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GI Issues Involving Gluten

Wheat allergy, non-celiac gluten sensitivity, and celiac disease all involve adverse reactions to gluten in the GI tract. Gluten is found in wheat, rye, and barley as well as in any hybrids made from these grains. Individuals with these conditions need to remove gluten from their diet to improve their symptoms. The prevalence of celiac disease is about 1%, but 6-13% of the population appear to have some type of gluten sensitivity.

Wheat Allergy

Wheat allergy is an IgE mediated allergy to any of the antigenic components of wheat. The allergic reaction happens relatively fast (within minutes to hours) after ingesting wheat. Symptoms can include rash, nausea, abdominal pain, itching, swelling of the lips and tongue, and even anaphylaxis.

Non-Celiac Gluten Sensitivity

Non-celiac gluten sensitivity is a poorly understood condition and there is a plethora of mis-information about its symptoms, diagnosis and treatment. This condition is not an immunoglobulin mediated disease. There are no tests or biomarkers to diagnose it. If non-celiac gluten sensitivity is suspected, tests are done to rule out celiac disease and gluten allergy. If these conditions are ruled out and gluten avoidance results in improved symptoms, then gluten sensitivity may be diagnosed. Signs and symptoms of gluten sensitivity are similar to those for celiac disease. Symptoms include GI discomfort, headaches, fatigue, joint and muscle pain, skin rashes, asthma, rhinitis, and some nutritional deficiencies.

Celiac Disease

Watch the video Celiac Disease Pathogenesis - Described Concisely and in Detail

Celiac disease is also called celiac sprue, non-tropical sprue, or gluten sensitive enteropathy. The word “sprue” refers to a condition found in the tropical regions of the world where an abnormal flattening of the enterocyte villi results in malabsorption problems. The cause of sprue is unknown, but it does not involve wheat or wheat products. Celiac disease has a similar appearance to sprue, but the flattening of the villi and malabsorption problems are due to an immunological reaction to gluten. The two portions of the digestive tract that are most affected by celiac disease are the duodenum and proximal jejunum.

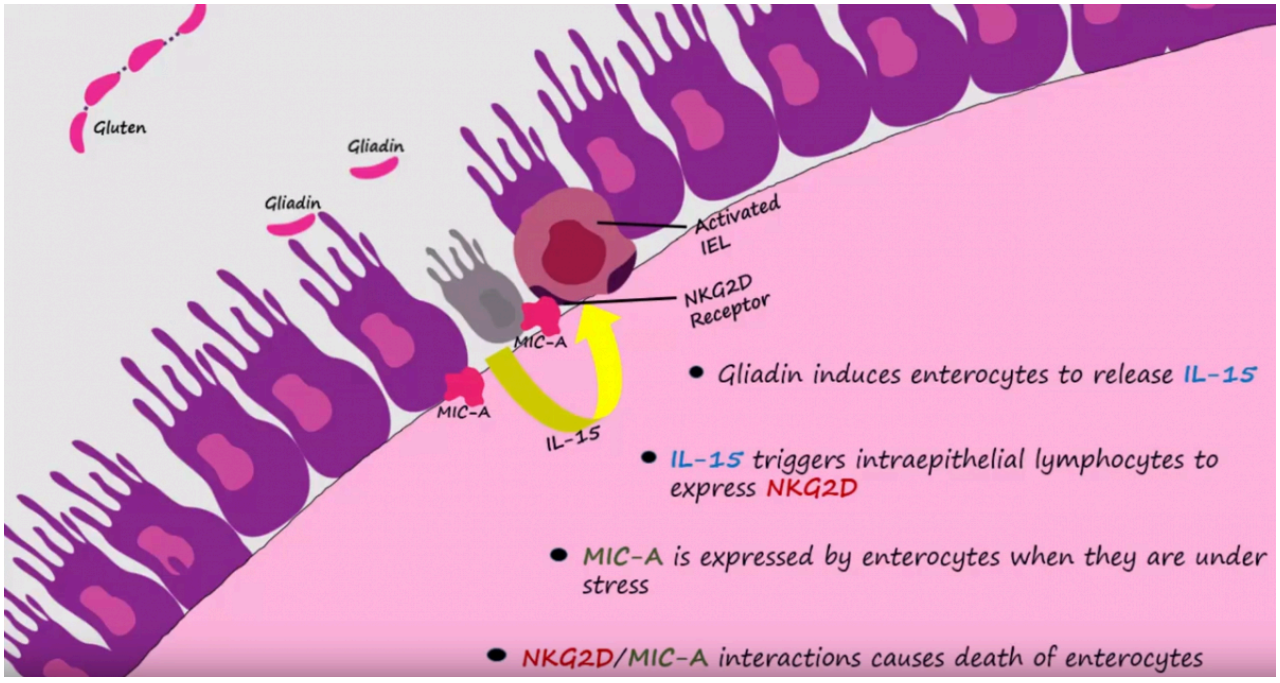
Gluten is a storage protein composed of two main subcomponents: **glutenin** and **gliadin**. Glutenin allows for elasticity in bread making while gliadin increases viscosity. Gliadin is not easily broken down by the intestinal proteases and is the substance that triggers the immune response in gluten-sensitive individuals. The destruction in the digestive tract that results from celiac disease is mostly caused by T-cells that have become activated when sensitive individuals are exposed to the gliadin. These activated T-lymphocytes then attack the enterocytes and are responsible for most of the damage to the intestine.

Gliadin exposure in gluten-sensitive individuals increases the release of **zonulin**. Zonulin is a protein produced by enterocytes in the small intestine and by the liver that regulates the function of tight junctions between enterocytes. Zonulin production is upregulated by the presence of inflammation. The binding of zonulin to the chemokine receptor

CXCR3 causes disengagement of zona occludens proteins within the tight junction complex. This results in the breakdown of tight junctions and a consequential increase in gut permeability sometimes referred to as "leaky gut." Gliadin can then enter the lamina propria and trigger an immune response. The enzyme **tissue transglutaminase (TTG)**, deaminates gliadin in the lamina propria. This deaminated gliadin is then presented by an APC on a MHC-II receptor called **HLA-DQ2/DQ8** and is much more immunogenic than regular gliadin. Expressing the HLA-DQ8 subtype increases the risk for having celiac disease. Helper T-cells will interact with this receptor and release cytokines that further contribute to the tissue damage. Helper T-cells also activate B-cells that produce antibodies against tissue transglutaminase, gliadin, and the endomysium. Anti-TTG, anti-gliadin and anti-endomysium antibodies can all be measured in the blood as part of the diagnosis for celiac disease.

Gliadin also causes enterocytes of the small intestine to express **IL-15**, which triggers the proliferation and activation of **intraepithelial lymphocytes (IELs)**. IELs are CD8+ T-cells that can be directly activated by antigen. They don't seem to need facilitation by helper T-cells. One hypothesis to explain this is that these cells were activated previously and have taken up a role as a memory cell in and among the enterocyte cells. The activated IELs then express **NKG2D**, which is a receptor for the ligand **MIC-A**. MIC-A is expressed by enterocytes under conditions of stress such as with bacterial infections, cancer, and gliadin or some other antigen exposure. The MIC-A/NKG2D interaction will cause the IEL to kill the enterocyte using granzymes and perforins that bring about cell lysis.

There are a lot of IEL cells in the gut epithelium. Some mammal models suggest 1 IEL for every 10 enterocytes.



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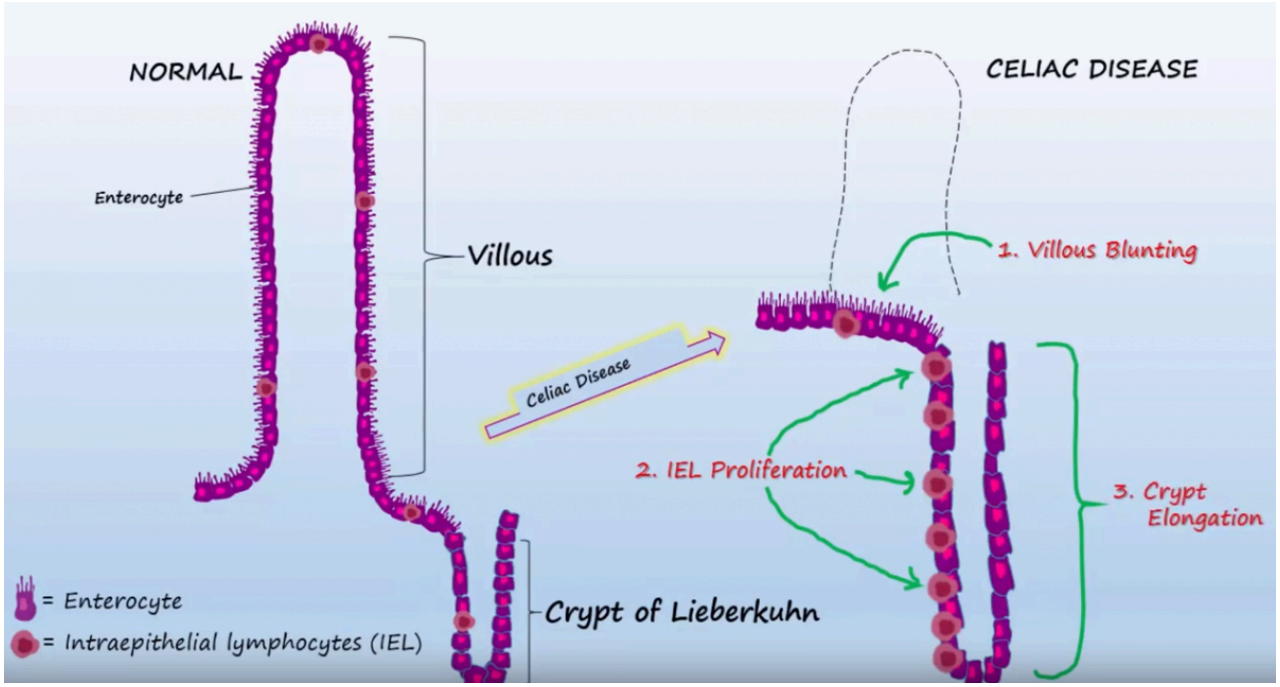
Several morphological changes that occur with celiac disease include villous blunting (no villi and thus decreased surface area for nutrient absorption), IEL proliferation, and crypt elongation (because of IEL proliferation). Four important clinical features that may be experienced by those with celiac disease include diarrhea, bloating, chronic fatigue, and anemia. Celiac disease causes a much higher risk of anemia because of malabsorption of iron (leads to iron deficiency anemia) and vitamin B-12 and folate (leads to megaloblastic anemia). Children with untreated celiac disease often have short stature because of the malabsorption of nutrients during crucial times of growth. Celiac disease causes an increased risk for cancer because of increased IEL proliferation (which can lead to lymphoma) and increased enterocyte division (which can lead to small intestine adenocarcinoma).



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Treatment for celiac disease is rather simple. It consists of eating a gluten free diet by avoiding wheat, barley, and rye products or foods that can be contaminated by these grains during processing. Adherence to a gluten-free diet allows the intestinal mucosa to completely heal.