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A different TRAP220 expression in distinct histologic subtypes of lung adenocarcinoma and the prognostic significance

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ABSTRACT

Adenocarcinomas are a very heterogeneous subgroup of lung cancers, in which oncogenesis is linked to different molecular events. Recent evidence suggests that the hormonal status may contribute to the pathogenesis of lung adenocarcinoma. TRAP220 is the main subunit of the TRAP/Mediator complex and it binds to nuclear hormone receptors in the presence of their cognate ligand, as a cofactor of the transcription machinery. Since TRAP220 is an essential coactivator that interacts directly with estrogen receptor β (ERβ), we examined the expression of TRAP220 protein to investigate its role in lung adenocarcinoma, with particular attention being paid to its different histologic subtypes and the ERβ expression. We performed immunohistochemical detection of TRAP220 and ERβ protein in eighty-seven tissue samples from lung adenocarcinoma patients by using a tissue microarray, and Western blotting was then done to confirm the immunohistochemical observations. TRAP220 immunoreactivity was observed in 27 (31.0%) of the 87 adenocarcinoma cases. Analysis of the TRAP220 expression by Western blotting confirmed the immunohistochemical results. The TRAP220 expression was more frequently positive in the non-solid subtypes (bronchioloalveolar, acinar, and papillary patterns) than that in the solid subtype ($P = 0.027$) and the TRAP220 expression was more frequently positive in the well-differentiated adenocarcinomas than that in the moderately or poorly differentiated adenocarcinomas ($P = 0.005$). The tumors with a negative TRAP220 expression were larger in size ($P = 0.048$) and they more frequently showed lymph node metastasis ($P = 0.002$), pleural invasion ($P = 0.026$) and an advanced TNM stage ($P = 0.012$). The frequency of the TRAP220 expression in the cases with an ERβ expression was significantly higher than that in those cases without an ERβ expression ($P = 0.003$). The Kaplan–Meier survival curves demonstrated that the patients with a positive TRAP220 expression had a significantly longer survival time than those patients with a negative TRAP220 expression ($P = 0.014$). The multivariate analysis revealed that a TRAP220 expression was an independent good prognostic factor ($P = 0.049$). Our data may be useful to understand the different biologic basis for the development and progression of the subtypes of lung adenocarcinoma.

1. Introduction

Adenocarcinoma is becoming the most common histologic type of lung cancer in both gender and the incidence of adenocarcinoma is increasing in many countries worldwide [1]. It is the most histologically variable, heterogeneous form of lung cancer, both between cases and within individual tumors, and the different forms probably have different biological behavior and this has potential therapeutic implications for the patient [2]. However, the mechanisms accounting for the observed high heterogeneity of lung adenocarcinomas are unknown. A recent study reported there was a strong association between the estrogen receptor β (ERβ) expression and the histologic grade of lung adenocarcinomas, suggesting a specific role for ERβ in the pathogenesis of the different histologic subtypes of adenocarcinomas [3]. The mechanisms modulating the expression and function of ERβ in lung cancer still remain unclear.

Human TRAP/Mediator is an evolutionarily conserved multisubunit coactivator complex that acts as a molecular bridge between gene-specific transactivators and the RNA polymerase

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II-associated basal transcription machinery, and TRAP/Mediator may be involved in a variety of human disease states, including cancer [4–6]. TRAP/Mediator consists of 25–30 subunits that are thought to assemble in relatively discrete modules [7]. TRAP220 (also known as Med1/PBP/DRIP220/CRSP220) is the main subunit of the TRAP/Mediator complex and it binds to nuclear hormone receptors in the presence of their cognate ligand, as a cofactor of transcription machinery [8]. It has been shown that ER interacts with the complete TRAP/Mediator complexes, both in vivo and in vitro, through the TRAP220 subunit [9,10]. TRAP220 is amplified in several ER-positive breast and ovarian cancer cell lines, and this suggests that it might also play an oncogenic role in the progression of steroid hormone-dependent cancer [11]. Dougherty et al. have reported that the TRAP220 expression in the lung adenocarcinoma cell lines from females was significantly higher than that in the cell lines from males, and so TRAP220 may contribute to the difference in estrogenic responsiveness of lung adenocarcinomas [12].

Considering the importance of estrogen in lung adenocarcinoma's tumorigenesis and the coactivator function of TRAP220 in the ER signaling pathways, we performed immunohistochemical detection of TRAP220 and ERβ protein in lung adenocarcinoma tissue samples by using a tissue microarray. The purpose of this study is to investigate the role of TRAP220 as related with the ERβ expression in lug adenocarcinoma, with particular attention being paid to its different histologic subtypes. In addition, we wanted to determine whether the immunohistochemical expression of TRAP220 could provide useful information as a novel prognostic option for treating primary lung adenocarcinoma. This study is the first study to critically determine the clinicopathological roles of the expression of TRAP220 in lung adenocarcinoma patients.

2. Materials and methods

2.1. Patients and tissues

Tissue samples were obtained from 87 Korean patients who underwent surgical resection for primary lung adenocarcinoma at Dong-A University Medical Center from 2000 to 2006. No preoperative chemotherapy or radiotherapy had been performed in any of these cases. Standard lobectomy and lymph node dissections were performed in every case. The cases that had any other malignancy occurring before or after the primary lung cancer were excluded from our study. The postoperative pathological staging was determined according to the 7th Edition of the TNM classification [13]. The clinical records, pathological reports and follow-up information were also obtained for all the cases. The institutional review board at Dong-A University Medical Center approved our study, and written informed consent was obtained from all the patients for surgery and to use their resected samples for research.

2.2. Histologic evaluation

The hematoxylin and eosin-stained slides of each case were reviewed by an experienced pathologist (M.S.R.) to confirm the original diagnosis, which was based on the revised World Health Organization (WHO) classification in 2004 [14]. The percentage of each histologic component (acinar, papillary, bronchioloalveolar and solid), in addition to the micropapillary component, was recorded. After estimating the amounts of each histologic subtype in increments of 10%, the tumors were classified according to the histologic subtype that represented the major component, as proposed by Motoi et al. [15]. The signet ring and mucinous bronchioloalveolar carcinoma (BAC) subtypes were not included in this study due to the limited number of samples (1 and 2 cases, respectively). We also recorded the least differentiated component as the differentiation grade when there was evidence of more than one grade of differentiation in a tumor, according to histological grading of the 2004 WHO classification [14].

2.3. Construction of the tissue microarray

One mm cores were removed from the representative major histologic subtype of the adenocarcinomas that had been previously formalin-fixed and paraffin-embedded. For all the arrays, 3 cores of different areas of the representative tumor were removed from each case and these were put in a new blank recipient paraffin block using a previously described method [16], and 4 μm-thick sections were taken for all the immunohistochemical staining. Full cross-sections from the paraffin blocks were used for 5 of the adenocarcinomas along with the adjacent normal lung tissue to confirm the staining patterns seen on the tissue microarray.

2.4. Immumohistochemistry

Immunohistochemical staining for TRAP220 and ERβ were performed on the tissue microarray slides by using the avidin–biotin–peroxidase complex method. Deparaffinization of all the sections was performed through a series of xylene baths, and rehydration was performed with a series of graded alcohol solutions. To enhance the immunoreactivity, microwave antigen retrieval was performed at 750 W for 30 min in Tris EDTA (pH 9.0). After blocking the endogenous peroxidase activity with 5% hydrogen peroxidase for 10 min, incubation with the primary antibody was performed for 1 h at room temperature. The primary antibodies used in immunostaining were rabbit polyclonal antibody directed against TRAP220 (CRSP1; Novus Biologicals, Littleton, CO) used at a 1:250 dilution and mouse monoclonal antibody directed against ERβ (PPG5/10; Serotec Ltd, Oxford, UK) used at a 1:50 dilution. An Envision™Chem™ Detection Kit (DakoCytomation, Carpinteria, CA) was used for the secondary antibody at room temperature for 30 min. After washing the tissue samples in Tris buffered saline for 10 min, 3,3′-diaminobenzidine was used as a chromogen, and then Mayer's hematoxylin counterstain was applied. Positive controls for TRAP220 and ERβ were normal adrenal gland and normal breast tissue, respectively. Negative control was obtained by substituting primary antibody with buffer.

2.5. Immunohistochemical assessment

The percentage and intensity of the immunoreactive tumor cells in each core were recorded and the final value of the positive tumor cells was determined as the mean of the immunoreactivity of the 3 cores. The presence of tumor tissue in at least 2 interpretable cores was required to include a case in the statistical analysis. All the slides were independently evaluated by an experienced pathologist (M.S.R.) and one of the authors (K.E.L.) without them having knowledge of any of the clinicopathologic data. There were only minor discrepancies in the evaluation. Those slides with discrepant evaluation were reevaluated under a multi-head microscope until a consensus evaluation was obtained.

TRAP220 immunoreactivity was defined as those showing a nuclear with/without cytoplasmic staining pattern of the tumor tissue with minimal staining background. ERβ immunoreactivity was defined as those showing a nuclear staining pattern of the tumor tissue. The percentage scoring of the immunoreactive tumor cells was as follows: 0 (0%), 1 (1–10%), 2 (11–50%) and 3 (>50%). The staining intensity was visually scored and stratified as follows: 0 (negative), 1 (weak, if it was a blush) and 2 (strong, if it was obviously positive at 20× magnification). A final score was obtained for each case by multiplying the percentage and the intensity score. Therefore, the tumors with multiplied score exceeding 4 (i.e., the

tumors with a strong intensity of >10% of the tumor cells) were recorded as having positive immunoreactivities for TRAP220 and ERβ; all the other scores were considered to be negative.

2.6. Western blot analysis

Eight adenocarcinomas (4 cases with a positive TRAP220 expression and 4 cases with a negative TRAP220 expression) were analyzed. All the tissue specimens were snap frozen within 20 min after excision and they were stored at −80 °C. The cryofrozen tissue samples were lysed in PRO-PREP™ protein extraction solution (iNtRON Biotechnology Inc., Korea), and then comparable amounts of protein were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis; the proteins were then transferred to a nitrocellulose membrane. The membrane was blocked in 5% nonfat milk for 1 h and then it was incubated overnight with an antibody against TRAP220 (1:500 dilution; Novus Biologicals, Littleton, CO). Anti-β-actin (clone AC-15, 1:2000 dilution; Sigma Chemical, St Louis, MO) was used for the loading controls. The signals from the primary antibody were amplified by HRP-conjugated anti-rabbit IgG (Chemicon, Temecula, CA); these amplified signals were detected with using Enhanced Chemiluminescence Plus (Amersham Pharmacia Biotech, Piscataway, NJ) and this was followed by autoradiography.

2.7. Statistical analysis

Associations between the TRAP220 expression and the clinicopathologic characteristics and the ERβ expression were analyzed using the χ^2 test or Fisher's exact test. Student's t test with Yates correction was used for the continuous variables. The survival probabilities were estimated using the Kaplan–Meier method and they were compared using the log-rank test. The overall survival time was defined as the time from the date of surgery to the date of death as a result of any cause. The patients who were alive at the date of the last follow-up were censored on that date plus one day. Multivariate Cox proportional hazard regression analysis was used to assess the prognostic significance of the TRAP220 expression and the other clinicopathologic characteristics on survival. Overall, 95% confidence intervals were used throughout the analysis. Statistical significance was defined as $P \leq 0.05$ (two tailed). All the statistical tests were performed with the Statistical Package, SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinicopathologic characteristics

The patients consisted of 53 men and 34 women, and they ranged in age from 28 to 74 years (median age: 59 years). Among the 78 patients who had a known smoking history, there were 41 never smokers, 11 former smokers (who had quit smoking more than 12 months before the diagnosis of lung cancer or before the interview) and 26 current smokers. The tumor size ranged from 1.0 to 9.5 cm, with forty-three cases involving tumors ≤3 cm in size, while 44 cases involved tumors >3 cm in size. There were 60 cases without pleural invasion and 27 cases with pleural invasion. There were 51 negative cases and 36 positive cases for lymphovascular invasion. There were 42 negative cases and 35 positive cases for lymph node metastases. According to the TNM staging system, 11 patients were stage IA, 28 were stage IB, 9 were stage IIA, 30 were stage IIB, 4 were stage IIIA and 6 were stage IIIB at the time of surgery.

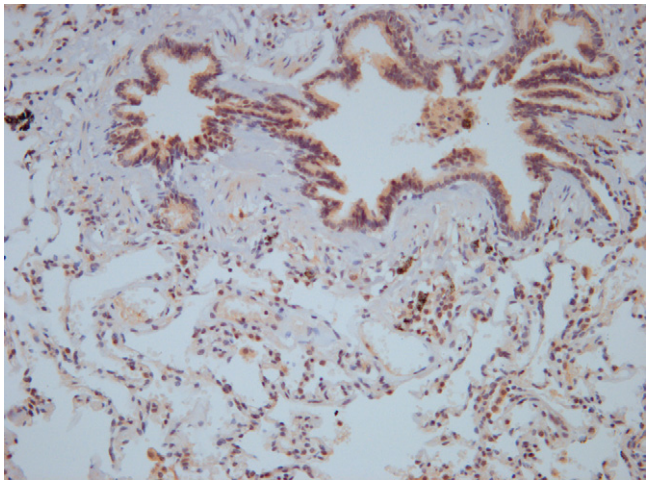

Fig. 1. In the adjacent normal lung tissue, the nonneoplastic bronchial and alveolar epithelial cells, stromal cells and endothelial cells were occasionally reactive for TRAP220 with strong intensity.

3.2. Histologic features

According to the 2004 WHO classification, 92.0% of the adenocarcinomas were the mixed subtype: 3 were pure papillary, 3 were pure solid and 1 was pure acinar. No pure BAC was identified. When classifying the tumors according to the major histologic components, the most common subtype was solid-predominant (33.3%), followed by papillary-predominant (29.9%), acinar-predominant (19.5%) and bronchioloalveolar-predominant (17.3%). However, the most common histologic pattern present in any amount was acinar, followed by papillary, solid and bronchioloalveolar. In regards to differentiation grade, the bronchioloalveolar pattern was virtually well differentiated except for a few cases, whereas solid pattern was poorly differentiated. Although all three (well, moderately, and poorly) grades were recognized among acinar and papillary patterns, acinar and papillary patterns were more commonly well or moderately differentiated. The tumor grade was well differentiated in 37 cases, moderately differentiated in 21 cases and poorly differentiated in 29 cases.

3.3. Immunohistochemical findings

All the cores for each tumor demonstrated similar staining characteristics. Seven cases had only 2 cores with enough tissue to evaluate. The staining patterns of the TMA cores showed concordant results with those of the 5 full cross-sections. The expression of TRAP220 protein was detected in the nuclei with/without cytoplasms of both the normal cells and the tumor cells. In the adjacent normal lung from the 5 full cross-sections, the nonneoplastic bronchial and alveolar epithelial cells, stromal cells and endothelial cells were occasionally reactive for TRAP220 with strong intensity (Fig. 1). In the tumor tissue, TRAP220 immunoreactivity was observed in 27 (31.0%) of the 87 adenocarcinoma cases. The expression was limited to only the tumor cells without any background labeling. The staining intensity and percentage were relatively well-concordant.

The expression of ERβ was detected in the nuclei of tumor cells and it was observed in 28 (32.2%) of the 87 adenocarcinoma cases.

3.4. Correlation between the TRAP220 immunoreactivity and the Western blot analysis

To confirm the immunohistochemical observations, Western blotting was performed with equal amount of the total lysates from

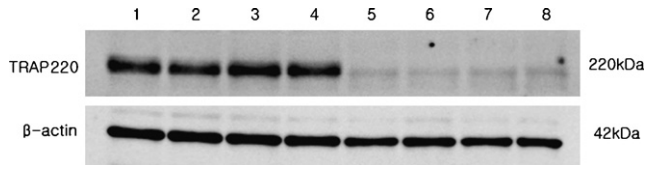

Fig. 2. Western blot detection of TRAP220 in the tumor tissues with a positive TRAP220 expression (lanes 1–4) compared with the tumor tissues with a negative TRAP220 expression (lanes 5–8). Equal amounts of protein were loaded and separated by sodium dodecyl sulfate-polyacrylamide gel electophoresis and the proteins were subsequently transferred to a nitrocellulose membrane. Immunodetection was performed with anti-TRAP220 antibody. Anti-β-actin antibody was used to control for equal loading. The Western blot analysis showed consistent results with the immunohistochemical study.

4 adenocarciomas with a positive TRAP220 expression and 4 adenocarcinomas with a negative TRAP220 expression. Although the Western blot analysis did not show completely clear bands due to contamination by imperfect microdissection of tumor, the Western blot analysis showed that the total levels of TRAP220 protein were increased in the tumor tissues with a positive TRAP220 expression, as compared with that of the tumor tissues with a negative TRAP220 expression, which was relatively consistent with the immunohistochemical results (Fig. 2).

3.5. Correlation between TRAP220 immunoreactivity and the clinicopathologic characteristics and the ERβ expression

The various clinicopathologic characteristics of the patients and their tumors were compared according to the TRAP220 immunoreactivity (Table 1). The mean tumor size was significantly larger in the cases with a negative TRAP220 expression than that in the cases with a positive TRAP220 expression ($P = 0.048$). A statistically significant association was found between the TRAP220 expression and the different subtypes of adenocarcinoma. The TRAP220 expression was positive in only 13.8% of the solid-predominant subtypes, but the TRAP220 expression was positive in 53.3% of the nonmucinous bronchioloalveolar-predominant subtypes, in 35.3% of the acinar-predominant subtypes and in 34.6% of the papillary-predominant subtypes ($P = 0.05$) (Fig. 3). The TRAP220 expression showed a different trend in the solid subtype as com-

Table 1
Correlations of the TRAP220 expression with the conventional clinicopathologic factors in 87 lung adenocarcinoma patients.

Clinicopathologic factors	TRAP220 expression		*P* value
	Positive ($n = 27$)	Negative ($n = 60$)	
Age	58.85 ± 7.52	57.67 ± 11.00	0.613
Gender			0.488
Male	18	35	
Female	9	25	
Smoking history (pack-years)[a]	16.88 ± 19.49	17.70 ± 18.87	0.644
Smoking status[a]			0.866
Never	12	29	
Former	3	8	
Current	9	17	
Tumor size	3.10 ± 1.17	3.80 ± 1.62	0.048
Predominant histologic subtype			0.05
Bronchioloalveolar	8	7	
Acinar	6	11	
Papillary	9	17	
Solid	4	25	
Differentiation grade			0.005
Well	19	18	
Moderate	4	17	
Poor	4	25	
Micropapillary component			0.356
Negative	12	34	
Positive	15	26	
Pleural invasion			0.026
Negative	14	46	
Positive	13	14	
Lymphovascular invasion			0.062
Negative	20	31	
Positive	7	29	
Lymph node metastasis			0.002
Negative	20	22	
Positive	7	38	
TNM stage			0.012
I	18	21	
II/III	9	39	
Estrogen receptor β			0.003
Negative	12	47	
Positive	15	13	

[a] 78 patients who had a known smoking history were analyzed.

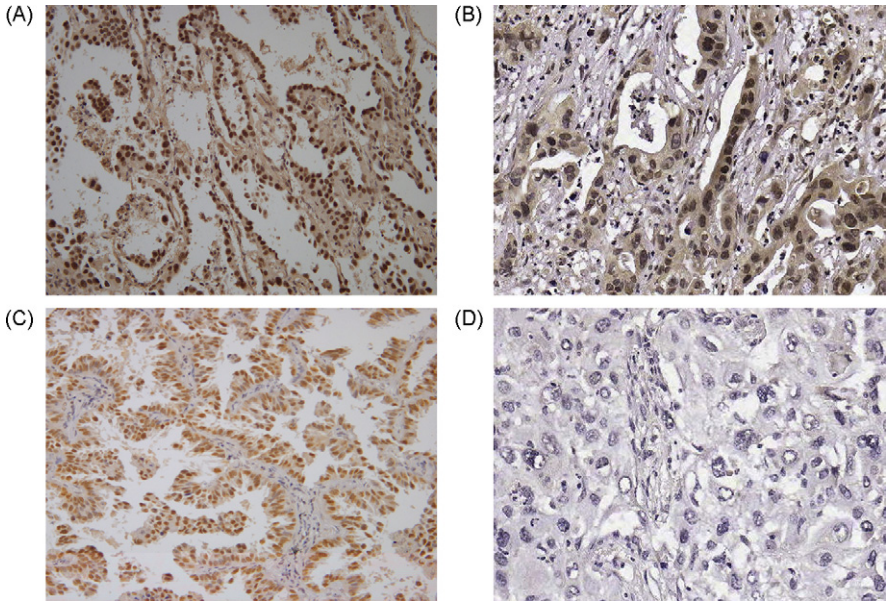

Fig. 3. Immunohistochemical findings of TRAP220 in the distinct subtypes of lung adenocarcinoma tissue. The TRAP220 expression was more frequently positive in the nonmucinous bronchioloalveolar-predominant (A), acinar-predominant (B) and papillary-predominant (C) subtypes than in the solid-predominant (D) subtype.

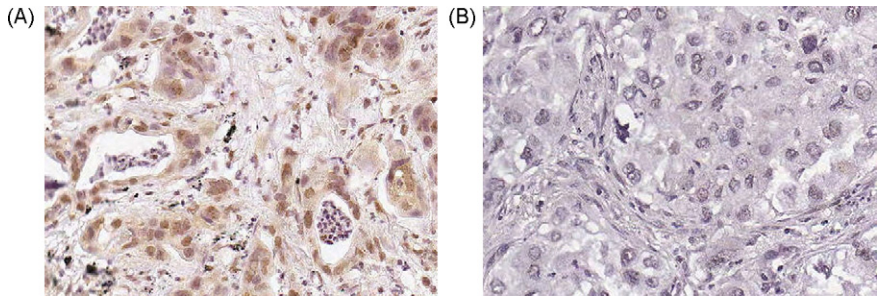

Fig. 4. Immunohistochemical findings of estrogen receptor β (ERβ) in lung adenocarcinoma. The case of acinar-predominant subtype with a positive TRAP220 expression (Fig. 3B) showed a positive ERβ expression (A), whereas the case of solid-predominant subtype with a negative TRAP220 expression (Fig. 3D) showed a negative ERβ expression (B).

pared to the non-solid subtypes (bronchioloalveolar, acinar and papillary patterns) ($P = 0.027$). A TRAP220 expression was more frequently detected in the well-differentiated adenocarcinomas than that in the moderately or poorly differentiated adenocarcinomas ($P = 0.005$). The tumors with a negative TRAP220 expression more frequently showed lymph node metastasis ($P = 0.002$), pleural invasion ($P = 0.026$) and an advanced TNM stage ($P = 0.012$). There was no significant association with age, gender, the smoking history (pack-years), the smoking status, a micropapillary component or lymphovascular invasion. The frequency of the TRAP220 expression in the cases with an ERβ expression was significantly higher than that in those cases without an ERβ expression ($P = 0.003$) (Fig. 4). Although there was no significant association between the ERβ expression and the histological subtypes, the non-solid subtypes tended to more frequently show a positive ERβ expression than the solid subtype ($P = 0.073$) and the well differentiated adenocarcinomas tended to more frequently show a positive ERβ expression than the moderately or poorly differentiated adenocarcinomas ($P = 0.086$). No significant association was found between the ERβ expression and the other clinicopathologic characteristics (data not shown).

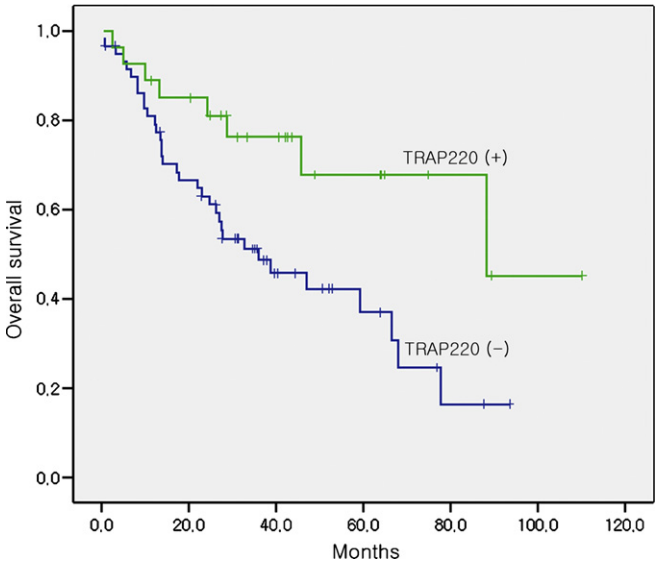

Fig. 5. The overall survival curves after surgical therapy grouped by TRAP220 expression, calculated by the Kaplan–Meier method. The positive TRAP220 expression group ($n = 27$; green line) had significantly longer survival than the negative TRAP220 expression group ($n = 60$; blue line) ($P = 0.014$).

3.6. The influence of the TRAP220 expression on recurrence and survival

Adequate clinical follow-up information was available for all 87 cases. The mean follow-up period of the 87 cases was 48.6 months, and this ranged from 7.2 to 110.3 months. Fifty-one (58.6%) were still alive, but 36 (41.4%) died during the follow-up period. Of the latter, 25 died of documented progressive lung cancer, 8 of respiratory dysfunction and 3 of other diseases. Forty (46.0%) had recurrences during the follow-up period: 9 had distant recurrences that included the liver, adrenal gland, brain and bone, and there were 31 locoregional recurrences. The mean duration from the surgery to the recurrence in these 40 patients was 26.5 months, and this ranged from 3.0 to 48.7 months. The 5-year survival rates of the patients with a positive and negative TRAP220 expression were 67.7% and 37.0%, respectively. The Kaplan–Meier survival curves demonstrated that the patients with a positive TRAP220 expression had a significantly longer survival time than those patients with a negative TRAP220 expression ($P = 0.014$) (Fig. 5). The multivariate analysis using the Cox proportional hazard model revealed that a TRAP220 expression was an independent good prognostic factor ($P = 0.049$) and lymph node metastasis and the TNM stage were also significant ($P = 0.038$ and $P = 0.033$, respectively. However, the histologic subtype (solid vs. non-solid) was only marginally significant ($P = 0.075$). The other clinicopathologic factors were not significant (Table 2).

4. Discussion

To the best of our knowledge, this is the first study in which the relationship between the TRAP220 expression and the clinicopathological features, with special attention given to the histologic pattern and the prognostic significance of lung adenocarcinomas, has been extensively investigated. The TRAP220 expression showed a different trend in the distinct histologic subtypes of lung adenocacinoma and it was an independent good prognostic factor for lung adenocarcinoma.

Adenocarcinomas are a very heterogeneous subgroup of lung cancers, in which oncogenesis is linked to different molecular

Table 2
Cox multivariate analysis to determine the independent prognostic value of different variables in relation to the overall survival of 87 lung adenocarcinoma patients.

Covariate	Risk ratio (95% confidence interval)	*P* value
Histologic subtype (non-solid vs solid)	0.923 (0.740–4.557)	0.075
Lymph node metastasis (− vs +)	1.701 (1.061–8.047)	0.038
TNM stage (I/II/III)	2.341 (1.684–9.572)	0.033
TRAP220 (+ vs −)	2.972 (1.427–4.611)	0.049

events. A recent study showed that specifying the major subtype in the mixed subtype adenocarcinomas led to meaningful correlations with the clinical and molecular features, including the smoking status, the gene profiling clustering and EGFR mutations [15]. In the present study, the TRAP220 expression showed a different pattern in the non-solid subtypes (bronchioloalveolar, acinar and papillary patterns) as compared to the solid subtype, which suggests that TRAP220 has a specific role in the pathogenesis of distinct histologic subtypes of lung adenocarcinoma, and it specifically drives different differentiative pathways. The TRAP220 expression could represent a useful marker for a more accurate histopathologic subclassification of adenocarcinomas, with important applications for the clinical behavior.

Lung adenocarcinoma has recently become the most frequent histologic type in women and nonsmokers, which suggests that other putative etiologic factors such as the hormonal status may play an important role in the development of lung adenocarcinoma [17,18]. ERβ has been shown to be expressed in both normal lungs as well as in lung tumors [3,19]. Ali et al. reported a different ERβ expression pattern in the distinct histologic subtypes of lung adenocrcinoma, with a low or negative ERβ expression in 68.2% of the solid subtypes and a high ERβ expression in 76.5% of the nonmucinous bronchioloalveolar subtypes, in 69.4% of acinar subtypes and in 61.2% of papillary subtypes [3]. Because TRAP220 has a coactivator function in ER signaling, we determined the level of the TRAP220 and ERβ expressions to examine the relationship between the ERβ and TRAP220 expressions and their role in lung adenocarcinoma. In the present study, the frequency of a TRAP220 expression in the cases with an ERβ expression was significantly higher than that in those cases without an ERβ expression. Furthermore, the TRAP220 expression showed a different pattern in the non-solid subtypes as compared to the solid subtype, which is a similar trend as that for the ERβ expression, as reported by Ali et al. [3]. This suggests a specific role for TRAP220 in the pathogenesis of different histologic subtypes of lung adenocarcinoma in relation to estrogenic responsiveness. In fact, it was suggested that ER might function through TRAP220 alone or through a different TRAP220 (sub) complex [20]. Estrogen-dependent activation of the cathepsin-D mRNA expression was blocked by TRAP220 siRNA [21]. TRAP220 was found to be amplified in ER-positive breast cancer tissues and cell lines, and so this suggests a possible oncogenic role for TRAP220 in steroid hormone-dependent cancer [11]. The TRAP220 expression was higher in the lung adenocarcinoma cell lines from females than males, and so this suggests TRAP220 may contribute to the differences in estrogenic responsiveness between the lung adenocarcinoma cells in females and males [12]. If biologic interactions between ER and TRAP220 promote growth of a subtype of lung adenocarcinoma, this signaling axis could offer a new target for the treatment of lung adenocarcinoma.

It is notable that TRAP220 is essential for physiological processes and embryologic development. TRAP220 is a direct binding target for a number of regulatory transcription factors involved in cell growth and differentiation [22]. Although very little is known about the regulation of the TRAP220 gene, the TRAP220 chromosome localization on locus 17q12–q21.1 suggests its involvement in human cancers [23]. The TRAP220 locus was found to be amplified in some breast cancers and TRAP220 may play a role in breast carcinogenesis [11]. The TRAP220 expression was elevated in half of the human prostate cancer tissues and TRAP220 plays a coregulatory role in the cell proliferation and survival of prostate cancer [24]. However, recent study revealed that TRAP220 knockdown in human melanoma cells in vitro increased the invasive properties and TRAP220 knockdown in melanoma cells in vivo switched the melanoma phenotype from non-tumorigenic to strongly tumorigenic in nude mice [25]. Furthermore, Gade et al. showed that TRAP220-expressing A549 human lung adenocarcinoma cells formed significantly fewer metastases compared with the controls and a majority of primary lung cancer tissues showed a consistent loss of the TRAP220 and tumor metastasis suppressor DAPK1 expressions; this suggests that TRAP220 loss contributes to the attenuation of antitumor responses and the promotion of tumor growth [26]. In the present study, we have shown that a subset of adenocarcinomas that revealed a negative TRAP220 expression was correlated with poor prognostic clinicopathologic factors, including the solid subtype, lymph node metastasis and an advanced tumor stage. The patients with a negative TRAP220 expression had a significantly shorter survival time than those patients with a positive TRAP220 expression. The fact that depending on the type of cancer, the TRAP220 expression could either increase as we herein demonstrated in non-solid lung adenocarcinoma, as well as in breast and prostate cancers as was previously demonstrated by others, or the TRAP220 expression could decrease in solid lung adenocarcinoma, should be taken into account. It seems that TRAP220 has a contradictory action in the pathogenesis of different histologic subtypes of lung adenocarcinoma. TRAP220 loss seemed to be necessary for dedifferentiation and progression in solid type adenocarcinomas, whereas TRAP220 overexpression seemed to be necessary for tumor proliferation in non-solid type adenocarcinoma. Therefore, the opposite promoting/inhibitory role of TRAP220 in tumors was once more present, and the role of TRAP220 is set by an undetermined histotype specificity. Further prospective immunohistochemical study for TRAP220 using full cross-sections of adenocarcinomas including various histologic components in the same tumor would allow us to compare the expression change of TRAP220 in different histologic components and to define the role of TRAP220 in the development and progression of lung adenocarcinomas.

5. Conclusion

Our findings suggest that TRAP220 plays an important coregulatory role in the development and progression of lung adenocarcinoma. It seems that the TRAP220 expression showed a different trend in the distinct histologic subtypes of lung adenocacinoma in relation to estrogenic responsiveness. We also hypothesize that TRAP220 is lost during dedifferentiation of tumor cells, suggesting that the lack of TRAP220 could be associated with aggressive biologic behavior. Therefore, our results highlight the fact that among the various molecular events associated with a tumorigenic phenotype of human lung adenocarcinomas, the level of the TRAP220 expression should be also taken into account. Taken together, TRAP220 may represent a new target for therapeutic intervention in a subset of human lung adenocarcinoma patients and in relation to the ER signaling.

Conflict of interest

None declared.

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