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Type 1 Diabetes

Research is a dynamic enterprise that generates a wealth of knowledge. It provides a forum for debating ideas and working them into evidence-based theories. The clinical trial setting puts these theories to the test and may lead to evidence-based medicines that can alleviate symptoms or cure disease. But the process of taking research from bench to bedside is a lengthy one, and demands not only vision but also years of hard work and dedication on the part of scientists, physicians and patients. This document presents some basic information about diabetes, and in so doing, frames the context for the discussion that follows about the future application of stem cells to treat type 1 diabetes. The content presented is by no means exhaustive and readers may wish to peruse additional web resources or speak with their physicians for more information.

About Diabetes

Diabetes mellitus includes a range of diseases that result in high blood sugar (glucose) or hyperglycemia. Two of the four broad clinical classes are type 1 and type 2 diabetes. While they differ in their causes and the major populations affected, they share the same propensity for causing chronic damage to multiple organ systems as the diseases progress.

The cause of type 1 diabetes remains a mystery. It is known that certain susceptibility genes, (e.g., major histocompatibility complex genes contributing to the immune response), combined with some kind of trigger -- environmental or infectious -- promote the autoimmune attack on beta cells of the pancreas. When this happens the body's own immune system destroys the beta cells which are vital for producing insulin, a hormone essential for regulating carbohydrate, fat and protein metabolism and uptake of glucose by the cells. So vigorous is the onslaught on beta cells that the body is left with very little or no insulin at all. The high levels of glucose circulating in the bloodstream inevitably wreak havoc on the blood vessels, eyes, kidneys, brain, nerves and heart. Type 1 diabetes is also called childhood or juvenile-onset diabetes because it most commonly affects children and young adults under 30. In reality the autoimmune attack on beta cells can happen at any age.

It remains difficult to tease out the cause of type 2 diabetes as no single risk factor is to blame. Instead a complex interplay of genetics, environment and lifestyle collide to impact one's risk of developing the disease. Although it is not currently possible to predict type 2 diabetes based on genetics, a genetic component is indisputable. The risk of inheriting diabetes climbs to nearly 40 per cent when both parents have it, and multiple genes are known to incrementally contribute to one's overall risk. The best-known implicated environmental factors are obesity, nutrition and exercise; hence the conventional description is that type 2 diabetes occurs in sedentary and overweight individuals later in life. The role obesity plays cannot be understated: approximately 80 per cent of all type 2 diabetics are obese. Certain ethnic populations (African American, Latino, Native American, Asian American and Pacific Islanders), and health conditions (hypertension, polycystic ovaries or a history of gestational diabetes) are also known risk factors. In susceptible individuals, the coincidence of risk factors leading to disease is twofold: the body gradually becomes resistant to insulin and the beta cells lose their ability to secrete it. The risk of developing type 2 diabetes most often increases with age, but it is becoming more common in children and young adults who are obese.

Diabetes is the fourth leading cause of death worldwide and it's on the rise. The burden of health on the population is staggering and shows no signs of abating. For the past two decades, the global prevalence has skyrocketed from 30 million in 1985 to 366 million in 2011. Men and women are equally at risk. If this trend remains unchecked, it is estimated to reach 552 million people by 2030. Today in Canada, the Canadian Diabetes Association estimates that approximately 9 million Canadians are living with diabetes or prediabetes.

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Symptoms and long-term effects

The onset of symptoms in type 1 diabetes can be sudden. Individuals may experience increased thirst, frequent urination, constant hunger, weight loss, blurred vision and extreme tiredness. If the condition is not diagnosed and treated in time with insulin, a person with diabetes could lapse into a life-threatening coma. People with type 2 diabetes may experience a similar, but often less pronounced, gamut of symptoms.

The long-term ramifications of living with diabetes are considerable: the risk of death is at least double for diabetics as compared with non-diabetics. Fifty percent of people with diabetes eventually die from cardiovascular disease, mostly attributed to heart disease or stroke, and 10 to 20 per cent of individuals succumb to kidney failure. Diabetes is also the leading cause of amputation of the lower limbs as a result of poor blood flow. Diabetic retinopathy is a type of adult blindness and occurs when there is an accumulation of damage to the blood vessels in the retina. After many years of diabetes, approximately two per cent of people experience blindness and 10 per cent experience severe visual impairments. Nerve damage, or neuropathy, is also evident in up to 50 per cent of diabetics, who commonly experience symptoms of tingling, pain, numbness or weakness in the hands and feet.

Treatment of type 1 diabetes

Unlike type 2 diabetes, type 1 cannot be prevented or managed through changes in lifestyle, such as exercising and eating healthier foods. The vast majority of people with type 1 diabetes (and about one-third with type 2) manage the disease by testing their blood sugar and injecting themselves with insulin multiple times daily. This may sound relatively straightforward but intensive management is needed to effectively design regimens that balance blood sugar levels, which can fluctuate for many reasons – including food intake, exercise, hormonal changes, growth periods, infections and even emotions. Despite even the best efforts to tailor the insulin dose, diabetics will invariably experience periods when blood glucose is lower or higher than it should be. When blood glucose is too low a person can experience cognitive impairment or coma. At the other end of the spectrum, blood glucose that is too high can lead to debilitating complications. As a result, individuals with diabetes often live 15 years less than non-diabetics.

In an effort to more tightly control blood glucose levels, researchers began to explore the possibilities of using cell-based therapies that would replace lost beta cells. The first efforts focused on whole pancreas transplants, which have been performed now for over 50 years. Although they have been shown to lead to insulin independence for several years, pancreas transplants to treat type 1 diabetes are not widespread for a number of reasons. Being a major surgery, the accompanying risk of mortality is one to three per cent and the complications that ensue include cardiac death and systemic infections. In addition, to prevent the body from rejecting the transplanted pancreas, recipients must take powerful drugs to suppress their immune systems for the rest of their lives, leaving them susceptible to infections and a range of other diseases. Many doctors feel that the immunosuppressant therapy could be a greater health threat than the diabetes, and will only recommend a pancreas transplant if the patient also needs a kidney transplant which would require life-long immunosuppressant drugs anyway.

The complications arising from whole pancreatic transplants opened the door to the idea of transplanting only pancreatic islets, the precious patches of tissue in the pancreas that actually contain the beta cells. In this procedure, doctors use special enzymes to separate the islets from two or more pancreases of deceased donors and then a few teaspoons of islets are injected into the patient's liver. This organ is chosen because of easy access via the portal vein, and the islets successfully graft there. Once implanted, the beta cells in the replacement islets begin to make and release insulin. This procedure is easier and far less invasive than whole pancreas transplants. However, patients still require powerful immunosuppressant therapy to (1) prevent their bodies from rejecting the foreign cells, and (2) prevent their immune systems from attacking and destroying the replacement beta cells as they did the originals. The traditional, steroid-based anti-rejection drugs, in addition to leaving patients susceptible to other diseases, also have a negative effect on insulin-producing cells and eventually may exhaust the cells' ability to produce insulin. Despite improvements such as the Edmonton protocol for transplanting islets, long-lived islet graft survival rates are still not satisfactory. Attempts to transplant islet cells from living donors are not practical as the procedure would put the donor at risk for type 1 diabetes, and islet cell transplants from animals sources, such as pigs, might provoke serious immune responses or even cause diseases in the transplant recipient. An unlimited source of islet cells would go a long way towards helping type 1 diabetics remain insulin injection free.

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Réseau de cellules souches

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Can Stem Cells Help?

Because type 1 diabetes results from the loss of a single cell type – the beta cells in the pancreatic islets – and because there is proof that just a few teaspoonfuls of islet cells can restore insulin production, the disease is a perfect candidate for a regenerative stem cell therapy. Stem cells have the potential to grow into any of the body's more than 200 cell types so finding the ones that can be coaxed into becoming insulin-producing beta cells or restoring the secretion of insulin has been foremost on the research agenda for decades.

In theory, stem cells offer many advantages over the current transplant therapies: donor availability would not be an issue, and the stem cells could produce an unlimited source of new beta cells. These attributes have fueled the search for the best type of stem cells and the signals required to promote their differentiation into beta cells, either directly in the patient or in the laboratory first before being transplanted. Key to the success of these endeavours is being able scale-up the production of stem cells to meet the demand of transplant therapies.

High on the list of candidate stem cells being studied to treat type 1 diabetes are embryonic stem cells, induced pluripotent (iPS) stem cells, spermatogonial stem cells, and adult stem cells.

Embryonic stem cells

Embryonic stem cells are pluripotent, meaning that they have the potential to turn into any cell type in the body. It is not surprising, then, that scientists around the world have been able to devise methods for turning both mouse and human embryonic stem cells into insulin-producing beta cells. What is most promising about this work is that that the newly formed beta cells are able to keep blood sugar in check after being transplanted into mouse models of diabetes. However, translating these results into clinical trials is not as easy as it might seem. Researchers must first devise rigorous strategies to separate the newly formed beta cells from any undifferentiated embryonic cells that retain the potential to form teratomas, a type of tumour. In addition to this hurdle, the ethical concerns about using embryonic stem cells continue to hamper their future as therapeutic agents.

Induced pluripotent stem cells

Induced pluripotent stem cells offer the advantages of embryonic stem cells without the controversy about the source. These cells can be reprogrammed from normal adult skin cells, and can also become the multitude of cell types found in the body. In 2010, researchers first provided proof of principle for the clinical applications of induced pluripotent stem cells. They were able differentiate induced pluripotent stem cells in the laboratory into insulin secreting beta-like cells which, upon transplantation, could normalize blood sugar levels in diabetic mouse models. Getting one step closer to using induced pluripotent stem cells in a clinic setting, researchers are devising ways to reprogram the starting skin cell population that are safer than the original retroviral technique, which carries the risk of tumour formation.

Spermatogonial stem cells

Another intriguing avenue of exploration was revealed in 2010 when researchers showed that sperm stem cells could be reprogrammed to become embryonic-like cells that could, in turn, make beta-like cells. This approach is interesting because the reprogramming agents are growth factors rather than viral genes, and also because the beta-like cells could lower high blood sugar in mouse models of diabetes. Spermatogonial stem cells, although male-centric, could potentially be a vast source of pluripotent cells.

Adult stem cells

The pancreas seems an obvious place to search for stem cells that make beta cells. Studies in rodents have identified a number of different routes by which such beta cells could be made: differentiation from non-beta cells in the pancreas, slow replication of mature beta cells or from early stem-cell like progenitors. Although these cells types are not easy to isolate from the pancreas, researchers are continuing their investigations. The priorities are to identify the cells in people with type 1 diabetes along with the factors that will coax them into becoming insulin-producing beta cells.

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The fact that liver and pancreas are derived from the same embryonic tissue, called endoderm, has prompted researchers to question whether the liver could also be a source of stem cells that could be reprogrammed to make beta cells. The appeal of this approach is that the liver has a tremendous capacity to regenerate so removing a small portion of it from a diabetic would not put the patient at mortal risk, and the beta cells grown from the liver would be patient-specific. The key, though, is to figure out which factors can encourage the growth of beta cells and how they can be grown in large quantities in the laboratory. While the results are encouraging, there are as yet no protocols that can expand the reprogrammed liver cells in the numbers required for transplant therapies.

When researchers refer to bone marrow stem cells they mean either hematopoietic stem cells or mesenchymal stem cells (for a more detailed description of mesenchymal stem cells, see the Clinical Trials section, below). Hematopoietic stem cells have the advantage of being tried and true in terms of bone marrow transplantation procedures and they have also been proven to support beta cell regeneration in damaged pancreas tissue. In addition, both hematopoietic and mesenchymal stem cells harvested from the bone marrow are able to inhibit the autoimmune response that brings about the destruction of beta cells. This is a very important finding given that newly formed beta cells, regardless of how they are made, will need to be protected from the same autoimmune responses that destroyed the pancreatic beta cells in the first place.

Canadian contributions

The most important contribution to date by Canadian researchers has been the development of the Edmonton protocol in 2006 for islet cell transplantation. The protocol not only validated the clinical path for cell therapy – in that it showed that a simple infusion of a few teaspoons of cells could effectively reverse type I diabetes – but it also solidified the goal of using stem cells to develop an unlimited supply of cells. The protocol has been used worldwide for islet cell transplantation, and researchers are now developing ways to encapsulate the transplanted cells to shield them from autoimmune attack that inevitably occurs.

At the same time that researchers are grappling with the best stem cells to use for treating type 1 diabetes, they are also looking for ways to ramp up the production of stem cells or beta cells in the laboratory in order to address the shortage of tissue for transplantation. Canadian researchers from the Alberta Diabetes Institute are spearheading the development of The Cell and Tissue Innovative Research Centre, a world-class GMP (good manufacturing practice) facility scheduled to open at the end of 2013. The facility will be able to expand any type of stem cell with the goal of providing ready access to unlimited numbers of high quality cells, including insulin-producing cells, for clinical trials. Using pig islet cells or pancreatic stem cells as sources, the researchers are devising transplantation strategies free of immunosuppressive drugs or with co-transplantation of cells that might protect the grafted cells. Researchers in British Columbia are buttressing these efforts by identifying factors that can promote the development of stem cells into fully functioning insulin-producing cells or that can expand pancreatic islet cells for transplantation. In the hopes of avoiding immunosuppressive agents all together, they are also devising methods to encapsulate the newly formed beta cells to isolate them from immune attack.

Scientists at the Montreal Diabetes Research Centre are taking a different tack by searching for genes that can turn on tissue repair in the pancreas. Comparing a normal mouse pancreas with one that was regenerating following surgery, they found a protein that seemed to be contributing to the regeneration. Diabetic mice without this protein cannot regenerate their pancreas but when the protein is administered it stimulates the formation of new insulin-producing islets, perhaps from resident stem cells. The group is further characterizing the protein to ascertain whether it would be a good candidate as a therapy for type 1 diabetes.

Clinical studies

Currently, the majority of clinical trials evaluating stem cell therapies to treat type 1 diabetes explore the use of hematopoietic stem cells from the bone marrow or mesenchymal stem cells from bone marrow or other tissues. For the most part, the stem cell transplants are autologous (patient specific), and the therapy includes administering drugs that first destroy patient's immune system. It is hoped that this approach will reprogram the immune system so that it will not attack the newly transplanted stem cells, giving them the opportunity to restore normal insulin production.

Soon to finish is the nine-year clinical trial sponsored by the University of Sao Paolo, Brazil, Northwestern University

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and Genzyme. The goal of this Phase I/II study is to test the safety and efficacy of autologous hematopoietic stem cell transplantation for early onset type 1 diabetes mellitus. In this trial, peripheral blood hematopoietic stem cells from the bone marrow were harvested from patients 12-25 years of age. After the patients received high doses of chemotherapy to destroy the immune systems, the stem cells were administered intravenously. Patients were monitored for five years with the hope that the treatment would offset the amount of exogenous insulin required to manage blood sugar levels. Other trials evaluating hematopoietic stem cells are in various stages of completion.

Clinical trials transplanting mesenchymal stem cells into type 1 diabetes patients take advantage of two assets these cells possess. Firstly, they have the regenerative potential to repair beta cells, and secondly they can modulate the immune system by inhibiting the responses that lead to the autoimmune attack on pancreatic beta cells. In the trials underway, the most common source of mesenchymal stem cells is bone marrow, but some studies are also investigating mesenchymal stem cells from cord blood or menstrual blood. If successful, these trials will not only prove the safety and efficacy of mesenchymal stem cells but also they could replace the need for immunosuppressive drugs in future transplant therapies. The field eagerly awaits the results of a large phase II clinical trial sponsored by Osiris Therapeutics (Genzyme) in which 60 patients were given Prochymal, a special human mesenchymal stem cell preparation.

Also on the horizon are trials where mesenchymal stem cells are being cotransplanted with pancreatic islets, which have already demonstrated clinical benefits in patients with type 1 diabetes. The rational for adding the mesenchymal stem cells is to improve the engraftment of the islet cells and to protect them from being damaged by the immune system. The hope is that this approach will promote beta cell function, thereby reducing or eliminating the requirement for exogenous insulin.

Web Resources

Readers may wish to peruse the recommended sites below for more information about type 1 diabetes and the possible applications of stem cells to treat this disease.

- Canadian Diabetes Association: http://www.diabetes.ca/
- JDRF (Canada): http://www.jdrf.ca/
- American Diabetes Association: http://www.diabetes.org/
- National Institute of Diabetes and Digestive and Kidney Diseases: http://www.niddk.nih.gov/
- Public Health Agency of Canada: http://www.phac-aspc.gc.ca/cd-mc/diabetes-diabete/index-eng.php
- International Diabetes Federation: http://www.idf.org/
- World Health Organization Diabetes Program: http://www.who.int/diabetes/en/