

Development of Vaccines in Celiac Disease Therapies

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Abstract. In Western countries, celiac disease is a relatively common genetic immune disorder. When a patient ingests foods containing gluten, the gluten protein acts as an allergen and can cause the patient to develop the disease. The disease is not directly fatal, but its onset can be very uncomfortable for the patient, and its complications may lead to an increased chance of developing certain cancers. A lifetime gluten-free diet has already been the standard course to prevent celiac disease symptoms, but it can be challenging. In past studies, researchers have attempted to prevent patients from developing or mitigating their condition through vaccines as a treatment. However, with research stagnating and clinical trials being canceled, the production of a celiac disease vaccine is currently experiencing a bottleneck. Fortunately, the treatment of celiac disease is not the only way to build tolerance through vaccines; other therapies under investigation as well as new vaccine design ideas may be effective in treating celiac disease. This review systematically summarizes the scientific status of the celiac disease and discusses the potential of vaccine as a promising treatment for celiac disease.

Keywords: Celiac Disease, Vaccine, Immune Therapy.

1. Introduction

Celiac disease is known as an intestinal tract disease affected by inherited chronic immunological conditions. Although some people appear asymptotically, gluten consumption causes patients to experience bloating, diarrhea, and other unpleasant symptoms. Additionally, celiac disease results in damage to the intestinal mucosa that is not immediately repaired, and most patients still have mild inflammation even when their diet is free of gluten [1]. Although celiac disease does not directly result in death, studies have shown that affected individuals are more likely than the general population to develop specific cancers. Additionally, celiac disease complications, such as autoimmune diseases, gastrointestinal disorders (including liver disease and pancreatic disease), and miscarriage in patients who have not yet received a diagnosis are concerning [2].

There are not many therapeutic options for celiac disease. A lifetime diet without gluten is the most traditional form of treatment. In fact, gluten-free diets are difficult to follow since not all eateries and retailers mark their food as containing gluten; gluten-free goods may also be more expensive; and gluten-free diets may also be lower in nutrients than conventional diets. And for some patients with severe celiac disease, gluten-free diets do not work [1]. These reasons, as well as the possible complications of celiac disease, have forced the search for new treatments for celiac disease.

This article gives a summary of the development of vaccines against celiac disease. Given that celiac disease is an immune disease, vaccines are a means of prevention or treatment. In a later article, the pathogenesis of celiac disease will be briefly described to better explain how vaccines work. Subsequently, the development of different types of celiac disease vaccines and the problems faced will be discussed.

2. Pathogenesis

Human leukocyte antigen (HLA)-DQ2.2, DQ2.5, or DQ8 expression on patient's antigen-presenting cells (APC) is the reason why celiac disease happens [1, 3-5]. Other than the haplotype of HLA-DQ2.2/2.5 or HLA-DQ8 presenting, additional genes, including several genes that regulate T-cell immune response, are also implicated [4]. Most of patients, about 95%, have the HLA-DQ2 gene [6]. When patients ingest gluten-containing food, the peptide chains produced by incomplete

digestion of gluten proteins in the intestine enter the small intestinal epithelium, where transglutaminase 2 (TG2) will deaminate them, and they will be negatively charged to bind to positively charged HLA-DQ2 and HLA-DQ8 [1,3,5], which activates specific $CD4^+$ T cells [3,5], thus stimulating Th1 cells to activate $CD8^+$ T cells, and will also stimulate the function of natural killer (NK) cells; encouraging Th2 cells to activate B cells, which then undergo plasma cell differentiation and generate anti-TG2 and antigliadin antibodies [3]. Interferon (IFN)- γ , interleukin (IL)-15, IL-2, and IL-21 are among the cytokines that are created in large quantities when T cells are activated, increasing the susceptibility of cells to being destroyed [1,4,5]. Among them, the high secretion of IL-15 drives the conversion of intraepithelial lymphocytes (IEL) into cytotoxic cells, leading to small intestinal epithelial damage and intestinal villi atrophy [1,4,5]. Intestinal villi atrophy may lead to irreversible malabsorption, and persistent inflammation of the small intestinal epithelium can cause celiac disease patients to face intestinal discomfort even in the absence of gluten intake (Figure 1).

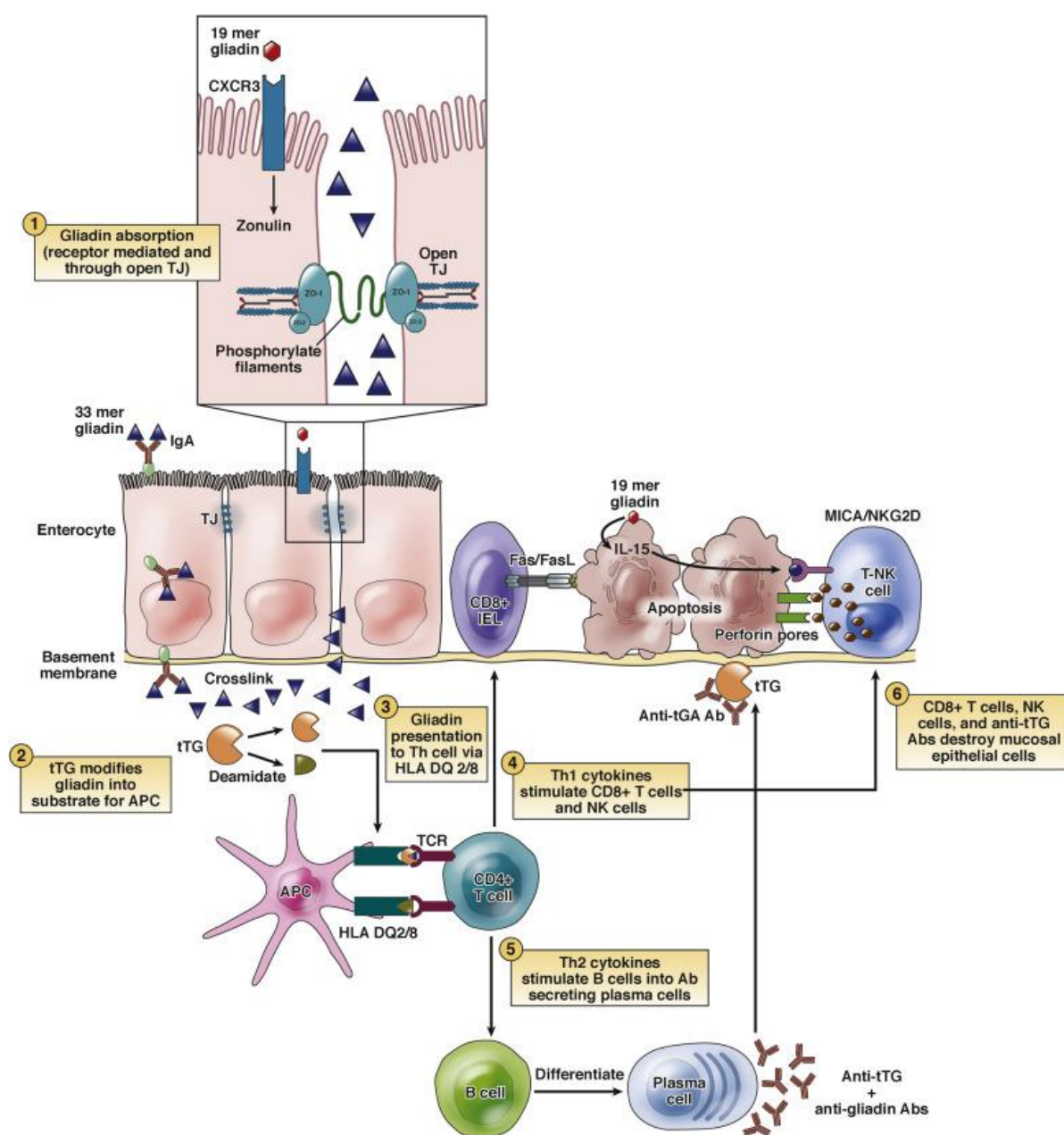


Figure 1. The Pathogenesis of Celiac Disease [3].

3. Vaccines in celiac disease treatment

3.1. Administration routes for vaccines

The therapeutic ideology of the celiac disease vaccine is based on establishing immune tolerance. Starting with a small dose of antigen exposure and gradually increasing the dose to gradually build up a tolerance to the specific antigen and reduce the immune response. It is not possible to use natural antigens directly in the treatment of celiac disease, such as consuming foods containing gluten, as this could exacerbate the condition in those who already suffer from it [7].

One idea is to still use oral administration to deliver gliadin to patients to build tolerance. To avoid exacerbation by direct intestinal exposure to the antigenic protein, gliadin was modified to be non-toxic [8] and delivered via genetically modified non-stereotypic, non-pathogenic bacteria [7,8].

Nasal administration has also been studied due to the proven association between the nasal mucosal system and the intestinal mucosal system [7]. Since the difference in antigen dose and antigen toxicity required for the nasal mucosal tolerance mechanism compared to the intestinal mucosa, a single α -gliadin obtained by purifying and processing wheat gliadin was found to be better able to induce immune responses and establish immune tolerance through the nasal mucosa [9].

The only celiac disease vaccine currently in clinical trials is NexVax2, developed by ImmunosanT, Inc. It includes 3 immunogenic gliadin peptides, each 15-16 amino acids in length, including the five most active gluten peptides known in the HLA-DQ2.5 gene-caused celiac disease [4,8]. Two of them are found in α -gliadin: DQ2.5-glia- α 1 and DQ2.5-glia- α 2; another two can be found in ω -gliadin: DQ2.5-glia- ω 1 and DQ2.5-glia- ω 2; one is found in hordein proteins: DQ2.5-hor3 [4,8]. The HLA-DQ2.5-TCR complex, which connects CD4⁺ T cells that induce specific immunity to gluten with antigen-presenting cells, is the target of the vaccine. This vaccine, unlike the two mentioned above, is administered by injection and by gradually increasing the dose to build up immune tolerance.

As shown in Figure 2, the left side shows that when patients ingest gluten peptides through diet, the peptide chains are recognized after being broken down by tTG into more immunogenic small molecules and activate CD4⁺ T cells, producing abnormal huge amounts of IFN- γ and IL-21, leading to inflammation and apoptosis of small intestinal epithelial cells. In contrast, injection of NexVax2 gradually builds tolerance, induces increased IL-10 production by CD4⁺ T cells, induces downregulation of immune responses by Regulatory T cells (Tregs), promotes wound healing, and enhances immune tolerance.

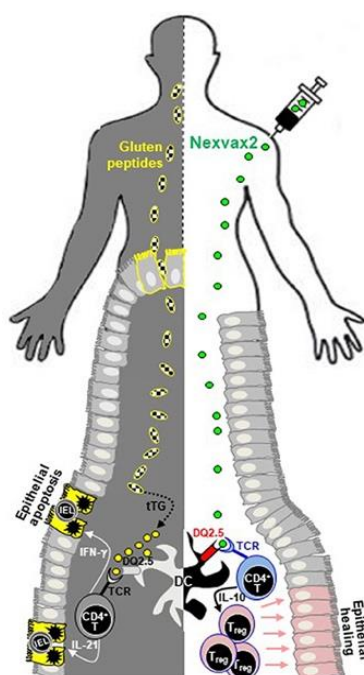


Figure 2. Mechanism of NexVax2 in Celiac Disease Patients [4]

3.2. Vaccines application

The oral administration of transgenic bacteria capable of delivering antigens has produced some effects in mouse models. A deamidated DQ8-specific gliadin epitope (DQ8d), a protein can trigger a DQ-8-mediated immunological response, was genetically introduced into *Lactococcus lactis* (LL) by researchers [10]. To establish immunological tolerance in DQ8-expressing celiac mice, this LL was designed to be given to NOD AB^o DQ8 transgenic mice [10]. In a mouse model, this approach successfully induced specific immunity [10]. Moreover, data from the study showed that this approach was able to induce immune tolerance in mice with reduced immune responses in antigen exposure, suppression of DQ-8-specific immune T-cell responses, IL-10 production, and reduced IL-12 secretion [10]. The strong ability to induce immune tolerance of LL may make it a promising vaccine for treating celiac disease.

The method of nasal mucosal administration also functions in mouse models. When animals expressing DQ-8 were given a pure recombinant version of α -gliadin via the nasal route, gastrointestinal stimulation with the same antigen revealed a significantly weaker immune response and suppressed T lymphocyte proliferation during gastrointestinal stimulation compared to the control group [9]. The immune response was also diminished when stimulated with wheat gliadin [9].

In contrast, NexVax2 has been studied in Phase I clinical trials with data on its effects in humans. Patients with celiac disease aged 18-70 years, with the gene encoding HLA-DQ2.5, were selected for the study in a crossover trial that is randomized, double-blinded, and placebo-controlled [11-13]. An oral gluten challenge was performed prior to initiation of dosing to screen participants who tested positive for interferon γ release and who passed a biopsy to continue the dosing trial [11-13]. Patients would then receive a placebo or a gradual increase from a low dose (3-60 μ g), administered twice a week, to a high dose (>300 μ g) [11-13]. The injection location was the lumbar abdomen [12,13]. The findings demonstrated that vaccination injections, even at low dose levels, may cause symptoms resembling those reported in celiac disease patients who have been exposed to the antigen gluten [11-13]. As the dose was gradually increased, patients gradually built up their tolerance, and even at the highest dose, tolerance was good, with less production of adverse events and relatively normal plasma cytokine levels [11-13]. Also, no deterioration was found in the intestinal histology of the participants before and after the experiment [11,12]. Some of the patients who received the vaccine showed a negative interferon release in the post-treatment to an oral gluten challenge, demonstrating the efficacy of the treatment [11]. However, ImmusanT discontinued the NexVax2 clinical study in 2019 because of findings from the phase II clinical trial showing that the celiac disease vaccine-treated group did not statistically differ from the patients with placebo treatment in terms of providing protection from gluten exposure [14].

4. Conclusions

The development of the celiac disease vaccine has not been smooth. Vaccines for oral or nasal administration are still in the experimental stage in mouse models and have not been further developed. Research on NexVax2 is on hold and entry into use is elusive. Because the sample size in the phase I trials was still too small, NexVax2 clinical trials in the phase II phase did not show statistical differences that are significant enough between the vaccinated and placebo groups [14]. In contrast, vaccines for celiac disease, which are based on the idea of establishing tolerance, have many problems. The first is the age of applicability. Even NexVax2 has only been tested in patients aged 18-70 years. It is still not known whether it is dangerous for young children as well as for the elderly. Also, it is questionable whether the same dose progression is used to build tolerance in patients of different severity. Patients with severe symptoms may not be able to use this approach to help them relieve their disease. There are also no studies to show how long the tolerance built up after vaccine treatment can be maintained and whether tolerance needs to be built up again with the vaccine after a period. Most fundamentally, how to minimize the incidence of adverse reactions at the time of vaccination while achieving the best vaccine results so that patients will want to be treated for celiac

disease in this way. These are questions that need to be addressed not only by NexVax2 but also by all the other types of celiac vaccines being studied.

In summary, vaccine research for celiac disease is at a bottleneck. The existing vaccines are few in type, target few targets, and still, focus on establishing tolerance as the basic strategy for making a celiac disease vaccine. At the same time, the stagnation of vaccine development and the unpromising results of clinical trials make celiac disease vaccine research seem to be at a dead end.

The good news is that building tolerance through vaccines is not the only solution for celiac disease. The use of enzymes that induce the complete breakdown of gluten proteins in the intestine or polymerize gluten proteins to block absorption; the inhibition of HLA or TG2 activity; the use of specific probiotics; immune cell targeting; the development of antibodies against pro-inflammatory cytokines to reduce the inflammatory response, etc. are all potential treatments for celiac disease [1,3]. These treatments under investigation may have more potential for development than vaccines, but again, they face very many difficulties and require the tireless efforts of researchers, as well as material and financial resources.

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