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Review

Celiac disease: Autoimmunity in response to food antigen

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ABSTRACT

Celiac disease (CD) is an increasingly common disease of the small intestine that occurs in genetically susceptible subjects by ingestion of cereal gluten proteins. Gluten is highly abundant in the modern diet and well tolerated by most individuals. In CD, however, an erroneous but highly specific, adaptive immune response is mounted toward certain parts of the gluten proteome. The resulting intestinal destruction is reversible and resolved upon removal of gluten from the diet. Post-translational modification (deamidation) of gluten peptides by transglutaminase 2 (TG2) is essential for the peptides to act as HLA-DQ-restricted T-cell antigens. Characteristically, deamidated gluten and the self-protein TG2 both become targets of highly disease specific B-cell responses. These antibodies share several peculiar characteristics despite being directed against vastly different antigens, which suggests a common mechanism of development. Importantly, no clear function has been ascribed to the antibodies and their contribution to disease may relate to their function as antigen receptors of the B cells rather than as soluble immunoglobulins. Adaptive immunity against gluten and TG2 appears not to be sufficient for establishment of the disease lesion, and it has been suggested that stress responses in the intestinal epithelium are essential for the development of full-blown disease and tissue damage. In this review we will summarize current concepts of the immune pathology of CD with particular focus on recent advances in our understanding of disease specific B-cell responses.

1. Introduction

1.1. The small intestine

The primary function of the small intestine is uptake of nutrients from ingested food. Food components are broken down into small fragments by digestive proteases in the intestinal lumen to allow for transportation across the epithelium. The small intestine has long finger-like protrusions termed villi, which increases the surface area available for nutrient uptake. Only a single layer of epithelial cells lines the small intestine, and this is subject to both mechanical stress and constant exposure to a wide range of foreign components. Maintaining a healthy epithelium is important not only for the uptake of nutrients, but also to prevent invasion of pathogens. Epithelial cells therefore have a high turnover rate and the entire epithelial cell layer is completely replenished within 3–5 days [1].

1.2. The mucosal immune system and oral antigens

The small intestine must be able to correctly categorize a variety of antigens; it must tolerate ingested food and beneficial microbes and at the same time recognize and keep potential pathogens in check. This is an extremely complex task that requires coordinated effort by the epithelial cells and the mucosal immune system. The primary sites for gut immune response induction are the Peyer's patches and the tissue-draining mesenteric lymph nodes. The production of secretory IgA constitutes a first line of defense through its sequestration into the gut lumen following transport across the epithelium by the polymeric Ig receptor. In addition to the luminal protection conferred by secretory IgA, the epithelial cell layer is continuously patrolled by intraepithelial lymphocytes (IELs) that position themselves in between the epithelial cells. The majority of these cells are CD8+ T-cell receptor (TCR) αβ+ and some are TCR γδ+. These cells play a vital role as a first line of defense against infections [2,3]. In the lamina propria, beneath the epithelial layer, CD11c+ CX3CR1+ dendritic cells (DCs) patrol the tissue and sample luminal antigens through direct uptake [4] or *via* goblet cells

Abbreviations: BCR, B-cell receptor; CD, celiac disease; CTL, cytotoxic T lymphocyte; DC, dendritic cell; Fn, fibronectin; IEL, intraepithelial lymphocyte; PC, plasma cell; TG2, transglutaminase 2; TCR, T-cell receptor.

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[5,6]. Antigen is also taken up through M cells, which are specialized epithelial cells located directly above the Peyer's patches. M cells allow for uptake of large components, including intact bacteria, and the Peyer's patches are believed to be the main inductive sites for IgA responses toward microbial antigens [7]. The continuous exposure to foreign antigens could easily lead to overt inflammation and tissue destruction. To prevent this, the majority of oral antigens are conceived as harmless or ignored by the immune system—a phenomenon termed oral tolerance [7]. In mice, oral tolerance is primarily induced by migratory CD103+ CD11c+ DCs that, following uptake of antigen, migrate to the draining mesenteric lymph nodes and present the antigen to naïve T cells [7]. These DCs cells have a tolerogenic phenotype as a result of homeostatic expression of TGF-β and retinoic acid by the healthy intestinal epithelium [8]. T cells that are primed by these DCs in lymphoid organs acquire an immunomodulatory phenotype and home to the small intestinal lamina propria where they continue to support a tolerogenic environment [9]. How tolerance is maintained in humans is less well understood. Notwithstanding, unless the ingested antigen provides danger signals and is perceived as a pathogen, it will not provoke an inflammatory immune response.

1.3. Lack of tolerance toward gluten in CD is accompanied by autoimmunity and tissue destruction

In celiac disease (CD), there is no oral tolerance to gluten. Rather, there is a massive, pro-inflammatory and pathogenic immune response toward certain parts the gluten proteome and also toward the intestinal tissue itself. Whether this is due to loss of tolerance or failure to establish tolerance is not known. By contrast, knowledge of the pathogenic adaptive immune response toward gluten in CD is comprehensive. In the following sections we will discuss the multiple components that underlie the pathogenesis of CD, including the potent and pathogenic CD4+ T-cell response toward post-translationally modified (deamidated) gluten and the highly disease specific B-cell responses toward deamidated gluten and the self-protein transglutaminase 2 (TG2). We touch upon the emerging role of B cells in immune pathology and current models of B and T cell collaboration in CD. As the adaptive immune response alone appears not to be sufficient to develop disease, we also discuss how epithelial cell stress, together with pro-inflammatory adaptive immunity, causes cytotoxic T cell (CTL) mediated tissue destruction in CD.

2. The clinical aspects of celiac disease

2.1. Prevalence, symptoms and diagnosis

The prevalence of CD has increased dramatically in many populations over the last decades. Part of this increase, but not all, is explained by increased awareness among primary physicians and the general public. Disease onset can occur at any age among genetically predisposed individuals, but typically it occurs between 1 and 2 years of age in children. Pediatric CD often presents with distinct clinical symptoms such as diarrhea, malnutrition and failure to thrive. In adults, a wide range of symptoms can occur and many are often diffuse and not readily associated with an intestinal pathology [10,11]. Further, some individuals may have serological and histological findings compatible with disease, but with no clinical symptoms. The diagnosis of CD today relies largely on serological detection of disease specific antibodies [12] and HLA genotyping [13]. Historically, however, and still so in all adults and some children, the final diagnosis is confirmed by histological evaluation of duodenal biopsies.

2.2. Histological changes in the small intestine

Clinical symptoms such as diarrhea and malnutrition most likely correspond to the structural changes that are found in the intestinal architecture upon ingestion of gluten in CD patients. The changes occur along a continuum, but are usually subdivided according to the classification system of Marsh [14]. A healthy intestine has long, slender villi and short, proliferative crypts, whereas the celiac intestine has shortened or blunted villi with enlargement of the crypts. In severe disease (grade Marsh 3b-c), the villi are completely absent with a flattened mucosa and a large increase in the lamina propria volume. This dramatically reduces the absorptive surface of the small intestine, resulting in poor uptake of nutrients. Similar morphological changes are found in other sprue-like conditions, such as tropical sprue and certain other enteropathies and is thus not unique for CD [15]. In addition to the structural changes, the number of immune cells increases dramatically in the celiac lesion. One of the first signs of disease that occurs in the absence of gross morphological changes is an increase in the number of IELs, particularly TCR γδ+ cells [16–18]. A second pathognomotic feature of CD is massive infiltration of plasma cells (PCs) [19–21]. Although the role of the TCR γδ+ IEL subset remains to be clarified, both IELs and B cells appear to be important players in immune pathogenesis.

2.3. Recovery upon removal of gluten from the diet

Gluten is the only factor we know of to date that controls CD. It is required not only for the disease to precipitate, but also to drive inflammation. Upon commencement of a gluten free diet, the morphology of the intestine normalizes and clinical symptoms are reduced. Such a rapid recovery of affected tissue probably derives from the highly regenerative potential of the small intestine, in particular the epithelial cells. However, in keeping with a pivotal role of the adaptive immune response, reintroduction of gluten to the diet rapidly recalls the pathogenic immune cells and subsequent induction of tissue destruction.

3. Genetic predisposition for development of celiac disease

CD develops in genetically predisposed individuals. By far the single most important genetic factor is MHC class II [22]. The majority of the patients express HLA-DQ2.5 (*DQA1*05, DQB1*02*) (~90%)[23]. The remaining patients express either HLA-DQ2.2 (*DQA1*02:01, DQB1*02:02*) or HLA-DQ8 (*DQA1*03, DQB1*03:02*) (~5% each) [13]. A strong dose effect has been observed for HLA-DQ2.5, as individuals that are homozygous for HLA-DQ2.5 have a higher risk for disease development than heterozygous individuals [24,25]. The HLA-DQ molecules predispose to disease by preferential presentation of gluten antigens to CD4+ T cells [26–28]. Although these predisposing HLA allotypes are necessary for disease development, they are not sufficient as they are highly prevalent in the general population. From GWAS studies, 39 additional non-HLA loci were found to be associated with CD [29,30]. Although the causative genes within most of these loci remain to be identified, almost all of the candidate genes are directly or indirectly implicated in regulation of various aspects of the immune system. Several of these have effects on regulation of T cells, such as IL21, IL2, CTLA4, CD28 and ICOS, whereas others may be involved in B-cell biology [31]. Notably, many of the non-HLA risk alleles are associated with other autoimmune diseases, such as type 1 diabetes and rheumatoid arthritis [32,33]. This substantiates the notion that CD has more features in common with autoimmune diseases than food allergies and other food-induced immune pathologies. It also points to involvement of multiple, common pathways in the development of tissue destruction and autoimmunity.