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The postnatal maternal environment influences diabetes development in nonobese diabetic mice

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Abstract

When nonobese-diabetic (NOD) mouse embryos were implanted into pseudopregnant mothers of a nonautoimmune mouse strain, the progeny had a reduced type 1 diabetes (T1D) incidence, suggesting that transmission of maternal autoantibodies is important for T1D development. Whether eliminating islet autoantibody transmission *in utero*, or postnatally (through milk), prevented T1D is unknown. Herein, we show that fostering newborn NOD mice on B-cell deficient NOD.Igμ−/− dams does not prevent T1D, demonstrating that postnatally transmitted islet autoantibodies are not required for disease pathogenesis. Additionally, NOD.Igμ−/− mice reared on NOD dams did not develop T1D, indicating that autoantibody transmission to B-cell deficient NOD neonates is insufficient to trigger T1D. Interestingly, newborn NOD mice that were reared by ICR (but not NOD or C57BL/6) dams had reduced T1D incidence, although not as reduced as that reported after embryo transfer to ICR mice, suggesting that both prenatal and postnatal factors contribute to the observed reduction in T1D incidence. Thus, NOD mice have different risks for developing T1D depending on the strain of their foster mother, and both prenatal and postnatal maternal factors, other than islet autoantibodies, influence their T1D incidence. The results may be relevant for understanding the increasing incidence of T1D and designing interventions.

Keywords: Autoantibodies; Maternal factors; NOD mouse; Type 1 diabetes; Milk; T1D

1. Introduction

Type I diabetes (T1D) results from insulin deficiency due to the autoimmune-mediated destruction of the insulin-producing β-cells. It arises from an incompletely understood interaction between β-cells, the immune system and the environment in genetically susceptible individuals [1,2]. Autoantibodies to β-cell antigens appear years before disease onset and remain detectable long after disease onset. Since the placenta expresses FcRn receptors that transport IgG maternal antibodies across the placenta [3], infants of mothers with T1D are often born with autoantibodies to insulin, glutamic acid decarboxylase, tyrosine phosphatase IA-2 and other β-cell antigens [4–7]. Postnatally, maternal IgG antibodies in breast milk are transported across the intestinal epithelium to the neonatal circulation, which is an important mechanism for protecting newborns from pathogens until their immune system matures [8–11].

Two studies recently reported that maternally transmitted autoantibodies may affect NOD mouse progeny's risk for developing T1D. Greeley et al. implanted NOD embryos into three types of non-autoimmune pseudopregnant mice: (1) NOD.Igμ−/− mothers (which are B cell-deficient); (2) immunoglobin transgenic NOD mothers which make antibodies only against hen egg lysozyme (α-HEL NOD mice); or (3) wildtype DBA mothers [12]. Approximately 15–25% of the female NOD mice arising from all three non-autoimmune mouse strains had T1D at the end of the observation period

Abbreviations: HEL, hen egg lysozyme; ICR, Institute of Cancer Research; NOD, nonobese diabetic mice; T1D, type 1 diabetes.

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(to 40 weeks of age), compared to about 60–70% of the controls. These observations led those investigators to suggest that maternal transmission of autoantibodies is a critical environmental factor influencing the risk for developing T1D. Kagohashi et al. also observed that NOD mice produced from embryo transfer into ICR and DBA mothers had a very low incidence of T1D, with only about 7% of the mice developing T1D by 40 weeks of age [13]. Interestingly, although these mice were protected from T1D, they developed insulitis significantly earlier than usual. These studies did not distinguish whether it was the elimination of autoantibody transmission *in utero*, postnatally, or both, that reduced disease incidence in the NOD progeny.

Therefore, we tested the extent to which elimination of islet autoantibody transmission postnatally through milk would effect T1D development in NOD mice. Our observations do not support the notion that transmission of islet autoantibodies through mother's milk represents a risk factor for T1D. In addition, we show that adopted NOD mice are differentially protected from T1D depending on the strain of their foster mother. When protection from T1D was observed, it was not as great as that reported after transfer of NOD embryos to that mouse strain, suggesting that prenatal factors can also modulate risk for T1D. We discuss the other factors in the prenatal and postnatal maternal environment that may modulate the T1D incidence of adopted NOD mice.

2. Methods

2.1. Mice

In our NOD mouse colony (originating from Taconic Farms) approximately 80% of female mice develop T1D by 35 weeks of age. Institute of Cancer Research (ICR) mice and C57BL/6 mice were purchased from Taconic Farms and Jackson Laboratories, respectively. The NOD.Igμ−/− mice were generously provided by Dr David Serreze (Jackson Laboratories). All mice were housed in microisolators with filter tops on a ventilated rack under specific pathogen free conditions. Serological tests included those for mouse hepatitis virus, ectromelia virus, parvovirus, pneumonia virus, Sendai virus, lymphocytic choriomeningitis virus, Theiler's encephalomyelitis virus, enteric reovirus, minute virus of mice, epizootic diarrhea of infant mice, *Mycoplasma pulmonis*, pinworms, *Aspiculuris* spp, *Syphacia* spp and fur mites. Bedding was changed in laminar flow workstations and personnel wore protective disposable garments. Animals were fed standard lab chow and water *ad libitum.* Principles of laboratory animal care (NIH publication no. 85-23, revised 1985; http://grants1.nih.gov/grants/olaw/references/phspol.htm) were followed. The University of California, Los Angeles Animal Research committee approved all animal care and procedures.

2.2. Fostering

Newborn NOD mice were switched within 48 h of birth onto a foster mother that had given birth within 48 h. About 30 newborn NOD mice (of both sexes) were raised on about 7 dams of each mouse strain. The mice were weaned at 4 weeks of age.

2.3. Diabetes diagnosis

Following weaning, only female mice were monitored for T1D. Urine glucose levels were checked weekly. After observing abnormal glucose in the urine, blood glucose levels were monitored twice weekly. Two consecutive blood glucose levels 300 mg/dL was considered as T1D onset. The mice were monitored until they were 45–52 weeks of age.

2.4. Statistics

Time to diabetes/percent with diabetes over time was computed using Kaplan–Meier survival (life table) methods. The p values for comparisons between groups were computed using the log rank test.

3. Results

3.1. Studies of postnatal exposure to islet autoantibodies through the milk

To examine whether postnatal transmission of islet autoantibodies through the milk plays a role in T1D pathogenesis, newborn NOD mice were switched within 48 h after birth to other NOD or NOD.Igμ−/− dams that had given birth within 48 h. The adopted NOD mice are designated as NOD/NOD or NOD/NOD.Igμ−/− mice, respectively. NOD.Igμ−/− mice are B-cell deficient and do not develop T1D since B cells are critical APC for disease pathogenesis [14–17]. The NOD/NOD mice displayed a typical incidence of T1D, indicating that the cross-fostering procedure itself had no effect on their risk for developing T1D (Fig. 1). We observed that the elimination of antibodies from the mother's milk did not influence long-term diabetes incidence in NOD/NOD. Igμ−/− mice (Fig. 1). Thus, autoantibodies in NOD mother's milk are not required for T1D development. This result contrasts with the results of Greeley et al., who found that NOD mice reared after embryonic implantation into NOD.Igμ−/− mice had about one-half the disease incidence of those implanted into NOD mothers. This suggests that prenatal factors, but not postnatal factors, either present, or absent from, the NOD.Igμ−/− maternal environment, protect NOD progeny from developing T1D. This protection may be due to eliminating prenatal exposure to islet autoantibodies, or other protective factors in the NOD. Igμ−/− mothers resulting from their derivation by backcrossing from C57BL/6 mice (see Section 4).

We also cross-fostered newborn NOD.Igμ−/− mice on NOD dams to determine whether postnatal transmission of islet autoantibodies was sufficient to cause disease in B cell-deficient NOD mice. None of the NOD.Igμ−/−/NOD mice developed T1D, indicating that transmission of islet autoantibodies through the milk to B cell-deficient NOD mice is insufficient to promote T1D (Fig. 1).