

# Diploid Wheats and Non Celiac Wheat Sensitivity

Subjects: **Food Science & Technology**

Contributor: Vera Rotondi Aufiero , Anna Sapone , Giuseppe Mazzarella

Non-celiac wheat sensitivity (NCWS) is a clinical entity induced by the ingestion of gluten that leads to intestinal and/or extraintestinal symptoms, and is diagnosed when celiac disease and wheat allergy have been ruled out. In addition to gluten, other grains' components, including amylase trypsin inhibitors (ATIs) and fermentable short-chain carbohydrates (FODMAPs), may trigger symptoms in NCWS subjects. Several studies suggest that, compared with tetraploid and hexaploid modern wheats, ancient diploid wheats species could possess a lower immunogenicity for subjects suffering from NCWS.

non celiac wheat sensitivity

diploid wheat

common wheat

amylase trypsin inhibitor

FODMAP

## 1. Introduction

Adverse reactions to food that result in gastrointestinal symptoms are common in the general population. Wheat has been found to be one of the most common factors inducing such symptoms.

In particular, some disorders are related to the ingestion of specific wheat components, such as gluten, FODMAPs, and ATIs. These disorders are known as wheat-related disorders that mainly involve CD, WA, and non-celiac gluten/wheat sensitivity [1].

CD is an immune-mediated disease triggered by the ingestion of wheat gliadin and related prolamins from other toxic cereals, such as barley and rye, that cause typical CD autoimmune enteropathy in genetically susceptible individuals [1]. WA is an IgE-mediated allergic reaction to the proteins found in wheat and other related cereals, such as barley and rye [1]. As defined by the 2015 Salerno Expert's Criteria, the term non-celiac gluten sensitivity (NCGS) is used to describe the clinical state of individuals who develop both intestinal and extraintestinals (headache, foggy mind, chronic fatigue, joint pain, tingling or numbness of the extremities, eczema) symptoms when they consume gluten-containing foods, and feel better on a gluten-free diet (GFD), but do not have CD or a WA [2]. Subsequently, it has been recognized that some components of wheat other than gluten proteins are potentially deleterious for NCGS patients, which include ATIs and FODMAPs. The terminology "NCGS" was then changed to "Non Celiac Wheat Sensitivity" (NCWS), which would exclude other relevant cereals, such as barley and rye [3].

The limited knowledge about the pathophysiology of NCWS, and the lack of validated biomarkers, are still major limitations for clinical studies, making it difficult to differentiate NCWS from other wheat-related disorders, as well as from other clinical conditions characterized by similar symptoms (for example, irritable bowel disease). Therefore, NCWS diagnosis is still based on clinical criteria and it can be confirmed only by a double-blind placebo-controlled challenge, a practice difficult to implement in routine clinical settings [2]. Several studies suggest that NCWS is an immune-mediated disease that likely activates an innate immune response [4].

Research is actively trying to find wheat varieties with absent or low immune-reactivity to be implemented in new strategies for the treatment and prevention of subjects suffering from wheat-related disorders. Preliminary evidence supports the assumption that the diploid wheat species, *Triticum monococcum*, compared to common wheat, *Triticum aestivum*, could possess a lower immunogenic potential for subjects suffering from NCWS [4][5][6].

## 2. Mucosal Immune Responses in NCWS

The precise pathogenesis of NCWS is still poorly defined; nevertheless, in several reports, it has been shown to be the presence of a gut immune activation, and where innate immunity could have a role in some subjects with this condition (**Table 1**).

**Table 1.** Gut immune activation in NCWS.

Gut Immune Activation in NCWS	References
<b>Innate immune response</b>	<ul style="list-style-type: none"> <li>• Sapone et al., 2011 [7];</li> <li>• expression of TLR2</li> <li>• production of innate immune cytokines</li> <li>• Sapone et al., 2011 [7]; Lammers et al., 2011 [8]; Junker et al., 2012 [9]; Vazquez-Roque et al., 2013 [10]; Di Liberto et al., 2016 [11]; Caminero et al., 2016 [12]; Zevallos et al., 2017 [13]; Iacomino et al., 2021 [14]; Cárdenas-Torres et al., 2021 [15];</li> </ul>
<b>Adaptive immune response</b>	<ul style="list-style-type: none"> <li>• production of IFN-<math>\gamma</math></li> <li>• production of TNF-<math>\alpha</math> and IL-17</li> <li>• Brottveit et al., 2013 [16]</li> <li>• Mansueto et al., 2020 [17]; Castillo-Rodal et al., 2020 [18]</li> </ul>
<b>Autoantibodies</b>	<ul style="list-style-type: none"> <li>• production of antigliadin IgG antibodies</li> <li>• Sapone et al., 2011 [7]; Carroccio et al., 2012 [19]; Volta et al., 2012 [20]; Uhde et al., 2016 [21]</li> </ul>
<b>Intestinal permeability</b>	<ul style="list-style-type: none"> <li>• Sapone et al., 2011 [7]</li> </ul>

Gut Immune Activation in NCWS	References
<ul style="list-style-type: none"> <li>high levels of CLDN4</li> <li>Increased transepithelial electrical resistance</li> <li>break of tight junctions and infiltration of the intestinal epithelium by T cells</li> <li>high levels of multiple permeability biomarkers (LBP, FABP2)</li> </ul>	<ul style="list-style-type: none"> <li>Hollon et al., 2015 [20]</li> <li>Fritscher-Ravens et al., 2014 [23]</li> <li>Uhde et al., 2016 [21]</li> </ul>
<b>Mucosal immune cells</b> <ul style="list-style-type: none"> <li>increased infiltration of eosinophils</li> <li>increased levels of mast cells</li> <li>intraepithelial lymphocytosis</li> </ul>	<ul style="list-style-type: none"> <li>Carroccio et al., 2019 [19]; Zanini et al., 2018 [24]</li> <li>Losurdo et al., 2017 [25]; Giancola et al., 2020 [26];</li> <li>Sapone et al., 2010 [7]; Brottveit et al., 2013 [16]; Volta et al., 2012 [20]; Carroccio et al., 2012 [19]; Carroccio et al., 2019 [27]; Zanini et al., 2018 [24]; Rostami et al., 2022 [28]</li> </ul>

antibody response may be a consequence of impaired gut integrity and permeability [29], reported in NCWS [7][21][22][29]. Notably, GFD leads to a normalization of multiple permeability biomarkers, demonstrating a link between diet, intestinal barrier, and systemic immune activation in NCWS patients. Additionally, gut microbiota analysis revealed a significant dysbiosis in NCWS patients, and some authors suggest that this could contribute to intestinal barrier dysfunction.

Other findings of gut mucosal inflammation in NCWS include an increased infiltration of eosinophils and mast cells in the gastrointestinal tract [19] [24][25].

At present, NCWS is characterized by a normal duodenal histological picture (Marsh 0 stage), even if an increase in CD3+ IELs (Marsh I) could be detected in some patients, as reported by researchers' own studies [7][28][30], supported by others [16][19][26][27][28].

### 3. Gluten Components

Wheat gluten is composed of two types of proteins called glutenins and gliadins, which in turn can be divided into high molecular and low molecular glutenins and  $\alpha/\beta$ ,  $\gamma$  and  $\Omega$  gliadins [31].

Gluten composition varies between species and cultivars, presenting high contents of proline-rich polypeptide residues, which make them resistant to proteolytic degradation in the gastrointestinal tract [32]. When these proteins are consumed by genetically susceptible individuals, a cascade of immune reactions is triggered, which result in damage of the small intestinal mucosa, resulting in CD. Its pathogenesis has classically been attributed to the activation of lamina propria CD4+ Th1 cells specifically reacting to immunotoxic gluten peptides, such as 33-mer [4].

In the early phase of CD, epithelial cells are likely destroyed via toxic gliadin peptides, such as 19-mer [28][33], that might activate the innate immune system, thereby upregulating interleukin IL-15 secretion [34]. Recently, it has been found that 33-mer peptide could also activate the innate immune system via TLR-2 and TLR-4 receptors, inducing the release of pro-inflammatory cytokines, such as IP-10/CXCL10 and TNF- $\alpha$  (Figure 1a) [35].

Therefore, since both innate and adaptive immunity are involved in CD pathogenesis, cereal suitable for a CD diet should be low in both classes of peptides. Among candidates, there are diploid wheat species, because of a reduced number of stimulatory epitopes of T-cell lines [36], and of the lack of a D-genome encoding the immunodominant 33-mer fragment [37], compared to common wheat.

*Triticum aestivum* has evolved from hybridization between the tetraploid species *Triticum turgidum* (AABB) and the diploid species *Aegilops tauschii* (DD) [37]. Due to its “simpler” genome with respect to *Triticum aestivum* and *durum*, *T. monococcum* contains a reduced number of epitopes and toxic peptides [38]. These findings may have implications for programs aiming to produce wheat species with no or low contents of gluten proteins, harmful to CD patients. Nevertheless, even if it should prove impossible to generate a wheat cultivar completely devoid of harmful proteins, a cultivar low in T-cell stimulatory sequences can possibly be tolerated by most CD patients. Moreover, the difference in gluten composition among diploid (AA), tetraploid (AABB) and hexaploid (AABBDD) wheat varieties may affect the resistant to cleavage by intestinal peptidases [39].

Researchers have previously investigated, in *in vitro* models, the immunological properties of gliadin protein from two monococcum cvs, Monlis and Norberto-ID331, in view of their possible use in CD patients [40]. Researchers found that partially digested gliadin proteins extracted from two monococcum lines, Monlis and Norberto-ID331, induced adaptive immune response in CD patients, whereas the innate immune response could be elicited only by gliadin from Monlis cv [40]. Subsequently, researchers have demonstrated, by proteomic analysis, that almost all immunotoxic gluten peptides from Monlis and Norberto-ID331, are *in vitro* degraded during digestion by gastric-duodenal and brush border membrane (GD-BBM) enzymes, whereas gluten immunogenic peptides from hexaploid *Triticum aestivum* resist intestinal [41]. Clinical trials have shown that *T. monococcum* is toxic for CD patients, but it was well tolerated by the majority of patients [42], suggesting a potential efficacy in patients suffering from other gluten-related disorders, such as NCWS.

Increased intestinal permeability in patients suffering from wheat-related disorders, could be an early events that precedes the onset of gut immune activation. In CD it was shown that myeloid differentiation factor 88 (MyD88), a key adapter molecule in the TLR/IL-1R signaling pathways, induces release of zonulin, a mediator of gut permeability, upon non-digested gliadin binding to CXCR3 on enterocytes, as a result inducing greater epithelial

permeability and subsequent paracellular gliadin passage to the gut mucosa [43] (Figure 1a). These data support the model for the innate immune response to gliadin in the initiation of CD. Similar mechanisms may also underlie the increased intestinal permeability reported in NCWS. As researchers have shown that *T. monococcum* gliadin had a marked susceptibility to gastrointestinal digestion, researchers can hypothesize that such mechanism, triggered by non-digested gliadin of common wheats, may not be elicited (Figure 1b). Thus, the innate immune response could be prevented.

## 4. Non-gluten components

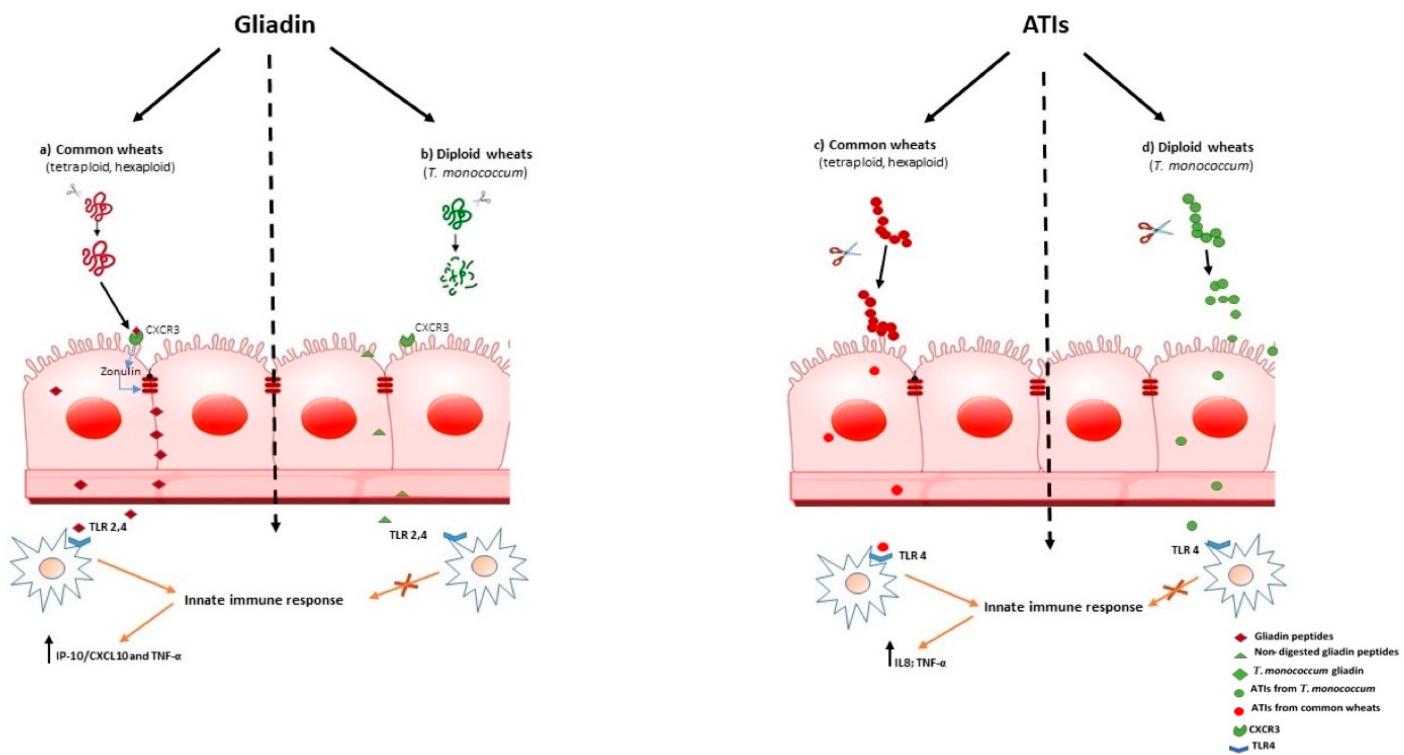
The non-gluten wheat proteins comprise a mixture of components with), such as ATIs, which may contribute to defence plant from pests and parasites.

To date, ATIs have been shown to be potent activators of the innate immune system response, engaging TLR-4 with release of proinflammatory cytokines in myeloid cells (IL-8 and IL-12), of both patients with CD and non-diseased controls. For their general TLR4 stimulatory activity, ATIs were suspected to have pathogenic roles in patients with wheat-related hypersensitivities such as NCWS or irritable bowel syndrome (IBS) [5][44][45]

Interestingly, it was found that modern wheat contains high concentrations of ATIs, compared with ancient diploid wheat [5][46][47][48]. Therefore, considering the pro-inflammatory effect of ATIs, *T. monococcum* wheat could retains a reduced immunostimulating activity for subjects suffering from wheat related diseases.

Zevallos and co-workers found that older wheat variants, as *T. monococcum*, had lower bioactivity than modern wheat [13]. More recently, researchers found that PC-digested ATIs purified from *Triticum aestivum* induced IL-8 and TNF- $\alpha$  secretion in organ culture of jejunal mucosa of treated CD patients, whereas the capability of ATIs from *T. monococcum* to stimulate innate immunity was meaningfully affected [49]. It has been reported that the resistance to gastrointestinal digestion is an important constrain in determining the immune stimulatory and toxicity properties of gliadin peptides [50]. Therefore, researchers' data suggest that the susceptible to enzymatic hydrolysis of ATIs from diploid *T. monococcum* resulted in a failure to induce the innate immune response (Figure 1d). In contrast, the stability to hydrolysis by human digestive enzymes of ATIs from hexaploid wheat, affects the activation of mucosal innate immune response (Figure 1c).

Therefore, researchers can hypothesize that a regular diet based on *T. monococcum* in NCWS patients, might prevent gut immune activation.



**Figure 1.** Schematic drawing that shows what happens in subjects with non-coeliac wheat sensitivity on *T. monococcum* based diet containing common wheat, according to researchers' hypothesis. **(a)** Interactions between non-digested gliadin peptides from common wheat and CXCR3 receptors in the intestinal epithelium trigger zonulin, release that leads to increased intestinal permeability. Therefore, non-digested gliadin peptides can reach the lamina propria and could activate the innate immune system via TLR-2 and TLR-4 receptors, inducing the release of pro-inflammatory cytokines; **(b)** As *T. monococcum* gliadin have a marked susceptibility to gastro-intestinal digestion, it can be hypothesized that such a mechanism, triggered by non-digested gliadin from common wheats, may not be elicited. Amylase trypsin inhibitors (ATIs) have been shown to be potent activators of the innate immune system in NCWS subjects. **(c)** ATIs from common wheats pass the intestinal epithelium and in LP stimulate TLR4 on macrophages, inducing the production of innate cytokines; **(d)** Considering that *T. monococcum* contains ATIs with a higher digestibility than modern wheat, the innate immune response could be prevented. Therefore, TM could retain a lower immunostimulating activity for subjects suffering from NCWS.

## 5. Beyond immunogenicity: nutritional features of diploid wheats

The increasing attention to the nutritional aspects of food has led to the search for alternatives to the traditional *T. aestivum* wheat.

Compared to modern wheats, diploid wheats showed a better nutritional quality and relevant potential for human consumption. In particular, ancient wheats contain higher levels of antioxidant compounds as  $\alpha$ - and  $\beta$ -carotenes, lutein, zeaxanthin, tocopherols, conjugated polyphenols, alkyl resorcinols and phytosterols, retinol, phosphorus, potassium, riboflavin and pyridoxine [51][52][53][54][55].

Moreover, ancient wheats had a lower quantity of dietary fibre and carbohydrate but a higher content of proteins, lipids (mostly unsaturated fatty acids), fructans, thiamine and a number of other B vitamins, zinc and iron [52][53][54][55][56], compared to modern wheats, that gives them properties useful in preventing some pathological conditions. Ancient wheats are still cultivated nowaday only in some areas of the world, including France, Germany, Austria, Hungary, Bulgaria and Italy, but the increasing interest to healthier foods has increased the popularity of their use and, consequently, has caused an increase in their production. For all these features the use of ancient wheats may become more relevant in human consumption, especially in the development of new or special functional foods with superior nutritional quality.

## 6. Conclusion

Gluten, and other wheat proteins, including ATIs and FODMAPs, have been identified as possible factors for generation of intestinal and extra-intestinal symptoms in subjects suffering from wheat-related disorders, such as NCWS. In particular, it is well-known that gluten and ATIs possess immune stimulating activity. Therefore, dietary exposure to the combination of gluten and ATIs exacerbates intestinal immune dysregulation and increase risk to develop wheat-related disorders. *T. monococcum*, the oldest and most primitive cultivated wheat, unexposed to genetic improvements, has been suggested to possibly exert a reduced immunostimulating activity compared to common wheats and, consequently, embodies the role of a fitting candidate to be introduced into the diet of such patients. Therefore, clinical studies on NCWS patients to assess the effects of a TM wheat-based foods diet are warranted.

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