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Gene therapy in diabetes: A review of case study conducted over mice to cure type 2 diabetes and obesity

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Abstract : Type 1 diabetes "(T1D) is characterized by the destruction of insulin-secreting beta cells in the pancreas, which results in insulin insufficiency and hyperglycemia. If they don't have daily insulin injections, these patients will die from diabetic ketoacidosis (DKA). T1D patients may benefit from a variety of gene therapy techniques, including viral vector and non-viral transduction, such as decreasing autoreactive T cells to minimize islet death (prophylactic) or substituting the insulin gene for patients (post-disease). The lack of cadaveric islets for transplantation and the associated immunosuppression necessitated the development of a novel strategy for attaining euglycemia. Despite extensive research on insulin ectopic expression and islet modification, no cure has yet to be discovered. In the treatment of Type 1 Diabetes (T1D)", numerous gene transfer techniques and a range of gene therapy procedures have been used, as well as possible novel treatments.

Key Words : Diabetes, Gene, Gene therapy.

Introduction

Chronically high blood "sugars are caused by insulin deficiency or insulin resistance, which are the root causes of diabetes mellitus (BGLs; hyperglycemia). Long-term hyperglycemia may lead to organ failure, such as neuropathy, nephropathy, retinopathy, peripheral vascular disease, morbidity, and mortality, as discussed by Sowers and Epstein, Klein and Vinik et al. Diabetic symptoms may emerge in a number of ways and at any age or stage of life when they first arise. Type 2 diabetes (T2D), which accounts for more than 80% of all cases in the United States, Canada, Europe, and Australia, is on the rise internationally. Other causes of diabetes include gestational diabetes, endocrinopathy, and post-viral infections", which account for the remaining 5–10% of people with diabetes.

Epidemiology.

Immunodeficiencies are more common in women than men. In most communities studied, there is no difference in the prevalence of T1D between sexes. Study after study has

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demonstrated that women are more likely than men to be diagnosed with type 1 diabetes. T1D was more common in men than in women in Jamaica, with a male to female ratio of 2:3. When compared to other studies, these findings contradict those of other organizations, which found that males were more likely than women to suffer from Type 1 Diabetes. A Boston survey of European populations aged 15 to 40 found a 3:2 male to female ratio. youngsters aged 6 and younger found the same thing. T1D is the most common type of diabetes among Americans under the age of 19 and accounts for around two-thirds of all new cases. Between the ages of 4 and 6, and between the ages of 10 and 14, T1D onset is at its peak.

A total of 246 million people throughout the globe have “diabetes (types 1 and 2). In the United States, the prevalence of type 1 diabetes (T1D) is 23.6 per 100,000 people. T1D is becoming more prevalent over the globe, with an annual rise of 2% in Europe, 5% in the Middle East, and 3% in Australia. More than 13,000 children and adolescents under the age of 19 are diagnosed with T1D each year”. 28 In the United States, the frequency is 2.0 per 1,000 people. Increased distance from the equator increases the chance of acquiring type 1 diabetes (T1D). According to the research, those who relocate from low incidence regions to high incidence areas are more likely to get T1D. Finland and Sardinia have the highest reported incidence of T1D, whereas Asia has the lowest. T1D prevalence varies widely among comparable geographic regions. There is a strong possibility that environmental variables have a role in a disease's prevalence. T1D is more likely to develop in a pregnant woman who has had a viral illness, had an immunization, had a poor diet, had a history of pre-eclampsia, or had neonatal jaundice. Low birth weight, on the other hand, lowers the chance of illness. T1D is hypothesized to be affected by the climate in which a person lives. However, research is inconclusive as to whether or not environment affects the “occurrence of type 1 diabetes (T1D). The incidence of some diseases is greater in certain ethnic groups in the United States than it is in others. Caucasian adolescents had the greatest rates, followed by African American and Hispanic adolescents. Asian/Pacific Islanders and Native Americans have the lowest rates.

Gene therapy

One of two methods—germ line or somatic manipulation—can be used to carry out genetic engineering. Somatic genetic manipulation only affects the person to whom the transgene is delivered, while genes are passed to kids through germ line genetic manipulation. There are

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two types of gene transfer: in vivo and in vitro. The vehicle for the transgene must be guided to the target cells, and the gene product must be shielded from immune assault in order for in vivo" administration to be effective. To perform genetic manipulation" on cells in vitro, the target cells must be readily withdrawn from the host and re-implanted.

Type 2 diabetes mellitus (T2DM) and its consequences have received a lot of attention in recent years. Over the last five years, we've released a comprehensive evaluation of the research on gene therapy for type 2 diabetes (T2DM). Three issues have been clarified as a result of this examination. For starters, what are the anti-diabetic genes and how do they work? Target genes, including those that regulate glucose homeostasis, improve insulin secretion or sensitivity, and alleviate diabetic-induced problems, are outlined in this paper. Second, how and where should the delivery be made? The merits and downsides of each of the basic strategies for delivering target genes into diabetic individuals are examined. Finally, what are the prospects for T2DM gene therapy research in light of these recent developments? This research might focus on a variety of unique targets in simultaneously, with a particular emphasis on combinational techniques. Finally, many of the genes implicated in the occurrence and progression of type 2 diabetes show considerable promise as future targets for gene therapy. The great efficacy and safety of probiotic oral administration of target genes for future T2DM gene therapy makes it a promising option for further development.

Gene transfer methods.

Several different techniques of gene transfer have been used. Approaches such as calcium phosphate co-precipitation, lipofection, microinjection, electroporation and biolistics are all examples of non-viral methods.

Gene therapy treatments.

Immunosuppression, apoptosis, ectopic gene expression, transplantation, and induction of tolerance may all be employed to maintain euglycemia.

Restoration of blood sugar levels after the death of pancreatic islet cells. Non-targeted gene expression occurs. Immune system attacks the pancreas in T1D, and numerous gene treatments aim to mimic -cell activities in cell types that aren't affected by the pancreas. To have ectopic gene expression, genes must be expressed in cells other than those where they ordinarily reside.

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Immunosuppressive therapies are avoided since the recipient of the transplant is the focus of genetic editing, "which may be an unlimited source of autologous cells. Pro-insulin transcription and translation, regulated maturation of pro-insulin to mature insulin, regulated storage and regulated release of mature insulin from -cells are all critical components of blood sugar regulation. Cells such as the hepatocytes, muscle, and the neuroendocrine system may be used to manipulate insulin producing cells in the absence of -cells.

The epithelial cells. Unlike islets, epidermal keratinocytes may be replenished indefinitely when used as autologous cells. Proinsulin that had been modified to enhance the cleavage of furin and a self-dimerization mutant of FK506-binding protein were genetically engineered to generate bioactive insulin in the presence of rampamycin. When disulfide bonds between C-peptide and the A-chain and B-chain are broken, C-peptide and mature insulin are released. Proteases are found in cells like keratinocytes and hepatocytes when mature insulin is required. An endoprotease found in abundance in the Golgi apparatus (furin) was inserted into the human insulin gene so that liver cells could transform proinsulin into mature insulin. The keratinocytes were evaluated in vitro for insulin secretion after being stimulated with rampamycin. 30 minutes after rampamycin was administered, insulin was detected in the supernatant", and insulin was no longer detectable 2–3 hours after rampamycin was withdrawn. Streptozotocin-injected diabetic mice were used to evaluate insulin-producing keratinocytes in vivo (STZ). Insulin was detected in plasma for up to four hours after rampamycin was administered to the animals. Animals in the control group that did not get rampamycin stimulation or cells transduced did not have insulin expressed in their plasma.

If Lei and his colleagues modified keratinocytes before Tian and his colleagues, they utilized a different retrovirus to create proinsulin in the C-peptide area between the A- and B-chains, rather than a lentivirus.

63 Enzyme-linked immunosorbent assays (ELISA) were used to identify the protein proinsulin in transduced cells (ELISA). The supernatant could not be used to determine the conversion of proinsulin to mature insulin, as was the case with the measurement of proinsulin. Keratinocyte proliferation requires mature insulin, which cannot be distinguished between insulin injected into the media and insulin exported from transduced cells. C-peptide, a byproduct of proinsulin conversion to mature insulin, was instead measured using an ELISA kit. Because keratinocytes had significant levels of proinsulin and C-peptide, insulin overexpression may be a viable

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option. K cells, an enteroendocrine epithelial cell type different from the others in the intestinal lining, are present in the intestinal lining. Because of their resemblance to -cells, they are ideal for reprogramming. “Cell line STC-1 was genetically modified to express insulin by Zhang and colleagues using a GIP promoter (pcDNA3-GIP-hIns). As a first stage, the ability of 64 STC-1 cells that had been transduced to generate insulin was assessed by measuring insulin production in high glucose solution (from 1 mM to 10 mM). STC-1-14 was administered to Stz-induced diabetic naked mice following an increase in insulin levels (10.8 IU/mL to 23.6 IU/mL) was seen in response to increased glucose levels.. After STZ injection, the mice's BGL levels climbed to 16.7 mM, and they began to lose weight. BGLs in mice receiving modified STC-1 cells returned to normal levels of blood glucose” and body weight on average 26 days following the transplant. After the transplant, the blood glucose level remained stable for an additional 49 days.

Case study : *(Source :[1] https://www.sciencedaily.com/releases/2018/07/180709104608.htm)*

[1] “A research team from the UAB led by Professor Fatima Bosch has managed to cure obesity and type 2 diabetes in mice using gene therapy. When an AAV bearing the FGF21 gene was administered to the liver, adipose tissue or skeletal muscle, it resulted in the genetic manipulation of these tissues to continually manufacture the FGF21 protein. Many organs release this hormone-like protein, which affects a wide variety of tissues in order to keep the body's energy metabolism running smoothly. The animal was able to lose weight and reduce insulin resistance, which is linked to the development of type 2 diabetes, by gene therapy.

Two separate mice obesity models, one produced by food and the other by genetic mutation, were effectively treated with this approach. Gene therapy may also be used to promote healthy aging and prevent weight gain and insulin resistance when delivered to healthy mice.

An improvement in insulin sensitivity and healthy aging was seen in mice treated with AAV-FGF21.

Using genetic alteration of three separate tissues (liver, adipose tissue, and skeletal muscle) to create the FGF21 protein, researchers were able to replicate their findings. This offers the treatment a lot of leeway since it enables the therapist to choose the most suitable tissue for the patient at any given moment, and it may be used on any of the tissues if necessary due to complications. According to Dr. Fatima Bosch, the study's director, the FGF21 protein is disseminated throughout the body when it is produced and secreted into the circulation.

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It is important to note that type 2 diabetes and obesity are increasing at an alarming pace worldwide, says UAB researcher Claudia Jambrina, a co-author of the study. Being overweight increases the chance of death, as well as a number of other health problems, including cardiovascular and immune system illness; hypertension; arthritis; neurological disorders; and certain forms of cancer;

As the first author of the publication and UAB researcher Veronica Jimenez explains, this is the first time that long-term reversal of obesity and insulin resistance have been accomplished after a single infusion of a gene therapy in an animal model that matches obesity and type 2 diabetes in people. The findings show that it is a treatment that is both safe and efficient.

When a high-calorie diet was followed for an extended period, gene therapy protected against the development of liver tumors, according to the study's findings.

When supplied conventionally, the natural FGF21 protein has a short half-life. As a result, the pharmaceutical industry has created FGF21 analogues/mimetics and has already begun clinical testing. FGF21 analogues/mimetics, on the other hand, need to be administered on a regular basis in order to achieve therapeutic advantages, although they may pose immunological concerns related with the administration of foreign proteins. While Dr. Bosch's team uses gene therapy to drive the mice to create long-term levels of FGF21, they do so without causing any negative side effects with only one injection.

Dr. Bosch's next step is to try this treatment on bigger animals before moving on to human clinical trials. Because of its effectiveness and safety, AAV-mediated gene therapy has been licensed for use in Europe and the United States to treat a variety of disorders. AAV-mediated gene transfer to the liver and skeletal muscle is also widely used in clinical practice. For these reasons, the treatment presented in this work serves as the foundation for future clinical translation of FGF21 gene transfer to treat type 2 diabetes, obesity, and associated comorbidities," says Dr. Bosch.

Conclusion :

UW School of Medicine and Public Health researchers found that inserting a short DNA sequence into diabetic rats' veins resulted in the development of cells that produce insulin. Blood sugar levels and glucose metabolism were regulated by these cells. Studies have shown that one injection may effectively manage blood sugar levels for over six weeks, which shocked

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the researchers. Diabetes type 1 may now be successfully treated for the first time using DNA-based insulin gene therapy, according to this research, which is the first of its kind.

Researcher Hans Sollinger remarked, "The diabetic rats had insulin and glucose levels that approximated precisely what you'd see in healthy animals" after getting treatment.

Gene-editing technique known as CRISPR has been used to treat mice with diabetes in other studies, as well. When it comes to the CRISPR type 1 diabetes trail, researchers are looking for genes that increase insulin production. After the therapy, the mice's blood glucose levels were observed to be lower. This research was conducted by Salk Institute scientists, who aimed to address concerns about gene cutting, which is still a hot-button issue.

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