

Focus on Celiac Disease

Celiac Disease as a Paradigm Shift in the Pathogenesis of Autoimmune Diseases



Alessio Fasano, MD
Director, Center for Celiac Research University of Maryland School of Medicine, (Baltimore, USA)
Professor of Pediatrics, Physiology, and Medicine

A common attribute of Celiac Disease and other autoimmune disease is the presence of pre-existing conditions that generate an autoimmune process. The first condition is genetic susceptibility for the host immune system to recognize, and potentially misinterpret, an environmental antigen presented within the gastrointestinal tract. Second, the host must be exposed to the antigen. Finally, the antigen is introduced to the gastrointestinal mucosal immune system following its paracellular passage (normally prevented by the competency of intercellular tight junctions) from the intestinal lumen to the gut submucosa. Most commonly before the manifestation of the disease, increased permeability causes an abnormality in the release of antigens that trigger the multiorgan process leading to the autoimmune response.

A hypothesis has been formulated to explain the pathogenesis of autoimmune diseases with the following three key points:

- Autoimmune diseases involve a miscommunication between innate and adaptive immunity
- One effect alone can not explain the complex events involved in the pathogenesis of autoimmune diseases. The presence of nonself antigens (environmental triggers) is necessary to perpetuate the process. Therefore this autoimmune response can be stopped and reversed if the trigger(s) is prevented or eliminated
- In addition to genetic predisposition and the exposure to the triggering nonself antigen, the third key element necessary to develop autoimmunity is the loss of the protective function of mucosal barriers that interface with the environment (mainly the gastrointestinal and lung mucosa)

Specifically in Celiac Diseases tight junctions are opened during the early life span of the disease, which is considered secondary to zonulin upregulation and results in severe intestinal damage (Fig. 1). The upregulation of the zonulin innate immunity pathway is induced by the introduction of the antigenic trigger gliadin. Gliadin has been shown to be also a potent stimulus for macrophage pro-inflammatory gene expression and cytokine release. Current studies suggest that signaling of both functions is independent of Toll-like receptor (TLR) 4 and 2, but is dependent on MyD88, a key adapter molecule in TLR/interleukin-1 receptor signaling. These data indicate that gliadin sets off intestinal permeability through a MyD88-dependent release of zonulin that enables paracellular translocation of gliadin and follows interaction with macrophages within the intestinal submucosa (Fig. 1). Gliadin interaction with macrophages initiates signaling through a TLR-like pathway, resulting in the establishment of a pro-inflammatory (T helper 1-type) cytokine milieu that results in mononuclear cell infiltration into the submucosa. Most likely permitting the interaction of T cells with antigen-presenting cells, including macrophages, leading to the antigen-specific adaptive immune response manifested in patients with celiac disease. By simply eliminating gluten from

the diet we immediately encounter: serum zonulin levels decrease, the intestine continues its barrier function, the autoantibody titers are normalized, the autoimmune process shuts off and, consequently, the intestinal damage, that results from the autoimmune process, fully repairs itself.

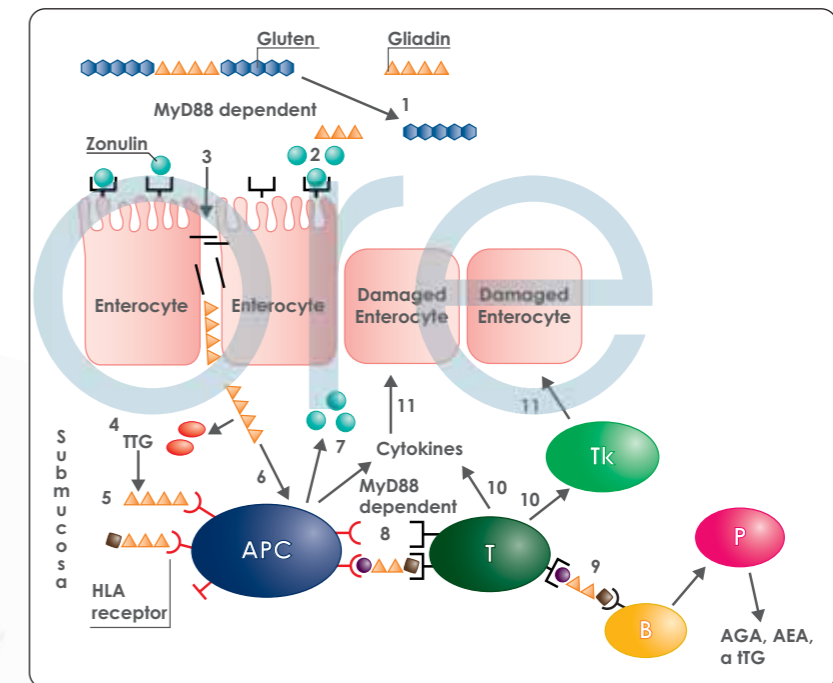


Figure 1: proposed role of abnormal intestinal permeability in the pathogenesis of celiac disease. Gliadin and its immunomodulatory/inflammatory fragments are present in the intestinal lumen (1), inducing an MyD88-dependent zonulin release (2) that causes opening of tight junctions and gliadin passage across the tight junction barriers in subjects with dysregulation of the zonulin system (3). Following tissue transglutaminase (TTG) deamidation (4), gliadin peptides bind to HLA receptors present on the surface of antigen-presenting cells (APC) (5). Alternatively, gliadin can act directly on antigen-presenting cells (6) causing MyD88-dependent release of both zonulin and cytokines (7). Gliadin peptides are also presented to T lymphocytes (8), followed by an aberrant immune response, both humoral (9) and cell-mediated (10) in genetically susceptible individuals. This interplay between innate and adaptive immunity is ultimately responsible for the autoimmune process targeting intestinal epithelial cells, leading to the intestinal damage typical of celiac disease (11). AEA, anti-endomysium antibodies; AGA, anti-gliadin antibodies; TG, thyroglobulin; Tk, T killer.

