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GENE THERAPY FOR DIABETES MELLITUS TYPE 1

Author Name: Ashutosh Budha Khairnar.

Designation: Student

Department Name: Pathophysiology.

Name of organization: Swami institute of pharmacy, Abhona, India.

Co-Author Name: Mrs. Pratiksha R. Patole.

Designation: Assistant Professor

Department Name: Pathophysiology.

Name of organization: Swami institute of pharmacy, Abhona, India.

Co-Author Name: Abhijit Kamlakar Kadam.

Designation: Student

Department Name: Pathophysiology.

Name of organization: Swami institute of pharmacy, Abhona, India.

Co-Author Name: Tejas Jagannath Bhadane.

Designation: Student

Department Name: Pathophysiology.

Name of organization: Swami institute of pharmacy, Abhona, India.

Co-Author Name: Jaydip Gopal Kapadnis.

Designation: Student

Department Name: Pathophysiology.

Name of Organization: Swami Institute of Pharmacy, Abhona, India.

ABSTRACT

As an autoimmune condition known as type 1 diabetes, your body assaults and kills the cells that produce insulin. This review focuses on the present state and potential applications of gene therapy in the treatment of T1DM. Gene therapy is one possible therapeutic option. The majority of studies that are presented on gene therapy for the treatment of T1DM use animal models and preclinical research. However, the efficacy of these treatments in humans has not yet been proven. Several gene-based treatments are now under investigation, including genetic vaccines, immune precursor cells, or vectors, transplanting cells that express certain genes, delivering gene therapy through stem cells, and overexpressing the genes and proteins necessary to combat T1D.

KEY WORDS: - Diabetes, Gene therapy, Insulin.

INTRODUCTION

Diabetes mellitus is a medical disorder that results in high blood sugar levels due to insulin resistance or insufficiency (BGLs; hyperglycemia). As a result of long-term hyperglycemia, organ failure can result from neuropathy, nephropathy, retinopathy, peripheral vascular disease, morbidity, and mortality, as well as end-stage micro- and macrovascular damage. Diabetes mellitus is a fatal condition that can manifest at different ages, in different ways, and with a wide range of clinical characteristics and presentations. [(1)] Diabetes is a long-term degenerative condition that affects the peripheral and autonomic nerve systems, the eyes, and the kidneys, causes quite specific long-term issues accounting for more c ases of adult amputations, end Adult cases of vision loss, end-stage kidney disease, and amputa-tions compared to any other illness. Furthermore, type 1 and type 2 Diabetes increases cardiovascular disease (CVD) risk by 2 to 5-fold. An increasing risk of some cancers during the past ten years, pancreatic, liver, colorectal, endometrial, and breast, among others, have Been added to the conventional diabetic vascular problems. [(2)] Hyperglycemia (increased blood sugar levels) is a symptom of Type 1 diabetes mellitus (T1DM), a chronic auto-immune condition brought on by an insulin shortage that results from the destruction of pancreatic islet cells1-4. One of the most prevalent endocrine and metabolic diseases affecting children is T1DM. The loss of -cells is a result of T1DM-related autoimmunity in the great majority of patients (70–90%); these individuals have autoimmune T1DM. This kind has a strong genetic component, and in a smaller percentage of individuals, no immune responses or autoantibodies are found, and the reason of cell death is unknown. In this Primer, the word "T1DM" refers to autoimmune T1DM unless otherwise stated. [(3)]

For the treatment, cure, or prevention of human illnesses, nucleic acids (DNA or RNA) are used in gene therapy. This can be accomplished using a variety of sophisticated tools, including naked oligonucleotides, viral and non-viral vector, depending on the type of disease, either by delivering a functional, therapeutic gene to replace the damaged or absent endogenous counterpart or by reducing the levels of a harmful defective gene product. [(4)] The development of T1DM is caused by multiple genes, which have been successfully identified by researchers during the past few decades. [(5)] Therefore, altering or manipulating these genes by gene therapy could potentially offer a more comprehensive disease management or perhaps cure T1DM. Despite the advantages that gene therapy might provide, there might also be drawbacks. [(6)]

Gene therapy is a method for treating illnesses by modifying one's deoxyribonucleic acid (DNA), which has a number of functions. Activating a disease-causing gene that isn't working as it should, replacing a disease-causing gene with a healthy copy of the gene, or adding a new or modified gene are all possible ways to treat disease. Gene into the body to help treat sickness. [(7)]

METHODOLOGY

A viable alternative to insulin injections for the treatment of T1D is gene therapy. The process of delivering or modifying genetic materials inside of a cell as a therapeutic method to treat disease is known as gene therapy. Its goal is to modify defective genes that are responsible for disease progression and so stop or stop the advancement of the disease. [(8)]

For gene therapy to be successful and last, it must be able to transfer nucleic acid sequences to the target cells effectively, allow the new gene to express properly and for a sufficient amount of time, and have no hazardous side effects. Delivering genes can be for gene therapy to be successful and last, it must be able to transfer nucleic acid sequences to the target cells effectively, allow the new gene to express properly and for a sufficient amount of time, and have no hazardous side effects. [(9)]

It's One of the best methods for delivering genes to the cells has evolved into viral vectors. They are designed to maintain the virus's ability to transmit genes while removing the pathogenicity of the infection. Viral vectors are more effective gene delivery mechanisms when compared to non-viral vectors. The cytotoxicity, inflammatory response, and immunogenicity must all be taken into account when creating a viral vector system, though.Viral vectors should be chosen with additional optimization depending on the therapeutic applications because there are various viral vectors utilised as gene delivery systems, and each system has advantages and disadvantages. [10]

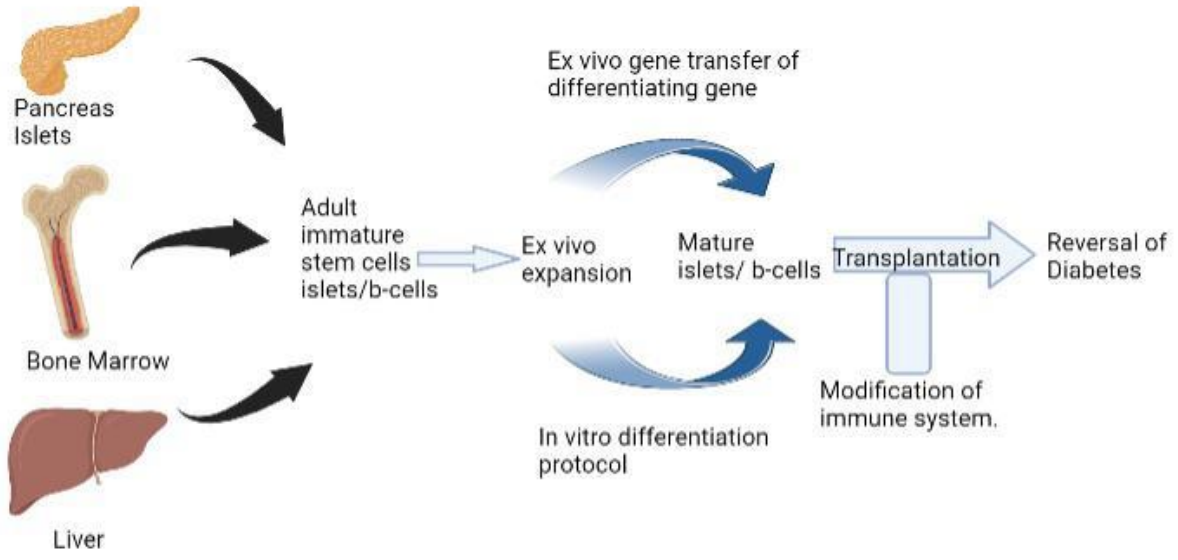

fig no.1 key components of cell-based gene therapy procedures for treating diabetes are represented schematically. [19]

By the above diagram demonstrating that the stem cells islets/b-cells collected from the pancreas, bone marrow, or either from liver and which further goes to the ex vivo expansion process by which propagates stem cell population and are transplanted into the human body which shows modulation of the immune system can show reversal of Diabetes.

EPIDEMIOLOGY

The prevalence of type 1 diabetes mellitus (T1DM) is rising globally, with significant regional variation in prevalence. Although the genetic component of T1DM is still unclear, the increased incidence is unlikely to be caused by this. Women typically have greater symptoms of autoimmune illnesses than men. The elusive factor that causes T1DM in today's youth is still undiscovered. The fluctuating incidence of the disease as well as its underlying aetiologies and pathophysiology are both believed to be caused by environmental or regional variables, according to ongoing epidemiological studies. [11]

T1D is a diverse condition characterised by the death of pancreatic beta cells, which results in a complete lack of insulin. A tiny percentage of cases are caused by the idiopathic failure or destruction of beta cells, while the majority of cases are caused by an autoimmune-mediated destruction of beta cells (type 1a) (type 1b). 5- 10% of all diabetes cases worldwide have T1D instances. [12]

The loss of the insulin-producing pancreatic beta cells appears to be the end result of an immunological response in genetically predisposed individuals after exposure to one or more environmental factors. The discovery of these elements ought to improve knowledge of the aetiology of the condition and support the creation of T1DM prevention measures.(13)

Global studies indicate that the incidence of T1D has increased by 2% to 5% worldwide, and that the prevalence of T1D in the United States is approximately 1 in, 300 at age 18 years. The studyof risk factors for T1D are an active area of research aimed at identifying genetic and environmental triggers that could be targeted for intervention. [14]

PATHOPHYSIOLOGY

To begin, it should be noted that type 1 diabetes is caused by an autoimmune attack on cells in the pancreas that secrete insulin. This observation is supported by the discovery of a chronic inflammatory infiltration that damages pancreatic islets at the start of type 1 diabetes symptoms. [15]

Patients with advanced illness have no insulin-producing cells in their pancreas, and the remaining cells cannot regenerate. Recent research indicates that although the majority of people with type 1 diabetes have few, if any, cells, there is evidence of -cell regeneration in new-borns and very young children. Analysis of pancreatic samples, serum, and peripheral blood lymphocytes acquired from type 1 diabetes patients provides a large portion of what we know about the pathophysiology of the disease. [16]

T1DM progresses through three stages. Asymptomatic stage 1 is characterised by greater than or equivalent to 2 pancreatic autoantibodies, normal fasting glucose, and normal glucose tolerance. The presence of more than two pancreatic autoantibodies and dysglycemia are stage 2 diagnostic criteria: Stage 3 includes clinical indications of diabetes or hyperglycemia as well as two or more pancreatic autoantibodies.Pediatric T1DM traditionally presents with hyperglycaemic symptoms, and one- third of cases present in DKA. Symptoms may appear suddenly at the time of opinion, especially in youthful people. However, it can come an exigency, If not assessed and treated snappily. Most frequently cases have hyperglycemia with polydipsia, polyuria and polyphagia. Youthful children may witness nightly enuresis. Polydipsia is associated with hyperosmolality and dehumidification due to increased urination. Blurred vision is possible because glucose can beget bibulous lump of the lens. Weight loss is also common. Lipolysis and ketone product increase along with muscle and fat breakdown. This causes muscle wasting, polyphagia, fatigue and weakness. Electrolyte disturbances may also occur. However, cases have DKA, which requires hospitalization and treatment with intravenous fluids, If these symptoms aren't detected. [17]

APPROACHES FOR GENE THERAPY IN TYPE 1 OF DIABETES

It may be possible to develop a treatment for type 1 (insulin-dependent) diabetes that would include replacing the cells that produce surrogate insulin. Long-term efforts to find a cure for diabetes have employed a variety of strategies, such as islet transplantation, stem cell regeneration, and insulin gene therapy, Insulin secretion from nonpancreatic cells, Ex vivo conversion of cells into functional b-cells.

1. Islet Transplantation

The idea of T1D cell relief remedy remained dormant for 80 times until 1972 when Ballinger and Lacy reversed chemical diabetes by island transplantation in rats(Shapiro, 2012). Following the success of steroid free immunosuppression transplantation of fresh mortal islands Island transplantation in Cases with type 1 diabetes can reduce or exclude the Insulin demand. Exenatide is a long- acting Glucagon- suchlike peptide- 1(GLP- 1) analog that increases Glucose- convinced insulin stashing and may increase the Mass of β cells. Roughly 70 percent of transplanted Type 1 diabetic cases achieved insulin independence. A clinical review at the BMJ in 2001 anticipated that transplantation of Langerhans islands would be the treatment of choice for utmost Type 1 cases diabetes by 2010. Island Transplantation is presently an option for a specific group Of cases with type 1 diabetes only those with Severe glycaemic liability, intermittent hypoglycaemia, and incognizance of hypoglycaemia(18)

More than 30 worldwide transplant facilities have carried out more than 750 islet transplants over the past ten years. Without a doubt, islet transplantation has progressed from an experimental method to lessen the effects of T1DM to a recognised standard of care clinical treatment. The treatment is only appropriate for patients with unstable glycaemic control who cannot be treated with standard conventional and intensive insulin regimens at this time. [19]

2. stem cell regeneration

One thing of regenerative medicine is the educational incorporation of adult cells into other forms of cells for Towel form and regeneration. One thing of regenerative medicine is the educational The regeneration of pancreatic β cells which produce insulin is a pivotal remedial strategy for diabetes. Maturity, β cell mass adding the capability to suit supplemental conditions. Shy insulin storing by β cells leads to Mellitus diabetes. Pancreatic insulin- producing β- cells have a long continuance, so they replicate truly little during a continuance in healthy conditions. Regeneration of pancreatic β- cell mass following either bane- or autoimmune- mediated destruction in immature rodents is probable, but the degree of recovery declines with age and is deficient in adultlife.Three regeneration modes were established According to the various cellular regeneration origins. In The first mode, the undifferentiated ancestor cells gain and separate as a tone- renewing source in Response to injury to repair the lost cell population. The Alternate separate, and also gain the largely defined remaining cells. Regeneration of lost or dysfunctional islet β cells in vivo Can fulfil the pledge of advanced treatment for Cases with diabetes. [18]

3. Insulin Gene Therapy

Modern insulin therapy can more precisely replicate the physiological release of insulin and help diabetic patients achieve improved glycaemic control. One approach to treating diabetes mellitus is gene therapy. Gene therapy for insulin replacement as a potential treatment for type 1 diabetes. The physiological regulation of the expression of the insulin gene is crucial, in addition to the use of a reliable and efficient gene transfer vector. Hepatocytes are the main therapeutic target for insulin gene therapy, which involves the targeted production of insulin in non-Hep cells. Rats can be successfully transfected with the human insulin gene via the gastrointestinal tract using chitosan nanoparticles. [18]

4. Insulin secretion from nonpancreatic cells

By converting nonpancreatic cells into insulin-secreting cells or by substituting other cells, such as epidermal, intestinal, hepatocytes, and myocytes, to deliver insulin, the gene therapy strategy can also be used to treat T1DM. Using lentivirus vector mediated Pdx-1 administration, Fodor et al. Investigated the ex vivo trans differentiation of primary hepatocytes to generate insulin secreting cells. After in vivo transplantation, it was seen that enough insulin was secreted to maintain glucose homeostasis for at least 8 weeks. However, despite the mice's hyperglycaemic condition showing significant improvements, moderate hyperglycemia was still shown in the fed state, which may be related to the small amount of cells that were transfixed. [20]

5. Ex vivo conversion of cells into functional b-cells.

Ex vivo conversion of non-b-cells into either insulin-producing b-cells or insulin-producing islet-like cell clusters has been shown to be possible in some recent ground-breaking investigations. Many organisations have previously documented that pancreatic duct cells of both human and rodent origin can be used to create insulin-positive cells in vitro. Additionally, they were successful in creating insulin-expressing cells. These investigations need to be strengthened because other researchers discovered that nestin served as a marker for non-endocrine cells. Multipotent pancreatic precursors from adult mouse pancreas that develop in vitro into both islet endocrine and neural lineages have been identified through clonal analysis. It's interesting to note that these islet lineage clones have insulin production that responds to glucose. [21]

FUTURE PROSPECTS

When a significant proportion of patients have T1DM. Gene therapy is a tactic used to maintain a near normal BG level in an effective, safe, and targeted manner. Achieving near normal BG levels is the major future goal of any therapy for T1DM.In order to insert genes into cells and create new cutting-edge gene therapy methods, the science of genetic engineering is also essential in this regard. A potential treatment for T1DM involves transplanting stem cells that express disease-fighting genes. [22]

The integration of gene therapy strategies, combining existing stem cell understanding with advancements in cellular and genetic engineering techniques, such as nuclear transfer and genome editing, is anticipated to be the next step towards stem-cell-mediated precision medicine for T1D.All of these elements can be combined to successfully build a programme for precision medicine in T1D. [23]

The only treatment for T1D, as immunotherapy methods have not been successful, is pancreatic or islet transplantation from donors. [24] Researchers have focused on using stem cells (SCs) to create insulin-secreting beta cells due to the pressing need for a much-anticipated -cell replacement. Due to its more specialised and targeted therapeutic approaches, SC-based treatments have expanded the possibilities for the treatment of T1DM. [25]

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