Cystic Fibrosis

Cystic fibrosis affects many organ systems, primarily the lungs, and is discussed in greater detail elsewhere (Chapter 10). Only the malabsorption associated with cystic fibrosis is considered here. Due to the absence of the epithelial cystic fibrosis transmembrane conductance regulator (CFTR), individuals with cystic fibrosis have defects in chloride and, in certain tissues, bicarbonate ion secretion. This interferes with bicarbonate, sodium, and water secretion, ultimately resulting in defective luminal hydration. Reduced hydration can occasionally lead to intestinal obstruction, but commonly results in formation of pancreatic intraductal concretions. The latter can begin in utero, and result in duct obstruction, low-grade chronic autodigestion of the pancreas, and eventual exocrine pancreatic insufficiency in more than 80% of patients. The result is failure of the intraluminal phase of nutrient absorption, which can be effectively treated in most patients with oral enzyme supplementation.

Celiac Disease

Celiac disease is also known as celiac sprue or gluten-sensitive enteropathy. It is an immune-mediated enteropathy triggered by the ingestion of gluten-containing foods, such as wheat, rye, or barley, in genetically predisposed individuals. Celiac disease has an overall worldwide incidence of 0.6% to 1%, but its prevalence varies widely between countries and regions. Some of these differences correlate with variation in wheat consumption, but the reasons for other disparities are not defined. While previously uncommon, the incidence of celiac disease in developing countries is growing, possibly as a result of adoption of Western diets.

Pathogenesis. Celiac disease is triggered by ingestion of gluten, which is the major storage protein of wheat and similar grains. The alcohol-soluble fraction of gluten, *gliadin*, contains most of the disease-producing components. Gluten is digested by luminal and brush-border enzymes into amino acids and peptides, including a 33-amino acid α-gliadin peptide that is resistant to degradation by gastric, pancreatic, and small intestinal proteases (Fig. 17-25). Some gliadin peptides may induce epithelial cells to express IL-15, which in turn triggers activation and proliferation of CD8+ intraepithelial lymphocytes. These lymphocytes express NKG2D, a natural killer cell marker and receptor for MIC-A. Enterocytes that have been induced to express surface MIC-A, in response to stress, are then attacked by NKG2D-expressing intraepithelial lymphocytes. The resulting epithelial damage may enhance passage of other gliadin peptides into the lamina propria where they are deamidated by tissue transglutaminase. These gliadin peptides interact with HLA-DQ2 or HLA-DQ8 on antigen-presenting cells and, in turn, can stimulate CD4+ T cells to produce cytokines that contribute to tissue damage.

While nearly all people eat grain and are exposed to gluten and gliadin, most do not develop celiac disease. Thus, host factors determine whether disease develops. Among these, HLA proteins seem to be critical, since almost all people with celiac disease carry the class II HLA-DQ2 or HLA-DQ8 allele. However, the HLA locus accounts for less than half of the genetic component of celiac disease. Remaining genetic factors may include polymorphisms of genes involved in immune regulation and epithelial function. These genetic variables may also contribute to associations between celiac disease and other immune diseases, including type 1 diabetes, thyroiditis, and Sjögren syndrome, IgA nephropathy, as well as neu-

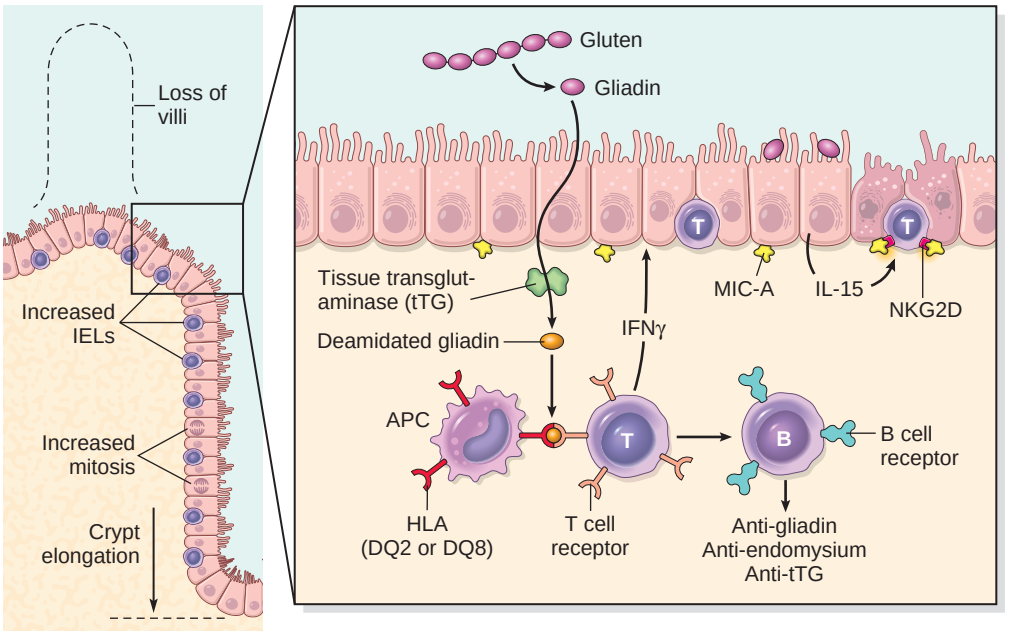

Figure 17-25 The left panel illustrates the morphologic alterations that may be present celiac disease, including villous atrophy, increased numbers of intraepithelial lymphocytes (IELs), and epithelial proliferation with crypt elongation (compare to Fig. 17-26). The right panel depicts a model for the pathogenesis of celiac disease. Note that both innate (CD8+ intraepithelial T cells, activated by IL 15) and adaptive (CD4+ T cells, and B cells sensitization to gliadin) immune mechanisms are involved in the tissue responses to gliadin.