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LENTIVIRUS THERAPY IN DIABETES MANAGEMENT: AN EMERGING THERAPEUTIC HOPE

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Abstract

Diabetes mellitus, a metabolic condition marked by persistent elevated blood sugar levels, affects approximately 422 million individuals globally, predominantly in low- and middle-income countries, contributing to 1.5 million deaths annually. Overcoming current hurdles in diabetes management involves optimizing existing therapies for glycemic control and improving healthcare delivery. The aim of this study is to examine the novel application of therapeutic lentivirus in diabetes management. Gene therapy, specifically utilizing lentiviruses, emerges as a promising avenue in diabetes management. Some lentivirus gene therapies that have been explored in diabetes management include; LentiINS, LentiVIP, Lenti GLP-1, LentiLacZ, LentiINSVIP, INSlentivirus. Research explored delivering the human proinsulin gene using a lentiviral vector (LentiINS), resulting in improved glucose levels in diabetic mice. LentiINS and an anti-inflammatory vector LentiVIP in a combinatory therapy (LentiINSVIP) proved effective in suppressing diabetes-related inflammation. Lentiviral vectors for VIP gene delivery showcased reduced glucose level and increased beta-cell proliferation. LacZ gene carrying lentivirus did not significantly improve symptoms in diabetic rats. Lentiviral vectors expressing furin-cleavable human insulin (INS lentivirus) in the liver demonstrated efficacy in reversing diabetes without pancreatic beta-cell transdifferentiation. Additionally, lentiviral vectors encoding GLP-1 exhibited anti-diabetic efficacy in a type 2 DM model. Lentiviruses thus emerge as versatile tools in innovative approaches for diabetes treatment, warranting further research and clinical trials to assess safety and therapeutic potential.

Keywords: Gene therapy, Insulin, hyperglycemia, Lentivirus, Diabetes Mellitus.

INTRODUCTION

Diabetes mellitus encompasses a set of metabolic conditions characterized by persistent elevated blood sugar levels, resulting from deficiencies in insulin secretion, insulin action, or both. The severity of symptoms varies based on the type and duration of diabetes. If left uncontrolled, diabetes can progress to serious complications, including stupor, coma, and in severe cases, death, often due to ketoacidosis or, more rarely, non-ketotic hyperosmolar syndrome[1]. The severity and duration of poorly controlled diabetes determine the variation in microvascular and macrovascular complications, encompassing nephropathy, retinopathy, neuropathy, and cardiovascular events, especially when coupled with comorbidities like dyslipidemia and hypertension [2].

According tosome researchers, gene therapy is broadly defined as treating diseases by introducing therapeutic genes into relevant cellular targets, correcting mutations or reprogramming cell functions [3]. Although both viral and non-viral vectors have been experimented with for treating type 1 diabetes mellitus and type 2 diabetes mellitus [4], viral vectors, particularly lentiviral vectors, exhibit clear superiority in gene delivery to target cells [5]. Lentiviral vectors, among the viral options, are gaining prominence as gene delivery vehicles in clinical trials[6]. Currently, therapeutic gene delivery via lentiviral vectors is actively being pursued for the treatment of both type 1 diabetes mellitus and type 2 diabetes mellitus. Recent investigations in liver-directed gene therapy demonstrated that lentivirus-mediated delivery of a furin-cleavable insulin gene to hepatocytes could satisfy basal insulin requirements in type 1 diabetes mellitus, aiming to eliminate the necessity for long-acting insulin analogs in diabetic patients [4].

This review explores the promising frontier of Lentivirus gene therapy as a potential breakthrough in the management of diabetes. Investigating the latest developments and scientific insights, it aims to provide a comprehensive overview of the therapeutic potential, challenges, and future prospects in utilizing Lentivirus gene therapy for diabetic management.

LENTIVIRUS THERAPY IN DIABETES MANAGEMENT

Lentiviruses are a family of viruses that are responsible for diseases like AIDS, which infect by inserting DNA into their host cells' genome. Many of such viruses have been the basis of research using viruses in gene therapy, but the lentivirus is unique in its ability to infect non-dividing cells, and therefore has a wider range of potential applications. Lentiviruses can become henceforth inherited by the host's descendants [4].

Mechanism of Action

The basic genes required for retroviral and lentiviral survival and function are the gag, pol, and env genes; gag encodes structural proteins, pol encodes enzymes required for reverse transcription and integration into the host cell genome, and env encodes the viral envelope glycoprotein [7].

There are several steps of lentiviral infection and replication in host cells. In the first step, the virus uses surface glycoproteins to attach to the outer surface of the cell. Specifically, the lentivirus attaches to the CD4 glycoprotein on the surface of the primary target cell [8]. The viral material is then inserted into the cytoplasm of the host cell. In the cytoplasm, viral reverse transcriptase transcribes the viral RNA genome to produce the viral DNA genome[9].The viral DNA then moves to the host cell's nucleus, where it is integrated into the host cell's genome by the viral enzyme integrase. From this point, the host cell begins to transcribe the entire viral RNA and express structural viral proteins, especially those that make up the viral capsid and envelope [8]. Once the lentiviral RNA and viral proteins are assembled and produced in sufficient numbers, the nascent virion is released from the host cell [9].

Lentivirus Therapy In Diabetes Management

Gene therapy, specifically utilizing lentiviruses, emerges as a promising avenue in diabetes management. Some lentivirus gene therapies that have been explored in diabetes management include; LentiINS, LentiVIP, Lenti GLP-1, LentiLacZ, LentiINSVIP, INSlentivirus.

LentiINS

It was hypothesized that suppressing diabetes-related inflammation and enhancing insulin gene expression through complementary gene therapy could improve the therapeutic efficacy of LentiINS in a rat diabetes model [4]. LentiINS, incorporating an insulin promoter to drive pancreatic beta-cell-specific proinsulin expression infected pancreatic beta cell line yielded significant levels of insulin secretion only at high glucose concentration. LentiINS injection into diabetic rats lowered fasting blood glucose levels.

LentiVIP

VIP, known for its anti-inflammatory and insulinotropic properties [10], was proposed for this purpose. While VIP has demonstrated efficacy in reducing the severity of diabetes in non-obese diabetic mice through shifting the proinflammatory cytokine profile and activating regulatory T cells [11,12], its potential to induce pancreatic beta cell proliferation after STZ-induced destruction of pancreatic islets remains unknown [13].

Authors assessed the therapeutic potential of an HIV-based lentiviral vector carrying the VIP gene (LentiVIP) in a multiple low-dose STZ-induced model of T1DM [4]. LentiVIP administration reduced hyperglycemia, improved glucose tolerance, prevented weight loss, and correlated with increased pancreatic beta-cell proliferation. Additionally, LentiVIP treatment led to decreased serum CRP levels, reduced serum oxidant capacity, and increased antioxidant capacity, indicating its role in suppressing diabetes-induced inflammation and promoting insulinotropic effects.

Lenti GLP-1

Glucagon-like pepetide 1 (GLP-1), a metabolic hormone, facilitates postprandial insulin secretion from the islets of Langerhans. It induces somatostatin secretion, inhibits glucagon release, slows gastric emptying, and reduces food intake, contributing to long-term weight loss. In type 2 diabetes (T2DM), the diminished incretin response to glucose and reduced GLP-1 secretion prompt compensatory measures. Some researchers developed a lentiviral vector (LentiGLP-1) encoding human GLP-1, testing its anti-diabetic efficacy in a T2DM model [4]. Results showed LentiGLP-1 administration in obese diabetic rats reduced blood glucose, improved insulin sensitivity and glucose tolerance, correlated with increased blood GLP-1, beta cell regeneration, and normalized triglyceride levels. These findings highlight the potential of GLP-1 gene transfer therapy for T2DM treatment.

LentiLacZ

LentiLacZ carrying the LacZ gene injected in STZ induced rats presented no significant improvement in blood glucose levels, weight loss, no increase in serum insulin levels. As expected, a faint insulin signal was detected in the pancreatic islets of LentiLacZ-injected rats, suggesting these islets were destroyed following STZ injection and correlating with higher levels of blood glucose [4].

LentiINSVIP

To achieve sufficient serum insulin levels for suppressing non-fasting plasma glucose and diabetes-related inflammation, a combinatory therapy involving LentiINS and an anti-inflammatory lentiviral vector (LentiVIP), LentiINSVIP, was necessary. The efficacy of glucose clearance was much greater in LentiINSVIP injected animals, suggesting LentiINSVIP-injected rats manifested a greater degree of glucose tolerance compared to LentiINS- or LentiVIP-injected rats alone. LentiINSVIP-injected rats displayed the highest serum insulin levels among the groups tested. Stronger insulin staining and enlarged islets were detected in LentiINSVIP-injected rats, correlating with the higher levels of serum insulin and lower blood glucose [4].

INS-Lentivirus

Pancreas or islet transplantation for type 1 diabetes is limited due to donor tissue shortage. Some authors explored an alternative gene therapy approach by expressing furin-cleavable human insulin in the liver of diabetic rats using INS-lentivirus [15]. This somatic gene therapy normalized blood glucose concentrations within days and maintained stability for a year, demonstrating efficient reversal of the diabetic state without transdifferentiation into pancreatic β-cells.

Researchers developed a lentiviral vector, LentiINS, incorporating an insulin promoter to drive pancreatic beta-cell-specific prexpression [4]. Intraperitoneal administration of the HIV-based LentiINS alleviated fasting plasma glucose levels, enhanced glucose tolerance, and prevented weight loss in streptozotocin (STZ)-induced diabetic Wistar rats.

To explore the anti inflammatory effect of the VIP gene some researchers tested the efficacy of LentiVIP in suppressing diabetes related inflammation [4]. VIP, known for its anti-

inflammatory and insulinotropic properties was proposed for this purpose.

LentiVIP administration reduced hyperglycemia, improved glucose tolerance, prevented weight loss, reduced serum C reactive protein levels and correlated with increased pancreatic beta-cell proliferation.

LentiLacZ carrying the LacZ gene was tested for its antidiabetic efficacy, In Contrast, LentiLacZ injected STZ induced rats presented no significant improvement in blood glucose levels, weight loss, no increase in serum insulin levels. To achieve sufficient serum insulin levels for suppressing non-fasting plasma glucose and diabetes-related inflammation, a combinatory therapy involving LentiINS and an anti-inflammatory lentiviral vector (LentiVIP), LentiINSVIP, was necessary. The efficacy of glucose clearance was much greater in LentiINSVIP injected animals, suggesting LentiINSVIP-injected rats manifested a greater degree of glucose tolerance compared to LentiINS- or LentiVIP-injected rats alone. LentiINSVIP-injected rats displayed the highest serum insulin levels among the groups tested.

Table 1: Lentivirus gene models and their corresponding proteins

LENTIVIRUS GENE MODEL	GENE	PROTEIN
INS-Lentivirus	Human Insulin Gene	Pre-proinsulin
Lenti GLP-1	Glucagon Like Peptide 1 Receptor Gene	Glucagon Like Peptide
LentiINS	Human Insulin Gene	Pre-proinsulin
LentiVIP	Vasoactive Intestinal Peptide Gene	Vaso Intestinal Peptide
LentiLacZ	Lac Z Gene	B -Galactosidase
LentiINSVIP	Human Insulin Gene/ Vasoactive Intestinal Peptide Gene	Pre-proinsulin/Glucagon Like Peptide

Table 2: Assessing the Treatment Outcomes of Various Lentivirus Gene Treatment Models in Diabetic Rats

References	Type of treatment	Classification	Frequency of Treatment	Duration of Treatment	Post Treatment Assessment Time	Outcome	Remark
Elsner et al. (2021)	INS Lentivirus	T1DM	Once	1 day	1 year	126mg/dL	Authors recorded quick reduction in diabetic hyperglycemia, normalized blood glucose concentrations through hepatic insulin expression.
Tasyurek et al. (2018)	LentiGLP-1	T2DM	Once	3 days	6 months	175mg/dL	Authors recorded reduction in blood glucose, improved insulin sensitivity and glucose tolerance, correlated with increased blood GLP-1, beta cell regeneration, and normalized triglyceride levels.
Erendor et al. (2021)	LentiINS	T1DM	Once	1 day	5 months	160mg/dL	Authors recorded reduction in plasma glucose levels, enhanced glucose tolerance, and increased body weight.
Erendor et al. (2021)	LentiVIP	T1DM	Once	1 day	5 months	220mg/dL	Author recorded reduction in hyperglycemia, improved glucose tolerance, prevented weight loss, and correlated with increased pancreatic beta-cell proliferation.
Erendor et al. (2021)	LentiLacZ	T1DM	Once	1 day	5 weeks	480mg/dL	Author recorded no significant improvement in blood glucose levels, weight loss, no increase in serum insulin levels
Erendor et al. (2021)	LentiINSVIP	T1DM	Once	1 day	5 months	120mg/dL	Author recorded greater degree of glucose tolerance, glucose clearance, much significant weight gain and reduction in blood glucose.

DISCUSSION

Study conducted by Elsner and his colleagues revealed the therapeutic efficacy of administering INSlentivirus in the management of T1DM [15]. He reported reduction of diabetic hyperglycemia and normalized blood glucose levels through hepatic insulin expression following administration of INSlentivirus. INSlentivirus carries the human insulin gene and uses the cytomegalovirus (CMV) promoter, which is a strong and constitutive promoter that can drive gene expression in various cell types. This accounts for the increase in hepatic insulin secretion. The therapeutic effect was maintained during an observation period of 1 year.

Tasyurek and his team demonstrated the efficacy of administering LentiGLP-1 in managing diabetes mellitus [14]. Following a treatment duration of 3 days and an observation period of 1 year, he did not only record significant reduction in blood glucose, improved insulin sensitivity and glucose tolerance which correlates with increased GLP-1 secretion in the blood. Normoglycemia was correlated with increased blood GLP-1 and pancreatic beta cell regeneration in LentiGLP-1-treated rats. Plasma triglyceride levels were also normalized after LentiGLP-1 injection. Collectively, these data suggest the clinical potential of GLP-1 gene transfer therapy for the treatment of T2DM.

Study conducted by Erendor and his colleagues assessed the therapeutic efficacy of two novel lentiviral vectors [4]. LentiINS, incorporating an insulin promoter to drive pancreatic beta-cell-specific proinsulin expression and a lentviral vector, LentiLacZ carrying the LacZ gene. Intraperitoneal administration of the HIV-based LentiINS alleviated fasting plasma glucose levels, enhanced glucose tolerance, and prevented weight loss in the diabetic rats. In contrast, LentiLacZ injected rats presented no significant improvement in blood glucose levels, weight loss, no increase in serum insulin levels. LentiINS-infected pancreatic beta cell line yielded significant levels of insulin secretion only at high glucose concentration compared to LentiLacZ-infected cells. In contrast to the LentiLacZ-treated rats, LentiINS injection into diabetic rats lowered fasting blood glucose levels.

This contrast may be due to the fact the LentiLacZ gene codes for the enzyme B galactosidase which catalyse the break down of lactose to galactose and glucose [16]. This implies that this gene will promote rise in glucose level due to the increase in glucose generation from lactose.

In a separate experiment Erendor suppressed diabetes-related inflammation and enhanced insulin gene expression through complementary gene therapy that could improve the therapeutic efficacy of LentiINS in a T1DM model [4]. LentiVIP, known for its anti-inflammatory and insulinotropic properties was proposed for this purpose [10]. LentiVIP demonstrated efficacy in reducing the severity of diabetes in diabetic mice through shifting the proinflammatory cytokine profile and activating regulatory T cells [11,12]. It also reduced hyperglycemia, improved glucose tolerance, prevented weight loss, and correlated with increased pancreatic beta-cell proliferation.

Erendor went further to achieve sufficient serum insulin levels for suppressing non-fasting plasma glucose and diabetes-related inflammation in T1DM rats using a combinatory therapy involving LentiINS and the anti-inflammatory lentiviral vector (LentiVIP), LentiINSVIP, was necessary [4]. The efficacy of glucose clearance was much greater in LentiINSVIP injected animals, suggesting LentiINSVIP-injected rats manifested a greater degree of glucose tolerance compared to LentiINS- or LentiVIP-injected rats alone. LentiINSVIP-injected rats displayed the highest serum insulin levels among the groups tested.

Although reduction in fasting blood glucose is consistent across all studies, the studies focused more on T1DM which could be due to the fact that since T1DM is believed to result from destruction of the insulin-producing β-cells in pancreatic islets that is mediated by autoimmune mechanisms [17], the lentiviral gene therapy aimed to permanently integrate their gene into genome of diabetic patients, allowing long-term stable gene expression with low immunogenic characteristics following pancreatic β-cells destruction [5]. But in general, the studies have demonstrated the effectiveness of lentiviral gene therapy in DM management with significant reduction in blood glucose concentrations, improved glucose tolerance, clearance and beta cell regeneration. Also, the efficacy of the treatment across the studies provides evidence of combinatory therapeutic success such that using two lentiviral genes rather than one resulted in increased therapeutic achievement.

CONCLUSION

This review highlights the therapeutic promise of lentiviral vectors for diabetes management. Intramuscular injection of insulin-encoding lentiviral vectors showed efficacy in treating type 1 diabetes. Novel vectors, LentiINS and LentiVIP, targeting pancreatic beta cells, demonstrated significant improvements in glucose levels and inflammation in diabetic rat models. Liver expression of furin-cleavable human insulin using INS-lentivirus offered an alternative gene therapy approach, efficiently reversing the diabetic state without pancreatic transdifferentiation. Overall, lentivirus-based therapies present diverse and promising avenues for addressing insulin deficiency and inflammation in diabetes management. Gene therapy using Lentiviral vectors has emerged as a promising therapeutic option for several conditions. Additional basic and clinical research to improve transduction efficiency and manufacturing are also still needed.

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