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REVIEW ARTICLE

Utilizing the Therapeutic Potential of Stem Cells in Celiac Disease

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ABSTRACT: Stem cells have been one of the most significant advances in recent medicine. They are cells that can uniquely differentiate into other body cells and self-renew, unlike other cells. This review discusses how these stem cells can impact a severe gastrointestinal and autoimmune disease known as celiac disease. Many studies describe that the most common stem cells for the treatment of autoimmune and gastrointestinal diseases such as celiac disease include mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and induced pluripotent stem cells (iPSCs). Stem cells are a highly effective treatment for celiac disease and should be utilized to create current therapies for those suffering from this severe condition. This review paper gathers data from numerous sources to compare treatments and conclude which is the most effective. Through our research, we found that MSCs have great potential for celiac disease treatment, and they have proven to be the most effective method in the full treatment of this disease. This paper outlines how various stem cells tackle celiac disease in patients by interfering with their autoimmune response to gluten using many methods, opening up new windows of knowledge for further research..

KEYWORDS: Disease Treatment and Therapies, Disease Detection and Diagnosis, Mesenchymal Stem Cells, Celiac Disease, Hematopoietic Stem Cells.

Introduction

Celiac disease is a lifelong autoimmune condition of the small intestine that is activated by the ingestion of gluten and is widespread in genetically susceptible individuals. This disease affects millions of people around the world, and its rates are growing by around 7.5 percent every year.[1] Celiac disease is a harsh condition that impacts 1.4 percent of the world's population and can lead to catastrophic disorders such as enteropathy-associated T-cell lymphoma (EATL), which has a five-year survival rate of around 20 percent. Some common symptoms of celiac disease include abdominal distension, diarrhea, nausea, malaise, anemia, and weight loss. However, it is possible to develop more severe symptoms of this disease, such as osteoporosis, fatigue, and neurological problems. While most patients receive symptoms of this disease, around ten percent of those with celiac disease have an asymptomatic type of celiac disease and exhibit nearly no symptoms.

In patients with celiac disease, the immune system mistakenly causes inflammation in the small intestine by wrongly recognizing gluten to be a dangerous substance in the body. When a patient consumes gluten, the major histocompatibility complex HLA-DQ molecules attach themselves to gluten peptides, which then introduce themselves to CD4+ T cells, leading to an inflammatory response.[2] During this response, the continued presence of the T- and B-cells ultimately leads to the destruction of enterocytes, which then leads to villous atrophy and malabsorption syndrome.[3] Diagnosis can be made through a series of blood tests that look for anti-tissue transglutaminase and anti-endomysial antibodies since they are common in those with this disease. Another less accurate form of diagnosis would be genetic testing for human leukocyte antigens HLA-DQ2 and HLA-DQ8. Still, it can only be confirmed through an endoscopy or biopsy of the small intestine, as it allows for a more detailed view of damage done to the small intestine.[4]

Although most patients with celiac disease can be treated through a gluten-free diet, this lifestyle is difficult for many patients to maintain due to its permanent nature and the increased presence of gluten in a variety of foods. Additionally, up to five percent of those with celiac disease develop a more serious form of this disease known as refractory celiac disease, in which symptoms are prevalent despite being on a gluten-free diet. This refractory stage of celiac disease leads to a drastic increase of intraepithelial lymphocytes, which can put patients at high risk of developing enteropathy-associated T-cell lymphoma (EATL), which has an incredibly low survival rate.[2]

Although there are many traditional therapies for this disease, these do not show promising results and usually have very severe side effects. Stem cell therapy is an emerging idea that has shown encouraging results in the treatment of many autoimmune diseases, such as this one, and this paper will dive deeper into the impact of these cells on celiac disease. In many clinical trials, stem cells have shown great success in preventing villous atrophy and decreasing inflammation in patients.[5] This type of success with such severe symptoms can promote new fields of research in stem cells such as this one. This comparative literary review goes over three different types of stem cell therapy: MSCs, HSCs, and iPSCs, and it gives an overview of why MSCs are preferred over other traditional therapies and stem cell treatments. This paper will cover how celiac disease

DOI: 10.36838/v7i7.11

affects the body, the current restorative options available for treatment, and how different stem cells help tackle this illness.

Discussion

The Epithelial Barrier:

Celiac disease is a lifelong intestinal enteropathy that gets activated once a patient consumes gliadin, a glycoprotein found in gluten. Gluten is a protein found in many ingredients such as wheat, rye, barley, and triticale. The protein gliadin is made up of multiple single-chain polypeptides that are joined by intramolecular disulfide bonds.[6] Some of these peptides contain certain amino acid sequences called proline-glutamine motifs, which are resistant to gastrointestinal enzymes, making them harder to metabolize and digest.[7] In a normal person, all the peptides not containing proline-glutamine would be digested and then excreted as waste. As for the peptides containing this amino acid sequence, they would either be digested like the rest of the peptides or pass through the epithelial barrier. However, even so, their passage would be so limited that no harm would occur. On the other hand, patients with celiac disease have a much weaker capability to break down gliadin due to a damaged epithelial barrier. This means that a more significant amount of digestion-resistant peptides are likely to cross the barrier, leading to an immune reaction. Gliadin is a substrate for tissue transglutaminase (tTG) deamination, which makes the gliadin peptides more immunogenic. This deamination does not trigger an immune response in those without celiac disease. However, in those with this disease, the deaminated gliadin is able to bind to the HLA-DQ due to the damaged epithelial mucosa, leading to an inflammatory immune response.[8] Lastly, this protein also impacts the epithelial mucosa's permeability, further damaging the immune system. Gliadin is just one of the many proteins that can wreak havoc in a person's body due to the damage to the epithelial barrier since it is a crucial body function.

The epithelial barrier is a physical and chemical barrier that regulates the movement of substances across the barrier, helping to ensure that the correct nutrients are absorbed. It also protects the body from external materials that could be dangerous to the body, such as environmental toxins and microbes. This system is driven by the epithelial cells, tight and adherent junctions, and the mucus layer that all come together to help maintain the epithelial barrier's selective permeability.[9] Celiac disease attacks this system, damaging its overall function and weakening its selective permeability. Those with this condition have more pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-1β.[10] These cytokines bind to receptors on intestinal epithelial cells, triggering many intracellular signaling pathways such as the MAPK (mitogen-activated protein kinase) pathway and the NF-κB (nuclear factor-kappa B) pathway to stimulate.[11] This stimulation causes these pathways to control the phosphorylation of tight junction proteins by taking over soccludin, claudins, zona occludens (ZO) proteins, and other protein kinases responsible for this phosphorylation.[12] The pro-inflammatory cytokines can then regulate the phosphorylation of the protein kinases through the pathways, destroying the tight and adherent junctions. The intense damage done to these junctions due to this illness leads to the increased permeability of the intestinal epithelial barrier so more dangerous substances, such as gliadin and other immunogenic substances, can get through the barrier. This further damages the patient's body. Celiac disease completely damages the epithelial barrier, destroying a very crucial body function.

Intraepithelial lymphocytes (IELs) are a segment of oligoclonal T lymphocytes located within the intestinal epithelium.[13] In normal epithelial mucosa, these cells greatly help maintain the operation of this system by monitoring it for any sign of damage and destroying anything that could harm the function of this barrier. In celiac disorder, however, exposure to gluten causes the intestinal epithelial cells (enterocytes) to release increased levels of cytokine interleukin-15 (IL-15). Upon exposure to the IL-15, the CD8+ TCRαβ+ IELs enhance the expression of receptors such as NKG2D and CD94-NKG2A on their cell surface. On the other hand, the enterocytes start to display stress-related ligands, such as MHC class I-related chains (MICA and MICB) and HLA-E, as a result of the gluten-induced stress that occurs as a reaction to the consumption of gluten. The NKG2D and CD94-NKG2A receptors on the activated IELs recognize these ligands and bind to them, triggering a cytotoxic reaction that results in the apoptosis of enterocytes.[14] This process that leads to enterocyte destruction is known as direct cytotoxicity. The persistent activation of IELs through IL-15 and the stress-related ligands leads to a chronic state of IEL activation.[2] This chronic state of activation propels the proliferation of the CD8+ TCRαβ+ IEL subset. This increased amount of CD8+ TCRαβ+ IELs produces increased levels of cytotoxic effector molecules, such as interferon-gamma (IFN-γ), perforin, and granzymes.[14] These cytotoxic molecules cause apoptosis in enterocytes through Indirect cytotoxicity. This combination of indirect and direct cytotoxicity is known as the dual cytolytic effect, in which the enterocytes become targets for destruction by the IELs. The dual cytolytic effect is one of the leading causes of villous atrophy and malabsorption syndrome, which are the main factors for the rest of the symptoms of celiac disease.

Celiac disease is incredibly damaging to the intestinal mucosa's function, ruining much of the body's innate immunity. The deterioration in the innate immunity of patients with this disease is a main factor for many symptoms of this disease, such as malabsorption syndrome and abdominal distention, causing lots of distress for those with this illness. While there are some traditional treatments to help with these symptoms for celiac disease they may not all be effective.

Current and Traditional Treatments for Celiac Disease:

Due to the severity and permanent nature of the disease, celiac disease treatments and therapies are constantly being developed by scientists for patients with this illness. While the most common way celiac disease is prevented in patients is through a strict, gluten-free diet, this method does not work for all patients and is not easy to maintain. So scientists are currently trying to develop better options. There are a multitude of methods by which celiac disease can be treated, such as anti-inflammatory drugs, the blockage of cytokines, genetic modifications, and many more, which will be further explored in the later paragraphs. This body section will dive deep into

DOI: 10.36838/v7i7.11

the current and developing treatments for celiac disease and assess their effectiveness in treating patients. (Figure 1)

One method to deal with celiac disease is by using genetically modified grains that lack the immunogenic epitopes that make people sick. However, this method is very challenging as gluten contains many of these said epitopes, and they are spread across the wheat genome in the genetic loci, making it impossible to perform deletion or silencing. Gluten is a complex group of proteins found in certain grains, not a gene. It is associated with various wheat genomes, including the 42-chromosome hexaploid genomes and the 28-chromosome tetraploid genomes. All these complex genomes evolved from simpler genomes, such as the 14-chromosome diploid genomes. A majority of these complex genomes, including the tetraploids and hexaploids, contain a peptide known as the 33-mer peptide, which is the most potent trigger of the HLA-DQ molecules and plays a key role in celiac disease pathogenesis.[15] While most wheat genomes contain this peptide or those similar to it, studies show that wheat with the simple AA and BB genomes lack this type of peptide and is, consequently, much less immunogenic.[15] This research has led to exploring mRNA interference technology to reduce the immunogenic gliadin peptides in patients.[16] While all of this seems promising, this solution's challenges and side effects make it seem far-fetched. A potential risk with this treatment would be the cross-contamination of this genetically modified wheat with normal wheat, undermining the effects of the solution. Another issue with this genetically modified gluten is that the modifications cause gluten to lose its baking capabilities. These issues, however, are not very severe, and so the real problem lies in the fact that scientists do not know what the immunogenic peptides in wheat are. So, it would be nearly impossible to take out all the immunogenic components of the grain without knowing all of these elements.

Glucocorticoids, also known as corticosteroids, are a type of steroid hormone that is used mostly for severe celiac patients who suffer from refractory celiac disease or EATL.[17] These hormones bind to glucocorticoid receptors within cells in the cytoplasm, which changes the structure of these receptors, causing them to activate.[18] The activated complexes then move to the cell nucleus, where they bind to glucocorticoid response elements (GREs) DNA sequences.[19] This binding then leads to decreased inflammation in a patient's body by slowing down the production of harmful lymphokines and reducing the proliferation of T and B cells. There are many different types of glucocorticoids, such as prednisone or budesonide, which all have their own advantages. Multiple studies show that this drug when combined with a gluten-free diet, can decrease the harmful effects on the body, but at a cost. While this drug has been proven to reduce the overall apoptosis rates in cells, it has also shown very harmful side effects, such as damaging the intestinal barrier through decreased epithelial cell regeneration.[15] This damage done to the epithelial barrier severely impacts the patient's body, rendering this treatment unproductive by scientists as the side effects are as bad as the actual disease.

Interleukin-15 (IL-15) is a cytokine that promotes the activation of IELs and plays a crucial role in the immune response during celiac disease. IELs, when activated by IL-15, cause intense damage to the intestinal barrier, so blocking IL-15 is hoped to prevent the inflammatory effects from taking place.[15] Some antibodies such as AMG 714 and NZV930 that target IL-15 are being tested to block this cytokine and are proving to work at doing this but are showing some severe negative possible side effects.[20] This is because IL-15 does not only cause intestinal damage but plays a crucial role in the function of Natural Killer cells and CD8+ T cells, which help maintain immune homeostasis and fight infections. So, by blocking the IL-15, we risk ruining the cytokine's positive functions.[21] Another issue is that celiac disease is a very complicated disease that involves multiple pathways, so just blocking one cytokine is not likely to be enough to help with this disease.

Interleukin-10 (IL-10) is an immunoregulatory cytokine that helps maintain the immune response to dangerous substances and helps sustain homeostasis in the body of ordinary people. However, this cytokine is deficient in those with celiac disease, which contributes to the inflammatory immune response to gluten. Increasing the amount of IL-10 is an idea being explored by scientists, and one way they plan to do it is through recombinant human IL-10 gene therapy.[22] This boost in the anti-inflammatory effects of IL-10 seems like the perfect solution, but the side effects are very severe for this type of treatment. Some consequences of this disease include flu-like symptoms, blood pressure changes, and possible damage to the immune system.[23] With these harsh symptoms, many scientists argue that the side effects outweigh the effectiveness of the treatment.

Transglutaminase 2 (TG2) is an enzyme that catalyzes the forming of many intermolecular isopeptide bonds, such as the one between glutamine and lysine.[24] It is also responsible for the deamination of gliadin peptides, which helps generate complexes that lead to an immune response to gluten. Studies reveal that T cells are more likely to recognize TG2-treated (deaminated) gliadin over non-TG2-treated (undeaminated) gliadin. Further studies also proved that when TG2 was blocked by cystamine, the T cells were a lot less likely to cause an immune response.[15] Overall, these studies confirm that by inhibiting TG2, it is possible to prevent the deamination of gluten peptides, greatly decreasing the immune response, but the problem arrives because TG2 is not only used for deamination. TG2 performs many functions, such as wound healing, cell signaling, cell differentiation, apoptosis regulation, angiogenesis regulation, helping with vascular function, and many more.[25] The risk of damage to any of these can lead to severe effects. For example, since TG2 enzymes impact apoptosis, this blockage could cause unintended cell death due to dysregulated apoptosis. TG2 enzymes also control vascular function, and the disruption of that system could damage tissue perfusion and oxygenation, which could lead to intense or even fatal harm to a person's body. After consideration of all of these consequences, this method is not very effective.

DOI: 10.36838/v7i7.11

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Treatments	**Treatment type**	**Approach**	**Method**	**Consquences**	**Practicality**	**Target**
Genetically Modified Grains	Gluten Modification	To use Ancient Wheat as a replacement for modern gluten, since it is less immunogenic than the evolved, complex wheat used now. (16)	The usage of mRNA interference technology to reduce the immunogenic gliadin peptides. (17)	There is a risk of cross contamination, a loss of the baking capabilities of gluten, and a lack of knowledge of what the immunogenic peptides in wheat are. (16)	This is not very likely to be used in the near future due to lack of knowledge on what the target peptides actually are.	Gluten peptides
Glucocorticoids	Anti-Inflammatory Drug	This drug binds to receptors in the body to decrease the inflammatory effect of celiac disease. (19)	The usage of this drug combined with a gluten-free diet provides decreased inflammation in a patient's body.	This causes a decrease epithelial cell generation along with serious damage to the epithelial barrier. Also, this method only works for refractory celiac disease patients. (16)	Considering that a main goal of celiac disease treatments is to decrease the epithelial barrier damage, this method is not very practical.	Glucocorticoid receptors
IL-15 Blocking	Cytokine Blocking	To block the cytokine IL-15 since IL-15 plays a big role in the inflammatory immune response of celiac disease. (14)	The usage of antibodies such as AMG 714 and NZV930 to block the cytokine IL-15. (21)	IL-15 has other helpful functions such as its big role in the maintenance of Natural Killer cells. By blocking this cytokine, we risk harming the beneficial functions it performs through Natural Killer cells such as maintaining homeostasis and helping fight infections. (22)	Since IL-15 is just one of the many pathways impacted by this disease, the blockage of this cytokine is not likely to make a difference. Also, the damage to such crucial functions make it an ineffective solution.	IL-15 cytokine
IL-10 Increase	Cytokine Increase	To increase the amount of the immunoregulatory cytokine IL-10, which is significantly less prevalent in those with celiac disease. (16)	The usage of recombinant human IL-10 gene therapy to increase IL-10 cytokines. (23)	Flu-like symptoms, blood pressure changes, and possible damage to the overall immune system. (24)	The risk of damage to the already inpaired immune system of patients makes this treatment pointless.	IL-10 cytokines
Transglutaminase 2 Blocking	Enzyme Blockage	To block the enzyme Tranglutaminase 2 since it is a main factor in the dysregulated immune response of this disease. (25)	The usage of the complex Cytamine to block the enzyme Tranglutaminase 2. (16)	Transglutaminase 2 also plays a huge role in many positive body functions such as wound healing, cell signaling, vascular function, apoptosis regulation, and many more. By blocking this cytokine we risk damaging any of these crucial body	The serious risk of severe side effects and even fatality makes this treatment completely irrational.	Trangluta minase 2 enzymes
				functiona which could lead to severe and even fatal effects. (26)		

Figure 1: ***Overview of Current and Traditional Treatments of Celiac Disease***
This table summarizes current and emerging treatments for celiac disease, highlighting their mechanisms, limitations, and practicality. While each approach targets different aspects of the disease, all face significant challenges that limit their effectiveness or feasibility for widespread clinical use.

Overall, while traditional and developing therapies for celiac disease show some promise in helping heal patients, in most cases, the side effects greatly outweigh the benefits. These treatments are only valuable for a worst-case scenario in which a patient needs to be treated to survive. In other cases, these therapies just prove to be ineffective in treating this disease because of how complex it is, as it is with the IL-15 therapy and probably many others. However, scientists have been developing a new method that tackles the complexities of celiac disease through a precise treatment known as stem cell therapy. This therapy is currently being developed, and it utilizes the stem cells in a person's body to treat the damage done to the patient's body.

Hematopoietic Stem Cells and Induced Pluripotent Stem Cells in Celiac Disease:

Stem Cells are an emerging therapy for celiac disease and are constantly proving to give positive results with minimal side effects. There are many different kinds of stem cells, and in this section, we will go over two of the three main types of stem cells that are being used to treat this disease. These stem cells are HSCs and iPSCs, and while they are both types of stem cells, they are very different in many ways, and both have unique properties. Both stem cells can help with celiac disease in many different ways, and in this section, we will go over how each stem cell impacts those with celiac disease and determine how effective each treatment is.

HSCs are a population of multipotent stem cells that reside primarily in the bone marrow and have the ability to differentiate into all the different blood cells in the body.[26] Three main types of HSCs are classified by their differentiation and self-renewal abilities. At the top of the HSC hierarchy are the long-term HSCs (LT-HSCs). These cells have a lifelong self-renewal ability and can repopulate the entire blood system.[27] Then are the short-term HSCs (ST-HSCs), which have a limited capacity to self-renew and cannot uphold blood cell production, or hematopoiesis, for long periods of time.[28] At the end of this hierarchy are multipotent progenitors (MPPs). These HSCs can differentiate into multiple blood cells but cannot self-renew.[29] HSCs have numerous qualities that make them an effective treatment for celiac disease. For example, HSCs can activate pericryptal myofibroblasts, vascular cells, and epithelial cells, all of which help maintain the intestinal mucosa. Additionally, tests done with HSCs on different kinds of diseases reveal that it is likely to work for celiac disease, and there is a possibility that it can induce immune tolerance. Furthermore, studies show that HSCs can not only help heal the intestinal mucosa but can also help recover the immune system by making it tolerant to antigens that would usually cause an immune response in celiac disease.[30] However, HSC treatment poses a risk of death, making it only a tool to save those from refractory celiac disease.

Refractory celiac disease is confirmed by continued malabsorption syndrome and intestinal villous atrophy while on a gluten-free diet for around half a year. Two types of RCDs have been identified: type one and type two. Type one refractory celiac disease, there is an increase in IELs, but none of these IELs display any signs of abnormalities.[31] In contrast, type two refractory celiac disease does include genetic abnormalities along with changes to the T-cell receptor and the aberrant phenotype on T-cells.[32] These aberrant T-cells are very dangerous and have a high chance of helping a patient develop EATL. To counteract the damaging effects of celiac disease, regulatory T-cells are increased, but IL-15 restrains their healing abilities.[33] While the traditional treatment for refractory celiac disease includes immunosuppressive therapies and nutritional support, these treatments have shown minimal impact in type two refractory disease, which has led to the consideration of HSC treatment. There were 2 studies done with 10 patients each on HSC autologous therapy, and both studies have shown promising results.[34] In these studies, the patients had significantly fewer aberrant T cells, partial healing to the intestinal mucosa, and recovery to a normal body weight, which immensely helped with the patient's health. However, some patients still developed EATL, so it can be determined that the aberrant IELs are greatly resistant to the HSC treatment. Also, most of the patients who developed EATL died, so while this strategy is mostly effective in those with type 2 refractory disease, it is not a solution for EATL patients. Furthermore, a couple more tests were run with auto-HSCT

DOI: 10.36838/v7i7.11

on thirteen patients between 2004 and 2010. One patient died due to complications in the transplantation of the auto-HSCT, but the majority of them received some improvement in their condition; 5 of them got their immune system "reset," and their epithelial barrier showed no complications. Another one of the patients did develop EATL but survived for much longer than usual EATL patients at around 7 years.[35] Overall, this treatment can help those with stage two refractory celiac disease and can delay the fatality of EATL, but the risk of death makes it only a solution in case of extreme need. On the other hand, an (HLA)-identical matched-sibling HSC allogenic treatment was run between two patients for celiac disease, and these patients experienced a cure for their celiac disease.[34] This meant that these patient's symptoms, serological markers, and all other effects of celiac disease were gone. In one of these patients, the abnormalities in their epithelial barrier also completely disappeared, freeing them of their condition. This proves that the allogenic HSC treatment completely resets the immune system and removes the damaged cells, replacing them with the ones from the donor. Furthermore, two other celiac disease patients also went through an allogenic HSC treatment to treat their Thalassemia major disease and were completely treated for their celiac disease.[34] They were reintroduced to a gluten-containing diet and showed no side effects or signs of celiac disease after 7 years. Another child who also received this HSC treatment received similar results, and after five years, they were still on a non-gluten-free diet.[34] However, with allogenic HSC treatment, there is a risk of developing Graft-versus-host disease (GVHD), in which the patient's body thinks the donor's cells are a dangerous substance and attacks them.[36] GVHD is a serious, life-threatening disease that causes symptoms all over the body, and in HSC transplantation, patients have around 30-70 percent of getting this disease.[37] Overall, while allogenic HSC transplantation seems to work, it should only be used to treat those in life-threatening conditions due to its intense risks. However, iPSCs may not be as bad as other emerging stem cell therapies.

Another emerging stem-cell therapy is iPSCs. iPSCs are pluripotent stem cells that can be made by reprogramming somatic cells within a person's body. These stem cells have the ability to differentiate into almost every cell in the body, including the three embryonic germ layers: the endoderm, mesoderm, or ectoderm.[38] In this therapy, the somatic cells are induced by transcription factors such as Oct4, Sox2, Klf4, and c-Myc, which causes them to become pluripotent.[39] Previously, pluripotent stem cells could only be derived from human embryos, raising some ethical concerns, so changing to somatic cells is a great breakthrough in this research. With this technology, we can produce almost any cell that a patient may need, eliminating the need for immunosuppressive therapies for celiac disease.

This therapy can help with celiac disease by decreasing the damage done to the T-regulatory cells (Tregs) in this disease. Tregs help to maintain a state of equilibrium in which the immune system does not mount a damaging response to a person's body. Tregs such as CD4, CD25, and Foxp3 positive, help regulate the T cell-mediated immune response; ensuring it does not go overboard can cause autoimmunity.[39] The Tregs also help to maintain peripheral tolerance by suppressing the overactivation of T-cells. These Tregs perform these functions by secreting a variety of inhibitory cytokines, such as interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), and interleukin-35 (IL-35).[40] These cytokines help suppress the proliferation of various immune cells, including T effector cells, B cells, and natural killer cells, helping maintain homeostasis and preventing a damaging immune response.[40] The Tregs are damaged in celiac disease and have fewer immunosuppressive abilities. So far, studies have shown that using autologous Tregs to suppress immune responses in multiple autoimmune diseases has proven successful. The problem arises when acquiring these Tregs since they are only visible in inflamed parts of the body.[41] Obtaining these Tregs from the inflamed site can cause unwanted inflammation in other body parts. Another issue is that it is difficult to cause the Tregs to proliferate, making it hard to gather enough Tregs to inhibit the immune response. On the other hand, it is possible to induce functional Tregs with iPSCs rather than having to collect them from the patient. Using this method, people can avoid all the complications of extracting Tregs from the patient while having the same effect. The immunoregulatory cytokines TGF-β and IL-10 were also shown in the Tregs developed by iPSCs, proving that they work the same as those accumulated from the body.[42] So far, animal studies with other autoimmune diseases have shown promising results in both autologous and allogeneic iPSC transfers.[42] This method of using iPSCs to utilize Tregs can help suppress the intense immune response in celiac disease patients. However, even with the use of iPSCs, there is a risk of tumor formation from small parts of undifferentiated cells.[43] While some scientists are trying to find ways to eliminate these undifferentiated cells, no method has shown great results for autoimmune conditions. Another risk with this method is that the reprogramming process may create abnormal Tregs, causing them to not work properly. Additionally, no tests have been done yet on celiac disease with this treatment, so while this may be a great tool in the future, it is too risky to use for a very long time, and considering its extreme side effects, it will take a while until scientists can come up with a safe way to use this so it can be implemented.[42] On the other hand, there has been much research on a new type of stem cell for celiac disease, known as MSCs.

Overall, the side effects of both of these treatments make them useless until all these consequences can be addressed, which would be nowhere in the near future. The lack of testing in iPSCs and the extreme consequences to the body in both of these treatments make them too risky to utilize. On the other hand, a new emerging stem cell therapy known as MSCs has shown promising test results with minimal side effects, making them a better option for this condition.

Mesenchymal Stem Cells in Celiac Disease:

MSCs are multipotent stromal cells with many properties and are currently being tested for celiac disease treatments.[44] These stem cells can differentiate into numerous cell types within multiple lineages, including the mesoderm, ectoderm, and endoderm lineage. MSCs are also plastic-adherent under

standard culture conditions. MSCs express CD105, CD73, and CD90 molecules but do not express CD45, CD34, CD14, CD11b, or CD19 and HLA-DR molecules.[45] These cells have a wide range of capabilities, from repairing tissues to decreasing inflammation, along with their ability to transform into multiple cell lineages, making them a valuable tool in future therapeutic research. These cells have been proven to have the same impact on the epithelial barrier as HSCs but have an advantage over them due to their greater immune abilities. MSCs lack many HLA molecules, such as CD40, CD80, and CD86, that can trigger a cytotoxic T-cell attack or cause the CD4 + T cells to activate. This makes them able to impact the immune system without the risk of a rejection response.[46] MSCs also help maintain immune tolerance through their anti-inflammatory and immunomodulatory properties. A mouse model done for colitis proved that MSCs were able to create Tregs to suppress the pro-inflammatory T-helper 1 cell (Th1).[47] This evidence proves that MSCs may influence the immune cells to make them more tolerogenic by creating a microenvironment known as a "quasiniche" through the secretion of various cells.[48] MSCs can induce immune tolerance through the paracrine release of protective substances such as indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), nitric oxide (NO), and many more.[49] HLA-G cells are another MSC substance that helps with immune system regulation through the apoptosis of CD8+ T cells, suppressing damaging NK cell activity, increasing the amount of Tregs, and many more functions. Overall, all of these functions of MSCs make it a useful solution for the treatment of celiac disease in many ways. (Figure 2)

The epithelial barrier involves a complex interplay of many substances to maintain selective permeability within the system, but, as stated before, celiac disease damages the tight and adherent junctions of this system, decreasing its selective permeability. To find a solution for this, some traditional therapeutic methods were tested, such as larozotide acetate, but after extensive tests, these did not show significant results.[50] In a study done on a mouse model of colitis, MSCs helped heal the epithelial barrier by reassembling claudins, which are one of the most important proteins of the tight and adherens junctions.[51] Certain MSCs also proved to help reduce the increased enterocyte apoptosis rate by protecting all the stem cells from radiation. Additionally, MSCs secreting Interleukin-16 (IL-6), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) caused the Fas receptor to be intercepted from reaching its ligand.[34] This is essential since when Fas connects to its ligand, it can activate the mediators caspase-3 and -8, which cause the apoptosis of enterocytes. Since the Fas receptor does not reach the ligand, the apoptotic effect is not reached. Overall, MSCs play a huge role in maintaining the function of the epithelial barrier and preventing damage to it.

Intraepithelial lymphocytes and NKs play a crucial role in the maintenance of the intestinal barrier, but the overactivation of these cells in celiac disease causes a damaging immune response. This issue causes scientists to turn to MSCs as a possible solution for this destruction. MSCs can reduce the expression of key activation receptors of natural killer cells NKp30, NKp44, and NKG2D and suppress IFN-y production, hindering NK cell cytotoxicity.[52] This inhibition of the NK cells impairs their ability to recognize and attack target cells so that the MSCs can do their job without getting killed by the NK cells. Also, although MSCs are recognized and destroyed frequently by IL-2-activated NK cells, the increased amount of IFN-y in the CD mucosa interferes with the destructive ability of these NKs. This means that the MSCs could properly function in the patient's body.[53] The MSC's impact on intraepithelial lymphocytes and NKs helps their ability to function and make an impact on the epithelial barrier.

Antigen-presenting cells play a huge role in celiac disease pathogenesis, making their regulation a significant concern for scientists. The strong binding of the HLA-DQ molecules on the dendritic cells to the deamidated gliadin peptides promotes the presentation of these peptides to CD4+ T cells.[54] MSCs can harm the monocyte differentiation into dendritic cells by a blockage in the G0 or G1 phase of the cell cycle or by the secretion of suppressive paracrine factors such as PGE2, IL-6, and monocyte-colony stimulating factor.[55] Also, the exposure of the MSCs to the fully mature dendritic cells can cause the dendritic cells to become less mature. Some ways this is confirmed is by the dendritic cells expressing less HLA class II, CD80, CD86, CD40, and CD83 molecules along with demonstrating an increase in their endocytic action.[34] This shift to more tolerogenic dendritic cells can decrease the proliferation of allogeneic T cells, which would, consequently, reduce inflammation in this disease. MSCs can immensely impact antigen-presenting cells, which helps decrease the inflammatory response in celiac disease.

T-cells are the main cells that drive the whole immune system response in celiac disease, so utilizing MSCs for this cell would greatly impact its whole function. Studies have shown that MSCs support the suppression of pro-inflammatory T-helper 1 response while skewing the T-helper 1 to T-helper 2 ratio more towards the T-helper two side.[56] Since T-helper 2 cells have anti-inflammatory effects, this would greatly help decrease the inflammation caused by the T-cells. MSCs can also inhibit the proliferation of gliadin-specific T-cells and increase the apoptosis rate for these cells. MSCs also have the ability to hinder pro-inflammatory cytokines that are directly involved in tissue injury, such as IFN-y and Interleukin-21 (IL-21).[57] All of these effects on T-cells from MSCs are done due to an enzyme known as IDO, which causes a lack of the amino acid tryptophan which is crucial for T-cell growth and activation.[58] Two other complexes that help with this T-cell MSC response are the PGE2 and NO mediators.[59] PGE2 helps with the skewing of the Th1 and Th2 ratio, while the NO mediator helps with the overall immune response of T cells. HLA-G molecules also help in the skewing of Th1 and Th2 cells and support the expansion of CD4+CD25highFoxP3+ regulatory T cells.2 Lastly, the reduction of tumor necrosing factor (TNF)-a, caused by MSCs, can prevent patients from getting a more severe form of celiac disease as there is an excess of (TNF)-a in those with refractory celiac disease.[60] Overall,

DOI: 10.36838/v7i7.11

MSCs' impact on the T-cell response may be the driving factor pushing this treatment to be further tested.

Regulatory T cells are a key asset in the modulation and maintenance of the immune response in celiac disease. The CD4+CD25highFoxP3+ T regulatory cells help achieve peripheral tolerance, helping preserve the harmless antigens outside the thymus and modulating the immune response in this area.[42] One experiment run on Crohn's disease or autoimmune enteropathy showed that a patient was successfully treated using an autologous MSC treatment. Since patients with Crohn's disease and autoimmune enteropathies experience an increase in regulatory FoxP3+ T cells in the intestinal mucosa and peripheral blood, just as do those with celiac disease, it is safe to assume that this could also work on celiac disease patients.[34] When the gliadin-specific T-cells were cultured together with MSCs, the levels of the immunomodulatory cytokine TGF-β increased, and so did the inhibition of IL-15.[61] The increase in TGF-β created modulating effects for the immune system, and the inhibition, not blockage, of IL-15, decreases the pro-inflammatory effects in this disease, showing that MSCs can use Tregs as a tool for inflammation in celiac disease.

B cells are white blood cells vital in the humoral immune response to celiac disease.[62] Intestinal plasma cells produce increased serum class A immunoglobulins (IgA) specific for gliadin and tissue transglutaminase, which plays a big factor in CD pathogenesis.[4] Studies have shown that the development of B-cells partially relies on MSCs and that these MSCs can impact the B-cell's activation and differentiation into plasma cells.[63] Also, in MSCs, IFN-γ stimulated IDOs cause the lack of the amino acid tryptophan, which is necessary for B-cell expansion.[2] The chemokines CCL2 and CCL7 secreted by MSCs bind to receptors on plasma cells, triggering a cellular signaling pathway that inhibits the STAT3 pathway.[64] By inhibiting STAT3 activity, MSCs can suppress plasma cell differentiation and immunoglobulin secretion. Overall, by decreasing B-cells' impact on the body, the MSCs help reduce the humoral immune response in CD.

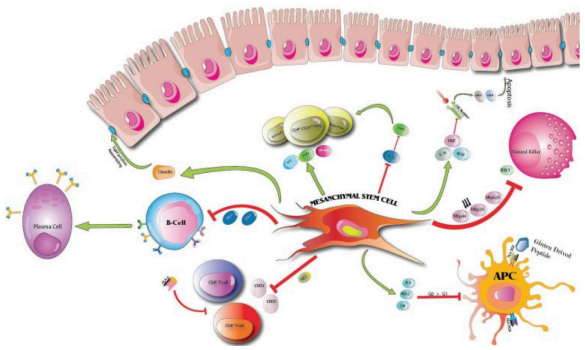

Figure 2: ***MSCs Modulation of Immune Response[2]***
This figure explains how MSCs (mesenchymal stem cells) regulate the immune response in celiac disease by interacting with immune cells like B cells and T lymphocytes Additionally, MSCs modulate claudin to maintain intestinal barrier integrity. Reproduced with permission from Moheb-Alian A *et al.* Gastroenterol Hepatol Bed Bench. 2016;9(Suppl1):S1-S7. Licensed under CC BY 4.0

Overall, MSCs have the most influence on celiac disease's immune response with minimal side effects. Unlike other stem cell therapies, MSCs impact many parts of the immune system, and they are easily accessible as they can be isolated from various adult tissues, which is a lot harder to do in other stem cell therapies. Furthermore, their exceptional differentiation and paracrine effects make them a more effective therapy than the others. Although MSCs have shown some potential side effects, such as consequences to the immune system and dysregulated differentiation, the risk of most of the side effects for MSCs is incredibly low and can be almost entirely eliminated through safety procedures. While it is true that further research and testing needs to be done before this can be implemented, considering the risk factors and the lack of success in other therapies, MSCs seem to be the most effective in curing this disease, and their incredibly high impact greatly outweighs its minimal risks.

Conclusion

As shown in this review, MSCs have incredible immune regulation abilities. They can target almost every part of the body affected by celiac disease, proving that they are the most effective treatment for this disease. While HSC transplantation poses a high risk of developing GVHD, in MSCs, this is, in fact, quite rare and can be prevented through necessary precautions. Furthermore, unlike iPSCs, MSCs have a shallow risk of tumor formation since they are not being reprogrammed like iPSCs are. Additionally, they do not pose any of the risks that traditional therapies do since they are not blocking any part of the immune system but are rather inhibiting it, eliminating the possibility of immune system dysfunction due to the blockage of particular systems. Furthermore, the low risks of MSCs and the high impact it has on the body make it a potential therapy for those with normal celiac disease. There has also been a test done on a 51-year-old woman with refractory celiac disease with MSCs, which yielded positive results as her symptoms disappeared and her intestinal mucosa was healing.[65] Also, there has been evidence that MSCs work on patients with diseases highly similar to celiac disease. For example, a 61-year-old woman with steroid-refractory adult autoimmune enteropathy and severe malabsorption syndrome was treated through an autologous MSC therapy.[66] Within a month, she lost all traces of celiac disease and also developed an increase in FoxP3+ Tregs. Furthermore, celiac disease also shares many properties with Type 1 diabetes, and MSCs have shown auspicious results in treating Type 1 diabetes, which implies that this treatment has a high chance of working in celiac disease, too.[67] However, before MSCs can be put to use, some important questions need to be addressed, such as how long the effectiveness of MSCs lasts. Due to the MSC's extensive range of immunomodulatory complexes and their ability to form a "quasiniche," they do not need to remain in the patient's body for long. Also, it is beneficial to mention that there have been no biological differences concerning which tissue the MSCs have been derived from. However, the invasiveness of this method and the potential constraints of gathering it from the bone marrow have led to the idea of gathering

placenta, and many more. These treatments will likely be the most impactful due to their increased proliferative capacities and high tolerogenic properties. Furthermore, before MSCs can be truly put to use, many things need to be worked out, like the standardization of the procedure and the dosage at which this will work.

Provide a summary of the results of your review concisely. Wrap up your review by drawing everything together and making sure it is clear what conclusions you draw about your topic or field of study based on the research studies you read and analyzed. This can include making suggestions for future research on the topic as part of your conclusion.

Acknowledgments

I would like to thank my mentors, Dr. Hamidreza Shaye, Taylor Hailstock, and the Indigo Research team.

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Suhani is a young author interested in possibly pursuing biotechnology in the future and was inspired to write about celiac disease due to her mother's complications with this condition.

DOI: 10.36838/v7i7.11