Use of Stem Cells for the Study and Treatment of Type 1 Diabetes

By

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled “Use of Stem Cells for The Study and Treatment of Type1 Diabetes” submitted by Safat Ahsan (18346094) of Summer, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree Bachelor of Pharmacy.

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Ethics Statement

This review adheres to the ethical principles of research and the relevant guidelines and regulations. The sources cited in this review were obtained by ethical standards, and their authors were properly cited. The goal of this review is to provide an objective and comprehensive analysis of type 1 diabetes treatment methods, with the ultimate aim of improving public health outcomes.

Abstract

Diabetes mellitus (DM) is a significant and prevalent chronic disease with high rates of morbidity and death. The loss of pancreatic cells characterizes type 1 diabetes mellitus (T1DM), For this reason, the body lacks insulin and becomes hyperglycaemic. Exogenous insulin cannot replace the endogenous insulin released by a healthy pancreas by administration or injection. To control blood glucose in T1DM patients, pancreas and islet transplantation have shown very satisfactory results. There have been efforts made to handle the rising number of T1DM patients. Patients who are suffering from T1DM can be treated with very positive results by using stem cell treatment. The objective of this study is to list the categories of stem cells that have the most supporting data for treating type 1 diabetes mellitus (T1DM).

Keywords: Diabetes Mellitus, Stem cells, Type 1 Diabetes, Mesenchymal Stem Cells, Insulin, Induced pluripotent stem cells

Dedication

This review paper is dedicated to my parents for their immense support and also to my supervisor. Also, friends whose unwavering support and encouragement have sustained me throughout this journey.

Acknowledgement

All praise to Almighty Allah, and I would like to commence by expressing my gratitude to Him for the continuous blessings.

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List of Acronyms

DM	Diabetes Mellitus
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
HLA	Human Leukocyte Antigen
CGM	Continuous Glucose Monitoring
iPSc	Induced Pluripotent Stem Cells
HSCs	Hematopoietic Stem Cells
MSCs	Mesenchymal Stem Cells
ESCs	Embryonic Stem Cells
SHH	Sonic Hedgehog
BMP	Bone Morphogenetic Protein
FGF	Fibroblast Growth Factor
VEGF	Vascular Endothelial Growth Factor
UCB	Umbilical Cord Blood
BM-MNC	Bone Marrow Mononuclear Cells
BM-HSC	Bone Marrow Hematopoietic Stem Cells
EBs	Embryoid bodies
DE	Definitive Endoderm
PKC	Protein Kinase C
RBC	Red Blood Cell
WBC	White Blood Cell
TGF	Transforming Growth Factor
TR-1	Thyroid Receptors-1
PARP	Poly-ADP-Ribose Polymerases

hiPSc	Human Induced Pluripotent Stem Cells
GLP-1	Glucagon-like Peptide-1
DPP-4	Dipeptidyl Peptidase IV
PDLN	Pancreatic Draining Lymph Node
TCRs	T cell receptors
Treg	T regulatory cells

Chapter 1 Introduction

1.1 Background

Diabetes mellitus (DM) is one of the world's fastest-growing public health issues in the twenty-first century. The International Diabetes Federation reported that 463 million people had diabetes worldwide in 2019. By 2030, this figure is anticipated to reach 538 million. (Raziye et al,2021). Type 1 and 2 diabetes mellitus are chronic conditions brought on by high blood glucose levels. Lack of insulin is the result of T1DM, the body's pancreatic beta cells that fail to produce enough insulin. It is believed that this reaction is caused by an accumulation of biological traits and influences from the environment that initiate the damaging autoimmune process, even though the precise cause of the reaction is unknown. (Atkinson et al,2014). Insulin resistance and beta-cell dysfunction are part of the pathophysiological mechanism in T2DM(Kolb,2005). Microvascular conditions like nephropathy, neuropathy, and retinopathy as well as macrovascular conditions like cardiovascular disease, peripheral vascular diseases, cerebrovascular accidents, and cerebrovascular accidents can all develop as a result of DM and have high morbidity and mortality rates. (Peng et al,2018). To manage hyperglycemia, insulin is given externally and other hypoglycemic drugs are being utilized, however, they don't follow internally generated insulin production, which can lead to fluctuating blood sugar levels and reacting hypoglycemia, and disruptions to the patient's work and daily life. (Peng et al,2018). As an alternative treatment option for DM, stem cell therapy, islet cell transplantation, and pancreas transplantation have all been given clinical approval for both T1DM and T2DM (Sherry et al,2011). As stem cells have immunomodulatory properties, multilineage distinction, and capacity for regeneration A highly encouraging new treatment choice for diabetes mellitus and its complications is stem cell therapy (Kalra et al,2014). Additionally, hepatic and pancreatic stem cells have been examined and treated T1DM patients with bone marrow-

derived stem cells and reported encouraging outcomes (Bhansali et al,2009). A type 1 diabetes diagnosis can profoundly change a person's way of life. When a person has type 1 diabetes, their pancreatic cells are destroyed, which prevents the body from producing insulin and makes them dependent on insulin replacement therapy. As a result, these patients either need continuous insulin infusion pumps or multiple daily insulin injections. (Ye L et al, 2017). Additionally, glucose level test is advised to be performed daily and control blood glucose levels. In order to achieve glycemic objectives, insulin therapies have advanced over a long period of time. Unfortunately, some patients continue to experience hypoglycemic events (Couri et al 2009). The use of type 2 diabetes medications in conjunction with insulin therapy for type 1 diabetes has been studied. These medications, which are used in conjunction with other treatments, are intended to assist people with type 1 diabetes in achieving their glycemic targets, controlling weight gain, reducing their risk of developing hypoglycemia, and living healthier lives. Although patients have benefited from these adjunct therapies, there are safety concerns (Ruloph M,2020).

1.2 Methodology

For this scientific review, All the information was compiled from a variety of reputable sources, including scholarly journals and databases such as PubMed, Web of Science, and Scopus, as well as renowned publications such as Google Scholar, MDPI, Cell, and Frontiers. To get precise information terms used such as "Stem Cell" and "Type 1 Diabetes" to narrow down on the most relevant papers. All the contents of pertinent publications and books were evaluated in order to get a comprehensive grasp of the issue. This approach, helps to identify critical knowledge gaps and formulate a research topic to assist fill them Furthermore, 80 articles have checked and skimmed through their techniques according to the topic then selected 40 articles from them to make this review. Next, a precise outline with key headers and subheadings were made to arrange this review. Using Mendeley Desktop to create in-text citations and references, this ensures that all sources were properly credited and quoted throughout the writing process

Chapter 2 Diabetes

2.1 What is Diabetes?

Diabetes is a chronic illness caused by either ineffective insulin use by the body or insufficient insulin production by the pancreas. The hormone that controls blood sugar levels is insulin. Hyperglycemia, commonly referred to as high blood glucose levels or high blood sugar, is a common consequence of uncontrolled diabetes that, over time, can cause serious harm to a variety of body systems, most notably the nerves and blood vessels. (Carlsson et al,2015). In 2014, the prevalence of diabetes among adults 18 years of age and older was 8.5%. In 2019, diabetes was directly linked to 1.5 million deaths, with individuals below the age of 70 accounting for 48% of these deaths. Increased blood glucose is the reason for around 20 percent of all cardiovascular deaths, and diabetes leads to more than 460,000 deaths from kidney failure. The number of deaths from diabetes, age-standardized, rose by 3% between 2000 and 2019. The countries with lower middle livelihoods, the death percentage from diabetes rose by 13% (World Health Organization,2019).

2.1.1 Types 1 diabetes mellitus:

Type 1 diabetes mellitus: People who have diabetes among them around 5 to 10% have type 1 diabetes. Although adults make up 20% of newly diagnosed cases of type 1 diabetes, most cases begin in children or teenagers. Diabetes can vary from country to country. for example, in China and some parts of South America among 1000 people less than 1 person has diabetes annually, whereas in Europe among 1000000 people 20 people annually (Sneddon et al, 2018). Most of the patients have symptoms associated with hyperglycemia, but some also have ketoacidosis in diabetics is a glaring sign of a drastic decrease. In type 1 diabetes, the pancreatic

islets of Langerhans are usually destroyed by an autoimmune response (Li et al,2018). Antibodies can exist for several years before the start of diabetes and may be associated with decreased insulin production. Some type 1 diabetes patients have genetic abnormalities related to the human leukocyte antigen (HLA) complex, which plays a role in antigens to autoimmune cells and initiating the synthesis of antibodies that can affect the body's own cells (autoantibodies). Instead of the creation of autoantibodies, it is believed that immune cells that have been sensitized to specific islet tissue components are what actually destroy the islets of Langerhans. Children whose parents have type 1 diabetes generally have a 2–5% chance of developing in themselves. (Britannica,2023).

2.1.2 Type 2 diabetes mellitus:

People who have diabetes among them 90% have type 2 diabetes and it is more common than type 1 diabetes. Around the world, the number of cases of type 2 diabetes is increasing gradually. Most of the time people who are adults have the tendency to have type 2 diabetes even though children and teenagers are also affected by it but the chance is low. (Barton et al,2012). Type 2 diabetes is more genetically predisposed than type 1 diabetes. For instance, type 2 diabetes is much more likely to strike identical twins than type 1 diabetes, and 7 to 14 percent of people with type 2 diabetes will also acquire the disease If both parents experience the same problem, this estimate increases to 45%; For type 2 diabetes unable to produce insulin and insulin deficiency caused because of obesity. Because insulin resistance is a common symptom of type 2 diabetes, obese patients often have serum insulin concentrations above normal When an obese person's body cannot produce enough insulin to respond appropriately to higher blood sugar levels, this can lead to hyperglycemia. In a diabetic person and a healthy

person in case of blood glucose level raises the same level then the healthy person secretes insulin higher than the diabetic patients. (Britannica,2023).

Gestational diabetes: Pregnancy-related gestational diabetes is defined as blood glucose levels that are higher than regular levels, but lower than diabetes-indicating levels. Women who have gestational diabetes while pregnant are more likely to experience pregnancy as well as delivery complications. Type 2 diabetes is more likely to strike these women later in life, and possibly even their children. Rather than waiting for symptoms to appear, gestational diabetes is diagnosed through a prenatal test (Britannica,2023).

Risk factors for diabetes:

- Have a history of diabetes in the family
- Older than 55 years old
- Have high blood pressure or overweight and older than 45.
- Have an Aboriginal or Torres Strait Islander ancestry and are over 35 years old.
- Have experienced gestational diabetes while pregnant
- Experience PCOS (polycystic ovarian syndrome) (Diabetes Australia, 2020).

2.1.3 Symptoms of type 1 diabetes:

- feeling extremely hydrated,
- urinating more frequently than usual, especially at night,
- experiencing extreme fatigue,
- gaining less muscle mass and weight and having thrush episodes frequently,
- distorting vision due to an alteration in the eye's lens (Papadakis,2022).

2.1.4 Challenges with T1D:

Challenge in Diagnosis: Because 5 to 15% of cases of adults suffer from T1DM, the prevalence of T1DM is underreported. When a disease first manifests, autoantibodies against islet beta-cell antigens are found. is the primary criterion for separating T1DM from T2DM. (Yamaguchi et al,2017). In between 85% and 90% of T1DM patients, one or more of the autoantibodies was present. For the purpose of giving proper care and avoiding complications, an accurate diagnosis of T1DM is essential (Teresa,2016).

2.1.5 Management:

T1DM has no known treatment, and insulin therapy is required for the rest of one's life. Maintaining normoglycemia, minimizing hypoglycemia, and lowering the risk of complications are the main objectives. A typical treatment strategy includes a customized insulin regimen and daily glucose monitoring. (Teresa,2016).

2.1.6 Existing therapies for T1D:

2.1.6.1Insulin Therapy:

Because type 1 diabetes destroys beta cells, it is a long-term condition. that eventually results in a total loss of insulin production. Inadequate islet cell repair mechanisms are another issue that ultimately compromises glycemic control (Kim et al,2010). As a result, the first-line therapeutic option for treating T1D at this time is insulin replacement therapy. In order to achieve their glucose-lowering effects, Banting and Best used animal pancreas crude extracts in 1921 when they first described the use of exogenous insulin as a treatment for T1D

(Banting,1922). Animal-derived crude insulin preparations for clinical use were commercialized shortly after in 1922. There were issues with the pharmacokinetics of insulin, chiefly because of insulin absorption. Additionally, it was noted that administered insulin didn't work as well as intended, which resulted in inconsistent glucose-lowering effects. (Richter et al,2002).

Limitations for Insulin Therapy:

Low blood glucose: Even though insulin is meant to lower blood sugar, sometimes its impact may prove more potent than you need. Hypoglycemia, also known as low blood sugar, is the most common side effect of insulin. When blood sugar falls below 70 mg/dL, this occurs. The correct dose of insulin must be administered in order to prevent hypoglycemia (Hindu ,2023).

2.1.6.2 Artificial Pancreas:

The management of T1D is becoming more and more dependent on technology. Capillary blood glucose meters, which offer progressively more precise point-of-care glucose measurements, weren't developed until the 1960s. (Thabit et al,2016). CGM devices entered clinical use in the late 1990s, enabling Interstitial glucose measurements in real-time and enhancing glycemic stability (Klonoff et al,2016). Small pumps were first used for continuous subcutaneous insulin infusion (CSII) in the 1970s (Tamborlane et al,1979). The size and functionality of the CSII devices are constantly being enhanced. The various insulin administration options currently available in devices include bolus infusions and variable basal rates. There are patch pumps that can be applied directly to the skin as well as pumps with individual infusion sets (Thabit H et al,2016).

Limitations for Artificial Pancreas:

There are a few significant restrictions on these studies The closed loops that solely rely on insulin, and patients who have severe hypoglycemic events were removed (Garg et al,2017). Patients with little awareness of hypoglycemia and insulin resistance were also removed from some studies (Garg et al ,2017). One major current limitation of closed-loop devices is lagging time. In CGM systems, which are now utilized in healthcare for determining the amount of glucose in the interstitial fluid, glucose is oxidized enzymatically (Ferri et al,2011). In patients with T1D, between blood glucose level and interstitial fluid, there is a delay of about 15 minutes. (Cobelli et al,2011). The majority of CGMs offer a blood sugar measurement every five minutes, which is an average of those devices' glucose levels prior to 5 min may cause the CGM itself to have a latency period. The total delay in the glucose concentration as reported by the CGM may be up to 20 minutes (Schoemaker et al,2015). During the first few days of using the CGM, there is decreased precision in measurement and a variable error in the measurement. Factors like skin temperature, pressure, and movement have an impact on accuracy. (Helton KL et al,2011). Despite the fact that the average difference of modern GCMs is getting closer to 10 percent, this happens because of changes in hypoglycemic range and glucose levels (Christiansen et al,2017).

2.1.6.3 Xenotransplantation of Islets:

Human whole pancreas and islet transplantation provides a different option for ensuring lifetime insulin independence, but there are practical difficulties related to a lack of donors (Millman et al,2016). Exciting possibilities exist for islet xenotransplantation to help with the shortage of donors. In human T1D patients, the first documented attempt to transplant porcine islets was made in 1994(Kenneth et al,2008). Results showed that C-peptide levels could be detected in the patient's urine up to 300 days after transplant. These had no appreciable impact on blood sugar levels, though. Since then, there have been a few small clinical studies that have highlighted the advantages of treating T1D with islets derived from pigs (Groth et al,1994).

Limitation of Xenotransplantation of Islets:

Since there hasn't been much long-term follow-up of islet recipients, there are additional safety issues that need to be taken into account. For instance, both in nonhuman primates and in patients, we and others have noticed hepatic structural changes after islet transplantation (Bhargava,2004). Immunohistochemical analysis and chemical shift MRI both showed glycogen buildup and localized steatosis. The liver transplant procedure has not been linked to any long-term negative effects on liver function, but the link between obesity, type 2 diabetes, and fatty liver disease that causes progressive fibrosis and eventually cirrhosis is alarming. The correction of defects in hepatic visualization It has been proposed that secondary hepatic effects can serve as indirect markers of islet function in cases where islet allografts fail (Han,2004).

Chapter 3 Stem cells:

A stem cell is a kind of cell in the body that can make itself into different types of cells (Alm,2023). When any cell of the body gets damaged stem cells can repair that damaged cell. There are special abilities of stem cells which can apart from other body cells:

- Stem cells have the ability of They have the capacity to split and regenerate over time.
- They are able to differentiate into specialized cells such as brain, blood, and muscle cells
- They cannot execute some body functions because they are not specialized (Bethesda,2016).

3.1 Types of stem cells:

Embryonic stem cells: Embryonic stem cells are located in the inner cell mass of the blastocyst, a mostly hollow ball of cells that forms in humans three to five days after a sperm fertilizes a cell from an egg. The more specialized cells found inside the inner cell mass are usually the ones that ultimately give rise to our whole body, including all of our tissues and organs. However, when the inner cell mass is removed and the cells are grown in specific lab environments, they maintain the characteristics of embryonic stem cells. (Silva,2022).

Tissue-specific stem cells: Compared to embryonic stem cells, tissue-specific stem cells are more specific, and are called somatic stem cells. Usually, they are able to generate different kinds of cells depending on the specific tissue or organ in which they are found (Brizzi et al,2012). Hematopoietic stem cells found in bone marrow can differentiate into platelets, white blood cells, and red blood cells (Badylak et al, 2009). On the other hand, brain cells, lungs, and liver are not produced by blood-forming stem cells, nor are stem cells in other tissues, blood, Skin, and the lining of the stomach are just a few of the body's organs and tissues that contain

tiny stores of tissue-specific stem cells. These cells are used to replace lost tissue from accidents or everyday activities (Tyler et al,2015).

Induced pluripotent stem cells: Induced pluripotent stem (iPSC) cells are created in research settings by converting tissue-specific cells, like skin cells, into cells that behave like embryonic stem cells. Scientists need IPS cells to gain a better understanding of both typical growth and the onset and progression of diseases. These cells are also used in the research and evaluation of novel drugs and therapies. Although they can both differentiate into all of the various kinds of body cells, iPS cells, and embryonic stem cells are not the same. Researchers are examining these variations and their implications (Lei Y et al,2013).

Hematopoietic stem cells (HSCs): From the hematopoietic stem cells the substance of blood like RBC, WBC, and platelets can be produced. Because HSCs are able to regenerate themselves, they can divide and create double of themselves. Between HSCs and mature cells, there are a number of progenitor cells that act as intermediaries. Before full maturation, these cells typically exhibit both their multipotent and lineage-committed properties. Due to its short lifespan, blood is a highly regenerative tissue, and BM promotes diverse cells' dynamic movement to maintain the homeostasis of blood cells. (Robert et al,2006).

Mesenchymal Stem Cells (MSCs): Adult stem cells of the type known as mesenchymal stem cells (MSCs) have a broad range of cell types that they can differentiate into. They can be isolated from fat, umbilical cord, placenta, and bone marrow. MSCs have a wide range of potential medical uses, from cancer treatment to regenerative medicine (Lai et al,2005). Additionally, MSCs have the ability to produce biological elements like skin, cartilage, and

bone, which can be used to treat patients with serious illnesses or injuries (Sigrist et al, 2003). MSCs are also being researched for their ability to deal with autoimmune diseases like Crohn's Disease and Multiple Sclerosis. With so many potential uses, it's no surprise that research on MSCs has emerged as one of the most exciting areas of modern medicine (Jayasinghe et al,2022).

There are some positive results in the treatment of type 1 diabetes by using MSC found in different parts of the body also known as adult cells, including fat, bone marrow, and umbilical cord tissue. This type of cell can be used to treat inflammation by influencing in body’s immune system. MSCs have the ability to control blood glucose levels by producing cells that can secrete insulin (Maahs et al,2010).

3.2 Studying T1D using stem cells - disease models:

Newer Ways of Modelling Disease Pluripotent Stem Cells: In order to develop strategies for beta cell preservation, test potential immune-modulatory therapies, and understand the pathogenesis of T1D, disease models are essential. Immune modulatory therapies have primarily been studied in vivo on NOD mice. While some of these therapies were successful in mice, they have typically not been as effective in treating human diseases. This emphasizes how crucial it is to have disease models that are species-specific and take into account the human disease process. In vitro disease models in humans might offer an additional experimental tool for researching the pathophysiology of human disease and developing potential therapeutic approaches (Kriti et al,2021). With the help of iPSC technology, it is possible to create patient-specific cell lines that can be differentiated into desired tissues and then applied to the study of disease pathology or perhaps even cell replacement therapy. Numerous types of diabetes have given rise to iPSCs, including T2DM diabetes linked to cystic fibrosis neonatal diabetes, various types of monogenic diabetes maturity-onset diabetes of the young, and T1D (Maehr et al,2009). Human models of diabetes brought on by monogenic illnesses like Wolfram syndrome and mutations in the insulin gene that impact beta cell development and function have been successfully created using iPSCs. These studies offered proof-of-concept information for improving the disease phenotype in addition to demonstrating the effectiveness of iPSC technology for modelling disease phenotypes (Egli et al,2014).

Chapter 4 Strategies to treat T1D using stem cells:

4.1 Regeneration of insulin-producing cells:

Induced pluripotent stem cells (iPSCs) undergo genetic modification through cellular mechanisms, transforming into cell products resembling embryonic stem cells (ESCs). ESCs, characterized by high expression of Sox2, Oct4, Klf4, c-Myc, and, are modified through retrovirus transduction in the genetic alteration process. This method facilitates the production of cell groups from adult cells that closely resemble human ESCs in terms of anatomy, cell proliferation rate, antibody, epigenetic modification profile, and telomere length (Takahashi & Yamanaka,2006).

The therapeutic strategy for treating Type 1 Diabetes (T1D) involves in vitro differentiation of stem cells into insulin-producing cells (IPCs). In humans, the primitive gut gives rise to dorsal and ventral protrusions, forming the embryonic pancreas, which later grows and fuses into the final pancreas. The adult pancreas consists of retroperitoneal glands, including the endocrine and exocrine compartments. The exocrine pancreas, comprising acinar cells, produces digestive enzymes, while the endocrine pancreas, forming islets of Langerhans, constitutes only a small portion (1-2%) of the organ and includes four cell types: somatostatin cells, insulin cells PP cells, pancreatic polypeptide cells, and glucagon cells (Sakhneny et al, 2019).

Induced pluripotent stem cells (iPSCs) and ESCs, due to their exceptional renewal ability, are promising candidates for differentiation into -cells. The differentiation process aims to identify stem cells with the ability to differentiate and self-renew, determine proliferative and instructive signals, and identify molecular signals maintaining physiological state and viability.

Various approaches have been employed, including, spontaneous differentiation with Nestin+ progenitor cell selection, and phosphatidylinositol-3-kinase (PI3K) inhibition. The differentiation process involves activating or inhibiting signalling pathways through successive cytokine or signalling modulator treatments in specific doses. Precise control of concentration, time, and duration of growth and differentiation factor treatment is essential to achieve mature IPCs in vitro (Ptasznik et al,1997).

Embryoid bodies (EBs): To mimic the structure of cells of the in vivo embryonic stage, it begins with the creation of embryoid bodies (EBs). The three main germ layers—the mesoderm, endoderm, and ectoderm are represented by the cell types that arise from the spontaneous differentiation of embryonic stem cells (Kossugue et al,2013). Since it is thought to dictate whether or not the final. Cells may transform into cells that produce insulin-producing cells (IPCs), the formation stage of EBs is vital. The chance of spontaneous differentiation into different cell types is influenced by the size of the EB, which affects the acquisition of precursor cells of different kinds (Candiello et al,2018)

Activating different signalling pathways to encourage cellular division and specialization is the focus of subsequent steps in the protocol, as the range of cell types arising from spontaneous differentiation is limited. The development through stages like definitive endoderm, pancreatic progenitors, and ultimately pancreatic endocrine cells and beta cells follow from this. Differential gene expression analysis can be used to monitor these in vitro differentiation stages, offering insights into the molecular mechanisms underlying the development of particular cell lineages (Candiello et al,2018)

Definitive Endoderm (DE): In the beginning, factors that activate the Nodal pathway are used because their signalling gradient causes the segregation of the endoderm (high nodal) and mesoderm (low nodal), serving an important role in endodermal formation. The gastrulation process is triggered by the modulation of the Wnt pathways, BMP, and FGF by nodal-mediated signalling. Activin A can therefore be used to simulate Nodal activity in vitro. Pancreatic endoderm remarkably lacks Sonic hedgehog (SHH) expression, an important signal of intracellular pattern. Activating signalling, a notochord factor, can lower Shh expression by chick endoderm while increasing the expression of insulin and Pdx1, enabling the development of the pancreas (Stafford D & Prince VE,2002).

Nevertheless, some investigations have revealed that activin A may also stimulate neuronal cells. Determining the activin A concentration is thus one of the most crucial factors for effective endoderm differentiation. Additionally, retinoic acid is essential for endoderm development at a stage between endoderm formation and the specification of pancreatic progenitors (Nostro et al,2011). The gut tube is produced by definitive endoderm after it has formed, and it is shaped into anterior and posterior fates by gradients of WNT, FGF, and retinoic acid (RA) signalling. It is stated that WNT signalling plays a direct and multifaceted role in intestinal specification and patterning. Cdx2, a crucial modulator of genes unique to the gut that plays a role in cell division and development, is induced by WNT signalling through direct action on definitive endoderm (Sherwood et al,2011). Studies have shown that WNT can work in conjunction with Activin signalling to promote the development of definitive endoderm, with Wnt3a treatment of cells achieving the best induction of differentiation in definitive endoderm (Kunisada et al,2012)

Pancreatic progenitors: The subsequent stage involves the induction of pancreatic precursor cells, which possess the capability to differentiate into all pancreas lineages, giving rise to functional endocrine and exocrine cell types (Ndlovu et al,2018). Research indicates the critical role of the FGF signalling pathway, originating from surrounding mesenchymal tissue, in shaping specific cell domains, emphasizing the pivotal role of mesenchymal tissues in the growth of pancreatic cell lineages. FGF10, a mesenchymal factor, plays a crucial role in pancreatic epithelium growth, acting as a mitogenic factor that fosters proliferation and enables pancreatic cells to multiply in vitro (Öström et al, 2008).

KGF, also known as FGF7, functions as a fibroblast growth factor promoting ductal cell proliferation. KGF stimulates specific signalling pathways in rat ductal cells, supporting beta-cell regeneration. KGF is frequently incorporated into stepwise differentiation media, contributing to the generation of PDX1+ and later PDX1+/NKX6.1+ pancreatic progenitors. Activation of protein kinase C (PKC) during -cell differentiation protocols has been reported to induce pancreatic precursors, as PKC activation influences growth factor production (Vasavada et al, 2007).

Transitioning to pancreatic endocrine cells: The primary objective of post-pancreatic precursor cell induction is to initiate endocrine cell specification. This involves inhibiting Notch signalling, enabling the expression of ngn3, thus initiating endocrine differentiation in PDX1+/NKX6.1+ progenitors (D'Amour et al,2006). Activation notch in Ngn3+ endocrine precursors hinder differentiation, and as these cells undergo endocrine differentiation, they become unresponsive to Notch. Ngn3+ cells, demonstrating proliferative potential, give rise to cells expressing islet-specific transcription factors like NEUROD, NKX6.1, and PAX6, making them promising candidates for endocrine progenitor cells. This stage involves specifying multipotent progenitors towards differentiated lineages, achieved by initiating and maintaining a specific gene expression profile using different combinations of transcription factors (Gao et

al,2019). Notch pathway inhibition, facilitated by gamma-secretase inhibitors like DAPT, is employed to obtain NGN3+ cells, while retinoic acid is thought to increase endocrine cell numbers and inhibit exocrine cell growth in a dose-dependent manner. Activin A, binding to the ngn3 gene promoter region, enhances ngn3 gene transcription through the Smad4 (TGF-/Smad pathway) (Gao et al,2019).

The effects of thyroid hormones on the growth of various endocrine glands, including the pancreas, are well known. The thyroid receptors TR-1 and TR-1 mRNAs were revealed to be differentially expressed at various stages of the embryonic murine pancreas. The pro-endocrine gene ngn3 had higher mRNA levels, and there were more -cells in cultures that had previously received triiodothyronine (T3) treatment, according to these researchers. Acinar re-programming into ductal-like cells, which will later differentiate into endocrine cells, was discovered to be the mechanism of T3 action. By administering various inhibitors, such as NOGGIN (BMP antagonist), to the., it is possible to prevent the alternative hepatic lineage differentiation pathway. It has been shown that NKX6.1 + progenitors from iPSC lines are effectively developed when EGF and nicotinamide signalling are combined with BMP pathway inhibition. (Sui et al,2013).

Following PDX1 induction, the small molecule ALK4/5/7 inhibitor SB431542 (SB) and Noggin were added to inhibit the TGF-/activin/nodal and BMP pathways. This additive effect led to a six-fold increase in INS expression compared to untreated cultures. The findings showed that after induction of pancreatic progenitors, inhibition of TGF-/activin-/nodal- and BMP signalling does promote differentiation to the endocrine lineage. Late in the differentiation protocol to produce stem cell-derived -cells, ALK5i and T3 were crucial players. Although treatment with Alk5i during the earlier stage of the protocol is required for a robust-like cell phenotype, inhibiting TGF- TGF-signalling during the protocol's final stage significantly reduces the function of these differentiated cells (Velazco et al,2019).

Mature β-cells: The goal of the final stage of pancreas proliferation is cell specification and maturation, producing a mass of cells that have the ability to produce insulin to lower the level of glucose, which is a hallmark of mature pancreatic beta-cells (Rezania et al,2014). Substances and molecules that have been shown to be effective in the adult pancreas are commonly used to achieve this cellular profile. It is well known that betacellulin, a member of the family of epidermal growth factors generated by growing pancreatic cells, increases Pdx1 and insulin production. Nicotinamide supplementation is frequently added to the culture medium during the later phases of in vitro differentiation of cultured human pancreatic cells in order to enhance the expression of somatostatin, glucagon, and insulin (Shing et al,1992).

Because of its antimicrobial properties, nicotinamide has been shown to protect islet cells from damaging stimuli and to encourage the development of pancreatic beta cells. Studies show that exposure to nicotinamide is essential for the differentiation of human pluripotent stem cells (hiPSCs) into pancreas endocrine progenitors (Woodford et al,2020). This is especially true for the inhibition of poly-ADP-ribose polymerases (PARP), which results in strong expression of nkx6.1. In a human ES cell line, pancreatic beta-cell differentiation has been successfully demonstrated with the addition of betacellulin and nicotinamide to modified differentiation protocols, all the while preserving PDX1 expression (Thowfeequ et al, 2007).

An intestinal incretin hormone called glucagon-like peptide-1 (GLP-1) binds to particular G protein-coupled receptors on pancreatic beta-cells to increase insulin secretion through cAMP-dependent pathways. As a result, GLP-1 is essential for the regeneration of -cell mass (Kieffer & Habener,1999). Exogenous GLP-1 stimulates the PI3-kinase-dependent pathway in Ins-1 cells to promote islet cell proliferation. Exendin 4, a long-acting GLP-1 analogue, is more clinically useful because it resists cleavage by dipeptidyl peptidase IV (DPP-IV), and it can also be used to encourage cell proliferation. Studies revealed that thyroid hormone along with

mafA causes cell maturation which is a physiological regulator. taking into account the significance of mafA indicates when the cell is matured (Prasadan et al,2016).

Thyroid hormone may therefore aid in the maturation of insulin-expressing cells derived from immature stem cells in vitro. Additionally, VEGF, which affects islet function and physiology, is thought to be primarily secreted by -cells in the adult pancreas. Therefore, exogenous VEGF supplementation has been linked to a decrease in cell apoptosis and the maintenance of cell mass (Weber et al,2008). Collagen and laminin are other crucial element that must be present during -cell differentiation and maturation. It has been demonstrated that the islet ECM controls islet morphology, insulin secretion, proliferation, and survival. Laminin and type IV collagen have also been found to be advantageous for cell function in vitro. It has been demonstrated that laminins increase the expression of hormones and transcription factors that are let-specific, including Pdx1, insulin1, insulin2, glucagon, and Glut2(Alberto et al,2018). Collagen has been linked in vitro studies to giving transplanted grafts the desired mechanical properties, enhancing scaffold performance, and, when combined with other ECM proteins like laminin, enhancing glucose-stimulated insulin secretion in pancreatic islets. As a result, providing islet matrix proteins to the in vitro differentiation process is a crucial factor in determining how matrix-bound signals are presented. This ensures that the microenvironment is more similar to that found in the native in vivo environment, which supports the maintenance of cellular viability (Stendahl et al,2009).

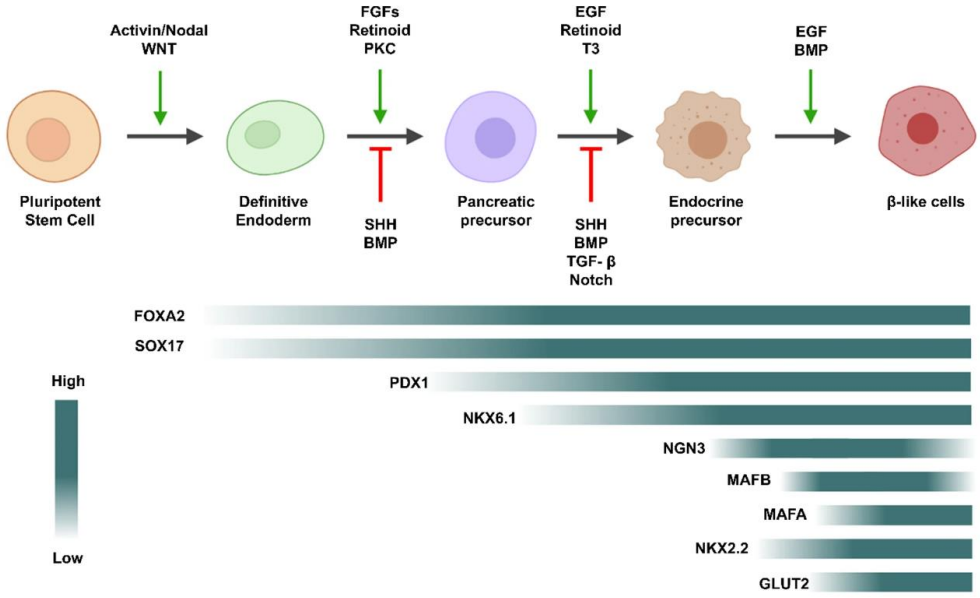

Figure1: Stem cell differentiation into insulin-producing cells (IPCs) extracted from (Frumento et al.,2017)

Diagram illustrating the signalling pathways that regulate every stage of β-cell differentiation as well as the expression levels of the primary transcription factor and useful proteins during β-cell maturation. The expression of MAFB and NGN3 is transient, whereas the expression of the other genes persists until maturity. BMP stands for bone morphogenetic protein; EGF, FGF, and PKC for protein kinase C; SHH, or sonic hedgehog; T3, or triiodothyronine; and TGF-β, or developing growth factor beta (Keymeulen,2017).

4.2 Immunomodulation-method:

The immunomodulation method is used to change our immune system so that it can increase or decrease our immune response in certain biological conditions. By using immunomodulation various kinds of diseases have been treated in recent years. (Cynthia et al,2019).

Insulin is produced from pancreatic β cells which are destroyed by the body's immune system resulting in a disruption of blood sugar balance and the development of type 1 diabetes (T1D) (Patterson et al,2009).

Islets Transplantation stem cells and immunotherapy: Immunosuppressive medications are necessary for organ and tissue transplants in order to avoid rejection of the donor organ by the person's immune system. (Monaco,2004). Compared to transplanting other organs, immunomodulation in the pancreas and islet transplantation is difficult. First of all, since autoimmune diseases are already present in T1D patients, immunomodulation is necessary to stop the growth of immune responses to donor alloantigen's and the return of autoimmune diseases. In fact, even with the use of proven immunomodulation therapies, a considerable portion of people with pancreas transplants experience autoimmune diseases to recur (Longoni et al,2010). Secondly, a number of immunosuppressants have the potential to harm the islets and induce resistance to insulin (Furth,2009). which makes them unsuitable for application during the islet or pancreas transplantation process (Li et al,2009). Third, immunosuppressants like rapamycin may result in T cell loss, which sets off a homeostatic response that genetically improves T memory cells in response to islet antibodies, thereby exacerbating autoimmune diseases (Monti et,2008). Fourth, mycophenolate fetidity could inhibit development, making it unsuitable for children even though it fails to result in T cell loss followed by memory cell growth (Balistreri et al,1995).

Because there are some limitations of immunosuppressive drugs led to find other techniques can change the immune response during islet transplantation (Koh et al,2010). It is found that MSC can manage to treat various diseases in patients who are not responsive to traditional immunosuppressive treatments (Blanc et al,2008). This can ensure that immunomodulation could be a more effective treatment than immunosuppression for illnesses caused by immune system malfunctions. Along with a low chance of side effects Additionally, MSC immunomodulation doesn't reduce the response of T cells to some specific virus (Dahlke et al,2008) preventing the higher risk of infectious complications that are frequently experienced by patients receiving standard immunosuppressive drugs (Abdi et al,2008).MSC can transplant islets under the kidney capsule extended period of time without the need for immunosuppressive drugs. Usually, the suitable location for mice is the portal vein (Mellgren et al,1986) But on the other hand human islet transplantation is primarily carried out through the portal vein (Merani et al T,2008). In rats receiving intraportal islet transplantation, there is a first decrease in glycaemic levels that is followed by a gradual recovery to hyperglycemia. Participants typically reach their pretransplant substantial glycaemic levels in 4 weeks, whether they are receiving MSC

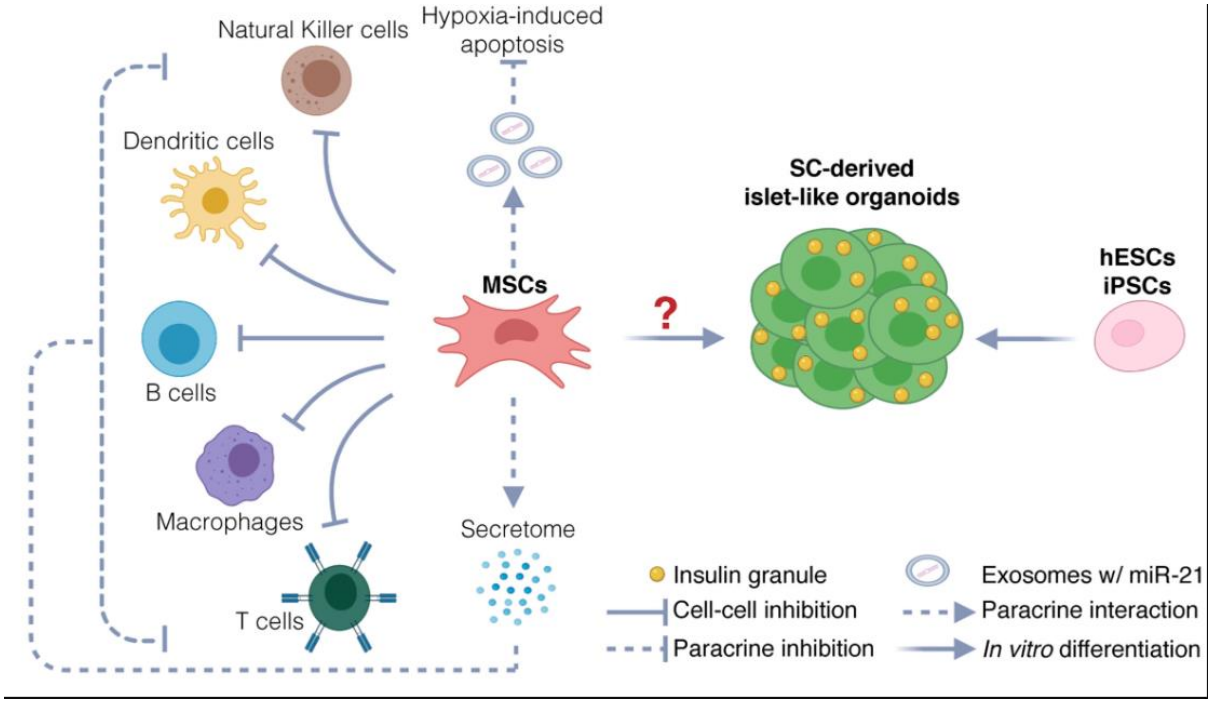

Figure 2: Possible therapeutic approaches. Possible methods encompass safeguarding native islets and reinstating the mass of β cells. Endogenous β cells could be safeguarded by MSCs through immunomodulation and prevention of hypoxia-induced apoptosis extracted from (De Klerk et al,2021).

Immunomodulation is mediated by a pair of processes: paracrine activity, which involves the secretion of growth factors, cytokines, and chemokines (secretome), and direct cell-cell interaction with immune cells. The release of exosomes containing miR21, which targets messenger RNAs involved in the hypoxia-mediated ER stress prior to apoptosis, may be used to inhibit hypoxia-induced apoptosis. It is unclear whether MSCs can be used therapeutically to create islet-like organoids and β cells derived from stem cells. Instead, to restore β cell mass, functional islet-like organoids are generated using hESCs and iPSCs (Song et al,2020).

treatment or immunosuppressive drugs (Longoni et al,2010). Secondly, MSCs that have been separated from various organs might have unique characteristics. The majority of patient work

has used MSCs taken from the bone marrow. Recent data suggests that MSCs separated from the umbilical cord and blood may also protect transplanted islets (Anzalone et al,2011). But when syngeneic islets were given to diabetic rats that had suffered -cell destruction from one large dose of streptozotocin, an autoimmune response to the transplanted islets was seen, leading to a gradual deterioration of grafted islets and control of glucose levels (Phinney et al,1999). The activation of T cells by cell-released antigenic substances may result from islet damage caused by streptozotocin, as illustrated in Figure 2. Later, transferred islets will be attacked and destroyed by activated T cells (Longoni et al,2010). Nevertheless, in transplanted rats, both MSC therapy and drug-induced immunosuppression cannot control glucose levels, indicating that other variables that are not connected to immunity might impact islet sustainability (Longoni et al,2010). The transplantation site might have an impact on islet longevity. Reduced oxygen levels in the liver and kidney capsules compared to the natural pancreatic surroundings could have a negative impact on islet function (Carlsson et al,2000). It is important that in response to glucose, the cells produce action potentials that raise the amount of calcium that enters via voltage-gated channels. To prevent the subsequent start of cell death by calcium buildup, cells have to discharge calcium, which necessitates the production of energy through oxidative digestion. (Carlsson et al ,2001). As a result, it is anticipated that the lack of oxygen in the liver will affect cell function by impeding the production of ATP from glucose, which will open the ATP-sensitive Kir6.2 potassium channels and lessen glucose sensitivity. In the end, the longevity of the cell may be affected by reduced ATP synthesis. Ischemic preconditioning of islets has reportedly been shown to increase their viability following the transplantation process (Echeverri et al Ij,2008). ischemia injury may cause liver integration hence it must be avoided after intraportal transplantation (O'Gormanet et al,2010). Furthermore, the process of islet isolation exacerbates the harm that results from the low oxygen level of the liver by damaging the vascular network that is essential to islet

function. There are currently significant efforts underway to enhance the islet isolation process through the use of a less invasive enzyme therapy, which could more effectively maintain cell interaction and avoid islet blood vessel damage from enzymatic therapy (Lukinius et al,1995).

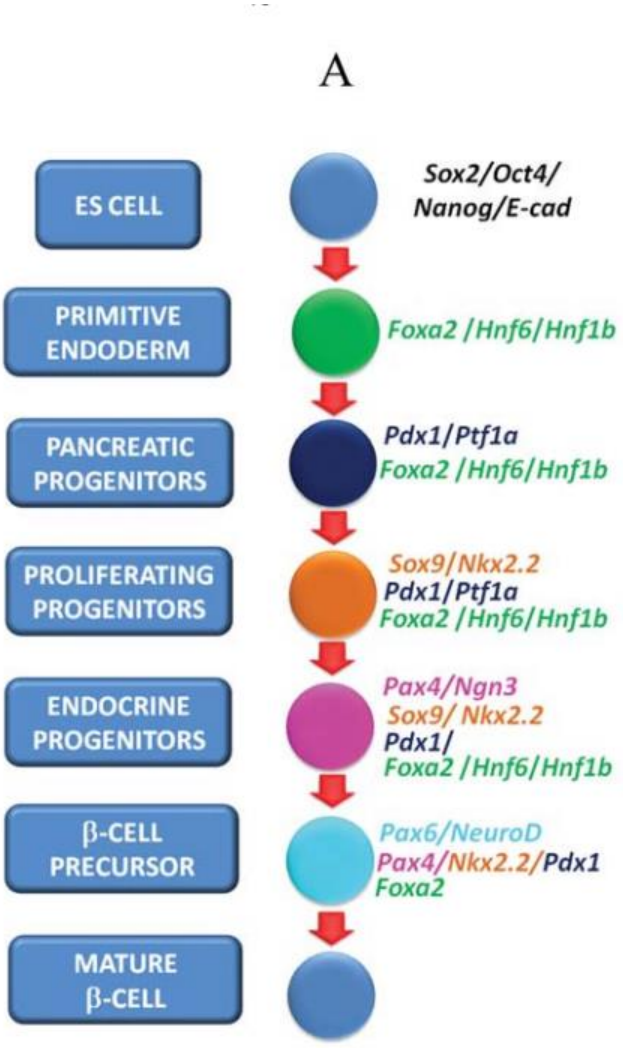

Figure3: Stem Cell-Based Immunomodulation in Type 1 Diabetes adopted from (Hogan et al,2009)

In vivo, ES cells produce the primitive endoderm, which expresses Foxa2, Hnf6, and Hfn1b in addition to other genes. In order to proceed, ES cells must be able to overcome the sonic hedgehog (Shh) signal produced by the nearby mesoderm. The pancreatic fate is then

*determined by the pancreatic duodenal homeobox Pdx1, which is expressed by pancreatic progenitors in the foregut. Additionally, Ptf1a adds to the pancreatic specification (Kroon E et al Kadoya K,2008). Ptf1a expression is downregulated by endocrine progenitors, whereas Ngn3 expression is upregulated. Prior to ultimate maturation, -cell precursors express Pax6 and Neuroid. For an in-depth analysis of the developmental stages associated with all origin*s (Oliver J et al,2008)

4.3 Replacing pancreatic ß cells:

Some of the recent researchers have found that the changing nature of beta-cell mass in vivo. Variations in metabolic demand impact the mass of beta cells in humans (M. Taneja et al,2000). This mass is initially elevated in those who are obese or have insulin resistance. In contrast, individuals with type-1 diabetes who are weight-matched exhibit a reduction in beta-cell mass (A.E. Butler et al,2003).

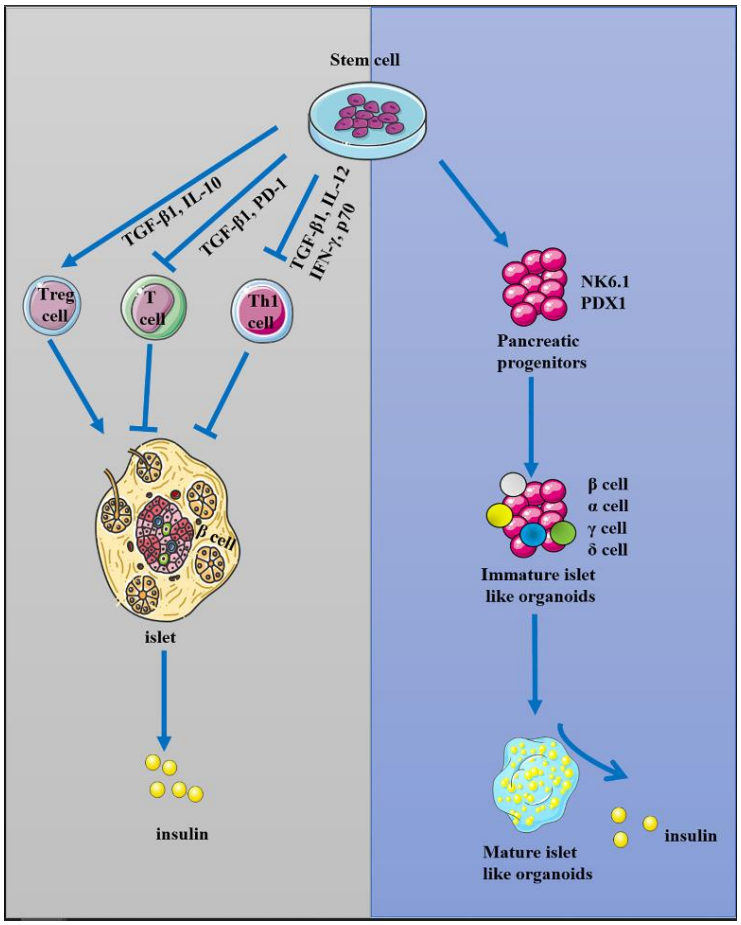

Figure 4: The potential role of stem cells in T1DM treatment. Stem cells were utilized for the preservation and regeneration of β-cells as well as for the restoration of immunotolerance by preventing T and Th1 cells and triggering T regulatory cells (Treg) adopted from (Wan et al,2022).

Stem cells regenerate immunotolerance by blocking T cell and Th1 cell immune responses through TGF-β and inflammatory pathways, and they can increase the mass of islets by differentiating into organoids that resemble β cells (Figure 4). Given that type 1 diabetes is characterized as an autoimmune disease that triggers the immune system to target and eliminate pancreatic β-cells, stem cell therapy for T1DM patients should take into account the immunomodulatory characteristics of the cells as well as their potential to differentiate into insulin-producing cells(Wan et al,2022).

The two main types of stem cells found in bone marrow are mesenchymal stem cells (MSC) and hematopoietic stem cells (HSC). As there has been a wide number of therapeutic applications of these 2 types of stem cells this is why these two are used widely in the treatment of various diseases (Pittenger et al,1999). Because they have the ability of their self-origin and easy ex vivo development, these two types of stem cells offer an effective means to avoid using antirejection medicinal products. Numerous investigations revealed that stem cells collected from bone marrow might develop into cells that produce insulin-producing β-cells (Chen et al,2008). The first natural stem cell clinical trial to treat type 1 diabetes was carried out by Voltarelli's group (Voltarelli et al,2007). After using high-dose immunosuppression, they transferred autologous nonmyeloablative HSCs into newly identified T1D patients. Increased the level of C-peptide after an average follow-up of 29.8 months after transplantation, and most patients attained insulin independence with satisfactory glucose control. Preserving the remaining mass of β-cells and promoting the body's natural processes for β-cell regeneration were the primary goals. Since MSCs and HSCs most likely lack the ability to differentiate in vivo into a sufficient number of β-cells, HSCs were employed to restore β-cell acceptance by immunosuppressive means and T-cell regeneration. It's still unclear exactly what mechanism of action this treatment uses. (Voltarelli et al,2008). The T1D patients have demonstrated transient elevation of C-peptide and partial independence from insulin along with auto

transplantation of bone marrow-derived MSCs without any PR immunosuppression. It is anticipated that the integration of distinguished β-cells and MSCs will enhance the therapeutic results. MSCs extracted from bone marrow and adipose and umbilical cord blood have features in common with each other (Haller et al,2008)

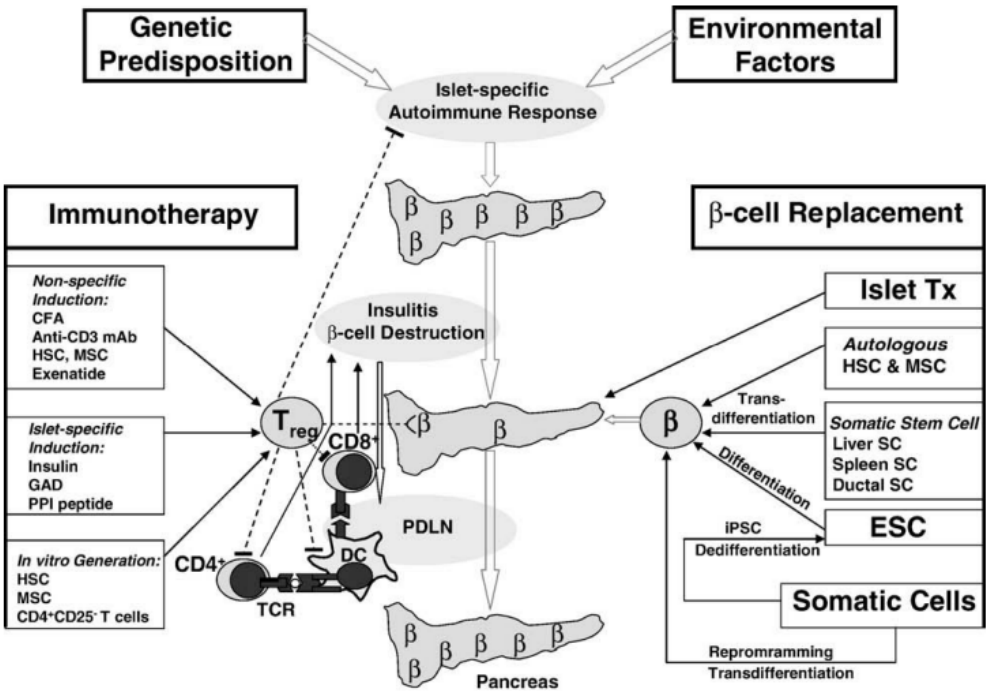

Figure 5: immunotherapy and ß cell replacement on T1D adopted from (D-S. Li,2009).

The direct cause of insulitis is an islet-specific autoimmune response, which is triggered by a variety of environmental factors in genetically predisposed individuals. Dendritic cells (DC) in the insulitis islets are activated by propreinsulin (PPI) peptide and ß cell peptide via MHC class II and HLA-A2, respectively. Activated DCs then move to the pancreatic draining lymph node (PDLN), where they use T cell receptors (TCRs) to present PPI peptide to CD8+T cells and ß cell peptide to CD4+ T cells. The islets are invaded by the activated CD4+ and CD8+ T cells, which then kill the ß cells that produce insulin (Sakaguchi et al Nomura T,2008). Dysregulation of

glucose metabolism mediated by ß-cell insufficiency is the ultimate result. The cause of T1D is addressed by immune intervention, which blocks the autoimmune attack on the islets by upregulating regulatory T cells (Treg) (shown by the dashed lines) (Tian et al,2009).

4.4 Clinical Trials result where stem cell is used to treat Type1 Diabetes:

Table 1 displays the attributes of the ten studies that were included. Since the research investigations took place in a wide range of nations. They were released between 2007 and 2017 and reflected a population from around the world. Patients who are suffering from T1DM (120 patients, six studies, average age 17.7 years) or T2DM (65 patients, four studies, average age 51.4 years) were evaluated for stem cell therapy (Bhansali et al,2009). Remarkably, only five trials had a treatment group that got stem cell transplantation and a control group that was given insulin or a placebo. There was a 6 to 29.8-month monitor period of time. (Bhansali et al,2017).

Regimen	Author And year	Country	Sample type	Sample size (cell therapy/ control)	Mean age (cell therapy /control)	Mean dose of injected cells	Mode of injection
BM-HSC	Ye 2017 (Ye et al,2017)	CN	T1DM	8 /10	18.86 /20.18	NA	IV
BM-HSC	Couri 2009 (Couri et al, 2009)	BR	T1DM	23	18.4	10.52 × l06/kg	IV

BM-HSC	Voltarelli 2007 (Voltarelli et al, 2007	BR	T1DM	15	19.2	11 × l06/kg	IV
BM-MNC	Bhansali2017(Bhansali et al, 2017))	IND	T2DM	10/10	44.5 /53	1 ×109/kg	Superior pancreaticoduodenal artery
BM-MNC	Bhansali 2009 (Bhansali et al, 2009)	IND	T2DM	10	57.5	3.5 × 108/kg	Superior pancreaticoduodenal artery
MSC	Liu 2014 (Liu et al, 2014)	CN	T2DM	22	52.9	1 × 106/kg	IV on Day 5+ splenic artery on Day 10
MSC	Hu 2013 (Hu et al, 2013)	CN	T1DM	15 /14	17.6/18.2	2.6 × 107/kg	IV
MSC	Bhansali 2017 (Bhansali et al, 2017)	IND	T2DM	10 /10	50.3 /53.5	1 × 106/kg	Superior pancreaticoduodenal artery

MSC	Carlsson 2014 (Carlsson et al, 2014)	SE	T1DM	9 /9	24 /27	2.75 × l06/kg	IV
UCB	Giannopoulou 2013 (Giannopoulou et al, 2013)	DE	T1DM	7/ 10	3.02/ 6.6	1.27 × 106/kg	IV
UCB	Tong 2013 (Tong et al, 2013)	CN	T2DM	3	41	2.88 × 106/kg	Intrapancreatic

Table 1: The comprehensive review of clinical trials for Stem cell-based diabetes therapy. UCB: umbilical cord blood; T1DM: Type 1 diabetes mellitus T2DM: type 2 diabetes mellitus; BM-MNCs: bone marrow mononuclear cells; IV: intravenous; m: months; MSCs: mesenchymal stem cells; BM-HSCs: bone marrow hematopoietic stem cells; NA: not available. Name of the countries given according to ISO country codes (Faten et al,2021)

Chapter 5 Challenges of using stem cells in T1D treatment:

Even though using stem cells TD1 diabetes can be treated there are some also have challenges that may arise:

a. The possibility of rejection of implantation is a significant barrier to the success of stem cell therapy. Nevertheless, one effective way to avoid the harmful immune response associated with T1D is to modify the makeup of immune cells and build psychological obstacles to shield the embedded cells from harm (Lena et al,2021).

b. Regrettably, stem cell therapy has a shortage of available pancreatic tissue, the challenges associated with isolating and maintaining beta cells' effectiveness, the long-term viability of the cells that are transplanted in vivo, and the ensuing high costs limit this strategy (Siwakoti et al,2021).

c. Uncontrollable T cell-induced can trigger the host's immune system and result in long-term issues like cancer and infections caused by viruses (Putman et al, 2012).

Chapter 6 Future Direction:

6.1 Exogenous Insulin Administration:

Exosomes derived from MSCs deliver biological molecules, like proteins and RNAs, into target cells or tissues in order to affect how they will develop (Teotia et al,2017). Exosomes are therefore referred to as the capable nanomedicine for the therapy of various diseases (Yin et al,2018). Intracellular multivesicular structures combine with the cell membrane when exosomes are released (Gomzikova et al,2019) biological compounds found in the MSC cytoplasm influence the intrinsic contents of exosomes. Thus, two highly prospective methods to boost the levels of therapeutic molecules in exosomes—preconditioning or genetic modification of MSCs—will allow for the production of superior exosomes with enhanced potential for therapy. In fact, in the T1DM rat model, exosomes from DFO-pretreated human BMMSCs significantly speed up skin wound healing. This improved PR angiogenesis results from exosomes' elevated microRNA (miR)-126 level. (Ding et al Xu J,2019). In T1DM rats, exosomes from human BMMSCs injected with atorvastatin promote PR angiogenesis controlled by the AKT/eNOS pathway, leading to skin wound repair (Yu M et al,2020). The enhanced therapeutic outcomes of preconditioned MSC-derived exosomes in models of diabetes imply that exosomes produced by MSCs that have been previously treated with antioxidant or hypoxia ought to have greater anti-diabetic effectiveness, which looks very promising for the treatment of diabetes in future (Wang B et al,2016).

Chapter 7 Conclusion:

Diabetes mellitus is a widespread health concern globally, with at least one family member in almost every household affected by this condition. While significant progress has been made in the medical field for managing diabetes, the available treatment options remain somewhat limited. However, the integration of stem cell therapy in the treatment of type 1 diabetes has emerged as a promising avenue, instilling newfound hope for individuals grappling with this chronic illness.

Despite being in the nascent stages of development, the utilization of stem cells in diabetes treatment is seen as a groundbreaking advancement. Experts anticipate that as research progresses, stem cell therapy will surpass traditional approaches and become the primary choice for managing type 1 diabetes. This innovative approach holds the potential to revolutionize the landscape of diabetes treatment, offering a more effective and sustainable solution for patients in the future.

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