STEM CELL TRANSPLANTATION: A FUTURE FOR DIABETIC PATIENT

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ABSTRACT

At the moment, it is difficult to know which source of stem cells has the greatest potential. The β-cell is a very complex and differentiated cell. Thus adult stem cells, particularly those coming from the pancreas, seem to be easier to fully differentiate in normal β-cell with precise glucose recognition and regulated insulin secretion. In contrast, embryonic stem cells are more difficult to differentiate, but proliferation is not a major problem. In addition, regardless of the origin of newly generated β-cells, these cells will need to function in other places besides the pancreas and will need to be protected from rejection and autoimmune destruction. Thus research on both adult and embryonic stem cells should be pursued, because embryonic stem cells will be crucial to improve the research in adult stem cells and vice versa.

Keywords: Stem cell, β-cell, autoimmune, embryonic cell

INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases in developed western countries as well as in developing countries, which has a prevalence of approximately 8% in much of Europe and in USA[1]. This metabolic disorder is primarily characterized by hyperglycemia along with disturbances of protein, carbohydrate, and fat metabolism, and relatively lesser or no secretion of the hormone insulin[2]. Due to the life styles and dietary habits of people of this generation the incidence of diabetes continues to rise throughout the world. It is expected that the diabetic population will increase to 221 million by 2010[3]. Type 2 diabetes will be accountable for the majority of the new cases and its population is expected to be doubled to 135 million by 2010. China, Indian subcontinent and Africa are likely to be its favorite destination[4].

The limitations of conventional therapy

Current diabetes drug therapies are not sufficient to provide tight control of blood glucose to avoid diabetic late complications in many cases[5]. Whole pancreas transplantation is an effective form of treatment but it has limited application because it entails major complicated surgical procedure and also requires long term immunosuppression. This failure to prevent the morbidity associated with diabetes places an enormous burden not only on patients and their relatives but also on society. The costs of treating late diabetic complications are set to escalate because of the predicted sharp rise in the number of people with diabetes. Thus, both patients and society have much to gain from development of improved treatment for diabetes.

Stem cells transplantation

Stem cells are undifferentiated somatic cell that is capable of differentiating into any specialized cell type.[7, 8] These cells are able to divide into specialized cells in culture for indefinite periods. These cells can turn into other type of cell, but not into anything, called pluripotent. Some cells can be turned into any other type of cell at all, called tolipotent. Human development begins when a sperm fertilizes an egg and creates an embryo, which contains many types of stem cell that are probably rare or absent in adult, called embryonic stem cell (ESC). In adult many tissues are able to renew themselves by growth of new cells from stem cells within tissue, called Adult stem cell(ASC).[8] Stem cells are found in human embryos, umbilical cords, placentas,[9] bone marrow, spleen, liver, gut, pancreas, and adipose tissue could soon be used as a source of stem cells for the use in transplant.[10] They have the potential to proliferate and differentiate into any type of cell and can be genetically modified in vitro, thus providing a renewable source of cells for transplantation. Stem cell transplantation is an effective treatment for diabetes, stem cells are extracted from a donor pancreas and injected into the portal vein of the liver but its use is limited by shortage of donor material. The recent success of clinical stem cell transplantation has stimulated by research into alternative sources of insulin producing cells.[6]

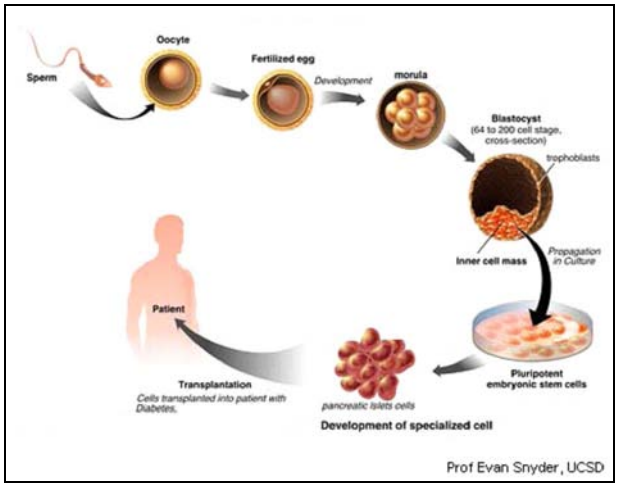
Alternative Sources of Insulin producing cell

The shortage of human donor pancreases for stem cell transplantation has led to a search for alternative sources of insulin producing cells. Several sources have been suggested from embryonic stem cell and adult stem cell like human pancreatic duct cells, fetal pancreatic stem cells, bone marrow derived stem cell, placental stem cell, liver stem cell, gastrointestinal stem cell and adipose stem cell.

1. Embryonic stem cells (ESCs)

Embryonic stem cells (ESCs) are derived from the inner cell mass of the developing blast cyst. Grown in culture, they have a stable karyotype and can differentiate *in vivo* into cells of endoderm, mesoderm and ectoderm origin and, thereafter, into cells that are specific for the various tissues in the body. Human and murine ESCs can generate embryoid bodies that contain cells with a β-cell-like phenotype *in vitro*.[11, 12] Differentiated ESCs can also lower blood glucose levels in rodents.[13, 14] Various groups have indicated that the number of insulin-producing cells during *in vitro* differentiation can be

enhanced by over expressing PAX4, PDX1 or NKX6.1 in ESCs.[14, 15, 16] An increase in the number of differentiated β cells can also be accomplished by culturing ESCs with differentiation factors. Murine ESC-derived embryoid bodies generate a population of cells that express insulin and PDX1.[17] The potential application of ESCs for producing β cells has brought optimism into the field of diabetic research. However, there is a downside that the lack of knowledge of normal differentiation is probably also responsible for the fact that at the moment products of stem cells that show many features of senescence such as multiple fragments of chromosomes are generated.[18] Moreover, change of culturing malignant cells during the differentiation process should be considered as a threat. ESCs closely resemble embryonic carcinoma cells, which can form teratocarcinomas. It has been shown that animals develop tumors when they are transplanted with ESC-derived insulin-producing cells.[19] Therefore, it follows that it is advisable to perform detailed efficacy studies on ESCs before proposing these cells as a suitable source of insulin-producing cells in the treatment of diabetes.



2. Adult stem cell

2.1. Bone-marrow-derived stem cells (BMSCs)

BMSCs are multipotent, capable of self-renewal and well known as a source of stem cells for blood cells. However, they can also differentiate into other cells, because BMSCs can migrate towards a site of damage[20, 21] and fuse with neighboring specialized cells to substitute damaged cells.[22] This, however, is probably a rare event in the pancreas.[23] Infusion of bone-marrow cells can restore chemically induced diabetes in mice.[24] Notably, however, it has not been indisputably shown that BMSCs differentiate into β cells. A recent study described engraftment of endogenous bone marrow in damaged islets.[25] However; the engraftment did not generate cells that express insulin or β-cell-specific transcription factors such as PDX1 or NKX6.1[25]. In spite of conflicting findings, the role of BMSCs in regenerative processes *in vivo* remains the subject of study because *in vitro* findings are promising.[24, 26] BMSCs that are cultured *in vitro* can produce *de novo* insulin and express insulin.[24, 26]

2.2. Placenta-derived multipotent stem cells (PDMSCs)

Placenta-derived multipotent stem cells (PDMSCs) from human term placenta were isolated and and demonstrated to possess multilineage differentiating capacity. PDMSCs, which are fibroblast-like cells, can be expanded *in vitro* and induced to differentiate into cells of various mesenchymal tissues, including adipocytes, osteoblasts, and chondrocytes. Chien et al. demonstrated PDMSCs can be used as an alternative resource for the generation hepatic progenitor cells.[27] However, whether the potential of PDMSCs included differentiation into insulin-positive cells which functionally secrete insulin *in vitro* and *in vivo* had been undetermined. But Chang et al. demonstrated that PDMSCs included differentiation into insulin-positive cells which functionally secrete insulin *in vitro* and effective control of blood glucose levels *in vivo.* [28]

2.3. Pancreatic stem cells

There is some evidence to suggest that pancreatic stem cells reside within pancreatic ductal cells, where they can differentiate and migrate to form new islets during both organogenesis and regeneration.[29] Ramiya et al. first described the generation of new islets from pancreatic ductal epithelial cells in vitro.[30] The authors grew pancreatic ductal epithelial cells manually isolated from prediabetic adult non-obese diabetic (NOD) mice in long-term cultures, where they were induced to produce functioning islets containing alpha (α), β and delta (δ) cells. These in vitro-generated islets showed temporal changes in mRNA transcripts for islet cell-associated differentiation markers, responded in vitro to glucose challenge, and reversed insulin-dependent diabetes after being implanted into diabetic NOD mice. Furthermore, a recent study demonstrated that fetal pancreatic ductal cells could differentiate into insulin-producing cells.[31] Liu et al. demonstrated that adult porcine pancreatic duct epithelial cells could differentiate into insulin-producing cells in vitro and these derived pseudo-islets were positive for expression of β-cells marker and could secrete insulin.[32] These data suggest that duct cells are a source of pancreatic progenitor cells. However, the specific cells in the pancreatic ducts that are the progenitors giving rise to the insulin-producing cells were not identified or characterized.

2.4. Liver stem cells

During embryogenesis the liver appear to arise from the same cell population located within the embryonic endoderm. It is assumed that the epithelial cell populations within the liver might share common stem cell populations. So liver stem cells would be another attractive source for new β cells. Zalzman et al. presented evidence that fetal human liver cells transduced with human telomerase (hTERT) and then PDX-1 produced cells with considerable amounts of stored and secreted insulin.[33] These cells not only secreted insulin in a regulated manner but also restored and maintained euglycemia for prolonged periods when transplanted into immunodeficient diabetic mice. Similarly promising results have been yielded with adult human liver cells. By using PDX-1 gene and soluble factors, Sapir et al. induced a comprehensive developmental shift of adult human liver cells into functional insulin-producing cells.[34] When transplanted under the renal capsule of diabetic, immunodeficient mice, these cells ameliorated

hyperglycemia for prolonged periods of time. Recently, Tang et al. succeed in reprogramming liver stem WB cells into pancreatic endocrine precursor cells by persistent expression of Pdx1- and Pdx1-VP16 mediated by lentiviral vectors. Upon transplantation into diabetic mice, these cells become functional insulin-producing cells and restore euglycemia.[35] Liver cells could thus provide another clinically relevant source of precursors to be used for the generation of transplantable insulin-producing cells.

2.5. Gastrointestinal adult stem cells (GI ASCs)

The gastrointestinal (GI) tracts have similar embryological origins in anterior endoderm and thus might derive from progenitors that differ in the expression of only a few (albeit crucial) genes. In the absence of Ptf-1a, endoderm-derived progenitors partially committed to the pancreatic lineage can develop into GI cells, including GI ASCs.[36] the plasticity of GI ASCs to act as islet progenitors has been investigated recently. Kojima and colleagues[37] transfected intestinal stem cells from the rat with genes encoding Pdx-1 and Isl-1, followed by exposure to the peptide betacellulin, which promotes pancreatic β-cell differentiation. The resultant cells made insulin, and reduced glucose levels *in vivo*, [38] illustrating at least proof of principle of this approach.

2.6. Adipose stem cell

Adipose tissue is abundant and easily accessible and could thus also harbor cells with the potential to differentiate in insulin producing cells. During the proliferation period, the cells expressed the stem cell markers nestin, ABCG2, SCF, Thy-1 as well as the pancreatic endocrine transcription factor Isl-1. The cells were induced to differentiate into a pancreatic endocrine phenotype by defined culture conditions within 3 days. Using quantitative PCR a down-regulation of ABCG2 and up-regulation of pancreatic developmental transcription factors Isl-1, Ipf-1, and Ngn3 were observed together with induction of the islet hormones insulin, glucagon, and somatostatin.[39]

CONCLUSION

Research in stem cell transplantation is set to develop rapidly. Future sources of β-cells derived from embryonic or adult stem cells offer an important potential on the road ahead to provide a cure for diabetes. At the moment, it is difficult to know which source of stem cells has the greatest potential. The β-cell is a very complex and differentiated cell. Thus adult stem cells, particularly those coming from the pancreas, seem to be easier to fully differentiate in normal β-cells with precise glucose recognition and regulated insulin secretion. In contrast, embryonic stem cells are more difficult to differentiate, but proliferation is not a major problem. In addition, regardless of the origin of newly generated β-cells, these cells will need to function in other places besides the pancreas and will need to be protected from rejection and autoimmune destruction. Thus research on both adult and embryonic stem cells should be pursued, because embryonic stem cells will be crucial to improve the research in adult stem cells and vice versa. Although stem cell research is on the cutting edge of biological science, it is still just beginning. Before the enormous potential and capabilities of stem cells can be developed for the treatment of diabetes, several goals need to be achieved by stem cell physiologists such as the establishment of the physiological basis for stem cell reprogramming, proliferation, differentiation, and self-renewal along with techniques to propagate them reliably and a consensus on the physiological criteria confirming the restoration of the tissue function following stem cell transplantation.

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