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Gene Therapy - An Overview

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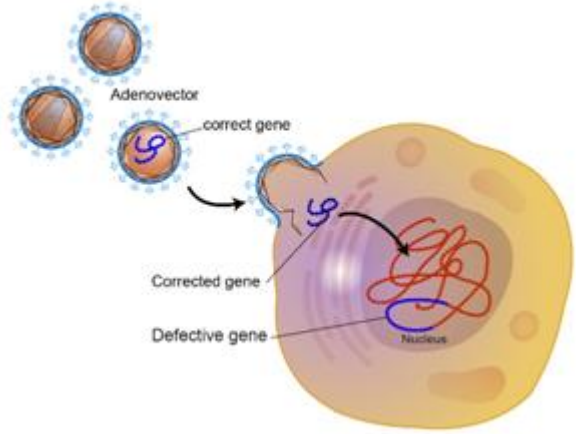
Abstract: ***Gene therapy is used to correct defective genes in order to cure a disease or help your body better fight disease. Researchers are investigating several ways to do this including Replacing mutated genes. Two decades after the initial gene therapy trials and more than 1700 approved clinical trials worldwide, but also learned to understand the concern that has persisted in society. Nevertheless, our knowledge continues to grow and during the course of time more safety data has become available that helps us to develop better gene therapy approaches.***

Keywords: Gene therapy, In vivo gene therapy, In vitro gene therapy, vectors in gene therapy

1. Introduction

Gene therapy is an experimental technique that uses genes to treat or prevent disease. In the future, this technique may allow doctors to treat a disorder by inserting a gene into patient's cells instead of using drugs or surgery.



The first attempt at modifying human DNA was performed in 1980 by Martin cline, but the first successful nuclear gene transfer in humans, approve by the National Institute of Health, was performed in May 1989. Between 1989 and February 2016, over 2,300 clinical trials were conducted with more than half of them in phase I.

Cell Types

1) **Somatic:** In Somatic cell gene therapy (SCGT), The therapeutic genes are transferred into any cell other than a gamete, germ cell, gametocyte or undifferentiated stem cell. Any such modifications affect the individual patient only and are not inherited by offspring. Indicated in Immunodeficiency's, Haemophilia, Thalassemia, Cystic Fibrosis
2) **Germline Gene Therapy (GGT):** Is when DNA is transferred into the cells that produce reproductive cells, eggs or sperm in the body. This type of therapy variants for the correction of disease causing gene variants that are certain to be passed down from generation to generation.

Approaches to gene therapy

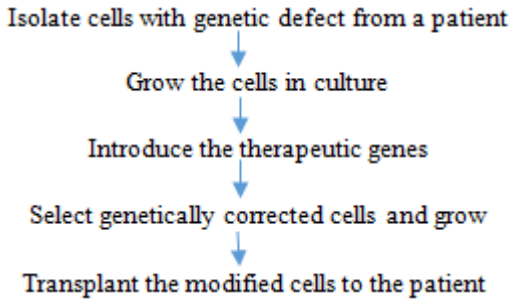
There are multiple approaches to gene therapy research. There are two potential methods of delivering the gene material:

In vivo gene therapy: Directly introduces the gene into the patient'seye using a vector, which is the only feasible method of accessing these particular cells of interest.

In vivo gene transfer is necessary when cultured cells cannot be re-implanted in patients effectively.

Example of in vivo gene therapy: In patients with cystic fibrosis, a protein called cystic fibrosis trans-membrane regulator (CFTR) is absent due to gene test, it can be treated by in vivo replacement of defective gene by adenovirus vector.

Ex vivo gene therapy: Harvests cells from the patient, genetically modifies them, and returns them to the patient. A few cell types may lend themselves well to ex vivo gene therapy, but may do not.



Example of ex vivo gene therapy: 1st gene therapy – to correct deficiency of enzyme, Adenosine De Aminase(ADA). Performed on a 4 year old Ashanti Desilva, was suffering from SCID-Severe Combined Immuno Deficiency. SCD caused due to defect in gene coding for ADA, which causes accumulation of deoxy adenosine and destroys T Lymphocytes which disrupts immunity, suffer from infectious diseases and diet at young age.

Vectors in Gene Therapy

To transfer the desired gene into a target cell, a carrier is required. Such vehicles of gene delivery are known as vectors. Two main classes are

a) Viral vectors
b) Non-viral vectors

Ideal Vector:

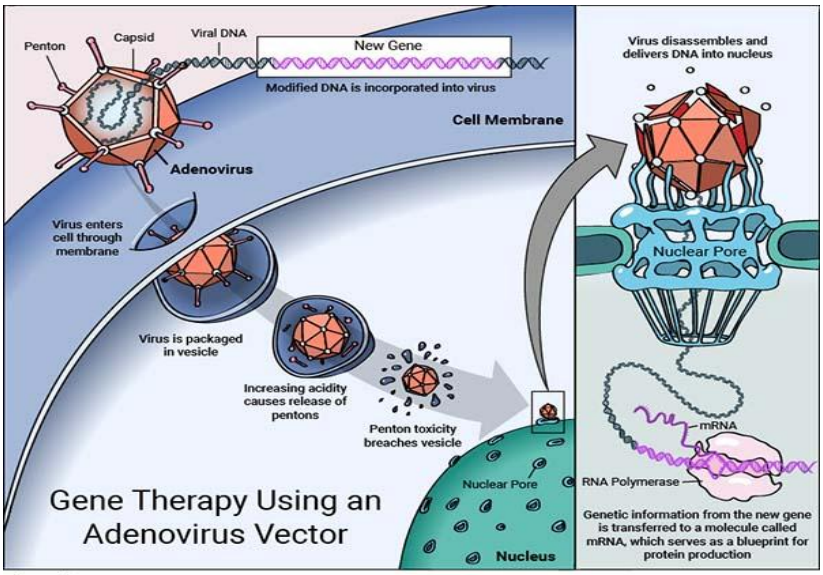
- Target the right cells
- Integrate the gene in the cells
- Activate the gene
- Avoid harmful side effects
- No universal vector exists

Viral Vectors

- Viruses introduce their genetic material into the host cells as part of their replication cycle.
- Remove the viral DNA and using the virus as a vehicle to deliver the therapeutic DNA.
- The viruses used are altered to make them safe, although some risks still exist with gene therapy.

Types of viral vectors: A number of viruses have been used for human gene therapy including..

- Retrovirus
- Adenovirus
- Adeno-associated virus
- Herpes Simplex Virus.



- Retrovirus vector system: The recombinant retroviruses have the ability to integrate into the host genome, Can carry a DNA of size less than 3.4 kb. Target cell-dividing.
- Adeno virus vector system: Adenoviral DNA does not integrate into the genome and is not replicated during cell division. Humans commonly come in contact with adenovirus, majority of patients have already developed neutralizing antibodies which can inactivate the virus. Target non-dividing, dividing cells.
- Adeno Associated Virus Vector System: It is a human virus, It is single standard. AAV enters host cell, becomes double stranded and gets integrated into chromosome. AAV is not currently known to cause a very mild immune response. Target – non-dividing, dividing cells.
- Herpes Simplex Virus Vector: Viruses which have natural tendency to infect a particular type of cell. The herpes simplex virus is a human neurotropic virus. This is mostly examined for gene transfer in the nervous system.

Advantages:

- Target specific types of cells
- They are very good at targeting and entering cells
- They can be modified so that they cannot replicate and destroy cells.

Disadvantages:

- They can cause immune responses in patients
- They can carry a limited amount of genetic material. Therefore, some genes may be too big to fit into some viruses.

Comparison of commonly used viral vectors in gene therapy

Virus	Gene material	Packing capacity	Chromosome Integration	Key principles
Retro virus	RNA	8 kb	Yes	Infects only dividing cells, persistent gene expression.
Adeno virus	ds DNA	30 kb	No	Efficient short term gene expression
Adeno associated virus	ss RNA	5 kb	No	Carry small amount of gene material
Lenti virus	RNA	8 kb	Yes	Infects both dividing and quiescent cells, persistent gene expression.
Herpes Simplex Virus	Ds RNA	40 kb	No	Strong tropism for neurons.

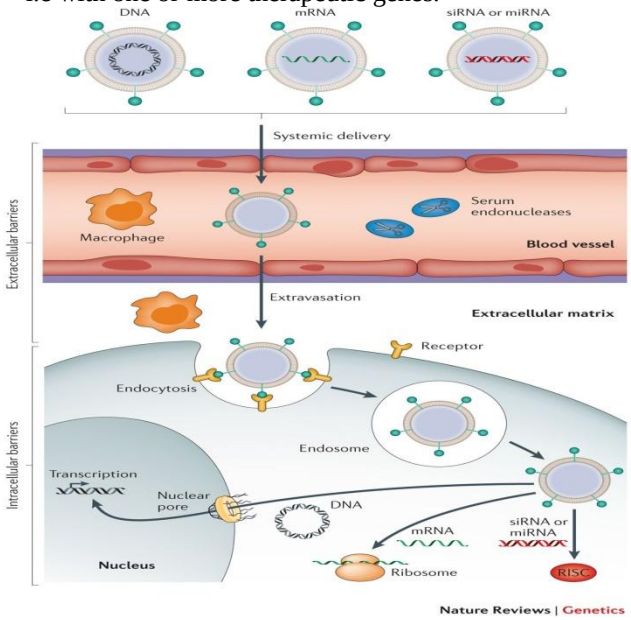
Non-Viral Vector System

a) Pure DNA Construct: Direct introduction of pure DNA construct into target tissue.
   - Efficiency of DNA uptake by cells and expression rather low.
   - Consequently, large quantities of DNA have to be injected periodically.

b) DNA Molecular Conjugates: Commonly used synthetic conjugate is poly-L-Lysine bound to specific target cell receptor.
   - Therapeutic DNA is then made to combine with the conjugate to form a complex.
   - It avoids lysosomal breakdown of DNA.

c) Lipoplexes:
   - Lipid DNA complexes
   - DNA construct surrounded by artificial lipid layer
   - Most of it gets degraded by lysosomes

d) Human Artificial Chromosome: Can carry a large DNA i.e with one or more therapeutic genes.



2. Methods of Gene Delivery

2.1 Physical Methods

1) Gene Gum: Employs a high-pressure delivery system to shoot tissue with gold or tungsten particles that are coated with DNA.
2) Microinjection: Process of using a glass micropipette to insert microscopic substances into a single living cell. Normally performed under a specialized optical microscope setup called a micromanipulator.
3) Chemical Methods: Using detergent mixtures: Certain changes chemical compounds like calcium, phosphates are mixed with functional cDNA of desired function.
4) The mixture is introduced near the vicinity of recipient cells.
5) The chemicals disturbs the cell membrane, widens the pore size and allows cDNA to pass through the cell.
6) Lipofetion: It is a technique used to iject genetic materials into a cell by means of liposomes.
7) Liposomes are artificial phospholipid vesicles used to deliver a variety of molecules including DNA into the cells.

Other types of gene therapy:

a) Gene Augmentation therapy: Most common form, foreign gene replaces missing or defective gene
   Ex: Replacement of defective P53gene by a normal one in liver cancer.

b) Gene Inhibition therapy: It id done to block the over production of some proteins. It is gain divided into two types
   - Antigens: Blocks transcription using anti-gene oligonucleotide.
   - Antisense: Blocks translation using anti sense oligonucleotide.

Indications of Gene Therapy:

- Blindness of inherited condition
- Parkinson's disease
- Cystic Fibrosis
- ADA- SCID
- AIDS
- Heart Diseases
- Cancer
- Haemophilia
- Thalassemia
- Diabetes
- Muscular Dystrophy

Purpose of Gene Therapy

- To introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein.
- If a mutated gene causes a necessary protein to be faulty or missing, gene therapy may be able to introduce normal copy of gene to restore function of the protein.
- It helps inactivating or "Knocking out" a mutated gene that is functioning improperly.

Advantages

- Gene therapy has the potential to eliminate and prevent hereditary diseases such a s cystic fibrosis, ADA – SCID etc..
- It gives someone born with a genetic disease a chance to life
- It is a possible cure for heart diseases, AIDS and cancer
- It can be used to eradicate diseases from the future generations.

Disadvantages

- Long lasting therapy is not activated by gene therapy, due to rapid dividing cells benefit of gene therapy is short lived.
- Immune response to the transferred gene stimulates a potential risk to gene therapy
- Multigene disorders
- Viruses used as vectors for gene therapy may cause toxicity, immune responses and inflammatory reactions in the host
- Disorders caused by defect in multiple genes cannot be treated effectively using gene therapy
- Costly Procedure
- Insertional mutagenesis of deaths – due to systemic inflammatory response system.

Genetic Counselling

Definition: Genetic counselling is a communication process which deals with the human problems associated with the occurrence or the risk of occurrence of the genetic disorders in a family.

Purposes:

- To comprehend the medical facts, including diagnosis, probable course of disorder and the available management.
- To appreciate the way hereditary contributes to the disorders and the risk of occurrence in specific relatives.
- To understand the option for dealing with the occurrence.
- To make the best possible adjustment to the disorder in an affected family members.
- To choose the course of action which seems appropriate to them in view of their risks and family goals, act in accordance with that decision.

3. Phases of Genetic Counselling

Assessment Phase:

- Initial interview with counselling and family for counselling
- Collect family history and other relevant history
- Physical examination
- Considering potential diagnosis based on collected information.

Diagnosis Phase:

- Chromosomal analysis
- Biochemical tests
- Molecular DNA tests
- X- rays, Biopsy test
- Immunological tests

Analysis Phase:

- Literature search and review of information
- Consultation with other experts
- Compiling of information and determination of recurrent risk.

Communication Phase:

- Communication of the results and risks to the counselee and to the family if appropriate
- Discussion of the natural history of disorder, treatment, anticipatory guidance
- Discussion of option and review of question
- Clear all doubts of the patients.

Referral and support Phase:

- Refer the individual to genetic specialist for further intervention ex: prenatal diagnosis
- Support of decision made by counselee
- Psychological support should be provided throughout the process
- Follow up and evaluation.

4. Role of nurse in Genetic Counselling

1) Receive client and family to make them comfortable in assessment room for genetic counselling.
2) Obtain prenatal, family and other family histories from individual and family
3) Identify families at risk, investigate the problems present in the family
4) Provide psychological support throughout the counselling
5) Provide information about hereditary pattern
6) Collect other related information from individual and family
7) Obtain an informed written consent for any planned genetic test / intervention
8) Encourage the individual and family to ask question as much as they can understand about all aspects of disorders, testing and management.
9) Ensure follow up and supportive services to individual and family during entire course of need.

5. Practical Application of Genetics in Nursing

1) Understands genetics basis of disease
2) Early and effective diagnosis of disorder
3) Contributes towards health promotion with genetic aspects
4) Prevention of genetic disorders
5) Management and care of genetic disorders
6) Genetic information and counselling referral services
7) Social and ethical issues in genetics.

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