

Increased expression of monoamine oxidase A is associated with epithelial to mesenchymal transition and clinicopathological features in non-small cell lung cancer

FEI LIU^{1,2*}, LIANG HU^{1,2*}, YUEFAN MA^{1,2*}, BINGYU HUANG^{1,2}, ZIHAN XIU^{1,2},
PEIHUA ZHANG³, KEYUAN ZHOU^{1,2} and XUDONG TANG^{1,2}

¹Institute of Biochemistry and Molecular Biology, Guangdong Medical University, Zhanjiang, Guangdong 524023; ²Guangdong Provincial Key Laboratory of Medical Molecular Diagnostics, Guangdong Medical University, Dongguan, Guangdong 523808; ³Institute of Plastic Surgery, Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong 524001, P.R. China

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Abstract. Monoamine oxidase A (MAOA), a mitochondrial enzyme, is closely associated with neurological disorders. Recently, MAOA has been linked to the progression of prostate cancer, hepatocellular carcinoma, and cholangiocarcinoma. However, MAOA was reported to have different effects on the progression of these types of cancer, and the role of MAOA in non-small cell lung cancer (NSCLC) progression remains unclear. The present study determined the expression of MAOA and epithelial to mesenchymal transition (EMT) markers in 45 pairs of NSCLC and matched non-tumor adjacent lung tissues, and further analyzed the correlation between MAOA expression and the EMT or the development of clinicopathological features. The results demonstrated that protein and mRNA expression levels of MAOA in NSCLC tissues were higher than those observed in the matched non-tumor adjacent lung tissues. Furthermore, the increased MAOA expression in NSCLC tissues was positively correlated with N-cadherin ($r=0.525$, $P=0.002$), Slug ($r=0.515$, $P=0.001$), and Twist ($r=0.448$, $P=0.008$) expressions, but negatively correlated with E-cadherin expression ($r=-0.387$, $P=0.01$). Additionally, the elevated MAOA expression in NSCLC tissues was associated with late stage NSCLC ($Z=-2.596$, $P=0.029$) and

lymph node metastases ($Z=-2.378$, $P=0.020$). These findings suggest that MAOA may have a role in promoting NSCLC progression by mediating EMT.

Introduction

Lung cancer, the leading cause of cancer-related deaths worldwide, is commonly divided into two categories, small cell lung cancer (SCLC) and non-SCLC (NSCLC), depending on its degree of differentiation and morphological characteristics (1,2). NSCLC accounts for ~80% of primary lung cancers, including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma (3). The 5-year survival rate of NSCLC is only 7% (4). Moreover, lymph nodes and distant organ metastasis are the main reasons leading to treatment failure in NSCLC patients with radical resection (5,6).

Epithelial to mesenchymal transition (EMT), a reversible biological process, is characterized by the loss of epithelial cell junction proteins (E-cadherin, Zo-1) (7,8), the gain of mesenchymal markers (vimentin, N-cadherin) (9,10), and the activation of transcription factors (Snail1, Slug, ZEB1, Twist) (11-15). Accumulating evidence indicates that EMT enhances tumor invasion, distant metastasis, and chemotherapy resistance in NSCLC, underscoring the need for a comprehensive understanding of the EMT function in NSCLC progression (16-19).

Monoamine oxidase A (MAOA), a mitochondria-bound enzyme, catalyzes the oxidative deamination of dietary amines and monoamine neurotransmitters, such as serotonin, norepinephrine, and dopamine (20,21). The functions of MAOA have been extensively studied in the context of neurological disorders, including mental depression, aggressive behaviors, and Parkinson's disease (22,23). Recent studies have indicated the role of MAOA in the progression of prostate cancer (24-30), hepatocellular carcinoma (HCC) (31), and cholangiocarcinoma (32). High Gleason grade or poorly differentiated prostate cancer exhibited increased MAOA expression (24), and the increased MAOA promoted prostate cancer metastasis (25,26). Furthermore,

Correspondence to: Professor Xudong Tang, Institute of Biochemistry and Molecular Biology, Guangdong Medical University, 2 Wenming Donglu, Xiashan, Zhanjiang, Guangdong 524023, P.R. China
E-mail: tangxudong2599@126.com; txd@gdmu.edu.cn

*Contributed equally

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overexpression of MAOA was found to dramatically down-regulate the expression of E-cadherin and upregulate the expression of vimentin and Twist at both mRNA and protein levels in prostate cancer (25). These studies suggested that MAOA might promote the progression of prostate cancer by mediating EMT. However, conflicting results were reported for HCC (31) and cholangiocarcinoma (32). Therefore, the role of MAOA may vary across cancer types, and therefore, it is essential to further understand the function of MAOA in other cancers.

Little is known about the function of MAOA in NSCLC. Accordingly, in this study, we investigated the expression of MAOA in NSCLC tissues and analyzed the association between the expression of MAOA and EMT or the development of clinicopathological features. We found for the first time, to the best of our knowledge, that MAOA protein and mRNA expressions in NSCLC tissues were significantly higher than those observed in the matched non-tumor adjacent lung tissues, and the increased MAOA expression was related to EMT, clinical stages, and lymph node metastases in NSCLC, suggesting that MAOA may be involved in mediating the progression of NSCLC.

Materials and methods

Reagents. Rabbit anti-human MAOA monoclonal antibody was obtained from Abcam (ab126751; Cambridge, UK). Mouse anti-human E-cadherin monoclonal antibody, rabbit anti-human vimentin, N-cadherin, Snail1, Slug, Zo-1, ZEB1 and Twist monoclonal antibodies, and horseradish peroxidase (HRP)-conjugated secondary antibodies were purchased from Cell Signaling Technology, Inc. (Beverly, MA, USA). The RNA extraction kit (RNAprep Pure FFPE kit) was purchased from Tiangen Biotech Co., Ltd. (Beijing, China). The reverse transcription (RT) kit (PrimeScript™ RT reagent kit) and qPCR analysis kit (SYBR Premix Ex Taq™ II) were obtained from Takara Biotechnology Co., Ltd. (Dalian, China).

NSCLC patients and control cases. NSCLC tissue specimens were obtained from 45 patients who were definitively diagnosed with NSCLC and had undergone curative surgery between 2007 and 2010 at the Affiliated Hospital of Guangdong Medical University (Guangdong, China). The matched non-tumor adjacent lung tissues (1 cm from the tumor) were also collected from the same patients, as the controls. Among these patients, the complete clinicopathological and histopathological data were collected from 30 cases. The patients that met the following criteria were enrolled. First, the patients were definitively diagnosed with NSCLC based on histological examinations. Second, the patients had not received chemotherapy, immunotherapy, or radiotherapy before pulmonary lobectomy. Third, the patients showed normal hepatic and renal functions and no abnormality of the endocrine system.

Ethics approval. Either the patients or their close relatives provided informed written consents. Our investigation received the ethic approval from the local Committee of the Affiliated Hospital of Guangdong Medical University. All

clinical investigations were performed according to the principles defined by the Declaration of Helsinki.

Immunohistochemistry. Immunohistochemical staining was performed on paraffin-embedded tissue specimens, including NSCLC and matched non-tumor adjacent lung tissues, from 45 cases. Briefly, paraffin-embedded tissue specimens were cut into 4- μ m sections, transferred onto Superfrost Ultra Plus slides, and placed in a 60°C oven overnight. The slides were deparaffinized with xylene, rehydrated in a descending alcohol series (100, 95, 90, 80 and 70%), and then rinsed with sterile distilled water for 5 min. Antigen retrieval was performed by boiling the tissue sections in citrate buffer (10 mM trisodium citrate, 0.05% Tween-20, pH=6) for 10 min. The slides were further treated with 3% hydrogen peroxide for 15 min to inactivate any endogenous peroxidase activity. After rinsing in phosphate-buffered saline (PBS), non-specific sites were blocked with normal goat serum for 15 min. The slides were subsequently incubated with primary antibodies (1:100) overnight at 4°C. One slide was incubated with PBS, as the negative control. After washing with precooled PBS, the slides were incubated with a secondary biotinylated antibody for 15 min at room temperature. The slides were washed with precooled PBS three times, and then treated with a streptavidin-biotin complex for 15 min at room temperature. The slides were then stained with diaminobenzidine (DAB), and counterstained with hematoxylin, before being observed and analyzed in a double-blind manner, under light microscopy, by two senior pathologists. Ten randomly selected fields were examined at x400 magnification and 100 cancer cells were counted in each field (total 10,000 cells) to determine the proportion of positive cells. A semi-quantitative analysis was performed to evaluate the protein expression levels as described previously (33,34). In brief, staining intensity was scored on a scale of 0 to 3, 0 for no intensity, 1 for low intensity (light yellow), 2 for moderate intensity (claybank), and 3 for high intensity (sepia). The cell positivity was scored on a scale of 0 to 4: 0, <5% cells stain-positive; 1, 5 to 25% cells stain-positive; 2, 26 to 50% cells stain-positive; 3, 51 to 75% cells stain-positive; and 4, >75% cells stain-positive. The scores obtained relative staining intensity and proportion of positive cells were multiplied together to generate a final score ranging from 0 to 12, interpreted as follows: 0, negative (-); 1 to 4, weakly positive (+); 5 to 8, moderately positive (++); 9 to 12, strongly positive (+++). The scores were evaluated by two pathologists.

RT-qPCR. Total RNA was extracted from paraffin-embedded tissue specimens using the TIANGEN RNAprep Pure FFPE kit and then converted to cDNA using the PrimeScript™ RT reagent kit (both from Tiangen Biotech Co., Ltd.). qPCR analysis was performed using SYBR Premix Ex Taq™ II (Takara Biotechnology Co., Ltd.), according to the manufacturer's instructions. All the primers were synthesized by Takara Biotechnology Co., Ltd., and are listed in Table I. The housekeeping gene β -actin was used as an internal control to normalize mRNA levels. The optimum reaction conditions for qPCR were as follows: Pre-treatment at 42°C for 5 min, initial denaturation at 95°C for 10 sec, followed by 40 cycles at 95°C

Table I. Primers for real-time quantitative PCR.

GenBank no.	Genes	Primer sequence (5'-3')	Length (bp)
NM_000240.3	<i>MAOA</i>	Forward primer AGTGAGCGAACGGATAATGG Reverse primer TGTTCATGGTTCAGCGTCTC	114
NM_004360.4	<i>E-cadherin</i>	Forward primer TTGCTACTGGAACAGGGACAC Reverse primer CCCGTGTGTTAGTTCTGCTGT	179
NM_003257.4	<i>Zo-1</i>	Forward primer GGATGTTTATCGTCGCATTGTA Reverse primer AAGAGCCCAGTTTTCCATTGTA	158
NM_001792.4	<i>N-cadherin</i>	Forward primer TTATCCTTGTGCTGATGTTTGTG Reverse primer TCTTCTTCTCCTCCACCTTCTTC	139
NM_003380.3	<i>Vimentin</i>	Forward primer TGGCACGTCTTGACCTTGAA Reverse primer GGTCATCGTGATGCTGAGAA	176
NM_005985.3	<i>Snail1</i>	Forward primer TCCTTCGTCCTTCTCCTCTACTT Reverse primer TGTTGCAGTATTTGCAGTTGAAG	155
NM_003068.4	<i>Slug</i>	Forward primer GCCTTTTTCTTGCCCTCAC Reverse primer GGTTTTGGAGCAGTTTTTGC	115
NM_030751.5	<i>ZEB1</i>	Forward primer TCCCCATCACCTCTAAACCTT Reverse primer CCCTGTTGCTTTGGTAGTGAA	122
NM_000474.3	<i>Twist</i>	Forward primer AGTCCGCAGTCATACGAGGAG Reverse primer GACCTAGTAGAGGAAGTCGATG	146
NM_001101.3	<i>β-actin</i>	Forward primer TGACGTGGACATCCGCAAAG Reverse primer CTGGAAGGTGGACAGCAGGG	186

MAOA, monoamine oxidase A.

for 5 sec, and 60°C for 31 sec. The experiment was carried out in triplicate.

Statistical analysis. SPSS 19.0 Windows software was used for statistical analysis. Quantitative data were presented as the mean \pm SD. The categorical variables were presented as frequency and percent rates, and the positive rates from two groups were compared using Chi-square (χ^2) test or Fisher exact probabilities ($n < 40$ or $T < 1$). Wilcoxon rank sum test was used to perform the statistical analysis on ordinal data. Spearman rank correlation coefficient was employed for the correlation analysis. P-value < 0.05 was considered to indicate a statistically significant difference.

Results

Expressions of MAOA and EMT markers in NSCLC and matched non-tumor adjacent lung tissues. Previous studies have demonstrated that prostate cancer and HCC exhibit completely different MAOA expression levels (24,31), and to date, MAOA expression has not been reported in NSCLC. To investigate the expressions of MAOA and EMT markers in NSCLC tissues, immunohistochemical staining was performed in 45 pairs of NSCLC and patient-matched non-tumor adjacent lung tissues. The protein expressions of MAOA, N-cadherin, vimentin, Snail1, Slug, ZEB1, and Twist were obviously enhanced in NSCLC tissues (Fig. 1A). The positive expression rates of MAOA, N-cadherin, vimentin,

Snail1, Slug, ZEB1, and Twist in NSCLC tissues were higher than those observed in the matched non-tumor adjacent lung tissues ($P < 0.01$, Fig. 1B; Table II), while the positive expression rates of E-cadherin, Zo-1, and EMT epithelial makers determined in NSCLC tissues were lower than those observed in adjacent normal lung tissues (Fig. 1A and B; Table II). To further investigate the mRNA expressions of MAOA and EMT markers, NSCLC and matched adjacent normal lung tissues from 30 cases were selected for RT-qPCR. Our results showed that the mRNA levels of MAOA, N-cadherin, vimentin, Snail1, Slug, ZEB1, and Twist in NSCLC tissues were significantly higher than those detected in non-tumor adjacent tissues. As expected, a significant decrease in E-cadherin and Zo-1 mRNA expressions was observed in NSCLC tissues ($P < 0.01$; Fig. 1C).

Moreover, the statistical distribution results further demonstrated that MAOA, vimentin, and Snail1 protein expressions were significantly stronger in NSCLC tissues than in adjacent normal lung tissues, whereas E-cadherin protein expression displayed the opposite trend ($P < 0.05$; Fig. 2).

Correlation between the expressions of MAOA and EMT markers in NSCLC. To study the role of MAOA expression in the EMT of NSCLC, a Spearman rank correlation coefficient test was performed to analyze the correlation between the expressions of MAOA and EMT markers in NSCLC. As described in Table III, although there was no relationship between the expression of MAOA and the expressions

Table II. The positive rates of protein expression of MAOA and EMT markers in NSCLC and non-tumor adjacent lung tissues.

Proteins	NSCLC tissues (%)	Non-tumor adjacent lung tissues (%)	χ^2	P-value
MAOA	71.1 (32/45)	40.0 (18/45)	8.802	0.003
E-cadherin	46.7 (21/45)	77.8 (35/45)	9.265	0.002
Zo-1	51.1 (23/45)	91.1 (41/45)	17.524	0.0001
N-cadherin	68.9 (31/45)	26.7 (9/45)	21.780	0.0001
Vimentin	44.4 (20/45)	17.8 (8/45)	7.465	0.006
Snail1	62.2 (28/45)	33.3 (15/45)	7.526	0.006
Slug	55.6 (25/45)	20.0 (9/45)	12.101	0.001
ZEB1	53.3 (24/45)	15.6 (7/45)	14.221	0.0001
Twist	64.4 (29/45)	22.2 (10/45)	16.335	0.0001

MAOA, monoamine oxidase A; EMT, epithelial to mesenchymal transition; NSCLC, non-small cell lung cancer.

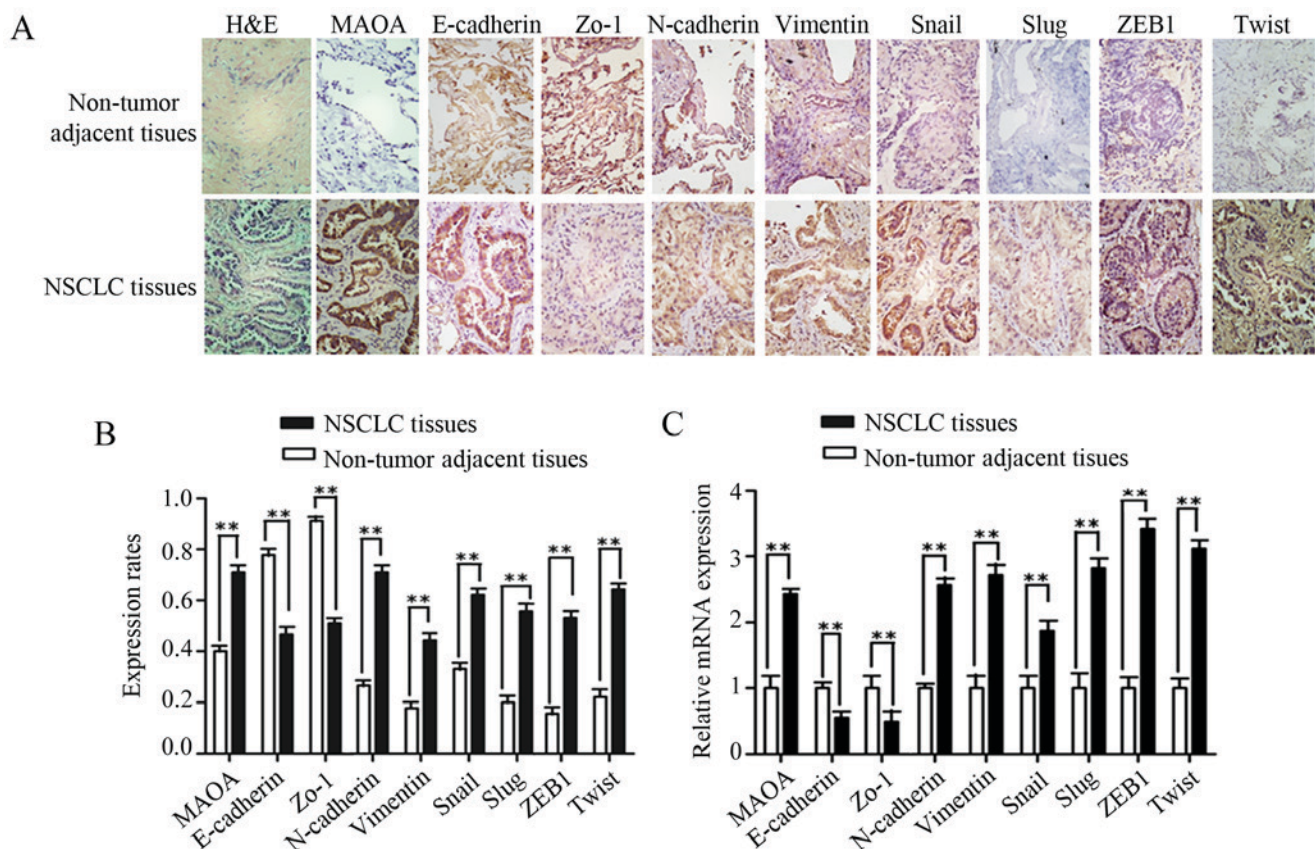


Figure 1. The expressions of MAOA and EMT markers in NSCLC and the matched non-tumor adjacent lung tissues. Immunohistochemistry and RT-qPCR were performed to analyze the expressions of MAOA and EMT markers. (A) The representative results of immunohistochemistry. Original magnification, x400. (B) The positive rates of protein expression, ** $P < 0.01$. (C) RT-qPCR results, ** $P < 0.01$. MAOA, monoamine oxidase A; EMT, epithelial to mesenchymal transition; NSCLC, non-small cell lung cancer.

of vimentin, Snail1, Zo-1, or ZEB1 ($P > 0.05$; Table III), the expression of MAOA was positively correlated with the expressions of the EMT mesenchymal marker N-cadherin ($r = 0.525$, $P = 0.002$) and the EMT transcription factors Slug ($r = 0.515$, $P = 0.001$) and Twist ($r = 0.448$, $P = 0.008$). Accordingly, MAOA expression was negatively correlated

with the expression of the epithelial marker E-cadherin ($r = -0.387$, $P = 0.01$; Table III).

Correlation between MAOA expression and the development of clinicopathological features in NSCLC. Thirty of the patients who were definitively diagnosed with NSCLC, and

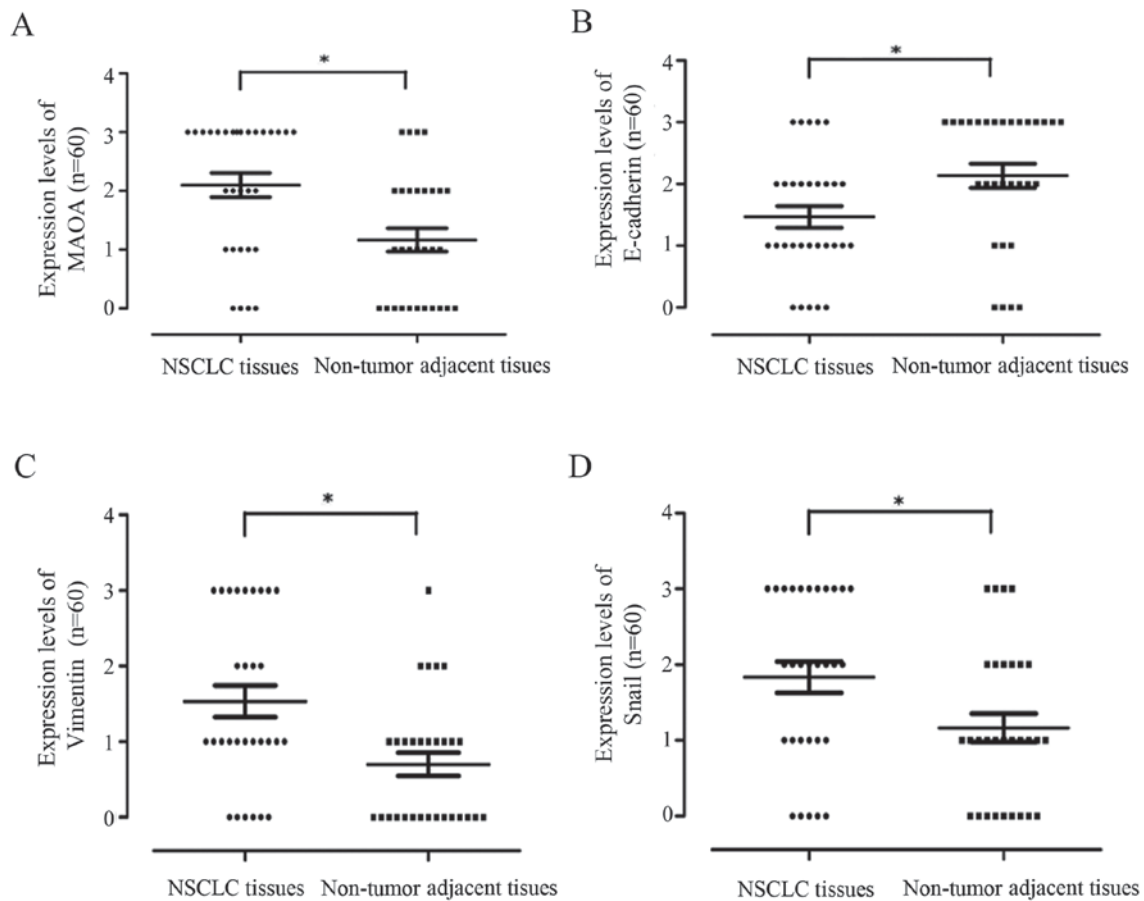


Figure 2. The statistical distribution of MAOA, E-cadherin, vimentin, and Snail1 expression levels in NSCLC and the matched non-tumor adjacent lung tissues. Wilcoxon rank sum test was employed for analysis of statistical distribution of protein expression levels of MAOA, E-cadherin, vimentin, and Snail1. (A) MAOA, (B) E-cadherin, (C) vimentin, and (D) Snail1. *P<0.05. MAOA, monoamine oxidase A; NSCLC, non-small cell lung cancer.

offered complete clinicopathological and histopathological data, were enrolled to analyze the correlation between MAOA expression and the clinicopathological features observed in NSCLC. A Wilcoxon rank sum test was employed to carry out the analysis of statistical distribution on the data obtained regarding the protein expression levels. Our results showed that the positive rate of MAOA expression in stage III was higher than that measured in stages I and II ($Z=-2.596$, $P=0.029$; Table IV). Additionally, the lymph node metastasis group exhibited a stronger MAOA expression level than the controls with no metastasis ($Z=-2.378$, $P=0.020$; Table IV). These results indicated that MAOA expression was significantly correlated with clinical stages and lymph node metastases. However, MAOA expression was not influenced by sex, age, degree of differentiation, or histological types ($P>0.05$; Table IV).

Discussion

MAOA, a monoamine neurotransmitter degrading enzyme, is well-known to be closely associated with impulsive aggressively, anxiety, depression, among other emotions, and is considered as an indicator of psychological status (22,23,35). Recently, several studies have been focusing on the relationship between MAOA expression and cancers (24-32). However, conflicting results were reported across different

types of cancer, including prostate cancer (24-30), HCC (31), and cholangiocarcinoma (32). MAOA was demonstrated as being highly expressed in high-grade aggressive prostate cancer, and capable of mediating prostate tumorigenesis and metastasis (24-27). Recently, MAOA was reported as a novel decision maker in apoptosis and autophagy processes occurring within hormone refractory neuroendocrine prostate cancer cells (28). Moreover, clorgyline, a MAOA inhibitor, was found to exhibit anti-oncogenic and pro-differentiation effects on high-grade prostate cancer cells (29), and the MAOA inhibitor-near-infrared dye conjugate was reported to reduce prostate tumor growth (30). These findings suggest that MAOA might play a key role in mediating prostate cancer progression. However, Li *et al* demonstrated that MAOA expression was remarkably downregulated in clinical HCC tissue samples (31), and that MAOA suppressed HCC metastasis by inhibiting the adrenergic system and its trans-activation of EGFR signaling (31). Huang *et al* also found that MAOA expression was inhibited by coordinated epigenetic and IL-6-driven events in human cholangiocarcinoma (32), and that overexpression of MAOA suppressed cholangiocarcinoma growth and invasion (32). In the present study, we demonstrated for the first time to our knowledge that MAOA protein and mRNA expression levels, positive rates, and statistical distribution in NSCLC tissues were dramatically higher than those recorded in the matched non-tumor

Table III. The correlation between MAOA expression and EMT in NSCLC.

Proteins	MAOA		Total	χ^2	P-value	r
	+	-				
E-cadherin				6.724	0.010	-0.387
+	11	10	21			
-	21	3	24			
Zo-1				0.795	0.372	-0.133
+	15	8	23			
-	17	5	22			
N-cadherin				10.020	0.002	0.525
+	27	4	31			
-	5	9	14			
Vimentin				3.380	0.066	0.274
+	17	3	20			
-	15	10	25			
Snail1				0.160	0.690	0.11
+	21	7	28			
-	11	6	17			
Slug				11.948	0.001	0.515
+	23	2	25			
-	9	11	20			
ZEB1				1.625	0.202	0.19
+	19	5	24			
-	13	8	21			
Twist				7.099	0.008	0.448
+	25	4	29			
-	7	9	16			
Total		32	13	45		

MAOA, monoamine oxidase A; EMT, epithelial to mesenchymal transition; NSCLC, non-small cell lung cancer.

adjacent lung tissues (Figs. 1 and 2; Table II). Moreover, we further found that MAOA expression was correlated with clinical stages and lymph node metastases, while no relation could be established with sex, age, degree of differentiation, and histological types (Table IV). Taken together, our results suggest that MAOA may play a role in promoting the progression of NSCLC.

EMT, a key step in invasion and metastasis, plays a crucial role in the progression of cancers, including NSCLC (16-19). Wu *et al* (25) demonstrated that MAOA expression in prostate cancer suppressed epithelial phenotype and promoted mesenchymal transition by decreasing the expression of epithelial marker E-cadherin, while increasing the expressions of mesenchymal marker vimentin and transcription factor Twist, indicating its association with EMT in prostate cancer. In the present study, we showed that the increased MAOA expression in NSCLC tissues was negatively correlated with E-cadherin expression, but positively correlated with the expressions of N-cadherin, Slug, and Twist (Table III),

Table IV. Correlationship between the expression of MAOA and clinicopathologic characteristics.

Variables	n	MAOA		P-value
		-	+	
Age (years)				0.691
<60	13	3	10	
≥60	17	6	11	
Sex				1.000
Male	21	6	15	
Female	9	3	6	
TNM stage				0.029
I+II	21	9	12	
III	9	0	9	
Differentiation				0.687
Poorly	11	4	7	
Moderately	19	5	14	
Pathologic type				0.704
Adenocarcinoma	12	3	9	
Squamous	18	6	12	
Lymph node metastasis				0.020
Negative	13	7	6	
Positive	17	2	15	
Total	30	9	21	

MAOA, monoamine oxidase A.

suggesting that MAOA may mediate EMT, leading to the progression of NSCLC.

In conclusion, we demonstrated for the first time, to the best of our knowledge, that MAOA expression was significantly increased in NSCLC tissues, which was positively associated with EMT, late stages and lymph node metastases of the cancer, thus supporting the notion that MAOA may play a role in NSCLC progression by regulating the EMT process.

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