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Comparative Analysis and Optimization of Stem Cell Therapies for Type 1 Diabetes: Evaluating Glycemic Control, Insulin Independence, and Adverse Effects

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Abstract

This paper will explore treatments for Type 1 diabetes by comparing embryonic stem cells, adult stem cells, and induced pluripotent stem cells through glycemic control, insulin independence, and other adverse effects. Diabetes is a detrimental disease that affects over 10% of the U.S. population, leading to chronic conditions such as damage to large and small blood vessels, which can increase the risk of a heart attack or stroke, as well as dilemmas with the kidneys, eyes, feet, and nerves. Given the limitations of standard insulin therapy, stem cell transplantation is a promising alternative; however, due to the novelty of the solution, researchers and doctors are not familiar with the most optimal way to treat diabetes. To alleviate and cure this degenerative disease through stem cell transplantation, we will optimize the efficiency of the process by deductively analyzing each stem cell through Continuous Glucose Monitoring (CGM) and monitoring HbA1c levels. We hope to enhance stem cell therapy for type 1 diabetes and save the lives of those suffering from this hoarding pandemic, so victims are effectively cured, not treated. The objective of this study is to find the most suitable stem cell for treating T1D (Type 1 Diabetes) using stem cell transplantation to ensure the safest and most effective route.

K**eywords**: Embryonic Stem Cells, Adult Stem Cells, Induced Pluripotent Stem Cells, Type 1 Diabetes

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Introduction

Stem cell research has become a groundbreaking innovation in modern medicine, providing novel solutions to some of the most complex medical challenges. Our rationale for this paper is to explore the potential of various stem cells in treating diseases with very sparse current treatments. This paper will focus on diabetes and the current treatments that are aimed at managing it. Both type 1 and type 2 diabetes involve the issue of high blood glucose problems in patients, but they differ in their causes and the medical approach taken to treat it. Type 1, usually found in younger patients, involves the lack of insulin produced due to an autoimmune attack on insulin-producing beta cells. In this variation, patients are subject to insulin therapy for the rest of their lives. In Type 2, which occurs mostly in adults, patients can produce insulin, but their cells cannot respond to it and absorb the glucose. This is combatted through various medications and sometimes insulin therapy.

Although some current treatments for T1D exist, they come with downsides. Current treatments include: Insulin replacement therapy is the use of an outside source of insulin, such as insulin made by recombinant DNA technology from bacteria. It can be administered through multiple daily injections or via insulin pumps paired with continuous glucose monitors. Although the replacement therapy aims to mimic physiological insulin release, it fails to provide long-term insulin independence. Artificial Pancreas is an automated insulin-delivery system in which the Continuous glucose monitor uses a sensor to take the glucose levels of the patient which is then sent to a program that calculates the need for insulin. Then the insulin pump attached to the patient will deliver small amounts of insulin to reach glucose homeostasis. This system has shown improvement in glucose control in patients however some concerns are attributed to high sensor replacement costs, buildup of scar tissue from microneedle insertion, and premature sensor failure. Immune Therapies include various strategies to stop or reverse the attacks on β cells. One approach is modifying T-cells by using antibodies such as the anti-cd3 and anti-cd20 antibodies to reduce the immune attack by T-cells. Another approach includes peptide and DNA vaccines aimed at training the immune system to tolerate insulin. Islet Transplantation is when donor islet cells are purified in labs and transplanted into the recipient's liver. Then the islets will produce insulin and restore glycemic control. Some drawbacks to this method include the risk of rejection, side effects of immunosuppressive drugs, and apoptosis of islet cells.

Due to there being more treatments available for Type 2, we decided to focus on ways to improve the standard of life for patients with Type 1 by conducting research on different types of stem cell therapies and comparing their advantages and drawbacks to emphasize the most beneficial variant.

Research Methodology

We were amazed by stem cell therapy in general practice: cardiology, immunology, and neurology. We trimmed it down to Cardiovascular and Pancreatic with a specific disease: Type 1 Diabetes. The main constraints were due to the novelty of this research and experiment, most data and medicine are new, thus the prolonged effects of stem cells are not yet measured and there is not much outside research. Throughout the research process, we vowed to bring only valuable and reliable information so the patient’s life would never be at

risk. We cited and brought information from PubMed and government organizations allowing us to propel our knowledge and research.

Embryonic Stem Cells

Embryonic stem cells (hESCs) are derived during embryo development - near the inner cell mass of a blastocyst. Occasionally they can be isolated from the umbilical cord to isolate the embryonic stem cells and then cultivated for weeks and even years (National Research Council [NRC], 2002). However, they are mainly taken and developed in IVF facilities (in-virto-fertilization), where during the process of fertilization, many unwanted embryos are created. Those not implanted are donated for research only through the consent of the donor. Discovered in 1981, these cells have become a focus in medicine to reverse any immuno or neurological disease using reverse therapy. Historically, Martin Evans and Matthew Kaufam are the first to cultivate embryonic stem cells from mice.

As of now, (hESCs) are being used in multiple regenerative therapies, such as spinal cord, diabetes, and Multiple Sclerosis (NRC, 2002). Fortunately, researchers around the world are continuing to aim their goal of safety and the ethical concerns regarding these types of stem cells due to the destruction of embryos and risk. While hESCs are the most versatile of all stem cells due to the lack of maturity; however, they raise a bioethical concern due to the process of retrieving embryonic stem cells.

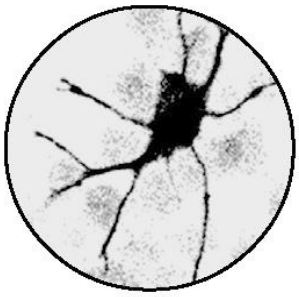

Figure 1: Embryonic Stem Cell

Source: National Academies Press (US). (2002). Embryonic stem cells. Stem Cells and the Future of Regenerative Medicine - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK223690/

Induced Pluripotent Stem Cells

Induced Pluripotent stem cells (iPSCs) are created by reprogramming adult cells, either found in the skin or blood, into an embryonic-like state. First developed by Shinua Yamanaka in 2006, iPScs were seen as a method to give patients specific cells without ethical concerns, meeting the best of both worlds (embryonic and adult) (Takahashi & Yamanaka, 2006). Currently, iPSCs are being applied in multiple drug discovery paths, where a new approach for regenerative medicine using engineering is taking hold (Robinton and Daley, 2012). iPSCs are unique in their ability to differentiate into any cell while simultaneously overriding ethical concerns. However, due to the novelty, there is a risk of disease and genetic mutations that

have been reported with the use of induced pluripotent stem cells. The advantages outweigh the disadvantages if we ensure long-term safety as the stem cell ages and divides.

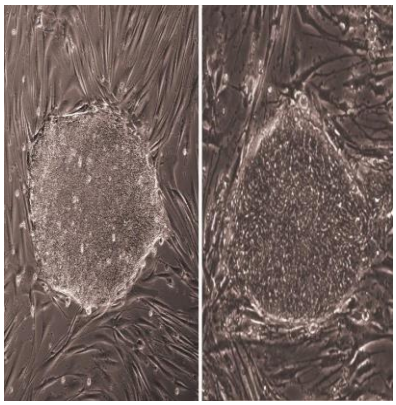

Figure 2: Induced Pluripotent Stem Cells

Source: Ring, K. (2016, February 22). CIRM-funded study suggests methods to make pluripotent stem cells are safe. The Stem Cellar. https://blog.cirm.ca.gov/2016/02/22/cirm-funded-study-says-methods-to-make-pluripotent-stem-cells-are-safe/

Adult Stem Cells

Typically found in bone marrow, adipose tissue, and the brain, adult stem cells play unlike embryonic stem cells, they are multipotent - limiting the variability the stem cell can become (Mayo Clinic, 2013). Around the 1950s, adult stem cells were discovered by scientists - James Till and Ernest McCulloch - realizing how they would revolutionize blood disorders. Today, adult stem cells continue to be used to fight blood-affiliated diseases, such as leukemia. However, adult stem cells are limited by their reduced differentiation capacity, allowing for less room for error but sometimes no results are apparent. There is a reduced risk of immune rejection, as most of the time the stem cells are harvested from the patient's body. Nonetheless, the patient still has to go through severe challenges and the process has to be used with an encapsulation device to not put the patient's life at risk with an immune rejection (Mayo, 2013).

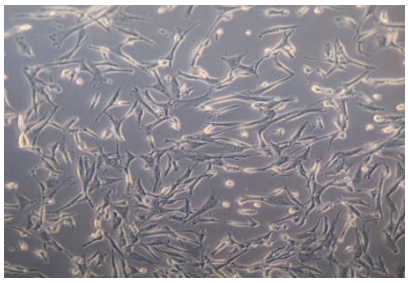

Figure 3: Adult Stem Cells

Source: Gartner, A., Pereira, T., Gomes, R., Lucia, A., Lacueva, M., Geuna, S., Armada-Da-Silva, P., & Colette, A. (2013). Mesenchymal Stem Cells from Extra-Embryonic Tissues for Tissue Engineering – Regeneration of the Peripheral Nerve. In InTech eBooks. https://doi.org/10.5772/53336

Glycemic Control

As mentioned, Type 1 diabetes is a chronic condition that—for now—permanently compromises the pancreas beta cells to produce insulin (a hormone that is secreted by the pancreas to the liver to take the glucose from the bloodstream and store it as glycogen). The autoimmune disease T1D mistakenly attacks the β cells of the pancreas and creates a lack of insulin. Glycemic levels are usually measured in mg/dl (milligrams per deciliter) and constantly involve measuring hemoglobin A1c levels (Hb1ac), which reflect the blood glucose level over a 2-3 month period as well as real-time CGM monitoring (Atkinson et al., 2001; Powers, 2021).

For example, if you eat a bowl of rice, the carbohydrates from your rice get broken down by analysis, and the small intestine makes glucose that enters your bloodstream. This causes an influx in glucose levels and requires the pancreas to create insulin to signal to the liver to transfer the glucose through a process of anabolic reactions. According to Atkinson et al. (2001), as a result, people must rely on a variety of therapies, including the ones already mentioned, but primarily on a lifetime of exogenous insulin therapy, in order to control their blood glucose levels. In addition to managing blood glucose levels through monitoring and insulin therapy, dietary strategies such as focusing on low glycemic index (GI) foods can significantly impact glycemic control. Low-GI foods produce a slower, more stable rise in blood glucose, which is crucial for preventing spikes and maintaining better overall glucose management (Brand-Miller & Buyken, 2020).

The goal is to achieve near-normal 72/108 mg/dl levels in glycemic control to minimize the risk of complications from prolonged hyperglycemia (Atkinson et al., 2001). Unfortunately, many patients still struggle to achieve optimal glycemic control due to factors such as variability in insulin absorption, individual differences in response to therapy, and the psychological burden of constant glucose monitoring (Powers, 2021).

Insulin Independence

Insulin independence is a crucial milestone for patients with type 1 diabetes since most individuals are taking insulin through a pump and are insulin dependent. They no longer require exogenous insulin therapy to maintain normoglycemia (a normal range of glycemic levels). This can be achieved through islet transplantation or stem cells that act as new beta cells. Islet (portion of tissue of pancreas) transplantation, while effective, has limited availability due to the scarcity of donors (Shaprio et al., 2000). Moreover, efforts aim to protect the remaining β-cells in individuals with recent-onset T1D, allowing younger individuals to achieve insulin independence (Powers, 2021). In short, the long-term survival of transplanted cells is still questionable, further studies are being conducted to find a viable option for a broader population of victims of T1D.

Lab Analysis

Embryonic Stem Cells

Because human embryonic stem cells (hESCs) may develop into beta cells that produce insulin, they have the potential for treatment for type 1 diabetes. Studies have shown that pancreatic endoderm produced from hESC "efficiently generates glucose-responsive endocrine cells after implantation into mice" in terms of glycemic control. According to research done by Baetge and colleagues, the majority of "(92%) of implanted mice expressing high levels of C-peptide before STZ treatment" were protected against hyperglycemia, which indicates a high degree of glycemic control (Wen et al., 2010). These hESC-derived cells could also produce insulin in response to glucose, an essential factor for patients' insulin independence. In certain research, "only 30% of animals showed an obvious rescue of their hyperglycemic phenotype," conveying that these cells vary in effectiveness (Wen et al., 2010).

By converting human embryonic stem cells (hESCs) into insulin-producing beta cells that can react to glucose levels, insulin independence through hESCs can be achieved, which potentially lowers or eliminates the need for exogenous insulin in type 1 diabetes (T1D). By this method, the lack of islets is capable of generating insulin for transplantation. Human embryonic stem cells have great potential as they have the ability of "self-renewal and differentiation to almost any specific cell type in the human body" (Hayek & King, 2016). In 2008, hESC-derived beta cells were shown to produce insulin functionally for the first time in mice. The ability to reprogram a patient's cells into beta cells was made possible due to the later development of induced pluripotent stem cells (iPSCs) in 2007. Refined procedures to generate insulin-secreting, glucose-responsive cells from hESCs are among the recent advances. Companies like ViaCyte have made great strides in creating techniques for producing pancreatic stem cells that turn into functional beta-like cells in vivo. These cells have exhibited the capacity to prevent hyperglycemia, which brings T1D patients closer to gaining insulin independence.

Insulin-producing beta cells in patients with type 1 diabetes (T1D) can be significantly restored by human embryonic stem cells (hESCs). However, there are several factors that limit the cells' utilization. For example, there is limited research on human embryonic stem cells "due to law restrictions in many countries" (Wan et al., 2022). Furthermore, there are difficulties in preserving the "survival, differentiation, and immunomodulatory ability of stem cells in vivo and in vitro" of these cells even though these cells can proliferate into beta-cell mass and develop into pancreatic generations (Wan et al., 2022). As potential solutions to the problems hESCs can bring, strategies like "far-red light, genetic engineering, biological material scaffolds, nanofiber tubular, combination treatment with insulin or other drugs, microcapsules, and co-transplantation with more than one of stem cells" are options that can help (Wan et al., 2022).

Induced Pluripotent Stem Cells

In research on type 1 diabetes (T1D), induced pluripotent stem cells (iPSCs) have demonstrated a great deal of potential for controlling glucose levels. In a crucial study, the liver tissue of a T1D mice model was transplanted with insulin-producing β-like cells produced from induced pluripotent stem cells (iPSCs). The blood glucose levels returned to

normal as a result of the "transplanted iPS-derived β-like cells were able to survive within the tissue environment where they were engrafted" (Soejitno & Prayudi, 2011). These transplanted cells were able to sustain normoglycemia during a four-month follow-up period, proving that β-like cells produced from iPSCs can successfully imitate the role of pancreatic β-cells in T1D. Furthermore, according to the early results from the group of T1D mice, normoglycemia was maintained for the remainder of the trial with "correction of hyperglycemia was achieved following transplantation (Soejitno & Prayudi, 2011). The extended duration of glycemic control was about "20-30% of the life expectancy of those mouse models," which shows that iPSCs have enough endurance to be an alternative treatment for type 1 diabetes.

Achieving insulin independence has been difficult in recent type 1 diabetes clinical trials using induced pluripotent stem cells (iPSCs). Unexpectedly, Vertex research found that a T1D patient receiving a single infusion of VX-880, a fully developed pancreatic islet-like cell treatment produced from stem cells, saw an amazing "91% decrease in daily insulin requirement" in less than 90 days (Rezania et al., 2012). Total insulin independence has not yet been attained. Similarly, no patient achieved complete insulin independence in trials employing ViaCyte's PEC-Direct; only "one patient had a >50% reduction in insulin requirements within one-year post-implantation" (Rezania et al., 2012).

Inconsistent results and difficulties with the immune system are side effects of using induced pluripotent stem cells (iPSCs) to treat type 1 diabetes (T1D). In the case of ViaCyte's PEC-Direct, for example, clinical trials found that although some patients required less insulin, the treatment's effectiveness was "primarily limited by a foreign body response to the device component," suggesting problems with the materials used in encapsulation devices (*Diabetes*, n.d.). Furthermore, participants in the Vertex trial needed "concomitant immunosuppressive therapy" to prevent immunological rejection, which resulted in certain adverse effects, even if a significant reduction in insulin reliance was observed (*Diabetes*, n.d.).

Adult Stem Cells

Mesenchymal stem cells (MSCs) are adult stem cells that have displayed the potential to enhance glycemic control in individuals with type 1 diabetes mellitus (T1DM0. For example, an intravenous injection of allogeneic umbilical cord-derived MSCs improved islet β-cell protection over 12 months, when compared to standard treatments in a 53-person clinical trial (Wan et al., 2022b). According to a different study, MSC treatment can enhance glycemic management by lowering blood glucose and HbA1c while raising C-peptide levels in patients. These results imply that MSC transplantation may be a treatment strategy that works well for controlling T1DM (Wan et al., 2022b).

The potential of adult stem cells to achieve insulin independence in the treatment of diabetes has been highlighted by recent findings. The report states that bone marrow MSCs can enhance insulin production by "injecting insulin levels into diabetic mice and downregulating hyperglycemia" (National Academies Press (US), 2002). Furthermore, the autoimmunity reverses itself, "islet cell regeneration is promoted, and blood glucose control is improved by monotherapy with human umbilical cord MSCs" (National Academies Press (US), 2002). The achievement of total insulin independence is still a work in progress, as proven by the fact that "successful hUCMS therapy for T1DM in NOD mice depended on the stage of the T1DM disease process" (National Academies Press (US), 2002).

There are drawbacks and possible side effects when using adult stem cells to treat diabetes. Even though "MSC xenotransplantation was not used in the clinics," the study points out that through immunomodulation and β-cell-like differentiation, "human-derived MSCs could alleviate diabetic symptoms" (National Academies Press (US), 2002). There are still difficulties, though, such as the possibility of "immune rejection," which makes stem cell therapy more difficult. Furthermore, MSCs' "autoimmune properties included the presence of increased Treg in T1DM," suggesting that although MSCs might lower blood sugar, they can also have intricate impacts on the immune system (National Academies Press (US), 2002).

Results and Conclusion

In the final analysis, we concurred that adult stem cells are the most reliable in terms of consistency in differentiation and have been tested out the longest out of all three types of cells, unlike embryonic. However, Induced Pluripotent Stem Cells, with more clinical trials and research done, may have the potential to be a viable treatment for T1B

Using the data above from the researched labs, we found the pros and cons for each category: glycemic control, insulin, independence, and adverse effects. Embryonic Stem Cells showed the most control over blood glucose levels in animals, however, Adult Stem Cells showed the most control in humans All three types of stem cells showed very little amounts of insulin independence. However, with more research and time, the results may be improved. Induced pluripotent cells have been shown to resemble pancreatic beta-cells. All types of transplants need to be monitored carefully through the use of an encapsulation device to prevent severe diseases such as liver or pancreatic cancer. For embryonic, some adverse effects include inconsistent differentiation in β-cells. For Induced pluripotent stem cells, adverse effects include side effects from immunosuppression and tumor formation.

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Conflict of Interests

The authors and editors of this article profess no conflict of interests

Contributions

All authors outlined and created this review - conducting the literature searchers and meticulously mediating the systematic review process. We interpreted and analyzed data, participated in research conferences and all conjured on the publication of this final research paper and or article.

Supplement Information

All authors participated in the 13th London International Conference, LIC. The publication of this article was not influenced by the Conference. During this conference, we were able to share and present our research and objectives with other scholars on the topic of stem cells.

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