Exosomal let-7e, miR-21-5p, miR-145, miR-146a and miR-155 in Predicting Antidepressants Response in Patients with Major Depressive Disorder Yi-Yung Hung^{1*}, El-Wui Loh²⁻⁵, Hong-Yo Kang^{6, 7}

¹Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital, and Chang Gung University College of Medicine, Kaohsiung, Taiwan; ian670523@cgmh.org.tw ²Center for Evidence-Based Health Care, Department of Medical Research, Taipei Medical University Shuang Ho Hospital, New Taipei City, Taiwan; lohew@hotmail.com ³Department of Dentistry, Taipei Medical University Shuang Ho Hospital, New Taipei City, Taiwan ⁴Cochrane Taiwan, Taipei Medical University, Taipei, Taiwan ⁵Craduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

⁵Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

⁶Graduate Institute of Clinical Medical Sciences, Chang Gung University, College of Medicine; hkang3@mail.cgu.edu.tw

⁷Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Abstract: The intracellular microRNAs that negatively regulate toll-like receptor 4 signalings in peripheral blood mononuclear cells were associated with major depressive disorder (MDD). However, the distribution of these microRNAs in exosomes as a biomarker of central nervous system diseases is just beginning to be explored. In the present study, we isolated serum exosomes from patients with MDD and healthy controls to explore the levels of exosomal microRNAs, in-cluding let-7e, miR-21-5p, miR-223, miR-145, miR-146a, and miR-155. We also investigated the changes of these exosomal microRNAs after antidepressants treatment and their association with clinical changes in Hamilton Depression Rating Scale. ANCOVA adjusted by age, sex, BMI, and smoking showed higher expression levels of miR-146a (p = 0.006) in patients with MDD com-pared to controls. Patients who achieved remission showed significantly lower let-7e, miR-21-5p, miR-145, miR-146a, and miR-155 levels before treatment and increased after antidepressants treatment compared with the non-remission group. Through receiver operating characteristic (ROC) analysis, let-7e, miR-145, and miR-146a reflected acceptable discrimination between the remission and non-remission groups, whereas miR-21-5p and miR-155 showed poor discrimination. These findings characterize that exosomal microRNAs may play essential roles in predicting antidepressants response.

	Mature microRNA Sequence	Assay Name	Assay ID
	UGAGGUAGGAGGUUGUAUAGUU	hsa-let-7e	002406
let-7e -(UGAGGUAGUAGGUUGUAUGGUU	hsa-miR-21-5P	000397
miR-21-5p -:	UCCCUGAGACCCUUUAACCUGUGA	hsa-miR-125a-5p	002198
miR-125a -4	GUCCAGUUUUCCCAGGAAUCCCU	hsa-miR-145	002278
miR-223 6	UGAGAACUGAAUUCCAUGGGUU	hsa-miR-146a	000468
miR-145 -	UUAAUGCUAAUCGUGAUAGGGGU	hsa-miR-155	002623
miR-146a 1	CAAAGAAUUCUCCUUUUGGGCU	hsa-miR-186	002285
miR-155 -3	UGUCAGUUUGUCAAAUACCCCA	hsa-miR-223	002295
Monn Whitnow II toot?			

Table 4. Difference of exosomal microRNA expression between remission and non-remission at baseline.

	Remission	Non-remission	
	(n = 16)	(n = 23)	<i>p</i> -value
let-7e	-0.727 ± 1.160	0.452 ± 1.611	0.001**
miR-21-5p	-1.390 ± 1.594	-0.384 ± 1.794	0.038*
miR-125a	-4.706 ± 1.411	-3.545 ± 1.493	0.018*
miR-223	6.704 ± 1.081	7.084 ± 0.910	0.093
miR-145	-1.700 ± 1.190	-0.763 ± 1.514	0.018*
miR-146a	1.051 ± 1.627	2.181 ± 1.583	0.004**
miR-155	-3.794 ± 1.408	-2.719 ± 1.576	0.042*

Table 2. Demographic and clinical characteristics of patients with major depressive disorder and health control.

Table 1. Primers for qRT-PCR.

	Depression before Treatment (n = 52)	Health Control $(n = 31)$	<i>p-</i> Value
Age (years)	42.52 ± 13.51	39.06 ± 7.95	0.199
Sex (M/F)	18/34	9/22	0.637
BMI (kg/m ²)	24.57 ± 4.56	23.24 ± 2.61	0.142
Smoking (yes/no)	20/32	2/29	0.002**
HAMD before treat- ment	23.35 ± 4.76	_	-
HAMD after treatment	7.53 ± 4.27	-	-

Results reported as a mean \pm SD or as a number; age and BMI were compared using Student's t tests; sex and smoking were compared by the chi-square test; ** *p* < 0.01

Table 3. The difference of serum exosomal microRNA expression between health control and major depression groups before and after treatment.

		Ι			II		III	I vs III	I vs II
	Depression		Depression		Hoalth control				
	before	treat	ment	after treatment		n = 21	<i>p</i> -value	<i>p</i> -value	
	<i>n</i> = 52		<i>n</i> = 39		n = 51				
let-7e	-0.243 ± 1.466		0.258 ± 1.268		-0.752 ± 1.351	0.443	0.044*		
Remission	-0.727	±	1.160	0.295	±	1.390		0.900	0.002§§
Non-remission	0.452	±	1.611	0.205	±	1.112		0.009¶,¶	0.278
miR-21-5p	-0.977 ± 1.730		-0.823 ± 1.459		-1.07 ± 1.18	0.605	0.581		
Remission	-1.390	±	1.594	-0.690	±	1.571		0.396	0.036§
Non-remission	-0.384	±	1.794	-1.036	±	1.302		0.122	0.098
miR-223	6.86 ± 1.019		7.140 ± 0.964		6.19 ± 1.68	0.127	0.102		
Remission	6.704	±	1.081	7.254	±	1.025		0.416	$0.014^{\$}$
Non-remission	7.084	±	0.910	6.976	±	0.874		0.007^{M}	0.278
miR-145	-1.316 ± 1.394		-1.068 ± 1.230		-1.58 ± 1.32	0.765	0.274		
Remission	-1.700	±	1.190	-1.009	±	1.308		0.693	0.003§§
Non-remission	-0.763	±	1.514	-1.154	±	1.145		0.149	0.179
miR-146a	1.515	1.515 ± 1.685 1.639 ± 1.681		81	0.10 ± 1.83	0.007*	0.592		
Remission	1.051	±	1.627	1.642	±	1.756		0.062	0.048^{s}
Non-remission	2.181	±	1.583	1.635	±	1.624		D.000¶	0.079
miR-155	-3.353 ± 1.554		-2.849 ± 1.627		-2.85 ± 1.67	0.126	0.048*		
Remission	-3.794	±	1.408	-2.780	±	1.840		0.081	0.004^{ss}
Non-remission	-2.719	±	1.576	-2.949	±	1.311		0.995	0.408



*,** : ANCOVA adjust with age, sex, BMI, and smoking; \P , \P : Mann–Whitney U test; \$, \$: Wilcoxon signed-rank test; *, \$ p < 0.05; **, \$, $\P p < 0.01$.