Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 4
NSCBM 2024

Gene Therapy for Treating Diabetes

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Abstract. Diabetes has already been a worldwide issue.it is a type of chronic disease with a high risk and a high number of cases. The main symptom of diabetes is not only the spike in blood sugar after eating and the difficulty in lowering it, but the numerous complications are also noteworthy. Currently, traditional treatments for diabetes include controlling sugar intake in the diet and insulin injection therapy. However, traditional diabetes treatments are not ideal. This is mainly due to the fact that diabetes is difficult to treat at the root of the problem and can only be regulated in the long term, not cured. But gene therapy offers us the possibility of treating diabetes in the long term or even permanently. This essay primarily begins with the various pathogenic pathways behind type 1 and type 2 diabetes, summarizes and analyzes some existing diabetes gene therapies that have been theoretically analyzed and experimentally verified. The pros and cons are compared, and the advantages and disadvantages are analyzed. Type 1 diabetes treated with gene therapy involves inhibition of false attacks by immune cells, ectopic expression of insulin-encoding genes, and repair of insulin-encoding gene activity. For type 2 diabetes, gene therapy focuses on increasing the sensitivity of insulin receptor cells to the insulin molecule. Overall, there is a variety of research on treating diabetes through gene therapy, but it is still in the experimental stage. I expect clinical trials to be on the agenda soon.

Keywords: Gene Therapy, type 1 and type 2 diabetes, immune cells, ectopic expression, insulin.

1. Introduction

Diabetes is a chronic illness that is highly prevalent and at high risk globally. From 2000 to 2019, diabetes death rates by age increased by 3%. Diabetes is responsible for an estimated 4.2 million deaths among those aged 20 to 79 years [1]. According to data published by WHO on April 5, 2023, the number of individuals diagnosed with diabetes increased from 108 million in 1980 to 422 million in 2014.

Diabetes is characterized by high blood sugar and can manifest as drinking more, eating more, urinating more. As diabetes affects the functional regulation of several organs, it can lead to weakness, drowsiness, excessive sweating, hypotension and tachycardia, thus affecting the patient's daily life. The immunity and resistance of diabetic patients are relatively low. Their bodies are weak for a long time. So, they may be infected by external bacteria and viruses. At the same time, diabetes can lead to kidney damage, cardiovascular health risks, peripheral blood vessels and nerves, and many eye problems.

Diabetes may be classified into two discrete kinds, specifically type 1 and type 2.

Type 1 diabetes mellitus is distinguished by an autoimmune reaction in which the immune system mistakenly directs its attack towards the beta cells, which are accountable for the production of insulin inside the pancreas. This process ultimately results in a complete lack of insulin [2, 3].

Due to the pancreas's little or non-existent ability to produce insulin, people with Type 1 diabetes are completely dependent on insulin treatment to survive. Monitoring blood glucose levels and carbohydrate counting are essential for managing Type 1 diabetes.

The precise ethology of this immunological response remains incompletely elucidated; nonetheless, it is plausible that genetic predisposition and environmental influences may contribute to its manifestation. The condition is commonly identified during childhood or adolescence; however, it

has the potential to manifest at any stage of life. Currently, there exists a dearth of validated methodologies for the prevention of Type 1 diabetes.

Type 2 diabetes primarily manifests as a metabolic disorder characterised by the development of insulin resistance, wherein the body's cells exhibit reduced responsiveness to insulin, leading to inadequate compensatory insulin production by the pancreas.

Initially, A significant number of individuals diagnosed with Type 2 diabetes effectively manage their illness by dietary adjustments, oral medications, and lifestyle modifications. Some may eventually require insulin or other injectable medications if their pancreas cannot produce enough insulin.

Risk factors include genetics, obesity, sedentary lifestyle, and poor dietary choices. It is usually diagnosed in adults, though it is increasingly being diagnosed in children and adolescents, primarily due to rising obesity rates.

In conclusion, diabetes, whether type 1 or type 2, is today regarded as a chronic illness that is not fully treatable with any current therapy. Once diabetes is acquired, it is accompanied by hyperplasia and an extremely strict lifestyle. Gene therapy, on the other hand, offers a new possibility to cure diabetes.

Gene therapy is a therapeutic modality within the field of medicine that entails the deliberate modification or manipulation of an individual's genetic material with the aim of mitigating or averting the onset of certain pathological conditions. It attempts to introduce new, healthy genes into the patient's cells to replace or repair defective genes that cause particular medical diseases. Gene therapy possesses the capacity to address a diverse array of genetic problems, encompassing hereditary ailments such as cystic fibrosis, muscular dystrophy, and some forms of cancer.

There are several methods of gene therapy, including:

Gene Replacement Therapy: the proposed methodology involves the introduction of a functioning and intact copy of a damaged gene into the cells of the patient, with the aim of replacing the faulty gene.

Gene editing technologies, such as CRISPR-Cas9, enable the exact manipulation or alteration of targeted genes inside an individual's DNA. This can be used to correct genetic mutations or make desired changes in the genome.

Gene Augmentation: Some gene therapies involve adding extra copies of a gene to increase its expression or function. This is often used to compensate for genes that are not functioning correctly.

Gene Silencing: This approach aims to "turn off" or suppress the activity of a specific gene that is causing a disease.

Research into the treatment of diseases through gene therapy has yielded significant results in cancer, blindness and eye diseases, neurological disorders, immune system disorders, and various rare genetic diseases such as haemophilia and muscular dystrophy.

Advantages of gene therapy for diabetes treating over traditional therapy methods

Therefore, compared to traditional therapies, gene therapy can provide targeted treatment that accurately targets the current genetic cause of diabetes or other causative factors for long-term or even permanent treatment. This provides the direction and possibility of a complete cure for diabetes. Moreover, gene therapy can be personalized and targeted according to the type and degree of diabetes and the patient's own situation.

This thesis begins with the development of traditional treatments for diabetes, combines the history of the development of gene therapy, The purpose of this study is to critically review earlier studies that used gene therapy as a therapeutic strategy to treat type 1 and type 2 diabetes, and summarizes a variety of potential methods for curing diabetes through gene therapy, taking into account the advantages and disadvantages.

2. Gene therapy for treating type1 diabetes

Diabetes is a group of metabolic illnesses characterized by increased blood glucose levels resulting from deficits in insulin production, insulin efficiency, or both. Diabetes is characterised by chronic hyperglycaemia, which has been linked to the long-term impairment, malfunction, and deterioration of several organs, including the eyes, kidneys, nerves, heart, and blood vessels [4].

Because of the differences between the pathogeneses and symptoms of patients affected by different types of diabetes, different ways of gene therapy can be carried out.

2.1. Theoretical foundation

Type 1 diabetes is widely acknowledged to result from an autoimmune reaction, when the immune system unwittingly directs its attack towards the pancreatic beta cells, which play a crucial role in the manufacture of insulin. And the lack of insulin leads to the blood sugar level out of control. By using gene therapy, we can repair the damaged beta cells in the pancreas and enable them to once again manufacture insulin or introduce genes coding for insulin making into cells of other organs. The aetiology of type 1 diabetes is predominantly attributed to autoimmune mechanisms, when the immune system erroneously targets and eliminates the insulin-producing pancreatic beta cells. So immune tolerance is also something necessary. In addition, preventing the immune cells from targeting and attacking beta pancreatic cells or the other types of cells we design for insulin producing is also significant. Gene editing can inhibit their activation.

2.2. Comparison of two therapy methods

Type 1 diabetes is a condition that arises due to the loss of pancreatic beta cells, which is primarily caused by the auto-aggressive action of T cells. The promotion of self-tolerance restoration facilitates the process of islet cell regeneration and subsequent recovery. Type 1 Diabetes is characterized by the destruction of β-cells. The condition of absolute insulin deficiency often manifests as the leading factor [4].

In traditional methods of treatments for diabetes type 1, the patients have to get insulin injection throughout a lifetime to control the blood level and ensure the food intake won't lead to blood sugar spike. They have to carry insulin injections by their sides as long as they are going take a meal.

But through gene therapy, there are some research fields for longtime and even permanent heal about type 1 diabetes.

2.3. Stopping the immune system from attacking incorrectly

In the scientific community, type 1 diabetes is mostly recognized as an autoimmune illness. The condition arises due to an aberrant immune response directed at the beta cells located within the pancreas. So, blocking this attack from the immune b cells to the pancreatic beta cells can effectively ease the extent of destroy of beta cells, preventing further deterioration of disease. If introducing dan coding for relative growth factors that can block the destroy, the disease can be controlled.

The use of transforming growth factor (TGF)-β1 has been demonstrated to effectively inhibit the autoimmune response responsible for the destruction of pancreatic islets, while concurrently facilitating the restoration of beta cell functionality in non-obese diabetic (NOD) mice exhibiting apparent symptoms of diabetes [5].

A replication-defective adenoviral vector, known as Ad, was engineered to encode the active version of human transforming growth factor-beta 1 (TGF-β1). This was achieved through the application of a targeted mutagenesis approach, resulting in the introduction of cysteine-to-serine mutations at certain locations, namely 224 and 226. The NOD mice with a predominant diabetes phenotype were administered Ad-hTGF-β1 by intravenous injection. The mice were administered an injection, and around 7 to 14 days later, they were subjected to the transplantation of 500 synthetic islet grafts beneath the kidney capsule. The study investigated the survival of islet grafts and the recovery of

native β-cell function. Treatment with Ad-hTGF-β1 extended the lifespan of islet grafts, but all untreated mice's synthetic islet grafts failed on day 17. Islet grafts from mice that received treatment had islets that were in good condition and were surrounded by CD4+ T cells that expressed Foxp3 and CD25. Treatment-empowered mice's natural pancreas had strong insulin staining. In a manner akin to synthetic islet grafts, the islets exhibited a conspicuous invasion characterised by positive expression of CD4, TGF-β1, and Foxp3 [5].

This work demonstrates that in diabetic NOD mice, systemic TGF-β1 gene therapy prevents the autoimmune that kills pancreatic islets, stimulates islet regeneration, and reverses diabetes [5].

The induction of immune tolerance is a widespread way which has already been taken on researching about the treatments of diabetes through reactions with immune system. Recent progress in comprehending disease processes and the accessibility of novel experimental data have paved the way for future strategies aimed at particularly addressing the prevention of progressive decline in beta cell activity and viability within distinct tissues. The current body of evidence indicates that the delivery of pancreatic autoantigens and associated peptides to individuals who have or are at risk for type 1 diabetes is a viable, secure, and well-tolerated approach. Mechanistic findings suggest favorable changes in pancreatic autoimmunity and signs of immunomodulation. Significant challenges remain in terms of dose and frequency of administration, the method of administration and the utilization of adjuvants. However, significant progress has been made in the field of tissue-specific and personalised medication for managing type 1 diabetes. This development will lay the groundwork for further research on the development of immune tolerance to treat pancreatic autoimmunity as well as the course and progression of the disease.

2.4. Ectopic expression of the insulin gene

However, in the case of type 1 diabetes, the rate at which β-cell breakdown occurs exhibits significant variability. This variability is shown to be quick in certain individuals, particularly babies and children, whereas in others, notably adults, the rate is comparatively slower [4].

So just stopping the attack to pancreatic beta cells is far from adequate for longtime cure. There should be more insulin produced by the body.

Reconstitution genes coding for insulin producing is an attempt which has been taken into experimental and preclinical stages more largely. There are several organs that can be chosen as the targeted organ for insulin action.

Liver is a choice which has already been taken into research extensively. The pancreas is considered the primary target organ for the action of insulin and plays a crucial role in maintaining glucose homeostasis and producing ketone bodies. The insulin 1 cDNA needs to be rescued through PCR [6].

There is substantial evidence from previous studies indicating that the transplantation of hepatocytes or the production of hepatic insulin in transgenic mice can effectively mitigate the impact of severe diabetes. In this study, the researchers effectively achieved persistent and limited expression of the rat insulin 1 gene in the livers of rats with severe diabetes by the utilization of an in vivo recombinant retroviral vector [6].

It is discussed about the importance of the liver in insulin action, glucose homeostasis, and ketone body production. Additionally, it discusses how to lessen the symptoms of severe diabetes by using hepatocyte transplantation or hepatic insulin expression in transgenic mice, as well as the PCR-based rescue of insulin 1 cDNA. Additionally, it highlights the use of a recombinant retroviral vector to cause the insulin 1 gene to express at a low level in the livers of rats with severe diabetes.

The liver plays a crucial role in insulin action. It is a major target organ for insulin, where insulin regulates various metabolic processes, including glucose uptake and storage, glycogen synthesis, and inhibition of glucose production. The liver also plays a role in ketone body production, which is an alternative energy source during times of fasting or low carbohydrate intake.

2.5. Insulin 1 cDNA Rescue by PCR

It appears that there is a need to rescue insulin 1 cDNA, possibly for further experimentation or gene expression studies. The Polymerase Chain Reaction (PCR) is a widely employed technique in the field of molecular biology for the amplification of targeted DNA sequences. which can include rescuing or replicating genes of interest.

2.5.1. Hepatocyte Transplantation

The passage mentions hepatocyte transplantation. This is a technique in which healthy liver cells (hepatocytes) are transplanted into a recipient with liver disease or dysfunction. In the context of severe diabetes, hepatocyte transplantation may have been used to introduce functional liver cells that can help regulate glucose metabolism.

2.5.2. Hepatic Insulin Expression in Transgenic Mice

Transgenic mice are genetically modified animals with specific genes introduced into their genome. It appears that in some studies, researchers have expressed insulin in the liver of transgenic mice to investigate its effects on diabetes. This approach allows researchers to study the impact of hepatic insulin production on glucose homeostasis and diabetes management.

2.5.3. Recombinant Retroviral Vector

A recombinant retroviral vector is a tool used for gene delivery. Within this particular setting, the insulin 1 gene was introduced into the liver of rats afflicted with severe diabetes. Retroviral vectors are commonly used in gene therapy and genetic research to deliver genes of interest into target cells for therapeutic or experimental purposes.

2.5.4. Conclusion

It is suggested that these approaches and techniques have been explored in the context of diabetes research, particularly in rodent models, to understand the role of the liver and insulin expression in glucose regulation and diabetes management. This type of research is valuable for advancing our understanding of diabetes and potential therapeutic interventions.

3. Gene therapy for treating type2 diabetes

Type 2 diabetes arises primarily due to impaired insulin secretion by pancreatic beta cells and insufficient responsiveness of insulin-sensitive tissues to the actions of insulin. In the context of this specific kind of diabetes, the efficacy of insulin injection is limited.

Decline the hydrocarbons intake and increase in physical activities and fitness can contribute to type2 diabetes remission [7]. Nevertheless, the molecular mechanisms that regulate insulin synthesis, release, and detection are subjected to rigorous regulation as a result of the vital role played by insulin release and activity in maintaining glucose homeostasis. So through gene therapy, modifying insulin sensitivity can be reached [8].

Nowadays there are several different directions of research on this mechanism.

Gene-based targeted nanoparticle formulations have been developed to stimulate adipose tissues for adiponectin (ADN) production.

The present work aimed to devise a gene-based targeted nanoparticle formulation with the objective of enhancing adipose tissue synthesis of adiponectin (ADN) and ameliorating insulin sensitivity in individuals diagnosed with type 2 diabetes [8].

The research was around the investigation of several cationic polymers, such as chitosan, poly(vinylimine), poly(L-lysine), poly(aminodiethylamine), and green tea catechins, in relation to their capacity for gene transport. Non-viral gene delivery vectors have been used to effectively transfect genes in both in vitro and in vivo situations. Examples of these vectors include lipid polymer

self-assemblers and hydrophobically modified cationic polymers. These vectors exhibit very weak gene interactions; however, they have proven to be useful in facilitating gene transport. This work aimed to enhance the internalisation of adipose homing peptide (AHP) in adipose tissue by covalently conjugating the free amino groups on chitosan-oleic acid polymers with AHP. The focus of this study is on the inhibition of prohibitin-1, a transmembrane protein that is specifically expressed in vascular endothelial cells of white adipose tissue. AHP-mediated nanoparticle targeting has been successfully delivered to adipocytes in various preclinical studies [8].

Previous studies have demonstrated that the use of a polymeric carrier for mini-circle adiponectin gene delivery resulted in a significant elevation in adiponectin levels, hence achieving the desired biological outcomes [9].

In addition, another research has been taken place through measuring the Preserved Ejection Fraction of mice to evidence that the Cholesterol-Lowering Gene Therapy can validly cure the type2 diabetes [10].

In this study, the investigators administered a high sucrose/high fat (HSHF) diet to C57BL/6J low-density lipoprotein receptor (LDLr)-/ mice with the aim of establishing an experimental model of high-density lipoprotein (HDL) associated with hypercholesterolemia and type 2 diabetes. Second, they assessed whether LDLr gene transfer mediated by serotype 8 adeno-associated virus (AAV8), which lowers cholesterol, The prevention of heart failure with preserved ejection fraction (HFpEF) can be accomplished by the utilization of AAV8-LDLr gene transfer. This approach has demonstrated a notable decrease in plasma cholesterol levels in both standard diet (SC) mice (66.8 ± 2.5 mg/dl vs. 213 ± 12 mg/dl) and high-sucrose high-fat (HSHF) animals (84.6 ± 4.4 mg/dl vs. 464 ± 25 mg/dl) ($p < 0.001$). The use of a diet rich in saturated fat and sucrose, commonly referred to as the high-saturated fat, high-sucrose (HSHF) diet, led to the manifestation of cardiac hypertrophy and pathological remodelling. However, these adverse effects were successfully mitigated with the implementation of AAV8-LDLr gene transfer. AAV8 null HSHF mice had 19.0% higher wet lung weights than AAV8 null SC mice ($p < 0.001$), and the AAV8-LDLr HSHF mice had normal lung weights. Pressure-volume cycling analysis showed that AAV8 null HSHF mice used in this study were consistent with a high rate of atrial fibrillation, whereas AAV8-LDLr HSHF mice had completely normal cardiac function. The results of treadmill exercise testing revealed a reduction in exercise ability among AAV8-null HSHF mice, whereas AAV8-LDLr HSHF mice had normal exercise capacity. The positive benefits of cholesterol lowering may be mediated via the reduction of oxidative stress and tumour necrosis factor-α levels. In summary, the implementation of AAV8-LDLr gene therapy has demonstrated efficacy in mitigating the occurrence of elevated atrial fibrillation [10].

The preceding paragraph outlines a scientific investigation that was carried out on mice in order to develop a model of heart failure with preserved ejection fraction (HFpEF) that is linked to hypercholesterolemia and type 2 diabetes mellitus. Additionally, the goal of this research is to investigate the potential therapeutic advantages of a gene therapy strategy that lowers cholesterol. To be precise, the adeno-associated virus serotype 8 (AAV8) will be utilized as a vector to deliver the low-density lipoprotein receptor (LDLr) gene.

The main goal of this research was to create a mouse model of heart failure with preserved ejection fraction (HFpEF) by feeding the animals a high-sucrose/high-fat (HSHF) diet, which is a diet heavy in fat and sugar. This diet has been previously linked to hypercholesterolemia and type 2 diabetes mellitus. The researchers aimed to examine the potential of the transfer of the LDLr gene using AAV8 vectors. in mitigating HFpEF in the experimental model.

The researchers aimed to examine the potential of AAV8-mediated LDLr gene transfer in mitigating HFpEF in the experimental model. The observed decrease in cholesterol levels exhibited a high level of statistical significance ($p < 0.001$).

The High-Sugar High-Fat (HSHF) diet elicited heart hypertrophy (enlargement of the heart) and pathological remodelling (changes in the heart's structure), the adverse effects were successfully

mitigated with the implementation of the transfer of the LDLr gene using AAV8 vectors. This suggests that the gene therapy had a protective effect on the heart.

The results of the treadmill exercise tests indicated that AAV8-null HSHF mice exhibited a decrease in exercise ability, but AAV8-LDLr HSHF animals demonstrated normal exercise capacity. This suggests that the gene therapy helped maintain physical function.

The study posits that the advantageous outcomes of cholesterol reduction by AAV8-LDLr gene therapy could perhaps be attributed to a decline in oxidative stress and a decrease in levels of tumor necrosis factor-α, which are factors associated with heart disease and inflammation.

In brief, the findings of this study conducted on mice provide evidence that AAV8-LDLr gene therapy is successful in reducing cholesterol levels and preventing HFpEF triggered by a diet high in sugar and fat. The gene therapy appears to protect the heart, reduce lung congestion, improve cardiac function, and maintain exercise capacity. These findings may have implications for potential treatments or interventions in humans with similar conditions. However, it's important to note that results from animal studies may not always directly translate to human outcomes, so further research is needed to validate these findings in clinical settings.

4. Conclusion

All in all, Gene therapy for treating diabetes is an area of ongoing research and development, primarily focused on Type 1 diabetes (T1D) and certain instances of severe insulin-dependent Type 2 diabetes (T2D). The primary goal of diabetic gene therapy is to achieve a durable or enduring resolution by either reinstating the regular functionality of cells responsible for insulin production or effectively managing glucose levels in the bloodstream. Several research have already been taken into experiments on rats and mice through different ways. that gene therapy for diabetes is still in the experimental and research stages. There are current clinical trials assessing the efficacy and safety of different gene therapy techniques. Challenges include ensuring long-term safety, preventing immune responses against the therapy, and fine-tuning the delivery methods. Gene therapy shows potential for the therapeutic management of diabetes although a definitive cure for diabetes using gene therapy had not yet been established. But research in this field continues to advance, and new developments may occur in the future.

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