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Stem Cells as Regenerative Medicines: In Treatment of Diabetes

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ABSTRACT:

In recent years, stem cell therapy has become a very promising and well-developed scientific research topic. High hopes have been raised as a result of medical treatment advancement. Stem cell origin is followed by controlled stem cell culture and derivation in the lab. This cutting-edge therapy represents a turning point in modern medicine since it offers a wide range of possibilities and gives hope to people with fatal conditions. Patients who have diabetes mellitus stand to benefit greatly from stem cell treatment. Research on the ability of human embryonic stem cells to differentiate into islet cells has revealed the developmental phases and transcription factors involved in this process. The clinical uses of human embryonic stem cells are nevertheless constrained by ethical issues and the potential for teratoma development. As a result, a lot of study has been drawn to alternative stem cell therapies such induced pluripotent stem cells, umbilical cord stem cells, and mesenchymal stem cells made from bone marrow. Future advancements in stem cell therapy may make this a workable diabetes cure.

Keywords: Embryonic stem cell, induced pluripotent stem cell, mesenchymal stem cell, diabetes.

INTRODUCTION:

STEM CELLS

A cell with the capacity to differentiate and self-renew potential A group of undifferentiated cells known as stem cells have the capacity to repeatedly divide (self-renewal), typically develop from a single cell (clonal), and differentiate into various cell and tissue types (potent). Stem cells come from a variety of sources with varied potencies. Pluripotent cells are developed from the inner cell mass of the embryo by embryonic stem cells, and induced pluripotent cells are created by reprogramming somatic cells. From all three germ layers,

pluripotent cells can develop into tissue (endoderm, mesoderm, and ectoderm). The mesenchymal stem cells that generate adipose tissue, bone, and cartilage are examples of multipotent stem cells that can develop into tissue from a single germ layer [1].

Because they are unspecialized cells and can divide asymmetrically, stem cells have distinctive qualities that make them stand out. Stem cells come in a variety of varieties based on their potency and/or uniqueness. A new type of treatment for many ailments is cell therapy. The only logical treatment approach seems to be the use of stem cells to restore failing tissues and organs, which has attracted enormous interest [2].

The potential of stem cell therapy is to overcome the drawbacks of existing therapeutic approaches. To fully utilise stem cells' potential, it could be required to modify their qualities. The ability to differentiate into multiple cell types and to divide in a process known as self-renewal enable stem cells [3].

REGENERATIVE MEDICINE

Regenerative medicine uses in vitro design and in vivo application to replace or treat damaged or diseased tissue or organs. It might be said that this area of medicine is relatively young. It is suggested to incorporate platelet-rich plasma (PRP). showed that PRP could cause the jaw's bone to regenerate. A portion of bone marrow-derived stem cells were found to be able to repair a number of mesenchymal tissues or organs throughout the same time period [4].

In contrast to conventional treatment, regenerative medicine aims to restore damaged tissue or organs. Tissue engineering, cellular therapies, medical technologies, and artificial organs are the methods employed to achieve these results in the present therapeutic strategy, which mostly focuses on treating the symptoms. Combinations of these methods can replace a permanently damaged organ or accelerate our natural healing process where it is most needed. When injured or infected by disease, our bodies have the innate ability to heal themselves. Regenerative medicine is a relatively new field that brings together experts in biology, chemistry, computer science, engineering, genetics, medicine, robotics, and other fields to find solutions to some of the most difficult medical problems faced by humankind [4].

This review describes the most current developments in ESCS, TSPSCS, MSCS, UCSCS, BMSCS, and iPSCS tissue engineering and transplantation methods used in regenerative medicine. This review also covers the use of stem cells for regeneration in animal conservation [5].

CLASSIFICATION OF STEM CELLS:

STEM CELL CLASSIFICATION BASED ON DIFFERENTIATION POTENTIAL

There are five primary categories of stem cells based on how differentiated they are.

1. **Totipotent Cells**

   The least distinct cells, known as totipotent or omnipotent cells, are present in the early stages of development. A fertilised egg and the cells from the first two divisions are totipotent cells because they can differentiate into both extraembryonic tissues like the placenta and embryonic tissues [6].

2. **Pluripotent cells**

   A stem cell is referred to as pluripotent if it can differentiate into nearly every type of cell, although not always. Embryonic stem cells and cells produced from the germ layers of the endoderm, mesoderm, and ectoderm at the beginning of embryonic development [6].

3. **Multipotent cells**

   Most tissues contain multipotent stem cells, which develop into different types of cells from a single germ layer. The most well-known multipotent cell is the mesenchymal stem cell (MSC). Bone marrow, adipose tissue, bone, Wharton's jelly, umbilical cord blood, and peripheral blood are just a few of the tissues from which they can be generated [7].

4. **Oligopotent cells**

   Oligopotent stem cells have the ability to self-renew and produce two or more lineages within a specific tissue. Hematopoietic stem cells, which can develop into both myeloid and lymphoid lineages, are a classic example of Oligopotent stem cells. Studies imply that the alveolar and bronchiolar epithelium in the lung may develop from bronchoalveolar duct junction cells [7].

5. **Unipotent cells**

   Unipotent stem cells have the ability to self-renew, differentiate into just one particular cell type, and create a single lineage, such as muscle stem cells, which exclusively produce adult muscle cells. Type I pneumocytes are produced in the lung by type II pneumocytes of the alveoli [7].

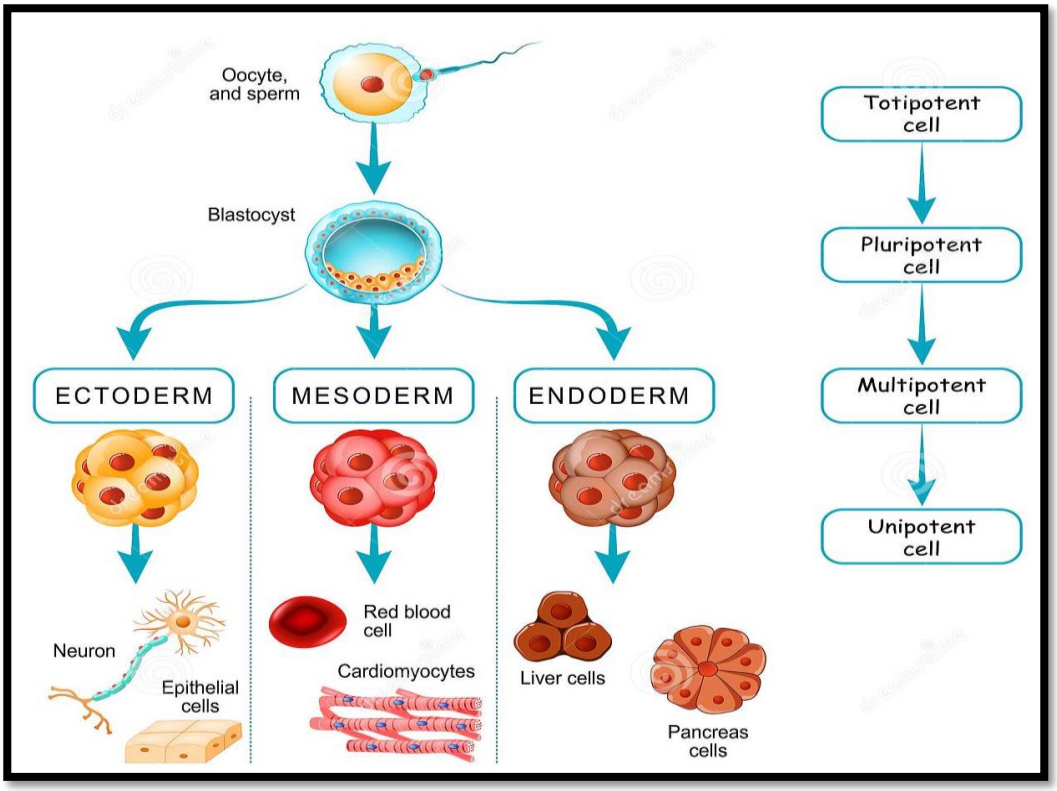


Figure no.1 Cell potency

STEM CELL CLASSIFICATION BASED ON ORIGIN

1. Adult Stem Cells

Adult tissue is the source of adult stem cells. MSCs and stem cells produced from foetal tissue, such as human amnion epithelial cells, are examples. These cells have been demonstrated to be anti-inflammatory and to improve animal damage repair. Although these cells have been developed into tissue from several germ cell layers in vitro, they have a limited capacity for differentiation [8].

2. Embryonic Stem Cells

As the name implies, embryonic stem cells are mostly derived from embryos that are in a developmental stage prior to the time when implantation would normally take place in the uterus. Blastocysts are often the source of embryonic stem cells. As a result of years of experimentation, numerous scientists have developed certain fundamental guidelines or "recipes" for the guided differentiation of embryonic stem cells to desired specialised cells [9].

3. Tissue-specific Stem cells.

Tissue-resident stem cells, which produce tissue-specific, terminally differentiated cells, are essential for several tissues and organs in the adult to regenerate and heal after injury. According to studies, these cells develop during ontogenesis and stay dormant until local cues trigger their proliferative, differentiating, or migrating processes. A "stem cell niche" is the home of tissue-resident stem cells. The microenvironment known as the stem cell niche regulates the self-renewal and differentiation of these cells. The niche is

crucial for stem cell homeostasis and tissue repair because there is mounting evidence that extrinsic signals from the microenvironment have a significant impact on stem cell function [10].

4. Induced pluripotent Stem cells

The most recent form of stem cell to be identified is induced pluripotent stem cells. Adult somatic cells that have undergone genetic reprogramming to achieve a "ESC-like state" are used to create iPSC's. These cells could develop into multiple cell types and shared characteristics with human ESCs, including shape, proliferation, surface antigens, gene expression, the epigenetic state of pluripotent cell-specific genes, and telomerase activity [10].

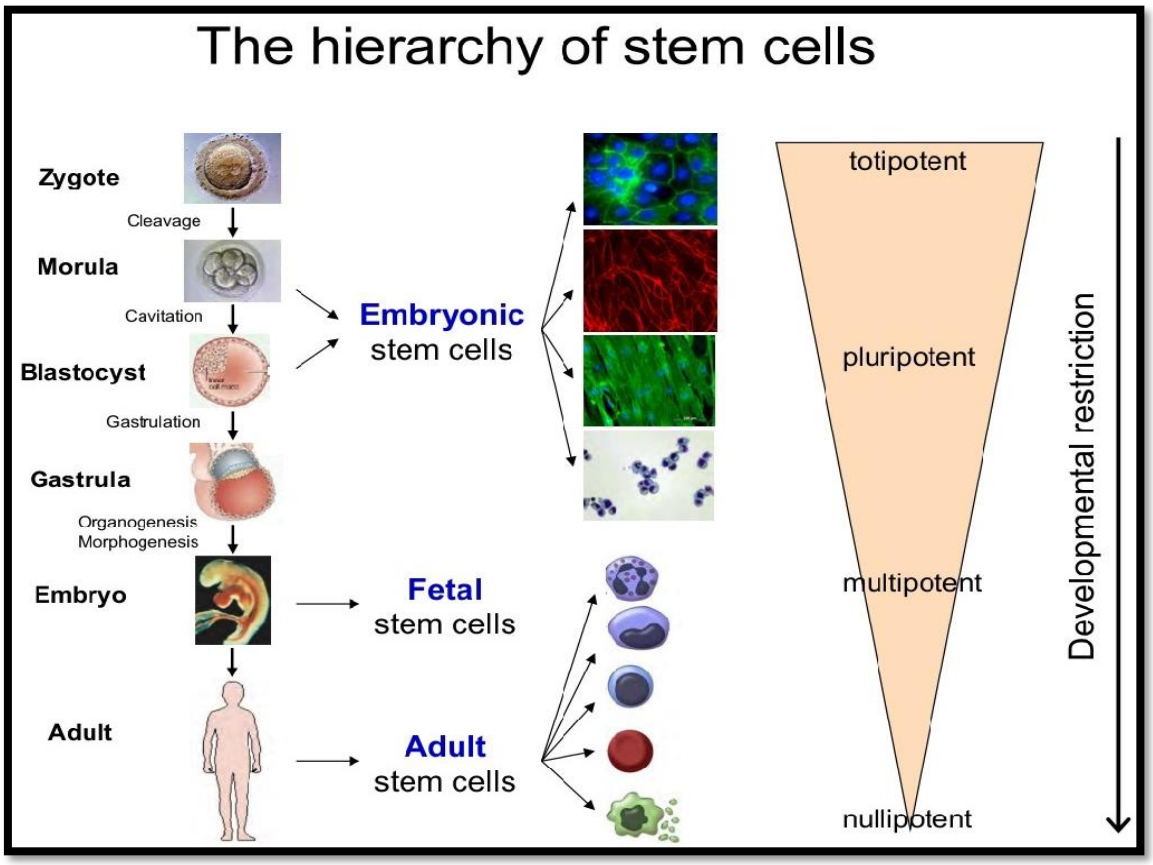


Figure no.2 The Hierarchy of Stem cells.

STEM CELLS AS REGENERATIVE MEDICINES: IN TREATMENT OF DIABETES

Diabetes is a serious health issue in underdeveloped nations. Every year, there is a significant increase in the disease's occurrence. The purpose of the present drugs is to regulate hyperglycemia levels and diabetes complications. Stem cells have the capacity to differentiate into any type of specialized cell and aid in the treatment of illness, particularly when they produce insulin-producing beta cells [11].

THERE ARE TWO TYPES OF DIABETES MELLITUSTYPE 1 AND TYPE 2

Type 1 diabetes is an autoimmune disease characterized by pancreatic β cells destruction and absolute deficiency of insulin: It accounts for approximately 5% to 10% of all cases, and is the most common subtype diagnosed in patients younger than 20 years of age.

Type 2 diabetes is caused by a combination of peripheral resistance to insulin action and an inadequate secretory response by the pancreatic β cells ("relatives insulin deficiency"): Approximately 90% to 95% of diabetic patients have type 2 diabetes, and the vast Majority of such individuals are overweight. Although classically considered adult onset the prevalence of type 2 diabetes in children and adolescent has been increasing at an alarming pace due to the increasing rates of obesity in these age groups. One piece of encouraging news is that the incidence of obesity in the U.S. in children of 2004 to 2010, a tipping of the scales that may signal a reversal of a troubling trend [12].

The malfunctioning of the pancreatic beta-cells can be linked to the pathophysiology of DM, whether type 1 or type 2. There are licensed treatments that improve beta-cell performance, but none that promote the regeneration of a lost or damaged beta cell. Studies have demonstrated that some chemicals, such as GABA and hormone, can re-programme beta-cells. These findings also highlight numerous unknowns that require investigation. Embryos, the placenta, and bone marrow are just a few of the biological sources from which stem cells for the treatment of DM are derived Another intriguing area of study is progenitor cells. These cells, like stem cells, can transform into a variety of adult human cell types, but unlike stem cells, they are not able to divide endlessly [13].

Pathophysiology of Diabetes Mellitus

A chronic, diverse metabolic illness with a complicated pathophysiology is diabetes mellitus. It is characterized by hyperglycemia, or increased blood sugar levels, which are caused by anomalies in insulin secretion, action, or both. Metabolic dysfunctions related to carbohydrates, fats, and proteins are brought on by hyperglycemia, which can present itself in many different ways. The majority of diabetes-related morbidity and mortality are caused by numerous microvascular and macrovascular diabetic complications that are frequently brought on by long-term hyperglycemia. The main biomarker for the diagnosis of diabetes is also hyperglycemia [14].

Diagnosis and Treatment

Insulin Therapy: Type 1 diabetes patients require many insulin injections each day to maintain acceptable insulin levels. Type 2 diabetes is frequently treated with insulin.

Insulin is classified into four types:

1. Rapid-acting
2. Short-acting
3. Intermediate-acting
4. Long-acting

Treatment Management of type 2 diabetes includes

1. Healthy eating
2. Regular exercise
3. Weight loss
4. Possibly, diabetes medication or insulin therapy
5. Blood sugar monitoring [15].

STEM CELL THERAPY FOR DIABETES:

The replacement of insulin-producing cells by the use of embryonic stem cells has been suggested as a potential cure for diabetes. has some initial success in differentiating cells from human embryonic stem cells (hESCs). Although these cells coexpressed glucagon and insulin and did not boost insulin production in response to elevated ambient glucose levels, they were not functionally mature. It's interesting to note that the implantation of these immature cells into mice encouraged the development of mature cells and stopped the hyperglycemia caused by Streptozotocin (STZ) [16].

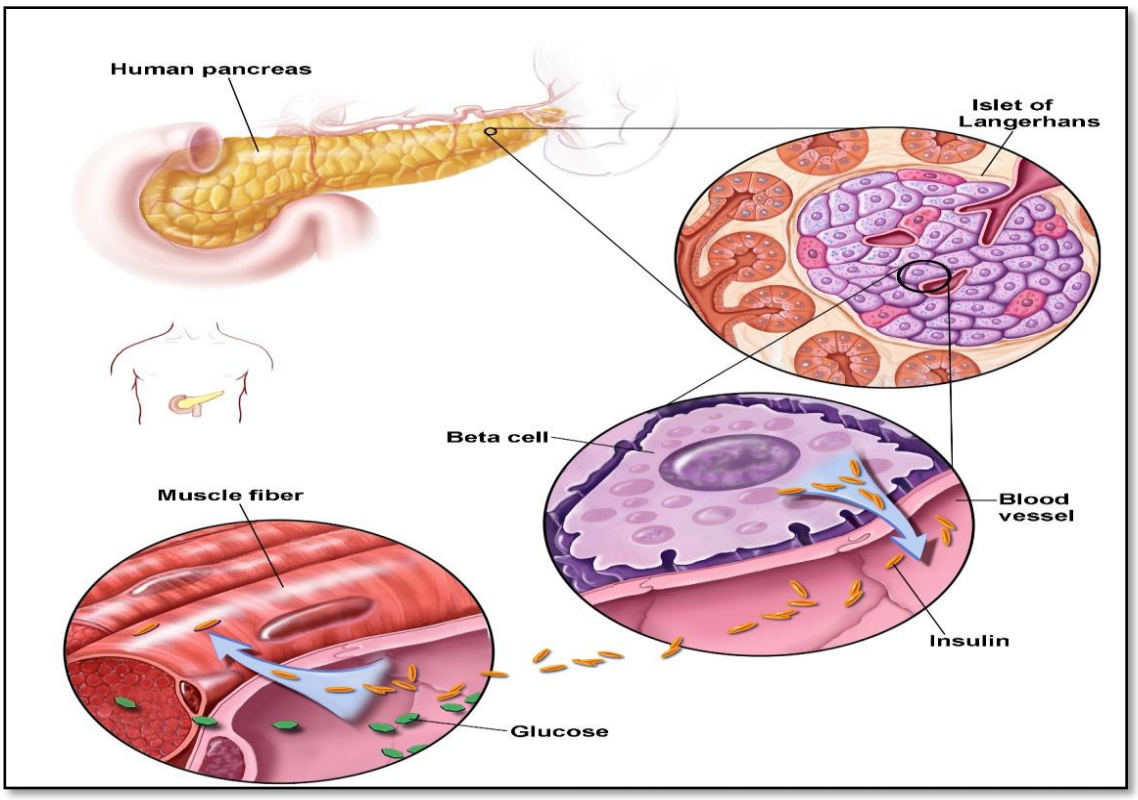


Figure no.4 How would stem cells help in diabetes?

Stem Cell Therapy for Type 1 Diabetes mellitus (DM)

Undifferentiated cells with the capacity for self-renewal, stem cells can develop into almost any type of tissue or organ. Based on where they came from, stem cells can be divided into four broad groups. Fetal stem cells, embryonic stem cells, adult stem cells, and induced pluripotent stem cells are the four types of stem cells (iPSCs). ASCs are unipotent or oligopotent, whereas iPSCs and ESCs are pluripotent stem cells (PSCs). Human embryonic stem cells (ESCs) and human induced pluripotent stem cells (iPSCs) are two types of PSCs that provide a reliable source of human cells at an extremely early developmental stage with the capacity to

generate any cell type in the adult body. iPSCs, human cord blood-derived multipotent stem cells (CB-MSCs), hematopoietic stem cells (HSCs), and MSCs were used to preserve -cells through islet protection and regeneration [17].

Another important role of stem cells is their capacity to restore peripheral tolerance to -cells through remodeling of the immune response as well as through inhibition of autoreactive T-cell function. In general, stem cells have the capacity to differentiate into organoids that resemble cells and can increase the mass of islets. They can also restore immunotolerance by blocking the immunological response of T cells and Th1 cells through TGF- and inflammatory pathways. When using stem cell therapy for T1DM treatment, it is important to take into account the immune modulatory properties of stem cells and their potential ability to differentiate into insulin-producing cells because T1DM is characterized as an autoimmune disease by activating immune cells to attack and destroy pancreatic beta-cells [18].

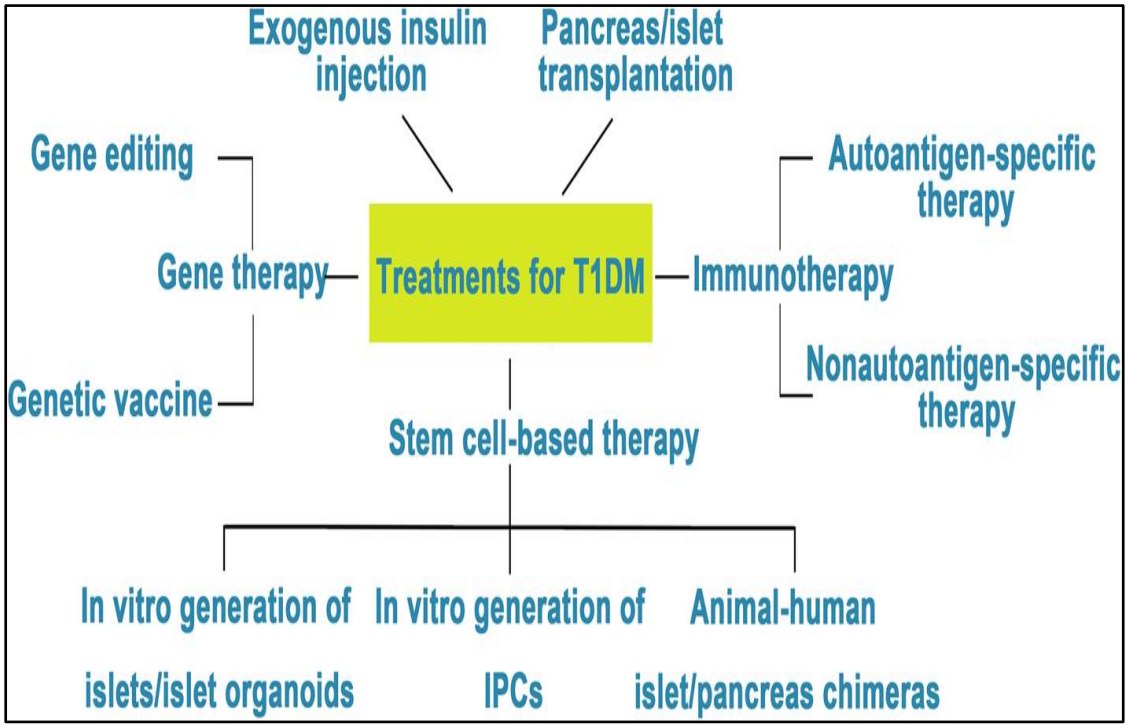


Figure no.5 Stem cell therapy for type 1 diabetes mellitus

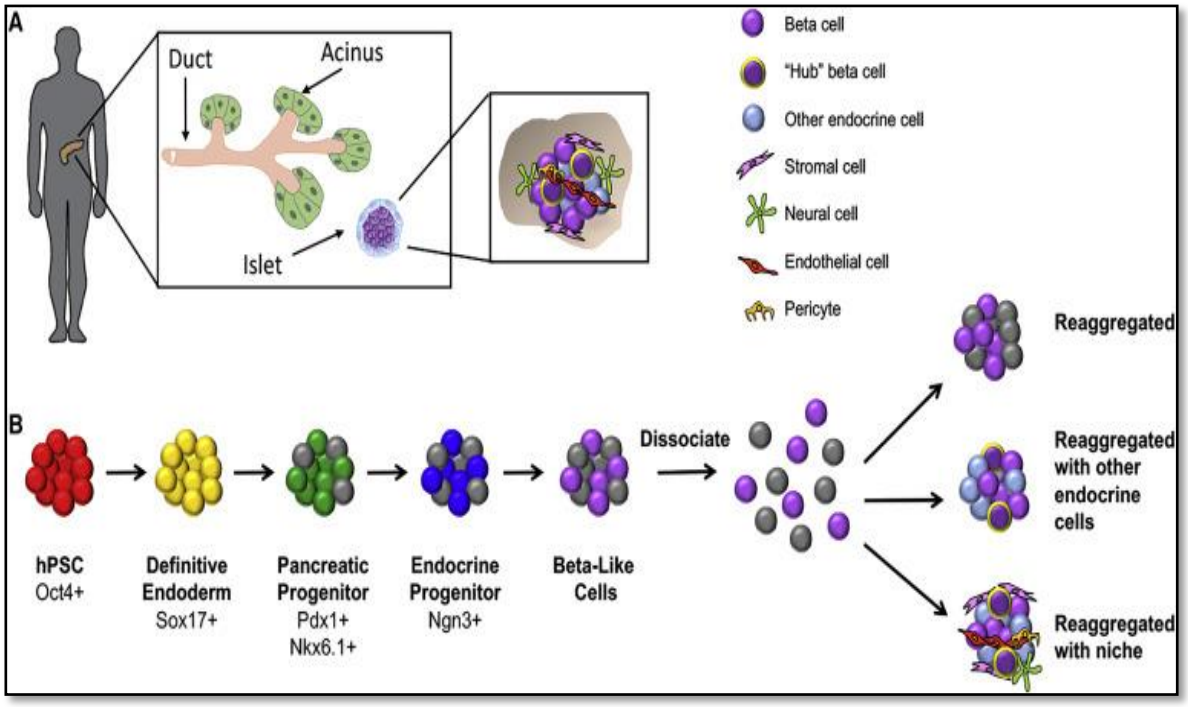


Figure no.6 Stem cell therapy on diabetes.

Stem Cell Therapy for Type 2 Diabetes mellitus (DM)

Diabetes Mellitus cellular treatments

Depending on their microenvironment, progenitor stem cells have the ability to self-renew and specialize into several cell types in vitro. For the therapy of T2DM, a variety of stem cell types are being studied. These include induced pluripotent stem cells, mesenchymal stem cells (MSCs), peripheral hematopoietic stem cells, bone marrow mononuclear stem cells (BM-MNSC) [19].

Using Mesenchymal Stem Cells for Treatment (MSC's)

The majority of stem cells employed in clinical trials today are mesenchymal stem cells (MSCs), also known as stromal stem cells. Multipotent adult stem cells (MSCs) can be produced from tissues in both adult and neonatal individuals. MSCs can be found in practically all tissues that have a perivascular region, although adult bone marrow is the most common source. MSCs are produced from the mesodermal germ layer and have the capacity to develop in vitro into Adipocytes, Osteoblasts, and Chondroblasts, which are all types of connective tissue. Numerous studies have also revealed MSCs that are generated from the neural crest, but given the high variability of MSCs, it is still unknown whether MSCs can also come from origins other than the paraxial mesoderm and the neural crest. MSCs have been categorized as an advanced therapeutic pharmaceutical product from a regulatory standpoint.

The therapeutic utility of MSCs in T1DM clinical trials is highly debatable, despite the fact that they are the most promising source for allogeneic cell treatment. In clinical settings, three different hypotheses have been investigated:

i. using pancreatic progenitors derived from MSCs that mature into functional cells capable of restoring normoglycemia.
ii. using undifferentiated MSCs to directly transdifferentiate into functional cells in vivo and
iii. using undifferentiated MSCs to support islet health and survival without differentiating into pancreatic progenitors.

There isn't enough information to date to conclusively prove that MSCs can develop into functional mature cells or organoids that resemble islets both in vitro and in vivo [20].

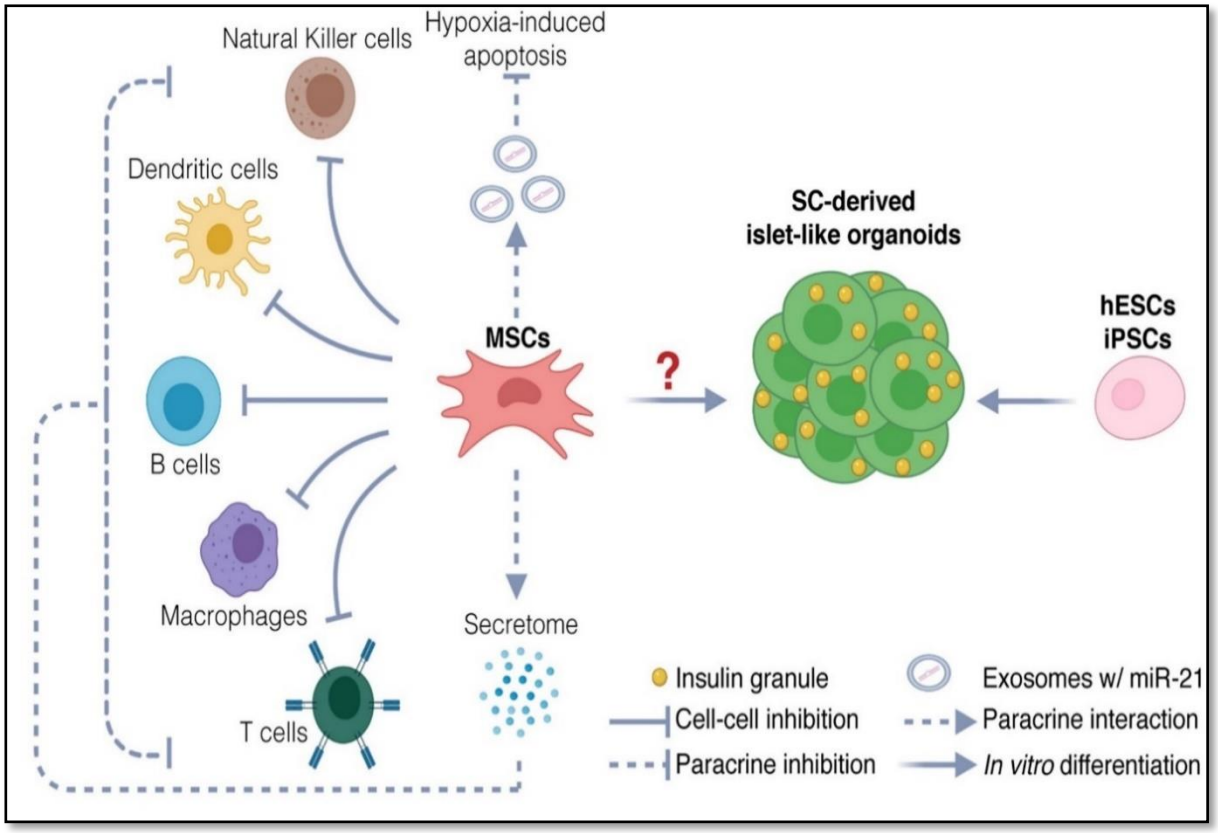


Figure no.7 Potential therapeutic mechanisms.

Potential strategies include restoring the bulk of cells and protecting endogenous islets. Through immunomodulation and prevention of hypoxia-induced death, MSCs could defend endogenous cells. Immunomodulation is effected by two different mechanisms: suppression by paracrine activity, which is caused by the production of chemokines, cytokines, and growth factors; and inhibition through direct cell-cell interaction with immune cells (secretome). Release of exosomes carrying miR21, which targets messenger RNAs implicated in the hypoxia-mediated ER stress before apoptosis, could be used to inhibit hypoxia-induced apoptosis. It is unclear if MSCs can be used therapeutically to produce islet-like organoids and stem cells. Instead, functioning islet-like organoids are created using hESCs and iPSCs to replenish cell mass [20].

Using Bone Marrow Mononuclear Stem Cells (BM-MNSC)

Depending on their microenvironment, progenitor stem cells have the ability to self-renew and specialize into several cell types in vitro. For the therapy of T2DM, a variety of stem cell types are being studied. These

include pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), peripheral hematopoietic stem cells, bone marrow mononuclear stem cells (BM-MNSC), and hematopoietic stem cells.

The BM-MNSCs comprise a variety of cells, including adult differentiated cells, MSCs, and hematopoietic progenitors. Peripheral infusion of marrow cells results in many modes of action. In addition to the bone marrow, stem cells also reside in wounded tissues where they are stimulated to release a variety of cytokines and growth factors. In ischemic areas, the BM-MNSCs increase angiogenesis and vascularization most likely through paracrine actions. Additionally, they most likely encourage the growth of the body's own stem cells, which aid in the healing process. Repair, vascularization of under-perfused regions, and control of the inflammatory and fibrotic processes are the end results [21].

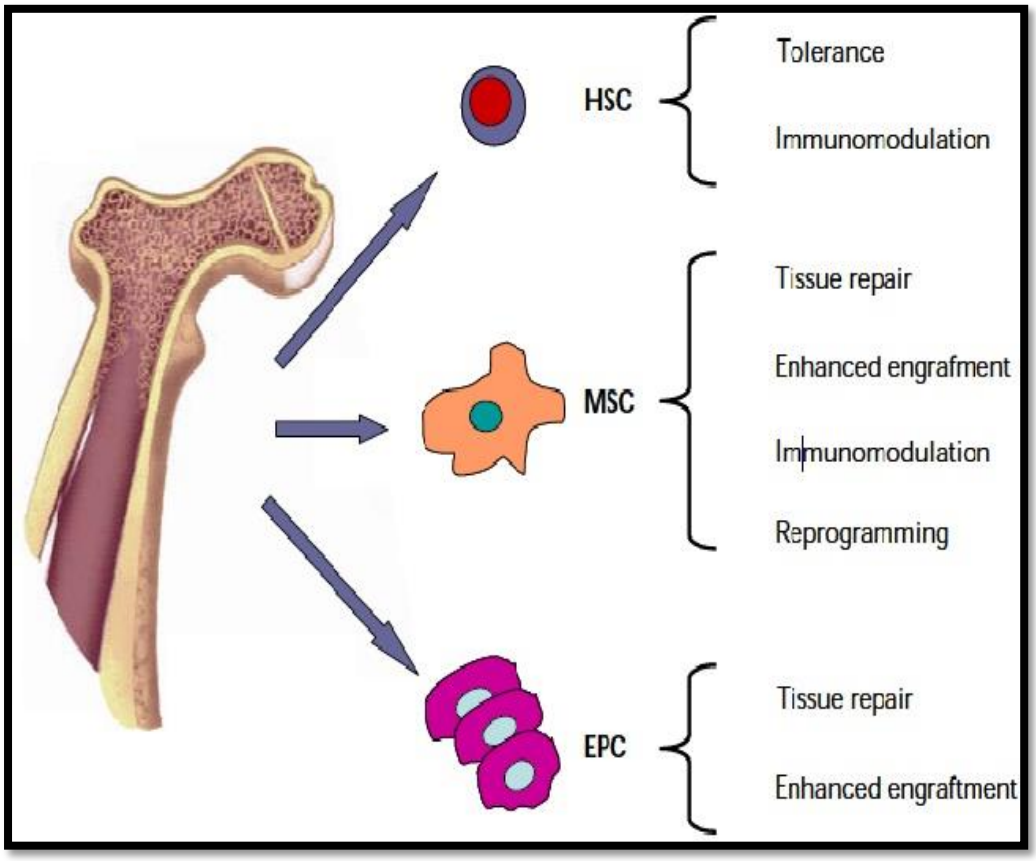


Figure no.8 Bone Marrow Mononuclear Stem Cells (BM-MNSC)

Stem cells can be found in injured tissues in addition to the bone marrow, where they are propelled to release a number of cytokines and growth factors. The BM-MNSCs promote angiogenesis and vascularization in ischemic regions, most likely by paracrine activities. Furthermore, they probably promote the body's own stem cells, which contribute in the healing process, to flourish. The final effects include repair, vascularization of under-perfused areas, and control of the inflammatory and fibrotic processes [21].

CONCLUSION:

CURRENT PROSPECTIVE

Undifferentiated cells called stem cells are essential for the development and regeneration of soft tissues as well as for body growth. The efficiency and safety of stem cells in treating a range of disorders, including diabetes, were demonstrated in the previous years through numerous research that either used stem cells exclusively or in combination with other therapeutic techniques. Transplanting BM-HSCs for T1DM and BM-MNCs with MSCs for T2DM led to the best therapeutic results. However, stem cell transplantation is not a promising option for Diabetic Ketoacidosis (DKA) patients.

FUTURE PROSPECTIVE:

With the first hESC-derived islet-like organoids transplanted in T1D patients, hESC and iPSC-based cell replacement therapies are now becoming a reality after decades of MSC-based clinical trials for both T1 and T2 diabetic patients. The numerous facets of stem cell transplantation, including the long-term safety of each encapsulating method, the ideal implant size to achieve a therapeutic effect, and the long-term survivability of the transplanted cells, require a significant amount of clinical testing at this time. It would be safer and easier to monitor transplants if cell survival in the subcutaneous and/or intramuscular spaces improved. A new and promising therapeutic approach for DM is cell-based therapy, such as stem cells, which are unspecialized cells that develop into specialized cells with a multi-lineage differentiation and regeneration capability that differs for different tissue types.

The metabolic disease group known as diabetes mellitus (DM), which causes excessive blood glucose levels, is very common in today's society. Diabetes and its effects are anticipated to cost the world significantly more by 2030, particularly in middle- and lower-income nations. The preferred form of treatment nowadays is evidence-based medicine, with a focus on lowering high blood glucose levels and reducing diabetic complications. For the treatment of DM, stem cell therapy provides a promising future. Studies have created regenerating beta-cells that closely mimic insulin-secreting cells, notwithstanding the difficulties currently associated with this course of therapy. There have been numerous sources of stem cells investigated.

A successful procedure would have an immediate impact and spare the patient from long-term pharmaceutical therapy and it’s Despite these formidable obstacles, the area of stem cell research is constantly making remarkable strides. There are now many diseases and ailments that can be treated using stem cell treatment. They appear to have a major influence on medical advancements in the future unavoidable negative effects.

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