Diet, Gut, and Type 1 Diabetes: Role of Wheat-Derived Peptides?

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The role of the gut and gut-associated lymphoid tissue in the development of type 1 diabetes has come into the research focus over the last 20 years. Accumulated evidence suggests that the gut is involved in the pathogenesis of this immune-mediated disease, and there seem to be several mechanisms by which such an effect may be mediated (1). Decreased microbial diversity in the gut, increased intestinal permeability, local inflammation in the gastrointestinal tract, and abnormal mucosal immune responses all may contribute to the appearance of β-cell autoimmunity and further progression to overt type 1 diabetes. The intestinal mucosa comprises the largest surface area in the body, and the gut-associated lymphoid tissue represents the most extensive immune organ. The gut plays accordingly a crucial role in the interaction between the host and the environment. Given that type 1 diabetes is the unfortunate consequence of the combined effects of the individual genetic setup and exogenous and host-related factors, it is not surprising that the gut might be involved in the process leading to clinical disease.

In this issue of *Diabetes*, Mojibian et al. (2) report that approximately half of the patients with type 1 diabetes, whom they studied, had a proliferative T-cell response to dietary wheat polypeptides and that the cytokine profile of the response was predominantly proinflammatory. A positive T-cell response to wheat polypeptides was associated with the HLA DR4-DQ8 haplotype but surprisingly not with the HLA DR3-DQ2 haplotype, which confers strong susceptibility to celiac disease. The investigators interpret their observations as reflecting a diabetes-related inflammatory state in the gut immune system associated with defective oral tolerance and a possible gut barrier dysfunction (Fig. 1). Accordingly, these observations add to the accumulating concept that the gut is an active player in the diabetes disease process.

The findings of Mojibian et al. also raise a series of questions. Are the observed T-cell responses to wheat polypeptides present in subjects with preclinical type 1 diabetes? The mean duration of clinical diabetes was 11.2 years in the 42 patients included in the present study. Accordingly, one cannot exclude the possibility that the observed T-cell responses to wheat polypeptides may reflect hyperglycemia-induced changes in the intestinal barrier function. No data were provided on glycemic control in the patients studied nor any comparison on the metabolic control between the patients with a positive T-cell response and those lacking such a response. It would be important to assess T-cell responses to wheat polypeptides in subjects with preclinical type 1 diabetes in order to exclude the possibility that the responses are secondary to the disease condition.

Another issue is why T-cell responses to wheat polypeptides could be seen in only approximately half of the patients. Would that indicate that the other half have developed clinical type 1 diabetes without any intestinal involvement? It is intriguing that other studies focusing on various aspects of the gastrointestinal system have also reported abnormalities in ~20–50% of the patients analyzed. Westerholm-Ormio et al. (3) found enhanced expression of HLA-DR and -DP, intracellular adhesion molecule-1, α4β7-integrin, interleukin (IL)-4, IL-1α, and γ-interferon in small intestinal biopsy samples from ~20–30% of children with type 1 diabetes, and they interpreted these findings as signs of intestinal inflammation. Auricchio et al. (4) observed higher density of intraepithelial $CD3^+$ and of γ/δ T-cells and lamina propria $CD25^+$ T-cells reflecting the activation of intestinal immunity in ~50% of the patients with type 1 diabetes. Sapone et al. (5) measured elevated serum levels of zonulin, implicated as one of the tight junction proteins, in 42% of patients affected by type 1 diabetes. Taken together, these observations imply that only a proportion of patients with type 1 diabetes do have signs of intestinal inflammation and increased permeability.

The study by Mojibian et al. raises the possibility that wheat could be the driving dietary antigen in two autoimmune diseases, i.e., celiac disease and type 1 diabetes. It is well established that celiac disease is induced, in genetically susceptible individuals, by the ingestion of gluten, the major storage protein of wheat and similar grains (6). Gliadin is the alcohol-soluble fraction of gluten that contains most of the toxic components. Undigested molecules of gliadin are resistant to degradation by gastric, pancreatic, and intestinal proteases in the human intestine and accordingly remain in the intestinal lumen after gluten ingestion (7). These peptides pass through the gut epithelial barrier of the intestine, possibly during enteral infections or when there is an increase in intestinal permeability for some other reason, and interact with antigen-presenting cells in the lamina propria. In patients with celiac disease, immune responses to gliadin fractions promote an inflammatory reaction, primarily in the upper small intestine, characterized by infiltration of the lamina propria and the epithelium with chronic inflammatory cells. Approximately 85–90% of the patients with celiac disease carry the HLA DR3-DQ2 haplotype, and a majority of the remaining patients carry the HLA DR4-DQ8 haplo-

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DOI: 10.2337/db09-0686

See accompanying original article, p. 1789.

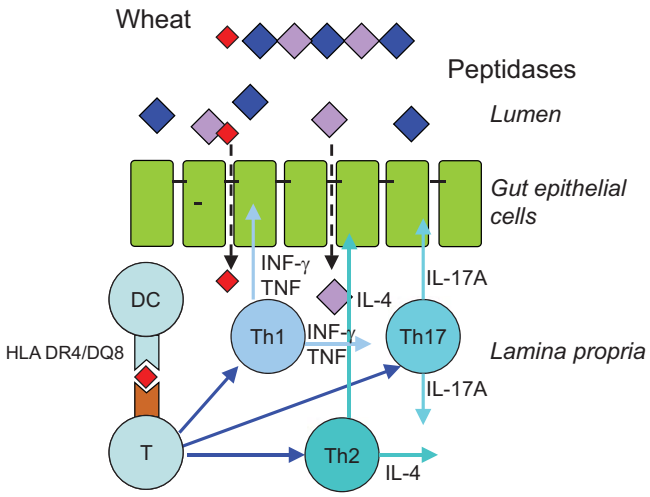

FIG. 1. Proposed pathway for a wheat-induced intestinal inflammation in patients with type 1 diabetes. Wheat polypeptides pass through the apical junction system from the gut lumen to the mucosa and are presented to T-cells by dendritic cells (DCs) in an HLA DR-restricted manner. The activated T-cells stimulate T-helper type 1 (Th1) cells to produce γ-interferon (INF-γ) and tumor necrosis factor (TNF), Th2 cells to secrete IL-4, and Th17 cells to secrete IL-17A. This cytokine cascade results in local inflammation.

type. Heterozygosity for the two aforementioned haplotypes seems to be associated with a decreased risk for celiac disease.

According to the present data, wheat polypeptides generated by chymotrypsin treatment of gluten resulted in vitro in a proliferative T-cell response in 42% of the patients analyzed. A majority of the responders were HLA DR3/DR4 heterozygous, whereas only one carried the HLA DR3-DQ2 haplotype in combination with a non–HLA DR4-DQ8 haplotype—the most common celiac disease–associated genotype. The response was characterized by a proinflammatory cytokine response dominated by increased secretion of γ-interferon, tumor necrosis factor, and IL-17A. The secretion of IL-4 and IL-6 was also increased; however, the investigators argue that the IL-6 was secreted most likely by non–T-cells given that the secretion was not inhibited by anti-DR antibodies. Taken together, these observations suggest that the described T-cell response differs from that characteristic of celiac disease. A critical issue is whether the wheat polypeptides tested here are naturally occurring antigens in the intestinal lumen. In addition to the difference observed in the HLA association, there are also other differences between the gut inflammation seen in patients with type 1 diabetes compared with the inflammation characteristics of patients with celiac disease. Overall, the inflammatory state seems to be a more active process in patients with celiac disease (3). One study focused on the density and function of T-cells in jejunal mucosa expressing the transcription factor Foxp3 perceived as a marker of regulatory T-cells. In children with type 1 diabetes, the densities of Foxp3-positive cells were low and did not show activation of Foxp3 transcripts (8). This was in contrast to celiac disease, where mucosal inflammation involving Foxp3 expression was noted. The absence of intestinal Foxp3 activation in type 1 diabetes provides a strong rationale for further investigation regarding whether impaired regulatory mechanisms could explain the subclinical intestinal immune activation and altered responses to dietary antigens seen in patients with type 1 diabetes. Such a mechanism may also be behind the proliferative T-cell response to wheat polypeptides and the associated proinflammatory cytokine response reported by Mojibian et al.

Although additional work is needed to verify that the observed phenomena are primary and present already in subjects with preclinical type 1 diabetes, these observations add to the growing evidence that dietary components may be involved in the disease process resulting in clinical type 1 diabetes by intestinal pathways. These may include effects on gut microbiota, intestinal permeability, and gut immune function as recently discussed by Vaarala et al. (1).

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

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