GENE THERAPY- A BRIEF REVIEW

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ABSTRACT

Gene therapy is an emerging field of biomedicine that has commanded considerable scientific and popular attention. As evolution is a continuous process with the advancement of the technology, the researchers are in continuous to understand the cellular and molecular basis of every disease. As in most of the diseases conventional method is not giving satisfactory results, thus focus is on gene therapylocated to treat not only inherited disease but also acquired ones.This review provides an update on gene therapy and its types with different gene transfer strategiesand disadvantages of gene therapy.

***KEY WORDS**: Gene therapy, diseases, medicine.*

INTRODUCTION

Gene therapy "the use of genes as medicine" involves the transfer of a therapeutic or workingcopy of a gene into specific cells of an individual in order to repair a faulty gene copy.Thetechnique may be used to replace a faulty gene, or to introduce a new gene whose functionis to cure or to favourably modify the clinical course of a condition.1

The objective of gene therapy is: to introduce new genetic material into target cells while causing no damage to thesurrounding healthy cells and tissues, hence the treatment related morbidity is decreased.1

Genes are specific sequences of bases that encode instructions to make proteins. When genes are altered so that encoded proteins are unable to carry out their normal functions, genetic disorders can result. Gene therapy essentially consists of introducing specific genetic material into target cells to compensate for abnormal genes or to make a beneficial protein without producing toxic effects on surrounding tissue. Transferred genes can be used for either reparative or pharmacological purposes.2

GENE iDELIVERY iSYSTEMS

The delivery system includes a vector that delivers a therapeutic gene into the patient's target cell. Functional proteins are created from the therapeutic gene causing the cell to return to a normal stage.

Gene delivery systems are categorized as:3

- Viral-based systems

- Non-viral-based systems
- Combined hybrid systems

VIRAL-BASED SYSTEMS

Viral-mediated gene delivery systems consist of viruses that are modified to be replication-deficient, but which can deliver DNA for expression. Adeno viruses, retroviruses, and lenti viruses are used as viral gene- delivery vectors.4

NON-VIRAL-BASED SYSTEMS

Non-viral gene delivery systems were introduced as an alternative to viral-based systems. One of the most important advantages of these systems is improved transfection. Non-viral systems are categorized according to preparation, as physical or chemical types. The most c om m o n phys ic al m et ho ds a re m ic r o - inject ion, electroporation, ultrasound, gene gun, and hydrodynamic applications. In general terms, physical methods refer to delivery of the gene via the application of physical force to increase permeability of the cell membrane.5

TYPES iOF iGENE iTHERAPY

There are 2 types of gene therapy:

1. Germ line gene therapy: where germ cells (sperm or egg) are modified by the introduction of functional genes, which are integrated into their genome. Therefore changes due to therapy would be heritable and would be passed on to later generation. Theoretically, this approach should be highly effective in counteracting genetic disease and hereditary disorders. But at present many jurisdictions, a variety oftechnical difficulties and ethical reasons make it unlikely that germ line therapy would be tried in human beings in near future.6

2. Somatic gene therapy: where therapeutic genes are transferred into the somatic cells of a patient. Any modifications and effects will be restricted to the individual patient only and will not be inherited by the patient's offspring or any later generation.7

GENE iTRANSFER iSTRATEGIES

Gene transfer protocols have been approved for human use in inherited diseases, cancers and acquired disorders. In 1990, the first successful clinical trial of gene therapy was initiated for adenosine deaminase deficiency. Since then, the number of clinical protocols initiated worldwide has increased exponentially.

Although systemic intravenous route can be applied to deliver the genetic material to the cells, local delivery methods are more commonly used.

a. Percutaneous injection: If paracrine effect of the gene product is therapeutic, vector solution can be injected percutaneously into the tissue around the vessel. This simple and locally effective technique can be efficacious for increasing the number

of capillaries within ischemic muscles.

b. Surgical method: This is the most common method used in the vascular gene therapy in animal models. In this procedure, the related vascular area is isolated by clamping from proximal and distal ends and its all side branches are ligated. The blood inside is drained and vector solution is injected into this isolated segment. After a certain time of incubation the vector solution is aspirated and the involved segment is washed unclamped, and ligations are removed. This technique has high transfection efficiency and only the isolated corresponding area is transfected. Its disadvantage is that it is an invasive procedure and the vessel is exposed to the straining effects of clamping and ligation of side branches.

c. Catheter systems: New catheter systems are developed to increase the interaction between vectors and end o t helial c ells . M echa nic a l o r elec tr ic ally strengthened catheters are needle injection catheter, iontophoretic electric current-enhanced balloon, and stent based systems.7

DISADVANTAGES iOF iGENE iTHERAPY

1. Short-lived nature of gene therapy: Before gene therapy can become a permanent cure for any condition, the therapeutic DNA introduced into target cells must remain functional and cells containing the therapeutic DNA must be long-lived and stable. Problems with integrating therapeutic DNA into the genome and the rapidly dividing nature of many cells prevent gene therapy from achieving any long-term benefits. Patients will have to undergo multiple rounds of gene therapy. Moreover, the new gene fails to express itself or the virus does not produce the desired response.
2. Immune response: Anytime a foreign object is introduced into human tissues, the immune system has evolved to attack the invader. The risk of stimulating the immune system in a way that reduces gene therapy effectiveness is always a possibility. Furthermore, the immune system's enhanced response to invaders makes it difficult for gene therapy to be repeated in patient.
3. Problem with viral vectors: Viruses, while the carrier

of choice in most gene therapy studies present a variety of potential problems to the patients such as toxicity, immune and inflammatory response and gene control and targeting issues. In addition, there is always the fear that viral vector, once inside the patient, may recover its ability to cause disease.

4. Multigenic disorders: Conditions or disorders that arise from mutation in a single gene are best candidates for gene therapy. Unfortunately, some of the most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis and diabetes, are caused by the combined effects of variations in many genes. Multigenic or multifactorial disorders would be especially difficult to treat effectively using gene therapy.
5. Insertional mutagenesis: The main problem that geneticists are encountering is the virus may target the wrong cells. If the DNA is integrated in the wrong place in the genome, for example in a tumor suppressor gene, it could induce a tumor. This has occurred in clinical trials for X-linkedSCID (Severe combined

immunodeficiency)patients in which hematopoietic stem cells were transduced with a corrective transgene using a retrovirus, and this led to the development of T-cell leukaemia in 3 of 20 patients.a

CONCLUSION

Thanks to the changes in medicine, pharmacological treatment rapidly progresses into newfields. There is an emphasis on the development of treatment methods to eliminateunderlying factors rather than to treat the symptoms of a disease. Therefore, research isincreasingly utilizing knowledge from the field of genetics. Gene therapy is in its infancy, and current genetherapy is primarily experimental, with most human clinical trials only in the research stages. Over time and with proper oversight, human gene therapy might become an effective weapon in modern medicine's arsenal to help fight diseases such as cancer, HIV/AIDS, diabetes etc.We can hope that the extensive animal studies and human clinical trials may become a clinical reality in the second decade of 21st century.

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