The advancement of gene therapy conjures up the hopes of treating psychiatric disorders

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Abstract

Gene therapy is a potential treatment of many incurable, lethal, and chronic diseases as psychiatric disorders. Competing with other kinds of medications, gene therapy -also known as gene alteration- has been seen as a prospective therapeutic solution as genetics contributes intensively to the origin of many disorders. The emergence of gene therapy was accompanied by controversial arguments about its unknown side effects and effectiveness that impeded the development of gene therapy. After a lot of experiments on mice and deliberate research in the world of genomics, the first genetic therapy on the human body was conducted on a young girl who was diagnosed with a rare genetic disorder in 1990. The treatment went successfully, and it has spurred the implementation of gene therapy in numerous health issues. Among many diseases that can be treated using gene therapy, psychiatric disorders are the most prominent as they are profoundly affected by gene defects. Depression, Bipolar, Alzheimer's, and OCD are examples of mental issues caused by defections in certain genes.

I. Introduction

For therapeutic purposes, genetics would be an effective solution. Gene therapy is the modification or manipulation of the expression of a certain kind of genes inside the cell body to change its biological behaviors to cure a specified disorder. But what makes biologists think of using genetics instead of using familiar medications such as pharmaceuticals?

The reason is that genetics have a profound, direct contribution to most diseases -genes can mutate during the growth of the body, and genes could be missed from the moment of birth also. Such genetic problems could disrupt a chronic health issue.

Gene therapy presents a promising attempt to treat different diseases such as leukemia, heart diseases, and diabetes. Also, gene therapy could be used to improve the immunity of a body during its fighting with immune destructive disorders like HIV [1].

II. Gene Therapy Overview

Gene therapy has erupted from the late 1960s and the beginning 1970s when the science of genetics was revolutionized. In 1972, Two genomics scientists Theodore Friedmann and Richard Roblin issued a paper named "A Gene therapy for human genetic disorders?"; their paper was pointing out that a genetic treatment is a potential cure for patients with incurable genetic disorders by merging a DNA sequence into a patient's cells. The paper encountered much disapproval as the side effects of gene therapy were unknown at that time. However, after deliberate research and experiments, in 1990 the first gene therapy trial on the human body went successfully. The therapy was conducted on a young

girl who was diagnosed with a deficiency of an enzyme called ADA, making her immune system vulnerable, and any weak infection could have killed her. Fortunately, that trail has paved the way for gene therapy to flourish as a treatment among other types of medications.

III. Gene therapy vs genetic engineering

A renowned misconception is that people think that gene therapy and genetic engineering are synonymous; nonetheless, they are different technologies. Gene therapy is a technique that aims to alter the DNA sequence inside malfunction cells to cure genetic defects. On the other hand, Gene engineering is used to modify the characteristics of a certain gene to enhance its biological functions to be abnormal. Genetically Modified Organisms are an obvious example of genetic engineering products. For illustration, the advancement of biotechnological techniques enabled scientists to develop a kind of modified cultivated products with certain abilities to cope with human needs such as a plant with less need for fertilizers and more prolific outcomes [3].

IV. Gene therapy stages

You might have imagined gene therapy as the injection of the patient with a syringe that has a gene to simply substitute the flawed gene inside the cell. Mainly that thought is right, however, the process is not that easy.

Before we would insert the isolated, intended gene inside the body, we must know a new agent called Vector. As we know, we aim to change an abnormal gene inside a cell by entering a new gene but inserting the gene directly into the cell always tends to fail. Therefore, scientists looked for a carrier that would insert the gene successfully into the cell. Vectors are a carrier that would infuse with the cell and release its genome, inclusive of the required gene inside the targeted cell. The most used vectors are Viruses because they can easily fuse with cells and inject their genome inside them. Despite the bad reputation of viruses, engineered modified viruses are not harmful to the body.

The way of how the viruses interfere with the cell depends on the kind of that virus. For example, Retrovirus fuses with the cell and integrates its genetic components inside the cell‘s chromosomes. On the contrary, Adenoviruses eject their components but without integrating them into chromosomes.

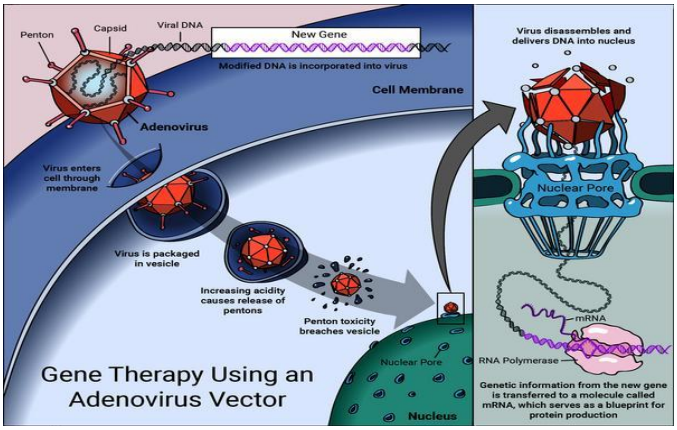

Figure 1: how the vector enters the cell’s nucleus

There are some other ways of injecting the body with vectors such as taking the cell outside the body and injecting it artificially with the vectors then returning it to the body [4].

V. Types of genetic therapy

There are two types of genetic therapy: somatic therapy and germline therapy. Somatic therapy is inserting the new gene in a somatic cell (cells that do not produce sperms or eggs). Somatic therapy does not ensure that the disease will not appear in successive generations, and it requires the patient to take it several times as its effect does not last long. On the other hand, germline therapy targets the reproductive cells which produce gametes that later develop into an embryo. Germline therapy occurs one time in life. It happens either in pre-embryo to treat genetic defects or it is used to treat a flawed adult sperm or egg before entering the fertilization process [5].

VI. Genetic therapy and psychiatric disorders

The productivity of individuals within their society is determined by their mental conditions. If they suffer from a mental issue, they will not behave well in their routines. Psychiatric disorders are a psychological and behavioral defect that causes disturbance in the functions, feelings, and perceptions of the brain. Ranging from sleep troubles to Alzheimer's, psychiatric disorders have many different forms, such as Depression, Schizophrenia, Bipolar disorders, and development disorders like ADHD [6].

Neuroscientists and researchers say that there are many factors attribute to the causation of chronic Psychiatric disorders. They classified those factors into two groups – minor factors and major factors. Minor factors, such as environmental and social influences, contribute less than those of the major factors [7].

Among many major contributors to psychiatric disorders, Genetics(heredity) is the most notable factor in all mental illnesses. According to advanced studies of genomics, Psychiatric disorders tend to be heritable, and mentally defective parents' offspring have a high susceptibility to receive a mental illness. Etiology, the science of causation of a disease, has shown that both Depression and Bipolar disorders have profuse genetic origins [8]. Depressive disorders have about 30-40% genetic contributions [9].

VII. What makes gene therapy the expected future approach for most of the psychiatric disorders?

Despite the continuous research and advances in medical treatment methods for various psychiatric conditions, a large number of patients remain unresponsive to current approaches. Development in human functional neuroimaging has helped scientists identify specific targets within dysfunctional brain networks that may cause various psychiatric disorders. Consequently, deep brain stimulation trials for refractory depression have shown promise. With the procedure and targets being advanced, that helped scientists use similar techniques to deliver biological agents such as gene therapy.

Identification of specific molecular and anatomic targets is important for the development of gene therapy. In gene therapy, the vehicles used to transfer genes to the neurons in the brain are modified viruses, called viral vectors. Viruses have the ability to transfer their genetic material to the target cells. That enables viral vectors to take advantage of that ability. The viral coat of the vectors is able to deliver a payload with the therapeutic gene efficiently while decreasing the proteins or viral genes that might cause replication and spread of the toxicity or inflammation of the virus.[11]

i. Depression

Neuroanatomic substrates and circuits of depression remain poorly understood although depression is one of the most widely studied psychiatric diseases.[11] Poor signaling of the neurotransmitter serotonin causes depression. Serotonin is trafficked by p11 protein in the living brain. The gene expresses a protein, which is p11, that binds to the serotonin receptor molecules carrying them to the cell's surface and positioning them to the neighboring cells.

A neurosurgeon, at Weill Cornell Medical College in New York, called Michael Kaplitt worked with Greengard and other researchers on an experiment that tested gene therapy's ability to cure depression in mice. Firstly, the researchers used a technique known as RNA interference to block the expression of p11 protein in the nucleus accumbens of two mice, which were known to be linked to depression. Next, they injected a viral vector, which carried the p11 gene, into the nucleus accumbens of the mice lacking the gene. In the end, they found that the viral vector helped undo the depression-like symptoms in the mice.[12]

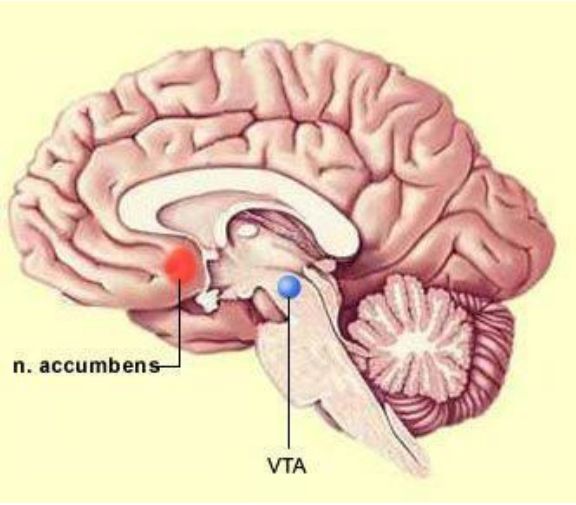

Figure 2: A human brain picture with labeled nucleus accumbens.[19]

ii. Addiction

In 1998, Carlezon et al. showed significant results in using gene transfer techniques to modify drug-seeking behavior in mice.[13] Although the addiction to other drugs has been studied well, we will talk here about cocaine addiction as an example. Rats treated with a 5-HT1B agonist were found to have reduced cocaine-seeking behavior. The reduced cocaine-seeking behavior was blocked by the 5-HT1B antagonist. But, at the same time, 5-HT1B agonist reduced sucrose seeking in mice as well. Therefore, that indicates that 5-HT1B agonist caused anhedonia or depression-like behaviors in mice in addition to reducing cocaine-seeking behavior.[11] Recently, scientists were able to use similar methods to modify ethanol intake in animal models targeting the expression of the aldehyde dehydrogenase gene (ALDH2) leading to a significantly altered alcohol-drinking behavior.[13]

iii. OCD

OCD, also known as obsessive-compulsive disorder, is present in 2% of the Earth's population. It is characterized by obsessions that lead to anxiety and some behaviors could relieve this anxiety. It is a heterogeneous disorder that cannot be identified by clear biological symptoms or environmental causes. Sapap3 is a protein that is expressed in high levels in the striatum. In rodents, a deficiency of Sapap3 in the lateral striatum produced an OCD-like phenotype. The lateral striatum is a cluster of neurons in the basal ganglia of the forebrain. Sapap3 KO mice exhibited OCD-like behaviors that were alleviated by selective serotonin reuptake inhibitor treatment.[11]

VIII. Gene therapy and p11 protein in treating Depression /Bipolar

i. Bipolar disorder and genetics

Bipolar disorder is a serious psychiatric disorder that is also known to have a strong genetic component. Adoption studies, segregation analyses, and twin studies have shown that the possibility of developing bipolar disorder, especially BP-1, is sometimes very high due to genetic factors. The identification of a specific gene that causes the bipolar disorder is difficult because it's not related to mendelian genetics, so it is more complex. Genome-Wide Association or GWA have started using dense SNP maps, also known as Single-nucleotide polymorphism, to study bipolar disorder. SNP mapping is the most dependable way to map genes because it is very dense. Baum et al used a two-stage strategy, he started with 461 bipolar cases and 563 controls, and he showed significant findings in a sample of 772 bipolar cases and 876 controls and found evidence for novel genes linked with bipolar disorder, including a gene for diacylglycerol kinase, which plays a main role in the lithium sensitive phosphatidylinositol pathway.[18]

One of the major things that most people with bipolar disorder experience is depression. Therefore, we can say that reducing depression symptoms with gene therapy may lead to significant alleviation of the seriousness of the bipolar disorder.

ii. What is p11 protein?

P11 is a kind of protein encoded by the gene S100A10. Its function is the intercellular trafficking of the transmembrane protein to the cell surface. Researchers found out that mice with a decreased level of p11 protein in their brains displayed a depression-like phenotype.[14] Moreover, they turned to the postmortem brains of 17 individuals, some of them had depression and others didn't. Finally, they discovered that the individuals, who had depression, had lower levels of p11. Therefore, we can say that p11 has a role in treating depression.[13]

iii. Sucrose preference test and anhedonia in mice

Anhedonia is the inability to experience joy from enjoyable activities and it is a symptom of depression. Sucrose preference test or SPT is a protocol used to measure anhedonia in mice. It was the reason why scientists were able to diagnose mice with depression. Therefore, they tested the injection of a viral vector containing p11 protein to cure depression. Rodents are known to naturally prefer sweet solutions when given a two-bottle free-choice regimen with access to both sucrose solution and regular water. However, when they experienced depression, they did not show a preference for the sucrose solution.

IX. Gene therapy pros and cons

Currently, gene therapy research has been ongoing for decades. Researchers say that it could be used to treat various diseases**.** However, they had to dive more into it to discover its pros and cons.

Gene therapy is sometimes better than other treatments because it has many advantages. For instance, its effects are long-lasting as the defective gene is replaced by a healthy one. Therefore, that healthy gene is the one that will be transferred to the offspring. Furthermore, germline gene therapy can be used to replace incurable diseases' genes in gametes. That results in eradicating genetic diseases such as Parkinson's disease, Huntington's disease, and Alzheimer's disease.

Conversely, gene therapy has several cons. For instance, it can go wrong because it is still under research. The immune system response can lead to inflammation or failure of the organ. In 1999, a clinical trial was conducted at the University of Pennsylvania on an 18-year-old man, who died at the end. In the clinical trial, the Ad5 vector was used to deliver the gene for ornithine decarboxylase, a deficient hepatic enzyme. An investigation by the university showed that the man died due to a massive immune reaction.[15] Moreover, it can be much more expensive than other treatments since it is a technologically-based therapy. Accordingly, socioeconomic segregation would emerge as the rich would be disease-free while others would be suffering.

X. Enduring with gene therapy is tough because it has many Ethical obstacles

i. Gene therapy: A double-edged sword

We must recognize that the power of gene therapy is not limited to the cure or prevention of genetic diseases. Many people support technologies that can avoid the birth of a child with a genetic disorder such as Tay Sachs disease, Down syndrome, or Huntington's disease, although this technology might result in aborting established pregnancies. Questions about gene therapy have gone beyond its ability to cure some defects. Some difficult questions became broadly included such as:

What kind of traits will an infant have?

How much will economic forces affect the hiring or insuring of individuals who are genetically at risk of having costly diseases?

How much data can be secured if an individual's genetic information is stored on computer disks?

The human genome project is a research project about the genes that structure and control functions in the human body. The United States government has created a panel of ethics experts to prevent the use of the knowledge for harm. In fact, this project is similar to the early research stages of nuclear science. Nowadays, nuclear power is known to be a double-edged sword. Therefore, the leakage of information about the human genome project may lead to massive annihilation.[16]

ii. Controversy against gene therapy

Critics assert that in a world that values physical beauty and intelligence, gene therapy may be exploited in a eugenics movement that promotes perfection. People with mental retardation will not be allowed to reproduce. That could lead to discrimination. The genetic profiles may be known by potential members of society which will result in the lack of privacy. Moreover, with the world valuing strengths, this could make special capabilities necessary for a person to be an active member of society. As a result, high standards of physical beauty, intelligence, and capabilities will be put which will result in inequality.[16]

On the other side, many scientists support the development of gene therapy because it will benefit

humankind and will enable them to save many human lives and alleviate their suffering.

iii. Justice in the distribution of gene therapy

If gene therapy is shown to be effective and safe in curing diseases, the rich will monopolize the treatment. Additionally, it might be used for various reasons, other than just correcting genes, such as controlling the traits and gender of an infant. The presence of special capabilities in a human would be normalized which will lead to the preference of rich people with perfect modified genes. On the other hand, middle and low-income families will be under pressure to achieve perfection and that will make them oppressed. In addition, they will not have the opportunity to be treated with gene therapy because it is going to be highly expensive.[16]

XI. Conclusion

As genetic diseases are increasing rapidly and may result in chronic health issues, gene therapy would be one of the most promising medications. In addition to its significant success in curing diseases such as leukemia, heart diseases, and diabetes, it was discovered that it could contribute to treating psychiatric disorders. Various psychiatric disorders were noticed to have a major genetic component. As a result, research has been ongoing to find whether gene therapy was scientifically appropriate to treat psychiatric disorders or not. Several experiments have been conducted on mice to measure the therapy's efficiency. Fortunately, these experiments have shown promise.

As the research has demonstrated, gene therapy has numerous merits that can benefit humankind. Nevertheless, it has many disadvantages that can result from the reaction of the immune system. Additionally, critics affirm that the therapy could go beyond correcting genetic defects. So, ethical issues might emerge as genetic information will not be secured and standards of special capabilities will be put. That can prevent many people from being active members of society.

To conclude, gene therapy is a double-edged weapon, however, further research on it will contribute to the eradication of many serious diseases.

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