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Gene therapy applications as treatment approach

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Abstract

What is gene therapy? It is one of the treatment methods developed to be used in the treatment of hereditary diseases. It is based on a plan to rearrange faulty gene functions with gene therapy, which is still very new research, or to replace faulty genes with healthy ones through gene transfer. The gene therapy method was first introduced by Martine Cline in 1970. Martine Cline also suggested that viruses can be vectors that can be used to perform gene transfer. In 1980, he showed that genes can be transferred by ex vivo and in vivo methods. Then, in 1990, two children were fully cured as a result of gene therapy with a retrovirus vector carrying the ADA gene by Michael Blaese and William French Anderson in severe combined immunodeficiency (SCID) disease, and thus the first successful gene therapy procedure took place.

Introduction

On being treated, some treatment modalities require expression of the corrective gene, but others may be expressed in a shorter time. Most gene delivery methods use viruses as vectors to deliver genes into cells, both in vivo and ex vivo [1]. The viral vector uses the viral genome to deliver the therapeutic gene to human body cells, thereby delivering the gene to the body. Scientists use a variety of viruses as potential vectors for gene transfer, such as adenovirus, which causes the common cold, influenza virus, called adeno-associated virus (AAV), which causes flu, herpes viruses, which cause herpes and some sexually transmitted diseases [2]. Scientists need to make sure that these viruses that will be used as viral vectors are genetically modified and inactivated so that they do not cause both a disease and spread throughout the body and infect other tissues. Most viruses infect human body cells by binding to and entering the cell, then releasing their genetic material into the stoplasm or nucleus in the human cell [3]. This genetic material is usually DNA, but some viruses contain an RNA genome. The infected human cell then acts as the host for the replication of the viral genome and the production of viral RNA and proteins. Viral proteins eventually combine to form more viral particles, and the host cell breaks down, the viruses are released and transmitted to other cells, and in this way the life cycle repeats. Viruses can be used very well as a therapeutic tool or vector in gene transfer [2-4]. For example, adenovirus can infect a wide variety of body cells quite effectively. Retroviruses such as lentivirus, even HIV, can be used as vectors because they enter the cell and copy their RNA genome into DNA and stay there permanently [5]. This process is called integration. The main reason for the use of retroviruses in gene transfer is that they can integrate therapeutic genes into the DNA of the human host cell. It ensures that gene therapy is permanent by permanently placing the genes in the chromosomes of the cells in the patient [6].

Germ cell gene therapy

In the human zygote, genetic modification of the germ cells is theoretically possible. Technologies applied in animals can in principle be applied to humans [7]. However, the aim here is germline gene therapy rather than human transgenesis.

Steps Followed in Germ Cell Gene Therapy;

- Totipotent embryonic cell isolation,
- Determination of the genetic structure of the embryo,
- culturing embryonic stem cells,
- Transfer of genetic material to embryonic cells,
- Selection of cells that receive the transfected gene,
- Selection of cells with the target gene integrated into the genome
- Marker removal
- Confirming genomic integrity
- Nucleus transfer,
- Reimplantation to the mother

The aim of germ cell gene therapy is to transfer the therapeutic gene to both body and germ cells. As a result, both the disease of the person will be eliminated and gametes with corrected genotype will be formed and healthy generations will be obtained [7]. In the germ cell gene therapy method, these changes can be transferred to future generations, since the genetic period made in the early embryo, gamete and zygote, which can form all the cells of the body, is applied with the genetic changes made in the embryo, gamete and zygote [7].

Somatic gene therapy

In somatic gene therapy, the therapeutic gene is transferred to somatic cells. Gene transfer to the patient's bone marrow, blood and skin cells is included in the category of body cell gene therapy [8]. As a result, the changes made at the level of genes and the changes made at different levels of gene therapy and the different effects of gene therapy remain only at the level of body cells and are not transferred to the germ cells and then to the next generations.

Gene Transfer Purposes Used in Gene Therapy

Transfer of genes to the recipient cell can be carried out in the laboratory (ex vivo) or in the patient's body (in vivo).

Ex vivo Gene Therapy; The cells are taken from the patient and the cloned gene is transferred by multiplying in the cell culture medium. The cells where the gene transfer takes place are selected and reproduced in vitro in cell culture and given to the patient [9]. The patient's own cells (autologous cells) are preferred as much as possible so that these cells are not rejected by the patient's immune system.

In Vivo Gene Therapy; It is the only option when in vitro culture of recipient cells is insufficient (e.g., brain cells) or when the cultured cells cannot be effectively re-implanted to the patient. The transferred gene can be delivered directly to the target tissue or the general circulation, but the vector used for delivery must be designed to be taken up only by the targeted cells or to express the gene only in the targeted cells. In this method, the success of in vivo gene therapy depends on the efficiency of gene transfer and expression (expression), since it is not possible to reproduce and select cells that have received or expressed the gene [9].

Results

How are gene therapy studies progressing?

From a chronological point of view, it is noticeable that from 1990 to 1999 there was a rapid increase in the number of clinical gene therapy trials Although there was a stable period for a short time in 2002-2003, there was a renewed increase in annual approved clinical gene therapy trials thanks to the path taken and the achievements of clinical trials in recent years [9].

In which countries is it made?

We can say that a clinical gene therapy trial has been conducted in 29 countries. The United States leads with 975 gene therapy clinical trials (63.4%). The United Kingdom ranks second with 184 studies (12%). These countries are followed by Germany (4.9%) with 76 studies, Switzerland (3%) with 46 studies, and France (2.7%) with 41 studies [10]. The numbers recorded in the clinical gene therapy database may be much lower than the actual numbers. For example, although it is reported that there is only one officially approved study in Russia, in reality it is known that a much larger number of clinical gene therapy trials are being conducted. In addition,

despite the fact that there are more than 50 studies in Canada, only 20 of them have been registered in the database of gene therapy clinical trials [10].

Targeted diseases

Gene therapy was initially developed as a method of treating hereditary single-gene diseases. However, today, the majority of gene therapy clinical trials (% 64.6), is one of the most common and deadly diseases; and multigenetic has a mechanism to treat cancer are used.

After all, at the moment, approaches to treating hereditary single-gene diseases give the most successful results in gene therapy clinical trials conducted so far, but it ranks third in the ranking, accounting for only 8.1% of total clinical trials [10].

Genes transferred to humans

In gene therapy clinical trials, more than 200 genes are transferred to humans using the methods mentioned above (viral and non-viral methods). It is necessary to say that the genes transmitted to humans in this way are mostly aimed at treating cancer, which is one of the most common and deadly diseases. In this context, the immune system genes that encode tumor antigens trigger (19.9%) was cytokine genes (% 18.7), tumor suppressor genes (% 10.8), pushed the genes that cancer cells to commit suicide (% 7.1), receptor genes (5.4 percent) of the genes in this study preferred one [10].

7.9% of the genes used in gene therapy clinical trials are genes encoding reproductive factors, and almost all of these genes are used to treat cardiovascular diseases. Genes used for gene transfer to treat hereditary single-gene diseases (deficiency genes) also make up 7.4% of the genes used in all trials [10].

As a result, although the gene therapy method is a new method, it is believed that if the research gives a positive result, it will greatly contribute to the treatment of many hereditary diseases [10].

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