TREATMENT OF GENETIC DISEASES

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INTRODUCTION

- Many genetic disorders characterized by progressive phenotype with no effective treatment available at the present.

- The most promising hope in treatment of such diseases is THE GENE THERAPY.
CONVENTIONAL APPROACHES TO TREATMENT OF GENETIC DISORDERS

• In reality, most genetic disorders can not be treated using this type of conventional methods of treatment.

• Examples of method used for treatment of genetic disorders are:
  • Protein/enzyme replacement
  • Drug treatment
  • Transplantation
    • Tissue transplantation
    • Stem cell transplantation
PROTEIN/ENZYME REPLACEMENT

• If the genetic disease is found to be caused by a deficiency in particular protein or enzyme, then replace this substance with be the logical and first line of treatment for such a disease.

• Replace of factor VIII in treatment of hemophilia.
• Drug was used in some genetic disease such as familial hypercholesterolemia to lower the cholesterol level in the body.

• Avoid certain drug and food in treatment of G6PD

• Codeine drug pain reliever
Tissue transplantation was an option in treatment of some genetic disease such as renal transplantation in adult polycystic kidney disease or lung transplantation in patient with cystic fibrosis.

Stem-cell transplantation or bone-marrow transplantation was used as an effective treatment of several genetic diseases such as:

- Sever combined immunodeficiency
- Lysosomal storage disease
- Fanconi anemia
GENE THERAPY

• Gene therapy can be defined as
  • The replacement of a deficient gene product
  • Correction of abnormal gene

• Gene therapy may be loosely defined as the transfer of genetic material to effect a desired biological response.

• This usually entails transfer of chosen cDNA (or genomic DNA), under the control of an appropriate promoter, into host cells.

• Once inside the cell, the host's transcriptional and translational tools effects production of the desired protein.
GENE THERAPY

- The first clinical trial of gene therapy was approved in 1989; it involved the transfer of human cDNA encoding adenosine deaminase to a patient with severe combined immune deficiency (SCID).

- Gene therapy can be carried out in two ways

  - Ex vivo: by treatment of cell and tissue from an affected individual in culture and reintroduction into the affected individual.

  - In vivo
GENE THERAPY
TECHNICAL ASPECTS OF GENE THERAPY

• Before any trial of gene therapy these are several aspects should be considered
  • Gene characterization
  • Targeted cell/ tissue
  • Vector system used
METHOD OF GENE THERAPY

- These can be divided into **viral** and **non-viral**

- **Non-viral** gene therapy
  - Naked DNA
  - Liposome-mediated DNA transfer
    - Receptor-mediated endocytosis
  - *Repair of mutation* in situ through the *cellular DNA repair mechanism*

- **Animal models**
- **Target organ**
METHOD OF GENE THERAPY

• Non-viral vectors principally comprise cationic liposomes, which are effectively cationic lipid bilayers
  • capable of enveloping (anionic) plasmid DNA.
• Liposomes can incorporate into cell membranes, liberating their DNA content into the cytoplasm.
• Liposomes have found favor in many quarters because they are
  • relatively easy to produce and administer, and
  • they do not carry the theoretical risks of oncogenesis or superinfection that may accompany the use of some viruses;
  • biologically not moving, and thus open to to repeated administration without inducing inflammatory or immune responses,
METHOD OF GENE THERAPY

• A major limitation of liposome vectors:
  • vast majority of the nucleic acid carried into cells is directed into, and degraded by, endosomes before reaching the nucleus;
  • the small proportion of DNA reaching the nucleus is usually only transiently and weakly expressed;
  • in the context of the lung, effective spreading of liposomes throughout the bronchial tree is difficult practically.
LIPOSOME-MEDIATED GENE THERAPY
VIRAL GENE THERAPY

- There are number of different viruses can be used to transport DNA into cells
  - Oncoretrovirus
  - Lentivirus
  - Adenovirus
  - Adeno-associated virus
  - Herpes virus
Retroviruses are potentially important vectors for gene therapy because viral DNA is integrated into the host genome, resulting in stable transfection thus avoid the need for re-administration.

Unfortunately, large-scale production of retrovirus for therapeutic purposes is technically difficult.

In addition, retroviruses are critically dependent upon cell division for transfection - this favors the use of retrovirus in the setting of malignant disease.
ADENOVIRUS

• Adenoviruses, efficiently transfect non-dividing cells.

• Have a natural tropism for respiratory epithelium making them ideal candidates for gene delivery to the lung.

• Adenoviruses can efficiently transfect cells of both the proximal and distal airways both in vitro and in vivo and once inside host cells, they efficiently access the nuclear membrane, and liberate their genetic material.

• Techniques have been devised to yield extremely high titers of adenovirus rendered incapable of replication, but capable of efficiently transfecting human cells.
ADENOVIRUS

• These techniques involve removing the only region of the adenoviral genome absolutely required for viral replication (the E1 region).

• Deletion of E1 also makes space for therapeutic transgene to be inserted.

• Generation of sufficient virus to allow transfection of organs in large mammals such as man, along with

• high levels of transgene expression, have made adenoviruses extremely attractive therapeutic tools.

• By far the biggest problem facing adenoviral gene therapy is inducing the host immune response.
ADENOVIRUS

- Adenoviral DNA adopts an epichromosomal, non-integrated location in the host nucleus, making transfection short-lived which means that re-administration is necessary for long-term therapy.

- Both cellular and humoral immunity present difficulty to the effective administration and readministration of adenovirus, principally in the form of MHC Class I restricted cytotoxic T lymphocytes which eliminate host cells transfected with virus, and neutralizing antibodies which eliminate virus entering the airways.

- Other theoretical concerns surround adenoviral gene therapy:
  - adenoviruses can disrupt the cell cycle in human cells;
  - they may cause fulminant pneumonia and decline in lung function in immunocompromised hosts;
### Retroviruses and Adenoviruses

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<th>Retroviruses</th>
<th>Adenoviruses</th>
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<tr>
<td>Small DNA can introduce up to 7kb</td>
<td>carry up to 36kb</td>
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<tr>
<td>Can only infect dividing cell e.g not CNS</td>
<td>Wide variety of cell types</td>
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<tr>
<td>Unstable</td>
<td>stable for treatment of specific tissues e.g RT</td>
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<td>can not purified</td>
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THANK YOU