DIABETES & STEM CELLS: FACT SHEET

INTRODUCTION: Regulation of Blood Glucose in Health

In health, blood glucose levels are tightly regulated to provide sufficient fuel for the brain while avoiding the adverse effects of high blood glucose. This regulation is accomplished through a closed-loop system between beta cells in the pancreatic islets and the liver, which releases glucose into the blood between meals and takes up and stores surplus glucose after meals.

Pancreatic beta cells have the unique property of sensing blood glucose levels and coordinating this with insulin secretion that is delivered into the hepatic portal vein, where it acts directly on the liver to constrain glucose release into the circulation. The amount of insulin needed for this process can vary five-fold between individuals who are insulin sensitive and those who are more insulin resistant, such as those with obesity.

DIABETES TYPES, CAUSES, AND CONSEQUENCES

Diabetes is defined by abnormally high blood glucose levels that result from relative or absolute insulin deficiency.

Diabetes may occur when pancreatic beta cells are lost due to an autoimmune-or inflammatory mediated process referred to as type 1 diabetes (T1D). The lifetime risk of developing T1D is approximately 0.5%, and this risk has been increasing over the last 20 years, especially in young children. T1D is fatal unless treated with injected insulin, and its onset can occur at any age. There is a strong genetic component linked to specific human leukocyte antigen (HLA) subtypes, consistent with the immune basis of T1D.

The most common form of diabetes, impacting as much as 20% of some populations, is type 2 diabetes (T2D). The incidence of T2D increases with age but can occur in childhood. T2D is caused by insufficient insulin secretion to meet the individual's needs. There is a wide range of contributions to insulin resistance (most commonly due to obesity and a sedentary lifestyle) and beta cell failure in individuals who develop T2D.

Patients whose primary issue is insulin resistance can often avoid the need for insulin treatment if the insulin resistance is overcome, for example, through approaches that induce weight loss. A minority of people with diabetes have rare single gene defects and can sometimes be managed by targeted oral therapy. In contrast, patients with significant beta cell failure - common in what is known as lean type 2 diabetes - often require long term insulin treatment.

Diabetes can also occur due to the surgical removal of part or all the pancreas, as well as in diseases characterized by chronic pancreatitis, including cystic fibrosis. Loss of blood glucose control typically occurs when more than approximately 50% (~0.4 grams) of the mean beta cell mass (0.8 grams) in an adult is lost.

Diabetes can lead to several long-term health complications. Some are referred to as microvascular complications, as they are the consequence of damage to small blood vessels. Potential microvascular complications include blindness (diabetic retinopathy), kidney failure (diabetic nephropathy), nerve damage (diabetic neuropathy) and brain damage (cerebral microvascular disease). There are also macrovascular complications of diabetes as a result of damage to large blood vessels. Potential macrovascular complications of diabetes include heart attacks, strokes and poor circulation in the legs and feet which can lead to pain and sometimes require amputation. The risk of these complications increases with higher average blood sugar levels over time, which are typically monitored by the extent that hemoglobin is glycosylated in red blood cells (HbA1C).

ADDITIONAL RESOURCES

About Stem Cells
aboutstemcells.org

American Diabetes Association
diabetes.org

Breakthrough T1D
breakthrought1d.org

MANAGING DIABETES BY INSULIN INJECTIONS

All individuals with T1D or post-pancreatectomy diabetes require lifelong insulin injections. A subset of individuals with T2D also needs insulin. Insulin can be delivered as intermittent subcutaneous injections or continuous subcutaneous insulin infusion by a device known as an insulin pump. The latter can now be electronically linked to a continuous glucose sensor, which instructs the pump on how much insulin to deliver to maintain glucose levels within a target range.

While the sophistication of insulin delivery systems available for diabetes treatment has increased, the requirement for lifelong daily insulin injections or infusion remains a significant burden for patients, particularly for those who begin this journey in childhood. Insulin delivered into subcutaneous tissue cannot reproduce the dynamics of insulin delivered into the hepatic portal vein. This leads to ongoing risks of life-threatening low blood sugar events (hypoglycemia) and inevitable high blood sugar levels after mixed meals.

PANCREAS AND ISLET TRANSPLANT PROOF OF PRINCIPLE

The proof of principle for replacing beta cells in diabetes was first demonstrated through organ donor (allograft) pancreas transplants, which can achieve insulin independence in individuals with T1D, post-pancreatectomy diabetes and those with T2D who require insulin. Since only about 1-2% of the pancreas is composed of islets, this approach has been refined by isolating the islets from the pancreas before transplanting them, most often delivered into the hepatic portal vein, where the surviving islets become vascularized after about a week. These studies also highlighted that providing approximately 0.4 grams of beta cells is sufficient to reverse diabetes, presenting a seemingly attainable target for the stem cell field.

As a proportion of islets are lost during isolation and transplantation, this approach often requires sequential transplants from multiple donors to achieve insulin independence. Both pancreas and islet transplants are limited by the number of available organ donors. Additionally, all recipients of pancreas transplants, and most recipients of islets transplants require lifelong immune suppression to protect against allograft rejection and, in T1D, against the recurrence of autoimmune destruction of beta cells. An exception is made for patients who have their own pancreas removed due to diseases of the exocrine pancreas and then have their own islets reinfused into the hepatic portal vein. This is an autograft and requires no immune suppression, although it is often only partially successful because too few islets can typically be retrieved from a diseased pancreas.

While the islet transplant approach has demonstrated the benefits of replacing beta cells in both T1D and T2D, as well as in individuals requiring total pancreatectomy, this approach is limited by the availability of donor organs. As a result, there has been an intense interest in the diabetes community regarding the potential for stem cell-based beta cell replacement for patients with diabetes who require insulin therapy.

CLINICAL TRIALS OF STEM CELL-DERIVED BETA CELL REPLACEMENT

Human embryonic stem cell-derived beta cell replacement

The first clinical trials in T1D were conducted by Viacyte, which deployed embryonic stem cell-derived pancreatic progenitor tissue in encapsulated devices implanted subcutaneously. The goal was for the transplanted tissue to further differentiate into functional beta cells after transplantation. The device was designed to protect the transplanted cells from allograft rejection and autoimmune-mediated loss. Unfortunately, this approach was unsuccessful due to the loss of cells within the device.

In subsequent studies, the pancreas progenitor-filled devices were implanted with perforations in the membrane to allow for vascular ingrowth, although patients were now required to undergo immune suppression[1,2]. This approach resulted in better cell survival, including a minority of cells that were endocrine and some that immune-stained for insulin. However, no patients became insulin independent, although a small amount of insulin responsive to glucose was detected in some cases.

In a different approach, Vertex conducted clinical trials in individuals with T1D who were vulnerable to severe hypoglycemia events. In this case, the differentiation protocol used further differentiated pancreatic progenitor cells into partially functional islets, with endocrine cells in proportions similar to those found in adult human islets[3]. The stem cell-derived islets were transplanted via the hepatic portal vein with immune suppression. This approach resulted in most patients becoming insulin independent within six months, with progressively restored glucose-mediated insulin secretion and full resolution of severe hypoglycemic events.

Vertex is now conducting studies with the same stem cell-derived islets encapsulated in a new device intended to mitigate the need for immune suppression. Data from these studies are not yet available.

Induced pluripotent stem cell derived beta cell replacement

The first report of an induced pluripotent stem cell (iPSC)-derived transplant intended to treat diabetes was a case report of an individual with T2D who developed a poorly differentiated metastasizing teratoma at the site of the injected iPSC-derived implant[4]. Two subsequent case reports from different groups in China involved patients with diabetes: one with T1D and one with T2D.

In the patient with T1D, the iPSCs were generated using an extrinsic small molecules approach rather than virally induced genes. The 25-year-old recipient had an 11-year history of C-peptide negative diabetes, which had been treated with insulin injections. She was on long-term immunosuppression for two prior liver transplants. The iPSC-derived islets were transplanted beneath the abdominal anterior rectus sheath, and the patient became insulin independent within three months. At the time of reporting, the patient had remained insulin independent for one year, and the implanted islets could be imaged by MRI[5].

The T2D case report involved a 59-year-old patient with a 25-year history of diabetes, who was also immunosuppressed at the time of the iPSC-islet transplant due to a prior kidney transplant for diabetic nephropathy. In this case, iPSCs were generated via viral vectors and then differentiated into islets that were transplanted via the hepatic portal vein[6]. The patient's insulin requirements decreased to zero by 11 weeks and he was able to stop taking oral diabetes medications within one year. However, it is difficult to fully establish the role of the transplanted islets in this individual, as he had retained some endogenous insulin secretion before the transplant and experienced non-trivial weight loss afterward - a well-established cause for reduced insulin requirement.

FUTURE DIRECTIONS

SC-islet can reverse type 1 diabetes, but for how long?

Impressive progress has recently been made towards the goal of achieving reproducible insulin independence and freedom from recurrent, life-threatening severe hypoglycemia events achieved in patients with T1D by Vertex. This life changing advance overcomes the shortage of organ donor islets and can achieve insulin independence with a single treatment, in contrast to the use of organ donor islets. It will be important to determine how long the stem cell-derived-islets can maintain insulin independence, and, if necessary, what strategies might be used to extend their function.

Is there a pathway to avoiding immune suppression?

For now, patients with T1D require concurrent immune therapy to protect the transplanted islets from allograft rejection and autoimmune loss of beta cells. Ideally, reversal of T1D by stem cell-derived-islets could be made widely available without the need for immune suppression. Stem cell-derived-islet cells are presumably equivalent to neonatal islets and are likely more resistant to endoplasmic reticulum stress than organ donor islets as beta cell endoplasmic stress enhances recurrent autoimmunity and cell loss in transplanted organ donor islets. Therefore, it is possible that the stem cell-derived -islets, particularly in the relatively immune-privileged site of the liver, may require lower and more tolerable levels of immune suppression than organ donor islets.

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The use of physical barriers to protect transplanted islets from immune attack has a long history, but to date, there has been no success, as the implanted tissue is lost after the device is walled off by fibrosis. Another approach under consideration is to render the transplanted stem cell-derived-islets immune-privileged by mimicking the molecular strategies deployed by cancer cells.

Can iPSC-islet cells reverse non autoimmune mediated diabetes without immune suppression?

To date, the only reports of iPSC-islet are single-patient case reports. Questions remain about the practicality of developing a personalized therapy for patients with diabetes.

- How reproducibly will differentiation protocols work with each cell line?
- Will regulatory authorities accept the use of each iPSC line without prohibitive safety testing?
- Will iPSC derived islets act as autografts, or could minor changes that occur during iPSC formation and differentiation elicit an immune response?

If iPSC lines can be reproducibly differentiated into functional islets and are tolerated as autografts, this approach could be highly attractive for patients with non-autoimmune-mediated insulin-dependent diabetes, such as those with pancreatectomy or T2D.

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