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Human Gene Therapy: A Brief Review

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Abstract: ***Genetic defects are caused by mutations in the genome that lead to defect in proper physiological functioning of the human body. Genetic defects cannot be corrected by medicines or surgery. Therefore, a new innovative research called gene therapy has come up to resolve the issue of gene defect to some extent. Gene therapy is a technique to insert gene of interest in place of mutated/ non-functional gene in to the target cells of human. Several methods have been discovered to achieve the target insertion of the desired gene. The target gene can be inserted using physical, chemical or biological methods and the route of transfer of gene can be in vivo or in vitro depending on the site of gene mutation in human body. The first successful trial of gene therapy has already been done on a patient suffering from 'severe combined immuno-deficiency syndrome'. Since then, numerous trials have been initiated to cure some life-threatening diseases such as cancer and cardio-related diseases along with blood related disorders. Though, gene therapy is considered a modern technique to correct any gene defect, many ethical and moral issues have also been raised against it.***

Keywords: Gene therapy, genetic defects, severe combined immune-deficiency syndrome, somatic cell therapy, germline cell therapy.

1. Introduction

Human Gene Therapy can be defined as the treatment of genetic disorder/disease via transfer of artificially corrected gene into cells of human, by adopting various transfer techniques. The gene transfer can be done outside the human body in the cells of patient grown in vitro or it can be inserted in the patient cells in vivo. The various methods adopted for gene transfer use viral and non-viral vectors. The viral methods are more efficient in gene transfer as compared to non-viral methods but since viral vectors can be immunogenic, they are less preferred over non-viral based methods. The first successful trial of gene therapy was carried out in 1990 by a French scientist, Dr. Anderson and his colleagues on a 4-year-old patient born and suffering from severe combined immunodeficiency syndrome (SCID).

Types of Gene therapy

Classification of gene therapy based on the type of cells selected for gene transfer:

1) Somatic cell therapy: The corrected/ functional copy of gene is inserted in the somatic cells (non-reproducible cells) of the patient via viral/ non-viral methods at the site of defect. The functional copy of gene is integrated in the somatic cells and provide functional copy of defective protein to the patient. This method is more acceptable as it targets the defective cells of the patient and the gene in such cases is not inherited by the progeny. Few disadvantages of somatic cell therapy are that the effect of this method is short lived. The cells in which the corrected gene is inserted are short lived and recycled by the patient body that results in the death of treated cells. Hence, patients have to undergo regular treatment over the course of their life to sustain the functional gene.

2) Germline therapy: The gene of interest is introduced at the initial stages of embryonic development (in vitro fertilization) and the progeny produced will have corrected gene inserted in the genome and will be able to pass to the progeny in future. This method introduces permanent changes that are inherited by the progeny and is done to remove the genetic defects permanently from the family or population. Since the introduction of gene is in germ cells and passed to future generations, this type of gene therapy is less acceptable by religious and scientific community.

Classification of gene therapy based on the method adopted for gene insertion:

1) Ex-vivo (outside the patient body): In ex-vivo gene transfer method, the target cells are treated outside the patient body in the laboratory under sterile conditions. The cells (generally dividing cells like bone marrow cells or blood cells) to be targeted are first collected from the patient body and grown in the laboratory for a particular time period followed by exposure to viral vectors that carry the gene of interest (corrected gene). The viral vectors transfer the functional gene in the cells of patient and then after growing them for few cell divisions, they are inserted back into the patient body via injection or by other means. The ex-vivo genetransfer method is more efficient as compared to in vivo gene transfer method as viral vectors are natural gene introducing vectors and hence show higher efficiency.

2) *In-vivo (inside the patient body)*: The in-vivo gene transfer method is done inside the host's body. The vector containing the desired gene is inserted via viral or injection method. The virus inserts the functional gene in defective cells by homologous recombination that results in production of normal/functional copy of gene. This method is less popular as compared to in vivo method due to its less efficiency and insertion of gene at random sites sometimes.

Viral vectors play a significant role in gene transfer as they are natural gene transfer agent for human cells. Various types of ***viral vectors-based techniques***that are employed in gene therapy are:

1) *Retroviral vectors:* Retroviruses have RNA as their genetic material. The enzyme, reverse transcriptase present in retroviruses changes the RNA to dsDNA and then the formed dsDNA is inserted in the host genome with the help of integrase. The host cell when divide, it will transfer the

genome along with virus DNA to its daughter cells. Retroviruses are the first viruses that were employed in the gene therapy of a patient suffering from SCID. Along with highly efficient nature of retroviruses for gene transfer, they can also cause cancer by converting a normal functioning gene in to oncogene by random insertion of its genome in the host cell. Therefore, despite several advantages, its use is ban in scientific community for gene therapy.

2) *Herpes Simplex virus:* Since, herpes simplex virus is a neurotropic virus (resides in neurons of nervous system), it is used for the gene transfer in nervous cells. A strain, HSV-1 carries a large genome that is beneficial for transfer of a long gene and few complications are reported for HSV as compared to other viral vectors.

3) *Adenovirus:* Another popular viral vector for gene therapy is adenovirus. These viruses cause intestinal, respiratory and eye infections. They transfer their DNA in the cytoplasm of host. Since, these viruses don't insert their DNA in the genome of host cell, they are considered less pathogenic as compared to other viral vectors. They are generally employed to treat cancer. Anadenovirus-based gene therapy named 'Gendicine' is used to correct p-53 created genetic defects leading to neck and head cancer approved by China in 2003.

Apart from viral based vectors, few ***non-viral based techniques*** are also employed to insert functional copy of gene in place of defective gene. Some of them are:

1) ***DNA injection:*** Naked DNA is transferred in the body of the host at the site of defective cells. Some successful trials have been carried out by transferring naked DNA via intramuscular injection to correct cystic fibrosis disease. It is not an efficient method as the target cells revert back to their previous condition due to unknown mechanism.
2) ***Gene gun:*** It is physical method of gene transfer in which DNA is coated on gold particles that are introduced in the target cells by gene gun (device that helps in penetration of DNA in the host cells by force application). It can be done only in ex-vivo method of gene transfer.
3) ***Electroporation:*** This method is equally effective like prokaryotic transformation. The electric current is used to displace the membrane of the target cell that led to uptake of DNA from the environment. The process is performed in a cuvette placed in electroporation machine.
4) ***Sonoporation:*** Just like electroporation, this method uses ultrasonic waves to incorporate the DNA into the cells. The principle is similar as electroporation where the waves displace the membrane resulting in uptake of foreign DNA.
5) ***Magnetofaction:*** Here, magnetic particles help in introduction of DNA in to the host cell. They make DNA complexes which come in contact with cell monolayer and hence taken up by the cell.

Advantages of gene therapy

Gene therapy has a great therapeutic potential in case of genetic diseases that cannot be cured by medicines. It helps in increasing the life expectancy of the patient by correcting the mutated gene or inserting a functional gene that could make a threshold level of molecule required for a normal physiological function of the body. It can also silence a cancer-causing gene. The potential of treating some genetic diseases for which no cure is prescribed like cystic fibrosis, AIDS, muscular dystrophy, sickle cell anaemia, heart diseases and cancer has made gene therapy an efficient method to cure incurable diseases. Gene therapy avoids continuous medication and clinic visits and hence reduces the suffering of patient.

Disadvantages of gene therapy

The gene therapy treatment is very expensive and is not affordable by a large mass of population. Glybera, a drug used during gene therapy is considered to be one of the most expensive drugs and hence not accessible by a major population. The DNA/ gene inserted has a short-lived nature and easily degraded by the cell machinery and hence not able to function after a certain period which results in reappearance of symptoms. The viral vectors used for gene insertion are also a risk factor as they aggravate the immune response of the host resulting in inflammation of the insertion site and sometimes the toxic gene carried by viral vector can be transferred along with gene of interest that can lead to other physiological problems in the host. The gene therapy trial if gone wrong then it can result in multiple defects such as multigene disorders, heart defects and other diseases. The lack of understanding in the future effects of gene is also a limitation in gene therapy related treatment. Unavailability of gene of interest to transfer to the host cell and exact location of defective gene is required for correction and proper insertion of the functional gene which is difficult to find out in certain cases. The gene therapy has its limitation in the correction of single gene disorder hence multiple gene defects cannot be corrected by this method.

To one side from scientific challenges in using gene therapy, ethical and moral issues are also an area of concern. In spite of some promising results shown by gene therapy, it raises several ethical and moral concerns. According to some people, gene therapy is differentiating between good and bad genes but since all genes are created by God, human has no right to decide which traits (genes) are normal and abnormal. The gene therapy can result in a development of society that would be apathetic to the people who are different. Also, despite knowing the fact that viruses are harmful for humans as they are continuously mutated and can end up in causing diseases themselves, how can they be inserted in humans who are already suffering from diseases. Somatic cell therapy is still acceptable by few groups but germline therapy is banned due to its role in permanent insertion of gene that can pass to future generations.

2. Conclusion

Gene therapy is an efficient and promising area to cure some incurable genetic and mutated gene related diseases. Although, gene therapy is an emerging field, still the wide and astonishing applications make it a desired technique. The research on gene therapy trials is in progress and in near future, scientific community would be able to conquer it and human community will be benefitted by its exciting and innovative therapeutic effects.

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