Is celiac disease an autoimmune disorder?

Ludvig M Sollid[1] and Bana Jabri[2]

Celiac disease, which results from an immune reaction to ingested cereal gluten proteins, has several autoimmune features. In particular, celiac disease patients produce highly disease specific IgA and IgG autoantibodies to tissue transglutaminase when they are on a gluten-containing diet, and they have small intestinal intraepithelial lymphocytes which can mediate direct cytotoxicity of enterocytes expressing MIC molecules in an antigen non-specific manner. Similar to typical autoimmune disorders, celiac disease has a multifactorial aetiology with complex genetics, and several autoimmune diseases are commonly presented by patients with celiac disease. Much has been learned about the immunology of celiac disease in recent years, and there is overwhelming evidence that the immune response to gluten is central to the pathogenesis. In light of this, the many autoimmune phenomena associated with celiac disease are thought-provoking, and they challenge us to rethink the boundaries between autoimmunity and immunopathology.

Addresses
[1] Institute of Immunology, University of Oslo and Rikshospitalet University Hospital, Rikshospitalet, N-0027 Oslo, Norway
[2] Department of Pathology, University of Chicago, Illinois 60637, USA

Corresponding author: Sollid, Ludvig M (l.m.sollid@medisin.uio.no)

Current Opinion in Immunology 2005, **17**:595–600

This review comes from a themed issue on
Autoimmunity
Edited by Jean-François Bach and Shimon Sakaguchi

Available online 7th October 2005

0952-7915/$ – see front matter

DOI 10.1016/j.coi.2005.09.015

Introduction

Celiac disease (CD; also called gluten sensitive enteropathy or celiac sprue) is a frequently occurring disorder that is precipitated in genetically susceptible individuals by the ingestion of wheat gluten and similar proteins of other cereals. For this reason the disease is often categorized as a food hypersensitivity or food intolerance disorder. CD, however, has several autoimmune features, of which the highly disease-specific autoantibodies to the enzyme tissue transglutaminase (TG2) are particularly striking. The production of these antibodies in CD is turned on and off depending on exposure to dietary gluten. So, is CD an autoimmune disease after all?

This review will discuss the key features of CD relevant to autoimmunity and how CD can lead us to rethink about the boundaries between autoimmunity and immunopathology.

Co-existence of celiac disease with autoimmune disorders

The co-existence of (auto)immune diseases with CD is striking, and there is an association of the disease with type 1 diabetes, Sjögren's syndrome, autoimmune thyroid disorders, connective tissue diseases and IgA deficiency. Common genes that predispose to autoimmunity, such as HLA alleles, could be the reason for the co-existence of the diseases. Similar to many autoimmune disorders, CD shows a gender bias with a female to male ratio of approximately 2:1. It has been suggested that prolonged gluten exposure in patients with CD increases the risk of contracting autoimmune diseases [1], although age is a confounding factor in this type of study, and the effect of prolonged gluten exposure has not been confirmed [2].

Celiac disease genetics: the archetypical pattern of autoimmune diseases

Most autoimmune diseases are multifactorial with the involvement of both HLA-linked and -unlinked genes and environmental factors. CD is a prototype of multifactorial disorders with complex genetics. Gluten is an obvious environmental factor, and HLA (MHC) is a well-characterized genetic factor. The majority of CD patients carry DQ2 (DQA1*05/DB1*02) and a minority carry DQ8 (DQA1*03/DB1*0302). Those very few patients who do not possess these DQ gene constellations typically carry genes coding for either chains of the DQ2 heterodimer (i.e. DQA1*05 or DB1*02) [3]. The relative contribution of HLA-linked versus -unlinked is estimated to be about 50:50 [4]. So far the outcome of the hunt for HLA-unlinked susceptibility genes in CD has been meagre, thus echoing the experience of other autoimmune diseases. Independent genome-wide linkage studies have demonstrated little overlap of linkage regions, with the exception of the HLA region on chromosome 6p21. Apart from the HLA region, the two most promising regions identified by linkage studies are 5q32 and 19p13 [5–7]. Still the culprit genes in these regions remain to be identified. Moreover, similar to many other (autoimmune) diseases, there is a weak association of CD with polymorphisms of the *CTLA-4* gene. It is unclear whether the underlying mutation is the same for all the CTLA-4-associated diseases.

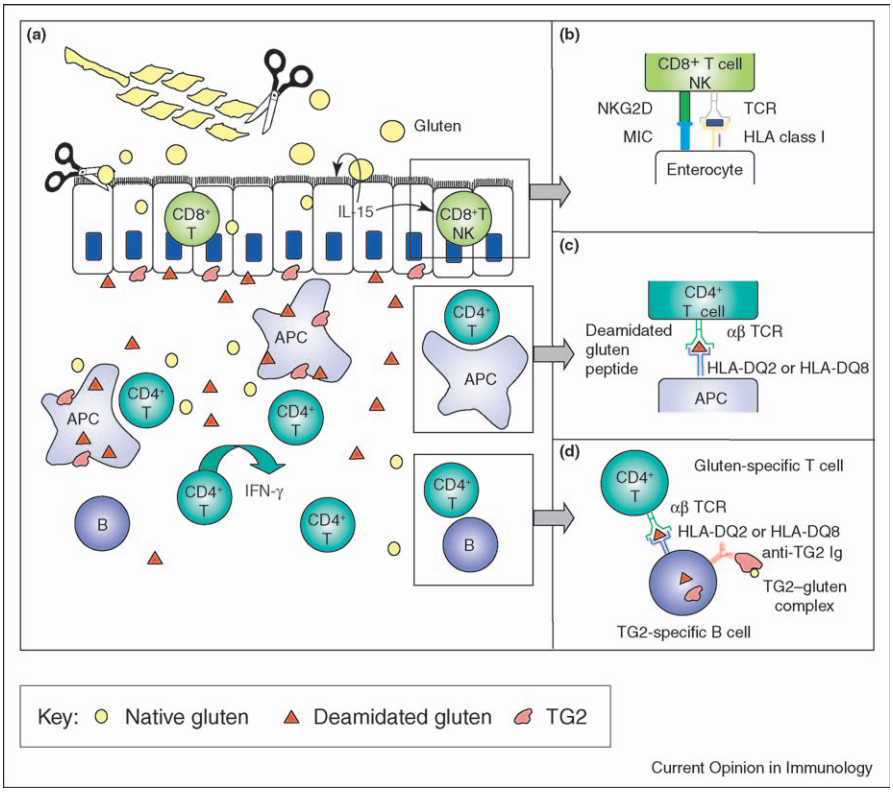
The fact that CD has the archetypical genetic pattern of autoimmune diseases is not in itself synonymous with CD

being an autoimmune disease. The polymorphisms involved in autoimmune diseases seem to be predominantly in genes with immune functions [8], and these polymorphisms have probably evolved because they were advantageous for fighting microbes. It is possible that these polymorphisms are also involved in shaping the immune response to the foreign antigen gluten.

CD4$^+$ T cells are a key component of the anti-gluten response

Gluten-reactive CD4$^+$ T cells can be cultured from small intestinal biopsies of CD patients but not from controls. These cells recognize gluten-derived peptides only in the context of DQ2 or DQ8, despite the many other MHC class II molecules expressed by CD patients (Figure 1a,d). The HLA association in CD can be explained by the preferential presentation of gluten peptides by these HLA molecules. The role of DQ genes as necessary, but not sufficient, factors for CD development suggests that the gluten-reactive CD4$^+$ T cells somehow control the immune response to gluten leading to celiac disease [9]. Remarkably, most of the celiac lesion T cells recognize gluten peptides that are post-translationally modified; certain glutamine residues in the T cell epitopes are converted to glutamate by a deamidation process mediated by the enzyme TG2. Some glutamine residues are specifically targeted by TG2, and the selectivity of the enzyme corresponds to the glutamine-to-glutamate conversions that are involved in T cell recognition. The deamidation process introduces negative charges to the gluten peptides, and both DQ2 and DQ8 have a preference for negatively charged anchor

Figure 1



The celiac small intestinal lesion. **(a)** The parts of the gluten proteins that are resistant to processing by luminal and brush border enzymes survive digestion and are transported across the epithelial barrier as polypeptides. Gluten peptides are deamidated by tissue transglutaminase (TG2). CD4$^+$ T cells in the lamina propria recognize predominantly deamidated gluten peptides, presented by HLA-DQ2 or -DQ8 molecules on the cell surface of the APC. In the epithelium there is infiltration of CD8+ T cells that express NK cell receptors, such as NKG2D. In the lamina propria there are B cells specific for gluten and TG2. **(b)** Intraepithelial T cells, by upregulation of NKG2D, can kill enterocytes expressing MIC molecules either by reducing the TCR activation threshold or by mediating direct killing. Gluten can induce NKG2D and MIC expression by stimulating the expression of IL-15. **(c)** HLA-DQ2 and -DQ8 molecules have a preference for binding peptides with negatively charged amino acids and thereby bind gluten peptides deamidated by TG2 with increased affinities. **(d)** A model of how gluten-reactive T cells control the formation of antibodies to TG2 by intramolecular help. This can happen in the lamina propria or, more likely, in the mesenteric lymph nodes. During the deamidation reaction, gluten peptides and TG2 form enzyme–substrate intermediates that are fairly stable (thiolester linkage). Such complexes of gluten and TG2 bound by surface immunoglobulin on TG2-specific B cells are endocytosed, and deamidated gluten peptides are released for binding to DQ2 or DQ8 molecules. After transport of the HLA molecules and their bound peptides to the cell surface, gluten-reactive T cells can recognize the deamidated gluten peptides and thereby provide T cell help to the TG2-specific B cell. The figure is adapted with permission from [57].