Abstract The integrity of the human genome is essential for maintaining the well being of an individual. Mutations, either caused by extrinsic or intrinsic means, that alters the genetic code can lead to genetic diseases, including, but not limited to, immature aging, developmental disorder, neurological disorder, cancer, etc. Traditional therapeutics may be able to treat or attenuate the condition of the genetic disease, but the mutated gene is still maintained in the patient’s genome and the root of the problem is not addressed. Gene therapy, or genetic replacement therapy, aims to treats the disease at the genetic level, either by introducing a wild-type sequence gene over the defective one or a gene that encodes a therapeutic protein. There have been great challenges in developing gene therapy treatment in a safe, effective and specialized way for treating different genetic diseases. We will discuss (1) what diseases are considered to be suitable for gene therapy, (2) currently available methods used in gene delivery, (3) the choice of different viral and non-viral gene delivery tools and how they can be introduced into the target tissues or organs, (4) the safety aspects of gene therapy and (5) challenges yet to be solved in increasing the success rate of gene therapy. We hope to introduce to the readers the latest advancement of the gene therapy field and further discuss challenges and difficulties in having a successful outcome of gene therapy.

Contents

26.1 Advent of Gene Therapy ........................................... 868
26.2 Diseases Considered Suitable for Gene Therapy ...................... 868
26.3 Gene Therapy Vectors ............................................... 868
26.3.1 Viral Vectors .......................................................... 868
26.3.2 Nonviral Vectors .................................................... 869
26.4 Factors Affecting the Success of Gene Therapy ........................... 870
26.4.1 Choice of Gene Delivery Vector .................................. 870
26.4.2 Route of Administration ........................................... 870
26.4.3 Integrating or Nonintegrating Vectors......................... 870
26.4.4 Therapeutic Means ............................................... 871
26.4.5 Regulation of Gene Expression .................................. 871
26.5 Safety Issues of Gene Therapy ......................................... 871
26.6 Difficulties in Achieving Successful Gene Therapy .................... 872
26.7 Conclusions .................................................................. 873

References ............................................................................ 873
26.1 Advent of Gene Therapy

Gene therapy, or genetic replacement therapy, is one of the most recent medical treatments for previously incurable genetic diseases [33]. The idea of gene therapy is to treat diseases by supplying genetic materials to modulate the pathophysiology caused by a malfunctioning gene in the patient’s genome, with the ultimate goal of achieving long-term cure in a single treatment. The completion of the human genome project complemented the field of gene therapy by providing an incredibly vast amount of genetic information for medical research [9, 10], and the better tools for diagnosis and the advancement in molecular biology assisted in accelerating the development of gene therapy in the clinics.

26.2 Diseases Considered Suitable for Gene Therapy

Several types of genetic diseases are considered suitable for gene therapy. Monogenic hereditary disorders, such as cystic fibrosis, adenosine deaminase (ADA) deficiency, hemophilia A and B, familial hypercholesterolemia, Canavan disease, muscular dystrophy, and X-linked SCID [39, 57], are good candidates for gene therapy treatment, because the disease treatment can be carried out by introducing the correct sequence of the mutated gene. With a better understanding of more complicated diseases, the feasibility of using gene therapy in treating inflammatory joint diseases, such as arthritis, neurological diseases, such as Batten’s, Parkinson’s and Alzheimer’s diseases, and various types of cancer, such as glioma, Lewis lung carcinoma, chronic lymphocytic leukemia, and cervical carcinomas [5, 30], has been demonstrated.

26.3 Gene Therapy Vectors

Even though the technology needed to synthesize genetic materials is readily available, the problem of developing gene delivery vehicles sufficiently efficient to transfer the DNA to all the target tissues remains challenging. An efficient gene delivery vector should fulfill the following criteria:

1. High safety level with minimal side effects
2. High efficiency and specificity
3. Large packaging capacity
4. Scalable to produce large quantities
5. Regulable to control gene expression

The two main categories of gene delivery vectors are viral and nonviral, and the most commonly used vectors, are discussed below.

26.3.1 Viral Vectors

Viral vectors are genetically modified viruses that have reduced pathogenicity while retaining the ability to infect cells. They usually consist of a modified viral genome, with a minimum amount of genetic material from the wild-type (wt) virus, packaged inside a capsid. Different viral gene delivery vectors (or viral vectors) offer various advantages that can be exploited to treat different diseases. In general, optimization of tissue tropism can be achieved by capsid mutagenesis, while long-term transgene expression is determined by the nature and the composition of the viral genome. Therefore, choosing the most suitable viral vector for each treatment is crucial to safe and effective gene therapy.

26.3.1.1 Adenovirus

Adenovirus (Ad) is a nonenveloped, double-stranded DNA virus with an icosahedral capsid diameter of 70–100 nm. Its vector genome is nonintegrating but remains episomal (to be discussed in Sect. 26.4.3) [44]. Among the few versions of Ad vectors developed in the past decade, the latest generation, the gutless vector, carries only the 5¢ and 3¢ inverted terminal repeats (ITRs) and the packaging signal (Ψ) as a minimal required cis element to generate the vector [40]. One of the few advantages of Ad vector is its large packaging capacity of up to 36 kb to accommodate either large or multiple transgene expression cassettes, ideal for the treatment of polygenic diseases. However, the major disadvantage of the Ad vector is that its systemic delivery can induce adaptive humoral and innate immune response, thus causing tissue damage and removal of infected cells by macrophages [18, 61]. This prohibits the use of Ad vector in establishing long-term transgene