

Abnormal expression and clinicopathologic significance of p120^{ctn} in lung cancer

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Summary. The aim of this study was to investigate the relationship between the expression of p120^{ctn} in human lung squamous cell carcinoma, adenocarcinoma and its clinicopathologic significance. The expression of p120^{ctn} in tumors and adjacent normal lung tissues from 143 patients was examined by immunohistochemistry and Western blot. Expression of p120^{ctn} occurs mainly in the cell membrane of normal bronchial mucosa. Abnormal expression of p120^{ctn}, including cytoplasmic and reduced membranous expression, was found in 114 of 143 specimens (79.7%) and was significantly associated with poor differentiation, high TNM stage, and lymph node metastasis ($P < 0.05$ for each) but not with histologic subtype. The Kaplan-Meier survival test revealed that abnormal expression of p120^{ctn} was related to poor survival ($P < 0.001$). A Cox regression analysis revealed that abnormal p120^{ctn} expression was an independent factor in predicting patient survival ($P = 0.024$). Compared with that in normal lung tissues, membranous protein level was lower in tumors ($P = 0.003$). Abnormal expression of p120^{ctn} is associated with tumor progression and poor prognosis in lung squamous cell carcinoma and adenocarcinoma. Reduced expression or even the absence of p120^{ctn} isoform 1 and 3 in tumor cell membranes may be responsible for the abnormal expression of p120^{ctn} that has been found in lung cancer.

Key words: Catenin, Lung cancer, p120^{ctn}, Prognosis

Introduction

Lung cancer is one of the most lethal malignant tumors, and the primary causes of this lethality include tumor recurrence and metastasis. Dysfunction of adhesion molecule and destruction of cell adhesion are the initial steps of tumor metastasis. p120-catenin (p120^{ctn}), a newly found adhesion molecule, may play an important role in tumor progression and metastasis. However, there is no data on its isoform expression and significance in lung squamous cell carcinoma (SCC) and adenocarcinoma in Chinese patients.

Originally, p120^{ctn} was identified as a tyrosine kinase substrate of *Src* and tyrosine, phosphorylated by several growth factors, such as EGF, PDEF, CSF-1, and Erb-B2 (Anastasiadis and Reynolds, 2000). As a member of the catenin family, which includes β - and γ -catenin, p120^{ctn} can bind with the cytoplasmic domain of E-cadherin (E-cad), not the β -catenin-binding domain (Yap et al., 1998; Thoreson et al., 2000). Depending on differences in the status of tyrosine phosphorylation, p120^{ctn} can be dynamically distributed in the cell membrane or the cytoplasm; thus, it has both positive and negative effects on cadherin-mediated cell adhesion and tumor progression (Mariner et al., 2001).

E-cad is a transmembrane protein, and its extracellular domain can cluster in a zipper-like form, through Ca^{2+} -dependent homophilic interactions, while its intracellular domain can form a complex with the catenins (β , γ , and p120^{ctn}) and can link to the actin cytoskeleton by binding α -catenin. Furthermore, E-cad regulates cell-cell adhesion and maintains cell structure. Abnormalities in such cadherin/catenin complex in structure or function will induce cell scattering and tumor metastasis (Herrenknecht et al., 1991; Nagafuchi et al., 1991; Rimm et al., 1995).

Dysfunctional expression of the E-cad pathway in non-small cell lung cancer (NSCLC) and its prognostic significance has been reported in several studies (Shibanuma et al., 1998; Smythe et al., 1999; Pirinen et

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al., 2001). Bremnes et al. used tissue microarray analysis to examine both the cadherins and the catenins and their prognostic significance in NSCLC (Bremnes et al., 2002). They concluded that reduced expression of E-cad and β -, α -, and γ -catenin, but not of p120^{ctn}, was associated with tumor progression and significantly shorter survival. To further address this question, we examined the expression patterns of E-cad, β -catenin, and p120^{ctn} and their prognostic significance for 143 patients with lung SCC and adenocarcinoma. In a previous paper, we reported that E-cad but not β -catenin was significantly related to shorter survival (Qiu et al., 2002). In the present study, our data demonstrate that p120^{ctn} is an independent prognostic factor for the survival of patients with lung SCC and adenocarcinoma. Several p120^{ctn} isoforms from cell membranous proteins are for the first time identified in these tumor samples.

Materials and methods

Case materials

This study was conducted with the approval of the local institutional review board at China Medical University. The primary tumors of 143 patients with lung SCC and adenocarcinoma who underwent complete resection (105 males and 38 females) in the First Affiliated Hospital of China Medical University were studied retrospectively. Of these samples, 80 were obtained between 1980 and 2001, and the complete follow-up for each patient was included in the prognosis analysis (ranging from 8 to 140 months); the other 63 samples were collected between November 2001 and September 2002. None of the patients had received radiotherapy or chemotherapy before surgical resection, and all were treated with routine chemotherapy after the operation. The mean age of the patients was 59 years (range, 26-87 years). All 143 specimens were reevaluated with respect to histologic subtype, differentiation, and tumor stage (Travis et al., 2004), which included 79 SCC (18 well differentiated, 28 moderately differentiated, and 33 poorly differentiated) and 64 adenocarcinomas (14 well differentiated, 30 moderately differentiated, and 20 poorly differentiated). The TNM staging system of the International Union Against Cancer (1999) was used to classify the specimens as stage I (n=29), II (n=9), III (n=96), or IV (n=9) (Watanabe, 2003). Lymph node metastases were identified in 88 of the 143 patients. Among these samples, 32 fresh specimens and corresponding normal tissue samples were used for Western blot analysis and were stored at -70°C immediately after resection (10 SCC and 22 adenocarcinomas from 24 males and 8 females; mean age of patients, 59 years).

Immunohistochemical assessment

Surgically excised tumor specimens were fixed with 10% neutral formalin and embedded in paraffin, and 4-

μ m-thick sections were prepared. Normal bronchial epithelium present in the tumor slides was used as an internal positive control. Immunostaining was performed by the avidin-biotin-peroxidase complex method (Ultrasensitive™, MaiXin, Fuzhou, China). The sections were deparaffinized in xylene, rehydrated with graded alcohol, and then boiled in 0.01 M citrate buffer (pH 6.0) for 2 min with an autoclave. Next, 0.3% hydrogen peroxide was applied to block the endogenous peroxidase activity and the sections were incubated with normal goat serum, to reduce nonspecific binding. They were then incubated with p120^{ctn}-specific mouse monoclonal antibody (1:200 dilution; Transduction Laboratories, Lexington, KY, USA) or mouse immunoglobulin (at the same concentration), as the negative control, at 4°C overnight. Biotinylated goat anti-mouse serum IgG was used as a secondary antibody. After washing, the sections were incubated with streptavidin-biotin conjugated with horse-radish peroxidase, and the peroxidase reaction was developed with 3,3'-diaminobenzidine tetrahydrochloride. Counterstaining was done lightly with hematoxylin, and the sections were dehydrated in alcohol before mounting.

Two investigators who were unaware of the clinical data examined all tumor slides randomly. Five views were examined per slide, and 100 cells were observed per view, at x400 magnification. Labeling scores were determined by the percentage of positive cells per slide (0%–100%), for membranous and cytoplasmic staining separately. In normal bronchial epithelium, p120^{ctn} showed a strong staining pattern in the cell membrane and little staining in the cytoplasm. Tumor tissues showed both staining patterns. Therefore, we semiquantitatively classified all the stained slides into 3 categories, according to the proportion of tumor cells that were immunoreactive for p120^{ctn}. When $\geq 90\%$ of the tumor cells stained for p120^{ctn} in the cell membrane, the case was defined as normal membranous expression. When $< 90\%$ of the tumor cells stained for membranous expression, the case was defined as reduced membranous expression. When $\geq 10\%$ of the tumor cells stained for p120^{ctn} in cytoplasm, the case was defined as ectopic cytoplasmic expression. Either reduced membranous expression or ectopic cytoplasmic expression was defined as abnormal expression of p120^{ctn}.

Western blot

Fresh frozen samples from 32 tumors and corresponding normal lung tissues were lysed with lysis buffer (50 mM Tris pH 7.2, 150 mM NaCl, 1 mM EDTA, and 1 mM DTT with 10 μ g/ml leupeptin, 10 μ g/ml aprotinin, and 1 mM PMSF) and were centrifuged at 12000 g for 20 min at 4°C. The sediment was placed in lysis buffer plus 1% Triton X-100, at 4°C overnight, and then was centrifuged again at 12000 g for 20 min at 4°C to extract membranous protein. Finally, the supernatants were stored at -20°C, and protein

concentrations were determined by the Bradford method. Forty micrograms of each sample was separated by 12% SDS-PAGE and then was transferred to a polyvinylidene fluoride membrane. The transferred samples were incubated with the anti-p120^{ctn} antibody at a 1:800 dilution, at 4°C overnight. After incubation with peroxidase-coupled anti-mouse IgG (HuaMei, Beijing, China), the proteins were visualized by an enhanced chemiluminescence system (HuaMei, Beijing, China). Autoradiograms were quantified by densitometry, and relative p120^{ctn} protein levels were calculated by comparison with the amount of β -actin protein.

Statistical analysis

SPSS version 11.5 for Windows was used for all analyses. The χ^2 test was used to examine possible correlations between p120^{ctn} expression and clinicopathologic factors. The Student t test was used to compare data from the densitometry analysis of the Western blots. The Kaplan-Meier method was used to estimate the probability of patient survival, and differences in survival between patient subgroups were further compared by means of the log-rank test. By use of a Cox proportional-hazards regression model, the possible prognostic significances of clinicopathologic variables were tested. Differences were considered significant when $P < 0.05$.

Results

Abnormal p120^{ctn} expression

Expression of p120^{ctn} occurs mainly in the cell membrane of normal bronchial epithelium. Of 143 lung cancers, 29 (20.3%) showed normal or preserved membranous expression only (Fig. 1a), and 114 (79.7%) showed abnormal expression, including reduced membranous expression (Fig. 1b), preserved membranous expression accompanied with ectopic cytoplasmic expression (Fig. 2a), and reduced or absent membranous expression together with ectopic cytoplasmic expression (Fig. 1c, 2b, and 2c).

Of 39 specimens with normal membranous expression, 10 cases (25.6%) showed cytoplasmic expression, while 68 (65.4%) of the 104 specimens with reduced membranous expression showed ectopic cytoplasmic expression ($\chi^2=18.07$; $P < 0.001$). No statistical difference was found in reduced membranous expression of p120^{ctn} ($\chi^2=0.86$; $P=0.354$) between adenocarcinomas (76.6%, 49/64) and SCC (69.6%, 55/79). Squamous cell carcinomas (63.3%, 50/79) showed significantly higher percentages of ectopic cytoplasmic expressions compared with adenocarcinomas (43.8%, 28/64, $\chi^2=5.45$, $P=0.020$). In additional experiments, we found that the staining patterns for p120^{ctn} were heterogeneous between bronchiolo-alveolar carcinomas (BAC)-like components and other histological components. Unlike other

histological components, the cancer cells in BAC-like region mostly showed normal membrane expression of p120^{ctn}, while only few cells had cytoplasmic and/or

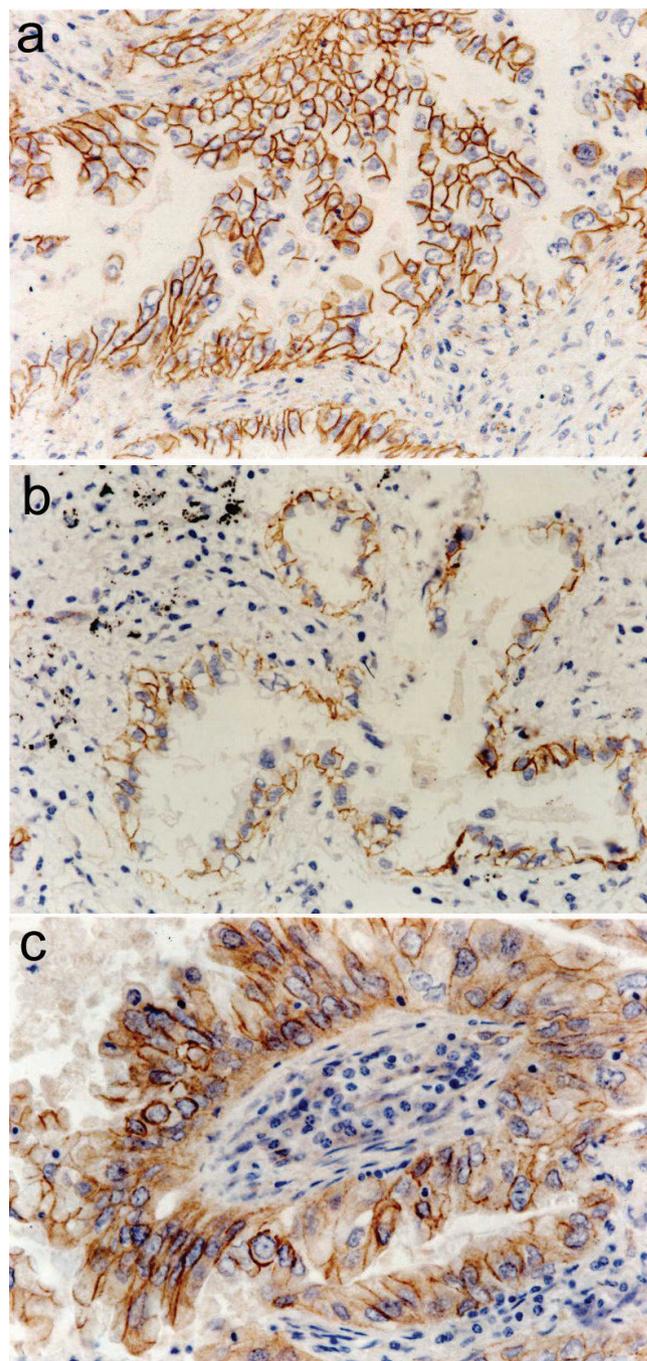


Fig. 1. Immunohistochemistry of p120^{ctn} in lung adenocarcinoma. Strong membranous immunostaining of p120^{ctn} was observed in a well-differentiated lung adenocarcinoma (a) and reduced membranous expression of p120^{ctn} (b). (c) showed increased cytoplasmic p120^{ctn} expression and reduced membranous expression in a lung papillary adenocarcinoma. x 400

reduced membrane expression of p120^{ctn}.

Next, we examined associations between abnormal expression of p120^{ctn} and clinicopathologic factors (Table 1). We found that abnormal p120^{ctn} expression occurred more frequently in samples with poor differentiation, advanced tumor stage, and lymph node metastasis ($P=0.041$, $P<0.001$, and $P<0.001$, respectively), while no significant associations were found with regard to age, sex and histologic type.

Abnormal p120^{ctn} expression and patient prognosis

The expression of p120^{ctn} and its relation to survival time were further analyzed among 80 patients with complete follow-up data. The patients with normal p120^{ctn} expression had a longer mean survival time (45.73 ± 12.10 months) and a higher 5-year overall survival rate (58.3%). For patients with abnormal p120^{ctn} expression, mean survival time was 24.57 ± 5.06 months and the 5-year overall survival rate was only 5.9%, which were statistically different from the patients with normal p120^{ctn} expression ($P<0.001$). Using the Kaplan-Meier method, we determined survival curves of lung SCC, adenocarcinoma, and both together (Fig. 3) and then compared them by using the log-rank test, which showed that the patients with abnormal p120^{ctn} expression had a poorer prognosis than those with normal or preserved p120^{ctn} expression ($P<0.001$ for lung SCC, adenocarcinoma and together). As shown by the results from the Cox proportional-hazards regression model (Table 2), abnormal p120^{ctn} expression, TNM stage, lymph node metastasis, and differentiation were significant predictive factors of overall survival ($P=0.024$, $P=0.002$, $P=0.048$, and $P=0.018$, respectively). Subgroup analyses with the Wald χ^2 test also demonstrated that abnormal p120^{ctn} expression, high TNM stage, poor differentiation, and lymph node metastasis indicated a worse chance of survival for patients with lung cancer ($P=0.023$, $P=0.001$, $P=0.017$, and $P=0.049$, respectively; Table 3). Other factors, such as age and sex, had no significant association with prognosis for patients with lung SCC and adenocarcinoma in this study.

Reduced membranous p120^{ctn} expression and aberrant isoforms

In order to examine p120^{ctn} isoforms and compare membranous p120^{ctn} expression between normal lung tissues and lung cancers, fresh frozen samples from 32 lung cancer specimens and corresponding normal lung tissues were subjected to Western blot. The average level of p120^{ctn} expression in normal lung tissue was significantly higher than that in the lung cancer specimens (3.11 ± 1.74 and 1.77 ± 1.31 respectively; $P=0.001$, $n=32$). P120^{ctn} has 4 isoforms (isoforms 1-4). In normal lung tissues, several specific bands that were 120 kDa (corresponding to isoform 1) and 100 kDa (corresponding to isoform 3) appeared, while the lung

cancer samples showed faintly stained bands or the absence of isoform 1 and isoform 3 (Fig. 4). Image analysis of Western blot results showed that the levels of

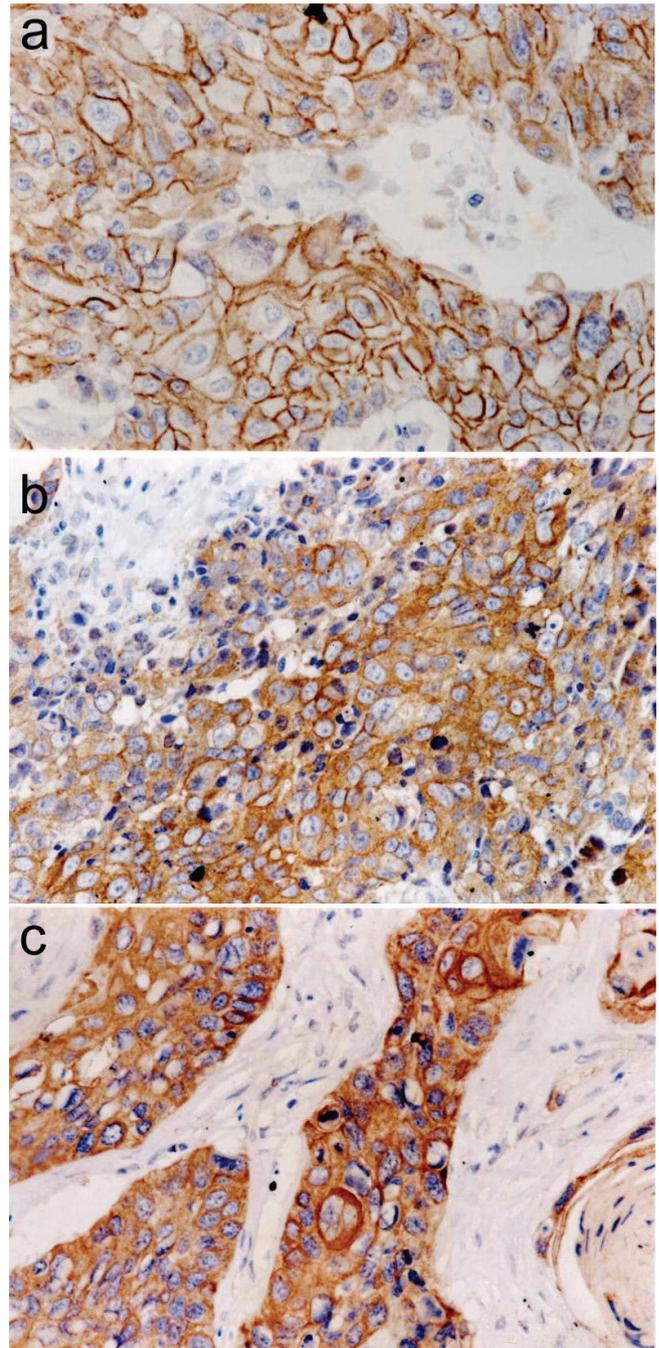


Fig. 2. Immunohistochemistry of p120^{ctn} in lung squamous cell carcinoma. (a) Normal membranous expression together with weak cytoplasmic staining in a moderately differentiated squamous cell carcinoma. Abnormal expression of p120^{ctn} could be either reduced membranous immunostaining associated with cytoplasmic expression (b) or only cytoplasmic staining without membranous expression (c). x 400

p120^{ctn} in lung cancer

isoform 1 and 3 in lung cancer were significantly lower than corresponding normal lung tissues (0.59 ± 0.87 vs 1.40 ± 1.45 for isoform 1, $P=0.005$, $n=32$; 1.40 ± 1.10 vs 1.91 ± 1.04 for isoform 3, $P=0.037$, $n=32$).

Additionally, we examined the relationship between the result of immunohistochemistry and western blot analysis using Spearman's correlation analysis. The results showed that the expression quantities of p120^{ctn} immunohistochemistry were significantly correlated with the total densities of p120^{ctn} bands of western blot analysis ($P=0.003$, Correlation Coefficient: 0.502;

$n=32$). The reduced membrane expression of p120^{ctn} staining also significantly corresponded to the reduction of p120^{ctn} isoform 1 seen in western blot analysis ($P=0.021$, Correlation Coefficient: 0.407, $n=32$). No correlation was seen between membrane expression and isoform 3 ($P=0.200$); cytoplasmic expression and isoform 1 ($P=0.257$); or cytoplasmic expression and isoform 3 ($P=0.892$). Therefore, the p120^{ctn} isoform 1 may be the most important isoform that is relevant to reduced membrane expression of p120^{ctn} in lung cancers.

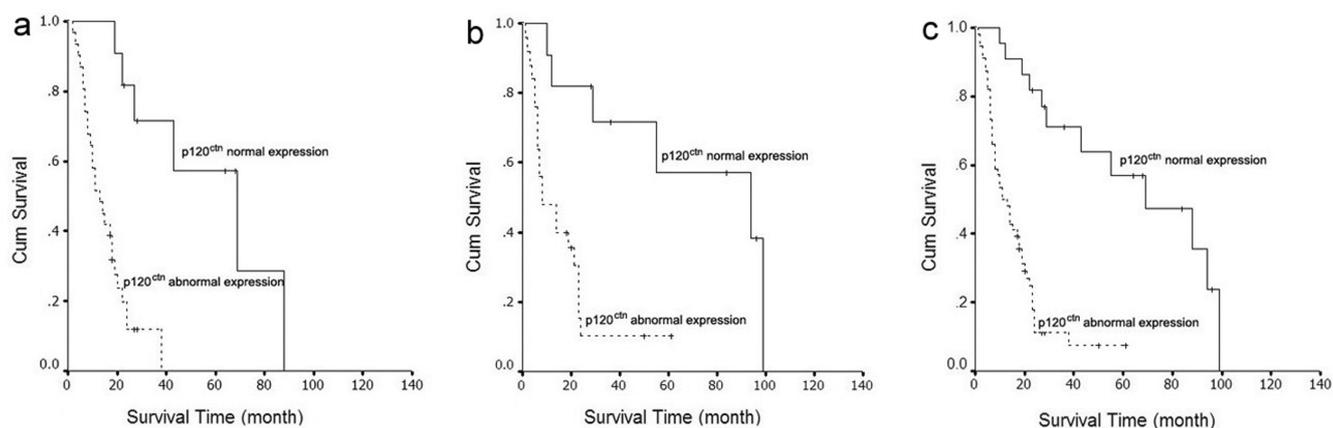


Fig. 3. Kaplan-Meier curve of the overall survival of 80 patients with lung SCC (a), adenocarcinoma (b) and both (c), stratified by normal or abnormal expression of p120^{ctn}. Abnormal p120^{ctn} expression was significantly correlated with poor survival (all $P < 0.001$).

Table 1. Expression of p120^{ctn} and clinicopathologic factors.

Parameter	p120 ^{ctn} abnormal express in SCC		p120 ^{ctn} abnormal express in Adenocarcinoma		p120 ^{ctn} abnormal express in all tumor samples	
		P		P		P
Age						
< 60	25 / 35 (71.4%)		21 / 26 (80.8%)		46 / 61 (75.4%)	
≥ 60	30 / 40 (80.0%)	0.386	36 / 42 (85.7%)	0.842	68 / 82 (82.9%)	0.269
Sex						
Male	46 / 58 (79.3%)		39 / 47 (83.0%)		85 / 105 (81.0%)	
Female	11 / 17 (64.7%)	0.359	18 / 21 (85.7%)	1.000	29 / 38 (76.3%)	0.542
Histologic type						
SCC					64 / 79 (81.0%)	
Adenocarcinoma					50 / 64 (78.1%)	0.669
Differentiation						
Well or moderate	32 / 45 (71.1%)		35 / 45 (77.8%)		67 / 90 (74.4%)	
Poor	25 / 30 (83.3%)	0.225	22 / 23 (95.7%)	0.122	47 / 53 (88.7%)	0.041
TNM Stage						
I or II	10 / 21 (47.6%)		9 / 17 (52.9%)		19 / 38 (50.0%)	
III or IV	47 / 54 (87.0%)	<0.001	48 / 51 (94.1%)	<0.001	95 / 105 (90.5%)	<0.001
Lymphatic metastasis						
Negative	17 / 30 (56.7%)		17 / 25 (68.0%)		34 / 55 (61.8%)	
Positive	40 / 45 (88.9%)	0.001	40 / 43 (93.0%)	0.018	80 / 88 (90.9%)	<0.001

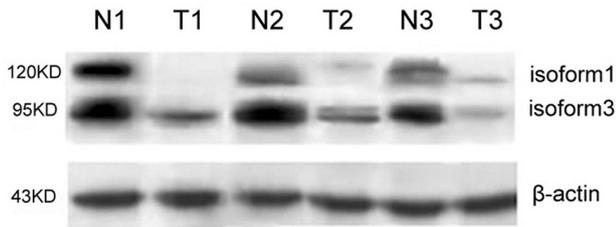


Fig. 4. Western blot analysis of p120^{ctn}. Compared with normal lung tissues, p120^{ctn} isoform 1 and 3 expression in cell membranes was apparently decreased or absent in tumor tissues. Densitometry analysis showed that the relative content of p120^{ctn} in the cancer tissue was significantly lower than that in normal lung tissues (mean \pm SEM, 3.11 \pm 1.74 and 1.77 \pm 1.31 respectively; n= 32 for each group; P = 0.001). Figure shows representative cases of Western blot analysis. "T" indicates tumors, and "N" indicates normal lung tissues.

Table 2. Cox proportional-hazards regression model for prediction of survival of 80 patients with lung cancer.

FACTOR	RISK	95% CI	P
Sex	0.942	0.497-1.785	0.854
Age	0.797	0.464-1.369	0.411
TNM Stage	6.161	2.001-18.972	0.002
Differentiation	0.491	0.272-0.886	0.018
Histologic type	1.106	0.636-1.922	0.722
Abnormal p120 ^{ctn} expression	0.369	0.155-0.878	0.024
Lymphatic metastasis	2.236	1.006-4.969	0.048

CI: confidence interval.

Table 3. Results of the forward-step Wald test.

FACTOR	RISK	95% CI	P
TNM stage	6.163	2.020-18.806	0.001
Differentiation	0.498	0.281-0.883	0.017
Lymphatic metastasis	2.203	1.002-4.844	0.049
Abnormal p120 ^{ctn} expression	0.376	0.162-0.875	0.023

CI: confidence interval.

Discussion

Altered expression of p120^{ctn} has been implicated in tumor progression in several malignant carcinomas, including cancers of the colon, bladder, stomach, breast, and lung (Thoreson and Reynolds, 2002). In the present study, we found no statistically significant difference in abnormal p120^{ctn} expression between adenocarcinomas and squamous cell carcinomas. Abnormal p120^{ctn} expression was significantly related to poor survival. For the first time, we demonstrate that reduced expression or even the absence of p120^{ctn} isoform 1 and 3 in tumor cell membranes may be responsible for the abnormal

expression of p120^{ctn} that has been found in lung cancer. In addition, cytoplasmic expression in SCC was significantly higher than that in adenocarcinomas.

Abnormal expression of p120^{ctn} may damage the function of the E-cad/catenin complex and affects related cell adhesion. As a result, this triggers tumor cells to detach from the primary site, invade surrounding tissues, and metastasize to lymph nodes and distant organs. Acquisition of cell dissociation and motility, induced by aberrations in the E-cad/catenin complex, could thus enhance the release of cancer cells from the primary site and affect the initial steps in the metastasis process. In contrast to one earlier report by Bremnes et al., (2002) our results reveal that abnormal expression of p120^{ctn} is an important pathologic alteration in the tumor metastasis process.

Membranous p120^{ctn} expression in normal tissues may activate Rho GTPase-Cdc42, which can bind to IQGAP1, an effector of Cdc42 (Noren et al., 2000). Free IQGAP1 negatively regulates cell adhesion by dissociating α -catenin from the E-cad/catenin complex and inhibiting the recognition of the cytoskeleton by the complex. Activated Cdc42 may interact with IQGAP1 and suppress its dissociating action. The former can maintain cell adhesion and cell structure. In another unpublished study, we found that, in lung cancers Cdc42 also showed reduced membranous expression or overexpression in the cytoplasm, which has significant consistency with abnormal p120^{ctn} expression (kappa = 0.493, P<0.001, data not shown here).

Thus far, few reports about the nuclear expression of p120^{ctn} in tumors are available. Daniel and Reynolds first observed that, in the cell nucleus, p120^{ctn} could connect with Kaiso, a transcription factor of the POZ/ZF (Pox virus and zinc finger) family (Daniel et al., 1999). Sarrjo et al. (2004) only found 4 of 67 cases of nuclear p120^{ctn} expression in breast cancer tumors. We did not find any nuclear p120^{ctn} expression in our samples.

Reduced membranous p120^{ctn} expression was also identified in our samples by Western blot analysis. The p120^{ctn} protein levels in cellular membranes were significantly higher in normal lung tissues than in lung cancers. The expression of large amounts of isoforms that have distinct biologic and tissue-specific functions may explain why p120^{ctn} can both positively and negatively affect cell adhesion. We found that isoforms 1 and 3 mainly presented in normal lung tissues, while isoform 1 expression was reduced or absent in lung cancer. The expression levels of p120^{ctn} isoform 1 shown by western blot analysis were positively correlated with p120^{ctn} membrane expression shown by immunohistochemistry. This result was consistent with the report by Montonen et al. and suggested that the expression of p120^{ctn}isoform 1 in cell membranes could help maintain cell structure and adhesion (Montonen et al., 2001).

The abnormal expression of p120^{ctn} has been related to an unfavorable outcome in several human cancers, although conflicting results have been reported. The

p120^{ctn} in lung cancer

abnormal expression of p120^{ctn} has been correlated with poor survival in a study of 68 patients with bladder cancer. On the contrary other studies did not find an association between abnormal p120^{ctn} expression and survival among 61 patients with gastric adenocarcinoma and 193 patients with NSCLC (Brien et al., 1998; Bremnes et al., 2002). In the present study, abnormal expression of p120^{ctn} was associated with poor patient survival. Additionally, Cox regression analysis showed that combination of the immunohistochemical results of p120^{ctn} and E-cadherin was also a significant predictive factor of overall survival in lung cancers (P=0.023). On the basis of our results and those of others, we suggest that abnormal p120^{ctn} expression is related to poor prognosis in tumor clinical stage and lymph node metastasis and p120^{ctn} expression is a significant factor in the prediction of survival for patients with lung cancer.

In summary, we conclude that lung cancers show a reduced membranous expression and ectopic cytoplasmic accumulation of p120^{ctn}. The faintly expressed or absent isoform 1 may be responsible for the reduced membranous p120^{ctn} expression observed microscopically in this study and frequently reported by others. Abnormal expression of p120^{ctn} is associated with poor patient survival and may be useful in predicting the progression of lung cancer. Further experiments are under way to clarify whether ectopic p120^{ctn} expression reflects alterations in the tyrosine kinase pathway.

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