10). Adoptive transfer has been demonstrated using young DP (8), cyclophosphamide–treated histocompatible RT1u non-BB (11) or athymic nude RT1u rats (12) as recipients. Transfer studies using young DP recipients have implicated both the CD4+ (13) and CD8+ (14) T cell subsets as being necessary for adoptive transfer. Since DP recipients possess

1Abbreviations used in this paper: BB/Wor, BioBreeding/Worcester; CAS, Con A-activated Lewis rat splenocytes; DP, diabetes prone; DR, diabetes resistant; IDDM, insulin-dependent diabetes mellitus; NOD, nonobese diabetic; SEE, staphylococcal enterotoxin E.
an endogenous cohort of autoreactive CD4⁺ and CD8⁺ T cells, these studies do not permit a precise determination of the cell type required for initiating the diabetogenic process. Experiments designed to discriminate between inductive versus effector events and to map each arm of the diabetogenic immune response to a specific MHC locus would require the use of non-BB, non–diabetes-prone RT1⁺ class I or class II congenic recipients in adoptive transfer studies. In non-BB RT1⁺ congenic recipients, one can measure de novo disease induction rather than the acceleration of a spontaneous disorder that would eventually occur in diabetes-prone BB recipients.

To investigate the basis for the MHC requirement in BB autoimmune diabetes, diabetes-inducing T cell lines were generated from the spleens of acutely diabetic DP rats. The diabetes transfer capabilities of the T cell lines were tested in syngeneic and class I or class II congenic non–diabetes-prone recipients. The ability of class I or class II congenic APC to activate the T cells in vitro for the adoptive transfer of diabetes in vivo was also assessed. The results presented herein explain, at least in part, the MHC genetic contribution to IDDM pathogenesis in the rat and shed light on the pathogenesis of β cell destruction.

Materials and Methods

Animals. BB/Wor DP and BB/Wor diabetes-resistant (DR) rats and inbred PVG.R8, PVG.R23, LEW1.1R2, and LEW1.W1R1 rats were raised at the University of Massachusetts Medical Center (Worcester, MA) under viral antibody–free conditions. Viral antibody–free LEW1.1R2 and LEW1.W1R1 breeding stock were obtained from the Central Institute for Laboratory Animal Breeding (Hannover, Germany).

Islet Cell Preparation. Islets were isolated from 90-d DR rats by the method of Gotot et al. (15). Pancreatic tissue was digested with 4 mg/ml collagenase P (Boehringer Mannheim Corp., Indianapolis, IN) for 25 min at 37°C. Islets were enriched on Histopaque 1077 (Sigma Chemical Co., St. Louis, MO) under viral antibody–free conditions. Viral antibody–free LEW1.1R2 and LEW1.W1R1 breeding stock were obtained from the Central Institute for Laboratory Animal Breeding (Hannover, Germany).

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riched on density gradients and recultured in CAS as a source of T cell growth factors. At the second round of antigen-specific selection, T cells were stimulated with whole BB/Wor islet cells and APC. Islet cell-reactive T lymphocytes were restimulated with either SEE and APC or with islet cells and APC. This protocol generates a population of T cells with potent diabetes transfer activity. A single intraperitoneal injection of 12–34 × 10⁶ T cells adoptively transferred diabetes into 21–28-d-old DP recipients in as few as 5 d after cell injection (Table 1), with a mean time to hyperglycemia of 7.9 d (n = 48). DP rats also develop spontaneous thyroiditis, although at a low and variable incidence (22). Diabetic recipients of T cell lines, however, did not develop thyroiditis (n = 48). Hyperglycemia was always accompanied by a β cell-destructive insulitis.

Only antigen-activated T cells transfer disease; unstimulated (resting) T cells transferred >5 d after antigen activation (with islet cells or SEE) did not induce adoptive diabetes (Table 1, line 4) or insulin. By single-color flow cytometry, the cell lines were comprised (at all time points tested) of 70–90% CD4+ and 10–30% CD8+ T cells (data not shown). Although DP rats have low, barely measurable levels of CD8+/CD5+ CTLs and increased numbers of CD8+/CD5+/3.2.3+ NK cells (23, 24), the T cell lines did not contain 3.2.3+ NK cells at any time. The cell lines proliferate in vitro in response to both islet cells and SEE (data not shown). One cell line (A91-1), also derived from acutely diabetic DP spleens, was initially selected and then repetitively stimulated in vitro with whole islet cells and APC, but it did not transfer diabetes or insulin into any of 28 DP recipients (21–25 d old) given 19–57 × 10⁶ T cells (data not shown). The initial in vitro activation step with SEE appears to select for T cells with both islet cell reactivity and diabetes transfer capabilities. Adoptive Transfer of T Cell Line-mediated Diabetes is MHC Class II Restricted and Independent of Class I Haplotype. To exclude the possibility that the T cell lines were simply accelerating or costimulating an endogenous immune process genetically present in DP recipients, T cell lines were transferred into RT1 congenic non-BB strains of rat. These congenics contain non-BB RT1u genes, in different allelic combinations on the genetic background of parental Lewis (RT11) and PVG (RT1q) strains. Neither the RT1u congenics nor their parental strains spontaneously develop insulitis or diabetes. To prepare congenic rats for BB/Wor T cell injections, recipients were treated with cyclophosphamide 24 h before transfer. Cyclophosphamide depletes T cells and enables RT1 congenic rats to accept the BB/Wor T cells, with which they share only partial genetic identity (11). Cyclophosphamide alone does not induce diabetes or insulitis in RT1 congenic rats (see Table 3).

Islet cell–activated T cell lines injected into PVG.R8 rats induced diabetes and insulin in 14 out of 17 recipients, with a mean time to hyperglycemia of 7.4 d (Tables 2 and 3). Pancreatic tissue sections taken from diabetic and control cyclophosphamide-treated PVG.R8 rats were immunostained for the localization of islet cell peptide hormones. Islets of Langerhans from diabetic rats exhibited destructive lymphocytic insulitis with depletion of insulin-producing β cells and sparing of glucagon-producing α cells (Fig. 1 C and D) and somatostatin-producing δ cells (data not shown). Cyclophosphamide-treated rats revealed no insulitis and had normal numbers and distributions of α, β (Fig. 1, A and B), and δ cells. Islet cell–activated T cells also transferred diabetes and insulitis into 9 out of 10 LEW1.WR1 rats (Table 3), with a mean time to hyperglycemia of 9.7 d and a mean blood glucose of 20.4 mmol/liter. Thus, BB/Wor islet cell–activated T cell lines have an in vivo specificity for insulin-producing β cells, even when transferred into a non-BB genetic environment.

When islet cell–activated T cells were transferred into PVG.R23 recipients, none of the rats developed insulin or diabetes (Table 3). T cells from the lines used in these experiments (at the same or a later passage) transferred dia-

### Table 1. BB/Wor Diabetes-inducing T Cell Lines

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Incidence of diabetes</th>
<th>Stimulus</th>
<th>Cell No.</th>
<th>Mean time to diabetes (d)</th>
<th>Mean blood glucose (mmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF-1</td>
<td>6/6</td>
<td>Islet cells</td>
<td>16-20</td>
<td>7</td>
<td>26.4</td>
</tr>
<tr>
<td>BF-1</td>
<td>3/3</td>
<td>SEE</td>
<td>32</td>
<td>5</td>
<td>25.0</td>
</tr>
<tr>
<td>BB-3</td>
<td>4/4</td>
<td>Islet cells</td>
<td>19</td>
<td>6</td>
<td>19.8</td>
</tr>
<tr>
<td>BB-3</td>
<td>0/4</td>
<td>None</td>
<td>22</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BB-3</td>
<td>2/2</td>
<td>Islet cells</td>
<td>12</td>
<td>8</td>
<td>15.7</td>
</tr>
<tr>
<td>BB-5</td>
<td>3/3</td>
<td>SEE</td>
<td>34</td>
<td>12</td>
<td>28.9</td>
</tr>
<tr>
<td>J193</td>
<td>2/3</td>
<td>Islet cells</td>
<td>17</td>
<td>7</td>
<td>27.9</td>
</tr>
</tbody>
</table>

T cell lines were activated for 3 d with islet cells/APC or SEE/APC as described in Materials and Methods. Blast-transformed cells were harvested on Histopaque 1077 and cultured for a further 2 d in 10% CAS. Resting T cells (no stimulus) were transferred after 2 passages in CAS. T cells were injected intraperitoneally into 21–28-d female DP rats. Recipients were monitored for 21 d for the development of hyperglycemia (blood glucose ≥13.8 mmol/liter). A total of 45 out of 48 DP rats injected with T cell lines developed diabetes, with a mean time to hyperglycemia of 7.9 d.
of 21 d for glycosuria and hyperglycemia (blood glucose > 13.8 mmol/liter).

To confirm the in vivo MHC restriction pattern obtained with islet cell-activated T cell lines, Con A–activated acutely diabetic DP spleen cells were also injected into cyclophosphamide-treated RT1 congenic rats. One spleen equivalent of Con A–activated cells transferred diabetes and insulitis into PVG.R8 and LEW1.WR1 but not PVG.R23 and LEW1.AR2 rats (Table 4). 13 out of 14 LEW1.AR2 recipients developed fulminating GVHD (manifested by wasting, anemia, and massive splenomegaly) 10 d after transfer. Two out of three DP rats concurrently receiving the same Con A–activated spleen cells developed diabetes at 10–11 d after transfer. Thus, cells with diabetogenic potential survived in LEW1.AR2 recipients, but without inducing hyperglycemia or insulitis.

As assessed by adoptive transfer, the cognitive or inductive phase of BB diabetes is MHC class IIα restricted and can proceed in the presence of either class I Aα or Cα gene products. Thus, the induction of transferred diabetes is dependent first upon CD4+ T cell recognition of β cell autoantigen in the context of class IIα in recipient target tissue (islet of Langerhans). These experiments do not, however, rule out a role for CD8+ CTL in the autoimmune attack leading to β cell destruction.

**Class II Restriction of BB Diabetes Operates at the Level of Interaction between Inducing T Cells and APC.** To examine the APC as a potential locus for the class IIα restriction, BB T cell lines were activated in parallel with sonicated BB islet cells and BB or RT1 congenic APC (irradiated spleen products for the successful transfer of BB/Wor diabetes.

### Table 2. Adoptive Transfer of Diabetes into PVG.R8 Rats by Islet Cell-activated BB/Wor T Cell Lines

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Cell No.</th>
<th>Incidence of diabetes (× 10^6)</th>
<th>Mean time to diabetes (d)</th>
<th>Mean blood glucose (mmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ju92</td>
<td>31</td>
<td>3/4</td>
<td>7</td>
<td>23.8</td>
</tr>
<tr>
<td>BB-5</td>
<td>39</td>
<td>6/6</td>
<td>7.5</td>
<td>25.2</td>
</tr>
<tr>
<td>092</td>
<td>16</td>
<td>3/4</td>
<td>8</td>
<td>17.9</td>
</tr>
<tr>
<td>092</td>
<td>29</td>
<td>2/3</td>
<td>7</td>
<td>24.6</td>
</tr>
</tbody>
</table>

T cell lines were activated for 3 d with islet cells and APC as described in Materials and Methods. Blast-transformed cells were harvested on Histopaque 1077 and cultured for a further 2 d in 10% CAS. T cells were injected intraperitoneally into 21–30-d female PVG.R8 rats treated 24 h earlier with cyclophosphamide, 180 mg/kg body weight. None of eight female PVG.R8 rats given 180 mg/kg cyclophosphamide alone developed diabetes or insulitis. All rats were monitored for 21 d for the development of glycosuria and hyperglycemia (blood glucose ≥ 13.8 mmol/liter).

The combined data from Tables 2 and 3 demonstrate that donor and recipient must share class II RT1α gene products for the successful transfer of BB/Wor diabetes. RT1α congenicity at only the class I RT1A or RT1C locus is not sufficient for T cell–mediated transfer of diabetes. Of importance is the observation that the adoptive transfer of autoimmune diabetes into class IIα congenic rats is independent of the class I haplotype; i.e., diabetes transfer occurs in the presence of class I Aα Cα (PVG.R8) or Aα Cα (LEW1.WR1) gene products.

### Table 3. Adoptive Transfer of Diabetes into MHC Congenic Rat Strains by Islet Cell-activated BB/Wor T Cell Lines

<table>
<thead>
<tr>
<th>Strain</th>
<th>RT1 haplotype</th>
<th>Cell No.</th>
<th>Incidence of diabetes (× 10^6)</th>
<th>Incidence of insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVG.R8</td>
<td>Aα B/ DαCα</td>
<td>16–39</td>
<td>14/17</td>
<td>14/17</td>
</tr>
<tr>
<td>PVG.R8</td>
<td>Aα B/ DαCα</td>
<td>0</td>
<td>0/8</td>
<td>0/8</td>
</tr>
<tr>
<td>PVG.R23</td>
<td>Aα B/ DαCαβ</td>
<td>27–36</td>
<td>0/14</td>
<td>0/14</td>
</tr>
<tr>
<td>PVG.R23</td>
<td>Aα B/ DαCαβ</td>
<td>0</td>
<td>0/11</td>
<td>0/11</td>
</tr>
<tr>
<td>LEW1.AR2</td>
<td>Aα B/ DαCα</td>
<td>36</td>
<td>0/7</td>
<td>0/7</td>
</tr>
<tr>
<td>LEW1.AR2</td>
<td>Aα B/ DαCα</td>
<td>0</td>
<td>0/10</td>
<td>0/10</td>
</tr>
<tr>
<td>LEW1.WR1</td>
<td>Aα B/ DαCα</td>
<td>28</td>
<td>9/10</td>
<td>9/10</td>
</tr>
<tr>
<td>LEW1.WR1</td>
<td>Aα B/ DαCα</td>
<td>0</td>
<td>0/7</td>
<td>0/7</td>
</tr>
</tbody>
</table>

21–30-d-old male and female RT1 congenic rats received cyclophosphamide, 180 mg/kg body weight intraperitoneally, 24 h before cell transfer. Control rats received cyclophosphamide alone. Rats were monitored for 21 d for glycosuria and hyperglycemia (blood glucose ≥ 13.8 mmol/liter).

### Table 4. Adoptive Transfer of Diabetes into MHC Congenic Rat Strains by Con A-activated Spleen Cells from Acutely Diabetic Diabetes-prone BB/Wor Rats

<table>
<thead>
<tr>
<th>Strain</th>
<th>RT1 haplotype</th>
<th>Diabetes</th>
<th>Insulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVG.R8</td>
<td>Aα B/ DαCα</td>
<td>19/23</td>
<td>21/23</td>
</tr>
<tr>
<td>PVG.R23</td>
<td>Aα B/ DαCαβ</td>
<td>0/17</td>
<td>0/17</td>
</tr>
<tr>
<td>LEW1.AR2</td>
<td>Aα B/ DαCα</td>
<td>0/14</td>
<td>0/11</td>
</tr>
<tr>
<td>LEW1.WR1</td>
<td>Aα B/ DαCα</td>
<td>5/5</td>
<td>5/5</td>
</tr>
<tr>
<td>BB/Wor DP</td>
<td>Aα B/ DαCα</td>
<td>24/27</td>
<td>25/27</td>
</tr>
</tbody>
</table>

Recipients were 21–30-d-old rats of both sexes. Each rat received one spleen equivalent of Con A–activated acutely diabetic DP spleen cells intraperitoneally or intravenously. Congenic rats received cyclophosphamide, 150–180 mg/kg body weight i.p., 24 h before spleen cell injections. For each experiment, rats were concurrently transferred into both congenic and BB rats. Recipients were monitored for 3 wk (BB rats) or 4 wk (congenic rats) for the development of hyperglycemia (blood glucose ≥ 13.8 mmol/liter).
Figure 1. Photomicrographs show adjacent pancreatic islet sections taken from PVG.R8 rats treated with cyclophosphamide alone (A, B) or cyclophosphamide followed 24 h later by an injection of islet cell-activated BB/Wor T cells (C, D). Tissues were fixed in Bouin's solution, and an immunoperoxidase technique was used for identification of insulin (A, C) and glucagon (B, D). The islets of cyclophosphamide control (A, B) reveal no evidence of insulitis. Insulin-positive β cells (A) and surrounding glucagon-positive α cells (B) are normal in appearance. The islets of the diabetic rat reveal an intrasitlet mononuclear cell infiltrate with almost complete destruction of the pancreatic β cells (C). Peripheral glucagon-positive α cells (D) are preserved in the diabetic PBV.R8 rats. A and B, ×200; C and D, ×170.

cells). The sonication step was added to deplete the islet cells of intact class II+ APCs of BB origin, as such cells are a normal component of the islets of Langerhans. After activation, equal numbers of T cells were injected into 21–25-d DP recipients, which were monitored for hyperglycemia for 15 d after cell injection. BB T cells activated in vitro with islet cell antigens and BB, PVG.R8 (B/D0), or LEW1.WR1 (B/D0) APC, but not PVG.R.23 (B/D0) or LEW1.AR2 (B/D0) APC, adoptively transferred diabetes (Table 5). Thus, BB diabetes-inducing T cells are class II restricted both in vivo and in vitro. The class II restriction appears to operate at the level of the interaction between inducing T cells and class II APC.

Discussion

BB autoimmune diabetes is an MHC-linked disease with a requirement for both CD4+ (13) and CD8+ (4, 14) T cells. To investigate the basis for the MHC requirement, diabetes-inducing T cell lines were generated from the spleens of acutely diabetic DP rats. When activated in vitro with whole islet cells and APC, the T cell lines have potent diabetes transfer activity, wherein a single injection of T cells adoptively transferred hyperglycemia into 21–28-d-old DP recipients in as few as 5 d after injection. Hyperglycemia was always accompanied by a β cell-destructive insulitis with sparing of the glucagon- and somatostatin-secreting islet cells. Although DP rats may also develop spontaneous thyroiditis (22), diabetic recipients of T cell lines never manifested any signs of intrathyroid lymphocytic infiltrates. Interestingly, the T cell lines can also be activated for diabetes transfer with the superantigen, SEE. The ability of a superantigen to activate diabetes-inducing T cells is reminiscent of a recent report suggesting a role for superantigen in human IDDM etiology (25).

To determine which type of T cell initiates the development of diabetes, BB/Wor T cell lines were injected into non–diabetes-prone RT1u class I or class II congenic recipients. Upon islet cell activation in vitro, the T cell lines rapidly transferred insulitis and diabetes into class II congenic rats. Recipients that are RT1u at only the class I A or C locus, but not at the class II B/D loci, did not develop diabetes after T cell transfer. The adoptive transfer of dia-
with class I hyperexpression and infiltrating CD8+ T cells and then present antigen to cell peptide-specific protein that is taken up by class II+ intraislet APC, which being invariant concomitants of the autoimmune attack BB rat cell peptide-specific CD8+ T cells do, however, express class I products in vivo, producing cell targets do not express detectable MHC gene products. In important in BB diabetes. Anti-CD8 mAb treatment re-
cytoxins in situ that ultimately lead to β cell cytosis (32). A formal demonstration of a role for CD8+ CTL in BB diabetes would depend upon the ability of islet cell-activated CD8+ T cells to adoptively transfer insulitis and hyperglycemia into class I+ congenic recipients, irrespective of the animals' class II haplotype. Finally, if CD8+ CTL are the final effectors of β cell cytosis, then the data presented above suggest that they can recognize β cell autoantigen in the context of either class I A+ (LEW1.WR1) or C+ (PVG.R8) gene products.

In the nonobese diabetic (NOD) mouse model of IDDM, both CD4+ and CD8+ spleen cell populations are also required for the transfer of diabetes into young NOD (33–35) or NOD-scid/scid recipients (36). However, the matter has not been further clarified by transferring spleen cells into other inbred strains of mice that are class I (H-2Kd) or class II (NOR/Lt [37], B10.H-2b [38]) congenic with NOD mice. Diabetes-accelerating CD4+ T cell clones have been described in the NOD mouse (39), but their ability to induce (as opposed to accelerate) diabetes in non-NOD MHC class II congenic recipients has not been reported. Furthermore, the acceleration of diabetes in NOD mice given CD4+ T cell clones is effective only if the recipients are <19 d of age (40). In contrast, BB T cells efficiently transfer diabetes into 21–30-d-old BB or class II+ congenic recipients.

The MHC contains the predominant genetic susceptibility factors for IDDM in humans (41, 42), the BB rat (7), and the NOD mouse (43, 44). In particular, MHC class II genes are associated with disease susceptibility in all three species (45–47). The manner in which the products of the IDDM-associated MHC genes influence the pathogenesis of diabetes is still unknown. The mechanism could be either at the level of thymic T cell selection or during peripheral immune response activation, both of which require appropriate peptide presentation by MHC molecules. Our data indicate that, in the BB rat, the MHC class II ge-

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Source of APC</th>
<th>Class II loci</th>
<th>Incidence of diabetes</th>
<th>Mean time to diabetes</th>
</tr>
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<tr>
<td>1</td>
<td>BB/Wor</td>
<td>B/D7</td>
<td>7/8</td>
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<tr>
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</table>
netic contribution to IDDM pathogenesis may be explained by binding of β cell peptide to permissive class IIα molecules, resulting in the activation of diabetes-inducing T cells. Specifically, BB T cells can be activated in vitro for the transfer of diabetes with islet cell antigens and class IIα-positive, but not class IIα-negative, APC (Table 5). The MHC class II restriction of BB diabetes thus operates at the level of interaction between inducing T cells and class IIα APC. These data lend support to the peptide affinity model for the class II genetic contribution to IDDM susceptibility: Susceptibility is caused by peptide presentation by a class II gene product that binds diabetogenic peptide, resulting in the activation of β cell-specific autoreactive T cells (48).

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