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Research Paper

Alternative Therapies for Diabetes Mellitus: From Gene Therapy to Epigenetic and Microrna Based Therapies

Medical Science

KEYWORDS : Diabetes mellitus, Gene therapy, Epigenetics, Stem cell therapy, mi RNA based therapy

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ABSTRACT

Several metabolic disorders and their associated complications including diabetes are mainly associated with the chronic low grade inflammation and enhanced oxidative/nitrosative stress. Reduction or correction of the enhanced glucose levels will help in the decreased diabetes associated co-morbidities. Several drug commodities, today used got several side effects leading to severe conditions. Hence present researchers are mainly focusing on other alternate therapies that can subside this metabolic disorder, that can naturally secrete insulin endogenous or enhance insulin sensitivity. Present review will give a brief picture about several alternative therapies that include; Stem cell therapy, Gene therapy, Nanoparticle (NPs) based therapies, Epigenetics and micro RNA (miRNAs) based therapies.

Summary

Several metabolic disorders and their associated complications including diabetes are mainly associated with the chronic low grade inflammation and enhanced oxidative/nitrosative stress. Hence reduction or correction of the enhanced glucose levels will help in the decreased diabetes associated co-morbidities. Insulin being a glucose regulator, any alternative therapies that can naturally secrete insulin endogenous or enhance insulin sensitivity will be of great use for the effected. Hence these approaches can hold a great role in mitigating diabetes and its associated complications.

1. Introduction

Diabetes mellitus, a metabolic disease or disorder that sets the toll for hyperglycemia to enhance oxidative/nitrosative stress alongside chronic low grade inflammation allied cellular dysregulation and dysfunctions. Several oral antidiabetic drugs like Insulin secretagogues, Rapid-acting prandial insulin releasers, Insulin sensitizers, Glucosidase inhibitors, new drug modalities and Amylin analogues having different mode of actions (Zyl, 2008). Most of these drugs have severe side effects like uncontrolled hypoglycemia, weight gain, lactic acidosis, osteoporosis, flatulence, abdominal discomfort and diarrhea that can harm the patients based on their diabetic complications (Zyl, 2008). As insulin itself can strongly act against glucose homeostasis, that can combat hyperglycemia, due to this reason other optional therapies that can naturally secrete insulin endogenous or enhance insulin sensitivity. The following are some optional therapies for endogenous insulin release or insulin longitivity which inhibit hyperglycemia and finally the oxidative/nitrosative stress besides low grade inflammation.

2. Stem cell therapy

Stem cell therapy; A future potential therapeutic approach which may change the face of the diseased and sufferings by intercession strategies that initiate the introduction of adult stem cells into the effected tissue for their treatment (Lindvall O, 2006). There are several types of stem cells like Haemopoietic, mesenchymal types which have the potential for the Type 1 Diabetes (T1D) therapy. Several sources produce different types of stem cells in the treatment of T1D which include; haemopoietic, mesenchymal stem cell from the adult stem cells, Cord blood haemopoietic and Cord blood/cord wall mesenchymal stem cell from the Umbilical Cord Stem Cells, blastocyst derived embryonic and Induced pluripotent stem cells from embryonic stem cells, pancreatic and their reprogrammed exocrine stem cells (Voltarelli JC, 2011). These stem cells can differentiate into insulin producing pancreatic β-cells by the manipulation in the culture protocols (Voltarelli JC, 2011).

3. Nanoparticle (NPs) based therapies

Diabetic patients maintain their blood glucose level by the injection of insulin into blood by the intravenous means, which generally happens during chronic stages of this metabolic disorder. This is generally followed due to the problems with the oral route due to the acid based destruction of insulin along with intestinal epithelium playing a barrier function for these hydrophilic drugs making this route useless for the consumption (A.H. Kraulanda, 2004). Hence attention should be given, for improving the drug in the paracellular transport (Lamprecht A, 2006). A proper delivery can be achieved with the help of nanoparticle based intestinal permeation enhancers like chitosan (CS), which protects the drug from harsh conditions (A. Arya, 2008). Additionally several natural polymers may be used for oral insulin delivery which is under study (Sonia T, 2012). Oral administration of insulin can also be achieved by the Microsphere system; acting both as protease inhibitor and intestinal permeation enhancers (Gerardo P. Carino, 1999).

4. Gene therapy

In order to regulate Diabetes mellitus, gene therapy based strategies has been targeted, yet they are unsuccessfully due to hurdles like vector-related toxicity and inability to physiologically regulate the insulin expression. But in the recent years the progression in the b-cells biology and the transcriptional cascade which has enabled in the in vivo and ex vivo gene therapies pooled with cell therapy are used in animal models of diabetes with significant success rate (Yechoor V, 2005). The parallel advancements in stem cell biology and immunology further opened up the prospects for the gene therapy allied for autoimmune diabetes.

5. Epigenetics and diabetic treatment

T2D and its severity occur due to the permutation in the insulin

secretion defect along side with the peripheral insulin resistance owing chiefly to hyperglycaemia, hyperlipidaemia and oxidative stress (Robertson RP, 2003). ROS that induce the oxidative stress have shown to effect the expression of multiple genes by rendering DNA methylation and their histone organizations (Cerda S, 1997). Epigenetics principally deals within the study of DNA and their histone modifications by methylation or acetylation along with the non-coding RNAs (ncRNAs), which significantly affect the phenotype by regulating the gene expression without altering the underlying sequence of DNA (Kaestner, 2012). This mechanism generally plays a crucial role during the pathogenesis of several complex metabolic syndromes like T2D and obesity that mainly add up due to the environmental factors along with the sedentary lifestyle (Kaestner, 2012). However recent improvements have shown that the epigenetic mechanisms have proven worthy for the endocrine cell differentiation and pancreatic islet functions. Discovery of several classes of histone-modifying enzymes(class I, IIa, IIb and III HDACs) along side with the assessment of their expression patterns by affecting the cell function largely provide us the importance of these enzymes and their scope in the developmental, functional maintenance of pancreatic tissue (Lenoir, 2011).

6. Micro RNA (miRNAs) based therapies

The recent focus of the research in the field of human genome and its annotation has lead the way to the discovery of small (~22 nucleotides), endogenous and ncRNAs in the cell, generally referred as miRNAs (Kumar M, 2012). These miRNAs can play a very important role in the therapeutic as well as in the pathogenesis of diabetes (Guay C, 2011). miRNAs like miR-375 which are mainly involved in the negative regulation of the glucose induced insulin secretions (Tang, 2008) and studies have shown that the homozygous deletion caused hyperglycemia with a reduction in the pancreatic β-cell mass and insulin, along with that an elevated α-cell number and plasma glucagon levels (Poy, 2009). These studies have given us the evidences that for normal pancreatic α- and β-cell turnover, glucose homeostasis and β-cell expansion in order to achieve the insulin level at the time of insulin resistance (Poy, 2009). Some other miRNAs like miR-9& miR-96 regulate insulin exocytosis in the pancreatic β-cells. The extensive role of several miRNAs as a post-transcriptional regulation of gene during diabetes and its complications convey us the idea that these may act like a probable biomarkers and drug targets for the prevention, treatment, and management of diabetes and its allied complications (Kumar M, 2012).

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