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Non-Celiac Gluten Sensitivity: How Its Gut Immune Activation and Potential Dietary Management Differ from Celiac Disease

*Vera Rotondi Aufiero, Alessio Fasano, and Giuseppe Mazzarella**

Non-celiac gluten sensitivity (NCGS) is a clinical entity triggered by the ingestion of gluten-containing grains leading to intestinal and/or extraintestinal symptoms that resolve once the gluten-containing foodstuff is eliminated from the diet, and it is diagnosed when celiac disease (CD) and wheat allergy (WA) have been ruled out. The limited knowledge about the pathophysiology of NCGS and the lack of validated biomarkers are still major limitations for clinical studies, making it difficult to differentiate NCGS from other gluten-related disorders (GRD). In the absence of clear-cut diagnostic criteria, NCGS is still mainly a diagnosis of exclusion. Several studies suggest that NCGS is an immune-mediated disease that likely activates an innate immune response. Moreover, it has recently been hypothesized that in addition to gluten, other components of wheat may be responsible for the symptoms observed in individuals without CD. This review aims at discussing available evidence related to the histological and immunological features in the gut mucosa of patients with NCGS and at outlining new dietary opportunities for these patients.

1. Introduction

The spectrum of gluten-related disorders (GRD) includes celiac disease (CD), dermatitis herpetiformis, gluten ataxia, wheat allergy (WA), and non-celiac gluten sensitivity (NCGS). As defined by the 2015 Salerno Expert's Criteria,[1] the term NCGS is used to describe the clinical state of individuals who develop both intestinal and extraintestinal symptoms when they consume gluten-containing foods and feel better on a gluten-free diet (GFD) but do not have CD or a WA. If these diseases have been ruled out, then NCGS should be considered. A double-blinded placebo-controlled gluten challenge (8 g day^{-1}), which includes a 1 week challenge followed by a 1 week washout using a strict GFD and crossover to the second 1 week challenge, has been recommended as the final step to confirm or rule out NCGS.[1] While this approach would provide the proper stringency for a diagnosis based on exclusion criteria and at the same time would rule out possible placebo/nocebo biases, its implementation in routine clinical settings is impractical and poorly acceptable to patients.[2,3] The most common symptoms, including bloating, abdominal pain, diarrhoea, tiredness, and headache, significantly overlap with those of irritable bowel syndrome (IBS). Such overlap could complicate patient selection for clinical studies, making the understanding of this disorder more challenging. It is estimated that the prevalence of NCGS in the general population is highly variable, ranging from 0.63% to 6%.[4]

Currently, in the absence of specific biomarker(s), the diagnosis of NCGS relies on the accurate assessment of clinical features, along with the exclusion of a WA and CD.[5] Therefore, the identification of reliable biomarkers for the diagnosis of NCGS is one of the more relevant issues that should be resolved. Furthermore, recent studies raised the possibility that in addition to gluten, other grains' components, including amylase trypsin inhibitors (ATIs) and fermentable short-chain carbohydrates (FODMAPs) may trigger symptoms. Whether it is gluten and/or other proteins in wheat that are responsible for the development of symptoms in NCGS patients remains to be determined. Nevertheless, it has been shown that FODMAPs cannot be entirely and exclusively responsible for the symptoms reported by NCGS subjects, since these patients experience a resolution of symptoms while on a GFD, despite continued ingestion of FODMAPs from other sources.[6] Furthermore, it is unlikely that all NCGS subjects are FODMAP-intolerant, as this condition could hardly explain the occurrence of extraintestinal manifestations such as fatigue, eczema, or depression. Finally, although FODMAPs can cause gastrointestinal symptoms (i.e., bloating, abdominal pain, and irregular bowel movements) secondary to their fermentation, they seem to inhibit rather than trigger intestinal inflammation.[7]

Preliminary data observed in NCGS would suggest that innate rather than adaptive immunity has a prominent pathogenic role. Our group has shown an increased expression of toll-like receptor (TLR) 2 and claudin (CLDN) 4 in NCGS subjects.[8] Additional

Dr. V. Rotondi Aufiero, Dr. G. Mazzarella
Immuno-Morphology Lab
Institute of Food Sciences
National Council Research
83100, Avellino, Italy
E-mail: gmazzarella@isa.cnr.it
A. Fasano
Mucosal Immunology and Biology Research Center and Center for Celiac Research and Treatment
MassGeneral Hospital for Children–Harvard Medical School
Boston, MA 02114-4404, USA

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Table 1. Summary of information available regarding the gut immune activation in NCGS.

References	
A)	**Histologic findings**
Sapone et al. *BMC Med.* 2011[8]	
Brottveit et al. *Am. J. Gastroenterol.* 2013[11]	
Sapone et al. *Int. Arch. Allergy Immunol.* 2010[12]	Increased number of CD3+ IELs
Volta et al. *BMC Med.* 2014[13]	
Carroccio et al. *Am. J. Gastroenterol.* 2012[14]	
B)	**Alteration of intestinal permeability**
Sapone et al. *BMC Med.* 2011[8]	Decreased (high levels of CLDN4)
Vazquez-Roque et al. *Gastroenterol.* 2013[9]	Increased (low levels of ZO1, CLDN1, and OCLN)
Fritscher-Ravens et al. *Gastroenterol.* 2014[30]	Increased (breaks in TJ protein)
Hollon et al. *Nutrients* 2015[31]	Increased (low TEER)
Uhde et al. *Gut* 2016[32]	Increased (high levels of FABP2)
C)	**Innate immune response**
Sapone et al. *BMC Med.* 2011[8]	Increased TLR2 expression
Vazquez-Roque et al. *Gastroenterology* 2013[9]	Increased TNF-α expression
Junker et al. *J. Exp. Med.* 2012[10]	Increased IL-8 and IL-12 expression
D)	**Adaptive immune response**
Brottveit et al. *Am. J. Gastroenterol.* 2013[11]	Increased IFN-γ expression
Sapone et al. *BMC Med.* 2011[8]	
Volta et al. *BMC Med.* 2014[13]	
Carroccio et al. *Am. J. Gastroenterol.* 2012[14]	Elevated AGA-IgG levels
Volta et al. *J. Clin. Gastroenterol.* 2010[33]	
E)	**Non-IgE-mediated food-related allergy**
Carroccio et al. *Am. J. Gastroenterol.* 2012[14]	Increased mucosal eosinophilic infiltration

IELs, intraepithelial lymphocytes; CLDN, claudin; ZO, zonula occludens; OCLN, occludin; TJ, tight junction; TEER, transepithelial electrical resistance; FABP2, fatty acid–binding protein 2; TLR, toll-like receptor; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; AGA-IgG, antigliadin antibody-IgG.

compelling evidence for the role of innate immunity in NCGS came from other groups, showing an increased production of TNF-α and IL-8.[9,10]

Nevertheless, recently, in an intestinal biopsy-based study, NCGS patients showed increased mucosal IFN-γ mRNA after a 3 day gluten challenge.[11] This indicates that the adaptive immune response may also play a role in the NCGS pathogenesis.

Taken together, these results suggest the presence of gut immune activation in patients with NCGS.

2. Histological Features

Currently, NCGS patients would have normal duodenal histology with the number of IELs <25/100 enterocytes (grade 0 according to the Marsh–Oberhuber modified classification), even if an increase in CD3+ IELs (Marsh I) could be detected in some patients, as reported by our own studies[8,12] corroborated by others (**Table 1**A).[11,13,14] These features greatly differ from the typical CD enteropathy in which small bowel biopsy remains an essential component for its diagnosis. In CD, mucosal pathologic features are variable, ranging from mild abnormalities, including intraepithelial lymphocytosis, to completely flat mucosa.[15] A GFD leads to complete regression of intestinal lesions. In CD, the increased number of CD3+ intraepithelial lymphocytes (IELs) represents the earliest morphological change.[16] IELs usually exhibit a cytotoxic phenotype, and their chronic activation leads to mucosal damage.[17] Specifically, CD8+ IEL-mediated killing of enterocytes is responsible for the typical villous atrophy of active CD.[18–20]

In our works,[8,12] small intestinal biopsy from NCGS patients revealed normal to mildly inflamed mucosa (Marsh 0 to 1), while all CD patients showed partial or subtotal villous atrophy with crypt hyperplasia. As expected, CD patients had increased numbers of CD3+ IELs (>50/100 enterocytes) compared to controls, while the number of CD3+ IELs in NCGS patients was intermediate between those of CD patients and controls in the context of relatively conserved villus architecture. Furthermore, the number of TCR-$\gamma\delta$ IELs, which is a typical feature of CD histopathology, was only elevated in CD subjects (>3.4/100 enterocytes), while in NCGS patients, the number of $\gamma\delta$ IELs was similar to that in controls.[12] Such observations have been reproduced by Brottveit et al.,[11] who found a significantly higher density of CD3+ IELs in duodenal biopsies obtained from NCGS patients than in those from healthy controls. This density was significantly less than the density of CD3+ IELs in treated CD patients. The reason for the increased IEL levels among NCGS patients remains unclear and should be addressed in further studies. However, Brottveit

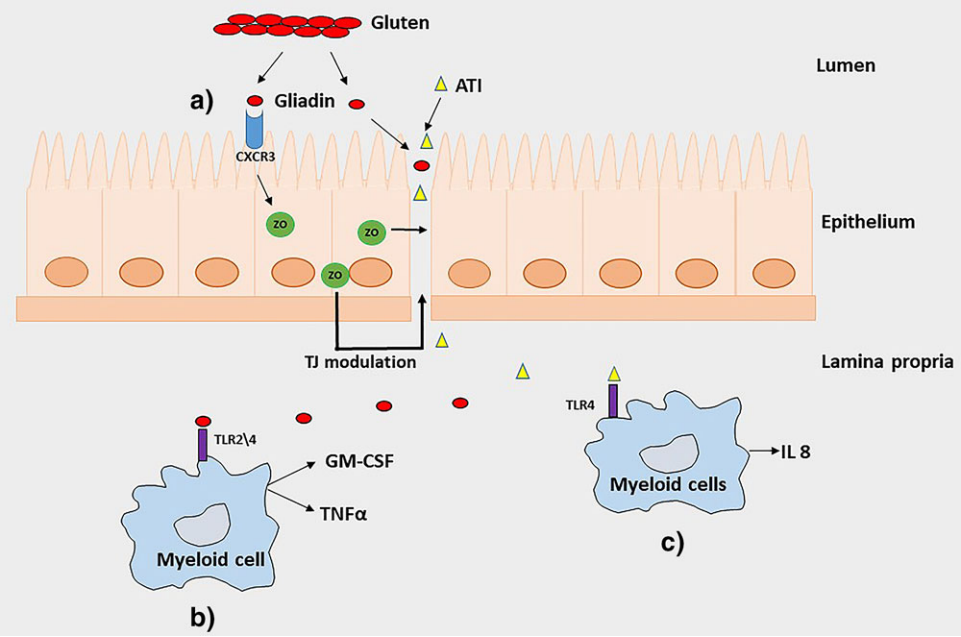

Figure 1. Schematic drawing showing possible steps leading to innate immune activation in subjects affected by NCGS. a) Gliadin peptides interact with the intestinal epithelium via the CXCR3 receptor and induce the release of zonulin, a molecule that increases gut permeability. This process facilitates gliadin and α-amylase/trypsin inhibitors (ATIs) trafficking from the intestinal lumen into the lamina propria, setting the stage for an innate immune response. b) Gluten peptides could activate myeloid cells (e.g., monocytes, macrophages, and dendritic cells) by undefined mechanisms or by binding to toll-like receptor (TRL) 2 or 4, inducing the production of tumor necrosis factor (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF). c) Furthermore, ATIs induce an innate immune reaction through the activation of TRL-4 on myeloid cells, leading to the release of pro-inflammatory cytokines such as IL-8.

et al.[11] suggested that the increased mucosal IFN-γ mRNA after a 3 day gluten challenge in NCGS subjects is related to the increased density of CD3+ IELs, as reported in CD patients.[21–23]

3. Intestinal Barrier Dysfunction

The gut mucosal barrier dysfunction may represent another potential mechanism involved in the pathogenesis of NCGS. While CD is consistently associated with increased small intestinal permeability,[24] contrasting evidence has been reported in patients with NCGS (Table 1B). In the intestinal epithelium, paracellular permeability is regulated by intercellular tight junction (TJ) proteins. CLDNs are integral TJ components that are critical for maintaining cell–cell adhesion in epithelial monolayers.[25–27] The overall balance of CLDN species expressed in a particular cell type helps to define the characteristics of its TJ. For instance, CLDN1 and CLDN4 are postulated to decrease TJ-dependent permeability, whereas CLDN2 is postulated to increase it.[28] In line with this notion, we have shown[6] that the NCGS mucosa expresses significantly higher levels of transcripts for CLDN4 compared to CD or controls. In contrast, other CLDN genes and other genes associated with TJ function (zonula occludens 1 and occludin) did not appear to be expressed differently in the NCGS or CD mucosa compared to controls.[6] Moreover, we have shown that small intestinal permeability, when tested with a lactulose/mannitol double sugar probe, was decreased in NCGS than in CD patients or even controls.[8] Together, these findings suggest that the distinct clinical features between NCGS and CD patients are associated with differences at baseline in mucosal barrier function and with apparent differences in the expression of CLDN4, which encodes a critical TJ component.[28]

Nevertheless, when exposed to gluten, even NCGS patients experience increased gut permeability, even if not as profoundly as registered in CD patients. The molecular bases of gluten-induced increased gut mucosal permeability are not entirely clear. However, our previous studies had identified α-gliadin peptides that interact with the intestinal epithelium via the CXCR3 receptor, causing release of zonulin, a molecule that regulates gut permeability.[29] We found that CXCR3 expression showed the same qualitative distribution in both CD and non-CD intestinal tissues, but its expression was higher in active CD.[29] This process would facilitate antigen trafficking from the intestinal lumen to the lamina propria via the paracellular pathway, setting the stage for an innate immune response and the features of NCGS (**Figure 1**a).

The role of gluten in causing loss of gut barrier has been also reported by Vazquez-Roque et al.[9] that, in a study published in 2013, showed that gluten ingestion can elicit gastrointestinal symptoms (GI) in non-CD patients, specifically, patients with diarrhoea-predominant IBS (IBS-D). The IBS-D patients, particularly those with the HLA-DQ2 and/or DQ8 genotypes, had more frequent bowel movements per day on a gluten-containing diet, and this diet was associated with increased small intestinal permeability. In these subjects, ingestion of gluten-containing grains increased gut permeability via reduced expression of intestinal epithelial TJ proteins, (zonula occludens 1, claudin-1, and occludin) without affecting intestinal transit time and histology.

This finding gave some insight into the role of the GFD in improving GI symptoms in IBS patients.

A recent study, using in vivo confocal laser endomicroscopy, has detected breaks in TJ and infiltration of the intestinal epithelium by T cells in patients with NCGS.[30] These changes occur within a few minutes after duodenal instillation of gluten, suggesting a rapid innate immune response in the intestine. Moreover, Hollon et al.[31] investigated intestinal permeability in human duodenal biopsies mounted in microsnapwells and luminally incubated with either gliadin or media alone. Changes in transepithelial electrical resistance (an index of intestinal permeability) were monitored over 120 min. Following gliadin exposure, both patients with NCGS and those with active CD demonstrated a greater increase in intestinal permeability than celiac patients in disease remission. The clinical significance of these findings remains to be elucidated. Another indication of gut mucosal barrier dysfunction in NCGS comes from a very recent study performed by Uhde et al.,[32] which showed that like patients with CD, NCGS patients also had elevated levels of fatty acid–binding protein 2 (FABP2), a marker of gut epithelial cell damage, suggesting compromised intestinal barrier integrity. The authors, in agreement with previous studies,[8,13,14,33] also observed an increase in IgG native gliadin antibodies in NCGS compared to the healthy control group, suggesting that such an antibody response may be a consequence of higher small intestinal permeability.

It is worth noting that the intestinal epithelial changes associated with NCGS may be more subtle in comparison with CD and might not be detectable by conventional light microscopy. Therefore, it may be useful to perform an ultrastructural analysis (e.g., by means of both scanning and transmission electron microscopy) so that such morphological anomalies can be detected, thus establishing a histologic diagnostic criterion to identify NCGS patients.

4. Immunological Features

In CD, the immune response against prolamins of toxic cereals involves both the adaptive and innate immune branches.[34] In the early phase of CD, epithelial cells are likely destroyed via toxic gliadin peptides, such as 19-mer, that might activate the innate immune system, thereby upregulating interleukin (IL)-15 secretion.[35] Therefore, immunoadaptive peptides, such as 33-mer, can enter the lamina propria, where the HLA class II molecules DQ2+ or DQ8+ present these peptides to T cells, which activate gluten-reactive T helper (Th) 1 cells and produce high levels of pro-inflammatory cytokines, particularly IFN-γ, a key cytokine in the downstream initiation of mucosal damage.[36]

The limited knowledge of the pathophysiology of NCGS and the lack of biomarkers are still major limitations for clinical studies, making it difficult to differentiate NCGS from other GRD. Furthermore, no data are available on the role of mucosal immune response in the pathogenesis of NCGS. There is an increasing interest in the role of the innate immune system in NCGS (Table 1C). This is based on the observation that intake of wheat-based products may provoke immediate reactions, which is too short of a timescale to be mediated by an adaptive immune response. In 2011, we observed that small intestine expression of TLR2 and, to a lesser extent, TLR1 was increased in NCGS subjects, compared to CD or controls, whereas there were no differences in markers of adaptive immunity.[8] Therefore, our findings provide evidence that the intestinal innate immune system might be involved in the development of NCGS. Moreover, in vitro experiments performed by our group,[37] identified an α-gliadin fragment that caused the release of IL8 that occurred only in a subgroup of non-CD subjects; peripheral blood mononuclear cells of the phagocytic lineage were the main source. This leads to recruitment of mononuclear cells to the intestinal lamina propria—possibly another key step in the activation of the innate immune response associated with NCGS.

More compelling evidence for the role of innate immunity came from Vazquez-Roque et al.,[9] who showed an increased production of tumor necrosis factor (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF) in the absence of IFN-γ production after in vitro PBMC stimulation with gluten fragments in non-celiac patients with diarrhoea-predominant IBS. Cytokine responses to gluten were not increased in the DQ2- or DQ8-positive patients. The lack of proliferation and IFN-γ expression and the increased production of TNF-α and GM-CSF not associated with DQ status, would suggest that non-T cells (e.g., monocytes, dendritic cells) could be directly stimulated by gluten. An involvement of TLR4 in the gluten-mediated antigen presenting cell (APC) activation has been suggested by Junker et al.[38] Furthermore, a recent work suggests that a pepsin digest of gluten can activate peripheral blood mononuclear cells and monocytes via TLR2 and TLR4 signaling[39] (Figure 1b). Further experiments are needed to determine which cell groups could contribute to this particular cytokine pattern in the periphery and whether the same cytokine profile is observed in the gut.

Another category of proteins identified as strong activators of innate immune responses are pest-resistance molecules in wheat known as α-amylase/trypsin inhibitors (ATIs). A recent study by Junker et al.[10] found that ATIs engage TLR-4 and release of pro-inflammatory cytokines in myeloid cells, for example, IL-8 and IL-12, of both patients with CD and non-diseased controls, as is expected for innate immune triggers (Figure 1c). Moreover, the authors also showed that the addition of exogenous ATIs to the organ culture of jejunal biopsies from treated CD induced an increase in IL-8 mRNA levels. The same group found in vivo, in ATI gavaged mice, an increased transcript levels of IL-15, an inflammatory cytokine that plays a pleiotropic role at the interface between innate and adaptive immunity in CD.[10] We plan to examine whether ATIs are also able to induce the production of innate cytokines such as IL-8 and IL-15 in NCGS biopsies.

Importantly, ATIs are present in commercial gluten and resist proteolytic digestion, such as by the gastric and enteric proteases pepsin and trypsin, maintaining the ability to activate TLR4 throughout oral ingestion and intestinal passage.[40] Plants other than wheat, rye, barley, and their early ancestors also contain inhibitors of amylase and trypsin-like activities, but show only minimal or no TLR4-activity.[40] Therefore, the terminology "NCGS" might more appropriately be termed non-celiac wheat sensitivity (NCWS) if the non-gluten proteins of wheat grain are proved to play a role in the pathogenesis of the disease. A GFD is also supposed to be ATI-free because avoidance of gluten necessarily involves avoidance of the implicated ATIs. In summary,

there is now evidence, although preliminary, that ATIs trigger innate immunity in both CD and NCGS.

While in CD there is a strong genetic association with the class II MHC haplotype, with approximately 95% of patients carrying HLA-DQ2 and the remaining 5% carrying HLA-DQ8, we reported that only approximately 50% of patients with NCGS carry HLADQ2 and/or HLA-DQ8,[8] a percentage slightly higher than the one detected in the general population. This questions the involvement of MHC-dependent adaptive immune responses in NCGS relative to CD. Moreover, we have shown no increase in adaptive immunity-related gut mucosal genes expression, including IL-6, IL-17, IL-21, and IFN-γ in NCGS.[8,12] Nevertheless, recently, in an intestinal biopsy-based study, NCGS patients showed increased mucosal IFN-γ mRNA after a 3 day gluten challenge.[11] This indicates that the adaptive immune response may play a role in the NCGS pathogenesis.

In support of a role of the adaptive immune system in NCGS, previous papers have shown that approximately 50% of NCGS patients are positive for antigliadin antibodies IgG (AGA-IgG; Table 1D),[8,13,14,33] which disappear quickly after implementation of GFD, together with improvement or resolution of symptoms.[41] However, there are some reports in literature suggesting that the detection of serum AGA-IgG may represent merely a nonspecific biomarker of loss of barrier function associated with the passage of non-self-antigens (in this case gliadin) that will induce in an immune response not related to the pathogenesis of the underlying condition.[42] Additionally, the lack of gluten-reactive T cells, and the lack of a strong association between HLA and NCGS suggests that the adaptive immune system in NCGS does not act in similar manner as seen in CD.

Other findings of a gut mucosal immune activation that might be specific to NCGS patients include an increased infiltration of eosinophils in the duodenum, ileum, and/or colon (Table 1E).[14] It is known that both IgE-mediated and non-IgE-mediated food-related disorders are characterized by eosinophilic infiltration of the gut.[43] Therefore, this study has shown that patients identified as having NCGS may have features of non-IgE-mediated food allergy when further checked. Moreover, this first demonstration of the colon's involvement in NCGS could explain why the main symptoms in these patients were lower (i.e., IBS-like ones) and not upper intestinal (i.e., dyspepsia-like one) ones and define a histology pattern pointing to a NCGS diagnosis.

5. New Dietary Opportunity for NCGS Patients

While in CD pathogenesis the immune response against prolamins of toxic cereals involves both the adaptive and innate immune branches, in NCGS pathogenesis, a prevalent role of the innate immune system was hypothesized. Therefore, a cereal suitable for a CD diet should be low in both classes of peptides. Research is actively trying to find wheat varieties with absent or low toxicity to be implemented in new strategies for the treatment and prevention of CD. Diploid wheat species are among the suitable candidates because of their low tendency to activate intestinal T cell responses in CD patients.[44,45] Compared with tetraploid and hexaploid modern wheats, ancient diploid *Triticum monococcum* ssp. *monococcum* wheat showed a marked reduction, or even a lack, of toxicity in in vitro cellular assays, which suggested their potential use as new dietary opportunities for CD patients.[46–48] However, additional studies are needed before the view is accepted that products from monococcum wheat are less toxic or nontoxic for CD patients. Furthermore, the existence of several variations of this ancient wheat with different gluten protein compositions also raised the question as to whether all varieties might be equally toxic for CD patients. We have investigated, in vitro, the immunological properties of 2 monococcum lines, Monlis and ID331, in view of their possible use in CD patients.[49] Our data showed that gliadin from monococcum lines, Monlis and ID331, digested by pepsin-trypsin (PT), activate the CD-T cell response and suggest that both lines are toxic for celiac patients. However, ID331 is likely to be less effective in inducing CD because of its inability to activate the innate immune pathways.[49] Subsequently, we demonstrated that gliadin proteins of Monlis and ID331 are sufficiently different from those of common *Triticum aestivum* wheat and have lower immune toxicity following in vitro simulation of human digestion.[50] Specifically, proteomics results demonstrated that several monococcum peptides, including known T cell epitopes, were degraded during the gastrointestinal treatment, whereas much of *T. aestivum* gliadin survived the gastrointestinal digestion.[50] Clinical trials have recently shown that monococcum is toxic for CD patients as judged on histological and serological criteria, but it was well tolerated by the majority of patients, suggesting that monococcum is not a safe cereal for celiacs, but that it may be of value for the prevention of CD or for patients with NCGS.[51] Interestingly, it was found that modern wheat contains high concentrations of ATIs, which activate innate immunity via TLR4, compared with ancient diploid wheat.[52] These data reinforce the hypothesis of the potential use of old cultivars as potential dietary options for NCGS patients. Therefore, considering a prevalent role of the innate immune system in NCGS pathogenesis, it might be anticipated that some lines of diploid wheat monococcum characterized by their minimal activation of innate immune pathways and reduced amount of gluten immune toxic peptides, could be used for the diet of NCGS patients. Furthermore, a regular diet based on ancient monococcum may delay the onset of CD, particularly in at-risk subjects such as first-degree relatives of celiac patients. Nevertheless, this hypothesis deserves further investigation in clinical setting.

Tritordeum, a novel cereal cultivar produced from hybridization between durum wheat (*Triticum durum*) and wild barley, may represent another alternative cereal for people suffering from NCGS. Tritordeum has the unique characteristic of having a gluten protein composition different from that of wheat, with lower levels of ω-gliadins. The results obtained suggest that, while not suitable for CD sufferers, tritordeum may be useful for those who wish to reduce their gluten intake, as NCGS patients.[53]

Recently, oats have been receiving increasing interest as human food, mainly because this cereal could be suitable for consumptions by CD patients. In 2011, we have investigated the immunogenic effect of avenins from two oat cultivars, Avena genziana and Avena potenza, by using in vitro organ culture models and intestinal gliadin-specific T cell lines from patients with CD. Our study showed that both cultivars do not display in vitro activities related to CD pathogenesis.[54] Other in vitro studies have shown that the immunogenicity of oats varies depending on the

cultivar used.[55,56] Recently, long-term cohort studies as well as short-term intervention studies have revealed that oats consumption by CD patients is safe, provided that the products are uncontaminated with wheat, barley, or rye.[57–59] However, although oats are generally considered safe for CD patients, their role in CD pathogenesis is still a matter of debate.[60] Furthermore, oats can be considered safe also for NCGS subjects due to their lower prolamin content[61] and for their lower ATI innate immune stimulatory activity.[52]

Another alternative treatment option to the GFD in patients affected by GRD could include the use of gene-editing technology in cereals.[62] Traditional mutagenesis and plant breeding have failed to obtain low-toxic wheat varieties for patients with GRD. More recently, it has been shown that the modification of gliadins' genes in bread wheat, using CRISPR/Cas9 technology,[63] efficiently reduced the amount of gliadins in the seed kernel, providing bread and durum wheat lines with reduced immunoreactivity for susceptible individuals.

6. Conclusions

The pathophysiology of NCGS is unclear. Many of the described observations seem to suggest that innate rather than adaptive immunity has a prominent pathogenic role in NCGS. However, differences in the immune response were observed among patients with NCGS that may justify the division in subgroups that react differently to foods, each characterized by a different pathogenesis and clinical course. Further studies are needed for a better understanding of the patho-mechanism, which might lead to the identification of biomarkers to properly diagnose and better define the different NCGS subgroups. Moreover, research on the potential pathogenic role of wheat components other than gluten, namely, ATIs or FODMAPs in NCGS, are also needed. Finally, ancient wheats, both for their reduced amount of gluten immune toxic peptides and low concentrations of ATIs, could be considered a new dietary approach for the management of patients with NCGS.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

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