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MAD2 Combined with Mitotic Spindle Apparatus (MSA) and Anticentromere Antibody (ACA) for Diagnosis of Small Cell Lung Cancer (SCLC)

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Background: MAD2 is the gene controlling mitosis. Many studies have assessed MAD2 in various types of carcinoma. Antinuclear mitotic spindle apparatus antibody (MSA) and anticentromere antibody (ACA) are related mitotic antibodies, playing roles in autoimmune diseases and carcinomas, but the expression of MAD2, MSA, and ACA in SCLC is unclear.

Material/Methods: We enrolled 70 SCLC patients, 72 non-small cell lung cancer (NSCLC) patients, and 65 pulmonary nodule (PN) patients. MAD2 expression was measured through agarose electrophoresis and qt-PCR. Antinuclear mitotic spindle apparatus antibody (MSA) and anticentromere antibody (ACA) were detected by indirect immunofluorescence (IIF).

Results: MAD2 was found both in SCLC and NSCLC. Interestingly, there was a significant difference found between SCLC and NSCLC using qt-PCR ($P<0.05$). The area under the ROC curve of MAD2 expression was 0.799, with medium diagnostic value. MAD2 expression was related to age, lymphatic metastasis, and survival time, but not with sex. The positivity for MSA and ACA by IIF assay were 37.20% and 34.00%, respectively, in the SCLC group, which were higher than in the NSCLC and pulmonary nodule groups ($P<0.05$). The kappa values of MSA and ACA with MAD2 expression were 0.73 and 0.65, respectively, with moderate consistency. Combining MAD2 with MSA and ACA enhanced the sensitivity and specificity for diagnosing SCLC.

Conclusions: MAD2 expression was found to be involved in carcinogenesis and prognosis of SCLC. The combination of MAD2 with MSA and ACA is useful for early diagnosis and shows promise in treatment of SCLC.

MeSH Keywords: Autoantibodies • Diagnosis • Mad2 Proteins • Small Cell Lung Carcinoma

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Background

Lung carcinoma has become the leading cause of cancer-related death worldwide. SCLC remains a major cause of carcinoma mortality, currently accounting for 13% to 15% of all lung carcinomas [1]. SCLC is characterized by a high proliferation rate and early metastasis. Outcomes have not changed dramatically, as the majority of patients are initially insensitive to chemotherapy and radiation therapy due to resistance. Thus, early diagnosis of SCLC is an urgent need.

It is reported that tobacco exposure is strongly correlated with the development of SCLC [1]. Growing evidence shows that carcinoma is related to chromosome instability (CIN) [2–4], and tobacco exposure can lead to DNA damage and *unattached* kinetochore [5]. The spindle assembly checkpoint (SAC) is a key controller of cell mitosis through the separation of daughter chromosomes. Once finding kinetochore *unattached, SAC is powered on* [6,7]. *Subsequently, cell mitosis does not switch to mitosis until the* kinetochore *is attached completely. Dysfunction of SAC leads to mis-segregation of daughter chromosomes. Later, CIN develops. The component of SAC covers MAD2, MAD1, BubR1, Bub3, and MSP1. Some studies have reported that the overexpression of* MAD2 *is detected continuously* in various types of carcinomas [8–10], but the expression of MAD2 in SCLC remains unknown. Therefore, detecting MAD2 *expression may be a potential tool for the diagnosis of SCLC.*

To date, many types of antibodies have been correlated with carcinoma [11]. ACA has been found in breast carcinoma, which targets centrosome antigens. In our laboratory work, MSA and ACA had high titers in SCLC [12]. The antigens of ACA and MSA play crucial roles in centromere formation and kinetochore organization. Antibodies appears earlier than tumorigenesis. The relationship of MAD2 with ACA and MSA in tumorigenesis is unclear.

In the present work, the expressions of MAD2, MSA, and ACA were measured. There were significant differences in MAD2 expression between SCLC and NSCLC. The combination of MAD2 with MSA and ACA obviously improved the sensitivity and specificity. Our results show that the combination of MAD2, MSA, and ACA is very useful in diagnosis of SCLC.

Material and Methods

Population

We enrolled outpatients and inpatients with lung tumors who attended the Second Affiliated Hospital of Nanchang University between December 2011 and December 2016. Of the 70 SCLC patients, 41 were males and 29 were females, ages 26–86 years (mean age 62 years). Of the 72 NSCLC patients, 37 were males and 35 were females, ages 35–84 years (mean age 64 years). As a negative control group, we used serum collected from 65 PN blood donors (32 males, 33 females, ages 32–87 years, mean age 59 years) who came to the same hospital for a physical check-up. SCLC was diagnosed according to the 2015 WHO Classification [13]. Inclusion criteria were: 1) informed, voluntary participation; 2) identified diagnosis, completing clinical, imaging, and pathological data; 3) complete patient data were available, and without other autoimmune diseases or other carcinomas; 4) in the healthy volunteers control group, the results of accessory examinations were normal, containing complete blood count, blood pressure, blood glucose, sternum, electrocardiograph, and hemopathy. Exclusion criteria were: 1) without specific tumor type or primary tumors; 2) with severe heart, lung, liver, kidney, other systemic disease, thyroid disease, and diabetes; 3) pregnancy or lactation, 4) noncompliance. Informed consent was acquired from each participant included in the study. The Hospital Ethics Committee approved the study.

Serum sample collection

We collected 3-ml fasting venous blood samples into tubes without any anticoagulant. After centrifugation at 1026 g for 15 min, serum was separated, divided into aliquots, and frozen at –80°C.

For mRNA analysis, we collected 2-ml fasting venous blood samples into tubes with EDTA. We extracted MAD2 mRNA with RNA Trizol reagent. Then, mRNA was saved at –80°C.

Detection of MAD2

For qRt-PCR analysis, we extracted mRNA of MAD2 using Trizol reagent (Takara Bio, Inc., Otsu, Japan). The concentration and purity of RNA was detected using a NanoDrop 2000 instrument (Thermo Fisher Scientific, Inc.). The RNA was transcribed into cDNA using a reverse transcription kit (Takara Bio, Inc., Otsu, Japan). The length of MAD2 mRNA was 163bp. GAPDH was used for internal reference and the length was 146 bp.
Primer sequence:
Upstream sequence 5- AGCTCCTTTTGACCTTCATTTC-3
Downstream sequence 5- TCCATTGCTTCATAGGTTCAAG-3
GAPDH sequence:
Upstream sequence 5-ACGGTGACATTTCTGCCACT-3
Downstream sequence 5-TGGTCCCGACTCTTCCCATT-3

Processing was performed under the following conditions: preheating of the mixture at 95°C for 5 min, followed by 35 cycles of denaturation for 30 s at 95°C, annealing for 30 s at 56°C, and extension for 1 min at 72°C, with a final extension for 7 min at 72°C.

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Table 1. Relationship between clinical parameters and *MAD2* expression.

Clinical parameters	N	MAD2		χ^2	P-value
		Positive	Negative		
SCLC	70	52	18	47.42	*P*<0.05
NSCLC	72	31	41		
PN	65	10	55		
Male	41	35	6	1.02	*P*>0.05
Female	29	22	7		
≥60	46	41	5	15.48	*P*<0.05
<60	24	11	13		
Lymphatic metastasis				3.00	*P*<0.05
Yes	50	40	10		
No	20	12	8		
Survival time(years)				8.71	*P*<0.05
≥5	17	8	9		
<5	53	44	9		
Smoking history				1.67	*P*>0.05
SCLC	37	13	24		
NSCLC	46	16	30		
PN	35	8	27		

SCLC – small cell lung cancer; NSCLC – non-small cell lung cancer; PN – pulmonary nodule.

Detection of MSA and ACA

MSA and ACA antibodies were detected by IIF with commercial kits from Euroimmun Company (Lübeck, Schleswig-Holstein, Germany). MSA was tested on snap-frozen sections of HEp-2010 cell lines. Detection of ACA was performed on Mosaic (Hep-2 cells). We placed 25 µL of diluted samples on slides and covered them. After incubation for 30 min at room temperature, the slides were washed. Then, FITC-anti-human IgG antibodies were added for 30-min incubation. Finally, the slides were covered with glycerin and then observed by fluorescence microscopy.

Statistical analysis

Statistical analysis was performed using SPSS 23.0 software (IBM Corporation, Armonk, NY, USA). Enumeration data are described in percentages. Because the results of qt-PCR for MAD2 mRNA were non-normally distributed data, we used the Kruskal-Wallis test to analyze the results of MAD2 expression in patient groups. The diagnostic efficacy of MAD2 for SCLC was assessed by receiver operating characteristics (ROC) analysis. Data on MSA and ACA from patient groups were assessed using the chi-square test. Consistency of MAD2, MSA, and ACA is represented by kappa value.

Results

Patients characteristics

We divided the 207 patients into the SCLC group (N=70), the NSCLC group (N=72), and the PN group (N=65). There were significant differences among the groups in MAD2 expression (P<0.05). Moreover, MAD2 expression was associated with age, lymphatic metastasis, and survival time (P<0.05). No significant association was found between sex and MAD2 expression (P>0.05). There were no distinct differences in smoking history and MAD2 expression among groups (*P>0.05*) (Table 1).

MAD2 expression and clinical value

Agarose electrophoresis showed that MAD2 was expressed in the SCLC group and the NSCLC group, but not in the PN group (Figure 1A). Then, we used qRt-PCR to measure the quantity of MAD2 expression (Figure 1B). We found obvious and significant differences between LC (SCLC and NSCLC) and PN (p<0.05). Interestingly, there were also significant differences between SCLC and NSCLC (p<0.05). Then, we hypothesized that MAD2 was a biomarker for SCLC and performed ROC curve analysis (Figure 1C), showing an AUC of 0.799. When the 95% CI was

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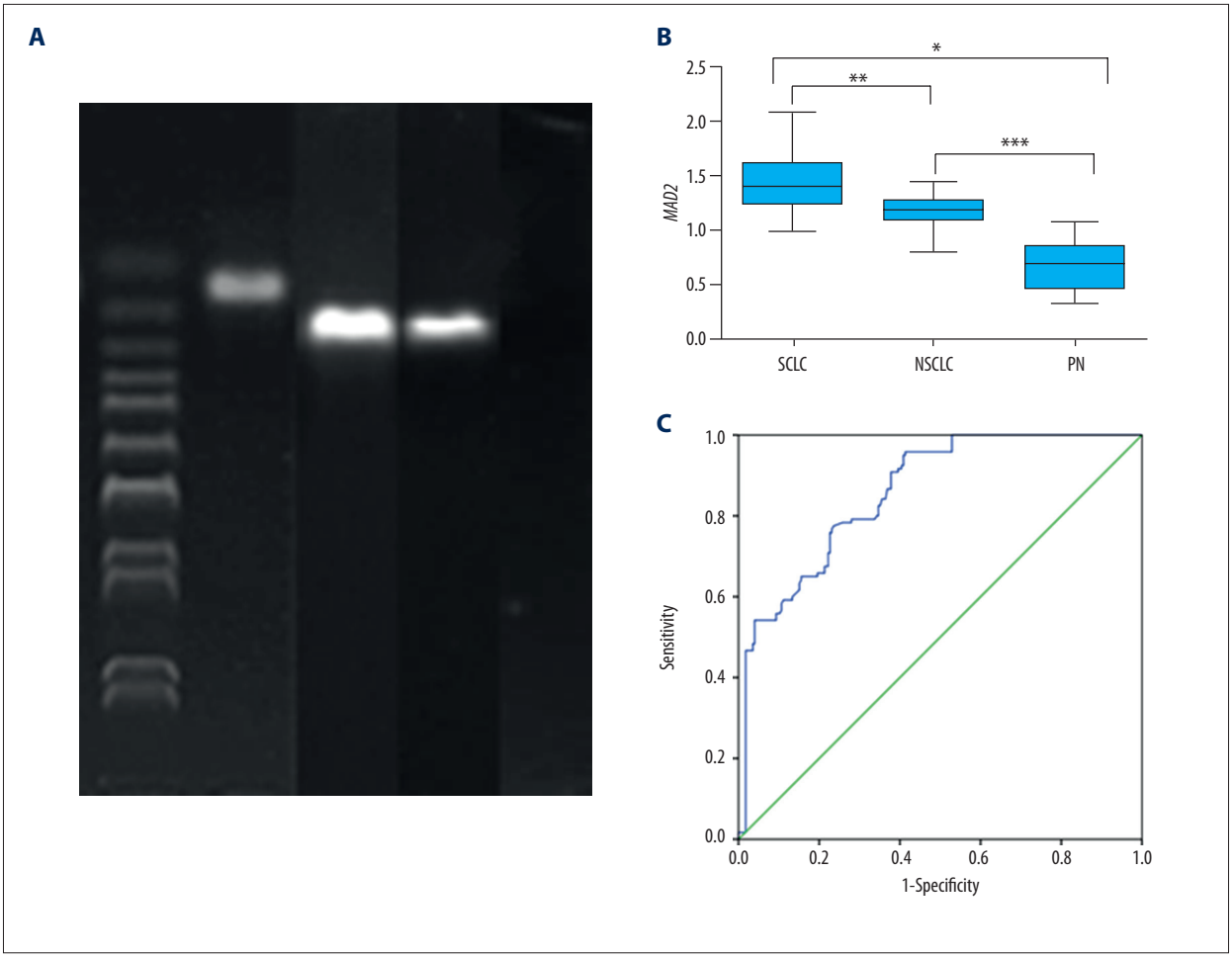

Figure 1. Agarose electrophoresis of MAD2 expression. MAD2 expression was assessed by agarose electrophoresis. GAPDH was used for internal reference and the length was 146 bp. The length of MAD2 was 163 bp. SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; PN, pulmonary nodule (**A**). MAD2 expression in SCLC, NSCLC, and PN groups. The quantity of MAD2 expression was assessed by qRt-PCR. * SCLC *vs.* PN, ** SCLC *vs.* NSCLC; *** NSCLC *vs.* PN, P<0.05 (**B**). ROC curve of MAD2 expression for the diagnosis of SCLC. 95% CI, 95% Confidential Interval (**C**).

1.380, the sensitivity and specificity were the best (53.32% sensitivity and 88.73% specificity).

MSA and ACA expression and clinical value

We divided the 207 patients into an SCLC group (N=70), an NSCLC group (N=72), and a PN group (N=65). MSA positivity was found in 26 patients in the SCLC group (37.20% of 72), patients in the NSCLC group (12.5% of 72), and 2 patients in the PN group (3.08% of 65).

The chi-square test showed a significant difference between the SCLC and NSCLC groups (P<0.05), and it was replicated in the SCLC and PN groups (P<0.05) (Figure 2A). ACA positivity was found in 27 patients in the SCLC group (38.57% of 70), 11 patients in the NSCLC group (15.28% of 72), and 4 patients in the PN group (6.15% of 65). The chi-square test showed a significant difference between the SCLC and NSCLC groups (P<0.05), as well as between the SCLC and PN groups (P<0.05) (Figure 2B). However, a significance difference was not found in the NSCLC and PN groups (data not shown). The sensitivity of MSA and ACA was 37.20% and 34.00%, respectively, and the specificity was 92.00% and 89.45%, respectively. The Youden index was 0.29 for MSA and 0.23 for ACA (Table 2).

MAD2 combined with MSA and ACA for the diagnosis of SCLC

When MAD2 was used as the criterion standard, the kappa values of MSA and ACA with MAD2 were 0.73 and 0.65, with high consistency (Table 3). Given the low sensitivity of MSA and ACA for the diagnosis of SCLC, combining MAD2 expression with MSA and ACA is an ideal choice. The sensitivity of parallel analysis was as high as 86.81% and the specificity of the serial

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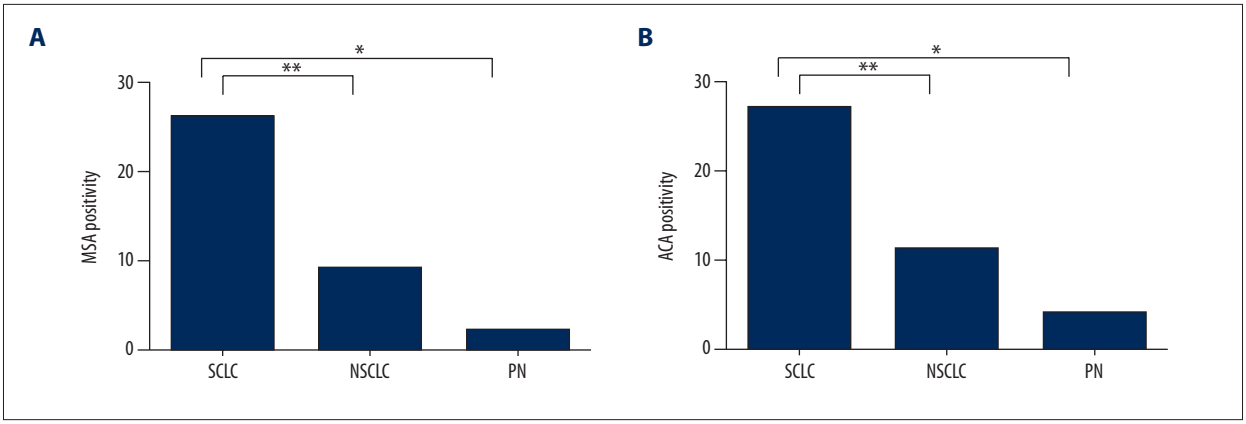

Figure 2. MSA positivity in SCLC, NSCLC, and PN groups. Chi-square analysis was used to measure the differences in MSA positivity among SCLC, NSCLC, and PN groups (**A**). ACA positivity in SCLC, NSCLC, and PN groups. Chi-square analysis was used to measure the differences in ACA positivity among SCLC, NSCLC, and PN groups. * SCLC *vs.* PN; ** SCLC *vs.* NSCLC, P<0.05 (**B**).

Table 2. The clinical value evaluation of MSA and ACA for the diagnosis of SCLC.

Group	Sensibility %	Specificity %	PPV	NPV	+LR	–LR	Youden index
MSA	37.20	92.00	0.45	0.89	4.65	0.68	0.29
ACA	34.00	89.45	0.36	0.88	3.22	0.74	0.23

PPV – positive predictive value; NPV – negative predictive value; +LR – positive likelihood ratio; –LR – negative likelihood ratio.

Table 3. Consistency analysis(*Kappa*) among *MAD2* expression with MSA and ACA.

Group	*MAD2* & MSA	*MAD2* & ACA
P	<0.05	<0.05
Kappa	0.73	0.65

Kappa: 0.4–0.6 as moderate consistency; 0.6–0.8 as high consistency; >0.8 as great consistency.

analysis was 96.82% (Table 4). MAD2 combined with MSA and ACA improved the sensitivity and specificity in the diagnosis of SCLC.

Discussion

Our study demonstrated that MAD2 expression was higher in SCLC patients than in NSCLC patients. MAD2 expression was associated with lymphatic metastasis and survival time. The area under the ROC for MAD2 expression in the diagnosis of SCLC was 0.799, with potential value for the diagnosis of SCLC. The consistency of the combination of MAD2, MSA, and ACA was high and enhanced the clinical value for SCLC.

CIN contributes to tumorigenesis. SAC performs a vital role in preventing chromosome mis-segregation. SAC monitors spindle microtubule structure, chromosome alignment on the spindle, and chromosome attachment to stockinette during mitosis [14]. MAD2, Bub1, and Bub2 form SAC together. After combining with Mad1, MAD2 changes into C-MAD2. Later on, mitotic checkpoint complex (MCC) is assembled by C-MAD2, Cdc20, BUBR1, and BUB3. The interaction between MCC and anaphase-promoting complex (APC) stops the cell from entering into anaphase [15]. MAD2 gene is highly conserved evolutionarily, with rare mutation. MAD2, inhibiting anaphase progression, stopped the proliferation of cells in culture and tumor xenografts. The expression of MAD2 varies in different types of carcinomas [16,17]. MAD2 is elevated in lung carcinoma [18]. In contrast, through phosphorylating SURVIVIN, MAD2 is

Table 4. Parallel and serial analysis of *MAD2* with MSA and ACA.

Group	*MAD2* & MSA	*MAD2* & ACA	Parallel analysis	Serial analysis
Sensibility %	68.75	66.59	86.81	64.31
Specificity %	91.21	91.21	81.31	96.82
Youden Index	0.60	0.59	0.68	0.61

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degraded in gastric carcinoma cells [19]. As exhibited in the present research, although MAD2 was detected both in SCLC and NSCLC, the quantity of MAD2 expression was higher in SCLC than in NSCLC ($P<0.05$). It is unknown why MAD2 expression varies in diverse carcinomas. The area under the ROC for SCLC was 0.799, which suggested we could distinguish SCLC from NSCLC based on the level of MAD2 expression. A study by Wang et al. identified the crucial role of MAD2 in the prognosis of carcinoma [20]. Consistently, MAD2 was associated with lymphatic metastasis and survival time in the present study. The reason may be that MAD2-positive tumors have a higher chance of developing persistent subclones to avoid remission and continue to grow. We found that MAD2 could act as a potential biomarker for SCLC. A number of studies have shown that autoantibodies can have low titers in tumorigenesis. These autoantibodies, targeting carcinoma antigen, could have an effect on receptors of carcinoma cells, thereby stopping cell proliferation [21,22]. They come into being in the early stage of carcinoma. Among them, autoantibodies (e.g., MSA and ACA) involved into the cell cycle have been tested frequently [12,23]. The tumor microenvironment is the cellular environment in which the tumor survives. In addition to cancer cells, different cells of either hematopoietic origin or from mesenchymal origin and cytokines form the tumor microenvironment together [24]. This influences tumor development, either due to a direct cross-talk with the tumor or by affecting immune cells functions. B and T cells derived from hematopoietic origin produce antibodies regulated by cytokines owing to induction of antigens [25]. A study reported that cytokines lead to T cell-dependent breakdown of tolerance, resulting in autoantibodies production [26]. In the present study, MSA and ACA were found to be correlated with SCLC, with 92.00% and 89.45% specificity, respectively. Nevertheless, MSA and ACA, detected by IIF, had low sensitivity.

Despite having certain advantages, MAD2 expression showed low sensitivity in qRt-PCR analysis. Hence, combining it with other biomarkers becomes unavoidable. The kappa values of MAD2 expression with MSA and ACA were 0.73 and 0.65, respectively, which shows that the combination of MAD2 expression with MSA and ACA is feasible. Parallel and serial analyses significantly enhanced the sensitivity and specificity. Further studies are needed to assess the function of MAD2 in induction of MSA and ACA.

Conclusions

MAD2 is elevated in SCLC, and MAD2 is related to prognosis and survival time of SCLC. Therefore, MAD2 could serve as a potential biomarker of SCLC. Due to the low sensitivity of MAD2 expression, cell cycle MSA and ACA were combined with MAD2 for the diagnosis of SCLC. This combination has high sensitivity and specificity for the diagnosis of SCLC.

Conflict of interests

None.

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