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Stem Cell Therapy for T1 D and T2 D Diabetic patients

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Abstract— Diabetes is a chronic condition that causes several diseases. Type 1 and Type 2 dependent diabetes are shown more concern in today's world. Type1 dependent patients suffers from inability of the Beta cells to produce insulin whereas Type 2 dependent patients suffers from insufficient insulin production. Diabetic Retinopathy, Nephropathy, Critical Limb Ischemia and impaired glucose tolerance are some of the major risk factors of Diabetes. Diabetic Retinopathy is a major complication of Diabetes causing blindness in working age adults. This article discusses some research methods involved in the generation of Beta cells carried out by certain authors, hypothesis and future works in this field.

Index Terms— Type 1 and Type 2 Dependent Diabetes, Beta cell regeneration, Immunosuppression, Human Embryonic Stem Cells(hESC), Human Induced Pluripotent Stem Cells(hiPSC), Human Pluripotent Stem Cells(hPSC), Transplantation.

1 Introduction

STEM CELL based regenerative therapy is seen as one of the most potential methods in treating T1 and T2 dependent diabetic patients. Growing pancreatic lineages from stem cells helps in disease modelling and drug delivery in diabetic patients. Recent researches involve deployment of Human Induced Pluripotent Stem Cells(hiPSC) in growing pancreatic lineages. This reduces the need of immunosuppression during transplantation of Beta cells into patients.

2 Methods

In this section, we review the methods of generating Beta cells and transplantation methods discussed in some research articles.

2.1 Generation of Insulin producing cells (Beta Cells) from Pluripotent Stem Cells

According to Yasushi et al.[1], the beta cells generated by treating stem cells with chemical compounds and growth transcription factors such as Nodal activin, Wnt, retinoic acid, hedgehog, fibroblast growth factor, epidermal growth factor, bone morphogenetic protein, when given a stimulus of Potassium Chloride (KCl) has not secreted suitable amount of insulin similar to adult beta cells but expressed somatostatin and glucagon similar to embryonic beta cells. The same process carried out by Yasushi et al.[1] in high cell density culture and cell aggregation cultures has resulted in generation of embryonic pancreatic endoderm similar to adult beta cells.

The authors in their article has referenced Assady et al.[6], who generated insulin producing beta cells from pluripotent stem cells which are closer to realisation. He has also referenced Rezania et al.[7], who added factors such as vitamin Protein kinase C pathway activators, R428 (selective molecule that inhibits tyrosine kinase receptor AXI) for generating beta cells which is less potent than adult human islets but improved blood glucose level after 16 days. They highlighted the works

Fig. 1. General outline of Diabetic Stem Cell Therapy

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of Pagliuca et al.[8], who generated beta cells by examining more than 150 combination treatments of more than 70 kinds of compounds. This resulted in insulin secretion and promoted the ability to handle intracellular Ca^{+2} with respect to changes in glucose concentration which is similar to adult beta cells. Jeffery et al.[2] has generated endocrine and beta like cells from pancreatic progenitors by signalling the stem cells with thyroid hormone, retinoic acid, and EGF and inhibiting of gamma-secretase, TGF-beta, Shh, Axl, BMP. The author has highlighted the microencapsulated allogenic hESC derived pancreatic progenitor product VC-01 transplanted into rodents by Viacyte, Inc. The authors Jeffery et al.[2] carried out several differential stages in attachment culture. They created clusters in

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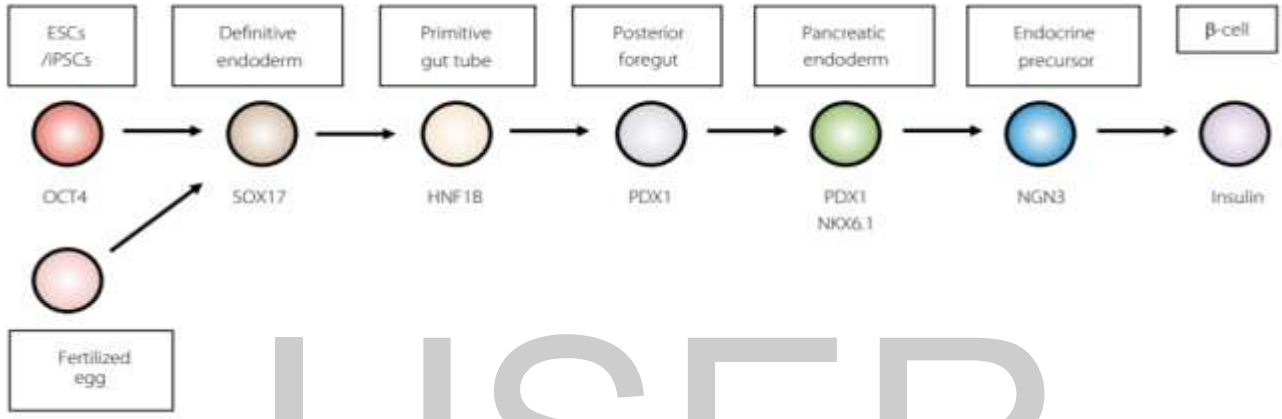

Fig. 2. Schematic diagram of the differentiation strategy to produce pancreatic endocrine lineages from such as human embryonic stem cells and induced pluripotent stem cells (hESCs/iPSCs) by mimicking in vivo development
(Image from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5835458/)

suspension culture, involved modulation of thyroid hormone gamma-secretase and TGF beta signalling. This has resulted in increased insulin production, glucose concentration, cytoplasmic Ca^{+2} concentration and C peptide. These beta cells produced from Human pluripotent Stem Cells expressed transcription factors such as NKX6-1, PDX1, MAFA, GLIS3, MNX1 (similar to adult beta cells except MAFA and GLIS3).

2.4 Transplantation of Beta Cells

The primary problem associated with transplantation of beta cells is immunorejection. Yasushi et al.[1] highlighted two methods that are used in transplantation of beta cells in their paper. In the first method, initially a pre-treatment is carried out to induce angiogenesis and then the cells are implanted. One such study was reported by Yasushi et al.[1], where a Nylon catheter is embedded into sub cutaneous tissues of host mice for 1 month before cell implantation which generated vascularised space and insulin producing cells are implanted once the inflammation diminishes. This has made the environment a less intolerant one for the implanted cells. The author referenced Szot et al.[9], who blocked T cell costimulatory pathways and prevented the rejection of xenogeneic implantation of hESC derived pancreatic cells into non diabetic incompetent mice by administering CTLA4 Ig and anti CD154 antibody. This model showed good therapeutic effects without immunorejection.

In another method, bio engineered device which was made selectively permeable to oxygen, nutrients and impermeable to immune cells were implanted which produced insulin in response to glucose concentration because of vasculogenesis. Yasushi et al.[1] reported a recent study where hESC derived beta cells encapsulated with alginate derivative, triazole- thiomorphine dioxide alginate has shown good therapeutic effects like glycaemic correction with immunosuppression for more than 170 days eliminating foreign responses and implanting fibrosis.

According to Jeffery et al.[2], micro and macro encapsulation with selective permeability to O_2, nutrients and blocking immune cells prevent the risk of immunorejection. The costimulation blockade with CTKLA4-Ig and monoclonal antibodies anti-CD40L prevents the rejection of HESC derived pancreatic progenitors in immunocompetent mice. Companies like Universal cells replaced Human Leukocyte Antigen (HLA1) locus with HLA-E and HLA-G to mimic pregnancy-based tolerance of allogenic tissue without triggering Natural Killer Cells based killing and deleted transcription factors which expresses HLA 2 (Not yet demonstrated). They have also used certain methods like inducing PDL-1 and CTLA4 to induce immune tolerance.

3 Challenges and Problems Involved

Jeffery et al.[2] in their paper highlighted that the human pluripotent stem cells (hPSCs) derived beta cells have the potential to contain residual undifferentiated hPSCs which can form

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teratomas. These kinds of problems are not present in short term transplantation but are more prevalent in long duration transplantations. One method suggested by Jeffery et al. to avoid the formation of teratomas is the removal of the cells that express hPSC surface markers by introducing an inducible suicide gene.

4 Solutions Provided

Jeffery et al.[2] referenced works and solutions provided by certain scientists in their paper. Rezania et al.[7] described the importance of Axl inhibitor R428 in achieving certain beta cell features. Russ et al.[10] deployed few factors and achieved differentiation of stem cells into beta cells in shorter duration. The author also highlighted the research work of an unpublished article where transplanted beta like cells for over a year and expression of Ki67 in insulin expressing cells suggests potential for long term graft function in immunocompromised mice. Phase 2 trials carried out by Gitelman et al.[11] with drugs like ATG have provided valuable results like suppressing TCR signalling and activation of T cells after transplantation which reduced the risks of immunorejection and need for immunosuppressive drugs. A recent research with CRISPR/Cas 9 technology has given high efficacy and fidelity results. Through this technology genetic defect can be fixed in patient derived Human induced pluripotent stem cells.

5 Hypotheses / Future Works

Umbilical cord cells and cells that are wasted during invitro fertilization can be used in generating beta cells. Wastage of those cells can be minimised and demand for pluripotent stem cells can also be reduced. A suitable nanomaterial can be used for transplanting beta cells into the patients. The nanomaterial must be designed in a way such that it must be biocompatible, selectively permeable to O_2 and other nutrients for maturation of beta cells and impermeable to immune cells such as T cells, etc. The beta cells are packed and encapsulated into this nanomaterial and delivered to the patients. The nanomaterial must also be signalled in a way that destroys the undifferentiated pluripotent stem cells thus preventing teratomas.

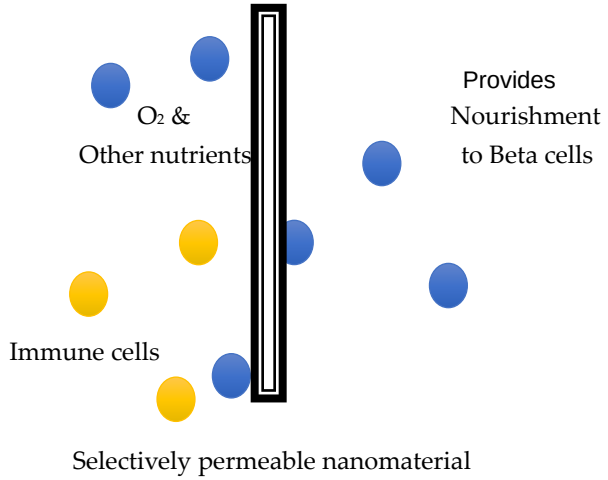

Fig 3. Design of the nanomaterial which selectively allows O_2 and other nutrients, blocking the entry of immune cells

6 Conclusions

Regenerating beta cells or pancreas for diabetic patients has been one of the most trending topics of research in the recent past. Researchers have shown that this method has reduced the risk of immunorejection and improved glycaemic conditions when carried out in diabetic and non-diabetic mice. Hypothesis and future works on nanomaterial-based beta cell delivery can be persuaded.

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