From grain to gut: the autoimmune puzzle of celiac disease

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Celiac disease (CeD) is a gluten-sensitive enteropathy with immune-mediated typical remodeling of the proximal small intestinal mucosa characterized by villous atrophy, crypt hyperplasia, and an increase in intraepithelial lymphocytes. Clinically, CeD presents with a broad spectrum of manifestations, ranging from classical symptoms such as chronic diarrhea and weight loss to more subtle or atypical symptoms, including anaemia or extraintestinal symptoms. CeD is genetically strongly linked to the human leukocyte antigen HLA Class II DQ2 and/or DQ8, which are expressed on antigen-presenting cells.

Glutens from wheat, rye, and barley are known as the nutritional triggers in CeD. Patients with CeD have gluten-specific antibodies, with the IgA subtype being more specific than IgG. An autoimmune component had long been suspected due to the presence of autoantibodies against endomysial tissue components. The identification of transglutaminase 2 (TG2) as major endomysial autoantigen in 1997 enabled the development of a highly sensitive and specific ELISA which revolutionized the diagnosis of CeD.

TG2 is a ubiquitously expressed enzyme involved in physiological processes such as matrix stabilization and apoptosis. Its expression is enhanced during wound healing, angiogenesis, and mechanical stress. In CeD, intestinal TG2 expression is markedly increased. TG2 enzymatically deamidates specific glutamine residues of dietary gluten peptides, a modification that increases their binding affinity to HLA-DQ2/DQ8 molecules, thereby enhancing the immune response. Additionally, TG2 catalyzes the cross-linking of glutens to extracellular matrix proteins, potentially prolonging their retention in intestinal tissues and contributing to sustained mucosal inflammation.

Dermatitis herpetiformis (DH) is the cutaneous manifestation in about 1-5% of CeD patients and is characterized by blistering papulovesicles that typically manifest on the elbows, knees, and buttocks. Most patients with DH experience only mild gastrointestinal symptoms and minor mucosal damage. In addition to circulating serum IgA autoantibodies against TG2, IgA against epidermal transglutaminase (TG3) are found in the skin of affected patients.

The treatment of CeD consists of lifelong adherence to a strict gluten-free diet. Even trace amounts of gluten can sustain mucosal damage. New therapeutic strategies include gluten-degrading probiotics, antibodies against interleukin 15 or TG2 inhibitors.