Maternal Immunization Protects Weanling LEW.1WR1 Rats from Autoimmune Diabetes Induced by Multiple Virus Infections

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Abstract

Viral infection may play an important role in the pathogenesis of human type 1 diabetes. We previously reported that MHC congenic (RT1u/u/a) LEW.1WR1 rats in the BRM colony develop spontaneous autoimmune diabetes at a low frequency (~2%) and are also susceptible to the induction of diabetes in response to environmental perturbations. In particular, LEW.1WR1 rats are highly susceptible to induction of diabetes after viral infection. The porovirus, Kilham rat virus (KRV; 105 PFU) induces diabetes in approximately 40% of animals. Infection with Coxsackie B4 virus (CoxB4; 108 PFU) induces diabetes in varying incidence (20-40%). Coxsackie B4 virus (CoxB4; 108 PFU) induces diabetes in up to 100% of animals. We previously demonstrated that infection of LEW.1WR1 dams with both KRV and RCMV prior to pregnancy (“maternal immunization”) protected pups from diabetes induced by inoculation of both viruses. To test if this novel strategy would work in weanling rats, we tested whether maternal immunization with RCMV alone would protect pups from RCMV-induced diabetes or KRV-induced diabetes. While we observed 62% induction of diabetes in pups in naïve females, none of the pups weaned from the immunized females developed diabetes (O). We further observed that maternal immunization with RCMV did not protect pups from KRV-induced diabetes – 62% of the pups weaned from RCMV-immunized females developed diabetes after KRV infection. These data demonstrate that maternal immunization with multiple viruses weakens the anti-virus-induced diabetes. The observed protection is virus-specific.

Background

Type 1 diabetes mellitus (T1D) is an autoimmune disease that remains exceedingly difficult to study in children. Despite intensive research in children and animal models, the causes of T1D remain unknown, and there are as yet no safe and effective methods for its prevention. Expression of T1D in humans is clearly modulated by environmental perturbations. Among individuals with high risk HLA alleles, only about 1 in 15 children in the general population and 1 in 5 with a first degree relative with T1D will develop disease. Additionally, the observation that the concordance for T1D among identical twins is approximately 40% supports the theory of an environmental trigger.

Among candidate perturbants, strong evidence suggests that viral infection is the most important, particularly in populations in which the prevalence is increasing. The association was first noted in the 1920s and 30s in children with several viral agents. Kilham rat virus (KRV) and Rat Cytomegalovirus (RCMV) both induce diabetes in ~40% of the animals. In the studies presented here, we demonstrate that maternal immunization can prevent diabetes induced by either one or two concurrent infections in weanling LEW.1WR1 rats. These data suggest that vaccination strategies directed at candidate viruses could be successful in preventing juvenile diabetes.

Methods

LEW.1WR1 Rats

- MHC haplotype RT1u
- Shares MHC Class II haplotypes common to all diabetic rats
- 2% incidence spontaneous diabetes
- Abnormal onset of hyperglycemia, glycosuria, proteinuria and ketonuria
- Normal immune cell profile
- Equally sensitive to environmental induction of diabetes

Maternal Immunization Experiments

As shown in Figure 1, 20-25 day old male and female BDxBR/Wor or LEW.1WR1 rats were infected (p) with the agents listed in Table 1. Following treatment, animals were killed for immunohistochemistry using an antibody that recognizes the RCMV early antigen. Serial sections were also stained with hematoxylin and eosin (H&E). Viral antigen (brown staining) was readily detected in salivary glands of infected animals while no viral antigen was detected in pancreata from the same animals.

Results

Table 2: Maternal Immunization is Effective and Specific in Protection from Virus-Induced Diabetes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Poly I:C</th>
<th>KRV</th>
<th>RCMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunized (RCMV, N=26)</td>
<td>0 (0%)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Immunized (KRV, N=13)</td>
<td>14 (100%)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Immunized (KRV+RCMV, N=10)</td>
<td>10 (100%)</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Conclusions

- The LEW.1WR1 rat is a new flexible model of both spontaneous and environmentally induced diabetes
- LEW.1WR1 rats reveal the potential of cytomegalovirus to induce diabetes
- Diabetes may be preventable by vaccines that target candidate pathogens
- The LEW.1WR1 rat model is ideally suited to test diabetes vaccination strategies
- Maternal immunization can provide effective and specific protection from virus-induced diabetes in weanling rats

References


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