CLINICAL IMPLICATIONS OF BASIC RESEARCH

Celiac Disease — The Villain Unmasked?

Ross McManus, Ph.D., and Dermot Kelleher, M.D.

Celiac disease (also known as celiac sprue and gluten-sensitive enteropathy) is a common autoimmune condition triggered by ingesting one of several related proteins found in wheat, barley, and rye: the gliadins, hordeins, and secalins. In susceptible persons, ingestion of these proteins leads to infiltration of the intestinal mucosa by both intraepithelial CD8+ lymphocytes and CD4+ lamina propria lymphocytes and, ultimately, to crypt hyperplasia and villous atrophy.[1,2] Symptoms vary — malabsorption of food by the intestine, diarrhea, and failure to thrive are typical in affected children, and symptoms in adults can include depression and anemia. A gluten-free diet alleviates these symptoms, although adherence to such a diet can be difficult. Shan and colleagues[3] have recently identified a peptide that probably initiates the disease, raising the possibility that strategic inroads can be made into the disorder.
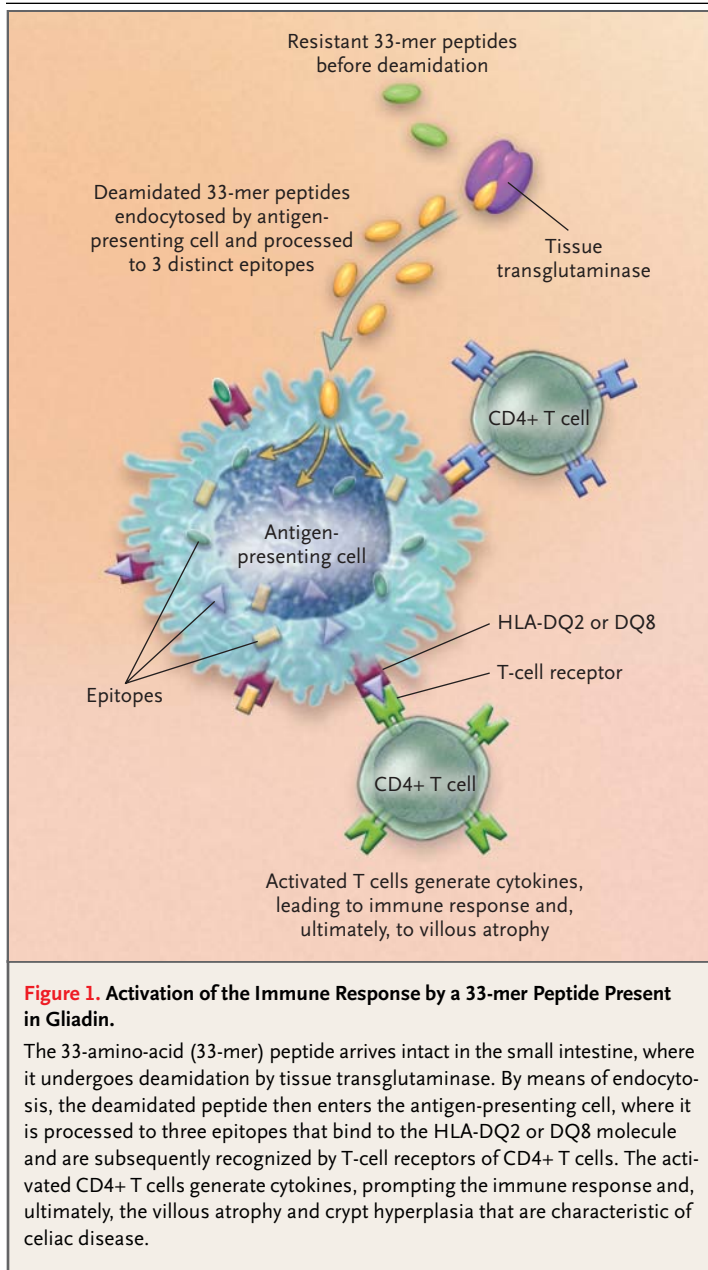
There is increasing evidence that CD4+ T cells mediate the pathogenic process in celiac disease. First, the principal determinants of genetic susceptibility are the highly variable HLA class II DQA and DQB genes located in the major histocompatibility complex. These genes (specifically the combination of variant alleles HLA-DQA1*0501 and DQB1*0201) encode the HLA-DQ2 class II protein molecule, which presents peptides to and binds CD4. A less prevalent determinant of susceptibility is the HLA-DQ8 variant. Second, HLA-DQ2–restricted T-cell clones that are specific for gliadin have been isolated from the small intestines of patients with celiac disease. However, these clones produce only small amounts of cytokines, and the mechanism by which gliadin peptides bind with high affinity to the HLA-DQ2–binding groove has only recently become clear.

The presence of endomysial autoantibody is another indicator of celiac disease, and the identification of tissue transglutaminase as the target of this antibody[4] has been enlightening. This enzyme is expressed on the subepithelial layer of intestinal epithelium, where it deamidates the glutamine residues in gliadin, resulting in glutamic acids. Deamidated peptides adhere strongly to the binding grooves of HLA-DQ2 and DQ8 molecules and elicit strong T-cell responses.[5]

Although the ingested proteins responsible for celiac disease may carry epitopes capable of activating T cells, they are also substrates for proteolytic degradation by gastrointestinal enzymes and thus should be fully digested before any exposure to the immune system could possibly occur. Therefore, the question of whether peptides constituting T-cell epitopes can survive the degradations of a low pH and proteolytic enzymes has critical implications for their functional relevance. Shan et al.[3] showed that one 33-amino-acid (33-mer) peptide survives transit through the digestive enzymatic milieu and arrives intact in the small intestine. In a series of elegant experiments, they demonstrated that this 33-mer resists digestion by gastric and intestinal proteolytic enzymes for extended periods in vitro. The peptide is resistant — both in vitro and in vivo — to digestion by brush-border enzymes of the small intestinal mucosa of rats and humans, although these enzymes normally reduce any remaining peptides to single amino acids or small peptides of about two or three residues before they are absorbed.

The 33-mer carries multiple copies of three epitopes that are immunogenic in patients with celiac disease (Fig. 1). Furthermore, the 33-mer has a very high affinity for tissue transglutaminase. Shan et al. found that once it was deamidated by tissue transglutaminase, the 33-mer elicited a response from each of 14 polyclonal T-cell lines derived from different patients with celiac disease. It therefore has many, if not all, of the properties required to initiate a response in patients with celiac disease. It

Figure 1. Activation of the Immune Response by a 33-mer Peptide Present in Gliadin.

The 33-amino-acid (33-mer) peptide arrives intact in the small intestine, where it undergoes deamidation by tissue transglutaminase. By means of endocytosis, the deamidated peptide then enters the antigen-presenting cell, where it is processed to three epitopes that bind to the HLA-DQ2 or DQ8 molecule and are subsequently recognized by T-cell receptors of CD4+ T cells. The activated CD4+ T cells generate cytokines, prompting the immune response and, ultimately, the villous atrophy and crypt hyperplasia that are characteristic of celiac disease.

Of potential therapeutic consequence is the finding that the 33-mer is broken down by a bacterial prolyl endopeptidase, raising the encouraging possibility of alternatives to a gluten-free diet (perhaps including genetic modification of the offending sequence) for the treatment of celiac disease. Successful clinical trials of such peptidases would provide final proof of the hypothesis that the 33-mer is central to the molecular pathologic process of celiac disease.

Despite these welcome findings, many questions remain. For example, up to 30 percent of persons of North European ancestry express HLA-DQ2, but celiac disease develops in only a small proportion of these carriers. There is some evidence, however, that the disease may be underdiagnosed, as reported by Mäki et al.[6] in this issue of the *Journal*. Although there is a pronounced familial aggregation of celiac disease, the pattern of inheritance is complex. Hence, it is clear that other genetic and possibly environmental influences have yet to be identified. The role of intraepithelial CD8+ lymphocytes (which do not bind class II molecules of the major histocompatibility complex) in the pathogenesis of the disease also remains to be determined. These questions notwithstanding, the identification of a pathogenetic pathway involving autoantibodies and cell-based immunity in celiac disease demonstrates the importance of research on principles of immunology and offers new hope for the understanding of other complex disorders.

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5. Molberg O, Mcadam SN, Korner R, et al. Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut-derived T cells in celiac disease. Nat Med 1998;4:713-7. [Erratum, Nat Med 1998;4:974.]
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survives the digestive tract, is a good substrate for tissue transglutaminase, is loaded onto HLA-DQ molecules, and activates T cells — which may then drive the characteristic immune response in the small intestinal mucosa. Similar peptide sequences are present in the hordeins and secalins.