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Stem cell therapy for the treatment of Type 1 Diabetes - Advantages and issues

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Introduction

Excess mortality due to complications in type 1 diabetes mellitus emphasises the significance of preventative strategies and the need for treatments[12]. In a particular study by Ruiz P. L. D. et al. (2022), the uncorrected rate of mortality from any cause for individuals with type 1 diabetes mellitus (T1DM), including children, was 11.7% per 1000 person-years.

Current treatment of Type 1 Diabetes

A chronic autoimmune disease, type 1 diabetes mellitus is marked by a deficiency in insulin and leads to hyperglycaemia[11]. Presently, no cure exists, and patients depend on insulin injections for life[14]. In England, patients get their prescription of insulin for free by using a medical exemption certificate[10]. In other parts of the world such as America, this is not the case. In the US in 2016, T1DM patients paid close to $6000 out of pocket for insulin[31]. Moreover, some older patients with dementia may forget whether they have or have not taken their insulin which can lead to hypoglycaemia or hyperglycaemia[2]. The discrepancies in the cost of treatment and difficulty taking current treatments are reasons that further strengthens the need for a cure.

Reason for stem cell therapies

Exogenous insulin that is administered cannot mimic the endogenous insulin that is normally secreted[6]. This is because exogenous insulin cannot regulate blood glucose levels physiologically. Usually, exogenous insulin is administered to ameliorate hyperglycaemia[6]. Stem cell therapies are being developed to produce beta (β) cell islet organoids in vitro and insulin-producing cells (IPCs) which in theory control blood sugar levels normally. This gives the hope that a cure can be found[6].

Causes of Type 1 Diabetes

While the aetiology of T1DM is not fully understood, some parts have been. Circulating immune T-cells are thought to mediate the destruction of β cells, the insulin producing cells of the pancreas[14]. More specifically, CD8+ and CD4+ T-cells and macrophages target β cells which ultimately causes hyperglycaemia[12]. Environmental and genetic factors destroy β cells as well[22]. In genetically susceptible individuals, one or more environment-related factors trigger the irreversible immunological destruction of β cells. These environmental factors include viruses such as gut microbiota, enteroviruses, and rubella. And in the diet, examples of these factors are cereals, and vitamin D[22].

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Diagnosis of Type 1 Diabetes

Type 1 diabetes usually starts in childhood or adolescence, but up to 50% of cases begin in adulthood[11]. Unfortunately, early onset T1DM is on the rise meaning that many more children are being affected[22]. The reason behind this rise is remains unknown[16]. Type 1 diabetes mellitus is diagnosed by measuring fasting blood glucose levels or measuring random blood glucose levels in an individual with symptoms[11]. These symptoms include polyuria, polydipsia, and polyphagia[4]. A positive result would be a concentration on or above 7.0 mmol/L (126 mg/dL) for fasting blood glucose and above 11.1 mmol/L (200 mg/dL) post satiation[11]. Glycated haemoglobin (HbA1c) indicates the level of glucose bound to haemoglobin in the blood[25]. Glycated haemoglobin (HbA1c) is less sensitive for diagnosis than the first two tests, so it is not used much for diagnosis of T1DM[11]. In a diabetic patient, HbA1c concentration will be above 48 mmol/mol (6.5%)[11]. This lack of sensitivity for diagnosis may be because HbA1c reflects the glycaemic history of the past two to three months[25]. This is good for long term complications associated with diabetes and for measuring chronic hyperglycaemia[25]. This indicates HbA1c is not effective for tracking dysglycaemia that progresses quickly.

Embryonic stem cells

Embryonic stem cells (ESCs) are pluripotent stem cells. From a blastocyst which is an early embryo, ESCs are separated from the inner cell mass[6]. In vitro, these ESCs can differentiate into many types of adult cells[6]. In therapeutics, ESCs have a significant potential to produce copious quantities of insulin producing cells (IPCs) e.g., β cells[7].

Aims of stem cell therapy

Generally, the aims of stem cell therapies are to replace β cells or control the autoimmune response to insulin-expressing cells[1]. Stem cell transplantation seems like a promising alternative to islet β cell transplantation which is a current treatment. While the latter is successful, it is not used as frequently because it relies on the availability and number of donors and the lifelong use of immunosuppressive drugs[30].

Induced pluripotent stem cells and hESCs in diabetic mice

Using Yamanaka factors, induced pluripotent stem cells (iPSCs) are reprogrammed from adult somatic cells into an embryonic-like pluripotent state. Human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) can be used to replace β cells. iPSCs and hESCs are both pluripotent stem cells[30]. The production of insulin producing cells from both ESCs and iPSCs involves the successive regulation of certain signalling pathways controlling the development of the pancreas[6].

In diabetic mice transplanted with greatly enriched pancreatic and duodenal homeobox 1 (PDX1+) pancreatic progenitor cells (from hESCs), normal blood glucose levels were restored[6,7]. This evidence therefore suggests that stem cell therapies and transplantations have the potential to reverse or prevent T1DM[1].

Production of insulin producing organoids and cells

hESCs and human induced pluripotent stem cells (hiPSCs) are sources of islet organoids in vitro and IPCs[6]. Organoids are 3D structures which are produced from stem cells[28]. Inside a 3D gelatinous chamber, induced pluripotent stem cells (iPSCs) are differentiated into insulin producing cells. This structure forms an organoid similar to an islet in humans. After the organoid, as seen in Figure 1, is activated using hormones and growth factors, the islet-like cells can produce insulin in response to glucose. These organoids are used for transplantation[8].

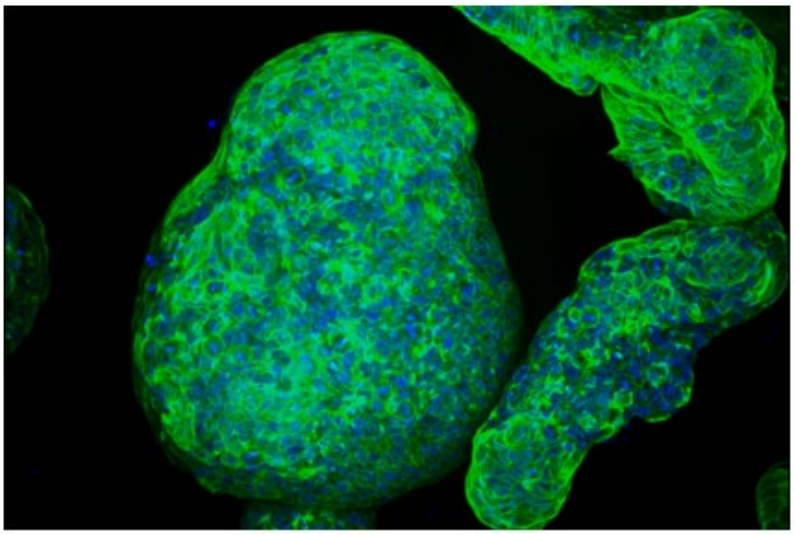

Figure 1: Growth of pancreatic organoids. Induced pluripotent stem cells (iPSCs) are being differentiated into insulin producing cells[29].

Research has shown that different islet types interact with each other, and this helps maintain glucose homeostasis[6]. Islet-like organoids which responded to glucose were created from human pluripotent stem cells (hPSCs)[15]. Experiments with conditions of elevated glucose stimulation suggest that 3D-induced IPCs, such as 3D islet organoids, are more sensitive to the stimulus of glucose than 2D induced cells[6].

In another study to produce β cells ex vivo, pluripotent stem cells and facultative progenitor cells from the pancreas and liver that are organ specific were used[1]. The generated β cells would be used for transplantation.

Advantages and disadvantages of using stem cells

However, there are many ethical issues concomitant with the use of embryonic derived stem cells due to their origin[7]. These stem cells are obtained as by the destruction of a human embryo which is the same as a human being to some scientists. However, other scientists hold the view that it would be against moral principles not to use embryos because they are quite beneficial for therapy and diagnosis of diseases. And some believe that is it okay to use embryos that are surplus and about to go to waste, but embryos should not be grown for the purpose of using them for research[9].

Moreover, human ESCs have teratogenic and tumorigenic potential[7]. Teratogenic potential means that it can cause abnormalities to a foetus during pregnancy[24]. And tumorigenic potential is when the stem cells for example are inclined to or do produce tumours[20]. The implication of this is when undifferentiated hESCS are transplanted *in vivo*, they can rapidly cause the creation of teratomas. A large benign tumour which consists of masses of disorganised differentiated tissue is called a teratoma[5]. Teratomas that have a core of malignant undifferentiated cells are called teratocarcinomas. These undifferentiated cells that are malignant are termed embryonic carcinoma[5]. Fortunately, hESC tumour dissemination is being addressed in modern technologies such as cell encapsulation[7]. In theory, cell encapsulation protects transplanted cells from rejection by the immune system using a membrane that is semi-permeable and artificial. This technique does not use immunosuppression which results in the elimination of numerous associated side

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effects[18,21]. Cell encapsulation precludes tumour dissemination because the encapsulated cells are sequestered[18].

Diabetic patient derived iPSCs

One advantage of creating patient-specific iPSCs for diabetics (DiPSCs) is that they can overcome immune mismatch and immune rejection which are current issues faced in stem cell therapy[6]. In a study by Millman et al., (2015, as cited by Chen S. et al. (2020)) human stem cells derived beta cells (SC-β), which were themselves derived from DiPSCs, were shown to resemble adult β cells in function[6].

One disadvantage of iPSCs is that the reprogramming processes for these stem cells have excessive costs and low efficiency due to the methodologies used. Now, small molecule gene inducers are being used and methodologies for reprogramming are being improved[7].

T1DM patients are diverse and thus a bigger number of stem cell lines that are compatible with a wide range of patients are required for future medical use[6]. Moreover, it was found using flow cytometry that only 15.9% of DiPSCs generate insulin producing cells compared to 25-50.5% of non-diabetic iPSCs[6]. This low result may be due to dysmetabolism causing epigenetic changes in T1DM[6]. These epigenetic changes will result in changes in insulin secretion[13]. Contrasted to hESCs, iPSCs have limited clinical utility due to incomplete maturation of cells that are differentiated, chromosomal aberrations and oncogenic potential[7].

Autoimmune issues

Autoimmune and alloimmune responses are still a big problem for cell replacement therapies with β cells derived from hESCs or iPSCs[6]. While encapsulation technology has progressed, the engraftment of β cells or transplanted pancreas progenitors that are derived from hPSCs still faces issues. These problems include engraftment rejection which is caused by the immune system. To overcome these difficulties, immune modulation techniques for hPSCs sound promising[6]. Currently, more immunosuppressive strategies are being developed. A few strategies involve eliminating certain Human Leukocyte Antigen (HLA) genes or specific HLA classes[6,27]. Some mesenchymal stem cells (MSC) also have immunosuppressive properties. In clinical trials in 2010, there was no definitive result about the use of mesenchymal stromal cells to modify the autoimmune response[1]. Contrastingly, by 2020, it was found that tolerogenic dendritic cells (MSC) and autologous haemopoietic stem cells (HSCs) that were modified in vitro had preservative effects[17]. Without hindering immune surveillance, these cells could protect newly created and endogenous β cells from the autoimmune response. This is done through the immunomodulatory properties the autologous stem cells possess which preserve β cells and limit autoimmunity[17]. However, further modification is required for the methods used to generate cells so that they can meet safety and quality standards in clinical purposes[17].

Efficacy of stem cell transplantation

One key question scientists are trying to answer is how effectual stem cell transplants are in treating T1DM. In early studies, there was no clear conclusion on the efficacy of stem cell transplants in T1DM patients[19]. In the review article by Madani S. et al. (2022), thousands of studies from 2000 to 2019 were featured. Among these an agreement was that MSC and HSC co-transplantation did significantly improve T1DM e.g. in HbA1c levels.

Conclusion

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β cell-like organoids made from human stem cells do seem promising in the treatment of T1DM. In previous studies, co-transplantation of MSCs and HSCs seemed to improve T1DM in the patients in the study[19]. In 2022, there were 6 clinical trials using hPSCs for the treatment of T1DM[26]. Most of the six clinical trials are measuring the efficacy, tolerability, and safety of certain hPSCs lines, e.g., VX-880, in T1DM patients[3]. The results of almost all of these trials have yet to be published so a general outcome cannot be made yet. More clinical trials of stem cell transplantation need to be done to see if this potential treatment option is safe for widespread use in humans. With more clinical trials and research, more of the limitations of stem cell therapy for type 1 diabetes mellitus could be overcome.

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