Gen therapy for diabetes type 1

What is gene therapy?

Gene therapy is a technique for correcting defective genes responsible for disease development. The most common approach for correcting faulty genes is to insert a “normal” gene into the genome to replace an “abnormal” disease-causing gene.

OBJECTIVES: The aim of this work is know the general appropriate modifications of viral vector to lead correctly the genetic material to the target cells.

BIBLIOGRAPHY:

CONCLUSIONS: In reference to the cure of type 1 diabetes, the authors demonstrate for the first time in a large animal model that this gene therapy approach has a beneficial therapeutic effect for up to 4 years. This is a major advance in the field of gene therapy for DM. rAAV-based gene therapy vectors represent one of the most promising gene therapy systems and gain increasing popularity.

Gene therapy treatments for type 1 diabetes

PREVENTIVE

Preventive gene therapy is based on exploit immunoregulatory networks to promote hyporesponsiveness of autoaggressive immune cells as a viable means of improving or restoring normoglycemia.

ADJUNCTIVE

Adjunctive gene therapies are based on reducing immune reactions or inducing immune tolerance in transplantation.

CURATIVE

Patients with an advanced stage of Diabetes type 1 cannot be restore normal insulin level production by preventive gene therapy, due to the high destruction of β-cell. Recovery from type 1 diabetes requires β-cell generation.

One approach to do so is by genetically engineering the endocrine pancreas in vivo to express factors that induce β-cell replication and neogenesis and counteract the immune response.

Insulin and Glucokinase gene transfer to skeletal muscle corrects diabetes in dogs

This approach, demonstrates that it is possible to generate a "glucose sensor" in skeletal muscle through coexpression of glucokinase and insulin. The genes were one-time intramuscular administration in diabetic dogs through adeno-associated viral vectors of serotype 1.

The liver enzyme glucokinase, compared to muscle glucokinase II in the skeletal muscle is not inhibited by glucose-6-phosphate, and shows kinetic cooperation with glucose. When expressed in skeletal muscle of transgenic mice, glucokinase remains active in the cytosol and facilitates glucose uptake only when blood glucose is high. However, during diabetes, constant basal levels of insulin are required to ensure the presence of GLUT4 on the cell membrane.

Therefore, the regulation of glycemia was achieved by coexpression in skeletal muscle of glucokinase and low levels of insulin.

Five diabetic dogs were treated with one of the following:

A. Insulin, administered twice daily. (Fig 6)
B. Intramuscular injection of the glucokinase gene alone (AAV-GcK). (Fig 7)
C. Intramuscular injection of the insulin gene alone (AAV-Ins). (Fig 8)
D. Intramuscular injection of both the insulin and glucokinase genes(AAV1-Ins/GcK) (Fig 9)

RESULTS

The efficiency of AAV infection has been improved through the use of certain serotypes of AAV that have different tropisms in vivo.

Figure 3. Production of AAV vectors. The two ITRs are the only AAV sequences preserved in the vectors, while transcriptional cassette (promoter + gene + polyadenylation site) substitutes the rest of the genome. [1]

Figure 4. Time and cell therapy strategies for type 1 diabetes. A number of strategies can be employed alone or in combination. Extracted from Gene- and cell-based therapeutics for type 1 diabetes mellitus. Gene therapy,2003;10.

Figure 5. The mechanism of glucose-stimulated insulin secretion from the β-cell. [3]

Figure 6. The dogs on twice daily insulin were better controlled but remained hyperglycemic. [2]

Figure 7. Expression of insulin alone. The ability to dispose glucose was only moderately improved. [2]

Figure 8. Expression of glucokinase alone caused hypoglycemia in overload glucose conditions. [2]

Figure 9. Expression of glucokinase and insulin. dogs quickly regained normoglycemia. [2]