Schizophrenia: Current Progress and New Treatment Perspective

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Keywords: Schizophrenia, NRG1, gene therapy.

Abstract: Schizophrenia is one of the common psychoses that would cause hallucinations, delusions, and other psychiatric symptoms. To better understand this disease and to develop various treatment strategies, it is essential to study the mechanism and factors of schizophrenia onset. Diagnosis is an essential part to definite psychiatry. For schizophrenia, the mainstream diagnostic approach emphasis on examining behavioral symptoms which are more accessible than examining physiological alteration. Emerging diagnosis that focusing on molecular change or structure abnormality, though not applied widely yet, could be a potential strategy in future. Genetic mutation and environmental factors could both impact on schizophrenia onset. NRG1(Neuregulin 1), a gene closely relates with neural signaling pathway and neural development, is thought to be associated with schizophrenia onset if it is mutated. Environmental factors that involve both antenatal and postnatal periods could also facilitate disease formation. Current treatment of schizophrenia relies on pharmacological approach along with psychological support. The development of gene-editing technology reveals the possibility of using gene therapy to treat mental diseases like schizophrenia.

1. Introduction

Schizophrenia is one of the most pervasive and chronic psychic disease around the globe with a prevalence rate of 7.2 per 1000 and has a general acknowledge that there is no difference in prevalence rate between male and female [1]. On the basis of the definition given by WHO, schizophrenia is a disorder which is having a mental illness on thinking, perception, emotions, language, sense of self and behavior, meanwhile experience hallucination as well as delusion [2].

The symptom of schizophrenia was recorded by several scientists around the world with differed describing of the disorder. It was originally defined as “dementia praecox” by Emil Kraepelin, who summarized a huge number of cases and found all patients suffered cognitive deficit. Eugen Bleuler concluded the symptoms by altering Kraepelin’s concept, and named this disorder “Schizophrenia” [3]. Schizophrenia also causes financial burdens to families, according to a data analysis towards 174,310 patients with schizophrenia in Brazil, the annual cost on the treatment was $US1811.92 ± 284.39 (mean ± Standard deviation) per patient [4].

Recent research reported that, NRG1 was believed to be highly associated with schizophrenia. NRG1 is a pleiotropic gene that encodes a membrane glycoprotein which is a member of growth factor family. This protein is used to coordinate and maintain the interaction between neuron, glia, and postsynaptic target, which are significant roles of making a mature synapse [5]. Meanwhile, the malfunction of NRG1 caused by mutation will damage the signaling pathway with a participatory receptor ErbB4.

Feasible treatment options can be brought out, for instance, psychological treatment using cognitive behavior therapy, pharmacological treatment using such drugs like tranquilizers, and genetic treatment. Considering the genetic basis of Schizophrenia onset, genetic therapy seems to be a promising approach. The gene-editing technology has been changed dramatically in the past decades. CRISPR/Cas9 system, as the latest gene-editing technology, could be conducted in a

relatively easy way for individual therapy. This article describes different therapies and demonstrates the potential of CRISPR/Cas9 in curing Schizophrenia.

2. Diagnostic Principle

2.1 Traditional Diagnostic approach

Currently, the mainstream schizophrenia diagnosis relies on the Diagnostic and Statistical Manual of Mental Disorders - fifth edition (DSM-5). According to DSM-5 [6], the diagnostic criteria include assessing key features of schizophrenia disorder including both positive symptoms and negative symptoms. Positive symptoms are delusions, hallucinations, disorganized speech and grossly disorganized or catatonic behaviour. While negative symptoms are normally described as affective flattening, alogia, and avolition. Patients who have two or more of these symptoms that last more than a month will be regarded as Schizophrenia. This approach is mainly conducted by exclusion, by determining patients' clinical features which are mainly collected from diagnostic interviews. Compare with other common Although this clinical feature-based method means the diagnosis is accessible and affordable for psychiatry experts, subjectivity might affect the reliability and stability. A review conducted by Palomar-Ciria [7] reported that even though schizophrenia has relatively higher diagnostic stability, factors such as gender, age, and severity of symptoms could still lead to an unstable diagnosis. Therefore, we introduce some emerging diagnostic approaches that are not widely applied yet to provide some new definitions of Schizophrenia at the pathognomy level.

2.2 Emerging Diagnostic approach

As a complex disease, schizophrenia shows some physiological changes such as metabolic changes, Immune system changes, and hormonal regulation changes [8]. For metabolic changes, blood test shows that schizophrenia patients will have higher fasting plasma level of glucose, insulin, and cortisol [9] and female schizophrenia patients would have higher plasma level of leptin [10]. It would be changed in the immune system for schizophrenia patients including a higher level of CCL2, IL-1, and IL-6 [11]. These methods indicate a physiological change in patients with schizophrenia. Although this method is still under development [12], it provides an inspiration for us to recognize schizophrenia in a biomarker way. Except for the blood test, cerebrospinal fluid is regarded as a marker accessible in living patients as well. The biomarker shows that schizophrenia patients have altered levels of S100B protein, GSK-3β, and SNAP25 [13]. Notably, along with a higher level of SNAP25 protein, their encoding mRNA level in schizophrenia patients also changed [14]. This research result indicates the genetic basis in schizophrenia onset. Neuroimaging is another reliable way to diagnose the brain structural and functional change in schizophrenia patients as well [15]. Using neuroimaging could help clinicians to identify substantive differences in brains between healthy people and schizophrenia patients. It is widely discovered that schizophrenia patients have a smaller cortical surface area and alteration in brain structure [15]. Despite current limitations in neuroimaging technology, it could be a potential diagnostic approach in future. All these methods, while less convenient for remote places where devices are not accessible, is helpful for us to identify the physiological change in schizophrenia patients. This biomarker could help us to inspire changes of molecular level happens in schizophrenia patients.

3. Pathogenesis of Schizophrenia

3.1 Molecular mechanism

Genetic basis of schizophrenia onset is a noticeable aspect in schizophrenia study. It has already been widely known that schizophrenia is a gene-related disease, showing a heritability estimate ranging from 80% to 85% [16]. Also, the prevalence rate of a child of a parent with schizophrenia is ten times higher than the common prevalence rate [17].

NRG1 is the gene coding neuregulin-1, a protein that involves several molecular functions and biological processes. Three main functions are highly related with schizophrenia development, which is regulating myelination, neural migration, and neurotransmitter receptors [18]. The process of myelination is conducted by Schwann cells, which is regulated by NRG1-ErbB signaling pathway [19]. In normal situation, this pathway could ensure the appropriate thickness and length of myeline so that the axons could conduct ideal saltatory conduction [20]. When there is mutation in NRG1 gene, abnormal NRG1 expression could result in impairment in myelination and result in problem in neural signaling, which could be related with psychiatry like schizophrenia [21]. Neural migration, another function that related with NRG1 signaling, is a vital process of nervous system. Appropriate migration of neural cells could ensure the correct structure and function of central nervous system and this process rely on the signaling pathway of NRG1 and ErbB receptors. In normal cases, NRG1 will activate ErbB2 and ErbB3 signaling pathway on glial cells to regulate and maintain these cells to conduct neural migration *(FIG. 1)* [22]. Research conducted by Ghashghaei et al discovered that blockage of this signaling pathway will disturb neurogenesis sites such as forebrain subventricular zones [23]. Regarding the function of neurotransmitter receptor, GWAS research conducted by Mostaid et al. studied the relationship between NRG1 and excitatory/inhibitory neurotransmission [24]. They suggested that abnormal expression of NRG1 will cause impaired neurotransmissions such as decreased activity in the frontal brain region that is responsible for attention, memory, and other executive function, and abnormal high activity in the hippocampus and certain subcortical areas. These neurotransmission problems could lead to schizophrenia's negative and positive symptoms relatively. Moreover, according to Mei and Xiong's review, the synapse formation, synaptic plasticity, and neuronal survival is also regulated by NRG1 [22]. If the NRG1 is affected, the CNS will undoubtedly be affected and cause schizophrenia.

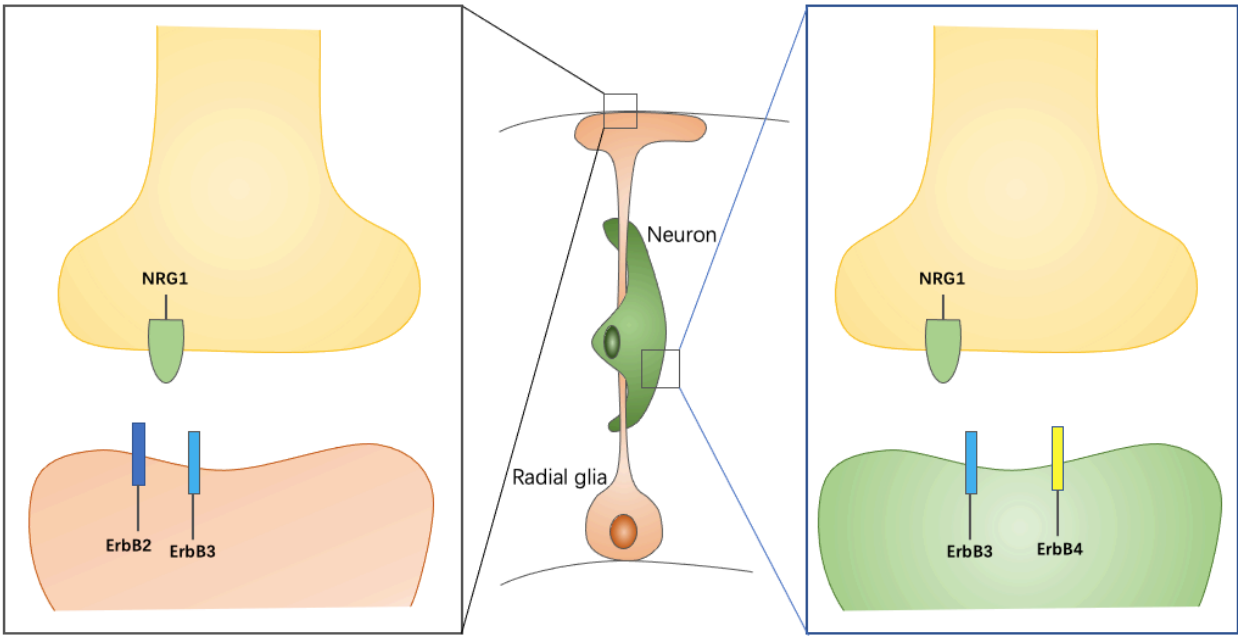

Figure 1. Neuron's release NRG1 to promote the formation and maintenance of glial cells

3.2 Environmental Factor

Despite the significant effects of genes on schizophrenia onset, environmental factors may also play considerable roles during this process. The neural system could be affected both antenatally and postnatally. One example of antenatal issues is hypoxia-associated obstetric complications, which usually happens in forms such as neonatal cyanosis and neonatal apnea. These events were reported to be associated with brain abnormalities, including neuronal death, white matter damage, and neural system development defects [25]. Antenatal brain impairment will affect neuron-associated gene expression, even reduce neonates' resistance to mental pressure when they grow up [26]. For postnatal factors, childhood trauma could be one of the most studied cases in schizophrenia patients.

Abusing, neglecting, parental death, and other types of social adversities are regarded to be strongly associated with psychosis, especially hallucinations, the positive symptom of schizophrenia [27]. In recent research, microbiome features on patients were also considered as a potential factor since the existence of the gut-brain axis reveals the relationship between the neural system and microbiome [28].

4. Treatment

4.1 Psychological treatment

Psychological treatment could relieve schizophrenia patients' symptoms by providing mental support and cognitive-behavioral therapy, which would be a promising treatment strategy. This treatment may include psychological interventions to conduct cognitive remediation, peer support services, and psychoeducation to help patients deal with delusions, hallucination, and social impairment [2]. Except for the major psychological causes before schizophrenia onset, the psychotic symptoms after disease onset could be stressful to patients as well, which is illustrated in Figure 2. This cycle may become perpetuating factor that hinders the effect of treatment [29]. Psychological therapy that mediates such a cycle could not only treat schizophrenia patients directly but can also reinforce other types of treatment. Nonetheless, psychological treatment is hard to assess on a quantity level. Inadequate randomization, small sample size, and other factors beyond clinical treatment could impact the result of the assessment. Even without such bias, the effect of psychological treatment is thought to be not significant enough in current research [30].

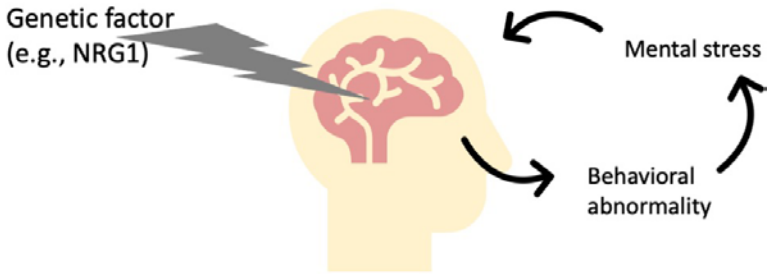

Figure 2. The stress-response circuity of schizophrenia patients. The symptoms patients have may lead to mental stress that enhance the severity of diseases [29].

4.2 Pharmacological treatment

Compare with psychological treatment, pharmacological treatment mainly focuses on amelioration in schizophrenia symptoms at the molecular level. The development of schizophrenia pharmaceuticals is currently in its third generation. These drugs are mostly functioning on serotonin receptors and dopamine-related pathways to mediate schizophrenia symptoms. Compare with the first generation of typical antipsychotic drugs that affect a wide range of receptors, the second and the third generation of atypical antipsychotics exhibit a more moderated effect on the human neural system. One example is the Brexpiprazole developed in the third generation that could partly activate dopamine and serotonin receptors [31]. Despite the side effects such as headache, somnolence, and weight gain, it is more tender than first-generation drugs. The Largactil, as the first-generation medicine, could block dopamine receptors in the brain without selectivity. Despite the high efficiency, first-generation drugs may cause severer side effects such as dystonia, akathisia, muscle breakdown [31]. Therefore, the doctor needs to identify patients' situations to decide what kind of medicine is best suited in each treatment case.

Except for side effects, pharmacological treatment may have other limitations. Stępnicki reported that nearly one-third of patients do not have mitigated symptoms after drug treatment [31]. The effect of drugs on negative symptoms is less significant than the effect on positive symptoms, which might hinder application of drugs during the treatment.

4.3 CRISPR as genetic treatment

Genetic treatment-related studies began in the later 1980s, conducted by Rosenberg et al. They used retroviral-mediated genes to treat tumor-infiltrating lymphocytes in humans [32]. This study inspired scientists to further study the potential for gene therapy. In the current stage, several strategies could be applied to conduct genetic treatment. In the past decades, there are three main gene-editing tools, zinc finger nucleases, transcription activator-like effector nucleases, and CRISPR-Cas9 [33]. Compare with the other two methods, CRISPR is more accessible for scientists to design, which might be more convenient when conducting personalized treatment [33]. CRISPR was first being identified in prokaryotes as an adaptive immune system. When prokaryotes identify invading genes, the CRISPR system would slice this invading gene and integrate this sequence [34]. Thus, prokaryotes could have higher resistance to this invading gene. Researchers optimized this potential system and created a powerful gene-editing tool for biological research in the past several years. Moreover, this brilliant CRISPR/Cas9 system make a great progress in the field of gene therapy.

CRISPR therapy is conducted by designing appropriate guide RNA that could bind Cas9 protein to the wanted sequence loci. The Cas9 protein will then slice the DNA sequence where it binds. The most important aspect of CRISPR treatment design is designing guide RNA. After identifying the genetic variant of schizophrenia patients, guide RNA for CRISPR could be designed based on the DNA sequence near mutation loci. Then, following the slice of mutated DNA, the corrected sequence was introduced to facilitate homologous directed repairing. To ensure the best effect, the protospacer adjacent motif (PAM) on guide RNA should be designed to be no more than 10 nucleotides far from the mutation points.

CRISPR has already been applied to clinical therapeutics. One significant instance is cancer immunotherapy that introduces gene-editing autologous T cells back to patients for more efficient tumour antigen [35]. Researcher successfully conducted CRISPR engineering immunotherapy, the inhibitory genes in T cells, collecting from patients, was disrupted with CRISPR-Cas9 and the tumor-targeting gene was introduced into the cells [36]. These gene-edited T cells would show higher efficiency in cancer treatment, revealing the potential of CRISPR technology as a therapy. Another successful case of using CRISPR therapy to treat a mutation-caused impairment is called Leber's congenital amaurosis 10 (LCA10), a disease that causes blindness [37]. Different from previous genetic therapy that edited in vitro cells and infused back these edited cells to patients, this LCA10 treatment was conducted by directly injecting the gene-editing system into the human body [37]. This improvement is a strong hint to applying CRISPR to neuronal system, as the administrated route is harder than other systems in the body. However, the technology of direct injecting gene-editing kits into the body is still immature and faces problem of safety and ethical concern. Any similar experiments that involve psychiatry disease treatment should be used in a more caring way.

5. Conclusion

Since the concept of Schizophrenia emerged, this mental disease has been studied by psychologists and neurologists for more than 100 years. In modern medical study, there have been both psychological symptoms and physiological symptoms for clinicians to diagnose schizophrenia patients. With the development of genetics and psychology, it is now possible for scientists to view both genetic and environmental factors that cause Schizophrenia onset. Clinical treatment of psychology and pharmacology is also discussed in this review. Then, the possibility of applying CRISPR to treat schizophrenia on a genetic level is proposed. With a modern understanding of schizophrenia, it is now possible to discover novel therapeutic strategies, such as gene therapy. As an immune system in prokaryotes, CRISPR is highly recommended gene-editing method to conduct schizophrenia treatment. By designing appropriate guide RNA, CRISPR could repair desired mutation on NRG1 gene, enabling patients to accessible personalized therapy. However, the application of CRISPR to neuronal system should be carefully studied since there is no such precedent.

The article reviewes the study of NRG1 and its corresponding CRISPR treatment. NRG1 mutation has already been known as a considerable reason for schizophrenia onset. This gene is closely related to the neurodevelopment process and signalling pathway. Therefore, a genetic approach to schizophrenia could be regarded as a promising strategy other than psychological and pharmacological treatment. The mainstream treatments of psychology and pharmacology, despite their efficacy, have limitations due to their nature. Genetic treatment like CRISPR treatment could be a complementary strategy for these mainstream therapies.

Still, how CRISPR should be applied to schizophrenia-related genes is uncertain. Especially when schizophrenia is not only related to genetic factors but also environmental and biological factors. The ethical problem of CRISPR treatment is an outstanding issue for scientists to consider since CRISPR gene-editing of schizophrenia will direct affect neuron cells. Neural cells are quite different from other types of cells because they are parts of the neural system. Treatment on neuronal system might cause uncontrollable aftermaths, if something unexpected occurs during the process. All these problems should be further evaluated before applying CRISPR to treat schizophrenia.

In terms of future research, how CRISPR could be applied to different types of cells should be studied. The neural system is delicate. Whether CRISPR gene editing could function on neuron as expected should be studied first, which could be conducted on animal models first (e.g., mice model). Ensuring the stability of CRISPR on neural-related cells is an essential task. Another future research topic is another gene related to schizophrenia onset. Except for NRG1, several other genes may be the candidates for this psychiatric disease. How these genes result in neural system impairment and whether such mutation could be recovered via CRISPR is a promising subject. Moreover, it might be possible for CRISPR to treat other psychiatric disorders with genetic basis like autism spectrum disorder, bipolar, and depression, if genetic treatment is feasible for schizophrenia.

In conclusion, the progress of schizophrenia-related knowledge enables scientists to easily recognize schizophrenia onset. With the development of genetics, it is possible to study the genetic basis of schizophrenia patients, which could be the breakpoint for novel treatment development. This article might provide a review of the possibility of such treatment.

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