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Application of Gene therapy in the perspective of the therapy of type 2 diabetes mellitus

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Diabetes mellitus is one of the main metabolic problems associated with an elevated level of blood glucose. Insulin play vital role in regulation of glucose level in the blood. Defect in insulin secretion /production is the etiological factor for type 1 diabetes whereas insulin resistance is for type 2 diabetes. These etiological factors are controlled by genetic and epigenetic factors. Several hypoglycemic oral drugs get used for the therapy of the type 2 diabetes. These drugs have some adverse side effects and need lifelong use. The recent advent of molecular genetics and big data analysis suggested several genes get associated with the type 2 diabetes. Aims of the current review are to explore the application and the prospect of gene therapy to combat fatal disorders. It is evident that these disorders are prevalent in low and middle-income countries. Further research on gene therapy in type 2 diabetes will explore immense future prospects for diabetes therapy and other problems of metabolism

Keywords: Diabetes mellitus, type 2 diabetes, hypoglycemic oral drugs, gene therapy, T2DM Gene therapy

1. Introduction

Diabetes mellitus, also known as diabetes is a very common metabolic problem in this century. According to the recent report in the year 2021, around 537 million people in the globe are affected by the disorders and it appears 9th major cause of death. Diabetes mellitusis an vital health problem in low income and mid income (LIMC) countries [1]. Diabetes mellitus is defined as a chronic metabolic problem associated with a high level of sugar in the blood. Diabetic ketoacidosis, hyperosmolar hyperglycemic state are the symptoms of acute complications and chronic complications include stroke, cardiovascular disorder, chronic kidney disorder, foot ulcers, retinopathy etc [2].

Our body utilizes sugars an energy source. In the case of diabetes, our body system is unable to take up sugar into its cells and extra sugars are accumulated in the bloodstream. Our endocrine system controls glucose levels of the blood by secreting hormones. Insulin and glucagon are the key players in blood glucose homeostasis. In response to blood, glucose level islet cells of the pancreas secrete the hormone. Pancreatic beta-cells (a type of islet cell) produces insulin and it exerts its effect on other tissue like adipose tissue, muscle tissue and red blood cells to absorb glucose from the blood to make it in normal level. On the other hand, glucagon which is secreted by pancreatic alpha cells mobilizes the glucose from liver cells to the bloodstream and maintain the blood glucose level.

Table 1. The number of people affected by Diabetes Mellitus worldwide. Data source: IDF Diabetes Atlas

Region	People with Diabetes
Africa	24 million
Europe	61 million
Middle east and North Africa	73 million
South East Asia	90 million
Western Pacific	206 million
North America and Caribbean	51 million
South and central America	32 million
Total	537 million

2. Review of Literature

2.1. Types of Diabetes

There are 2 main types of diabetes prevalent worldwide: type1 diabetes (T1DM) and type2(T2DM) diabetes mellitus [3]. TIDM is defined as a metabolic problem due to insulin deficiency.

T cell-mediated killing of pancreatic beta-cells is the main cause pathogenesis of the disorder. The process is triggered by persistent enteroviral infections. Biomarkers of T1DM are Glutamic acid decarboxylase, zinc transporter 8 and insulinoma-associated protein 2, [4]. There are three stages of the pathogenesis of T1DM. The stages are defined telepresence or absence of hyperglycemia and hyperglycemia-associated symptoms. Although no complete cure for diabetes is possible and patients depend on the insulin injections for life long. Beta-cell replacement is an alternate approach but possesses several limitations and complications to the patients [5].

T2DM is defined by insulin secretion deficiency by pancreatic islet cells and tissue insulin resistance (IR) [6]. Both genetic and environmental factors play an vital role in the onset of T2DM. Obesity is directly associated with the onset of the disorders. Various inflaming mechanisms, including high free fatty acid (FFA) release and adipokine deregulation, promote adipose tissue promotes for insulin resistance [7]. Complicacy arises in the therapy of T2DM because of the fact that our body cannot utilize the insulin effectively in this condition. In the early stage of the disorder, control of diet and physical exercise are effective strategies for disorders control. Dysregulation of the immune system and adipokine synthesishave been reported as pathophysiological factors for T2DM [8].

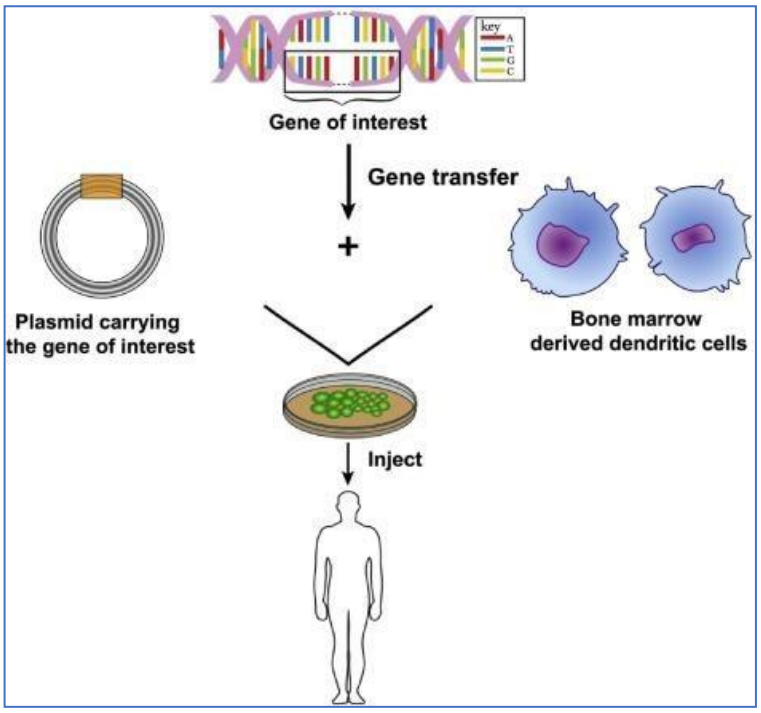
2.2. The emergence of gene therapy

Several oral hypoglycemic agents are used as the main therapeutic regimens for the therapy of T2DM because of its insulin resistance [9]. On the other hand, insulin injection is the main therapeutic strategy for T1DMtherapy. There are 4 classes of hypoglycemic drugs that are used for T2DM therapy [10]. These drugs have adverse side effects and not get approved for the therapy of diabetic pregnant women. Therefore, alternative for T2DM therapy is necessary to combat the disorders. Gene therapy is a cutting-edge approach

for correcting or compensating the function of defective or abnormal genes through the introduction of genetic manipulation [11]. Gene therapy is used for several disorders including cancers, neurological disorders, retinal problematic [12-14]. Gene therapy can be introduced both in somatic and germ cells through in vivo or in vitro transfer.

Figure1: Schematic diagram of gene therapy

The gene of interests is identified and characterized and engineered into a plasmid vector. The resulting genes are introduce in biological system via bone marrow derived dendritic cells (15).



Germline and somatic manipulation are the common platforms for gene manipulation. Gene transfer system can be categorized into two main approaches one is in vivo transfer and second one is in vitro transfer. The appropriate target cells and the immunogenic response for the vehicle is very much vital for in vivo gene delivery [15].

2.3. Target identification

Genomics studies enable to the identification of several genes associated with T2DM [16]. KCNJ11 is a vital component of the ATP-dependent potassium channel and its mutation leads to the onset T2DM [17]. Many genetic polymorphisms have been reported to antidiabetic drug responses. The SLC2A2 genes encoding and organic transporters get associated with glycemic response to Metformin. On the other hand, sulfonylureas response is well associated with SLCO1B3 and KCNQ encoding genes [18-20]. In T2DMgene remedy, nucleotide-binding oligomerization domain-like receptor protein 3 is a potent target. In mouse model it is reported that inhibition of NLRP3 protected pancreatic beta-cells from cell death and prevents T2DM development [21, 22].

2.4. T2DM Gene therapy

Gene remedy for diabetes primarily focuses on T1DM and is mediated by several delivery systems. Viral and non –viral-mediated transductions are common approaches for the same [23]. Gene therapy prevents

pancreatic beta-cells destruction or the replacement of the insulin gene by suppression of T cells [24]. Gene and linkage-based studies identified very few T2D risk genes, but the advent of genome-wide association studies identified multiple genes that play roles in T2DM [25]. Potential targets for T2DM were identified in 75 independent genetic loci. [26].

2.5. Genes regulating glucose homeostasis

Glucose transport in muscle and liver tissue is mainly controlled by Glucose transporters (GLUTs). GLUT4 and GLUT2 have been reported as probable targets for T2DM gene therapy. Glucose Absorption from kidney into the blood stream get control by sodium-glucose co-transporters (SGLTs) established as targets for T2DM [27]. Fibroblast growth factors (FGF) play vital roles in glucose homeostasis and are potential target to T2DM gene therapy [28]. Recent studies demonstrated that SIRT6 playas major role in control of blood sugar in T2DM. SIRT6 induces pancreatic insulin secretion and inhibits gluconeogenesis in the liver. SIRT6 is considered as vital target for treating T2DM [29].

2.6. Genes improving insulin secretion or sensitivity

Several genes have been identified as the regulator for insulin secretion and sensitivity. Glucose-dependent insulin secretion is regulated by Glucagon-like peptide 1 and its analogues [30]. G protein–coupled receptors (GPCRs), mainly the incretin receptors and the bile acid receptor GPBAR1 are the potent target for T2DM [31]. Furthermore, the inhibition of inflaming kinases IKKε and TBK1 have been reported to improve insulin sensitivity in T2DM patients. Immunotherapy with the proinflaming cytokine IL-1β exhibits the role in the maintenance of blood glucose level and insulin sensitivity [32].

2.7. Genes ameliorating diabetes-induced complications

T2DM has various complications and affect various organ. One of the common complications for T2DM patients is Diabetic kidney disorder (DKD). Blood serum isolated from DKD patients exhibited elevated level of Transforming growth factor alpha (TGF-α). T2DM triggered the onset of Diabetic cardiomyopathy (DCM) and is associated with NLRP3 inflammasome mediated cell death [34]. The onset of diabetic nephropathy (DN) can be ameliorated by globular adiponectin (ADPN) gene therapy [35]. Moreover, microRNAs play vital role in various of diabetes-associated complications such as nephropathy, retinopathy, myocardial injury and wound healing. Small RNAs possess great targets for therapeutic gene intervention for T2DM and its complications [36].

2.8. Prospect of Gene Therapy in T2DM

The concept of the gene therapy approach to diabetes was introduced after the cloning and expression of the insulin gene [37]. At that time it was thought that non-insulin-producing cells can be converted to insulin-producing β cells by recombinant DNA technology and can be used for insulin production in both types of diabetics [38, 39]. Several cell lines were used (fibroblasts, hepatocytes, myocytes etc) for artificial insulin-producing cells. Interestingly, those cells remain unresponsive to glucose with the physiological secretion of insulin. Thus exogenous insulin injection remain the common therapy for the therapy of diabetes. Other therapeutic approaches that aim to genetically manipulate beta-cells by genetic engineering to produce a protection factors for beta-cell protection. In diabetes beta-cells are destroyed by cytokines and nitric oxide from macrophage. Cytotoxic T cells released apoptotic factors (perforin and Fas ligand) that cause cell death to beta-cells in diabetic patients [40]. The genetic manipulation approaches have some advantages e.g. less toxicity, fewer immune reactions etc. Molecular biological research on transgenic gene expression using next-generation mammalian vectors improve the prosperity of gene therapy for the management of disorders.

3. Conclusions

Gene therapy in T2DM is a promising field for therapeutic intervention. However, gene therapy for T2DM are limited to few target genes and its effect was determined in animal model only. The genome-wide analysis of T2DM using next-generation sequencing with large number of samples will provide the landscape of genomics for the disorders. Genetic modulation generally achieved by two mechanism 1. Loss of function and 2. Gain function. Small interfering RNA (siRNA), micro RNA is used for inhibition of targets. Clustered regularly interspaced short palindromic repeats (CRISPR) is new techniques for genetic manipulation. These approaches can be used for genetic engineering to target the genes for T2DM.

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