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Review Article

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Schizophrenia Cureness and Gene Therapy

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1. Introduction

In this paper, it will be tried to briefely talk about Schizophrenia(cause and effects). In these years, mental illness cureness such as other sciences has improved.. It will be discussed the main methods for this illness.

2. Material and Methods

2.1 Multifactorial Disorders

Many people are ssusceptible to diseases that have a multifactorial basis- a genetic component plus a significant environmental influence. Hearth disease, diabetes, cancer, alcoholism, ertain mental illnesses such as schizophrenia and bipolar disorder, and many other diseases are multifactorial. In these cases, the hereditary component is polygenic.

2.1.1 Many Nervous System Disorders Can Now Be Explained in Molecular Term:

Disorders of the nervous system, including schizophrenia, depression, drug addiction, Alzheimer's disess, and Parkinson's diseas, are a major public health problem. Together, they result in more hospitalizations in the United States than do hearth diseas or cancer. Until receltly, hospitalization was typically the only available treatment, and many affected indivvvviduals were institutionalized for the rest of their lives. Today, many disorders that alter mood or bahaivor can be reated with medication, reducing average hospital stays for these disorders to only a few weeks. Nevertheless, many challenges remain with regard to preventing or treating nervous system disorders, especially Alzheimer's disease and other disorders that lead to nervous system degeneration.

Major research efforts are under way to identify genes that cause or contribute to disorders of the nervous system. Identofying such genes offers hope for identifying causes, predicting outcomes, and developing effective treatments. For most nervous system disorders, however genetics contributions only partially account for which individuals are affected. The other significant contribution to disease comes from environmental factors. Unfortunately, such environmental contributions are typically very difficult to identify. To distinguish between genetic and environmental variables, scientists often carry out family studies. In these studies, researches track how family members are related genetically, which individuals are affected, and which family members grew up in the same household. These studies are especially informative when one of the affected individuals has either an adopted sibling who I genetically unrealated or an identical twin, as we'll see for the disorder schizophrenia, our next topic.

2.1.2 Schizophrenia

Approximately 1% of the world's population suffers from this illness, a severe mental disturbance characterized by psychotic episodes in which patients have a disorted percepted of reality. People with schizophrenia typically experiancehallucinations(such as " voices" that only they can hear) and delusions (for example, the idea that others are plottingto harm them). Family studies have revealed a very strong genetic component for schizophrenia. However, the diseas also subjected to environmental influence, since an individual who shares 100% of his or her genes with a twin schizophrenia has only a 48% chance of developing the disorder. Despite the commonly held notion, schizophrenia does not necessarily result in multiple personalities.

One current hypothesis is that neuronal pathways that use dopamine as a neurotransmitter are distrupted in schizophrenia. Supporting evidence comes from the fact that many drugs that alleviate the symptoms of schizophrenia block dopamine receptors. In addition the drug amphetamine, which stimulates dopamine release, can produce the same set of symptoms as schizophrenia. Recent genetic studies suggest a link between schizophrenia and particular forms of the complement protein C4, an immune system component.

2.1.3 Schizophrenia and Dopamin System

Schizophrenia comes in many varieties. One of the most common types is seen in the person who hears voices and has delusions, intense fear, or other types of feeling that are unreal. Many schizophrenics are highly paranoid, with a sense of persecution from outside sources. They may develop incoherent speech, dissociation of ideas, and abnormal sequences of thought, and they are often withdrawn, sometims with abnormal posture and even rigidity.

There are reasons to believe that schizophrenia results from one or more of three possibilities : multiple areasthe cerebral cortex prefrontal lobes in which neural signals have become blocked or where processing of the signals becomes dysfunctional because many synapse normally excited by the neurotransmitter glutamate lose their responsiveness to this transmitter; excessive excitement of a group of neurons that secret dopamine in the behaivioral centers of the brain, including in the frontal lobes; and/or abnormal function of a crucial part of the brain's limbic behavioral control system centered around the hippocampus [1-3].

Dopamine has been implicated in schizophrenia because schizophrenic-like symptoms develop in many patients with Parkinson's disease when they are reated with the drug called L-dopa. This drug releases dopamine in the brain, which is advantageous for treating Parkinson's diseases but at the same time it depresses various portions of the prefrontal lobes and other related areas.

It has been suggested that in persons with schizophrenia, excess dopamine is secreted by a group of dopamine secreting neorons whose cell bodies lie in the ventral tegmentum of the mesencephalon, medial and superior to the substantia. Nigra. These neurons give rise to the so called mesolimbic dopaminergic system that projects nerve fibers and dopamine secretion into the medial and anterior portions of the limbic system, especially into the hippocampus, amygdala, anterior caudate nucleus, and portions of the prefrontal lobes. All these areas are powerful behavioral control system.

An even more compelling reason for believing that schizophrenia might be caused by excess production of dopamine is that many drugs that are effective in treating this illness, such as chlorpromazine, haloperidol and thiothixene, all either desrease secretion of dopamine at dopaminergic nerve ending ordecrease th effect of dopamine on neurons.

Finally, possible involvement of the hippocampus in schizophrenia was discovered when it was larned that in persons with schizophrenia, the hippocampus is often reduced in sie, especially in the dominant hemisphere.

In ths section we continue other ways of cureness by introducing Gene therapy.

2.1.4 Gene Therapy

The final application of recombination DNA technology in medicine that we consider is Gene therapy. This is the name originally given to methods that aim to cure an inherited disease by providing the patient with a correct copy of the defective gene. Gene therapy has now been extended to include attempts to cure any disease by introduction of a cloned gene into the patient. First, we will examine the techniques used in gene therapy, and then we will attempt to address the ethical issues.

2.1.5 Gene Therapy for Inherited Disease

There are two basic approaches to gene therapy: germline therapy and somatic therapy. In germline therapy, a fertilize egg is provided with a copy of the correct version of the relevant gene and reimplanted into the mother. If succeful, the gene is present and expressed in all cells of the resulting individual. Germline therapy is usually carried out by microinjection of a somatic cell followed by nuclear transfer into an oocyt and theoretically could be used to treat any inherited disease.

Somatic cell therapy involve manipulation of cells, which either can be removed from the origism, transfected, and then placed back in the body, or transfected in situ wothour reoval. The technique has most promise for inherited blood disease.(e.g. haemophilia and thalassaemia), with genes being introduced into stem cells from the bone marrow, which give rise to all the specialized cell types in the blood. The strategy is to prepare a bone extract containing several billions cells, transfect these with a retrovirus, based vector and then reimplant the cells. Subsequent replication and differentiation of transfectants lead to the added gene being present in all the mature blood cells. The advantage of a retrovirus is that this type of vector has an extremely high transection frequency, enabling a large proportion of the stem cells in a bone marrow extract to receive the new gene.

Somatic cell therapy also has potential in the treatment of lung disease such as cystic fibrosis, as DNA cloned in a virus vector or contained in liposomes is taken up by the epithelial cells in the lungs after introduction into the espiratory tract via an inhaler. However, turnover of the epithelial ells means that gene expression occurs for only a few weeks and as yet this has not been developed into an effective means of treating cystic fibrosis.

With those genetic diseases where the defect arises because the mutated gene does not code for a functional protein, all that is necessary is to provide the cell with the correct version of the gene. Removal of the defective gene is unnecessary. The situation is less easy with dominant genetic disease, as with these it is th defective gene product itself that is responsible for the disease state, and so the therapy must included not only addition of the correct gene but also removal of the defective version. This requires a gene delivery system that promotes recombination between the chromosomal and vector, borne versions of the genes, so that the defective chromosal copy is replaced by the gene from the vector. The technique is complex and unreliabl, and broadly applicable producedures hve not yet been developed.

2.1.6 The Ethical Issues Raised by Gene Therapy

Should gene therapy be used to cure humasn disease? As wit many ethical questions, there is no simple answer. On the one hand, there could surely be no justifiable objection to the routine application via a respiratory inhaler of correct versions of the cystic fibrosis gene as a means of managing this disease. Similarly, if bone marrow transplants are acceptable, then it is difficult to argue against gene therapiesaimed at correction of blood disorders via stem cell transfection. And cancer is such a terrible disease that the withholding of effective treatment regimens on moral grounds could itself be criticized as immoral.

Germline therapy is a more difficult issue. The problem is that the techniques used for germline correction of inherited disease are exactly th same techniques that could be used for germline manilulation of other inherited characteristics. Indeed, the development of this technique with animals has not been prompted by any desire to cure genetic disease, the aims being to 'improve' farm animals, for example by makin genetic changes that result in lower fat content. This type of manipulation, where the genetic constitution of an organism is changed in a directed, heritable fashion, is considered by many people to be unncceptable in humans, and is currently banned in over 40 countries. However, it was announced in 2018 that twin children had been born following modification of a fertilized egg cell by gene editing with a programmable nucleaseto improve resistance to HIV. The states justification was that the male parent was HIV positive and so could conceivably pass the virus to his offspring via his sperm, although there are existing strategies not involvinggene therapy to prevent father- offspring transmission of HIV. The furore generated by announcement of this work has prompted calls for a worldwide moratorium on research into human germline editing, so that the ethical issues can be fully disussed and agreement reached on the rules and regulations which must be followed if this work is to permitted.

2.1.7 How Gene Therapy Works

Sometimes the whole or part of a gene is defective or missing from birth. This is typically referred to as a genetically inherited mutation.

In addition, healthy genes can change (mutate) over the course of our lives. These acquired mutations can be caused by environmental exposures. The good news is that most of these genetic changes (mutations) do not cause disease. But some inherited and acquired mutations can cause developmental disorders, neurological diseases, and cancer.

Depending on what is wrong, scientists can do one of several things in gene therapy:

• They can replace a gene that is missing or is causing a problem.
• They can add genes to the body to help treat disease.
• Or they can turn off genes that are causing problems.

To insert new genes directly into cells, scientists use a vehicle called a "vector." Vectors are genetically engineered to deliver the necessary genes for treating the disease.

Vectors need to be able to efficiently deliver genetic material into cells, and there are different kinds of vectors. Viruses are currently the most commonly used vectors in gene therapies because they have a natural ability to deliver genetic material into cells. Before a virus can be used to carry therapeutic genes into human cells, it is modified to remove its ability to cause infectious disease.

Gene therapy can be used to modify cells inside or outside the body. When a gene therapy is used to modify cells inside the body, a doctor will inject the vector carrying the gene directly into the patient.

When gene therapy is used to modify cells outside the body, doctors take blood, bone marrow, or another tissue, and separate out specific cell types in the lab. The vector containing the desired gene is introduced into these cells. The cells are later injected into the patient, where the new gene is used to produce the desired effect.

There are a variety of types of gene therapy products, including:

• **Plasmid DNA:** Circular DNA molecules can be genetically engineered to carry therapeutic genes into human cells.
• **Viral vectors:** Viruses have a natural ability to deliver genetic material into cells, and therefore some gene therapy products are derived from viruses. Once viruses have been modified to remove their ability to cause infectious disease, these modified viruses can be used as vectors (vehicles) to carry therapeutic genes into human cells.
• **Bacterial vectors:** Bacteria can be modified to prevent them from causing infectious disease and then used as vectors (vehicles) to carry therapeutic genes into human tissues.
• **Human gene editing technology:** The goals of gene editing are to disrupt harmful genes or to repair mutated genes.
• **Patient-derived cellular gene therapy products:** Cells are removed from the patient, genetically modified (often using a viral vector) and then returned to the patient.

In March 2022, the U.S. FDA released the draft guidance for industry Human Gene Therapy Products Incorporating Human Genome Editing. The purpose of this draft document was to share preliminary FDA thoughts about proper implementation and control of human genome editing (GE) in therapeutic product development and to invite commentary from the scientific community about potential improvements to the guidance. Numerous scientific organizations and interested parties, including the American Society for Cell and Gene Therapy and the International Society for Cell Therapy, among others, provided feedback to the FDA about how to improve the clarity and utility of the guidance. On Jan. 29, 2024, the FDA released the final version of the guidance document.

Gene therapy is the administration of genetic material to modify or manipulate the expression of a gene product or to alter the biological properties of living cells for therapeutic use. Gene therapies offer the potential to treat diseases or conditions for which no or few treatments exist. They are being studied to treat cancer as well as genetic, infectious, and other diseases. FDA considers any use of CRISPR/Cas9 gene editing in humans to be gene therapy.

Gene therapy products are regulated by the FDA's Center for Biologics Evaluation and Research (CBER). Clinical studies of gene therapy in humans require the submission of an investigational new drug application (IND) prior to their initiation in the United States, and marketing of a gene therapy product requires submission and approval of a biologics license application (BLA). Clinical trials of gene therapies can be found at www.clinicaltrials.gov. FDA has also approved certain gene therapy products.

FDA is aware that gene therapy products intended for self-administration and "do it yourself" kits to produce gene therapies for self-administration are being made available to the public. The sale of these products is against the law. FDA is concerned about the safety risks involved. Consumers are cautioned to make sure that any gene therapy they are considering has either been approved by FDA or is being studied under appropriate regulatory oversight.

2.1.8 Gene Therapy and Schizophrenia

Schizophrenia gene therapy is a potential treatment option for schizophrenia that aims to restore the communication between neurons in the brain. It involves infusing a benign virus programmed with specific DNA into precisely targeted areas of the brain. This technique has been shown to reduce delusions and hallucinations, and improve cognitive function in rats that model schizophrenia.

It has been found that the majority of genetic changes occur in non-protein-coding regulatory RNA (ncRNA), particularly micro RNA (miRNA) and long non-coding RNAs (lncRNA). miRNA and lncRNA are two regulatory ncRNAs that do not code proteins and differ in function, location, and size. miRNAs play important roles in post-transcriptional destabilization of messenger RNA (mRNA), translational suppression, or regulation of both molecular mechanisms [4, 5]. lncRNAs are defined as nonprotein-coding regulatory ncRNAs longer than 200 nucleotides (nt) in length. Although the function of lncRNAs is not as well understood as the function of miRNAs, recent studies have provided a better understanding of their role and have shown an association with psychiatric disorders such as autism, bipolar disorder, and major depression, including schizophrenia [6-10]. Since miRNAs and lncRNAs are highly expressed in brain tissue because they regulate genes necessary to maintain brain development and function, as abnormal brain development and maturation has been proven to be linked to schizophrenia. For example, manipulation of schizophrenia-associated miRNAs such as miR-132/miR-121 and miR-219 has demonstrated changes in neuronal activity and brain plasticity at synapses [11-13]. Further studies have revealed that these miRNAs directly regulate the synthesis of proteins required for synaptic plasticity or interact with factors likely to regulate permanent neuroplastic changes [13, 14]. These recent findings of schizophrenia-associated miRNAs suggest that dysregulation of miRNAs and targeted genes is crucial for our understanding of the underlying biological causes of schizophrenia. Considering the multitude of miRNA alterations and their broad impact on target genes in schizophrenia, schizophrenia-associated miRNAs may be significant in the pathogenesis of schizophrenia. In past years, an increasing number of schizophrenia-associated ncRNAs such as miR-137, lncRNA Gomafu, etc. have been identified, and genetic changes in these ncRNA genes have strengthened the implications for the pathogenesis of schizophrenia [8, 15-17]. However, the functional roles of these genetic variations in the development and progression of schizophrenia are not yet well understood. In fact, the functioning of these ncRNAs in schizophrenia development and the correction of genetic changes in genomic DNA that are key to developing new treatments for schizophrenia and the effective manipulation of these ncRNA genes have not been realized due to insufficient technology. In light of new developments, it will be possible to create or correct mutations in animal models using new genetic tools in genomic DNA, including coding and non-coding regions in schizophrenia, which will be the key to developing new treatments for schizophrenia. In recent years, a large number of miRNAs and lncRNAs associated with schizophrenia have been identified and characterized, thanks to a range of advanced technologies, including next-generation sequencing, high-resolution microarray, and genotyping. Understanding the genetic variations of ncRNAs in the development of schizophrenia has benefited from advanced technology and new tools from biology and other fields of science. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated nuclease 9 (Cas9) (CRISPR/Cas9) is a recently developed revolutionary gene editing technology that can effectively manipulate non-coding regions of genomic DNA in human cell lines and animal models.

2.1.9 CRISPR/CAS9 and Methods

Originally well described as an adaptive immune defense mechanism in bacteria, the CRISPR/Cas9 system is an emerging revolutionary and viable method for precise genome editing of a variety of organisms, including plants, animals, and even humans. With this method, genomic DNA stretches can be edited easily and precisely. The key feature of the modified CRISPR/Cas9 system is the use of double gRNA, which creates two breaks at certain sites and allows deletion of a larger fragment.

Due to a number of advantages, the CRISPR/Cas9 system provides a new perspective on developing animal models for schizophrenia research. With the help of the CRISPR/Cas9 system, specific mutations of the target ncRNA gene can be introduced into the embryo and the restorative form of the ncRNA gene can be reintroduced into the gene in a rat or mouse embryo. The rat or mouse and their offspring will contain the mutation or restoration of the original form, allowing researchers to directly compare the symptoms of the resulting experimental and control groups.

The created animal models can also be used to test the efficacy of drugs or other potential therapeutic approaches in the treatment of schizophrenia. In fact, it usually takes up to two years for the animal model created by conventional procedures to acquire certain mutations in the offspring because multiple breeding steps are needed, while generating the animal model using the CRISPR/Cas9 approach is less costly and takes about two months.

Moreover, in combination with template DNAs and the use of multiple gRNAs, the CRISPR/Cas9 system can introduce any number of mutations into the embryo of an animal or its offspring. With these promising results in mammalian and human cells, CRISPR/Cas9 holds great therapeutic potential for treating human inherited diseases, including schizophrenia and perhaps other inherited mental disorders.

3. Result

As this survey on schizophrenia cureness ways, it proved gradually in future we should see the gene therapy methods for cureness of this illness.

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