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Laryngeal mask airway insertion anaesthesia and insertion techniques

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Current trends in type 1 diabetes mellitus - stem cells and beyond

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Abstract

Search for a cure for type-1 diabetes mellitus has lead to many avenues of research, all having the same objective: to replace the lost beta cells and prevent their further destruction by the immune system. Transplantation of islets of Langerhans seems closer to achieving this goal with the recent introduction of new improved immunosuppressive protocols including monoclonal antibodies against the T-lymphocytes. But the need for acquiring beta cells in large numbers rather limits this approach. With the recent advancement in stem cell technology, it may be possible to gather enough stem cells for transplantation purposes. In this regard, embryonic stem cells have shown the greatest promise due to their capacity for unlimited proliferation and differentiation into any cell type. This review discusses the current direction of research regarding diabetes mellitus type-1, while explaining the progress being made in stem cell usage in finding a cure for the disease.

Introduction

Diabetes Mellitius is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin. The prevalence of diabetes mellitus is increasing all over the world and at the present pace of increase it is anticipated that by the Year 2030 the world will have over 366 million diabetics.[1] Late diabetic complications will cause considerable morbidity in 5-10% of these patients and place an enormous burden on the society. Identifying methods to treat or cure the disease, along with efforts to prevent its development, will be a key in stemming this pandemic as both patients and society have much to gain from development of improved treatment protocols for diabetes.

Type-1 (insulin-dependent) diabetes is a chronic disease affecting genetically predisposed individuals, in which insulin-secreting ß-cells within pancreatic islets of Langerhans are selectively and irreversibly destroyed by autoimmune assault. In the treatment of this condition insulin from exogenous sources has to be given resulting in strict adherence to dietary rules as well as sometimes causing erratic glycaemic behavioru. Attempts have been made to restore normal or near normal metabolic control by various means. These include islet transplantation[2], insulin gene therapy[3] and beta cell regeneration.[4] Much progress has been made in islet isolation technology and less toxic immunosuppressive therapy but the problem lies in obtaining sufficiently large numbers of purified islet cells from cadaveric donors. Insulin gene therapy focuses on converting non-beta cells into insulin producing cells by way of introducing insulin synthetic and secretory techniques. This in a way avoids the body's immune system but there is no way as yet to control the insulin secretion in response to a glycemic load. Regeneration of pancreatic beta cells is now possible given the recent advancements in stem cell technology. The obvious advantage of using stem cells is that they can self-replicate and differentiate into any cell type including the insulin producing beta cells and

therefore can be used to treat diabetes mellitus.

Review

Current therapeutic options for Type 1 diabetes mellitus: For the past 80 years the treatment of type 1 diabetes mellitus had been confined to the use of Insulin injectable or the recently introduced inhaled form[5] the latter still under consideration. Even with thrice daily insulin injection along with daily blood glucose monitoring, normal glycaemic control cannot be achieved.[6] Ideally a system should be devised to sense the blood glucose concentration and intelligently administer the required amount of insulin when needed. This can be achieved by an implantable, glucose-sensing insulin delivery system. Because of the recent advances made in computer technology, in particular miniaturization of computer chips and insulin pumps, it may be possible in future, to develop an implantable computer driven, "closed loop" insulin delivery system.[7]

Pancreatic transplantation is another option but the patient has to take immunosuppressive therapy that have their own side effects. Therefore, whole pancreatic transplantation is now attempted usually in cases where renal transplantation is also being done.[8] The latest trend in the treatment of diabetes mellitus type 1 has been the transplantation of islets of Langerhans only. The procedure involves injecting islets into the portal vein. To prevent rejection of islets, steroid immunosuppression is used, but this leads to a much higher need for insulin to control the hyperglycaemia and success is had in only a few percent of the cases. Recently James Shapiro[9] and his colleagues in Edmonton, Alberta, Canada, developed a protocol, now called the Edmonton protocol, using larger amount of islet cells and a different immunosuppression method. This lead to success in the majority of cases initially but a five year follow up showed only 10% maintaining insulin independence.[10,11] Much work needs to be done in refining this protocol as it can become in the near future, a cure for type 1 diabetes mellitus. One of the major problem with this approach is finding enough donors as the procedure requires 2 to 4 cadaveric donors. A further modification to islet transplantation is microencapsulation of human islet allograft and injecting them intra-peritoneally. It is a simpler procedure and has yielded good results.[12] An alternate source of islets could be xenografts but this has been associated with the complications of hyperacute graft rejection. With new improved immunosuppressive regimens and the development of genetically engineered animals this risk has been reduced, however, the possiblity of transmitting unknown zoonotic infections to the host recipient remains.[13]

Another source could be the conversion of non-beta cells into insulin producing beta cells by way of manipulating with the genetic makeup of the cell. Sapir et al[14] by transducing hepatocytes with a single gene, were able to influence them to transdifferentiate into human beta cells. The gene under study was the pancreatic and duodenal homeobox gene-1 (Pdx-1).[15] Several researchers have now shown that this gene is a transcription factor required for the normal beta cell development.[16] As human hepatocytes were used for the study the question of graft rejection due to allograft or xenograft did not arise. Also liver cells due to their inherent quality are easily cultivated in vitro and able to proliferate rapidly into large enough numbers to be transplanted as insulin producing islet cells in patients with type 1 diabetes mellitus.[17] Similar experiments have been done utilizing human bone marrow derived mesenchymal stem cells. After first infecting them with PDX-1, using recombinant adenovirus as a vector, these cells were successfully stimulated to produce insulin.[18]

Stem Cells

What are stem cells? "Stem cells" is a term used to describe precursor or unspecialized cells that can give rise to multiple tissue types. These cells have two important characteristics. They have the ability to renew themselves for long periods without differentiating into specialized cells. And they can, when given the proper signals, differentiate into cells representative of all three body lineages: ectoderm, mesoderm, and endoderm. There are many potential sources for stem cells. Embryonic stem cells are derived from very early stage of the embryo, the blastocyst stage.[19] Embryonic germ cells are collected from foetal tissue at a somewhat later stage of development (from a region called the gonadal ridge), and the cell types that they can develop into may be slightly limited. Still later, stem cells can be found in many adult tissues, the adult stem cells, functioning as a continuing source of mature cells for that particular region.

Potential sources of stem cells

Human embryonic stem cells: Stem cells represent a renewable alternative source of insulin-producing cells. Pluripotent human embryonic stem cells have the potential to proliferate indefinitely in culture[20] and have the ability to differentiate into any cell type of the body including beta cells thus providing a cure for diabetes type 1. Removal of cells from the feeder layer and growing them in suspension leads to the formation of embryoid bodies.[21] These are clumps of embryonic stem cells consisting of cells from all the three germ layers. Researchers have found out that subjecting the embryoid bodies to various growth factors, including nerve growth factor, leads to their expression of certain genes such as Pdx-1 which is found expressed throughout the epithelium of early pancreatic buds and

plays a role in the development of pancreas.[16,22] These genes can be regarded as cell markers helpful in identifying the insulin secreting cells.

Ethical issues are involved regarding the usage of human embryonic stem cells for the purpose of transplantation. To overcome this problem, some researchers have isolated a population of stem cells from human cord blood, a plentiful source with simple collection procedures. These cells express embryo stage specific marker, SSEA-4, and the multi-potential stem cell marker, Oct4. Upon proper stimulation these cells can be turned into insulin producing cells.[23]

Human embryonic stem cells, due to their high proliferative capacity, have the potential to form teratomas in the recipient.[24] Moreover, depending upon the source of these cells, they can be rejected by the host immune system.

Immunologically competent embryonic stem cells: Type 1 diabetes mellitus results from T cell-mediated autoimmune destruction of pancreatic insulin-producing ß cells. This will remain a problem even when stem cells are transplanted from outside sources. To overcome this problem cloning technology can be applied, where nucleus of the patient's own somatic cell is taken and inserted into an enucleated human egg and allowed to develop into the blastocyst stage. The embryonic stem cells derived thus from the inner cell mass are immunologically competent thereby avoiding allogeneic host versus graft reactions and the need for immunosuppressive therapy. These cells are cultured in vitro and allowed to expand to produce the billions of cells needed for transplantation therapy.[25]

Adult pancreatic stem cells - do they really exist? Another potential source of stem cells is found in the adult tissue. These cells are responsible for cell turnover or repair of tissues under normal circumstances. During foetal development, these cells can be identified by their characteristic markers such as Pdx-1, which is specific for beta cells. After birth and later in adult life, controversy exist as to the presence of stem cells in the pancreas.[26] Recent research, however, has shown the presence of stem-like cells within both the adult pancreas islets and pancreatic ducts by identifying a separate marker called nestin, normally found in developing neural cells. Further differentiation of the cells, into liver or pancreatic cells, depend upon the type of growth factor added to the medium.[27]

Although adult stem cells have the obvious advantage of having fewer ethical issues involved and are non-immmunogenic being part of one's own body, the main disadvantage is that they are not easy to cultivate and are much less prolific than embryonic stem cells.[28]

Only beta cells or all cells of the Islets: The normal response of the body to a glycaemic load is an initial quick release of insulin followed by a slower gradual discharge in order to fine tune the blood glucose level. Research has revealed that this pattern is not followed when only the beta cells are transplanted, however, control is achieved by transplanting all the cells of the islets. This is due to the fact that the islet cells influence each other via gap junctions in controlling the release of insulin from beta cells according to the physiological needs which would not be possible by transplanting beta cells alone.[29,30]

Autoimmunity: Even if we achieve in gathering enough beta cells by any means for transplantation, the problem of autoimmunity may still be there. One way to avoid detection by the immune system theoretically is to downregulate the expression of the major histocompatibility complex antigens present over the surface of the cell. In this regard a potential advantage of using embryonic stem cells is that they are more amenable to genetic alteration than are adult stem cells. In addition, it has been found that the expression of major histocompatibility complex antigens is inherently much less on embryonic stem cells than on adult stem cells.[31,32] Another promising area of research is monoclonal antibodies against particular T cell involved in the process of autoimmunity. Recent advancement in this regard is the development of a drug Thioredoxin-4; an anti-CD3 humanized monoclonal antibody, which is about to enter its phase III clinical trials. It has been shown that when administered for a course of six days, Thioredoxin-4 slowed deterioration of beta cells as well as decreased the amount of insulin needed from outside.[33,34]

Conclusion

With the rise in the incidence of diabetes mellitus and its added burden to the society, it is imperative that a cure be found for the disease. Research is going on in various directions from improving the quality and delivery of insulin to forming new beta cells. Stem cell technology has revolutionalized this scenario and the goal of finding a cure for diabetes seems to be within reach. In this regard, human embryonic stem cells seem ideal for the purpose as they fulfill the requirement of being easily available and able to divide rapidly to large enough numbers to be used for any practical purpose. Legal and ethical issues are still there, causing stem cell research to turn its head towards adult stem cells. Moreover, it may take many years to convert this research into a clinically useful application within reach of mankind. In the meanwhile we will have to find new ways to monitor blood glucose and administer insulin, maybe without the painful needle.

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