Original paper

Folia Neuropathologica

LncRNA HOTAIR in exercise-induced neuro-protective function in Alzheimer's disease

Jianxia Lu[1,2*], Lihua Liu[1,3*], Jin Chen[2], Juan Zhi[2], Jiabin Li[4], Le Li[2], Zhongli Jiang[1]

[1]Department of Rehabilitation Medicine, the Affiliated Sir Run Run Hospital of Nanjing Medical University, Nanjing, China, [2]School of Rehabilitation, Jiangsu Vocational College of Medicine, Yancheng, China, [3]Department of Neurology, Jurong Hospital Affiliated to Jiangsu University, Jurong People's Hospital, Jiangsu, China, [4]Department of Rehabilitation Medicine, the First People's Hospital of Yancheng City, Yancheng, China

[*]*Jianxia Lu and Lihua Liu contributed equally to this work.*

Folia Neuropathol 2022; 60 (4): 414-420 *DOI: https://doi.org/10.5114/fn.2022.118961*

Abstract

Introduction: *Exercise is effective in Alzheimer's disease (AD), which is characterized by neuro-degenerative progress with increasing morbidity. The present study aimed to explore whether HOTAIR participated in the regulation of exercise in AD.*
Material and methods: *A relative expression of serum HOTAIR was detected using quantitative real-time polymerase chain reaction (PCR). The diagnostic significance of HOTAIR on distinguishing AD patients was evaluated by receiver operating characteristic (ROC) curve. Correlations between HOTAIR expression and Mini-Mental State Examination (MMSE) score or Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) score were analyzed with Pearson's test. Logistic regression analysis was applied to investigate factors as independent indicators for HOTAIR expression.*
Results: *In AD patients, the expression of HOTAIR was increased, and it could function as a diagnostic marker in AD patients. The expression of HOTAIR was associated with MMSE score and ADAS-Cog score in AD patients before exercise. Exercise ameliorated the cognitive impairment and reduced the relative serum expression of HOTAIR. Exercise was proved to be an independent indicator of HOTAIR expression.*
Conclusions: *HOTAIR was a possible biomarker for indicating AD patients, and it was correlated with MMSE scores and ADAS-Cog results. Exercise might moderate AD progress via controlling HOTAIR.*

Key words: *HOTAIR, Alzheimer's disease, exercise, diagnosis, cognition.*

Introduction

Alzheimer's disease (AD) is a common neuro-degenerative brain disease of dementia [14]. As a consequence of raised life expectancy, the incidence of dementia is increased worldwide and becomes one of the biggest global public challenges [6]. More importantly, COVID-19 disease may exacerbate the trajectory of deaths resulting from AD [1]. AD is the most prevalent form of dementia [15]. Neuro-psychological scale tests, imaging examinations, and biomarker detection of cerebrospinal fluid, are the three main methods for the diagnosis of AD [10,16]. However, cerebrospinal fluid detection is an impaired method, and it is difficult to promote it as a routine test. Searching for biomarkers of AD in blood might enrich the existing diagnosis theory. Loss of physical exercise is one of the most general preventable risks of AD [20]. Exercise has been considered as a management and prevention strategy for AD patients [4]. Aerobic exercise of six months can ameliorate memory performance and inhibit hippocampal atrophy, indicating that exercise may be ben-

Communicating author:
Zhongli Jiang, Department of Rehabilitation Medicine, the Affiliated Sir Run Run Hospital of Nanjing Medical University, No. 109 Long Mian Avenue, Nanjing, 211166 Jiangsu, China, phone: +86-138-5189-8370, e-mail: jiangzhongli_njmu@163.com

eficial for AD patients [21]. Therefore, the underlying mechanism attracts our attention.

Non-coding RNAs (ncRNAs) are substances that can predict or reflect changes in specific biological processes, including exercise. For obese children and adolescents, exercise can protect endothelial dysfunction by inhibiting the expression of long non-coding RNA (lncRNA) MALAT1 [33]. A previous study reveals, exercise may participate in hippocampal neurogenesis and prevent cognitive decline by downregulating miR-135a-5p [23]. All these pieces of evidence provide that exercise can suppress the progression of diseases and improve the recovery of normal function via regulating the expression of specific ncRNAs. In addition, several research on clinical roles of lncRNAs in AD patients have been published. In a study by Fotuhi *et al*., the expression of BACE1-AS was reduced in plasma samples compared with healthy controls, and BACE1-AS was considered a biomarker in predicting AD patients [11]. Zhang *et al*. reported that the expression of lncRNA MAGI2-AS3 was elevated in AD patients, and it was associated with the severity of AD [31]. LncRNA HOTAIR has been broadly examined in numerous investigations. In *in vivo* and *in vitro* Parkinson's disease models, the expression of HOTAIR is enhanced and its' overexpression aggravates dyskinesia, which indicates that HOTAIR may participate in neuro-degenerative disorders [3].

Considering the previous results of publication, our hypothesis was that HOTAIR was associated with exercise in Alzheimer's patients. We purposed to detect the expression and clinical appliance of HOTAIR in AD. The diagnostic value of HOTAIR for AD patients as well as the connections between HOTAIR and cognitive function in AD patients were evaluated. Moreover, the expression of HOTAIR in AD patients before and after exercise was detected as well as the associations between HOTAIR and exercise were certified in this publication.

Material and methods

Participants and sample extraction

We collected 79 healthy subjects and 82 patients with AD from the First People's Hospital of Yancheng City. All healthy individuals, who took regular examination volunteered to participate in this study. AD patients were confirmed by the revised NINCDA-ADRDA criteria [8]. Patients with vascular dementia, malignant tumors, systemic inflammatory dysfunctions, cerebral trauma, or serious nervous system diseases were limited to this study. All participants or their families signed informed consent forms. Our design and experiments of this study were approved by the ethics committee of the First People's Hospital of Yancheng City. All AD patients were randomly divided into exercise group and matched group. Forty-three patients in the exercise group underwent a three-month bicycle training, with 70% of maximum heart rate. Other 39 AD patients in the matched group took a three-month healthy consultation. Blood samples were collected from each group of patients. For AD patients, blood samples, Mini-Mental State Examination (MMSE) score, and Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) score were collected before and after three-month experiment. The collected blood samples were used to extract serum specimens.

RNA extraction and quantitative real-time polymerase chain reaction

Total RNA samples were isolated from serum samples using a total RNA extraction kit (BIOTEKE, Beijing, China). TRIpure LS reagent was mixed with serum sample, and the mixture was separated with chloroform, precipitated with isopropanol, and then washed with 70% ethanol. Next, RNA precipitate was air-dried and dissolved in RNase-free water, and gDNase (TIANGEN, Beijing, China) was used to remove residual genomic DNA from RNA samples. Concentration and purity were detected using Nanodrop 2000. About 1 μg RAN specimens with OD260/280 of 1.8-2.0 were transcripted to synthesize cDNA. The reverse transcription kit applying in this experiment was Quantscript RT kit (TIANGEN, Beijing, China). ABI 7500 quantitative real-time polymerase chain reaction (qRT-PCR) system was used to assess the relative expression of HOTAIR, and GAPDH was used as a reference gene. The following primers were used: HOTAIR 5'-GCAGTGGAATGGAACGGATT-3' (forward), 5'-CGTGGCATTTCTGGTCTTGTA-3' (reverse); GAPDH 5'-GGAGCGAGATCCCTCCAAAAT-3' (forward), 5'-GGCTGTTGTCATACTTCTCATGG-3' (reverse). Talent qPCR premix (TIANGEN, Beijing, China) was applied in this detection. Relative expression was calculated by 2(-deltadeltaCt) method.

Statistical analysis

All experimental data were analyzed with GraphPad and SPSS software. All data were exhibited as number or mean ± standard deviation. Student's *t*-test was applied to analyze the differences between two groups. Receiver operating characteristic (ROC) curve was conducted to predict the diagnostic possibility of HOTAIR. Correlations between HOTAIR expression and MMSE score or ADAS-Cog score were confirmed by Pearson's test. Logistic regression analysis was used to analyze factors responsible for the changes in HOTAIR expression. The criterion for statistical significance was $p < 0.05$.

Table I. Subjects' basic clinical information

Indicator	Subjects (N = 161)		P-value
	Healthy subjects (n = 79)	AD subjects (n = 82)	
Age (years)	65.15 ±6.04	65.32 ±5.95	0.861
Gender (male/female)	36/43	46/36	0.182
BMI (kg/m^2)	24.08 ±2.61	24.58 ±2.57	0.223
FBG (mg/dl)	103.13 ±11.50	100.70 ±11.16	0.176
DBP (mmHg)	82.11 ±10.35	82.07 ±9.76	0.980
SBP (mmHg)	123.96 ±13.74	121.17 ±15.31	0.226
TC (mg/dl)	195.38 ±8.57	194.55 ±9.53	0.564
TG (mg/dl)	125.26 ±115.16	128.24 ±17.57	0.252
MMSE score	29.39 ±0.65	20.35 ±2.91	< 0.001
ADAS-Cog score	4.14 ±2.77	21.41 ±8.32	< 0.001

AD – Alzheimer's disease, BMI – body mass index, FBG – fasting blood glucose, DBP – diastolic blood pressure, SBP – systolic blood pressure, TC – total cholesterol, TG – triglycerides, MMSE – Mini-Mental State Examination, ADAS-Cog – Alzheimer's Disease Assessment Scale-Cognition. Data are expressed as n or mean ± standard deviation

Results

Baseline information of all subjects

Baseline characteristics were collected and analyzed to reveal the differences between healthy controls and AD patients. As shown in Table I, the average age of 79 healthy people was 65.15 ±6.04 years, and the average age of 82 AD subjects was 65.32 ±5.95 years. There were no obvious differences in age, gender, body mass index (BMI), fasting blood glucose (FBG), diastolic blood pressure (DBP), systolic blood pressure (SBP), total cholesterol (TC), and triglycerides (TG) between the healthy group and the AD patients (Table I, $p > 0.05$), which indicated comparable data between the healthy group and the AD group. However, MMSE score in AD patients was lower than that in the healthy group, and ADAS-Cog score in AD patients was higher than that in the healthy subjects (Table I, $p < 0.001$).

Elevated expression of HOTAIR in AD patients and its' diagnostic accuracy

To estimate the expression of HOTAIR in 82 AD patients, qRT-PCR was carried out. As seen in Figure 1A, the expression of HOTAIR increased in the AD patients relative to 78 healthy individuals ($p < 0.001$).

ROC curve was used to analyze the diagnostic significance of HOTAIR on distinguishing AD patients from healthy individuals. As seen in Figure 1B, the area under

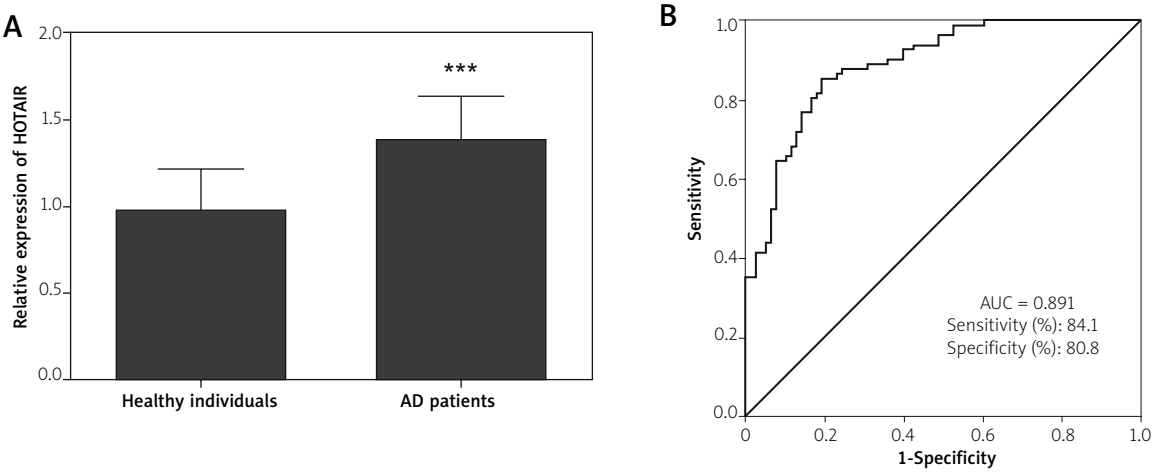

Fig. 1. A) Expression of HOTAIR was significantly increased in 82 Alzheimer's disease (AD) patients compared with 78 healthy individuals. **B**) The expression of HOTAIR showed a high possibility of diagnosing AD patients. ***$p < 0.001$.

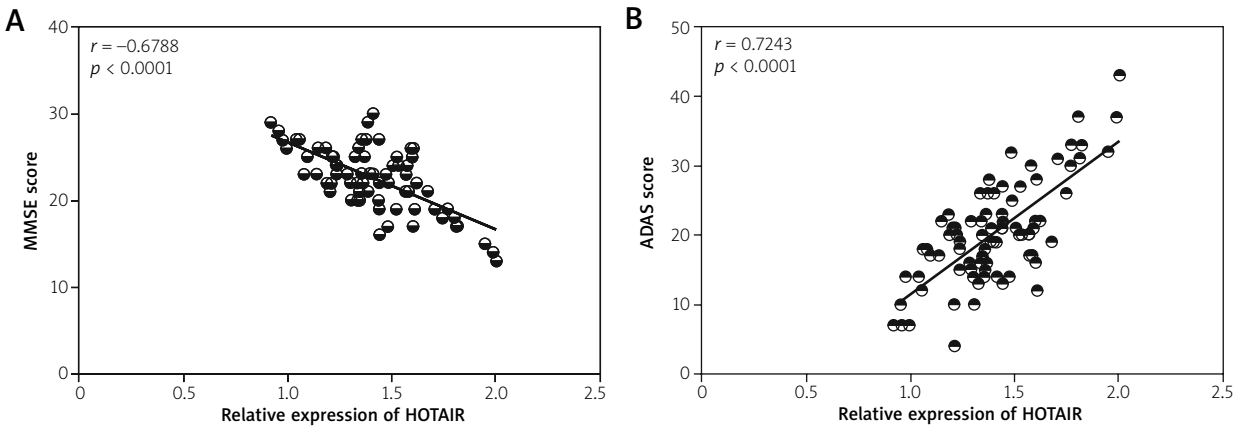

Fig. 2. Correlations between cognitive scores and HOTAIR in 82 Alzheimer's disease (AD) patients before exercise. **A**) The relative expression of HOTAIR was linked to MMSE score; **B**) An association between expression of HOTAIR and ADAS-Cog was found in AD patients.

the curve of HOTAIR was 0.891, indicating HOTAIR might be helpful in diagnosis of AD patients. Besides, the sensitivity of 84.1% and specificity of 80.8% further confirmed the diagnostic accuracy.

Correlation of serum HOTAIR level with MMSE score and ADAS-Cog score

The correlations between the level of HOTAIR and cognitive tests in 82 AD patients were evaluated before exercise. The expression levels of HOTAIR were correlated with the MMSE scores in AD patients (Fig. 2A, $r = –0.6788$, $p < 0.001$), and were related to the ADAS-Cog scores in AD patients (Fig. 2B, $r = 0.7243$, $p < 0.001$).

Beneficial influence of exercise in AD

All AD patients were divided into two groups, including 39 matched patients and 43 exercise patients. Further analysis was performed to confirm the correlation between clinical parameters and exercise. Before exercise, no significant differences were observed between the matched group and the exercise group (Table II, $p > 0.05$). After exercise, the average MMSE score in the exercise group was significantly higher than that in the matched group (Table II, $p < 0.001$). The average ADAS-Cog scores in the exercise group decreased in comparison with the matched group (Table II, $p = 0.032$).

Expression of HOTAIR in AD patients before and after exercises

In order to analyze the expression change of HOTAIR in AD patients before and after exercise, we detected HOTAIR expression in all AD patients before and after 3 months. In comparison with the matched group, expression levels of HOTAIR in the exercise group decreased significantly after three-month exercises (Fig. 3, $p < 0.001$). However, in the matched group,

Table II. Changes of various indexes in patients with Alzheimer's disease (AD) before and after exercise

Indicator	Before exercise		*P*-value	After exercise		*P*-value
	Matched group	Exercise group		Matched group	Exercise group	
BMI (kg/m^2)	24.27 ±2.47	24.86 ±2.64	0.299	24.61 ±2.67	24.60 ±2.70	0.983
FBG (mg/dl)	101.39 ±11.60	100.07 ±10.83	0.597	101.41 ±11.69	97.93 ±11.89	0.186
DBP (mmHg)	81.59 ±9.21	92.51 ±10.33	0.672	82.41 ±9.99	80.21 ±10.13	0.326
SBP (mm Hg)	121.97 ±15.28	120.44 ±15.48	0.654	120.05 ±13.23	124.35 ±13.83	0.155
TC (mg/dl)	194.79 ±9.25	194.34 ±9.89	0.833	194.17 ±9.48	194.91 ±8.36	0.711
TG (mg/dl)	128.64 ±16.34	127.89 ±18.81	0.848	128.68 ±14.68	127.85 ±15.21	0.801
MMSE score	19.76 ±2.86	20.80 ±2.88	0.083	19.54 ±3.53	22.60 ±3.78	< 0.001
ADAS-Cog score	22.13 ±8.89	20.77 ±7.82	0.463	21.79 ±8.32	17.70 ±8.55	0.032

AD – Alzheimer's disease, BMI – body mass index, FBG – fasting blood glucose, DBP – diastolic blood pressure, SBP – systolic blood pressure, TC – total cholesterol, TG – triglycerides, MMSE – Mini-Mental State Examination, ADAS-Cog – Alzheimer's Disease Assessment Scale-Cognition. Data are expressed as n or mean ± standard deviation

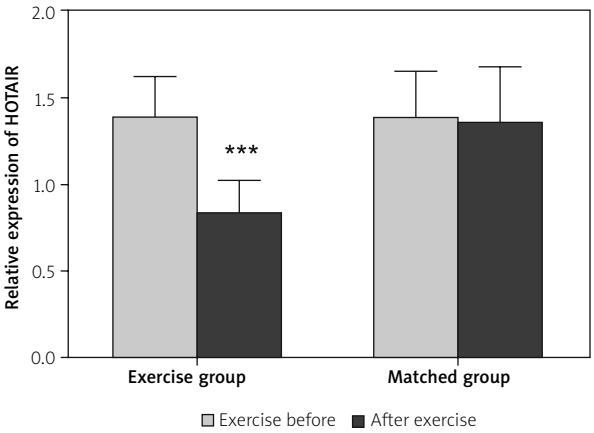

Fig. 3. HOTAIR was at a low level in 43 Alzheimer's disease (AD) patients after exercise compared with HOTAIR level in these patients before exercise. The difference in HOTAIR expression was not statistically significant in matched group; ***$p < 0.001$.

the difference in HOTAIR expression was not statistically significant (Fig. 3, $p > 0.05$).

Exercise as an independent indicator of HOTAIR expression

As seen in Table III, we used multivariate logistic regression analysis to evaluate the effects of age, gender, body mass index (BMI), diabetes, hypertension, hyperlipidemia, and exercise on HOTAIR expression, and found that exercise was significantly associated with HOTAIR expression (OR = 0.134, 95% CI: 0.046-0.393, $p < 0.001$).

Table III. Association of different variables with the occurrence of lncRNA HOTAIR expression level

Variables	OR	95% CI	*P*-value
Gender (male and female)	1.245	0.427-3.632	0.689
Age (years)	2.061	0.734-5.788	0.170
BMI (kg/m^2)	1.341	0.478-3.766	0.577
Diabetes	0.573	0.202-1.623	0.294
Hypertension	1.464	0.520-4.122	0.470
Hyperlipidemia	0.362	0.123-1.065	0.065
Exercise	0.134	0.046-0.393	< 0.001

BMI – body mass index

Discussion

As a progressive neuro-degenerative disease, AD is characterized by multidomain cognitive dysfunction, including deterioration in thinking and independence [2]. The risk of AD is dependent on age, lifestyle, causal gene mutations, and infection [24,25]. Labeling, clinical presentation, and imaging methods were broadly utilized within the current state of AD diagnostics [26,29]. Specific biomarkers have their predominance in recognizing AD, since they may diagnose AD patients before clinical diagnose of primary symptoms [18]. Regular physical exercise seems to be beneficial for Alzheimer's patients by suppressing several pathophysiological pathways implicated in AD [19]. Exercise may act as a novel preventative and/or therapeutic management for progressive AD by fortifying beneficial molecular instruments [7]. Nevertheless, the mechanism underlying exercise in AD is unclear.

In the present study, the expression of HOTAIR was raised in Alzheimer's patients compared with the healthy individuals, indicating that AD progression might contribute to the enhanced expression of HOTAIR. Moreover, the results of ROC curve revealed that HOTAIR might be used as a diagnostic biomarker in the clinical identification of Alzheimer's patients. The clinical utility of ncRNAs has been investigated by hundreds of researchers. Yang *et al.* reported that a panel of miR-135a, miR-193b, and miR-384 serves as an early diagnostic biomarker of AD [30]. LncRNA BACE1 is a promising indicator in distinguishing Alzheimer's patients [9]. MMSE and ADAS scores were used as important methods to evaluate the mental situation of AD patients in several reports [5,22]. A lower MMSE score and higher ADAS-Cog score indicated more severe cognitive impairment [28]. The mechanism underlying exercise in AD has been explored by some authors. For example, the exercise meliorates MMSE and ADAS-Cog scores, and inhibits the raised expression of lncRNA SNHG14 [13]. In another investigation of AD patients, the levels of miR-129-5p were enhanced induced by physical exercise, and correlations were identified between miR-129-5p and ADAS-Cog and MMSE scores [17]. Therefore, we further analyzed the association between HOTAIR and cognition. Our investigation indicated that the expression of HOTAIR was correlated with the MMSE score and ADAS score, which discovered that HOTAIR might ameliorate AD by cognition recovery.

Physical activity is related to maintenance or advancements of brain normal function by lessening the hazard of AD [12]. In the present study, we found the MMSE score was elevated in the exercise group compared with the matched group, providing that

three-month bicycle training could meliorate the progression of AD. The ADAS-Cog score was lessened in the AD patients after 3-month exercise, which elucidated that exercise might be beneficial to Alzheimer's patients. Besides, several experiments on the associations between exercise and ncRNAs have been carried out. In a report on vascular cognitive impairment, aerobic exercise alleviated the learning impairment in mice model by regulating TUG1 [27]. In Parkinson's disease, aerobic exercise training alters the motor performance of animal models by changing the expression of lncRNA LOC102633466 and lncRNA LOC102638670 [32]. Paronetto *et al*. validated the expansionary effect of physical activities in attenuating abnormal lncRNA MALAT1 expression by improving the levels of SOD1 and SOD2 antioxidant genes [2]. In the exercise group, the expression of HOTAIR in patients after exercise was decreased, which suggested that exercise might reduce the expression of HOTAIR. Furthermore, multivariate logistic regression analysis was conducted to analyze the correlation between exercise and HOTAIR. This finding showed that exercise was an independent marker in forecasting HOTAIR expression. Our analysis results can be beneficial to novel therapeutic targets and research strategies of AD. However, small sample size and no further studies on the molecular mechanisms were the limitations of this research.

In conclusion, the expression of HOTAIR was ascended in Alzheimer's patients, and HOTAIR was an alternative diagnostic biomarker for AD patients. The items of cognitive function were linked to the expression of HOTAIR. The cognitive situation of Alzheimer's patients was meliorated due to exercises. The expression of HOTAIR was declined in AD patients after three-month exercises. Exercise was an independent indicator for HOTAIR expression in Alzheimer's patients who undertook exercise.

Funding

This work was supported by National Key Research and Development Program "China's elderly disability prevention and intervention management network and technology research" (No. 2020YFC2008505).

Disclosure

The authors report no conflict of interest.

References

1. 2021 Alzheimer's disease facts and figures. Alzheimers Dement 2021; 17: 327-406.
2. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. Molecules 2020; 25: 5789.
3. Cai L, Tu L, Yang X, Zhang Q, Tian T, Gu R, Qu X, Wang Q, Tian J. HOTAIR accelerates dyskinesia in a MPTP-lesioned mouse model of PD via SSTR1 methylation-mediated ERK1/2 axis. Mol Ther Nucleic Acids 2020; 22: 140-152.
4. Cass SP. Alzheimer's disease and exercise: a literature review. Curr Sports Med Rep 2017; 16: 19-22.
5. Cheng J, Yang H, Zhang J. Donepezil's effects on brain functions of patients with Alzheimer disease: a regional homogeneity study based on resting-state functional magnetic resonance imaging. Clin Neuropharmacol 2019; 42: 42-48.
6. Crous-Bou M, Minguillón C, Gramunt N, Molinuevo JL. Alzheimer's disease prevention: from risk factors to early intervention. Alzheimers Res Ther 2017; 9: 71.
7. de Freitas GB, Lourenco MV, De Felice FG. Protective actions of exercise-related FNDC5/Irisin in memory and Alzheimer's disease. J Neurochem 2020; 155: 602-611.
8. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007; 6: 734-746.
9. Feng L, Liao YT, He JC, Xie CL, Chen SY, Fan HH, Su ZP, Wang Z. Plasma long non-coding RNA BACE1 as a novel biomarker for diagnosis of Alzheimer disease. BMC Neurol 2018; 18: 4.
10. Fiorini M, Bongianni M, Benedetti MD, Monaco S, Zanusso G. Reappraisal of Aβ40 and Aβ42 peptides measurements in cerebrospinal fluid of patients with Alzheimer's disease. J Alzheimers Dis 2018; 66: 219-227.
11. Fotuhi SN, Khalaj-Kondori M, Hoseinpour Feizi MA, Talebi M. Long non-coding RNA BACE1-AS may serve as an Alzheimer's disease blood-based biomarker. J Mol Neurosci 2019; 69: 351-359.
12. Fuller OK, Whitham M, Mathivanan S, Febbraio MA. The protective effect of exercise in neurodegenerative diseases: the potential role of extracellular vesicles. Cells 2020; 9: 2182.
13. He Y, Qiang Y. Mechanism of autonomic exercise improving cognitive function of Alzheimer's disease by regulating lncRNA SNHG14. Am J Alzheimers Dis Other Demen 2021; 36: 15333175211027681.
14. Hodson R. Alzheimer's disease. Nature 2018; 559: S1.
15. Holmer J, Aho V, Eriksdotter M, Paulin L, Pietiäinen M, Auvinen P, Schultzberg M, Pussinen PJ, Buhlin K. Subgingival microbiota in a population with and without cognitive dysfunction. J Oral Microbiol 2021; 13: 1854552.
16. Lee KH, Kwon DE, Do Han K, La Y, Han SH. Association between cytomegalovirus end-organ diseases and moderate-to-severe dementia: a population-based cohort study. BMC Neurol 2020; 20: 216.
17. Li Z, Chen Q, Liu J, Du Y. Physical exercise ameliorates the cognitive function and attenuates the neuroinflammation of Alzheimer's disease via miR-129-5p. Dement Geriatr Cogn Disord 2020; 49: 163-169.
18. Lloret A, Esteve D, Lloret MA, Cervera-Ferri A, Lopez B, Nepomuceno M, Monllor P. When does Alzheimer's disease really start? The role of biomarkers. Int J Mol Sci 2019; 20: 5536.
19. López-Ortiz S, Pinto-Fraga J, Valenzuela PL, Martín-Hernández J, Seisdedos MM, García-López O, Toschi N, Di Giuliano F, Garaci F, Mercuri NB, Nisticò R, Emanuele E, Lista S, Lucia A, Santos-Lozano A. Physical exercise and Alzheimer's disease: effects on pathophysiological molecular pathways of the disease. Int J Mol Sci 2021; 22: 2897.

20. Meng Q, Lin MS, Tzeng IS. Relationship between exercise and Alzheimer's disease: a narrative literature review. Front Neurosci 2020; 14: 131.
21. Morris JK, Vidoni ED, Johnson DK, Van Sciver A, Mahnken JD, Honea RA, Wilkins HM, Brooks WM, Billinger SA, Swerdlow RH, Burns JM. Aerobic exercise for Alzheimer's disease: a randomized controlled pilot trial. PLoS One 2017; 12: e0170547.
22. Mullins RJ, Mustapic M, Chia CW, Carlson O, Gulyani S, Tran J, Li Y, Mattson MP, Resnick S, Egan JM, Greig NH, Kapogiannis D. A pilot study of exenatide actions in Alzheimer's disease. Curr Alzheimer Res 2019; 16: 741-752.
23. Pons-Espinal M, Gasperini C, Marzi MJ, Braccia C, Armirotti A, Pötzsch A, Walker TL, Fabel K, Nicassio F, Kempermann G, De Pietri Tonelli D. MiR-135a-5p is critical for exercise-induced adult neurogenesis. Stem Cell Reports 2019; 12: 1298-1312.
24. Richard Armstrong A. Risk factors for Alzheimer's disease. Folia Neuropathol 2019; 57: 87-105.
25. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, Cummings J, van der Flier WM. Alzheimer's disease. Lancet 2021; 397: 1577-1590.
26. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. Int J Nanomedicine 2019; 14: 5541-5554.
27. Wang J, Niu Y, Tao H, Xue M, Wan C. Knockdown of lncRNA TUG1 inhibits hippocampal neuronal apoptosis and participates in aerobic exercise-alleviated vascular cognitive impairment. Biol Res 2020; 53: 53.
28. Wang Q, He C, Zhu Y, Zhang Q, Zhang Z, Xie C. Cortical atrophy mediates the accumulating effects of vascular risk factors on cognitive decline in the Alzheimer's disease spectrum. Aging 2020; 12: 15058-15076.
29. Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. F1000Res 2018; 7: F1000 Faculty Rev-1161.
30. Yang TT, Liu CG, Gao SC, Zhang Y, Wang PC. The serum exosome derived microRNA-135a, -193b, and -384 were potential Alzheimer's disease biomarkers. Biomed Environ Sci 2018; 31: 87-96.
31. Zhang J, Wang R. Deregulated lncRNA MAGI2-AS3 in Alzheimer's disease attenuates amyloid-β induced neurotoxicity and neuroinflammation by sponging miR-374b-5p. Exp Gerontol 2021; 144: 111180.
32. Zhang X, Wang Y, Zhao Z, Chen X, Li W, Li X. Transcriptome sequencing reveals aerobic exercise training-associated lncRNAs for improving Parkinson's disease. 3 Biotech 2020; 10: 498.
33. Zhao W, Yin Y, Cao H, Wang Y. Exercise improves endothelial function via the lncRNA MALAT1/miR-320a axis in obese children and adolescents. Cardiol Res Pract 2021; 2021: 8840698.