

Review Article

Celiac Disease and the Potential of Stems Cells as Treatment

Samantha Albano¹, Vincent S Gallicchio^{1*}

¹Department of Biological Sciences, College of Science, Clemson University; Clemson, South Carolina, USA

*Correspondence author: Vincent S Gallicchio, Department of Biological Sciences; 122 Long Hall, College of Science, Clemson University Clemson, South Carolina, USA; Email: vsgall@clemson.edu

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Abstract

Celiac disease is characterized by having a broad spectrum of clinical presentations ranging from asymptomatic cases to classical gastrointestinal manifestations of disease and cases of severe progression in refractory celiac disease and the development of certain types of cancers. The age of onset of disease also varies greatly, with genetics, environmental and immunological factors. While this autoimmune disease currently affects 1% of Western populations, cases have been increasing globally due to presence of gluten in westernized diets and improved diagnostic testing and awareness. The only current treatment for celiac disease is a strict lifelong adherence to a gluten free diet; however, patient reports suggest they are not satisfied with quality of life and clinical improvement involving only dietary treatment and future routes of treatment should be explored. The overall lack of understanding of a complex model of this disease has led to notable obstacles when conducting clinical trials investigating future treatments. Stem cells play a crucial role in the human body as they could help regulate inflammation that is often associated with autoimmune disorders by regenerating and differentiating into several different cell types. Mesenchymal stem cells and hematopoietic stem cells are highly proliferating, while mesenchymal stem cells can cross the HLAQ barrier and prevent an adverse immunological response in patients. For this reason, stem cells, especially mesenchymal stem cells, are prime candidates for investigation of future treatments designed with a goal of restoring the epithelial barrier and preventing villous atrophy while reducing inflammation.

Keywords: Celiac Disease; Refractory Celiac Disease; Stem Cells

Abbreviations

CD: Celiac Disease; RCD: Refractory Celiac Disease; EATL: Enteropathy-Associated T-Cell Lymphoma; IEL: Intraepithelial Lymphocytes; IL-6: Interleukin-6; IL-15: Interleukin-15; TGG: Tissue Transglutaminase; SPF: Specific Pathogen Free; GFD: Gluten Free Diet; TJ: Tight Junction; ISC: Intestinal Stem Cell; PC: Paneth Cell

Introduction

What is Celiac Disease?

Celiac Disease (CD) is an autoimmune disease that affects primarily genetically predisposed individuals [1]. This heritable disease is characterized by affected individuals having an immune reaction triggered by the ingestion of gluten. It varies widely when it comes to clinical manifestations; while some individuals suffer from minimal symptoms or even asymptomatic presentations of the disease, most patients experience severe malabsorption issues and associated malnutrition and excessive weight loss. Anemia, diarrhea, and abdominal issues among other gastrointestinal symptoms are also common.

Celiac disease is interesting since it varies widely in age of onset of disease. Onset can occur years before diagnosis and both genetic and environmental factors play a role in the presentation of this disease. Proper diagnosis of CD requires the presence of

duodenal villous atrophy samples are often acquired colonoscopically or endoscopically [1,2]. In blood work samples, individuals with CD are also known to have circulating levels of antibodies against tissue transglutaminase [1,3]. Genetic predisposition and dietary exposure to wheat and gluten containing proteins, an adaptive immune response as well as microbial dysbiosis all lead to the presentation of celiac disease [3].

Epidemiology of Celiac Disease

Celiac disease is an autoimmune disorder characterized by an autoimmune response in genetically susceptible individuals in response to gluten. Celiac disease affects an average of 1% of the population with more female prevalence and is primarily in those of European origin [4-6]. CD is more often found in first degree CD relatives and in other at-risk groups such as patients with Down syndrome, type 1 diabetes, or IgA deficiency [7]. Clinical presentations of celiac disease are greatly varied on a case-by-case basis with classical gastrointestinal symptoms such as malabsorption to non-classical gastrointestinal symptoms and asymptomatic subclinical cases. Therefore, most patients with celiac disease experience misdiagnosed or a delay in diagnosis that can delay treatment and worsen symptoms. Systematic reviews based on population-based data suggested that the incidence of celiac disease has increased over the past three decades, which could be attributed to an increase in the detection rate and modernization related changes in dietary practices that increase the amount of dietary gluten containing ingredients [8].

Diagnosis

Diagnosis depends on a positive serology (IgA anti-transglutaminase 2 and anti-endomysia antibodies) and villous atrophy in the small intestine revealed via biopsy as no antibody test provides a specificity of 100% [7-9]. These tests are not easily available in many parts of the world, limiting numbers of found cases in developing areas. The only current treatment known for celiac disease is following a strict gluten free diet for life. However, there are many challenges in adhering to this diet such as lack of availability, high cost, and cross-contamination associated with this very restrictive diet [11]. Though this disease has serious implications if a gluten free diet is not followed, follow-up protocols and disease management have not been clearly outlined by healthcare professionals. These challenges offer opportunities for future research.

Severe Complications of Celiac Disease

Refractory Celiac Disease (RCD) is a more complex form of CD. This autoimmune disorder is resistant or unresponsive to treatment with a strict adherence to a gluten free diet for 12 months [12,13]. While treatment with a gluten-free diet is sufficient in restoring the functionality of villi in average patients with celiac disease, patients with refractory disease are resistant to all current treatment options available and experience amplified symptoms of the disease while being at risk for further health complications down the line. A small percentage (1-2%) of the people with celiac disease develop RCD; they are almost always found in the older age demographic [12,14]. The symptoms of RCD are often more disabling than that of regular CD. Patients are known to have inflammation and ulceration of their middle portion of the small intestine which is known as ulcerative jejunitis. Ulcerative jejunitis can be visualized endoscopically and is often an indication or warning that the disease may progress into more serious conditions such as Enteropathy-Associated T-cell lymphoma (EATL) [12,15]. The link between refractory celiac disease and intestinal lymphoma provides motivation for an alternative form of treatment for celiac disease. While the exact cause of refractory celiac disease is not known, the body's immune system, T lymphocytes and Intraepithelial Lymphocytes (IEL) are all involved. In celiac disease, T-cells are responsible for the recognition of gluten and are activated and proliferated [12]. When gluten is removed from the diet, T-cells return to normal levels within the bloodstream. However, in the case of RCD, T-cells can be activated in the absence of gluten and continue to cause intestinal injury [12]. Cytokines are known to help regulate communication within the immune system. In the case of RCD, there is an increase in the proinflammatory cytokine, interleukin-15 (IL-15) [16]. This increase helps to increase the toxicity of IEL cells which contributes to the severe intestinal damage that is linked with the transition from RCD to intestinal lymphoma [12,17]. This disease can be divided into Type I and Type II, with Type I generally indicating a better prognosis than Type II.

Role of Gluten

While celiac disease is extremely heritable, the presence of gluten in the average diet is the primary environmental factor that leads to the onset of this disease. Gluten is a prolamin storage protein found in wheat, rye, and barley [1,18]. In healthy individuals, gluten, which contains large proportions of glutamines and prolines, is not able to be completely digested by peptidases. Peptides up to 33 amino acids in length enter the lamina propria of the small intestine. In affected individuals, an

immune response occurs by the enzyme Tissue Transglutaminase (TGG) [1]. This intense reaction is not only to gluten, but also some non-gluten proteins in wheat. While the understanding of the immune response to non-gluten proteins is unclear, there is thought that amylase trypsin inhibitors may result in epithelial cell damage that occurs as a result of gluten sensitivity [19]. While the removal of gluten on a dietary basis could alleviate the symptoms associated with disease, in patients with RCD and T-cells that can be activated in the absence of gluten, other factors play a role in the severity of presentation of disease.

Genetic Factors

Genetic factors are widely understood to play a large role in the development of celiac disease. The heritability of this disease is evidenced by familial occurrences and a high concordance rate amongst monozygotic twins [1]. Close to 100% of patients diagnosed with CD have certain variants of the HLA class II genes HLA-DQA1 and HLA-DQB1. In combination, these genes encode for the α and β chains of the heterodimer proteins DQ2 and DQ8 that are expressed on the surface of antigen presenting cells [1,20]. Over 90% of patients with CD are DQ2 positive with the remaining patients being positive for the DQ8 gene [1,21]. Geographical variability in the prevalence of these two genes, DQ2 and DQ8, has been reported, with higher incidence rates in individuals of European origin.

Role of the Microbiome

Effects on the commensal microbiota have been known to contribute to the prevalence of food allergies as well as support the development in tolerance of food allergens for certain affected individuals [22]. The importance of interactions between genes and diet and the ways these factors interact with an individual's microbiome could be important to investigate when considering preventative or therapeutic treatments [1,23]. While the recent increase in CD incidence can be partly attributed to better diagnostic testing and earlier diagnosis, additional factors such as intestinal microbiota alterations have been shown to play a role in its pathogenesis [24]. According to the hygiene hypothesis, the rising incidence of CD as well as other autoimmune disorders can be attributed to lifestyle and environmental changes that have reduced exposure to pathogens resulting in an imbalance in the gut microbiota's ability to regulate between tolerance and eliciting an immune response to certain stimuli [25]. In a study published in 2015 by The American Journal of Pathology, specific microbiota compositions and their influence in immune responses to gluten in mice expressing the DQ8 gene were investigated [24]. Germ-free mice, clean Specific-Pathogen-Free (SPF) mice colonized with a microbiota that did not include opportunistic pathogens and Proteobacteria, and conventionalized SPF mice that had a complex microbiota including the opportunistic pathogens [24]. It was found that clean SPF mice had weakened responses to gluten in comparison with germ-free mice and conventionalized SPF mice. Germ-free mice showed proinflammatory gliadin-specific T-cell response and antibiotic treatment that led to increased Proteobacteria enhanced gluten-induced immunopathology in conventionalized SPF mice [24,26]. Ultimately, this study suggests that in individuals with genetic susceptibility, there may be interactions with the microbiota that may increase the risk of CD.

The goal of a Gluten Free Diet (GFD) in patients with CD is to relieve the symptoms associated with gluten consumption. However, GFD treatment has not been completely effective in the restoration of a normal digestive tract flora in CD patients. After two years of following GFD, the duodenal mucosal flora of CD patients had not fully recovered; pathogenic bacteria declined, however, beneficial bacteria counts were still low [25]. Bifidobacterium and Lactobacillus counts were decreased, while Enterobacteriaceae and Escheria coli increased in those following GFD [25]. From this study it can be concluded that more efforts should be made to restore the microbiota to a fully functional state to better treat patients with CD.

Current Treatment Options for Celiac Patients

The only current treatment known to be effective in the treatment of celiac disease is a strict Gluten Free Diet (GFD) for life in hopes that it can support the regrowth of intestinal villi and increase functionality of the small intestine while limiting the negative intestinal and extraintestinal symptoms of CD. GFD is also believed to reduce likelihood of developing severe complications and letting the disease further develop [25]. While this diet can offer protection for patients, it is associated with decreased quality of life, psychological problems as well as fear of involuntary contamination with gluten, vitamin and mineral deficiencies and severe constipation [25]. In 2019, 40% of patients diagnosed with CD stated they are not satisfied with their current treatment regimen and would like to explore alternatives to treatment [25]. Though clinical trials are currently in progress, only few exploring larazotide acetate and gluten-specific proteases from a bacterial mix (ALV003) have reached the later stages of clinical trials [25,27,28]. Larazotide has been suggested to aid in gluten-related symptom control rather than

restoring the proper function of the epithelial barrier in CD patients [27]. ALV003 has been shown to have the ability to target gluten and degrade it into digestible particles before it reaches the duodenum [28]. Since this has only been effective with small amounts of gluten, this method of treatment would protect against potential cross contamination and not offer the ability to reintroduce gluten into the diet of patients diagnosed with CD. The idea that many patients are still symptomatic after strict adherence to the GFD calls for a need to develop non dietary therapies, such as the use of stem cells in potential treatment of CD. In addition, there are no current treatment options available for those with RCD, and therapies are needed to prevent the transition from celiac disease into certain types of intestinal lymphoma.

Discussion

Role of the Epithelial Barrier in Celiac Disease

Intestinal barrier function plays an important role in the proper maintenance of overall human health. The intestinal epithelium functions as a barrier between the external environment and the more closely regulated internal environment of the digestive tract. When the gut becomes leaky or more permeable, there are a variety of health issues that are associated, such as various human diseases like inflammatory bowel disease and celiac disease [29,30]. While CD is often characterized by villous atrophy and crypt hyperplasia being responsible for the presentation of disease, a defective epithelial barrier in patients often contributes to the pathophysiology of the disease as well. The epithelial layer maintains a balance between nutrient absorption and the prevention of microorganisms; Tight Junction (TJ) complexes are cell-cell adhesions made of proteins that seal the intraepithelial space and regulate the permeability of various ions and solutes [31-33]. Not only do these structures play a role in barrier function and integrity, but they also have impacts on various cellular processes such as cell proliferation, migration, differentiation, and cell survival [31-33]. In patients with celiac disease, they experience disruption in their tight cell junctions that are not completely recovered after adherence to a GFD. Zonulin, the most well-known physiological regulator of TJ permeability, is altered in autoimmune conditions that have associated TJ dysfunction such as CD [33-36]. The permeability of the epithelial barrier is increased due to the gliadin-dependent activation of the zonulin pathway in enterocytes that causes the cytoskeleton to reorganize and tight junctions to open where undigested gluten proteins move through the barrier [37]. These undigested proteins are ultimately deamidated by TG2 which leads to villous atrophy and intestinal lesions [38]. Also in celiac disease, Paneth cell activity is disrupted. This disruption causes a reduced level of lysozyme secretion into the crypt allowing for mutated ATG16L1 to cause altered secretory granule secretion and unregulated autophagy [31]. Additionally, in cases of complicated CD, there has been shown to be a decrease in antimicrobial α -defensins [31]. However, it is currently unknown whether these alterations in epithelial cells are caused by the genotype of individuals with CD or if they develop because of disease progression [31,32]. Overall, the increased gut permeability in individuals with celiac disease increases the risk of harmful microbes and other pathogens invading the gastrointestinal tract as well as limit cell proliferation that could be important in restoring the overall function of the small intestine [39,40]. Developing methods of repairing the epithelial and mucosal barrier are thus imperative to restoring overall health and quality of life in patients with autoimmune disorders such as CD.

Intestinal Stem Cells in Celiac Disease

Stem cells are characterized by their ability to differentiate into many various cell types and lineages through cell divisions. Stem cells play a principal role in tissue regeneration and homeostasis, making them an important topic to investigate in a wide spectrum of clinical conditions, such as celiac disease. Due to the role of the gastrointestinal tract in digestion, it is constantly exposed to harsh mechanical and chemical conditions such as high pH. These characteristics are maintained due to the ability of the digestive tract to self-renew in healthy individuals. Gut integrity is supported by mucosal proliferation, with most epithelial cells being replaced every three to five days [41,42]. This epithelial renewal is driven by intestinal stem cells (ISCs) that are found within intestinal crypts at the origin of the crypt-to-villus hierarchical migratory pattern [43,44]. These cells give rise to fully differentiated villus epithelial cells that are responsible for different functions as secretory cells such as goblet cells, enteroendocrine cells and Paneth cells (PC), or absorptive enterocytes [45-47]. It has been observed in recent years that ISC differentiation to PCs and goblet cells is disturbed in patients with CD which can result in a defective mucosal barrier and excessive permeability in the epithelial barrier that can be attributed to the excessive inflammation and villous atrophy associated with active CD [43,48]. Additionally, natural antibiotics, such as defensins, are limited in patients with CD. Beta-defensins are lacking in celiac patients and negatively correlated with the degree of villous atrophy which suggests that in increased numbers, defensins may possess the ability to help impede bacterial infiltration [43,45]. While molecular mechanisms regarding the deregulation of ISC differentiation in CD is still a topic of investigation, a study conducted by Capuano et al. found a

downregulation in the Notch pathway and KLF4 signals as well as a reduction in goblet cells in the epithelial tissue of patients with CD adhering to a GFD as compared to the controls [49-51]. One of the aims of the GFD is the restoration of epithelial barrier function; however, the lack of efficacy attributed to this diet has led to the exploration of alternative forms of treatment using stem cells. Stem cell biology largely focuses on therapies focused on the repair of injured tissues, which in the case of CD, could be used to restore the functionality of the gastrointestinal tract and lead to overall increased quality of life while reducing the likelihood of developing further malignant complications.

Mesenchymal Stem Cells as Potential Therapeutic Approaches in Celiac Disease

While hematopoietic stem cells and mesenchymal stem cells both may regenerate and differentiate into numerous cell types and contribute to overall homeostasis, mesenchymal stem cells offer more promise for the treatment of celiac disease since they are highly proliferating and multipotent while lacking immunogenicity [49,52,53]. Since CD is an autoimmune disorder, immune reaction is an important factor to consider in potential treatment options. Human clinical trial evidence has suggested that Mesenchymal Stem Cells (MSCs) can target nearly all pathogenic pathways and mechanisms involved in CD [49,50,54]. MSCs are plastic adherent under standard transfer conditions, they differentiate into many cell types such as adipocytes, osteoblasts and chondroblasts and express CD105, CD73 and CD90 while lacking surface expression of CD45, CD34, CD14, CD11b, CD19 and HLA-DR [49,55]. MSCs are more suitable for transplantation than hematopoietic stem cells due to their lack of expression of MHC class 2 and the absence of CD40, CD80, and CD86 which gives MSCs the ability to cross the HLA barrier [49,56]. Their anti-inflammatory properties help prime naive cells towards becoming tolerogenic and the expression of HLA-G allows MSCs to expand regulatory T-cells [49,50].

Patients with refractory celiac disease can benefit from treatment with MSCs as well. MSCs inhibit the secretion and function of IL-15 which protects from forming EATLs. By resembling claudins, MSCs can maintain the integrity of the epithelial barrier which can prevent the infiltration of unwanted pathogens [49,57]. MSCs could prevent villous atrophy as they secrete IL-6, HGF, and VEGF which disrupts the activation of caspase-3 and caspase-8 that are responsible for apoptosis of enterocytes that are causal of villous atrophy [49]. Excessive IFN- γ found in the mucosal environment in CD makes the environment favorable for MSCs to be accepted through transplantation [49,50]. MSCs can prevent the G0 to G1 phase progression of monocytes from differentiating into dendritic cells as well as secrete IL-6, PGE2 and CSF which can shift mature dendritic cells towards a more tolerogenic profile; overall helping to avoid the activation of T-cells and help to reduce inflammation [49,50]. Mesenchymal stem cells can target almost all mechanisms involved in the pathogenesis of CD, making them a prime consideration for future stem cell therapy treatments in CD. Limitations with MSCs include that they require a very specific mucosal environment to function properly, they must be obtained from sources that have unlimited donors, and they have an extremely large size which means they could potentially be caught in certain organs like the lungs [50,58].

Clinical Study #1

A clinical study was conducted to evaluate the efficacy of autologous hematopoietic stem cell transplantation in refractory disease with aberrant T-cells [59]. Thirteen patients (4 men, 3 women, mean age of 61.5 years old) diagnosed with RCD type II were evaluated [59]. Patients with CD were refractory when symptoms of malabsorption due to villous atrophy persisted or recurred after strict adherence to a gluten free diet for over a year. This diagnosis was classified as type II when 20% or more aberrant T-cells were present [59]. Patients with RCD II do not respond well to treatment and are most likely to develop non-Hodgkin's lymphoma [59,60]. Many physicians consider RCD II to be a low-grade form of lymphoma that does not generally have a good prognosis. In patients with RCD, the number of intraepithelial lymphocytes is raised which leads to the development of T-cell lymphoma [59]. They were not included if any other cardiac, pulmonary, renal, or hepatic disease was present. All patients exhibited genetic markers of celiac disease; four patients were DQ2 homozygous and three were heterozygous for the gene [59]. This strategy was investigated because autologous hematopoietic stem cell transplantation is an effective treatment for patients with severe autoimmune disease that have been successful in patients with other diseases such as multiple sclerosis, rheumatoid arthritis, and Crohn's disease [59]. In the study, hematopoietic stem cells were harvested from peripheral blood and given to patients through subcutaneous injection for four consecutive days [59]. Patients followed a conditioning regimen (fludarabine given orally for 5 days and melphalan given intravenously for 2 days) to regulate the depletion of T-cells [59]. The World Health Organization performance criteria was used to evaluate the changes in patients' health after the study. Nutritional status, changes in weight and stool frequency along with relevant biochemical markers were all noted, and an endoscopic and histological

examination of the small intestine was performed (3, 12 and 24 months after transplantation), duodenal biopsies were taken to measure the IEL levels after transplantation [59]. Before transplantation, most patients suffered from persistent diarrhea and weight loss with failure to respond to a GFD [59]. They also had a high presence of aberrant T-cells in the small bowel mucosa and cases of ulcerative jejunitis. Patients were seen to have increased levels of uptake in the small intestine and the procedure was well tolerated with an average recovery time of only 20 days [59]. All patients showed clinical improvement with regards to stool frequency, abdominal pain and other clinical markers, it was seen endoscopically that there was a disappearance in the erosions in the jejunum of patients who had ulcerative jejunitis before treatment and all types of T cell lymphocytes decreased [59]. This procedure offers future hope for the treatment of celiac disease. It was well tolerated in all patients and there was substantial clinical improvement seen in all patients. The initial response was rapid (within 3 months) and the duration of remission up to now has been promising, however, follow-up is too short to permit firm conclusions as to the efficacy for this treatment in the long term, long-term follow-up, and additional pilot studies with larger groups of patients are needed to confirm its efficacy [49,59].

Additional Clinical Studies

A study conducted in 2022 further suggests induced immunoablation with high dose chemotherapy with regeneration of naive T lymphocytes transplanted via autologous hematopoietic progenitor cells as a potential therapeutic approach [61,62]. This technique has been proven effective in other autoimmune disorders such as multiple sclerosis and thus has become a topic of interest in celiac disease. The initial analysis of seven patients with RCD II has shown that this treatment is well-tolerated [61,63]. A reduction in aberrant T-cells was seen via duodenal biopsy as well as reports of improvement in clinical well-being and biochemical markers for a mean follow up period of 15.5 months [61,64]. One patient died 8 months after transplantation due to progressive neuroceliac disease [61,64]. This data demonstrates that autologous hematopoietic stem cell transplantation shows promise in patients with RCD II as they can achieve histological remission [61,64]. However, further investigation will need to take place to establish a course of treatment for individuals who fail to respond to stem cell therapy histologically as they are at higher risk of EATL development and further complications. In a case report by the Mayo Clinic, a 51-year-old woman with RCD II underwent repeated serial infusions of autologous mesenchymal stem cells [59]. She did not experience any adverse effects and a dramatic improvement in her clinical condition was seen. The patient was monitored for malabsorption indexes, mucosal architecture, and percentage of aberrant intraepithelial lymphocytes was scheduled for the time of enrollment, at each infusion, and after 6 months [64]. Determination of mucosal expression of interleukin IL-15 and its receptor was also performed. Expansion of MSCs was feasible, and the patient underwent 4 systemic infusions of 2×10^6 MSCs/kg body weight 4 months apart [64]. The aberrant IEL population persisted, which could be explained by the inhibitory effects of IL-15-stimulated cells by mesenchymal stem cells [64]. In the patient, the expression of IL-15 pathogenic pathway was blocked, giving hope for the future of treatment of RCD with serial MSC infusions.

Case Study - Personal Report

I was diagnosed with celiac disease at age nineteen, after the confirmation of diagnosis via serological blood tests as well as biopsy acquired endoscopically and colonoscopically. I experienced largemouth ulcers that inhibited my ability to effectively communicate as well as eat for weeks at a time. These mouth ulcers in combination with a constant rash present across the lower region of my face are not classical presentations of celiac disease, leading to misdiagnosis for nineteen years. Around age 18, I lost twenty pounds and became anemic due to malabsorption issues when my provider suggested to be tested for celiac disease. When the tests came back positive, I received a phone call from my gastroenterologist indicating positive test results, however, I was not given any further information regarding a future course of treatment. Treatment for celiac disease consists of adherence to a gluten-free diet in hopes to return abnormal biological markers within normal levels. While I occasionally have lab work done to assess the efficacy of GFD, I have never experienced results within levels considered normal which suggests an alternate form of treatment is necessary to fully alleviate markers of my clinical condition and increase overall quality of life. Future providers should consider alternate forms of treatment, such as the use of stem cell therapy, to effectively treat celiac disease for current and future patients like myself.

Conclusion and Future Considerations

The increasing prevalence and patient dissatisfaction regarding the only current treatment option for celiac disease continues to be a developing problem in our Western civilization that is dominated by a gluten rich diet. Individuals with refractory celiac

disease are at higher risk of developing further complications such as various types of lymphoma, highlighting the need for more advanced treatment options for this autoimmune disorder. It is imperative to understand the crypt/villus axis in patients with CD and how this relates to the epithelial-mesenchymal stem cell transition that is impaired in patients [41]. While *ex-vivo* gastrointestinal organoids have been used to illustrate the pathophysiology of disease, the complex model of celiac disease including environmental, genetic, and immunological factors must be further understood in order to move forward in clinical trials. The ability of stem cells to proliferate and differentiate into a variety of specialized cell types offer promise in stem cell therapy infusions as forms of treatment as seen in various clinical trials. Mesenchymal stem cells with their lack of immunogenicity and ability to target almost every aspect of the pathogenic pathway of CD are thought to be the best therapy; however, more clinical trials with more participants with varying presentations of disease are needed to establish the efficacy of this treatment moving forward. Additionally, stem cell therapies are well-known to be effective in chronic inflammatory pathologies, not limited to celiac disease. Autoimmune diseases, like CD, typically group together and share many of the same mechanisms, such as inflammatory pathways, that lead to disease progression. Therefore, the investigation of stem cell therapy as a treatment for CD and the deeper understanding of a model of a complex autoimmune disease can lead to further understanding of other complicated diseases, such as Crohn's Disease.

Conflict of Interest

The authors have no conflict of interest to declare.

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