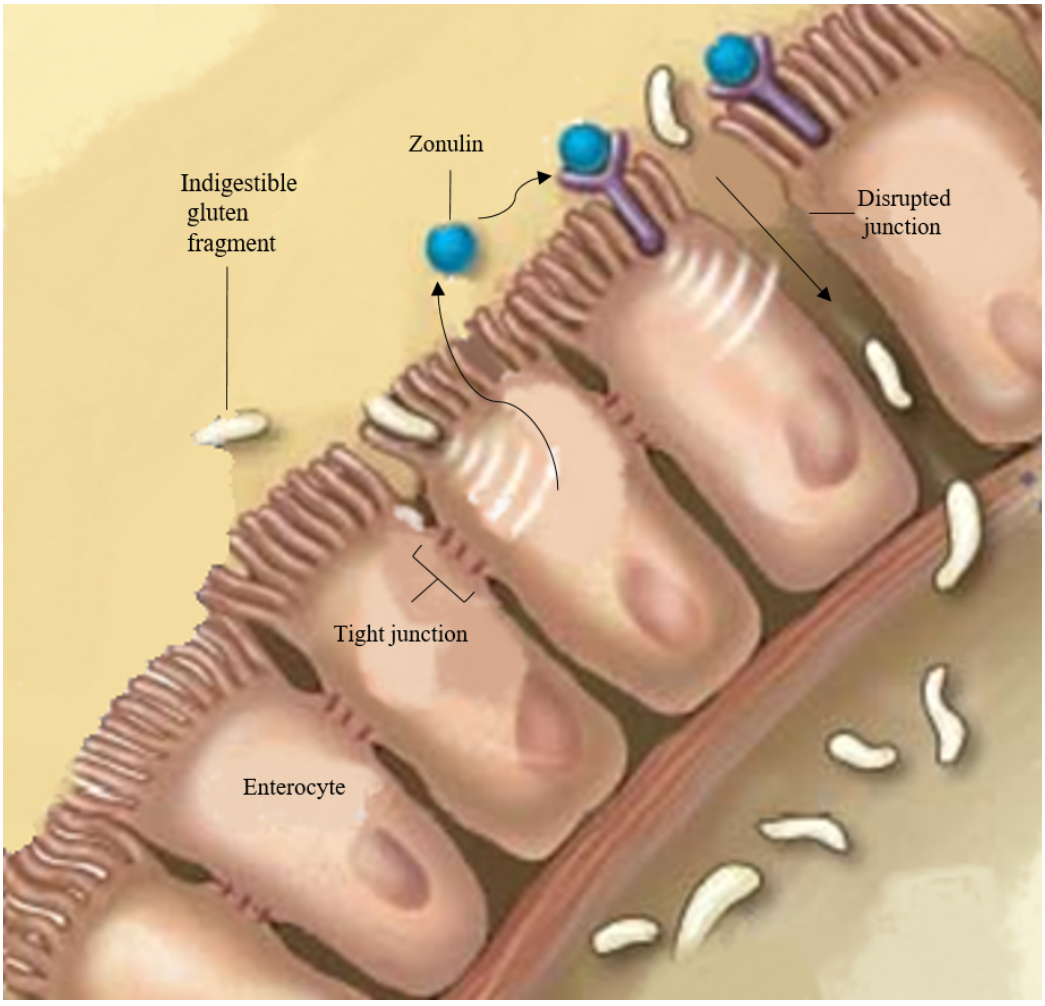
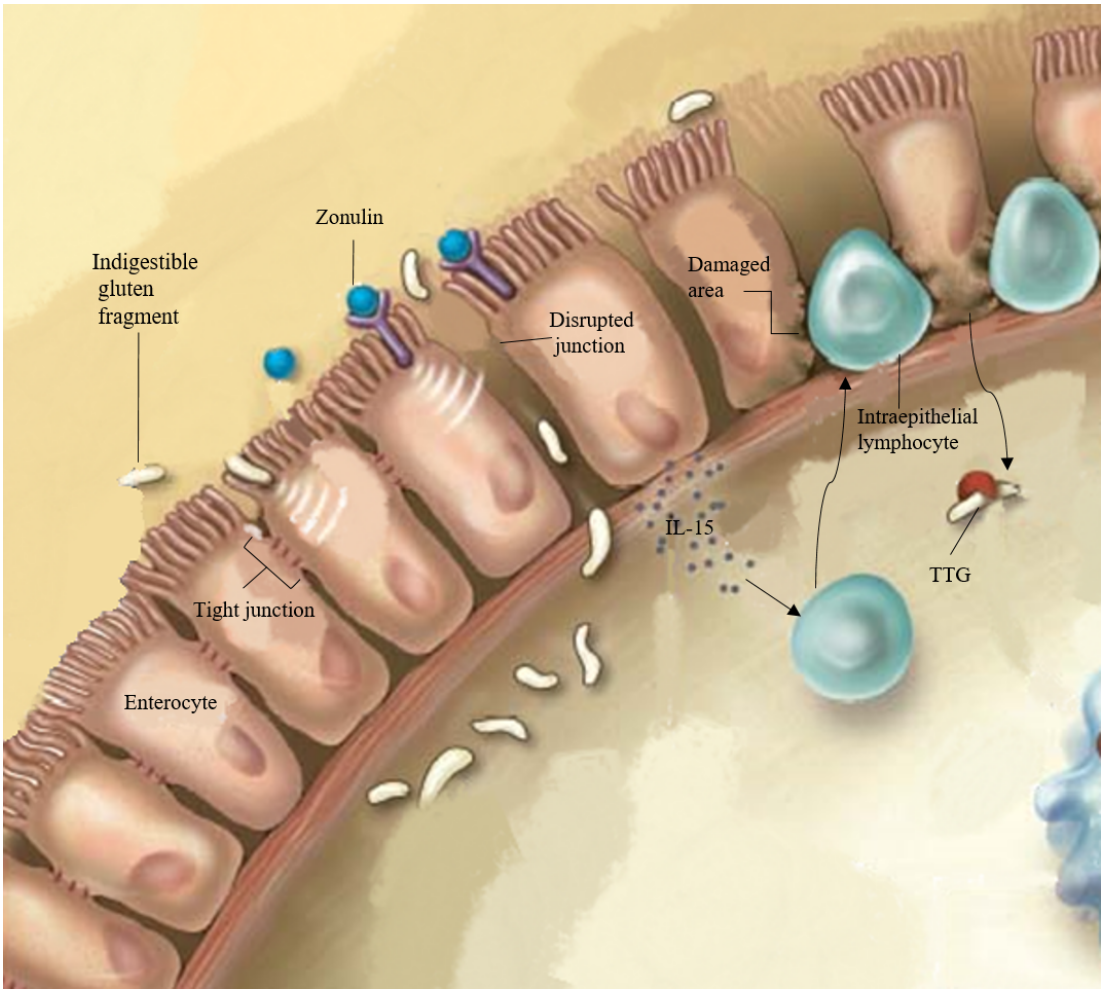
The Problem: Celiac Disease

Celiac Disease (CD) is a prevalent autoimmune disorder, affecting approximately 75 million people around the globe. The disease pathway is triggered by the introduction of gluten in the small intestine, leading to inflammation, abdominal discomfort, diarrhea, and other symptoms. Gluten is a protein found in grains such as wheat, barley, or rye.

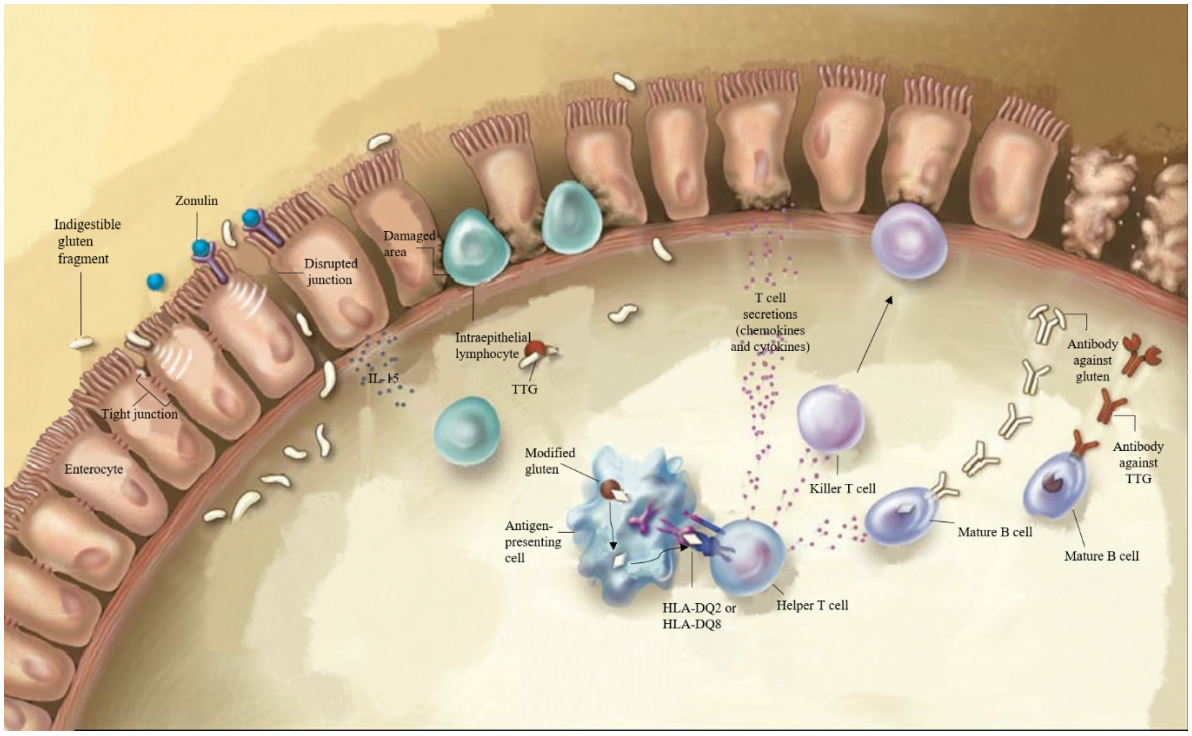
Celiac disease has three main pathogenic factors: an environmental trigger (gluten), genetic predisposition, and abnormal intestinal permeability. The current pathogenesis is hypothesized as follows: when gluten is digested, it is first broken down into its two component parts: glutenin and gliadin. In the small intestine, gliadin binds to the protein CXCR3 on the enterocytes and causes the release of zonulin proteins. Zonulin then binds to the EGFR and PAR 2 on the enterocytes, triggering a signal transduction cascade that loosens the gap junctions between the cells. This increase in intestinal permeability is termed “leaky gut”.



The gliadin then moves past the enterocytes due to leaky gut into the lamina propria, triggering an innate immune response characterized by the release of IL-15 by the enterocytes. This cytokine induces apoptosis of enterocyte cells. This also is characterized by the intraepithelial lymphocytes that are spurred once they encounter gliadin and other antigens and cause damage to the surrounding cells. As the gliadin peptide resides in the lamina propria, it is modified by transglutaminase 2 (TTG) through a deamination process.



It is here where the immune response is more severe in individuals with the gen that codes for either the HLA-DQ2 or HLA-DQ8 protein. The deaminated gliadin-TTG complex is recognized by antigen-presenting cells (APG) in the lamina propia if the APG has either the HLA-DQ2 or HLA-DQ8 protein. Once recognized, the APG displays the complex to helper T-cells, spurring three responses: 1) the helper T cell secretes pro-inflammatory chemokines and cytokines, 2) the helper T cell spurs killer T cells to directly attack enterocytes, and 3) B cells develop and release antibodies against both gliadin and the TTG protein.



These processes all contribute to the major indicators of Celiac Disease: the flattening of the villi in the intestine—leading to poor absorption of nutrients—and the prevalence of increased intestinal permeability—leading to increased inflammation in the gut. These effects manifest in symptoms such as diarrhea, abdominal discomfort, constipation, and fatigue. More serious reactions to gluten can manifest themselves in reproductive problems, ataxia, and neuropathy.

Reference

http://www.feingold.org/Research/PDFstudies/CeliacArticleAug2009.pdf