

Spontaneous Running Wheel Improves Cognitive Functions of Mouse Associated with miRNA Expressional Alteration in Hippocampus Following Traumatic Brain Injury

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Abstract Traumatic brain injury (TBI) is an insult to the brain that results in impairments of cognitive and physical functioning. Both of human research and animal studies demonstrate that spontaneous exercise can facilitate neuronal plasticity and improve cognitive function in normal or TBI rodent models. However, the possible mechanisms underlying are still not well known. We postulated that spontaneous running wheel (RW) altered microRNA (miRNA) expressions in hippocampus of mice following TBI, which might be associated with the improvement in cognitive functions. In the present study, acquisition of spatial learning and memory retention was assessed by using the Morris water maze (MWM) test on days 15 post RW exercise. Then, microarray analyses in miRNA files were employed, and the expressional changes of miRNAs in the hippocampus of mice were detected. The results showed that spontaneous RW exercise (i) recovered the hippocampus-related cognitive deficits induced by TBI, (ii) altered hippocampal expressions of miRNAs in both of sham and TBI mice, and (iii) miR-21 or miR-34a was associated with the recovery process. The present results indicated that an epigenetic mechanism might be involved in voluntary exercise-induced cognitive improvement of mice that suffered from TBI.

Keywords Traumatic brain injury · Spontaneous running wheel · Cognitive functions · miRNA

Introduction

The majority of deaths and disabilities from trauma occur with traumatic brain injury (TBI). TBI is known to result in deficits in spatial learning and memory. After TBI, cognitive impairments, such as problems with memory, orientation, attention, executive functions, and problem-solving, are often prominent and long lasting (Dikmen et al. 2009). These cognitive deficits affect the recovery of motor function and affect daily life.

Many studies have reported that physical exercise is the most effective method to improve cognitive function and brain health. It is suggested that spontaneous exercise may be therapeutic in the management of CNS injury, by reducing the degree of initiatory damage, limiting the degree of secondary neuronal death, improving neuronal plasticity and cognitive function, promoting recovery, and promoting neural repair as well as behavioral rehabilitation (Griesbach et al. 2009; Itoh et al. 2011). Though it is well demonstrated that practice of physical exercise increased adult hippocampal neurogenesis and enhances behavioral performance in rodents, the possible mechanisms underlying are still not well known (VanLeeuwen et al. 2010).

Studies on the mechanisms demonstrate that exercise (i) suppresses neuronal and hippocampal apoptosis; (ii) inhibits astrocytic reactions; (iii) increases neural stem cell proliferation and neurogenesis; (iv) attenuates proteasome activity; (v) decreases the protein levels of myelin-associated glycoprotein (MAG) and Nogo-A; and (vi) reduces the productions of free radicals and upregulates Na(+) or K(+)-ATPase enzyme activity in the brain (Griesbach et al. 2009; Szabo et al. 2010; Itoh et al. 2011; Truettner 2013). Recent reports also reveal

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that physical exercise modulates the function of the nervous system through epigenetic alterations to DNA, such as histone modifications, DNA methylations, expression of microRNA (miRNA) regulations, and changes of the chromatin structure (Ntanasis-Stathopoulos et al. 2013). It is well established that miRNAs are very important regulators of biological processes, such as development, cellular differentiation, and tumor generation. As a high throughput global analysis tool for detecting miRNA expression profiling, miRNA microarray is usually employed in recent researches and will facilitate the study of the biological function of miRNAs. However, the alterations of miRNA profiles induced by spontaneous exercise after TBI in the hippocampus are unknown.

The present study detected the expressional changes of miRNAs in the hippocampus in TBI mice after voluntarily exercise training by using microarray analyses. Mice were subjected to TBI and housed with voluntarily access to running wheel (RW) or immobilized RW for 2 weeks and then preceded for experimental analysis. Acquisition of spatial learning and memory retention was assessed using the Morris water maze (MWM) test on days 15 post RW exercise. Then, the hippocampus was collected and subjected to microRNA analysis.

Material and Methods

Animal Grouping

The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (Bethesda, MD, USA; NIH Publication No. 85-23, revised 1996).

Adult male C57BL/6J mice (4–4.5 months) were purchased from Kunming Medical University. Mice were housed with ad libitum access to food and water and exposed to a 12-h light/dark cycle.

The mice were group housed and allowed to acclimatize to their environment for 1 week prior to commencement of the experiments. Then, animals were divided into two groups: animals that received sham operation (sham) and animals that received a brain injury (TBI) described as following. Both of sham and TBI mice were then individually housed in cages equipped with a RW each (sham-runners and TBI-runners). The sedentary control, sham-non-runners, and TBI-non-runners were exposed to immobilized RW ($N=7$). The cages equipped with RW (diameter=12 cm, width=5 cm; Nalge Nunc International, Rochester, NY, USA) used for the voluntary exercise rotated freely and was attached to a receiver that monitored the number of revolutions (Vital Viewer Data Acquisition System software, Mini Mitter, Sunriver, OR, USA). The mice were allowed to exercise ad libitum in individual cages with unlimited access to the running wheel.

The mean number of revolutions was calculated for each night (7 p.m. to 7 a.m.), given that this was the most active period.

TBI Model

Animals underwent anesthesia with 3.6 % chloral hydrate by intraperitoneal injection and fixed on a stereotactic platform. Following skull was opened, the corticomotor area in cerebral cortex exposed. A mouse model of TBI was developed using a device that produces controlled cortical impact (CCI), permitting independent manipulation of tissue deformation and impact velocity. The left parietotemporal cortex was subjected to CCI [2 mm tissue deformation and 6.0 m/s (moderate)] or sham surgery (Rosi et al. 2012). After injury, the incision was closed with interrupted 6-0 silk sutures, anesthesia was terminated, and the animal was placed into a heated cage to maintain normal core temperature for 45 min post-injury. All animals were monitored carefully for at least 4 h after surgery and then daily. Surgeries for individual studies were performed by the same model expert within a short timeframe (3 days) to minimize experimental variation, with control and treated groups randomly intermingled.

Behavior Functional Evaluations

A MWM paradigm was employed to assess spatial learning by training mice to locate a hidden, submerged platform using examination visual information, and conducted exactly as described previously (Loane et al. 2009). The test was conducted at 15–20 days after injury immediately followed running, and each mouse was tested for three trials per day for six consecutive days. The time required (escape latency) to find the hidden platform with a 90-s limit was recorded by a blinded observer and tracked using TOPSCAN (Clever Sys Inc.). A probe trial of 90 s was given 1 day after the final learning trial. The percentage of time spent in the quadrant where the platform was previously located was recorded.

miRNA Microarray Analysis

The 7th generation of miRCURY™ LNA Array (v.18.0) (Exiqon) contains 3,100 capture probes, covering all human, mouse, and rat microRNAs annotated in miRBase 18.0, as well as all viral microRNAs related to these species. In addition, this array contains capture probes for 25 miRPlus™ human microRNAs.

Mice from the four groups ($n=3$) were killed by cervical dislocation and decapitated. Hippocampus were removed quickly (within 60 s) and frozen in -70 °C isopentane until processed for further analysis. After carefully rinsing in cooled PBS, the tissues were homogenized on ice in TRIzol (Invitrogen, Carlsbad, CA). Total RNA was isolated using

TRIzol and miRNeasy mini kit (QIAGEN) according to manufacturer's instructions, which efficiently recovered all RNA species, including miRNAs. RNA quality and quantity were measured by using nanodrop spectrophotometer (ND-1000, Nanodrop Technologies), and RNA integrity was determined by gel electrophoresis.

After RNA isolation from the samples, the miRCURY™ Hy3™/Hy5™ Power labeling kit (Exiqon, Vedbaek, Denmark) was used according to the manufacturer's guideline for miRNA labeling. After stopping the labeling procedure, the Hy3™-labeled samples were hybridized on the miRCURY™ LNA Array (v.18.0) (Exiqon) according to array manual. Following hybridization, the slides were achieved, washed several times using Wash buffer kit (Exiqon), and finally dried by centrifugation for 5 min at 400 rpm. Then, the slides were scanned using the Axon GenePix 4000B microarray scanner (Axon Instruments, Foster City, CA).

Scanned images were then imported into GenePix Pro 6.0 software (Axon) for grid alignment and data extraction. Replicated miRNAs were averaged, and miRNAs with intensities >30 in all samples were chosen for calculating normalization factor. Expressed data were normalized using the median normalization. After normalization, differentially expressed miRNAs were identified through fold-change filtering. Hierarchical clustering was performed using MEV software.

Statistical Analysis

Values are means±SE. Between- and within-group differences were tested using a repeated-measures ANOVA. Post hoc paired *t* tests were used to assess intragroup interaction effects between groups when the ANOVA models produced significant main effects. Significance level was predetermined to be $P<0.05$ unless otherwise indicated. All analyses were done with SPSS version 14.0 software.

Results

Behavior Evaluation

In non-injured mice, the voluntary runners (sham-runners) showed more preference to the hidden platform than the non-runners (sham-non-runners) from the 2nd day (16dpo) to the end of the test (Fig. 1, $P<0.05$). However, all mice that suffered from TBI showed significantly delayed in escape latency from the 2nd day (16dpo) of the test, when compared with that of non-injured mice ($P<0.05$). Among the injured mice, the runners (TBI-runners) spent fewer time to find the platform than that of TBI-non-runners ($P<0.01$) from 16dpo to 20dpo (Fig. 1).

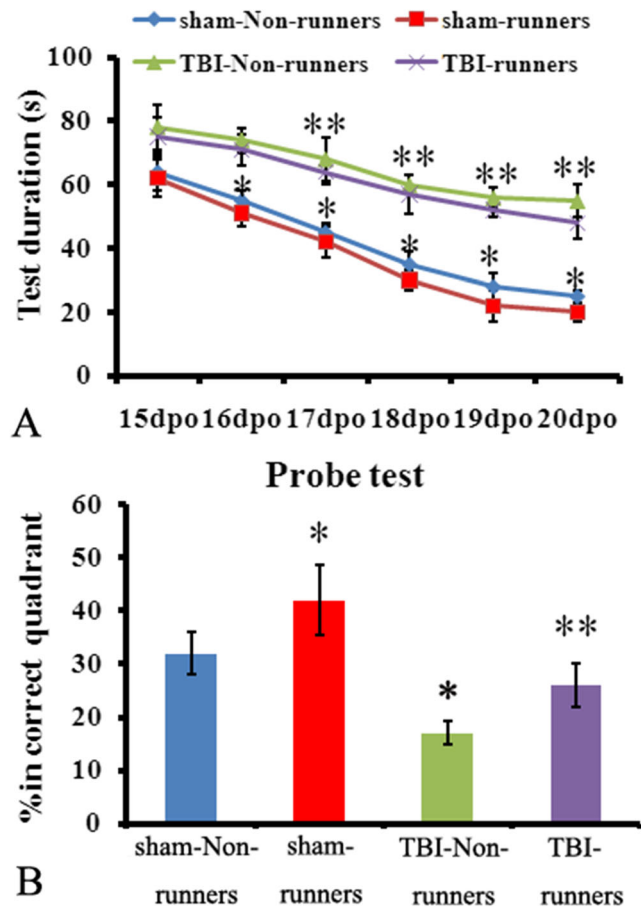
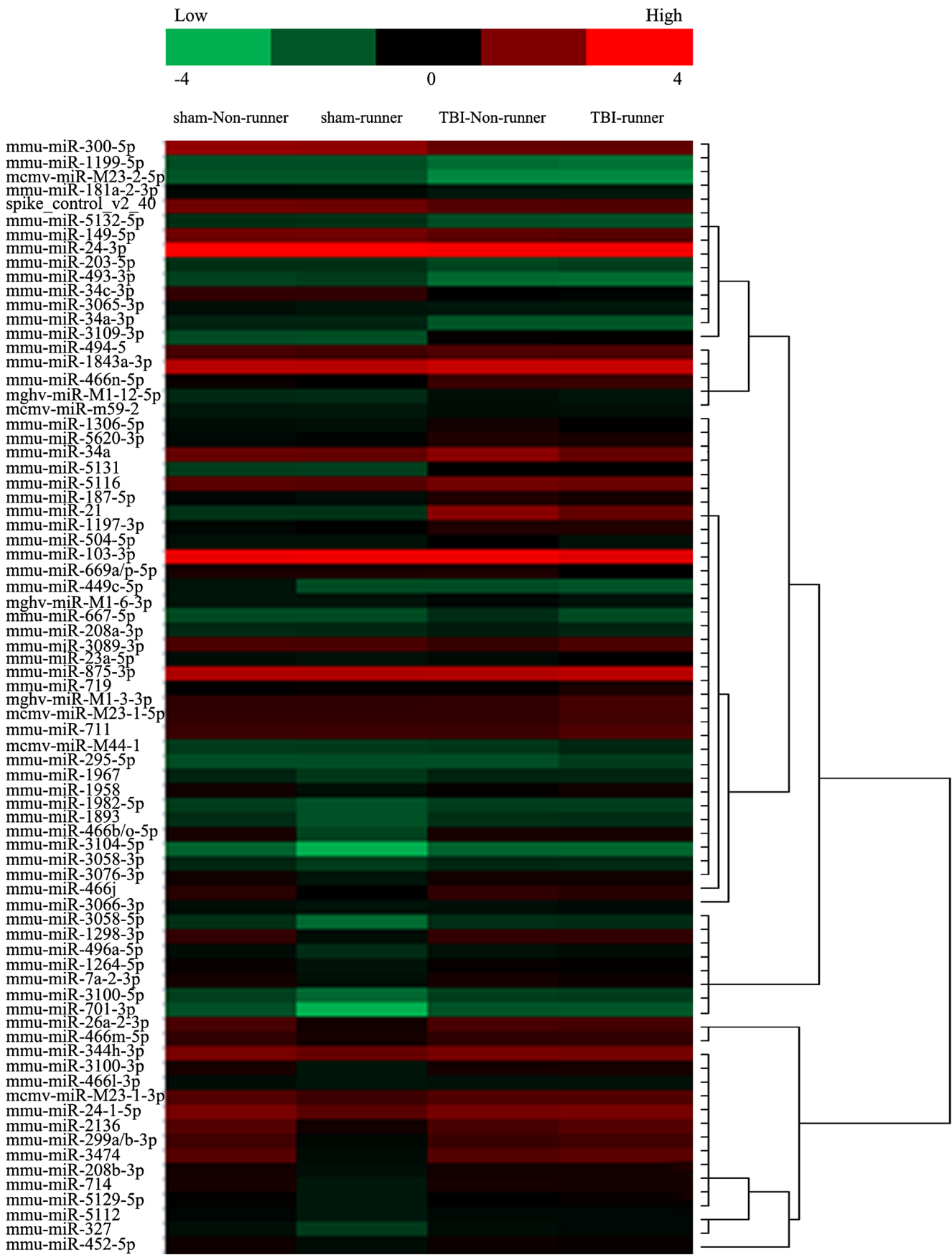


Fig. 1 Behavior changes evaluated by MWM test. (a) The escape latency (s) after hidden platform. (b) The percent in the target quadrant of mice from the four groups. Mice in injured groups had significant learning impairments on all 6 days of the test, whereas the behavior of injured runner group mice was distinguishable from injured non-runner group mice ($P<0.05$). Runner group mice showed more preference to either the target platform or to the correct quadrant than that of non-runner group in the test ($P<0.05$). Values plotted are means±SD ($n=8$). Number symbol, vs injured non-runners; asterisk, vs non-injured runners

Voluntary Exercise Induced miRNA Differential Expressions in Hippocampus of TBI Mice

To identify differentially expressed miRNA, we performed a fold-change filtering among the samples obtained from the four groups. The heat-map of the miRNA expression profile in these groups was generated by hierarchical clustering. The color gradient of the heat-map represents the log of the relative expression of miRNAs to their mean expression over all

Fig. 2 The heat-map of hierarchical cluster dendrogram of significant differentially expressed miRNAs of the groups. The heat-map shows the hierarchical cluster dendrogram of significant differentially expressed miRNAs of the sham-non-runner and sham-runner groups and TBI-non-runners and TBI-runner samples ($P<0.01$). The differentially expressed miRNAs were listed in Tables 1, 2, and 3. Red and green color scale represents high and low expression, respectively



conditions with red indicating overexpression and green indicating underexpression. Hierarchical cluster analysis of these miRNAs demonstrated that either the non-runners or runners from sham or TBI groups each expressed a shared subset of miRNAs (Fig. 2).

Effects of TBI on the alterations of miRNA expression profiles in sham-operated or TBI mice were detected. In the non-runners, expression levels of 27 miRNAs were different between sham and TBI injured mice, in which 13 miRNAs were upregulated and 14 miRNAs were downregulated ($P < 0.05$, Table 1 and Fig. 2).

As shown in Table 2 and Fig. 2, RW exercise following TBI differentially changes the level of several miRNAs, upregulating the level of some of them and downregulating the level of others. The data showed that 18 miRNAs were differently modulated between the TBI-non-runner and TBI-runner groups. Among which, eight miRNAs were upregulated, and ten miRNAs were downregulated ($P < 0.05$, Table 2, Fig. 2). We also identified 32 miRNAs that were differently

Table 1 Differentially expressed miRNAs between sham and TBI mice

miRNA ID	Fold change (sham vs TBI)	<i>P</i> value
mmu-miR-300-5p	2.38	0.007232
mmu-miR-1199-5p	3.42	0.005271
mcmv-miR-M23-2-5p	7.19	0.000454
mmu-miR-181a-2-3p	1.79	0.023162
spike_control_v2_40	1.71	0.020613
mmu-miR-5132-5p	3.52	0.004516
mmu-miR-149-5p	1.37	0.023161
mmu-miR-24-3p	1.23	0.035644
mmu-miR-203-5p	2.34	0.007235
mmu-miR-493-3p	4.57	0.000513
mmu-miR-34c-3p	2.67	0.006323
mmu-miR-3065-3p	1.39	0.010235
mmu-miR-34a-3p	6.85	0.006596
mmu-miR-3109-3p	0.05	0.001323
mmu-miR-494-5p	0.88	0.005549
mmu-miR-1843a-3p	0.73	0.006054
mmu-miR-466n-5p	0.41	0.007139
mghv-miR-M1-12-5p	0.37	0.009231
mcmv-miR-m59-2	0.63	0.005365
mmu-miR-1306-5p	0.42	0.006215
mmu-miR-5620-3p	0.39	0.008132
mmu-miR-34a*	0.38	0.006356
mmu-miR-5131	0.09	0.000646
mmu-miR-5116	0.61	0.004024
mmu-miR-187-5p	0.40	0.006921
mmu-miR-21*	0.01	0.000364
mmu-miR-1197-3p	0.42	0.007024

Table 2 Differentially expressed miRNAs between TBI-non-runner and TBI-runner groups

miRNA ID	Fold change (TBI-non-runners vs TBI-runners)	<i>P</i> value
mmu-miR-504-5p	1.981962	0.007295
mmu-miR-103-3p	1.333085	0.005369
mmu-miR-669a-5p/mm-miR-669p-5p	1.7031	0.005923
mmu-miR-449c-5p	1.343683	0.005517
mghv-miR-M1-6-3p	1.515913	0.006054
mmu-miR-21*	2.014291	0.002308
mmu-miR-667-5p	3.504043	0.000104
mmu-miR-208a-3p	1.470457	0.006032
mmu-miR-3089-3p	0.68387	0.007235
mmu-miR-34a*	0.856563	0.008136
mmu-miR-23a-5p	0.674392	0.006346
mmu-miR-875-3p	0.841638	0.007235
mmu-miR-719	0.707759	0.006596
mghv-miR-M1-3-3p	0.693971	0.005323
mcmv-miR-M23-1-5p	0.751136	0.007901
mmu-miR-711	0.679609	0.006054
mcmv-miR-M44-1	0.498651	0.004039
mmu-miR-295-5p	0.497307	0.003217

modulated between the sham-non-runner and sham-runner groups, in which 20 miRNAs were upregulated, and 12 miRNAs were downregulated ($P < 0.05$, Table 3 and Fig. 2). We focused on the two miRNAs, miR-21 and miR-34a, which were different between the sham-non-runner and TBI-non-runner groups, as well as between the TBI-non-runner and TBI-runner groups (Tables 1 and 2, Fig. 2).

Discussion

The present data showed that spontaneous RW exercise (i) recovered the hippocampus-related cognitive deficits associated with TBI and (ii) induced hippocampal expression changes in miRNAs between sham and TBI mice model, as well as between TBI with spontaneous RW exercise and TBI-non-runner groups. These results indicated that miRNA modulation mediated by voluntary RW exercise might be involved in the cognitive improvement of mice that suffered from TBI.

Our MWM results showed that TBI produced significant and irreversible long-term deficits in cognitive abilities of mice, which is consistent with previous study (Ettenhofer and Barry 2012; Zohar et al. 2003). However, the runners that received voluntary wheel-running exercise ameliorated their cognitive performance in learning the MWM following TBI in the present study. Reports establish that cognitive

Table 3 Differentially expressed miRNAs between sham-non-runners and sham-runners groups

miRNA ID	Fold change (sham-non-runners vs sham-runners)	<i>P</i> value
mmu-miR-1967	2.188935	0.003221
mmu-miR-1958	2.565155	0.003019
mmu-miR-1982-5p	2.323445	0.003123
mmu-miR-1893	4.316719	0.002013
mmu-miR-466b-5p/ mmu-miR-466o-5p	22.44289	0.000004
mmu-miR-3104-5p	21.37279	0.000038
mmu-miR-3058-3p	2.352078	0.003101
mmu-miR-3076-3p	2.997281	0.002912
mmu-miR-466j	2.184315	0.003235
mmu-miR-3066-3p	1.316873	0.008017
mmu-miR-3058-5p	9.848381	0.000446
mmu-miR-1298-3p	4.507181	0.001235
mmu-miR-496a-5p	3.471840	0.002196
mmu-miR-1264-5p	2.477477	0.003323
mmu-miR-7a-2-3p	2.676722	0.003901
mmu-miR-3100-5p	5.133896	0.001054
mmu-miR-701-3p	46.20254	0.000001
mmu-miR-26a-2-3p	2.638082	0.003077
mmu-miR-466m-5p/ mmu-miR-669m-5p	1.707838	0.007554
mmu-miR-344h-3p	1.394329	0.007643
mmu-miR-3100-3p	3.475755	0.002015
mmu-miR-466l-3p	0.757204	0.006123
mcmv-miR-M23-1-3p	0.653652	0.005023
mmu-miR-24-1-5p	0.547279	0.004356
mmu-miR-2136	0.299486	0.002321
mmu-miR-299a-3p/ mmu-miR-299b-3p	0.230639	0.002136
mmu-miR-3474	0.131734	0.001026
mmu-miR-208b-3p	0.396877	0.002931
mmu-miR-714	0.266016	0.002513
mmu-miR-5129-5p	0.384892	0.002813
mmu-miR-5112	0.485557	0.003954
mmu-miR-327	0.174051	0.001135
mmu-miR-452-5p	0.462897	0.004056

dysfunctions are frequently associated with impaired hippocampal function, which could be improved by early rehabilitation both in TBI patients and animals (Wilde et al. 2007; Andelic et al. 2012). Previous evidences also revealed exercise (i) increases the number of new neurons and regulates levels of neurogenesis; (ii) prevents and protects from brain damage; and (iii) regulates anatomical changes that support brain plasticity through its effects on genes encoding for neurotrophins and other proteins (Cotman and Berchtold 2002; Koo et al. 2013). Though it is well demonstrated that

practice of physical exercise increased adult hippocampal neurogenesis and enhances behavioral performance in rodents, the possible mechanisms underlying are still not well known (VanLeeuwen et al. 2010). We proposed an epigenetic mechanism might be involved in voluntary RW exercise-induced cognitive amelioration of mice that suffered from TBI.

MicroRNAs (miRNAs) are an important class of non-coding regulatory RNAs providing an epigenetic mechanism for the regulation of protein expression levels of target genes. It is demonstrated that miRNAs play an imperative role in the maintenance of healthy cellular function mainly by binding to their target mRNAs, resulting in mRNA degradation or preventing protein translation (Zacharewicz et al. 2013). The primary role of miRNAs is to specifically inhibit protein expression, and this can be achieved either by degrading specific mRNA species or by repressing protein translation (Humphreys et al. 2005). Overall, mRNA degradation accounts for the majority of miRNA activity.

Previous researches revealed that exercise significantly altered a number of miRNAs involved in monocyte functions associated with vascular health (Radom-Aizik et al. 2014) and in cardiovascular adaptation processes after endurance exercise (Mooren et al. 2014). Microarray studies in animal models of TBI have also revealed significant changes in miRNA expression within the hippocampus of rodent after a TBI (Hu et al. 2012; Redell et al. 2009). Exercise following spinal cord injury (SCI) has shown promise as a means to improve functional recovery, and research suggests that miRNAs can mediate this recovery process (van den Brand et al. 2012).

However, there were few studies that revealed the hippocampus expressional alterations of miRNAs induced by voluntary RW exercise following TBI in mice. Our data showed that there were numerous differential expressions of miRNAs in hippocampus between injured and sham mice, as well as between TBI-runners and TBI-non-runners. Hierarchical cluster analysis for miRNA profiles in this study suggesting an epigenetic mechanism may help elucidate the procedures involved in exercise-related improvement in cognitive functions of mice that suffered from TBI.

Interestingly, the present data showed the expressions of miR-21 and miR-34a upregulated in injured non-runners, which were downregulated by voluntary RW exercise in TBI-runners. Previous reports showed upregulated miR-21 expression in the hippocampus and cerebral cortex in rodent after TBI, suggesting that miR-21 could be involved in the intricate process of TBI course (Redell et al. 2011; Rosi et al. 2012). Moreover, others have demonstrated that overexpressed miR-21 in transgenic mice attenuated the beneficial hypertrophic response to SCI, whereas inhibition of miR-21 augmented the astrocytic response after SCI (Bhalala et al. 2012). miR-21 targets and blocks the pro-apoptotic

protein programmed cell death protein 4 and PTEN, which is a negative regulator of the AKT-mammalian target of rapamycin (mTOR) pathway involved in regeneration of neurons after injury (Redell et al. 2009). We proposed that voluntary RW exercise induced the cognitive improvement of TBI mice, might be resulted from miR-21 regulation in hippocampal.

miR-34a, which is originally discovered as a potential tumor suppressor that is downregulated and induces apoptosis in neuroblastoma cells, is subsequently shown to be a transcriptional target of p53 protein (Welch et al. 2007; Raver-Shapira et al. 2007). In addition, the role of p53 is associated with cognitive robustness, by increasing the survival of neurosphere regulating glucose metabolism, as well as neuronal apoptosis, eliminating deleterious, damaged neurons to make room for neurogenesis in the brain (Roemer 2010; Meletis et al. 2006). It is also demonstrated that p53-dependent apoptotic mechanisms underpin the neuronal and cognitive losses accompanying mild TBI (Rachmany et al. 2013). Given the fact that voluntary RW exercise reversed the upregulation of miR-34a after TBI, our data indicated that the spontaneous RW cognitive induced improvement in TBI mice might be through a miR-34a/p53 regulated way. However, further investigation is necessary.

Given these, we proposed that spontaneous RW following TBI induced improvement in cognitive function through miRNAs alteration in the hippocampus of mice. The present data also suggested that miR-21 or miR-34a either alone or in combination with other miRNAs was associated with this recovery process. However, further experiments are needed to determine the acute roles and the possible mechanisms underlying.

Disclosure No competing financial interests exist.

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