Intestinal Immunity and Type 1 Diabetes
[Article]

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INTESTINAL IMMUNE ACTIVATION IN TYPE 1 DIABETES

The link between the gut immune system and type 1 diabetes (T1D) has been suggested by studies that have demonstrated that dietary factors modify the disease in animal models of autoimmune diabetes (1,2). In BB-rats and NOD-mice, a diet of hydrolysed proteins decreased the indicence of the spontaneous autoimmune diabetes. A nondiabetogenic diet resulted in a switch to Th2 type cytokines from Th1 type response, which promotes cytotoxic activity, in the islet infiltrating T cells. In NOD-mice, islet-infiltrating lymphocytes express [alpha]4[beta]7-integrin, which is a homing receptor to the gut mucosa, and antibodies blocking this receptor prevent diabetes (3,4). Furthermore, mesenterial lymphocytes transfer diabetes from NOD-mice to NOD/scid-mice (5).

In humans, autoreactive T-cells may originate from the gut immune system. For example, T-cells derived from the pancreas of a patient with T1D adhered to mucosal and pancreatic endothelium (6). Autoreactive T-cells from patients with T1D expressed gut-associated homing receptor [alpha]4[beta]7-integrin, whereas their tetanus toxoid reactive T-cells did not (7). The reports of enhanced immune responses to dietary cow-milk proteins suggest an increased activation of the gut immune responses and dysregulation of oral tolerance in T1D (8).

We have studied intestinal biopsy samples from children with T1D but without signs of celiac disease (i.e., anti-trasglutaminase antibodies or increased number of intraepithelial lymphocytes) (9). Intestinal immune activation manifested as

increased expression of HLA class II molecule and ICAM-1 throughout the epithelial cells. We found that densities of IL-4 and IL-1[alpha] positive cells were increased in the lamina propria in patients with T1D and normal mucosa. Also, the IL-4 mRNA-positive hybridization signal was higher in lamina propria in patients with T1D and normal mucosa than in control children. We have studied further biopsy samples from children with T1D by real-time RT-PCR (Vaarala, unpublished data). When a large panel of cytokines and chemokine receptors was studied, we found that mRNA levels of IL-18 were significantly increased in biopsy samples from children with T1D and without signs of celiac disease. In contrast, the levels of IL-18 mRNA were decreased in biopsy samples from patients with celiac disease, whereas increased expression of IFN-[gamma] and CD25 was found in celiac disease. In patients with T1D and so-called potent celiac disease (i.e., increased number of intraepithelial lymphocytes), increased expression of CCR9 and TGF-[beta] was found in biopsy samples. Our results suggest that the inflammatory activation of intestinal immunity related with T1D is a separate entity from that seen in celiac disease. Our findings of intestinal immune activation in T1D were not restricted to the patients with DQ2 genotype, which is the most common HLA class II genotype in celiac disease. Furthermore, the up-regulation of HLA class II molecules on epithelial cells together with the cytokine activation profile associated with T1D indicates a role for intestinal epithelial cells and monocytes in the pathogenesis of T1D. The activation of IL-4 is somewhat unexpected since it is associated with Th2 immune response. IL-4 is also linked to antigen presentation and it has been reported to enhance the antigen uptake by macrophages.

ORAL TOLERANCE TO DIETARY INSULIN AND THE RISK OF T1D

Our results of the dysfunction of gut immune system may explain the link between cow-milk exposure and T1D; the aberrant immune responses to cow milk proteins may develop in individuals with dysfunction of gut immune system and oral tolerance.

Our studies show that infants who have been exposed to cow-milk formulas before the age of three months have higher levels of insulin-binding antibodies and T-cell reactivity to insulin than infants who have been exclusively breast-fed (10,11). Both antibody and T-cell response to bovine insulin showed cross-reactive with human insulin. Accordingly, an environmental trigger of insulin-specific immune response in humans is dietary bovine insulin. Bovine insulin differs from human insulin by three amino acids. Immunogenic nature of bovine insulin in humans was recognized when bovine insulin was used for the treatment of diabetic patients and resulted in high levels of insulin-binding antibodies. Since bovine insulin differs from human insulin it can be considered a "modified self-antigen," which may escape tolerance induced to self-insulin in the thymus.

The induction of insulin-specific immunity by cow-milk insulin is a physiological response to a new antigen encountered in the diet. Foreign dietary antigens induce a systemic antibody and T-cell responses, which decline with age indicating the development of immune tolerance to food antigens. Immune tolerance to dietary antigens does not always develop or it may be lost, such as in food allergies and celiac disease. It is of interest that in both diseases the target tissue is not restricted to the gut as the disease lesions are also found in other organs. In our follow-up study of children at increased genetic risk of T1D, the levels of bovine insulin-binding antibodies increased in the children who developed islet cell auto-antibodies, wheras in the children who remained autoantibody negative, the levels remain stable or decreased in most cases (10). This suggests that the children who develop islet cell autoimmunity may have a failure in tolerance induction to dietary insulin.

CONCLUSION

The origin of the autoimmunity leading to the destruction of insulin producing beta-cells is not known. Several studies suggest that a link exists between the

gut immune system and the islets infiltrating lympocytes. Inflamed pancreatic islets express the same adhesion molecules involved with the homing of gut-associated lymphocytes. Enhanced immune reactivity to cow milk proteins in the patients with T1D suggests aberrant regulation of the gut immune system in this disease. In the patients with newly diagnosed T1D, anti-GAD-reactivity was found in the subpopulation of lymphocytes expressing gut-associated homing receptor [alpha]4[beta]7-integrin. Furthermore, we have shown that children with T1D have markers of intestinal immune activation. The dysfunction of gut immune system and poor regulation of oral tolerance in children with T1D could explain the link between cow milk exposure and T1D: the aberrant immune responses to cow milk insulin may develop in individuals with dysfunction of gut immune system and oral tolerance.

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