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Regenerative Medicine : A Promising Approach In Overcoming Diabetes As An Increasing Economic Health Burden

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Abstract

Diabetes mellitus is a serious public health issue, particularly in developing nations due to the cost associated with its management and its debilitating complications. Patients with diabetes mellitus type 1 are insulin-dependent due to complete loss of insulin producing beta cells in the pancreas and require a well-balanced regimen of insulin injections for life-time. The patients with diabetes mellitus type 2 also require insulin therapy in later stages of disease. In these patients insulin helps by correcting the insulin deficiency, however, the root cause of the disease still persists. Regenerative therapy is now offering solutions and hope to people with insulin-dependent diabetes. This paper gives an outline of the currently used methods in regenerative medicine that aim to re-establish the functional beta cells and restore the body's original ability to regulate blood glucose levels.

Keywords: Diabetes mellitus; beta cells; insulin; regenerative medicine; stem cells;

1.0 INTRODUCTION

Diabetes is a global public health problem that threatens the economy of all nations, particularly the developing nations. According to the International Diabetes Federation, at least 285 million people worldwide are affected by diabetes, and by the year 2030, the number is expected to reach 438 million. Nearly two-third of all diabetes cases occurs in low- and middle-income countries. (Zhang et al. 2010) Asia accounts for 60% of the world's diabetic population (Chan et al. 2009). The costs associated with the

management of diabetes are enormous. It was estimated that diabetes accounts for 12% of health expenditures globally, or at least $376 billion—a figure expected to hit $490 billion in 2030 (Zhang et al. 2010).

The current therapeutic approaches in the management of diabetes primarily aim to control high blood sugar level without addressing the primary cause of elevated blood sugar level. Considering the huge cost associated with the management of diabetes mellitus, it is now crucial to explore the newer technologies that may help in correcting the root cause of the disease. These approaches may benefit patients by eliminating the risk of long-term complications on one hand and saving on the cost associated with life-long management on the other hand. In this paper we present a brief outline of the currently used technologies in regenerative medicine that aim to address the root cause of diabetes mellitus.

Diabetes mellitus: Types and current management

Diabetes mellitus is of two types. The most common type of diabetes that generally has onset during adulthood is largely a lifestyle disease, and is known as diabetes mellitus type II. Genetic makeup also plays a role in development of diabetes mellitus type 2. At the onset, patients with type 2 diabetes have elevated blood sugar levels as the body's sensitivity to insulin is reduced. Insulin is a hormone produced by the beta cells of pancreas in response to meals and its primary function is to facilitate utilization of glucose in the body. Hence, in people with diabetes type 2, body fails to utilize glucose despite presence of insulin. At this stage the treatment generally consists of oral administration of antidiabetic drugs. With progression of disease, patients also develop insulin deficiency and treatment now often requires administration of insulin.

Another type of diabetes that generally affects children and adolescents results from inability of the pancreas to produce insulin and there is absolute insulin deficiency. This inability of the pancreas is due to loss of specific cell, known as the beta cells of pancreas. In majority of cases, destruction of beta cells results from body's abnormal immune response towards beta cells. The causes of abnormal immune responses are not yet entirely understood, however, scientists believe that both the genetic and environmental factors are important triggers. Its onset has nothing to do with diet or lifestyle and as there is absolute deficiency of insulin, the only treatment is insulin injections for the lifetime.

Both type 1 and type 2 diabetes are associated with dangerous and debilitating complications. In a multinational study, 50% of people with diabetes die of cardiovascular disease, primarily heart disease and stroke (Morrish et al. 2001). Several other complications of diabetes include damage to kidneys, nerves and retina. Living with diabetes, particularly diabetes type 1 is a constant challenge. Patients must carefully balance insulin doses with eating and other activities throughout the day and night. They must also measure blood-glucose level by pricking their fingers few times a day. Despite all precautionary measures, people with type 1 diabetes still run the risk of dangerously high or low blood-glucose levels, both of which can be life threatening.

Regenerative medicine in diabetes

Although, insulin injections help patient with diabetes to survive, the root cause of the disease still persists. Hence, regeneration of pancreatic beta cells is the answer for definitive treatment of insulin-dependent diabetics. The purpose of regenerating beta cells is to restore the number of pancreatic beta cells to regain the body's original ability to regulate blood glucose levels. Hence, regenerative technologies in medicine are now offering solutions and hope to people who are suffering from conditions due to irreparable damage to tissues and organs.

There are two commonly investigated methods for regenerating lost beta cells of pancreas. In one method beta cells are first prepared in laboratory and then are implanted in the patient's body (Ex vivo approach). Another method aims to regenerate beta cells in the body by introducing genes and some factors that help in regenerating beta cells (In vivo approach).

Ex vivo approach

Ex vivo approach uses stem cells for regenerating beta cells of pancreas. Stem cells can be considered the mother cells that are capable of self-renewing as well as multiplying and developing into any other type of cell such as those of blood, heart, bones, skin, muscles, brain etc. Because of their ability to replenish other cell types, they act as an internal repair system. Stem cells by themselves are unspecialized cells i.e. they cannot perform any specialized function of the body until they transform and specialize into other cell types. The process by which unspecialized stem cells become specialized cells is known as differentiation and it occurs in several steps. What triggers the cell differentiation still remains incompletely understood. Scientists believe that internal triggers that reside within the gene could have a role to play. At the same time there can be external factors such as chemicals secreted by other cells, contact with neighboring cells or some molecules in the microenvironment of these cells. Answers to several questions regarding differentiation remain unknown. For example: which is the stronger trigger-genes or the external factors; do all cells differentiate in response to similar triggers; are there any specific factors that trigger differentiation of stem cells into specific specialized cells? Answers to these questions would greatly benefit development of stem cell based therapies for specific diseases.

There are different sources of stem cells and accordingly stem cells can be of 3 different types:

Embryonic stem cells: These stem cells, as the name suggests, are derived from embryos. Scientists were first able to obtain stem cells from mouse embryo in 1981. Further studies on these cells led to discovery of methods to derive stem cells from human embryo in 1998. Embryonic stem cells are derived from embryos that develop from a fertilized egg in an in vitro fertilization clinic and then donated for use in research with informed consent of the donor. They are not obtained from the fertilized eggs in a woman's body. The cells from human embryo are grown or cultured in a plastic laboratory dish containing a nutrient broth, known as culture media. Once the cells survive and multiply, they can be sub-cultured into several fresh dishes. Embryonic stem cells that have proliferated in culture for a long time without differentiating, and are capable of differentiating into specialized cells are referred to as an embryonic stem cell line. Scientists expose these undifferentiated stem cells in culture to specific triggers to allow there differentiation into specific cell types such as insulin secreting beta cells.

Adult stem cells: These are found in the adult tissues or organs. They can renew themselves and may differentiate into all of the major specialized cell types of the tissue or organ. Their primary roles in a living organism are to maintain and repair the tissue in which they are found. The most commonly used example is the bone marrow. Research is ongoing to find optimal methods that can allow rapid growth of adult stem cells in laboratory and also the recipes to direct their differentiation into specific cell type. As compared to embryonic stem cells, adult stem cells can differentiate only into the different cell types of their tissue of origin. Since the adult stem cells are very few in a mature organ, it is difficult to find them and they are also difficult to grow compared to embryonic cells.

Induced pluripotent stem cells: These are the adult cells that have been genetically reprogrammed to an embryonic stem cell–like state. They behave like embryonic stem cells and features that differentiate them from embryonic cells are not fully known.

There are several reports of using all three types of stem cells, especially in animals, to regenerate beta cells that can produce insulin (Hori et al. 2002; Lumelsky et al. 2001; Nir et al. 2007; Takahashi et al. 2007). However, it still remains difficult to accurately direct differentiation of any of these cell types and produce mass quantities of insulin producing beta cells. Furthermore, their effectiveness and possible adverse effects in patients remain to be determined.

In vivo approach

In vivo approach is based on creating insulin secreting beta cells by manipulating cells that exist in the body. The technique uses genes that produce differentiating factors. These differentiating factors target adult stem cells that exist in liver and are of pancreatic beta cell lineage i.e. they can differentiate into insulin secreting beta cells. Hence, the in vivo approach uses adult stem cells that exist in the body and hence is considered more physiological. There is no requirement for transplanting the cells or tissue and hence the method is noninvasive. Ethical issues are also not a big concern with this technique as is the case with the in vitro approach. However, there are several unresolved issues such as control of in vivo differentiation and safety and efficacy of these methods.

This approach seems to be particularly useful in patients with diabetes mellitus type 2 who have not lost the beta cell mass completely. Scientists have shown that pancreatic beta cells retain the self-propagating properties and can be triggered to proliferate by differentiating factors. Some studies have shown that GLP-1, a hormone from gut, stimulates proliferation of beta cells (Xu et al. 1999; Brubaker et al. 2004). There are also reports suggesting methods that employ introduction of genes into cells of completely different lineage and stimulate them to develop into insulin secreting cells. This approach may be useful in patients with diabetes mellitus type 1 who have completely lost the pancreatic beta cells.

2.0 CONCLUSIONS

Management of diabetes and its long-term complications remains a challenge for physicians and patients. Regenerative medicine that aims to re-establish the insulin secreting mass of beta cells of pancreas

provides great hopes as a new treatment modality. Current status in this field is rapidly developing; however, several technological details are yet to be explored. Moreover, further scientific investigation into the disease etiology, diagnostic tools for early detection and monitoring are also crucial. Perhaps the integrated approach involving several research fields is the key in making regenerative medicine achieve its purpose of completely curing diabetes mellitus.

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