Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

The role of schizophrenia susceptibility candidate gene miR137 in psychiatric diseases

Autor: Ping Zhang
Institut / Klinik: Zentralinstitut für Seelische Gesundheit Mannheim (ZI)
Doktorvater: Prof. Dr. D. Bartsch

Background: Schizophrenia (SCZ) is a severe psychiatric disorder that affects approximately 1% of the worldwide population. It constitutes a major socioeconomic burden for the local health systems. The exact etiology of SCZ is still unknown. In addition to environmental factors, genetic factors are assumed to play an important role in the development of the SCZ. It has a high heritability and involves multiple candidate genes. Among them, micro RNA 137 (miR137) has been identified to be a candidate gene for SCZ susceptibility by a large-scale genome-wide association study (GWAS) in 2011 with the strongest genetic association. After that, a series of studies suggest that miR137-mediated dysregulation is a previously unknown etiologic mechanism in SCZ. In order to investigate the role of miR137 in SCZ *in vivo*, a transgenic rat line constitutively overexpressing miR137 was generated in our lab.

Methods: Firstly, in order to confirm the generation of miR137 overexpression transgenic rat (miR137 TG) model, polymerase chain reaction (PCR) was performed to verify the deletion of STOP cassette in the conditional miR137 transgenic rat ($miR137^{cond}$) line. Real-time reverse transcription-PCR (qRT-PCR) was used for the quantification of miR137 overexpression in the brain of miR137 TG rats. In order to verify the expression of L10a-eGFP in the brain of miR137 TG rats, both DAB staining and immunofluorescent assay were carried out. Then neurochemical analyses of punched tissues from different brain regions were performed, trying to explain the behavioral deficits of miR137 TG rats. Furthermore, microarray analyses were performed to investigate the regulation of target genes of miR137.

Results: PCR analyses verified the deletion of STOP cassette in the $miR137^{cond}$ line, thus the generation of miR137 overexpression rat model was confirmed. qPCR revealed significant increase of miR137 mRNA in miR137 TG rats to about 13.7 fold of wild type levels. Both DAB staining and immunofluorescent assay demonstrated the ubiquitous expression pattern of L10a-eGFP in the whole brain of miR137 TG rats. In neurochemical analyses, a significant decrease of noradrenalin concentration in prefrontal cortex in miR137 TG rats was observed. The dopamine, 3, 4-dihydroxyphenylacetic acid and homovanillic acid concentrations in amygdala in miR137 TG rats were significantly decreased. A significant decrease of serotonin concentration in caudate putamen, a significant increase of 5-hydroxyindoleacetic acid concentration in nucleus accumbens, caudate putamen, hippocampus and ventral tegmental area in miR137 TG rats was observed. The serotonin /5-hydroxyindoleacetic acid concentration ratio in caudate putamen and hippocampus was significantly decreased. In microarray analyses, 24 up-regulated (>=1.5 fold) and 21 down-regulated (<=－1.5 fold) genes were identified in miR137 TG rats with significance ($p<0.05$).

Conclusions: The miR137 overexpression transgenic rat line which has been successfully generated in our lab is a new and valid translational SCZ-relevant psychiatric disease model. These molecular biological, morphological and neurochemical data further supplement the full view of this model and its role in SCZ.