Review Article

Advances Towards Regenerative Medicines for Diabetes

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ABSTRACT

Diabetes along with its broad spectrum of complications is considered to be a metabolic disease that has a high morbidity margin leading to the poor quality of life. Despite the fact that current diabetic treatments significantly decrease clinical symptoms, they are not curative, which results in a lifelong chronic insulin dependence that does not stop the additional effects linked to diabetes. The increased rise in the number of diabetes cases has led to the search for better therapeutic approaches for diabetes with the help of innovative methods. This article explores advancement in regenerative medicines for diabetes with their focus on pancreatic islet transplantations, stem cell remedy and various regenerative approaches for the action towards diabetes. Furthermore, it also discusses about the various clinical trials and research study related to islet transplantation, and many regenerative treatments for diabetes treatment. Overall, it emphasizes on the innovative approaches and also address the limitations of current diabetic treatment and improve clinical possibilities.

Keywords: Islet transplantations, regenerative medicine, stem cells, cellular reprograming.

INTRODUCTION

Diabetes is an autoimmune condition which is characterized by constant elevated blood sugar levels because the body is not producing enough insulin to meet the body's needs. A combination of environmental and genetic variables which are responsible for the development of diabetes, which currently affects 463 million adults around the whole world and is anticipated to impact 700 million people by the year 2045[1]. In present the available treatment and approaches for diabetes is solely focused on lowering the blood glucose level and not on the main factors responsible for hyperglycemia. Keeping in consideration the cost that is associated with the management of diabetes in terms of diet, medication and good health practice it has now become very important to look for simpler and cost-effective alternative for newer advances and technologies that can help improve lifestyle and rectify the cause of this disease. These various approaches can eradicate the risk for long term complications and treatments, it can also help save expenses related to lifelong management. Diabetes is an incurable condition that impacts the body's ability to utilize food as energy. Around most of the food we eat is transformed by our body into sugar or glucose, which is subsequently released into the bloodstream. When there is increased blood glucose level the pancreas releases out insulin as a response. Insulin functions as an essential component to allow glucose from the blood stream to enter the cells in the body and be used as an energy source. There are 3 major types of diabetes: -

Type I Diabetes Mellitus (T1DM) is a chronic ailment usually affecting children and young youth where their body does not have the capability to produce insulin is produced. Insulin is a hormone produced and secreted by the beta cells of langerhans that is present in the pancreas. Its function to utilize the glucose produced in our body after every meal that we consume but abnormal immune response with regards to beta cells of langerhans directs to the inability of the pancreas to produce required amount of insulin leading to insulin deficiency. The cause for this unusual immune response is not yet recognized nevertheless its onset is not related to lifestyle or diet. Environmental factors and genetics can be the starting point for the development of this disease. As the body is incapable of producing insulin, insulin injections for a lifetime are the treatment being used until date. Type II diabetes mellitus (T2DM) is most prominently as it generally has its onset during adulthood and it is well known because of its relation to lifestyle. When a person suffers from type II diabetes it means that their body is not able to use the produced adequate amount of insulin (insulin resistant), thus not able to keep their normal blood sugar level. During this condition the body is not able to employ glucose like it's supposed to resulting on high level of glucose in the blood thus leading to hyperglycemia and many other complications. This condition develops over many years thus its onset during adulthood. Treatment for this condition usually consist of oral ant diabetic drugs. Gestational diabetes mellitus (GDM) is another sort of diabetes affecting expectant women, normally the blood glucose is normal but if it reaches a certain level then they are said to have gestational diabetes. It affects about 5 out of 100 women. The body metabolism changes during pregnancy where the body takes longer time for glucose in the blood stream to get absorbed in the body as stated by Claes Hellerström's Pathophysiology of Gestational Diabetes has been qualified for the primary work starting

in 1963 on changes of body organs like pancreas during pregnancy and lactation in a mouse model[2].

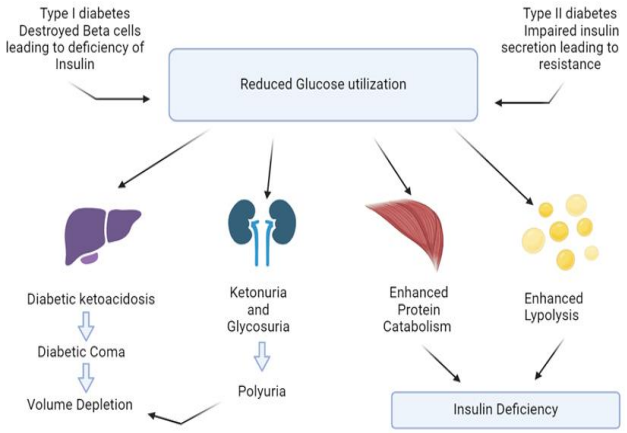

Figure 1: Pathophysiology of Diabetes

At present the standard drug treatment for GDM include changing diet and proper medication, for T2DM oral hyperglycemic drugs along with proper specified diet, and exercise are the first line of treatment and for T1DM frequent daily dose of exogenous insulin injection is required. Nonetheless exogenous insulin injections is said to be a non optimal treatment as it was assessed that less than forty percent of patients are able to maintain the glycemic state and continue it for a lifetime[3]. Many other problems associate with diabetes comprising of kidney disease, cardiovascular disease, eye damage, nerve damage, skin problems, infection, dental problems etc. Living with diabetes is a difficulty as it affects and hampers with daily life style also the expenses for drugs each month[4].Though drugs and insulin can maintain glycemic level and decrease complications related to diabetes it is not a cure. Despite all precaution measure people with T1DM still has a chance of being hypoglycemic or hyperglycemic which can be dangerous hence, in order for a definite and specific treatment various regenerative advances can be followed. Regenerative medicines is an approach to replace, revitalize tissues or organ damage that was caused due to diseases, injury, age or other related factors. Its main goal is to treat diseases and its symptoms without the use of medication and long tedious procedures. Regenerative medicine also helps to understand the basic biology and pathogenesis of various diseases. There are various advancement for handling of diabetes with the help of regenerative medicine.

1. a. Pancreatic islet Transplantation

As the name itself suggest this procedure is a transplantation technique where human pancreatic cells are isolated and transplanted to the recipient just like any other organ transplantation procedure. For over 30 years this technique has moved from rare successful procedure to frequently routine process with expected results for particular patients of choice suffering from T1DM whose condition is not stable with the help of standard choice of treatment. To date 1,500 patients have undertaken transplantation of islet in approximately 40 international centers[5]. Only patients who is suffering from T1DM and complication of hypoglycemia or hyperglycemia despite several corrective measures are the major indicators for islet transplantation. The recipient of this procedure must not be under any immunosuppressant drugs due to prior organ transplant. Inclusion criteria consist of patients having T1DM for more than five years and above eighteen years of age to avoid risk of immunosuppressant to children. Exclusion criteria includes patients with high BMI (< 30kg/m) or weight above 90kg or patients who require more than higher than0.1U/kg of insulin in order to avoid excess insulin requirement[6,7]. Currently, deceased donors are the source of transplantation where human pancreatic islets are used. In order to preserve pancreatic capsule integrity, donor pancrease procurement must be done with extreme caution. It should also reduce handling time must be reduced and increase the blood flow of oxygenated blood before cross-clamping of aorta[8].The process of islet isolation, purification, and transplant outcomes all depend significantly on the selection of ap propriate[9]. For islet processing, The perfect pancreas donor is similar for islet and whole-pancreas transplantation[10]. Ages between twenty to fifty, BMIs >30 kg/m2, and normal hyperglycemic levels at the time of organ donation are among the characteristics of pancreas donors that are associated with successful islet cell isolation[11-15]. The techniques used to obtain pancreas for transplantation of islets are similar as that of whole-pancreas transplantation; however, since surgical ligation is not required for islet transplantation, blood vascular preservation following organ removal is not required. The pancreas, along with a portion of the spleen, should be removed en bloc and triple-bagged in cold preservation solution of histidine-tryptophan ketoglutarate for sterile transference to the islet isolation center after donor thoracic organs have been cross-clamped and harvested for transplantation. Pancreas should be removed before any other abdominal organ to reduce the duration of ischemia[16,17]. After intraductal pancreatic perfusion with blends of enzymes, the pancreas is broken down by the help of an enzymatic digestion process that is mechanically increased with continuous flow. Centrifugal density gradient purification is then used to separate the islets. SOPs must be strictly followed in order to guarantee the viability and quality of the finished islet product[18]. The separated islets are then incubated for 24 to 72 hours after being put in culture media. Before the transplantation, immunosuppressive therapy is introduced to the patient. Islet culture lowers dead or apoptotic cells, which contributes to increased purification[19]. The recipient then receives a transplant of the purified islets, typically into the liver through the portal vein. Immunosuppression might not be necessary in cases of autotransplantation after finished pancreatectomy. A number of factors, including the size of the transplanted islets, early engraftment, and avoiding complications, influence how smoothly the transplant proceeds. After transplantation, patients are monitored for graft function, insulin independence, and potential complications. Continued

follow-up is essential in order to assess the ability and sustainability of glycemic control achieved through the islet transplantation[20].

1. b. stem cell therapy:

Stem cells are uniform dedifferentiated cells present in the embryonic state during fetal development which stays up to adulthood giving rise to different cells and organs, acting as a constituent feature for development. Stem cells can be utilized for therapy purpose that is cellular therapy where diseased and damaged tissues can be replaced with modified cells which can help regenerate organs. The important attribute of stem cells is to proliferate, to prepare clones and be potent where the cells can be distinguish into different types. These stem cells can be characterized into various cells depending upon its origin and differentiation potential. In terms of differentiation potential they are differentiated into 5 groups: -

a. Totipotent cell: They are the most undifferentiated tissues, which are existing in the earliest phases of progress. As the embryonic and extra embryonic tissue are developed, a fertilized oocyte plus the cells from the first 2 divisions are totipotent cells that generate an embryo and placenta[21].

b. Pluripotent : Entirely every organs and tissue arise from the three germ layers—the ectoderm, endoderm, and mesoderm which can be transformed by pluripotent stem cells to form cells[22]. Pluripotent stem cells, or ESCs were the first to be generated with the help of the inner mass of blastocyte[23].

c. Multipotent: Multipotent stem cells is present in almost every tissue, which can convert into numerous types of cells from one single germ layer. Numerous tissues can be used to make them, such as the marrow of the bone, fat, bone, tissues, Wharton's jelly, peripheral blood, and umbilical cord blood[24].

d. Oligopotent: Such stem cells have an ability to self-renew and establish several lineages within a single tissue. They can differentiate into lymphoid, myeloid genetic lines and hematopoietic stem cells[25].

e. Unipotent: Unipotent stem cells, are those found in muscles, can regenerate themselves, specialize themselves into a single unique cell type, and create a single heredity that gives rise to and no other cells than adult muscle cells **[26,27].**

When it comes to origin of cell then it is further divided into 4 groups

a. Embryonic stem cells (ESCs): Pluripotent (ESCs) originate from the inner mass of the blastocyst, which occurs within 5 to 7 days after fertilization also known as a stage of pre-implantation[23].

b. Matured stem cells: Adult matured tissue is the source for this cell. It has been established that these cells reduce inflammation and improve damage repair in animal models[28,29]. All three of the budding layers' tissues along with placenta can provide mature stem cells. Matured stem cell transplantation has proven in numerous trials to repair damaged organs in vivo, including bone tissue[30].

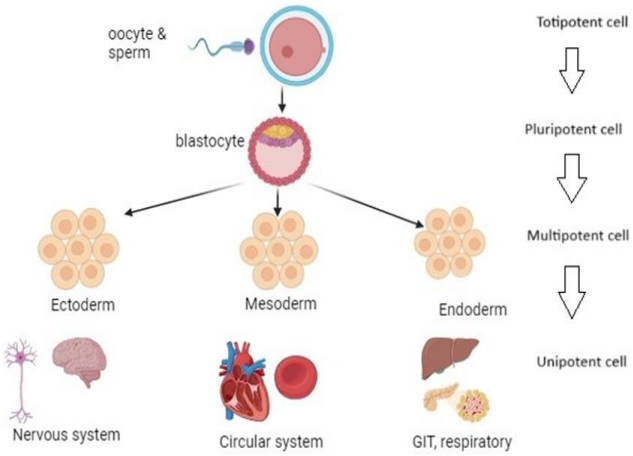

Figure 2: Hierarchy of stem cells

c. Tissue resident stem cells: This type of cells generate tissue-specific, cells with terminal differentiation which are essential for the renewal and restoration of some matured tissues and organs after injury[31]. According to past research, these types of cells are thought to be inactive during ontogenesis and proliferate, differentiate, or migrate only in response to external stimuli [32,33]. The environment known as the stem cell niche oversees the restoration and variation of these cells[34]. An increasing number of research indicates that external factors from the microenvironment have a substantial impact on the function of stem cell niche is essential for homeostasis of stem cell and tissue repair[35,36]. While most tissue-resident stem cells are inactive, during injury and repair they are triggered by certain signals[37]. Stem cells have made an important contribution to contemporary medicine because of their wide range of applications in basic science and the chances they present to create novel treatment approaches for use in clinical settings[38]. Research has been done on cell treatment for nearly all degenerative diseases. Several diseases, including diabetes mellitus, have already shown favorable results from preliminary research and clinical trials[39,40]. Regenerative medicine and cell therapy both have a factor to reflect on. Immunorejection is still something to think about. Tumor genesis can result from genetic instability. The stem cells' capacity for adaptability and self-renewal may give rise to cancer in the host tissue[41].

1. c. Cell sheet transplantation

Cell sheet treatment function by in vitro growth of cells to create a framework resembling a sheet while preserving cell-cell connections and extracellular matrix ECM. With this technique, cells can be transplanted without the need of frameworks, which are frequently utilized in traditional tissue engineering but may result in negative outcomes including immunological rejection or inflammation. This method of transplantation involves the following steps:-

1. **Cell Cultivation**: Cells are grown on a special surface that allows them to form a cohesive sheet.
2. **Sheet Harvesting**: The grown cell sheet is then separated from the surface without the use of enzymes, preserving the ECM and cell connections.
3. **Transplantation**: The intact sheet of cell is then transplanted straight onto the damaged tissue or organ.

As a method of delivering cells, cell sheet engineering may play a more sophisticated part in the goal of cell treatment for diabetes, by using temperature sensitive cultured dish in order to establish endogenous insulin secretion[42], created islet cell sheets of rats, which were then implanted into recipient rats' subcutaneous spaces. Streptozotocin-induced diabetic SCID mice had their diabetes restored by islet graft, which also preserved the ability to sense and release insulin[43].After the convergent MSCs were transplanted into diabetic SCID mice[44], seeded rat islets onto the MSCs. The maintenance of islet function was shown to be protected by MSCs sheets.

Additional research in this area suggested that fibroblasts and adipose tissue derived stromal cells (ADSCs) could take the place of MSCs as supportive cells[45]. In order to overcome the limitation on implantation locations, other sites were used instead of just subcutaneous transplants. It was demonstrated that the peritoneal wall[46] and hepatic surface were suitable for islet implantation. In the meantime, it has been shown that islets made from human MSCs, human embryonic stem cells (hESCs), and human chemically induced pluripotent stem cells (hCiPSC-islets) are effective in glycemic control improvement and endogenous insulin secretion restoration [47,48]. The preservation of the ECM and cell junctions is crucial because it maintains the cells' natural environment, which is essential for their function and communication. This technique has shown promise in regenerating various tissues and organs like cornea, liver and heart by providing a more natural combination of resettled cells into the patient's body[49]

1. d. Cellular reprogramming

The term "cellular reprogramming" describes the act of changing a cell's fate, or changing its kind. Genetic engineering has advanced to the point where cellular reprogramming is now possible. To accomplish this, mechanisms like transcription, transgenes, zinc figure nucleus can be used to manipulate and reengineer cellular DNA[50]. The pancreatic islet is a expert organ that performs both exocrine and endocrine activities. Exocrine cells, which constitute of islets, have a high ability for regeneration, in the event of acute pancreatitis, the exocrine pancreas can heal quickly. On the contrary, the endocrine cells, which make up only five percent of pancreatic islet, are not very good in regenerating[51]. In the pancreas of mice, expressed three essential transcription factors to produce β-like cells in site. The reprogrammed cells had resemblance to β-cells when it comes to size, shape, and ultrastructure. They also produced insulin to control blood glucose levels and exhibited a number of genes necessary for β-cell functions, according to PCR research[52].

Beta like cells can be produced by using transduced matured exocrine cells along with vector contain lentiviral coded with MAPK and STAT3[53]. Overexpression of MAPK and STAT3 resulted in a significant increase of neurogenin 3, a transcription factor that promotes the β-cell lineage in undifferentiated pancreatic cells and upregulates many other endocrine markers[54]. Furthermore, it could be possible that the increased cell-to-cell interaction resulting from cultivating the cells in a 3D Matrigel framework enhanced the transdifferentiation process' efficacy. Upon engrafting these cells into immunocompromised animals, they were able to manufacture insulin and take on certain β-cell functions, as seen by the upregulation of proteins that are essential for controlling blood glucose levels[55].

1. e. β cell regeneration

Dedifferentiation, transdifferentiation, and islet neogenesis of the already differentiated cells are all processes associated with β-cells regeneration. Presently available treatments for type 1 diabetes include insulin pumps, numerous injection schedules, and insulin analogs; nevertheless, they frequently fall short of the desired glycated hemoglobin levels. There have been decades of talk about stem cell therapy and islet transplantation[56]. It was first shown more than 40 years ago that islet cell transplantation could successfully restore blood glucose in diabetic rats[57]. However, default of the graft along with low β-cell can be caused by various factors such as islet death, engraftment, anoxia, and islet loss after transplantation. Significant barriers to the extensive use of islet transplantation also include lack of donor islets and affordability. Hormones such as growth hormone (GH), insulin, glucagon, glucagon-like peptide-1 (GLP-1), gastrin, cholecystokinin (CCK), prolactin, and gastric inhibitory polypeptide (GIP) have all been reported to be linked with β-cell mass. Development and characterization are regulated by them[58]. GH, prolactin, and placental lactogen have been reported to increase proliferation of β-cells and insulin gene expression in T1D and in vitro GIP, GSTP, and CCK hormones were found to improve proliferation of β-cell in the T2D model, but not in the T1D model, as indicated by the investigations[59]. In the T2D model, GIP is involved in both in-vitro and in-vivo model for β-cell proliferation and survival. Furthermore, these hormones delay the emptying of the stomach and increase the release of insulin[60]. Gastrin, a hormone-like substance found in the gastrointestinal tract, promotes β-cell neogenesis by enhancing the dedifferentiation and reprogramming of pancreatic cells that act on the CCK B receptor. The growth hormone secretagogue (GHS) receptor is liganded by ghrelin. It is well established that in T1D patients, ghrelin contributes to blood glucose regulation by stimulating secretion of insulin and ß-cell proliferation. By focusing on locations downstream of peroxisome proliferator-activated receptor (PPAR-), GHS also has other metabolic effects[61]. Because of these

characteristics, GHS is a good choice for the therapeutic management of diabetes. In the future, this approach might take the place of insulin injections.

2. CHALLENGES AND FUTURE DIRECTIONS

There are many challenges facing the field of regenerative medicine for diabetes, especially when it comes to restoring the function of beta cells that produce insulin. Determining the safety of stem cell therapy is the main obstacle. Immune rejection or uncontrolled proliferation of cells must be avoided. Immunosuppressive measures and human donors are necessary for current therapies such as pancreatic or islet transplantation. The goal of regenerative medicine is to accomplish comparable results without these requirements. While pharmacological therapy for beta cell regeneration has made progress, there is still a barrier in turning these discoveries into diabetes treatments that are clinically feasible. This involves overcoming past challenges like a lack of donor organs and the high cost of transplant techniques. Stem cell therapy involves ethical issues, particularly when it uses embryonic stem cells. One major problem is developing pharmacologic strategies that allow remnant beta cells to proliferate and regenerate while maintaining normal function. None of the diabetic medications currently on the market can stimulate the growth or regeneration of human beta cells. Although it is now possible to create beta cells from stem cells, these type of cells still need to improve in terms of how well they process pro-insulin and respond to glucose in order to operate like mature beta cells. These difficulties illustrate how difficult it is to treat diabetes with regenerative medicine. Still, research is being done to address these problems and try to give diabetic patients safer and more effective medications.

CONCLUSION

Regenerative medicine is a revolutionary field that is based on the power of biology, chemistry and advanced technology, hence it offers a possibility to treat or replace tissues of organ damage due to age, disease, or trauma. Moreover, it becomes less complicated to understand the fundamentals of biology and to choose the right strategy for treating diseases. Discussed here are the various approaches on regenerative medicine techniques such as stem cell therapy, pancreatic islet transplantation, cell sheet transplantation, cell reprogramming and beta cell regeneration, all of which can have promising future in the medical field. This gives us the impetus and a way to pave the way for treatments to fit the individual's condition of a patients based on their genetic traits and hence we are able to improve the outcome. Despite some obstacle such as ethical doubts, small number of donors, liability and problem with existing medications, many ongoing research and clinical trials are still studying the issue deeply to overcome these hurdles. The regenerative medicine world is filled with hope as this type of medication has enormous potential for the present and the future in treatment of a large number of complicated conditions.

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