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Stem Cell Technology for the Treatment of Diabetes

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Abstract

Diabetes is the disease that is most common throughout the world. In this disease, there is high level of glucose due to the low production of insulin. Due to the limited number of donor for pancreas, stem cells technology has been used to produce insulin producing pancreatic cells. This article describes different ways of producing the pancreatic islets using different stem cells. By using these different stem cell technologies there was the production of insulin but the Beta cells that were produce from human fetal pancreatic stem cells gave the good results. In future, it could be possible that there will be the excellent cure for the diabetes using these stem cells technologies. These technologies will help us to fully eradicate the diabetes from the roots.

Introduction

Diabetes is a disease in which our blood glucose levels are high. Mostly glucose comes from the foods that we eat. Hormone that is involved in glucose transport into our cells to get energy is insulin. In diabetes, our body does not able to make insulin it is called diabetes type 1. In the Type 2 body is not able to use glucose [1]. A number of new techniques have been used in the past to treat he diabetes in the past these include improved insulin delivery and glucose monitoring systems, whole pancreatic and islet cell transplantation, and new methods for ß-cell generation either from pancreatic ducts or stem cells, or through genetic engineering [2-10].

Patients with diabetes have been characterized by relative lack of insulin producing pancreatic β-cells, as a result they are unable to establish normal blood glucose level [11]. Islet transplantation has been effective therapy for producing sustained insulin level in the patients [12,13]. Due to the lack of donor for the islets transplantation, this technique has been widely used. Human embryonic stem cells (hESCs) are has been a good alternative source of this treatment and numerous groups of cells have been used to differentiate in to insulin producing pancreatic Beta cells [14-23]. Knowledge of pancreas development is based on Model organisms [24-27] but we have not been fully recognized the pattern of pancreas development.

A strategy has been used in which the Human embryonic progenitor cells have been differentiated *in vivo*. Human fetal islet-like cell clusters successfully matured into glucose producing cells in mice [28], suggesting that a similar approach may be feasible for hESC-derived cells.

The diabetics can be cured by the re-plenishment of beta cells by the trans-plantation of Islets [13,29]. Tran-planted Islets can be collect from the two to three donor's pancreatic donors with exceeding ten thousand islets equivalent(IEQ)/kg [12]. One of the limits of the islets transplantation is the storage of the donors organs. By the use of stem cell technology this issues is address well. Stem cells have the capacity of self-renewal and the potential of differentiating into various cell types. The generations of insulin-producing cells from the human embryonic stem cells (ESC) and induced pluripotent stem cells (iPS) have challenges till now [30]. Lumelsky [31] and Assady [32] found that beta cells can be produced by the application of different physiological condition from the islets structure *in-vitro* from ESC. Cells produced by this method have many issues like low insulin production and lack of response to glucose. They can also cause the diseases like risk of cancer, controversial ethical issues and functional deficiency. Cells produced from iPS have such problems. Human adult stem cells can also be used for the production of insulin producing cells.

Expanded mesenchymal stromal cells from human umbilical cord and placenta, and differentiated them into functional islets *in vitro* [33,34] reported that islet-like cell aggregates derived from stem cells in human adipose tissue ameliorated experimental diabetes in mice. This is insufficient for the clinical applicable. It is shown that stem cells are present in the pancreatic duct and islets, that have the ability to differentia into the pancreatic exocrine and endocrine with number of pancreatic stem cells increase upon the destructive immune response. So, that pancreatic stem cells are used for the formation of functional endocrine cells *in vitro* condition. Pancreatic stem cells differentiating into endocrine cells have pancreatic duodenal homeobox- 1(PDX-1) and neurogenin 3. From the work of Bonner-Weir et al. showed that human pancreatic duct cells expanded and differentia into glucose responsive islet tissue *in vitro* given ITS (insulin, transferrin, selenium), nicotinamide and keratinocytes growth factor [6]. Ramiya et al. isolated murine pancreatic ductal epithelial cells into culture and induced them into functional islets containing alpha, beta and delta cells [5]. From these results, it is shows that some changes in the mRNA for the islets cells that differentia into some markers, response to glucose *in vitro* and reversed insulin de-pendent diabetics into the mice. Pancreatic cells isolate from the adult pancreas show low proliferative than the fetal pancreatic cells *in vitro* [35,36]. Human fetal pancreatic cells also have the ability to differentiate into the insulin-producing cells *in vitro*. Human fetal cells not have this ability but also have to correct high blood glucose efficiency in diabetic animals [37-39].

The limitation of the conventional treatments

In many current cases, diabetic complications are not controlled by the drugs because they do not provide sufficient control on the blood glucose level [40,41]. Whole pancreas transplantation was an effective treatment but it had some serious issues like surgery and long term immunosuppression. The failure of many conventional processes was a sad situation not only for the patient and relatives but also for the whole society. The cost of the treatment was very high due to the increase in the number of the patients of diabetes. So, the development in the treatment of the diabetes was very important for the patient and society also.

Islet cell transplantation

This treatment for the diabetes was effective one but the limitation for this treatment was that the donor cells were not easily available or shortage of them. So, for type 1 diabetes allogenic transplantation had been explored. Extraction of the islet cells from the donor pancreas and cells were injected into the portal veins of the liver. This procedure repeated two to three times and patient hospitalized for two to three months. This type of treatment improved the diabetic patient condition, if successful [42]. But the limitation for this type of treatment was that the people who were already immunosuppressed for the other type of treatment like kidney transplantation were not suitable for this transplantation of islet cells [43]. It was also possible that the immunosuppression itself the cause of the inhibition of proper functioning of islet cells or it also induced peripheral insulin resistance [44]. As a result, only 10% of the patients had been seen insulin independent on the International Islet Cell Transplantation Registry after the transplantation [43]. Promising results had recently been rumored from transplantation of huge amounts of island cells from body pancreases that were not HLA matched into seven patients with diabetes type 1 or had multiple hypoglycemic episodes or uncontrolled polygenic disorder despite compliance with the prescribed hypoglycemic agent treatment [45]. All the patients showed standardization of glycated heamoglobin concentration and lasting independence from the insulin injection at a median of eleven months follow up. The islet cells were pure i.e. they are free from the foreign proteins, and this, combined with a glucocortcoid free from the immunosupressive regimen, with success prevented rejection. Notably, each host versus graft and immune rejection reactions were apparently avoided. This was a tiny uncontrolled study, however, and its encouraging results ha to be compelled to be confirmed in larger irregular controlled trials. Even if any studies make sure the effectiveness of this approach, the requirement to get 2 to 4 donor pancreases for every patient and also the uncertainty concerning long term side effects from immunosuppression probably to limit its application to patients with terribly poorly controlled diabetic disorder.

Alternative sources of islet cells

Due to the shortage of the donor of the islet cells there was the search for alternative sources. several sources are suggested:

- From pigs
- Induction from human pancreatic duct cells
- Fetal pancreatic stem cells
- Induction of insulin producing B cells and each one has its own benefits and downsides.

Xenogeneic islet cells

Porcine islet cells are instructed as a virtually unlimited offer of insulin hormone manufacturing cells for transplantation. However, the medical specialty barrier to xenogeneic graft is well bigger than the barrier to human grafts. The development of the transgenic pigs was a great approach because due to these techniques we get the humanized pigs that have the more characteristics like the human cells. Xeno antigens were not present in such type of transgenic pigs but not required for their survival and the technology would possibly even permit production of pigs one by one matched for recipients HLA sort. The problem for this type of grafting is the risk of the retrovirus of the porcine which after this made the human their host. Retroviruses lead to permanent infection, and there were reports that porcine endogenous retroviruses from porcine cell lines and lymphocytes would infect human cells *in vitro* [46,47]. So, the US Food and Drug Administration concerned about this fact and stopped the trial with the porcine xenograft until the already transplanted people had the infection or not. Although 10 Swedish patients were transplanted with these porcine endogenous cells but not acquired any sort of infection [48]. Another type of research performed that was recent one in this a transgenic mouse is transplanted with the endogenous porcine islet and showed infection in almost all cells but this mouse was diabetic and highly immunodeficient [49]. Expansion and transdifferentiation of the duct cells of pancreas whereas the character of the pancreatic duct stem cells continues to be uncertain, recent advances during this space prompted a high level meeting sponsored by the National institute of Health on stem cells and pancreatic duct gland development [49]. It had been reported by the Peck et al. that pancreatic ductal epithelial cells that are isolated from adult non-obese diabetic mice can be grown in long term cultures and induced to produce functioning islets [5]. These *in vitro* generated islets were capable of lowering blood sugar concentrations to close traditionally when transferred in the diabetic non-obese mice. In the three-month duration of the study mice remained norm glycemic. Human cells of pancreatic duct were also developed and produced *in vitro* but they did not show any proper result when transplanted inside the body [50]. This promising line of analysis was being pursued by many laboratories. Not solely would the use of adult donor ductal cells avoid the disputation of the fetal cells however there were fewer biological issues related to certain alpha cells from duct cells than from, as an example, embryonic stem cells.

The use of a cell precursor and fetal pancreatic stem cells

Few years ago, vast improvements have made in empathetic fetal endocrine growth. These gives significant guide further efforts produce islet cells *in vitro*. The identification of endocrine predecessor cells in developing pancreas and regulation of differentiation by definite cellular pathway raises stirring probability that modulation cellular signaling can used *in vitro* to grow and distinguish endocrine precursor cells, taken either from embryonic pancreas from aborted fetuses or using pancreatic duct cells. Once molecular facts are solved culture conditions can developed to supply unlimited number of allogeneic a cell for trans-plantation.

In 2013 the fetal pancreatic cell was used to produce active insulin producing cells that was a excellent work by the biotechnologists. In this work, they took the fetal pancreatic progenitor cells from the aborted embryos and they firstly isolated them by identification of the pancreatic progenitor cells by using different markers e.g. PDX1 and NGN3. Then they provided them the media and performed culturing.

Some islets like structures were formed and the started to produce insulin producing cells. Then they checked the function of those cells. By observing the results these cells showed the high efficiency than the normal cells of the body. So, these fetal cells have the best proliferation and differentiation ability than any kind of other cells [54].

Embryonic stem cells

Stem cells are powerful biological units have utilized for decades in numerous features of biology. The mammalian body contains 200 different cell types, which all derive from fertilized egg cell. The fertilized human egg distributes and rise the primary embryo, at blastula stage, comprises cluster of totipotent cell from clonal embryonic stem cells derived. Such ESC proliferated in-definitely *in vitro* and can induced to differentiate into numerous different lineages *in vitro*, containing cardiomyocytes and neural cells, but differentiation into endodermal cell types has not described. The stem cells follow appropriate develop-mental pathway in order become insulin producing cells. Soria et al. by using embryonic stem cells transfected with insulin promoter, resulting insulin producing cells from mouse ESC which permitted them selectively make insulin producing cells.

Nevertheless, this procedure gives rise proliferating cells, and potentially malignant cells, rather than matures, post mitotic cells. However, this trial shows that embryonic stem cells differentiate along pancreatic endocrine path. These embryonic stem cells are being used to produce functional Beta cells and transplanted to patient for the treatment of diabetes as shown in the Figure 1.

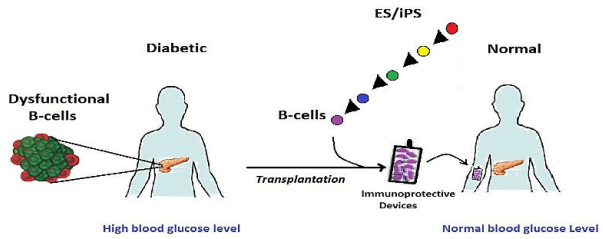

Figure 1: Formation of beta cells from IPS or ES cells and then transplantation to patient.

Induced pluripotent cells

IPS have high replicative capacity and pluripotency, these cells can be differentiated in to the insulin producing cells. These cells are highly similar to ES cells that have high differentiation ability. These are also able to maintain the normal telomere length. These cells can also differentiate in to the three germ layers that can also aggregate to form embryoid body. These three germ layers ectoderm, mesoderm and endoderm can be differentiated in to the different kinds of cells. so, we can also make the pancreatic beta cells form these cells that can be used for the treatment of diabetes. This process is also shown in the Figure 1.

Therapeutic cloning

The transfer nucleus of somatic cell from breast tissue into a donor oocyte from which nucleus has re-moved is used to clone mammalian species. The oocyte is re-placed by nucleus transfers genetic info of donor. This method used to clone Dolly sheep. Blastocysts can establish *in vitro* from oocytes and ESC that genetically identical to donor. The produced cells from embryonic stem cells established have organized supply of oocytes to produce therapy for diabetes. Then these cells (ESs) are collected at the embryonic stage. This development will avoid need of therapeutic cloning as shown in Figure 2.

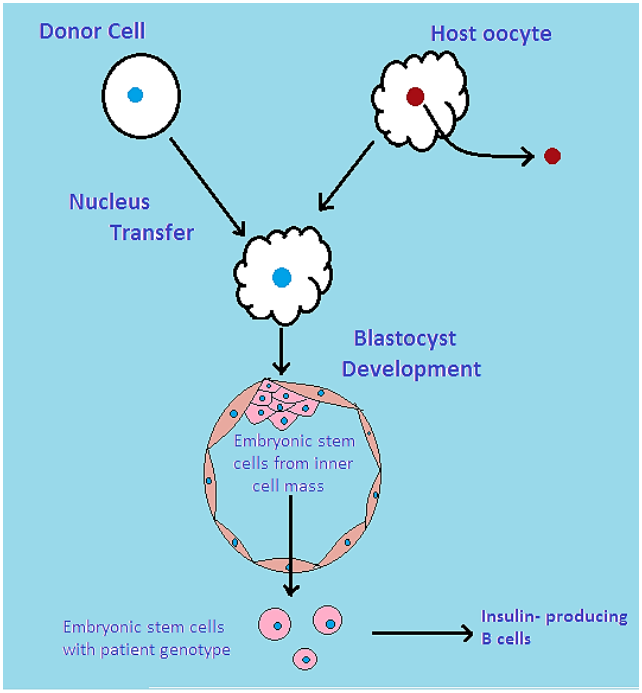

Figure 2: Oocyte is injected with the donor nucleus and developed in to blastocyst stage *in vitro* and then embryonic stem cells are collected at blastocyst stage.

Mesenchymal stem cell therapy

Stem Cell therapy provide handsome alternative to islet cell transplantation in type 2 diabetic patients. Mesenchymal stem cell therapy is best among autologous adult stem cells. Mesenchymal stem cells are less pluripotent than embryonic stem cells it renders the efficiency of MSCs to be differentiated into insulin secreting stem cells. Moreover, MSCs can be isolated different sources like umbilical cord, bone marrow and pancreatic stroma. MSCs can be obtained from the patient for autologous transplant. This of course can also be the case for ESCs if reproductive cloning techniques are followed; however, autologous MSCs from diabetic patients are still remarkably different from ESCs, because of prolonged exposure to hyperglycemia. Studies in transgenic mice showed that stem cells engineered to produce insulin did much more efficiently in hyperglycemic environment. MSCs are niche cells. Their traditional role in the bone marrow is the formation of the stroma and facilitation of growth, differentiation, and engraftment of HSCs.

Islets derived from human fetal pancreatic progenitor cells

From 10 to 12 weeks post conception pancreas is composed of many tube like structures that are confined within loose mesenchymal

stroma. These tube like structures are composed epithelial cells that are CD133 positive but insulin negative that indicate progenitor cells. After digestion with XI collagenase, the mesenchymal tissue was destroyed and islet-like structures were harvested. The progenitor-containing clusters adhered after 24 hours and the progenitor cells began expanding. These cells exhibited monolayer growth and proliferated quickly in medium containing bFGF, EGF and LIF, and confluent cells were epithelial-like.

Conclusion

By using these different kinds of stem cell technologies, we can make the insulin producing cells that will be helpful in the cure of diabetes that is worldwide disease. Out of all the stem cells fetal pancreatic cells are the best-known stem cells that have high efficiency than any other stem cells. Human fetal pancreatic stem cells have excellent capacity for proliferation; these may be induced to differentiate into insulin-producing cells resulting in the formation of islet-like structures *in vitro*. These are capable of secreting insulin and help to reduce hyperglycemia after transplantation in diabetic animals and resulted islets might become a potential source for islets transplantation in treatment for diabetes. In future, the time is near when there will be the fully cure of diabetes that is seem to be the cause of the most deaths now.

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