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Review



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Editorial note：*Schizophrenia is one of the most complex psychotic disorders. However，the fundamental nature of schizophrenia remains elusive. Recently，advances in the translational research make researchers begin to rethink the approaches they used for schizophrenia. The basic research which has been focusing on genetic mechanism is turning to integrate the need of clinical diagnosis and treatment. This review focuses on the advances in study of early diagnosis，personalized treatment，environmental risks identification and prevention of schizophrenia. Readers will understand the recent advances and future studies of translational research of schizophrenia in China in these aspects by reading this review.*

Translational research for schizophrenia in Chinese

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Abstract　Schizophrenia is one of the most complex psychotic disorders. Despite years of research，the fundamental nature of schizophrenia remains elusive. Recently，advances in the translational research make researchers begin to rethink the approaches they used for schizophrenia. The basic research which has been focusing on genetic mechanism is turning to integrate the need of clinical diagnosis and treatment. Research emphasis thus will be put on the study of early diagnosis，personalized treatment，environmental risks identification and prevention of schizophrenia. This review will introduce the recent advances and future studies of translational research of schizophrenia in China in these aspects.

Key words　schizophrenia，translational research，China

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Schizophrenia is one of the most common and severe psychotic disorder with complex causes and clinical features. After over a century of research, the fundamental nature of schizophrenia is still poorly understood. In recent years, few breakthroughs have been made in the understanding of the molecular basis of schizophrenia as a result of considerable research related to genome-wide genetic and epigenetic investigation as well as extensive studies at the transcriptional level. Schizophrenia is generally viewed as the result of a complex interaction between numerous predisposing genes and environmental factors affecting prenatal and postnatal neurodevelopment. In the study of how environmental factors and susceptibility genes interact and thus affect the neural development, results so far failed to explain its mechanism despite a number of animal experiments conducted[1]. On the other hand, after about half a century of medication developed from typical antipsychotics to atypical antipsychotics, there is little evidence that the pharmacological treatments have substantially improved outcomes for most people with schizophrenia. Therefore, the research bottleneck and unsatisfactory outcomes of clinical treatment make researchers begin to rethink the approaches they used and seek for new concept for better understanding schizophrenia and new treatment solutions[2].

Recently, the concept of "translational medicine" has been advanced in the field of international medicine. The translational medicine, aims to bridge the gap between basic and clinical research, is a two-way approach used to translate discoveries in the basic sciences into practical applications and to translate the clinical observations to research foci for basic sciences, eventually to translate results from clinical studies into everyday clinical health promotion and disease prevention[3-5]. In China, although the translational medicine is still in the early stage of development, the research of translational medicine is strongly emphasized in many scientific fields and vigorously supported by state grants, thus is becoming the major focus of future research[6]. In the translational research of schizophrenia, the basic research which has been focusing on genetic mechanism is reconsidered to integrate the need of clinical diagnosis and treatment[7]. Efforts thus will be put on the study of early diagnosis, personalized treatment, environmental risk factors identification and disease prevention of schizophrenia, for the purpose to reduce the incidence rate and postpone the onset of schizophrenia and improve the treatment outcomes. Also, multidisciplinary collaboration will be further enhanced to better understanding of the fundamental nature of schizophrenia. This review introduces the recent advances and future studies of translational research of schizophrenia in China about these aspects.

1 Development of molecular diagnostics and personalized medicine

One of the largest problems associated with the ongoing treatment of schizophrenia is the wide variability in patients' clinical response of any given antipsychotic. Identification of factors underlying individual differences in various antipsychotic drugs response is the major aim for researchers. As early as before the start of the NIH roadmap for translational medicine[8], cooperative research units from universities, institutes, hospitals and pharmaceutical companies have been established in China in an effort to search for candidate genes of schizophrenia and genes related to drugs response. Studies about associations between antipsychotic drugs response with genetic polymorphisms of a series of drug target genes, such as 5HTR1A[9], 5HTR3A[10], HTR7[11], DRD2[12], HRH3[13], drug transporters including 5HTT[14], DAT1[15] and drug-metabolizing enzyme including CYP2D6[16], CYP3A4[17] have been conducted. However, there are still some limitations in such studies. The first one is difficulties in replicating finding from association studies from diverse populations, therefore a further confirmation with significant sample sizes will be needed. Second, lack of approaches for molecular classification and stratification of schizophrenia failed to effectively evaluate the dose efficiency underling certain genetic background. Furthermore, most studies are still around single gene analysis in the Chinese population. Given the polygenic nature of schizophrenia, a larger scale identification of genetic variation in multiple genes is essential to develop genetics-based diagnosis and therapeutic tests[18]. Moreover, adopting integrated approaches to investigate genomic, epigenetic and proteomic background represent a unique opportunity for the prediction of response to antipsychotic drugs through investigating molecular factors associated with specific symptoms and side effects. Eventually, such approaches could drive choices of antipsychotic medication based on the likelihood of clinical response according to a particular patient's molecular profile, are leading to a bright future for advances in personalized medicine[19,20].

2 Identification of biomarker for early diagnosis of schizophrenia

The onset of schizophrenia typically occurs in late adolescence or early adulthood. The early symptoms of schizophrenia are subtle and often overlooked by the patients. Difficulties in the early detection cause delayed treatment and lead to poorer long-term outcomes for pa-

tients with schizophrenia. Consequently, there is currently an emphasis on attempting to reduce the incidence of schizophrenia by means of early detection and intervention. Currently, an early clinical diagnosis for very high risk of schizophrenia is based on having attenuated positive symptoms and increased genetic risk (having an ill family member)[21]. However, accurate identification for people with very high risk of developing schizophrenia in preclinical stages presented a much greater challenge. Researchers therefore started to focus on developing combinatorial approaches to seek integrative biological markers for schizophrenia[22]. For example, neuroimaging studies provide compelling evidence of gray matter volume reduction and enlargement of lateral ventricles in patients with schizophrenia. Nikolaos *et al* used structural magnetic resonance imaging to track changes in brain structure at high risk individuals, effectively increased the prediction rate of the patients[23]. In addition, functional magnetic resonance imaging (fMRI) became more widely accepted in studying abnormal regional brain activation in high risk subjects during performance of specific cognitive tasks, thus constituted a powerful tool to explore the predictive cognitive vulnerability markers to discriminate patients from healthy individuals. Shen *et al* developed an analysis method based on machine learning to extract highly discriminative functional connectivity features using fMRI data and applied as classifier to discriminate schizophrenic patients from healthy controls, which achieved a high accuracy rate[24]. Furthermore, combining neuroimaging and genotyping data is expected to lead to a better selection of biomarker[25,26]. However, no such research was reported in China.

Moreover, significant differences in the level of small molecules in central and peripheral systems between schizophrenia and healthy controls have been identified as a result from large-scale gene expression analysis, metabolic and protein profile analysis[27,28]. A series of validation have also been conducted in the Chinese population. For example, researchers found that concentration of S100B protein in the peripheral blood of schizophrenic patients was significantly higher than the control group[29]. Whereas, levels of BDNF[30], antioxidant[31], NGF[32] and IL-2[33] were significantly lower comparing to the control group. However, substantial inter-individual variation in such biomarker profiles makes it difficult to define range of concentration for normal and disease individuals, thus make it impossible for a single biomarker to achieve sufficient specificity as diagnostic marker. Therefore, splitting schizophrenia in homogeneous genetic groups and clinical subphenotypes will be critical in the identification of biological markers. For detect of high-risk individuals, on the other hand, a highly integrated analysis of all types of biomarker assay data and long-term follow-up clinical data should be carried out to find key biomarkers which reflect dynamic alterations related to the disease process.

3 Investigation of environmental risks and prevention of schizophrenia

Accumulating evidence from recent studies suggests that environmental risk factors play significant role in the etiology of schizophrenia and epigenetic mechanism is involved in schizophrenia. Epidemiological studies in the West indicate that prenatal exposure to infection, toxin, nutritional deficiency and stress are associated with later-life schizophrennia[34,35]. Other common risk factors for schizophrenia include low socio-economic status, childhood trauma and adolescent depression[36,37]. In China, studies of schizophrenia after the Chinese famine proved that prenatal exposure to severe nutritional deficiency may increase the risk of schizophrenia[38-40]. Other surveys, however, lack precision at the individual hospital level or in limited regions. The differences in the socio-economic environments, eating habit, early care and education system between China and the West highlight the importance of the socio-cultural factors with Chinese characteristics in the onset and course of the disorder. In addition, Chinese researchers reported an earlier onset age and a rising incidence of schizophrenia[41], which is drawing the attention to the issues rising from the drastically social and environmental changes in recent years. National surveys in China are therefore urgently needed to further explore the prevalence and risk factor of schizophrenia in China. With the results of national wide investigation, novel preventive strategies will be developed to eliminate of putative risk factors, reduce the incidence of this disorder and eventually improve the health outcomes.

Developing translational animal models to mimic human behavioral tasks altered in schizophrenia and to further quantitatively measure the environmental effect on the neurodevelopment have been challenging[42]. Related research in China is still on the beginning. Li et al found that early exposure to virus in mice in embryonic development caused marked enlargement of lateral ventricles in adulthood, supported the hypothesis that there is a causal relationship between prenatal immune challenge and emergence of ventricular abnormalities relevant to schizophrenia in adulthood[43]. In addition, studies of the dynamic interaction between epigenetic factors and susceptibility genes of schizophrenia are still in a relatively early phase in China. Extensive investigation of epigenetic al-

teration in schizophrenia needs to be conducted in the future, which is likely to lead to the development of epigenetic therapy.

4 A multi-disciplinary approach to enhance translational research of schizophrenia in the future

The complexity in the fundamental nature of schizophrenia makes that any single research will be limited and one-sided. The future research will be conducted at the multi-systemic level and emphasize the importance of collaboration between research units. First of all, overall planning should be carried out and the division of labor with individual research unit should be implemented for the purpose of a nation-wide epidemiology study of schizophrenia as well as the expansion of the clinical data and sample banks. Secondly, a multi-disciplinary approach based on knowledge interactions between neurobiology, immunology, physiology, biophysics and other disciplines should be developed to find new biomarkers to aid the diagnosis and evaluate the treatment effect of schizophrenia. Furthermore, a network should be built with the aid of bioinformatics and computational science to integrate the countless data from genomics, proteomics, metabolomics, and neuroimaging for a better understanding of the etiology of schizophrenia. In short, how to translate the comprehensive results of basic research in schizophrenia into simplified standards of conduct and procedures for clinical need is the main object of translational research for schizophrenia in China, which will be fulfilled under the co-efforts of the Chinese researchers.

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