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A Review on Gene therapy on Cancer

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ABSTRACT

Gene therapy is a contemporary therapeutic intervention with recent positiveresults and regulatory approvals either completed or expected in the next several years for various conditions. The evolving view is that gene therapy will ultimately offer hope across a range of otherwise debilitating or difficult to-treat conditions. The renaissance in gene therapy has seen major development of both non-viral and viral vectors and accelerated preclinical studies and clinical trials. It is therefore timely to address the progress in gene therapy through a special issue presenting reviews on non-viral and viral vectors including relevant updates on applications on herpes simplex virus (HSV) and adeno-associated virus (AAV) vectors. Thus, the purpose of this review is to summarize the general concepts of gene therapy with a specific focus on monogenic rare disease in hematology and central nervous system disorders where burgeoning therapies are currently entering clinical investigations and approaching regulatory approval.

Gene therapy (use of genes as medicines) is basically to correct defective genes responsible for genetic disorder by one of the following approaches. Gene therapy states and remains an experimental discipline and many researches remain to be performed before the treatment will realize its potential. He ideal design of a gene therapy strategy would first take into account the molecular basis of a disease process and then effectively tailor gene transfer techniques to mitigate toxicities and improve the effectiveness of existing therapies.. A gene therapy strategy modelled after the ADA protocol could play a role in delivering neuronal growth factors to the nervous system of patients with neurodegenerative disease. Cells from various tissues could be removed from a patient, be grown intissue culture where they could be stimulated to replicate, be genetically modified with retroviral vectors carrying a gene of therapeutic importance, and then be implanted into a brain with the intent to increase the local delivery of biologically active molecules. Genetic medicines are simple in concept, but challenging to make a therapeutic reality. We first outline thegeneral concepts that are applicable to genetic medicines. Gene therapy has the potential to eliminate and prevent hereditary diseases such as cystic fibrosis and is a possible cure for heart disease, AIDS and cancer. A gene therapy strategy known as viral-directed enzyme prodrug therapy has used retroviral vectors to eliminate some types of experimental brain tumorsin rodent model. Finally, from an ethics standpoint, it is important to consider whether medicine should surrender to the rule of technology or commit to a more responsible steering of the course of progress.

Keywords: Gene therapy, Retroviral, Genetic medicines, Hereditary diseases

INTRODUCTION

Gene therapy (also called human gene transfer) is a medical field which focuses on the utilization of the therapeutic delivery of nucleic acid into a patient's cells as a drug to treat disease.[1][2] The first attempt at modifying human DNA was performed in 1980 by Martin Cline, but the first successful nuclear gene transfer in humans, approved by the National Institutes of Health, was performed in May 1989.[3] The first therapeutic use of gene transfer as well as the first direct insertion of human DNA into the nuclear genome was performed by French Anderson in a trial starting in September 1990. It is thought to be able to cure many genetic disorders or treat them over time.

Gene therapy typically involves the insertion of a functioning gene into cells to correct a cellular dysfunction or to provide a new cellular function.[1] For example, diseases such as cystic fibrosis, combined immunodeficiency syndromes, muscular dystrophy, hemophilia, and many cancers result from the presence of defective genes. Gene therapy can be used to correct or replace the defective genes responsible. Gene therapy has been especially successful in the treatment of combined immunodeficiency syndromes, showing lasting and remarkable therapeutic benefit.[2-4]

For gene transfer, either a messenger ribonucleic acid (mRNA) or genetic material that codes for mRNA needs to be transferred into the appropriate cell and expressed at sufficient levels. In most cases, a relatively large piece of genetic material (>1 kb) is required that includes the promoter sequences that activate expression of the gene, the coding sequences that direct production of a protein and signaling sequences that direct RNA processing such as polyadenylation. A second class of gene therapy involves altering the expression of an endogenous gene in a cell. This can be achieved by transferring a relatively short piece of genetic material (20 to 50bp) that is complementary to the mRNA. This transfer

would affect gene expression by any of a variety of mechanisms through blocking translational initiation, mRNA processing, or leading to destruction of the mRNA. Alternatively, a gene that encodes antisense RNA that is complementary to a cellular RNA can function in a similar fashion.

Gene Therapy History

The first clinical study using gene transfer was reported.[5] Rosenberg and his colleagues used a retroviral vector to transfer the neomycin resistance marker gene into tumor-infiltrating lymphocytes obtained from five patients with metastatic melanoma. These lymphocytes then were expanded *in vitro* and later re-infused into the respective patients. Since this first study showed that retroviral gene transfer was safe and practical, it led to many other studies. Indeed, since 1989, more than 900 clinical trials have been approved worldwide.[6] What made gene therapy possible between 1963 and 1990 was the development of recombinant DNA technology.

In 2003 as well as in November 2005 China approved the first gene therapy drugs for the treatment of certain malignant tumors. A first European application for the approval of a gene therapy drug for the treatment of an aggressive brain tumor was submitted to the European Agency for the Evaluation of Medicinal Products (EMEA) in 2005. Despite continued great difficulties in the technical implementation, the successes of gene therapy can doubtlessly be confirmed today. For example, successful therapies have been developed during the past five years for patients with severe hereditary immunodeficiency diseases. These treatments are visibly beneficial to these patients with life-threatening conditions. The death of a patient in the USA in 1999 as a result of a very high systemically administered dose of adenoviralvectors were tragic events that were viewed by the public as a setback for gene therapy. Nevertheless, the same principles apply to gene therapy as to other medical interventions: Effective procedures are associated with potential side effects which can be reduced by improving the procedures when the underlying mechanisms are understood. German scientists have made important contributions in this field, from basic research of the vector-host interaction to clinical studies. Among other things, in 2006 they reported on the correction of a severe immunodeficiency in adult patients through gene therapy.

Vectors

Facilitating the transfer of genetic information into a cell are vehicles simply called as vectors. Vectors can be divided into viral and nonviral delivery systems. The most commonly used viral vectors are derived from retrovirus, adenovirus and adeno-associated virus (AAV). Other viral vectors that have been less extensively used are derived from herpes simplex virus 1 (HSV-1), vaccinia virus, or baculovirus. Nonviral vectors can be either plasmid deoxyribonucleic acid (DNA), which is a circle of double-stranded DNA that replicates in bacteria or chemically synthesized compounds that are or resemble oligodeoxynucleotides. Major considerations in determining the optimal vector and delivery system are (a) the target cells and its characteristics, that is, the ability to be virally transduced ex vivo and reinfused to the patient, (b) the longevity of expression required and (c) the size of the genetic material to be transferred.

Viral Vectors

Retroviruses-

A class of viruses that can create double-stranded DNA copies of their RNA genomes. These copies of its genome can be integrated into the chromosomes of host cells. Human immunodeficiency virus (HIV) is a retrovirus.

eg:- One of the problems of gene therapy using retroviruses is that the integrase enzyme can insert the genetic material of the virus into any arbitrary position in the genome of the host; it randomly inserts the genetic material into a chromosome. If genetic material happens to be inserted in the middle of one of the original genes of the host cell, this gene will be disrupted (insertional mutagenesis). If the gene happens to be one regulating cell division, uncontrolled cell division (i.e., cancer) can occur. This problem has recently begun to be addressed by utilizing zinc finger nucleases[7] or by including certain sequences such as the beta-globin locus control region to direct the site of integration to specific chromosomal sites.

Adenovirus[8]

To avoid problem of inserting genes at wrong sites, some researchers have turned to other types of viruses. A class of virus with double stranded DNA genome that can cause respiratory, intestinal and eye infection (especially the common cold). When these viruses infect a host cell, they introduce their DNA molecule into the host. The genetic material of the adenovirus is not incorporated into the host cell's genetic material. The DNA molecule is left free in the nucleus of the host cell, and the instructions in this extra DNA molecule are transcribed just like any other gene. Adenovirus also can infect a broader variety of cells than retrovirus, including cells that divide more slowly, such as lungs cells. However, adenovirus also are more likely to be attacked by the patient's immune system and the high levels of virus required for treatment often provoke an undesirable inflammatory response. Despite these drawbacks, this vector system has been promoted for treating cancer of liver and ovaries and

indeed the first gene therapy product to be licensed to treat head and neck cancer is Gendicine, adenoviral product.[9]

Polymeric gene carriers

Synthetic polycationic polymers have gained wide attention as non-viral vectors for gene delivery. A number of reviews and book issues have already been published which illustrates various mechanisms through which they act and also various biochemical and therapeutic aspects of these systems. Polyplexes form these polymers spontaneously as a result of electrostatic interaction between phosphate groups of DNA and oppositely charged groups of polycationic polymer.[22-24]

PEI (polyethyleneimine) is more appropriate as it has set a gold standard for nonviral gene delivery. Their ability, to condense large DNA molecules and eventually leading to homogenous spherical molecules of 100nm size or less as, they are capable of transfecting into cells efficiently for both *in vitro* and *in vivo*.[23] The other synthetic polymers showing promising results in gene delivery are poly-L-lysine. It is one of the first polymers to be studied for nonviral gene delivery because of its peptidic nature i.e.it is biodegradable and hence it is more suitable for in vivo use.[25] Imidazole containing polymers have been reported to have efficient transfection properties. -amino groups of poly-Lysine were modified. In various approaches with histidine or other imidazole-containing structures proved to be better transfecting agents than the unmodified poly-L-lysine.[26-28] Transfection and cytotoxicity studies were carried on amino methacrylate polymer where quaternary amine groups are connected to uncharged hydrophilic polymer of similar structure which is poly (N-Hydroxypropylmethacrylamide)-b-poly(trimethylaminomethylmethacrylate) (PHPMA-b-PTMAEM). It was found that while toxicity has not been changed much but the transfection efficiency has been increased with the addition of PHPMA block.[29]

Physical Methods to Enhance Delivery

1. Electroporation

Electroporation is a method that uses short pulses of high voltage to carry DNA across the cell membrane. This shock is thought to cause temporary formation of pores in the cell membrane, allowing DNA molecules to pass through. Electroporation is generally efficient and works across a broad range of cell types. However, a high rate of cell death following electroporation has limited its use, including clinical applications.

2. Gene Gun

The use of particle bombardment, or the gene gun, is another physical method of DNA transfection. In this technique, DNA is coated with gold particles and loaded into a device which generates a force to achieve penetration of DNA/gold into the cells.eg:- 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-linked severe combined immunodeficiency (X-SCID) patients, in which hematopoietic stem cells were transduced with a corrective transgene using a retrovirus, and this led to the development of T cell leukemia in 3 of 20 patients.[33]

3. Sonoporation

Sonoporation uses ultrasonic frequencies to deliver DNA into cells. The process of acoustic cavitation is thought to disrupt the cell membrane and allow DNA to move into cells.

4. Magnetofection

In a method termed magnetofection, DNA is complexed to a magnetic particles and a magnet is placed underneath the tissue culture dish to bring DNA complexes into contact with a cell monolayer.

Chemical Methods to Enhance Delivery

1. Oligonucleotides

The use of synthetic oligonucleotides in gene therapy is to inactivate the genes involved in the disease process. There are several methods by which this is achieved. One strategy uses antisense specific to the target gene to disrupt the transcription of the faulty gene. Another uses small molecules of RNA called siRNA to signal the cell to cleave specific unique sequences in the mRNA transcript of the faulty gene, disrupting translation of the faulty mRNA and therefore expression of the gene.

2. Lipoplexes and polyplexes

To improve the delivery of the new DNA into the cell, the DNA must be protected from damage and (positively charged). Initially, anionic and neutral lipids were used for the construction of lipoplexes for synthetic vectors.

3. Dendrimers

A dendrimer is a highly branched macromolecule with a spherical shape. The surface of the particle may be functionalized in many ways and many of the properties of the resulting construct are determined by its surface. In particular it is possible to construct a cationic dendrimer, i.e. one with a positive surface charge. When in the presence of genetic material such as DNA or RNA, charge complimentarily leads to a temporary association of the nucleic acid with the cationic dendrimer. On reaching its destination the dendrimer-nucleic acid complex is then taken into the cell via endocytosis.

4. Hybrid methods

Due to every method of gene transfer having shortcomings, there have been some hybrid methods developed that combine two or more techniques. Virosomes[34] are one example; they combine liposomes with an inactivated HIV or influenza virus. This has been shown to have more efficient gene transfer in respiratory epithelial cells than either viral or liposomal methods[35] alone. Other methods involve mixing other viral vectors with cationic lipids or hybridising viruses.

Gene transfer delivery system

Several methods have been developed to facilitate the entry of genetic materials (transgenes) into target cells,using various vectors. They are broadly divided into two major categories: viral (or bacterial) and non-viral vectors Viruses usually bind to target cells and introduce their genetic materials into the host cell as part of their replication process. As they enter target cells,

they can carry a load of other genetic material called “transgenes”. For non-viral vectors, different approaches have been utilized, using physical, chemical, as well as other modes of genetic transfer. Transferring genetic material directly into cells is referred to as “transfection”,

while moving them into cells carried by a viral or bacterialvector is termed “transduction”. Non-viral approaches have the advantage of safety and easy modifiability, but have a lower transfection efficiency compared to viral vectors.

Physical mediated gene transfer

DNA genetic material that is coated with nanoparticles from gold or other minerals, and with their kinetic energy supplemented by compressed air or fluid (gene gun), or using ultrasound, can force the genetic material into the target cell, followed by the release of DNA into its nucleus. They are best suited for gene delivery into tissue or in case of gene vaccination [23].

The electroporation gene therapy approach aims to achieve cellular membrane disruption with high-voltage electrical pulses, resulting in the formation of nanoporesthrough which naked DNA, foreign genetic materials, and even chemotherapeutic agents can enter cells [23,24]. This approach is best suited for plasmid DNA-based gene transfer therapy with the advantage of effectiveness in a vast array of cell types, ease of its administration, lack of genome integration with the risk of malignancy, as well as the low potential for unwanted immunogenicity [22].

Electroporation is presently being tested in several clinical trials, especially on patients with malignant melanoma, prostate cancer, colorectal cancer, and leukemia [22].

Viral mediated gene transfer

Viruses are small particles that contain either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA), and may be single-stranded (ss) or double-stranded (ds). The viral structure consists of a genome surrounded by a protective protein coat (viral capsid) which helps the virus attach to

host cell receptors, and prevents viral destruction by cell nuclease enzymes. Some viruses may also have a lipid bilayer envelope derived from the host cell’s membrane, and an outer layer of viral envelope made of glycoprotein. A complete viral particle (virion) by itself is unable

to replicate. For propagation, the virus needs to insert its genetic material into a host cell, in order to acquire metabolic and biosynthetic products for viral transcription and replication.

Gene therapy implementation

Once genetic materials are transferred into target cells and incorporated into nuclear genetic DNA, they may induce silencing, down-regulation, modification, or repair of the target cell genes. Depending on the intensity of the gene expression, it may lead to cell death and tumor

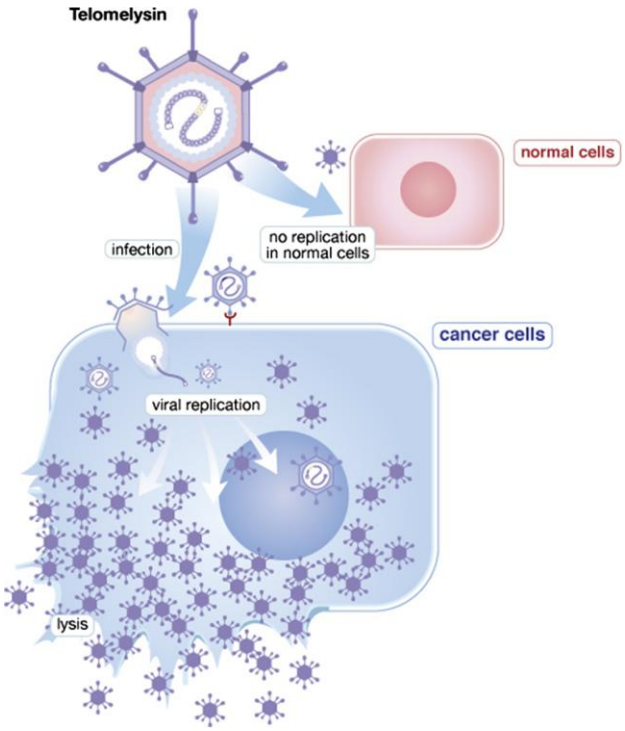
necrosis (as with the suicide gene), or impaired cell growth with tumor regression (as with the silencing gene). Modification of the gene may improve the response from subsequent cancer therapy, such as chemotherapy, immunotherapy, or radiation. Repair of the target gene may help in preventing subsequent malignancy or cancerrelatedcomplications such as thrombosis. They may alsobe helpful in the future by preventing hereditary cancer syndromes.

Gene silencing

This has been achieved through specific delivery of a small interfering double-stranded RNA (siRNA) into target cells, and subsequent duplex formation of RNA-induced silencing complex (RISC) that destroys messenger-RNA (mRNA), thus leading to interference with RNA functions and protein synthesis within the target cells . Through the appropriate design of siRNA, it is theoretically possible to use the technology in silencing any gene in the body, providing a greater therapeutic potential in cancer therapy as well as in the management of other medical disorders

such as the hepatitis B virus, human papilloma virus, hypercholesterolemia and liver cirrhosis . As siRNAdoes not interact with chromosomal DNA, it does have a lower risk of inducing target cell gene alterations and possible mutagenesis. It is highly specific against target genes, with low systemic toxicities, and does not induce multidrug resistance. Furthermore, these genes can induce potent gene silencing of many cancer-related genes, leading to tumor regression, but do not abolish abnormal genes. siRNA therapy can be administered directly into tumors; however, for systemic administration, it is somewhat difficult as a naked siRNA protein is liable for host-mediated clearance by enzymatic degradation, renal filtration, and host cellular phagocytosis. Several delivery systems for siRNA have been developed to protect them from enzymatic degradation, and facilitate their effect in silencing specific genes. Examples of siRNA systemic delivery system presently in clinical trials include CALAA-01 (Calando Pharmaceuticals) for patients with malignant melanoma , and ALN-VSPOI (Alnylam Pharmaceuticals)

for liver cancer and solid tumors . However, limited success has been achieved mainly due to relatively high toxicity and low transfection efficiency



Gene modification

This may be helpful in improving cancer therapy results, such as with radiation therapy. Radiosensitizing gene therapy promotes transgene expression in tumor tissue, thus increasing tumor sensitivity to radiation with better tumor control. In contrast, radioprotective gene therapy distributes transgenes and their products to surrounding normal tissue, thus limiting radiation induced toxicities to normal tissue . The concept of combining both approaches is presently being investigated in several preclinical studies.

Gene repair

This can be achieved using zinc finger nuclease attached to the lentiviral vector. Once the viral vector enters the nucleus,it binds to a specific location in the double-stranded DNA, breaking it at specific location, with subsequent endogenous repair mechanisms, to create a newly edited double-stranded DNA [23]. Other technological approaches include transcription activator-like effector nucleases (TALENs) , and clustered regularly interspaced short palindromic repeats (CRISPR) . Gene therapy for mitochondria Gene therapy may also be directed to cytoplasmic organelles such as mitochondria. The mammalian mitochondria are responsible for metabolic functions. Nearly 300 of the known mutations causing metabolic diseases are secondary to disorders affecting the mitochondrial genome [23]. Several approaches have been used to transfer genes successfully into cell mitochondria.

Gene Therapy in Diseases

Gene Therapy for Oral Squamous Cell Carcinoma

The current treatment strategies for oral squamous cell carcinoma (OSCC) include a combination of surgery, radiation therapy and chemotherapy. However, surgical resection of tumors frequently causes profound defects in oral functions such as speech and swallowing as well as in cosmetic aspects. Chemotherapy is associated with well-known toxicity and has demonstrated no clear impact on the survival of patients with recurrent oral cancer. Recurrence develops in approximately one third of the patients despite definitive treatment. Two thirds of the patients dying of this disease have no evidence ofsymptomatic distant metastasis. Therefore, local and regional disease control is paramount, underscoring an urgent need for more effective therapy.

Several reports have indicated that the combination of radiation and gene therapies has synergistic suppressive effects on various cancer cells, including colorectal, ovarian, nasopharyngeal and head / neck cancer cells. Gene therapy can also be used as an adjuvant to surgery (at the resected tumor margins). This review highlights various gene therapy methods that are available for combating OSCC.

Gene Therapy in Periodontics

Periodontal diseases have a broad spectrum of inflammatory and destructive responses, and are thought to be multifactorial in origin. Genetic variance has been considered as a major risk factor for periodontitis. With the advent of gene therapy in dentistry, significant progress has been made to control periodontal disease and reconstruct the dentoalveolar apparatus.[Gene therapy is a field of Biomedicine. A broad definition of gene therapy is the genetic modification of cells for therapeutic purposes. Genes are specific sequences of bases present in the chromosome that form the basic unit of heredity. Each person’s genetic constitution is different and the changes in the genes determine the differences between individuals. Some changes usually in a single gene, may cause serious diseases. More often, gene variants interact with the environment to predispose some individuals to various ailments.

The goal of gene therapy is to transfer the DNA of interest, for example, growth factor and thrombolytic genes into cells, thereby allowing the DNA to be synthesized in these cells and its proteins (termed recombinant protein) expressed. Gene therapy may involve (1) supplying or increasing the expression of a mutant gene that is insufficiently expressed (e.g., to treat enzymatic deficiencies); (2) blocking a gene that is detrimental (e.g., using antisense constructs to inhibit tumor proliferation); or (3) adding a foreign gene to treat a situation beyond the capability of the normal genome (e.g., introduce an enzyme into a cell or tissue that allows the tissue to become more sensitive to the effects of a pharmacologic agent).

CONCLUSION

Most scientists believe the potential for gene therapy is the most exciting application of DNA science, yet undertaken. How widely this therapy will be applied, depends on the simplification of procedure. As gene therapy is uprising in the field of medicine, scientists believe that after 20 years, this will be the last cure of every genetic disease. Genes may ultimately be used as medicine and given as simple intravenous injection of gene transfer vehicle that will seek our target cells for stable, site-specific chromosomal integration and subsequent gene expression. And now that a draft of the human genome map is complete, research is focusing on the function of each gene and the role of the faulty gene play in disease. Gene therapy will ultimately change our lives forever.

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