PRIMEVIEW

COELIAC DISEASE

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Coeliac disease was historically defined as an immune-mediated enteropathy that is driven by the ingestion of dietary gluten. However, coeliac disease is increasingly recognized as a systemic disorder characterized by diverse extraintestinal manifestations.

EPIDEMIOLOGY

Before the 1990s, coeliac disease was considered an uncommon disorder, limited largely to children in western Europe. Since then, the implementation of specific serological tests has led to the recognition that coeliac disease is a major global public health problem, and that the prevalence of coeliac disease is increasing. Screening studies indicate that coeliac disease affects ~1% of the European population. Similar studies performed in areas with high levels of European ancestry have yielded comparable prevalence figures. Coeliac disease remains rare in far east Asia and sub-Saharan Africa; however, large epidemiological studies are lacking from these regions. Notably, screening data suggest that for each clinically diagnosed patient there are 5–10 undiagnosed seropositive individuals.

Coeliac disease almost exclusively occurs in individuals with human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8 haplotypes. However, the presence of these HLA haplotypes is not sufficient for disease development.

MECHANISMS

Wheat gluten is a complex mixture of proteins named gliadins and glutenins

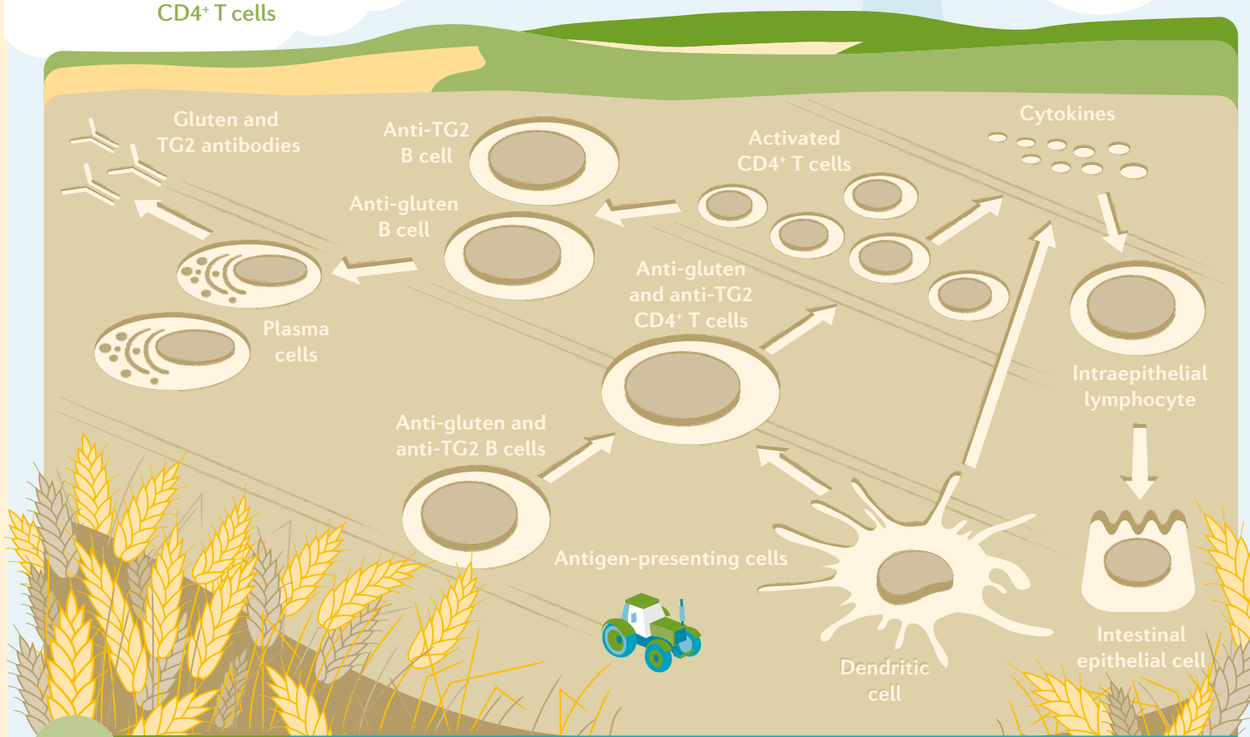
Gliadins and glutenins are resistant to gastrointestinal proteolytic processing, leading to the generation of long gluten peptides

Gluten peptides are deamidated by transglutaminase 2 (TG2), which enhances the binding affinity of gluten peptides to HLA-DQ2 and HLA-DQ8

Gluten peptides presented by HLA on antigen-presenting cells activate gluten-specific $CD4^+$ T cells

Activated $CD4^+$ T cells induce production of anti-gluten and anti-TG2 antibodies

Cytokines, such as IL-15, activate intraepithelial lymphocytes to kill intestinal epithelial cells, thus contributing to enteropathy



OUTLOOK

The diagnosis of coeliac disease is proceeding towards non-invasive procedures. In symptomatic children with high levels of TG2-autoantibodies, small intestinal biopsy samples are no longer required, and trials are underway to see if this approach can be adopted in other patient subgroups. Several drugs are in development, including drugs to correct the intestinal barrier and inhibit modification of gluten by TG2, enzymes to digest gluten and monoclonal antibodies to block IL-15. A vaccine is also being developed aiming to induce regulatory T cell responses.

DIAGNOSIS

The clinical signs and symptoms of coeliac disease may include severe or mild gastrointestinal symptoms and/or signs of malabsorption, or extraintestinal manifestations such as dermatitis herpetiformis, arthritis, peripheral neuropathy or anaemia. Moreover, some seropositive individuals are asymptomatic. As such, a diagnosis of coeliac disease is based on serological tests and small intestinal morphology. Serological assays include those to detect TG2-autoantibodies and antibodies against deamidated gliadin peptide. Individuals who are seropositive and symptomatic can undergo gastroscopy to obtain a small intestine biopsy. The diagnosis is confirmed upon histological demonstration of villous atrophy, crypt hyperplasia and infiltrates of intraepithelial lymphocytes.

MANAGEMENT

Coeliac disease can be effectively managed in most patients by life-long adherence to a strict gluten-free diet. However, in practice, this diet is difficult to maintain and requires a lot of knowledge and motivation from patients, and their friends and families. Dietary lapses may prevent normalization of small intestinal morphology; therefore, patient follow-up is important. A small proportion of patients with coeliac disease can develop complications, such as refractory coeliac disease (defined as villous atrophy and ongoing symptoms in the presence of a gluten-free diet), enteropathy-associated T cell lymphoma, certain types of non-Hodgkin lymphoma or intestinal adenocarcinoma.

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Written by Shimona Starling; designed by Neil Smith