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Popular Article

Viral Vector: An emerging tool for gene therapy

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Abstract

The science of gene therapy has achieved huge success in the last few decades. The technique has given a new ray of hope to the patients who are suffering with lethal genetic diseases. The viral vector-based strategy of gene therapy has permitted scientists and doctors to create potent advanced therapeutic platforms. Past few years have revolutionized the field of gene therapy by the development of numerous drugs based on viral vectors that have gained regulatory approval for clinical applications. Presently, there are three major viral vector-based strategies, which are based on adeno, adeno-associated and lenti virus. However, there are certain challenges which silently limit the evolution of these approaches.

Keywords: Gene therapy; genetic diseases; viral vector

Introduction

Gene therapy is defined as a medical approach for the treatment of any genetic disease by the introduction of specific cell function-altering genetic material into a patient. There are four more popular strategies of gene therapy available: somatic cell gene therapy, germline gene therapy, In-vivo gene therapy and Ex-vivo gene therapy (5). The somatic cell gene therapy can be performed by replacement of therapeutic transgene in place of mutated gene. The changes that is being made through somatic cell gene therapy remains lifelong, but it cannot pass to forthcoming generations. However, in case of germline gene therapy, before splitting the embryo, target gene can be introduced in germ cells (sperm or egg cell), fertilized egg cell or embryo. Subsequently, the modifications made in the DNA of these cells can pass into the upcoming generations. Because of playing with live embryos, this technique has been termed as unethical. In-vivo gene therapy, includes insertion of the exogenous gene directly into defective cell. However, in case of Ex-vivo gene therapy, cells are collected from

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patients and modified in lab followed by re-introduction of altered cells inside the patients (Fig. 1). There are four basic approaches for gene therapy: gene replacement, gene editing, gene silencing and gene addition.

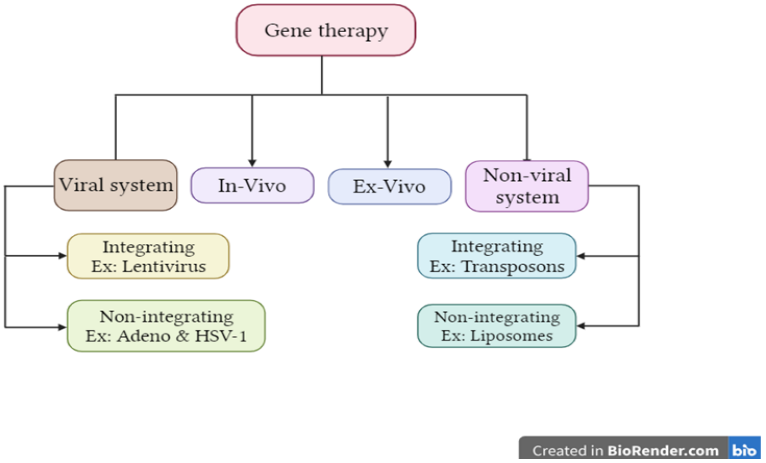

Figure 1. Overview of gene therapy strategies

History

Dr. S. Rogers has performed the first gene therapy trial, in 1973, who treated two blood relative sisters those were suffering from hyperargininaemia (4). The treatment was totally depended on his prior observations that patients with Shope papilloma virus had decreased serum arginine levels. However, before the 90s the viral vector-based gene therapy was less popular. F. Anderson has employed one clinical trial using Ex- vivo strategy for the treatment of a patient named Ashanthi DeSilva, who had adenosine deaminase deficiency-severe combined immunodeficiency disease (ADA-SCID). He has administered transformed T cells carrying recombinant retrovirus-ADA gene in that therapy. Moreover, Adeno-associated viral vector-based gene therapy has been used for the treatment of choroiderema disease during the year 2014. Therefore, so many viral vector drugs have been permitted by FDA to perform the gene therapy for various diseases.

Gene therapy vectors

The vehicle used to introduce the transgene is termed as vector. Currently, there are two types of vectors available: viral and non-viral. The utility of the vector depends on: size of the transgene, efficiency of the delivery, stability, longevity of the transgene and level of expression. These both type of vectors is again classified into two subcategories- integrating and non-integrating. Integrating vectors includes: Lenti virus, Retro virus and transposons while, non-integrating includes: Adeno virus, Adeno-associated virus, Herpes simplex virus-1, Baculo virus, liposomes and nanoparticles (3). Here, we will discuss regarding viral vectors which are most commonly used for gene therapy such as Adeno virus, Adeno-associated virus and Lenti virus-based vectors.

Adeno viral vectors

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Adeno virus is a non-enveloped, icosahedral protein capsid that accommodates a 26 to 45 kbp linear, double-stranded DNA genome and it has hairpin-like inverted terminal repeats (ITRs) that differ in length (30–369 bp). It is known to mostly cause infections of the upper respiratory tract but can also infect other organs such as the brain and bladder. It encodes ~35 proteins that are expressed in the early (E1a, E1b, E2, E3 & E4) and late phases (L1-L5) of viral gene transcription (2). Being used as a vector it has several qualities like: high transduction efficiency in both non-dividing and dividing cells; extra chromosomal persistence; vast tropism for various tissue; and large scale production system (1). So many generations of Adeno viral vectors are available based on number of genes deleted and insert size. The first-generation vector was engineered by replacement of the E1A/E1B gene with targeted transgene that can be up to 5.0 kb in length while E1/E3 double deletion freed up more space for the transgene cassettes. Due to certain drawbacks with first-generation vectors, researchers developed second generation by further deleting other early genes such as E2a, E2b, or E4. In 2003, Gendicine was approved as world's first commercialized gene therapy drug for the cancer treatment. Subsequently, ONYX-105 (dl1520) and H101(oncorine) have gained commercial approval in China during the year 2007.

Adeno-associated viral vector

Adeno-associated virus (AAV) was developed by B. Atchison in 1965 as a contaminant of Adeno virus preparations. As a depend parvovirus, AAV lacks the essential genes needed for replication and expression of its own genome. The AAV genome itself, is a single-stranded DNA that houses four known open reading frames (ORFs). The first cloned of the AAV genome into expression plasmids was done by Samulski. He found that transfer of these cloned plasmids into mammalian cells in the presence of Adeno virus could produce infectious viruses. Since the first demonstration, multiple vector designs have been reported. The first Adeno associated viral vector-based gene therapy was performed in human through delivery of cystic fibrosis transmembrane regulator gene. Till date, three AAV-based gene therapy drugs are available worldwide commercially. The first AAV-based gene therapy for the treatment of lipo-protein lipase deficiency was Glybera. It has gained regulatory approval for commercialization in 2012 (7). Subsequently, Luxturna and Zolgensma came in market during the year 2017.

Lenti viral vector

Lentivirus genus come under the *Retroviridae* family. Retroviruses are spherical, enveloped, ss-RNA viruses that are ~100 nm in diameter. It comprises of common essential core protein genes, such as gag, pol, and env. The lentiviral particle encapsidates two positive sense-strand RNAs that are bound by nucleocapsid proteins. Lentiviral vectors can integrate in genome and permit long-term gene expression. Additionally, they have a packaging space up to 9 kb. The first-generation vector contains entire viral genome within the therapeutic cassette, including the viral core, regulatory protein coding

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sequences and accessory regulatory genes. In the case of more than two plasmid based vector, the env gene is replaced by the vesicular stomatitis virus (VSV-G) glycoprotein that is separately provided by a second plasmid. To perform the large scale manufacturing of lentiviral vectors certain steps are needed such as intricate production, purification, and quality assessment. The first commercially available lenti viral vector based drug is Kymriah that can be used for the treatment of paediatric B-cell leukemia. The second chimeric T- cell based drug approved by the FDA for the treatment of refractory large B cell lymphoma is Yescarta (6).

Challenges

Currently, several types of viral vectors are available for multiple clinical and preclinical applications. However, an important challenge that it is facing remains regarding prevalence of pre-existing immunity. Additionally, this vector-based gene therapy has three major obstacles such as immunogenicity, cellular toxicity and risk of insertional mutagenesis.

Conclusions and future views

The future for viral-based vectors is extremely good and bright which has the ability to address numerous genetic diseases. In order to avoid the pre-existing immunity against adeno viral vector, several strategies can be employed such as serotype exchange or epitope masking. In addition to that, various adeno viral vector of animal importance can be used to limit cross-reactive immunity. Presently, advancement in CRISPR/Cas system and the associated pre-clinical successes has improved the potential of AAVs. Recently, evolution in the non-integrating lentiviral vectors development have greatly reduced the risk of insertional mutagenesis. To overcome the existing challenges, exploration into viral biology, as well as advanced and interdisciplinary approaches are needed.

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