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Research Report

Temporal lobe epilepsy induces differential expression of hippocampal miRNAs including let-7e and miR-23a/b

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ABSTRACT

To understand the role of miRNAs in the molecular mechanisms of temporal lobe epilepsy (TLE), we investigated the changes in microRNA (miRNA) expression profiles of chronic TLE rat models. MiRNAs microarray analysis results showed that 125 miRNAs were detected in the hippocampus of lithium-pilocarpine-induced TLE rats and normal rats. Compared with normal rats (control group), 23 of the 125 miRNAs were expressed differentially in TLE rats including 5 down-regulated miRNAs (let-7e included) and 18 up-regulated miRNAs (miR-23a/b included). Furthermore, let-7e and miR-23a/b analysis in rat hippocampus were performed by real-time quantitative polymerase chain reaction at 0 h, 1 h, 6 h, 12 h, 24 h, 2 days, 7 days,10 days, 30 days,50 days after induction of status epilepticus (SE). let-7e was detected down-regulated expression at 0 h, 1 h, 6 h, 2 days, 7 days, 50 days after SE and up-regulated expression at 12 h, 24 h, 10 days, 30 days after SE, which was significantly up-regulated expression at 24 h after SE (10.49 folds, $P<0.01$). miR-23a/b was detected down-regulated at 0 h, 1 h, 6 h, 12 h, 2 days, 7 days, 10 days, 30 days after SE and significantly up-regulated at 24 h (4.49 folds $P<0.01$), 50d (2.4 folds, $P<0.01$) after SE. TLE alters the expression levels of a subset of miRNAs in the hippocampus and these deregulated miRNAs may be involved in the pathogenesis of epilepsy directly or indirectly. Also the temporal change of the let-7e and miR-23a/b expression in the epileptogenesis indicated their underlying functions on TLE.

1. Introduction

Temporal lobe epilepsy (TLE) is one of the most common medically intractable neurological disorders. The pathogenesis of TLE is associated with the structural and functional changes of hippocampus and limbic system, which is characterized by selective neuronal cell loss and mossy fiber sprouting (Thom, 2004, Riban et al, 2002, Shibley and Smith,

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Abbreviations: AD, Alzheimer's disease; miRNA, microRNA; qPCR, quantitative polymerase chain reaction; SE, status epilepticus; TLE, temporal lobe epilepsy; TLR, toll-like receptor

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2002). However, the exact molecular pathogenic mechanism of TLE still remains unclear.

MicroRNAs (miRNAs) represent a family of small (22–24 nucleotides), endogenous noncoding RNAs, which post-transcriptionally regulate target gene expression by binding complementary sequences in the 3′-untranslated region (UTR) of target messenger RNAs (mRNAs), either mediating translational repression or directing mRNA cleavage(Obernosterer et al, 2006). Increasing evidence highlights the functions of miRNAs participating in the underlying molecular mechanism in neurological diseases such as Parkinson's disease and Alzheimer's disease (Lukiw, 2007; Hébert and De Strooper, 2007). Recently, several miRNAs have been found to be differentially expressed in TLE models (Aronica et al, 2010, Liu et al, 2009).

In this study, we found two miRNAs, let-7e and miR-23a/b to be differentially expressed in the hippocampi of TLE model rats. let-7e has been regarded as a post-transcriptional regulator during neural cell specification (Wulczyn et al, 2007). The down-regulated expression of let-7e was reported in many neoplastic diseases and neurological disorders (Dahiya et al, 2008; Li et al, 2009; Davis et al, 2007), but the definite functions of let-7e are still unknown. miR-23a/b was proven to be restricted to astrocytes during neural specification (Smirnova et al, 2005) and one of the mediators regulating cell growth and apoptosis pathways (Cheng et al., 2005). Also miR-23a/b was identified as a negative regulator of lamin B1 contributing to the process of oligodendroglia development and myelin formation (Lin and Fu, 2009).

To understand the role of miRNAs in the molecular mechanisms of temporal lobe epilepsy (TLE), we first investigated the unique miRNA expression profiles in the hippocampus of lithium-pilocarpine-induced chronic TLE rats models compared to normal rats. Furthermore, in order to study how these differentially expressed miRNAs dynamically changed during the epileptogenesis course, we detected the expression of let-7e and miR-23a/b (they were verified as a down-regulated expression miRNA and a up-regulated expression miRNA in the chronic stage of TLE in our study) in the hippocampus of TLE rats at different time points after status epilepticus (SE) (Fig. 1).

2. Results

2.1. *miRNA microarray analysis*

A miRNA microarray chip (including 349 unique miRNA probes) was used to detect the control and TLE rat ($n=3$) samples 60 days

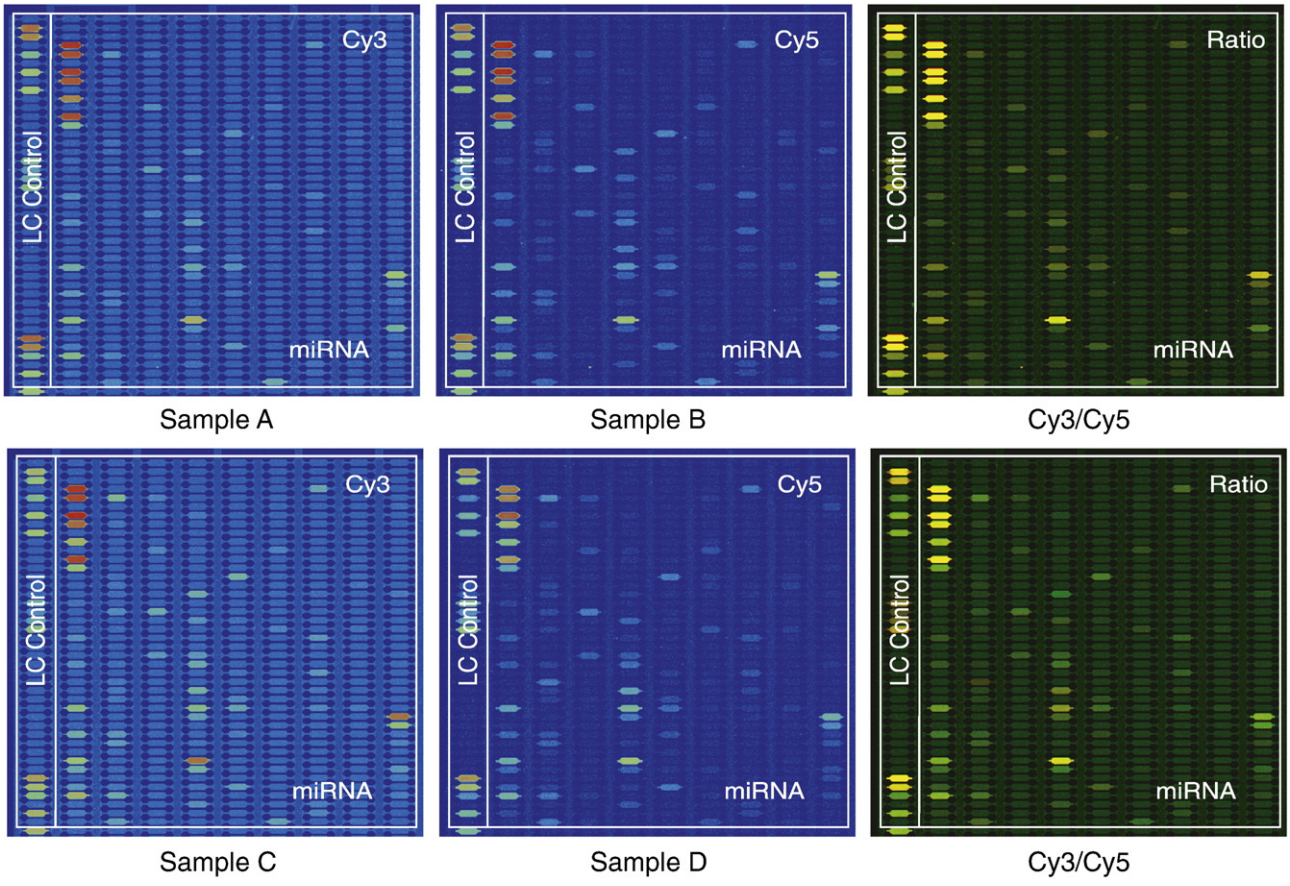

Fig. 1 – Representative regions of miRNA microarray images. Sample A depicts normal rat and Samples B, C, D represent TLE rats (2 months post-SE). From Cy3 and Cy5 images we can directly read miRNA profiles and from the ratio images we may get a quick sense of differential expressions between the corresponding samples. In the Cy3/Cy5 ratio image, when Cy3 level is higher than Cy5 level the color is green; when Cy3 level is equal to Cy5 level the color is yellow; and when Cy5 level is higher than Cy3 level the color is red.