Review

Adaptive and innate immune responses in celiac disease

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Abstract

Celiac disease (CD) is a complex small intestinal disorder due to a dysregulated immune response to wheat gliadin and related proteins which leads to a small intestinal enteropathy. It is generally accepted that CD is a T-cell mediated disease, in which, gliadin derived peptides, either in native form or deamidated by tissue transglutaminase, activate lamina propria infiltrating T lymphocytes which release proinflammatory cytokines. Recent studies indicate that gliadin contains also peptides able to activate an innate immune response. In particular, they induce a selective expansion of IEL, particularly TCR$\gamma/\delta+$ and CD8 + TCR $\alpha/\beta+$ lymphocytes bearing the CD94 NK receptor, as well as a strong epithelial expression of MICA molecules which interact with NKG2D receptor expressed on TCR$\gamma/\delta+$ and NK cells. Most of the events of innate immune activation events are inhibited by antibodies neutralizing IL-15, thus confirming the key role of this cytokine as a mediator of intestinal mucosa damage induced by ingestion of gliadin. It remains to be established to what extent the ability of gliadin peptides to activate innate immunity relates to other biological properties exerted not only on celiac cells and tissues; the specificity of celiac patients is probably related to their genetic make up.
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Contents

1. Introduction

Celiac disease (CD) is a common and complex disorder of small intestine leading to permanent intolerance to wheat

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gluten and related proteins of other edible cereals i.e. barley and rye [1]. Greater clinical awareness and availability of accurate serological tests have led to the recognition that this condition is very common, affecting approximately 1 in 100 persons in both Europe [2] and North America [3]. Both environmental and genetic factors contribute to the complexity of the disease characterized by a mild to severe enteropathy. From a clinical point of view, CD has a wide spectrum of gastrointestinal and extraintestinal manifestations, in some cases being completely symptomless. Twin and family based studies have clearly suggested a strong genetic component with risk attributable to HLA and non-HLA factors. Possession of the alpha chain DQA1*05 and beta chain DQB1*02 alleles is almost mandatory to develop CD [4]. A gene dosage effect has been shown and related in functional studies to the amount and type of DQ2 molecules able to present gliadin peptides to Th1 cells [5]. Linkage studies have identified chromosomal regions (e.g. 2, 5q, 19) likely to contain disease genes [6]. It is generally accepted that CD is a T-cell mediated disease [1], in which, gliadin derived peptides either in native form, or de-amidated by tissue transglutaminase, activate lamina propria infiltrating T lymphocytes which release proinflammatory cytokines, in particular γ-interferon, leading to profound tissue remodeling. Interestingly, recent studies, indicate that gliadin contains peptides able to activate a non-T mediated (innate) immune response [7,8]. The involvement and the interplay of both adaptive and innate immunity in CD pathogenesis are the focus of this minireview.

2. Adaptive immune response in CD

2.1. CD4-mediated Th1-skewed immune response

In CD the general consensus is that gliadin acts as an antigen recognized by the adaptive immune system. To date, several peptides derived from various gluten proteins, including α- and γ-gliadins and recently glutenins, have been reported to stimulate CD4+ T lymphocytes selectively isolated from small intestinal mucosa of CD patients [9–12]. Importantly, T cell lines and clones from intestinal mucosa of CD patients recognize gliadin-derived peptides in the context of the disease-associated HLA-DQ2 and -DQ8 restriction molecules [13,14]. By contrast, no evidence of T-mediated reactivity against dietary gliadin has been reported in normal, non-celiac mucosa ([13,14], Gianfrani, C., unpublished). Moreover, it has been shown that gliadin-specific T lymphocytes from CD intestinal mucosa are mainly of Th1/Th0 phenotype and release, following gliadin recognition, prevalently pro-inflammatory cytokines, dominated by γ-interferon [13,15,16]. γ-Interferon-dependent signaling pathways have been found to be enhanced in CD. Signal transducer and activator of transcription 1 (STAT1) [17] and interferon regulating factor 1 (IRF1) have both been found more expressed in untreated CD and in treated CD mucosa in vitro challenged with gliadin [18]. IL-10 is also upregulated, not to

same extent as γ-interferon, the IL-10/γ-interferon ratio being significantly lower in untreated CD [16]. IL-10 producing, gliadin-specific T cells have been identified in the CD small intestinal mucosa showing a cytokine pattern peculiar of Tr1 cells (IL-10+, IL-2^{low}, IL-4−, γ-interferon+) (Gianfrani et al., submitted for publication), but their frequency in the different disease phases (treated versus untreated) remains to be assessed.

2.2. Gliadin epitopes recognized by CD4+ cells

Gliadin is a mixture of almost 40 different proteins, albeit with a high grade of aminoacid sequence homology, characterized by a high content of the hydrophobic aminoacids glutamine and proline. Tissue transglutaminase (TG2), a Ca++ dependent enzyme, catalyzes both in vivo (epithelial brush border and subepithelial TG2) and in vitro the de-amidation of specific glutamine residues to glutamic acid, and enhances stimulatory capacity of gliadin-derived peptides by strengthening the binding to the HLA-DQ2/8 grooves [1]. Recent studies have identified in the sequence motifs QXP the glutamine residues which are preferentially substrate of TG2-mediated deamidation. This represents an important tool for the prediction of toxic gliadin peptides [19]; similarly, this analysis might prove useful to screen wheat varieties to identify potential non-toxic grains. It has recently become clear that the repertoire of gluten peptides involved in the disease pathogenesis is greater than appreciated previously; it may be different in children and adult patients [12]. Although there are at least 50 T cell stimulatory epitopes in gluten proteins, a unique 33-mer peptide is the more immunogenic since it harbors six in part overlapping epitopes; moreover, it is resistant to the enzymatic degradation by gastric, pancreatic and brush border peptidase [10]. It might reach in an intact and stimulatory form the immune districts of intestinal mucosa [10,20]; furthermore, the 33-mer peptide does not require further processing in APC for T cell stimulation as it binds to DQ2 molecules with a pH profile that promotes extracellular binding [21].

2.3. CD8+ gliadin-specific immune response

As mentioned before, the massive infiltration of intestinal celiac mucosa, particularly of the epithelium, by CD8+ T lymphocytes represents one of the diagnostic hallmarks of CD and is observed even in mild forms of CD lesions. CD8+ T lymphocytes recognize peptides of 8–12 aminoacid length in the context of HLA Class-I molecules. Peptides interact with HLA-Class-I molecules through specific aminoacid and in determined positions known as binding motifs which vary depending on the type of HLA Class-I molecules [22]. On the basis of the capacity of a panel of gliadin peptides to bind HLA-A2.1 molecules, we recently identified a peptide, mapping the 123–132 position of A-gliadin (A-gliadin 123–132, QLIPCMDVVL, pA2) which is selectively recognized by CD8+ T lymphocytes from HLA-A2.1-positive

celiac patients [23]. This peptide induced γ-interferon production and cytotoxic activity by peripheral blood mononuclear cells from treated CD patients. Moreover, pA2-specific cells were isolated from small intestine biopsies of patients either on gluten-free and on gluten-containing diets [23]. Furthermore, pA2 was found to be immunologically active in organ cultures of treated intestinal mucosa (Mazzarella et al., unpublished). Taking into account that all together HLA A2, A3/11, B7 superfamily cover more than the 90% of Caucasian population [24], it would be of great interest to expand a such analysis to these common HLA Class-I types, in order to identify novel gliadin-derived, CD8 T epitopes. Although the role of gliadin-specific CD8+ T cells in the damage of CD intestinal mucosa still remains to be fully elucidated, these findings suggest that, similarly to what happens in the pathogenesis of type 1 diabetes, CD8+ T cells infiltrating celiac mucosa, together with CD4+ T cells, may play an important role in CD pathogenesis.

3. Innate immune response in CD

3.1. Biological properties of gliadin peptides

More recently attention has been directed on the possible involvement of innate immune mechanisms in CD. A significant amount of data produced during the last decades suggest a biological activity exerted by some gliadin peptides. Different in vitro models have been implemented to study the ability of gliadin peptides to interact with cell lines and organs, and to damage in vitro the celiac intestinal mucosa; among them the agglutination of K562(S) cells [25], the interference with differentiation of the in vitro developing fetal rat intestine [26], the organ culture of celiac small intestine [27]. Interestingly, a strict correlation was found for a number of cereal proteins and gliadin peptides between the activity in such systems and the in vivo toxicity for celiac patients. Over the years other biological properties have been associated with gliadin peptides: induction of apoptosis in Caco-2 cells [28], increase of nitric oxide and γ-interferon dependent-cytokine production by mouse peritoneal macrophages [29], reorganization of intracellular actin filaments [30]. Very recently, direct and specific effect of dietary gliadin and peptic fragments inducing maturation of bone marrow derived dendritic cell has been described [31]. It is still unknown to what extent all these properties relate to the ability of some peptides to act as activators of innate immunity mechanisms, and ultimately to the in vivo toxicity for celiac patients.

3.2. Gliadin peptide 31–43

Old studies in the organ culture of mucosal explants from untreated celiac patients showed that the toxicity resides in the NH_2-terminal fragment of A-gliadin. In particular peptide 31–43 was able in such an in vitro system, to prevent the restitution of enterocyte height which normally occur in 24–48 h

of culture with medium alone [27], this phenomenon showing a good correlation with the number of apoptotic epithelial cells. The toxicity of gliadin peptide 31–43 was demonstrated both in vitro, in organ culture of treated biopsies [32], and in vivo feeding studies [33]. Similar results have been obtained in vivo on small intestinal [34] and oral [35] mucosae with the peptide 31–49. Despite its capacity to activate an immune response in CD mucosa (enhanced expression of HLA-DR in the epithelium and CD25+ cells in the lamina propria), this peptide does not appear to stimulate a T-mediated response, since a pool of overlapping peptides spanning the region 1–58 of α-gliadin failed to stimulate either gliadin-specific T lymphocytes isolated from CD intestinal mucosa [36] or peripheral blood mononuclear cells from CD patients after an oral challenge with wheat gliadin [37]. It has been recently demonstrated that gliadin peptides elicit EGF-like effects on different cultured cell types [30]. The 31–43 peptide, interfering with EGF receptor inactivation and then prolonging EGF activity, enhances some of its biological activities, such as actin rearrangement and induction of cell proliferation. Persistent EGF receptor activity induced by gliadin might amplify the effects of cytokines, such as IL-15 (see below) released in the early phase of the immune response.

Recent studies from Maiuri et al. [7] have shown that p31–43 is able to stimulate an innate immune response, simultaneously enhancing the stimulatory capacity of dominant gliadin T-cell epitopes, p57–68, p62–75. More specifically, p31–43 induced after only 3 h of in vitro challenge of treated CD mucosa, expression of message for ICAM-1 and HLA-DR in lamina propria cells and after 24 h of culture, an increase of COX-2, and expression of both CD25 on mononuclear cells (monocytes and macrophages) and CD83 on dendritic cells in the lamina propria compartment. The involvement of p38 MAP kinase pathway in the induction of COX-2 and CD25 was also demonstrated. Interestingly, no significant increase of expression of the activation markers CD25 and CD69 was found in CD3+ cells following incubation with p31–43 alone or with the immunodominant p57–68 or p62–75 peptides, taken singularly. In contrast, the authors found that lamina propria T cells were fully activated following the incubation with p57–68 or p62–75 if it was preceded by a short pulsing with p31–43, thus suggesting that the early activation of the innate immunocompetent cells may favour the capacity of gliadin peptides to stimulate the Th-mediated immune responses. Interestingly, all these events of innate immune activation were inhibited by antibodies neutralizing IL-15, thus confirming the key role of this cytokine as a mediator of intestinal mucosa damage induced by ingestion of gliadin. In fact, the same Authors had previously suggested that IL-15 mediates most of epithelial changes induced by gliadin challenge [38].

3.3. IL-15

IL-15, produced mainly by monocytes/macrophages, dendritic and epithelial cells, is a pro-inflammatory cytokine

involved both in adaptive and in innate immunity. Memory CD4+ and CD8+ T cells, NKT, NK, and TCRγ/δ+ cells expand following stimulation with IL-15 [39]. Furthermore, IL-15 is also a potent growth factor for the intraepithelial lymphocytes (IEL) [40], whose density is significantly increased in CD, representing its hallmark. Interestingly, a recent study from Cerf-Bensussan and co-workers, showed that IL-15 is highly expressed not only in lamina propria cells but also in the intestinal epithelium of untreated CD patients and in patients with refractory celiac sprue, a premalignant condition, characterized by a massive IEL infiltration in particular of abnormal TCRγ/δ+ cells [41]. The finding that in CD IL-15 is not secreted but bound to enterocyte cellular membrane, strengthened the hypothesis that IL-15 produced by epithelial cells, could be the main factor orchestrating the selective expansion of IEL, particularly TCRγ/δ+ and CD8 + TCR α/β+ lymphocytes bearing the CD94 NK receptor, as described in previous studies [42,43]. It is noteworthy to mention that, in normal condition, intestinal TCRγ/δ+ cells recognize stress-inducible, MHC Class I-like molecules MICA and MICB, expressed on damaged epithelial cells [44]. MICA and MICB proteins interacting with NKG2D receptor expressed on TCRγ/δ+ and NK cells, are found to activate innate cytotoxic and cytokine production responses. By contrast, the MICA ligation of NKG2D on CD8 + TCR α/β+ enhances the adaptive, antigen-specific cell-mediated responses [45]. Importantly, a very recent study indicate that MICA molecules are strongly expressed on epithelial cells of CD patients with acute disease and upregulated both in the epithelium and LP of treated following gliadin or gliadin-derived peptide 31–49 challenge [8]. Also in this case IL-15 seems to play a crucial role. These studies pinpoint the fundamental role of innate immune response in the damage of intestinal mucosal tissues in CD, primarily due to the cytolysis of epithelial layer mediated by MICA/NKG2D activated IEL [8].

4. Conclusion

The information reviewed here suggest that both innate and adaptive immune responses contribute to the mucosal damage in CD. There are some consolidated notions: the role played by IL-15 in a number of phenomena triggered by gliadin, namely expression of stress-induced molecules on the epithelium, the infiltration of the epithelium by cells which interact with such molecules exerting cytotoxic activity, activation of dendritic cells, probably reduced apoptosis of resident T cells. On the other hand, a Th1 skewed immune response, mainly but not only CD4+ mediated, to some gliadin peptides, favoured by their reduced digestion and by their deamidation by tissue transglutaminase, has been characterized and it is likely to be responsible for the profound mucosal remodeling of the celiac mucosa. However, there are also many unanswered questions. First, it is completely unknown what renders gliadin (and in particular some of its peptides, e.g. p31–43) such a special molecule acting as a stress protein for the epithelium. There are many evidence suggesting that this protein has special biological properties which exerts not only on celiac cells and tissues; what renders celiac patients particularly susceptible is probably related to their genetic make up. The other fundamental question attains to the interplay between innate and adaptive immunity; it has been shown in in vitro systems that the activation of innate mechanisms sets the stage for the subsequent activation of the adaptive response. Possible mechanisms are the activation of dendritic cells; to this regard it has been recently shown that wheat gluten induces a unique pattern of cytokines and chemokines in dendritic cells. At the same time it has proposed that MIC could be induced also on lamina propria monocuclear cells and also in this compartment the NKG2D-MIC axis could play role. In all cases the threshold also for adaptive immune response to gliadin, possible only in subjects with the relevant HLA haplotype, would be lowered [46]. Again the question why only a small proportion of these develop the disease remains unanswered.

A concluding note concerns the possible consequences of these information on the development of new therapeutic strategies alternative to the gluten-free diet. A number of players have been identified possible target of therapeutic interventions. There is little doubt that the growing knowledge on the mechanisms underlying this so common food intolerance will lead in the future to a cure more accepted by the patients.

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