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Coeliac disease

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Abstract

Coeliac disease is a gluten-sensitive enteropathy characterized by villous atrophy, hyperplastic crypts and increased numbers of intraepithelial lymphocytes which are reversed by gluten withdrawal. Diverse autoimmune disorders are frequently associated with the disease, and patients also carry an increased risk of gastrointestinal malignancy. This review is aimed at outlining the current knowledge on the contribution of the innate immunity to the whole progress of coeliac disease, catalogued as the prototype of an immune-mediated response dominated by the activation of the adaptive immune system. The accumulated data suggest a model in which the gliadin moiety triggers the upregulation of costimulatory molecules on antigen presenting cells in the lamina propria, and the generation of specialized functions on intraepithelial lymphocytes. In the lamina propria, gliadin effects are essential for the generation of a robust T cell response while in the epithelial compartment, gliadin effects confer both innate-like and TCR-mediated cytotoxicity strongly contributing to tissue injury.

Keywords: Coeliac disease; Genetic factors; Gliadin; Innate and adaptive immunity

Contents

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1. General characteristics

Coeliac disease (CD) is a chronic inflammatory intestinal disorder with multifactorial etiology. Human leukocyte antigens (HLA) and non-HLA genes together with specific dietary peptides (present in wheat, rye and barley), and additional environmental factors are involved in disease development. A particular polymorphism among HLA class-II genes identifies a specifically associated haplotype. In particular, greater than 97% of coeliac individuals have the DQ2 and/or DQ8 heterodimer encoded by the *DQA1*0501* and *DQB1*0201* genes in *cis* or *trans* configuration, compared to about 40% of the general population [1]. Therefore, the absence of these markers has a high negative predictive value. This pathology is considered one of the most common inherited diseases with a prevalence of almost 1% in western populations, which ranged from 5% to 15% in high-risk groups (type 1 diabetes, first-degree relatives, symptomatic or asymptomatic iron-deficiency anemia and osteoporosis) [2].

2. Natural history, clinical manifestations and possible complications

Over the last 15 years, the viewpoint on CD was transformed from the concept of a rare disease affecting primarily children of northern European ancestry with gastrointestinal symptoms, to an extraordinarily common disorder of people of all ages worldwide with symptoms affecting multiple organ systems. The mean age at which patients are diagnosed with CD has also changed from the first few years of life to middle adulthood [3]. There is some controversy on the long-term consequences of CD in undiagnosed or inadequately treated patients. Among the areas of greatest concern, we can mention the association of CD with gastrointestinal lymphomas and other cancers, the development of associated autoimmune diseases, the consequences of persistent osteoporosis, and the effect on growth, pubertal development, fertility, and successful pregnancy. The clinical manifestations of CD vary markedly with the age of the patient, the duration and extent of the disease and the presence of extra-intestinal pathologic conditions. A high index of suspicion is required for the diagnostic since most patients do not have overt gastrointestinal symptoms. Therapy in CD relays on a lifelong gluten-free diet [4]. Refractory CD refers to the persistence of symptoms and intestinal inflammation despite a gluten-free diet [5]. Some complications of CD are usually observed in adults after many years of disease and in the context of ulcerative jejunitis. Enteropathy-associated T cell lymphoma (EATL) develops in 7–10% of patients with long-standing CD, usually in the context of a refractory condition. Though this rare T cell lymphoma occurs much more frequently in patients with CD, the overall association with all non-Hodgkin lymphomas does not represent a great enough risk to justify early mass screening in celiac patients [6].

3. The association with other autoimmune diseases

The association of CD with autoimmune diseases, particularly type 1 diabetes and autoimmune thyroid disease has been widely reported, reaching a ten-fold increase in patients with CD compared with the general population [7]. Less clear is the link between CD and Sjögren syndrome, primary biliary cirrhosis, Addison disease, autoimmune chronic active hepatitis, cardiomyopathy, and peripheral neuropathy not due to B-12 or vitamin E deficiency. When both CD and autoimmune disease occur in a patient, CD is most often silent. Usually after the autoimmune disease is recognized, diagnosis of CD results from serologic screening in high-risk populations. However, the question whether the early diagnosis and treatment of CD reduces the risk of developing other autoimmune diseases is still open to debate. The prevalence of autoimmune diseases is closely related to the previous period of gluten exposure and the age of initiation of the gluten-free diet, children diagnosed and treated before 2 years of age have little subsequent risk [8].

4. Gamma–delta intraepithelial lymphocytes form part of the innate immune response

The mucosa of CD patients is characterized by a high proportion of intraepithelial T cells (IEL) bearing gamma–delta chains of the antigenic T cell receptors

($\gamma\delta^+$IEL) [9] which do not regress with the withdrawal of gluten, and are considered as mucosal markers of CD latency [10]. These cells form part of innate immunity because: i) they do not require HLA expression for antigen recognition, and instead, ii) respond to stress proteins [11]. $\gamma\delta^+$IEL influence epithelial cell proliferation and differentiation, but we are still far from completely understanding the role that these cells play in CD. The current understanding of the immunopathogenic mechanisms involved in CD highlights the role of the adaptive branch of the immune system, strongly supported by: i) the genetic association to the HLA system, and ii) the central role of T cells [12]. Though an ample body of evidences pinpoint to innate immunity [13,14], the role of IEL bearing alpha–beta chains of the antigenic T cell receptors ($\alpha\beta^+$IEL) and also of $\gamma\delta^+$IEL remains by far more controversial than the role ascribed to T cells in the lamina propria (LP).

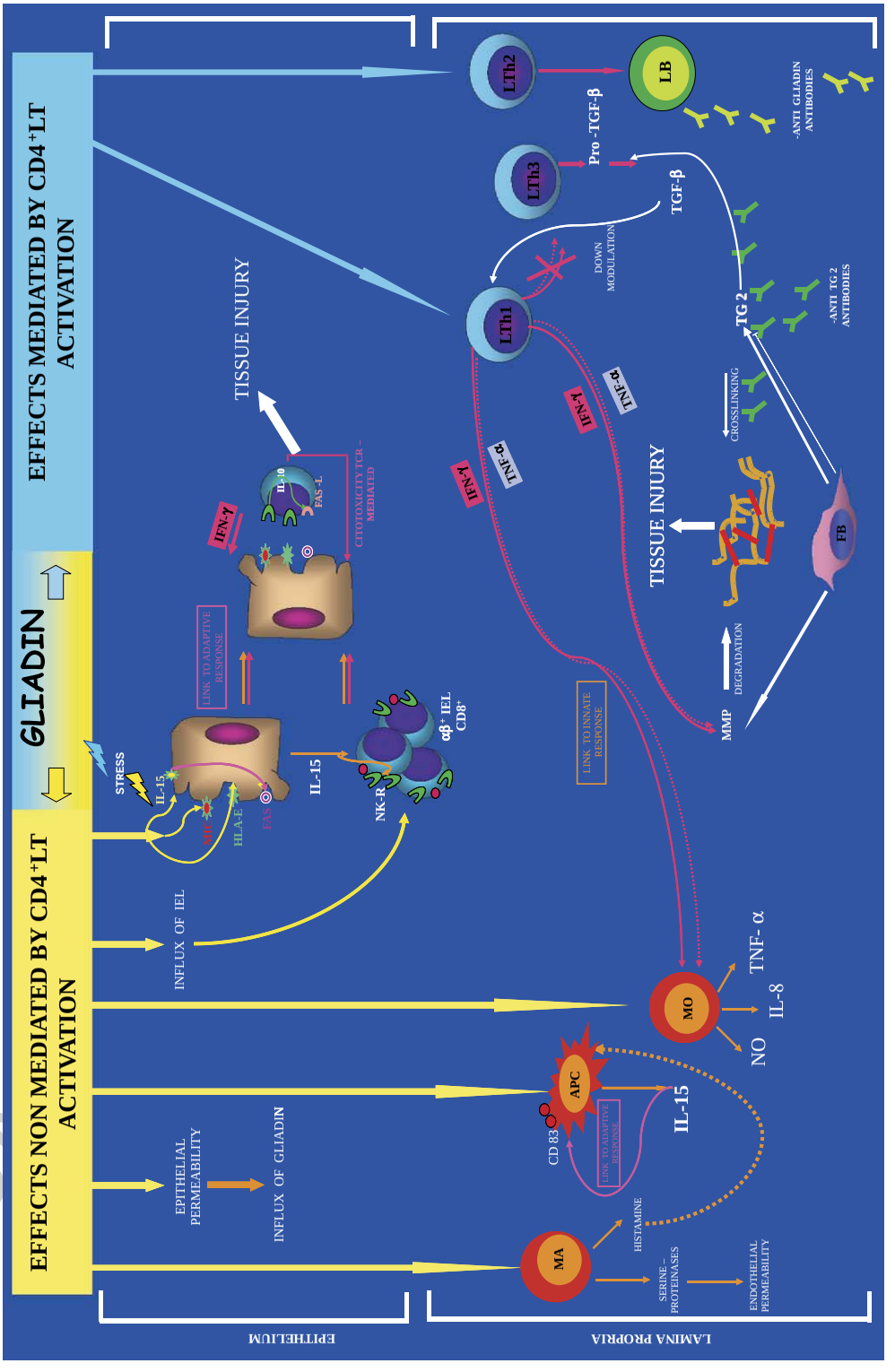
5. Gliadin: the master key for the development of tissue injury

Recognition of self-antigens by T lymphocytes (LT) is a central event in autoimmunity. Tissue transglutaminase 2 (TG 2) was identified as the main endomysial autoantigen in CD [15], however it becomes autoantigenic only after interacting with gliadin in the LP. The multiple factors that shape the anti-gliadin response in CD were defined by investigation of the effects of gliadin: i) on in vitro small intestine biopsy cultures, and ii) on individual components of the immune response. It must be stressed that the topics separately summarized in Sections 5.1 and 5.2 (see bellow) actually interact during the immunopathogenic course of CD (see Fig. 1).

5.1. Effects of gliadin mediated by the activation of LT $CD4^+$

Gliadin is taken up preferentially by dendritic cells (DC) in the LP of the small intestine. DC migrate and interact with antigen-specific LT $CD4^+\alpha\beta^+$ in mesenteric lymph nodes, and afterwards, LT return to the mucosa as effector cells. It was only 3 years ago that the primary initiator of the inflammatory response to gluten in CD patients was defined as a 33-mer peptide of α-gliadin which is stable towards breakdown by gastric, pancreatic, and intestinal brush-border membrane proteases [16]. The antigenic recognition is facilitated after intact peptides are deamidated by TG 2 that converts the abundant glutamine residues to glutamic acid, and thus renders them negatively charged [17]. In this state, the gliadin peptides are more efficiently bound to the specific and positively charged HLA DQ2 or DQ8 receptors on the surface of the antigen-presenting cell (APC). Once TG 2 was identified as the endomysial autoantigen, it was deduced that gluten-specific LT might help TG 2-specific LB by linked recognition of TG 2-gluten "neo-antigenic" complexes. This could explain how exposure to the dietary antigen controls the formation of anti-gliadin and anti-TG 2 autoantibodies [18].

The characteristics of an intestinal inflammatory response depend on the cytokines involved during the response. CD histological lesion is associated with a marked infiltration of Th1 cells dominated by the synthesis of IFN-γ and TNF-α among other pro-inflammatory cytokines [19]. An exaggerated Th1 type response triggers mucosal tissue injury with a characteristic epithelial cell shedding and loss of villi. In ex vivo organ cultures gliadin stimulates the expression of IFN-γ regulatory factor-1 (IRF-1), a transcription factor that drives the differentiation and function of Th1 cells [20] and also the expression of signal transducer and activator of transcription-1 (STAT-1) and T-bet, two transcription factors that mediate downstream effects of IFN-γ [21]. The presence of IFN-γ and TNF-α contributes to tissue injury through the downmodulation of the transforming growth factor (TGF)-β [22] secreted by LTh3 (an unique subset of the intestinal mucosa). As a consequence, the anti-inflammatory effects of TGF-β are abrogated by both proinflammatory cytokines. Maduration of TGF-β requires the enzymatic activity of TG 2 (synthesized by myofibroblasts) and in consequence, the pathogenic role of anti-TG 2 autoantibodies is partly associated to the interference with its enzymatic activity [23]. The physiological homeostatic balance of matrix metalloproteinases (MMPs), a family of endopeptidases involved in tissue remodeling, its inhibitors and the protein cross-linking enzyme TG 2 in the extracellular space [24] is disrupted by gliadin-induced T cell activation. The upregulation of IFN-γ and TNF-α destabilizes this



homeostatic balance and contribute to mucosal degradation. Of note, MMP that under physiological conditions are only produced by the IFN-γ and TNF-α stimulation of myofibroblasts, are constitutively expressed in active CD patients [25]. The main features summarized in this section are shown in Fig. 1.

5.2. Effects of gliadin non-mediated by the activation of LT CD4$^+$

Among the early effects of gliadin on the small intestinal mucosa of CD patients, the activation of eosinophils and mast cells [26] and also the increase of histamine secretion [27] deserve a special mention. Serine proteinases from activated mast cells promote vascular permeability and recruit inflammatory cells [28]. It was described that transamidation between histamine and gliadin exerted by TG 2 results in the scavenging of bioactive histamine and in the loss of T cell-stimulatory effect. When the concentration of gluten or histamine decreases, the hydrolysis of those conjugates produces a sustained release of both bioactive histamine and deamidated T cell-stimulatory peptides [29]. Thus, activation of mastocytes and the TG 2-mediated activity on histamine might contribute to shape the anti-gliadin response. Other LT activation-independent effect of gliadin is the promotion of increased epithelial cell permeability that could in turn induce the influx of potentially immunostimulatory molecules into the gastrointestinal tract, including gliadin itself [30]. Though the vast majority of food components do not elicit intestinal inflammation, peptidic fragments of gliadin upregulate TNF-α, IL-8 and nitric oxid production by monocytes [31] and also IL-15 and CD83 expression by APC [32]. The rapid kinetics of infiltration of T cells in the surface epithelium after the addition of gliadin to biopsy cultures [33,34] has important consequences on tissue injury. It is accompanied by the expression of MHC class I chain-related genes (MIC) and HLA E molecules on enterocytes [11] and also by the upregulation of Fas and the increase of epithelial apoptotic cells [35], two events mediated by the early expression of IL-15. This proinflammatory cytokine upregulates the expression of activating NK receptors on IEL (mostly αβ$^+$IEL) [36,37] that coactivate TCR-mediated responses of IEL, induces IFN-γ expression and promotes FasL-mediated cytotoxicity towards enterocytes. Epithelial cytotoxicity is the consequence of endogenously expressed IL-10 by IEL [38]. Of note, the proliferation of NK receptor-bearing IEL promoted by IL-15 [39], has been implicated in the pathogenesis of intestinal lymphoma. The main features summarized in this section are shown in Fig. 1.

6. Conclusions

Gliadin has a key role in the development of CD through mechanisms that are in part mediated by activation of CD4$^+$LT. The effects non-mediated by CD4$^+$LT activation are primarily associated with the innate immune system while effects non-mediated by CD4$^+$LT primarily activates the adaptive immune system. Downstream effects of both branches are mutually related. Interestingly, IFN-γ (a product of the adaptive response) reinforces some of the effects of the innate response triggered by gliadin on monocytes. Also, the maduration of APC mediated by IL-15 (an innate response to gliadin) facilitates subse-

Fig. 1. Gliadin: the master key for the development of tissue injury. The figure shows the interaction between the innate (orange arrows) and adaptive (pink arrows) branches of the immune response in the development of CD triggered by gliadin. Boxes indicate the links between innate and adaptive responses. Gliadin exerts effects mediated (white blue arrows) and non-mediated (yellow arrows) by activation of CD4$^+$LT, both in the epithelium and in the lamina propria of the small intestinal mucosa. Effects of gliadin *mediated by activation* of CD4$^+$LT includes the differentiation of CD4$^+$Th1 and Th2 cells (to simplify, the inductive phase of the adaptive response is omitted). Once activated, CD4$^+$Th1 cells secrete cytokines (IFN-γ and TNF-α) that interfere with the downmodulatory effect of TGF-β on LTh1, reinforces the activation of monocytes and upregulate matrix metalloproteinases (MMP) leading to tissue injury. CD4$^+$Th2 cells drive the production of anti-gliadin and anti-tissue transglutaminase 2 (TG 2) antibodies which interfere with TG 2 action (see text). Effects of gliadin *non-mediated by activation* of CD4$^+$LT includes activation of mastocytes (MA) that could regulate the presentation of deamidated gliadin peptides to APC (see text), increase epithelial permeability, activate antigen presenting cells (APC) by upregulation of costimulatory molecules (CD83), activate monocytes (MO), increase the influx of intraepithelial lymphocytes (IEL) and upregulate the expression of IL-15, stress molecules (MIC, HLA-E) and Fas (mediated by IL-15) on enterocytes surface. IL-15, in turn, upregulates the expression of NK receptors (NK-R) (mostly on αβ$^+$ CD8 IEL). The interaction between enterocytes and IEL coactivates TCR-mediated cytotoxicity (through Fas/Fas-L recognition and mediated by endogenous IL-10), and also induces IFN-γ expression leading to tissue injury. FB: myofibroblast.

quent adaptive T cell responses. In addition, IL-15 (cytokine of the innate system) induces TCR-mediated cytotoxicity towards enterocytes and synthesis of IFN-γ by IEL via the upregulation of NK receptors. These mechanisms constitute links between both innate and adaptive immunity in CD.

The causative molecular pathways underlying the pathogenesis of CD are still poorly understood. Additional genes that could reveal pathways not previously implicated in the pathogenesis of CD remain to be further explored.

Take-home messages

- CD is a multifactorial gluten-sensitive enteropathy that affects genetically susceptible individuals.
- Of great concern are its effects on growth, bone metabolism, fertility and pregnancy and its association with other autoimmune diseases.
- Gliadin triggers tissue injury through $CD4^{+}$LT activation-dependent and -independent mechanisms.
- Those mechanisms disrupt both innate and adaptive branches of the immune response.
- The identification of new genes primarily involved is needed to unravel new aspects of coeliac disease pathogenesis.

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