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Original Article

Aberrant expression of karyopherin α-2 (KPNA2) contributes to poor prognosis of non-small cell lung cancer

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Abstract: KPNA2 has been researched in the development, progression and prognosis in various cancers. However, the prognostic value of KPNA2 expression in NSCLC patients remains limited. We evaluated the KPNA2 expression by immunohistochemistry in resected NSCLC patients. Of the 196 cancer tissue samples, there were 94 (48%) specimens with positive expression of KPNA2, and the remaining 102 (52%) with negative expression. We found that expression of KPNA2 correlated with gender, histological type, differentiation, T-stage, lymph node metastasis, and TNM stage (all P<0.05), respectively. The overall survival (OS) for patients with KPNA2 positive expression was significantly poorer than patients with negative expression (P<0.001). Moreover, there was significant between KPNA2 expression and progress-free survival (PFS) (P=0.025). Furthermore, we found that NSCLC patients staged I-II with KPNA2 positive expression had a poorer overall survival than that with negative expression (P<0.001), whereas the difference was not discovered in patients staged III-IIV (P=0.243). Multivariate analysis showed the TNM stage (III-IV/I-II) (HR: 1.039; 95% CI: 1.015-1.063, P=0.001) and KPNA2 expression (Positive/negative) (HR: 2.012; 95% CI: 1.183-3.423, P=0.010) were independent prognostic indicators of poor survival for resected NSCLC patients. In summary, our results have shown that KPNA2 expression is associated with lung cancer progression, and is an independent prognostic factor for poor outcome in NSCLC patients.

Keywords: Non-small cell lung cancer, KPNA2, prognosis

Introduction

Lung cancer is the leading incident cancer with the highest mortality in China [1]. Non-small cell lung cancer (NSCLC) is the major histopathologic subtype of lung cancer [2]. Recent years, significant advances have made in diagnosis and treatment for lung patients [1, 3], however, the prognosis remains poor.

Multitude of complex process have been involved in the development of cancer, and nucleocytoplasmic transport plays an important role in cancer biology and may as therapeutic potential target [4], which involved in several cancer processes, including the cell cycle control [5], apoptosis [6, 7], gene expression [8] and signal transduction [9].

Karyopherin α-2 (KPNA2), a member of the karyopherin-α protein family, is an adaptor protein which has an important role in nucleocytoplasmic transport through large Nuclear Pore Complexes (NPCs) [10]. With the help of KPNA2, macromolecules more than 40 kDa can be shuttled between the cytoplasm and nucleus [11], by recognized cargo proteins via their nuclear localization signal (NLS) [12]. Furthermore, KPNA2 may be involved in tumorigenesis, and previous studies have identified that nuclear expression of KNPA2 is overexpressed and associated with poor prognosis in patients with small hepatocellular carcinoma [13], gastric adenocarcinoma [14], esophageal squamous cell carcinoma [15], breast cancer [16], colorectal cancer [17], and bladder cancer [18]. KPNA2 may be as a novel biomarker for cancer [19].

In non-small cell lung cancer (NSCLC), previous researches have suggested that overexpression of KPNA2 is associated with several clinicopathological features and poor outcome [20,

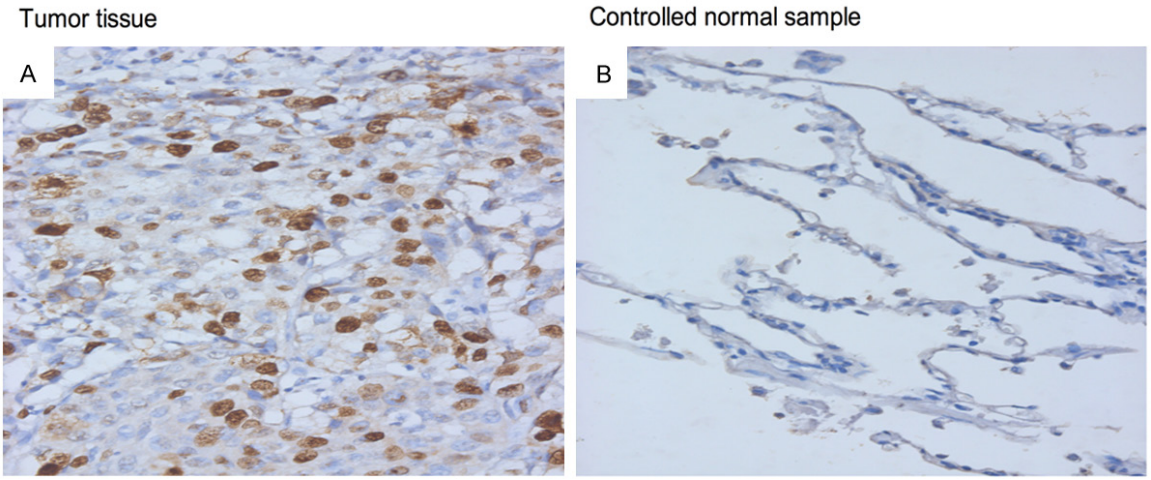

Figure 1. KPNA2 was overexpressed in lung cancer tissues. The positive expression of KPNA2 in one NSCLC patient's cancer tissue (A) and the compared normal control sample (B). (magnification: ×400).

21]. While the prognostic significance of KPNA2 expression in NSCLC patients remains poor. In present study, we evaluated the expression of KPNA2 based on immunohistochemistry (IHC) in 196 resected NSCLC patients, and we aim to investigate whether the expression of KPNA2 is associated with the clinicopathological features and survival.

Materials and methods

Patients and tumor specimens

From January 2008 to December 2011, pathologicly conformed NSCLC patients who undergwent a complete resection from West China Hospital, Sichuan University were enrolled in our study. No patients had previous lung cancer or other malignant cancer, received previous radiotherapy and chemotherapy. All patients have complete clinical records. Finally, a total of 196 tumor samples and their tissue sample adjacent to the tumor tissue were obtained. We retrospectively recorded the following features, including age, gender, smoking status, the presence of viseral plural invasion (VPI), differentiation (Moderate to well or poor) and the histological type (including adenocarcinoma (ADC), squamous cell carcinoma (SCC) and others) according to the World Health Organization classification for NSCLC [22], T stage (T1, T2, T3, or T4), lymph node metastasis (Yes or No), and TNM stage (I-II or III-IV stage) according to the tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer [23]. Overall survival (OS) was defined as the time from primary surgery to death and progression-free survival (PFS) was defined as the time from primary surgery to tumor recurrence or progression.

Immunohistochemistry (IHC)

All specimens were immediately fixed in 10% formalin and embedded in paraffin within 12-24h after surgery, and all paraffin tissues were made of 4 μm slices. The instruction of immunohistochemical staining was performed according to the previous literature [20]. Antigen retrieval treatment was done at 95°C for 16 min in sodium citrate buffer (pH 8.0). Primary antibody was anti-KPNA2 antibody (1:250 dilution, Abcam). For a negative control, phosphate-buffered saline (PBS) replaced the primary antibody, and the staining showed no immunoreactivity. Secondary antibodies of Dako Envision were purchased from Dako Corporation.

Scoring of KPNA2 expression by immunohistochemistry (IHC)

All the stained slides were scanned and evaluated by two independent pathologists, who were blind to the knowledge of the patient clinical status. The dual-rate semi-quantitative method was used for all slides according to the previous studies [24, 25]. KPNA2 is a nuclear protein [16, 26], and we evaluated the expression of KPNA2 in nuclei of cancer cells. The total score included stained intensity and

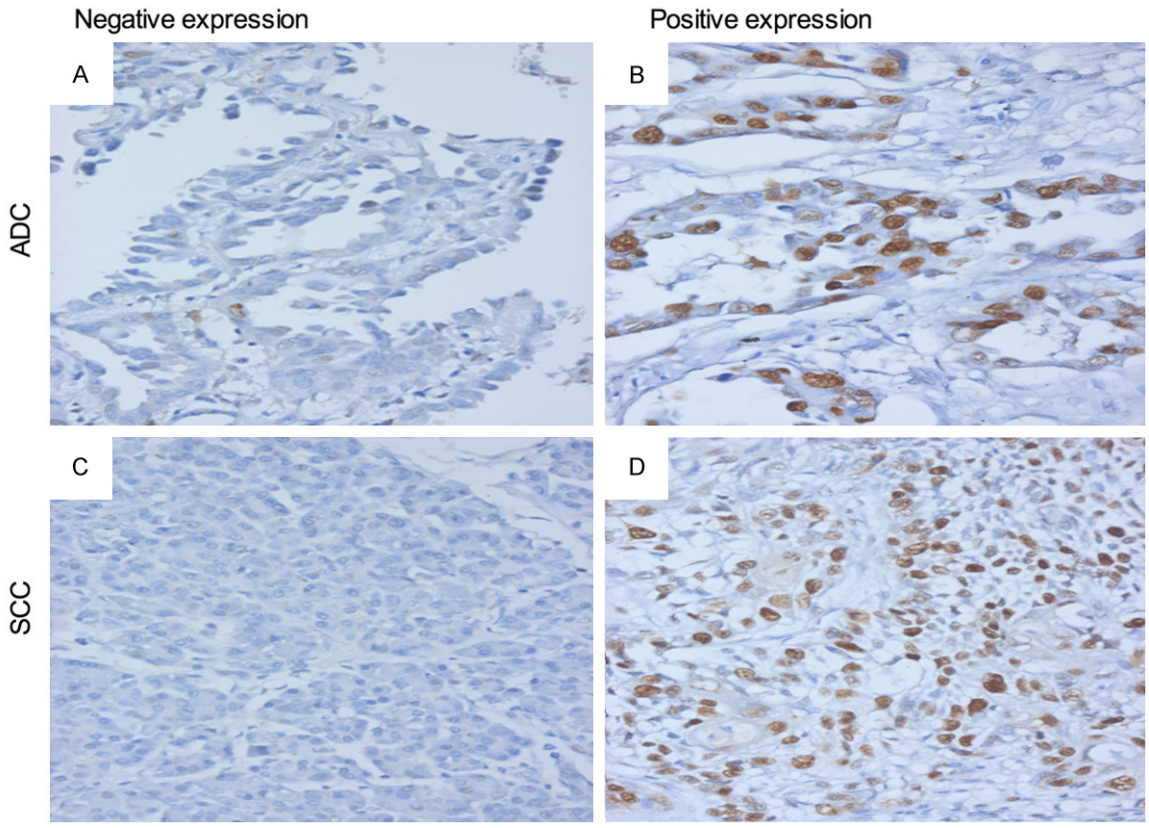

Figure 2. The expression of KPNA2 in NSCLC specimens, KPNA2 presents negative expression in patients with adenocarcinoma (ADC) (A) and squamous cell carcinoma (SCC) (C), and positive expression in patients with ADC (B) and SCC (D). (magnification: ×400).

stained area. The intensity score was divided into four categories as follows: 0, no staining; 1, yellow staining; 2, brown staining; and 3, dark brown. The proportion of cells with nuclear KPNA2 staining was evaluated by examining at least 2,000 cancer cells in 6 representative areas. The area score was divided into five categories as follows: 0, ≤5% of tumor cells; 1, 6% to 25% of tumor cells; 2, 26% to 50% of tumor cells; 3, 51% to 75% of tumor cells; 4, >75% of tumor cells. In our study, the total score more than 4 was defined as positive expression.

Statistical analysis

Statistical calculations were performed by using the SPSS 19.0 for Windows (SPSS Inc., Chicago, III) and Graphpad Prism 6. The χ^2 test was used to analysis the association of clinicopathologic characteristics with KPNA2 expression. The Kaplan-Meier method was used to analysis the impact of KPNA2 on OS and PFS, and the log-rank test was performed based on the differences. Multivariate Cox regression analysis was used to identified the independent prognostic factors. *P* value <0.05 was considered statistically significant.

Results

The expression of KPNA2 in lung cancer tissue and controlled normal samples

We investigated KPNA2 expression in 196 human NSCLC tissues and the controlled normal samples by IHC. As shown in **Figure 1**, KPNA2 positive immunostaining was only observed in the nuclei of the cancer cells, whereas all the compared control tissues showed negative staining. The KPNA2 negative and positive immunostaining in patients with adenocarcinoma and squamous cell carcinoma were showed in **Figure 2**. Of the 196 cancer tissue samples, there were 94 (48%) specimens with positive expression of KPNA2, and the remaining 102 (52%) specimans with negative expression.

Table 1. Baseline characteristics of study subjects according to the expression of KPNA2

Characteristics	N. (%)	KPNA2 expression		*P* Value
		Negative (N=102)	Positive (N=94)	
Age (Years)				*0.898*
≤60	126 (64.3)	66	60	
>60	70 (35.7)	36	34	
Gender				*.020**
Male	136 (69.4)	63	73	
Female	60 (30.6)	39	21	
Smoking status				0.004
Yes	91 (46.4)	37	54	
No	105 (53.6)	65	40	
Histologic type				*.019**
ADC	72 (36.7)	28	44	
SCC	108 (55.1)	64	44	
Other	16 (8.2)	10	6	
Differentiation				*.004**
Poor	102 (52.0)	43	59	
Middle-Well	94 (48.0)	59	35	
VPI				0.872
Presence	101 (51.5)	52	49	
Absence	95 (48.5)	50	45	
T stage				*.020**
T1	35 (17.9)	23	12	
T2	120 (61.2)	64	56	
T3	29 (14.8)	8	21	
T4	12 (6.1)	7	5	
LN metastasis				*.002**
Yes	72 (36.7)	27	45	
No	124 (63.3)	75	49	
TNM stage				
I-II	139 (70.9)	83	56	*.001**
III-IV	57 (29.1)	19	38	

ADC, Adenocarcinoma; SCC, Squamous cell carcinoma; VPI: visceral plural invasion; LN: lymph node; N: numbers; *statistically significant.

Relationship between the expression of KPNA2 and clinicopathological characteristics

The relationship between the expression of KPNA2 with clinicopathological characteristics was demonstrated in **Table 1**. The expression of KPNA2 correlated with gender (P=0.020), smoking (P=0.004), histological type (P=0.019), differentiation (P=0.004), T-stage (P=0.020), lymph node metastasis (P=0.002), and TNM stage (P=0.001), respectively. Overall, overexpression of KPNA2 was associated with patients with adencarcinoma (44/72, 61.1%) and higher tumor grade (staged III-IV) (38/57, 66.7%). However, no significant difference was observed between the KPNA2 expression and othercharacteristics, such as age and VPI.

The expression of KPNA2 and patients' survival

The Kaplan-Meier was used to evaluate the association between KPNA2 positive expression and survival. And the overall survival (OS) and progress-free survival (PFS) was showed in **Figure 3**. The 5-year overall survival rate was 54.2% for KPNA2 positive patients and 78.1% for KPNA2 negative patients, and the overall survival for patients with KPNA2 positive expression was significantly poorer than patients with KPNA2 negative expression (**Figure 3A**, P<0.001). Moreover, there was significant between KPNA2 expression and progress-free survival (PFS) (**Figure 3B**, P=0.025), patients with KPNA2 positive expression more likely to be recurrence or progression.

Furthermore, we found that NSCLC patients staged I-II with KPNA2 positive expression had a poorer overall survival than that of negative expression (**Figure 4B**, P=0.002), whereas the difference was not discovered in patients staged III-IIV (**Figure 4A**, P=0.243).

The univariate and multivariate analysis of 196 lung cancer patients were showed in **Table 2**. Univariate cox regression analysis showed that gender, smoking status, differentiation, lymph node metastasis, TNM stage, and KPNA2 expression were significantly associated with the overall survival (all P<0.05). Furthermore, multivariate analysis showed the TNM stage (III-IV/I-II) (HR: 1.039; 95% CI: 1.015-1.063, P=0.001) and KPNA2 positive expression (Positive/negative) (HR: 2.012; 95% CI: 1.183-3.423, P=0.010) were independent prognostic indicators for resected NSCLC patients.

Discussion

In the present study, we investigated the clinicopathological and prognostic significance of KPNA2 expression in resected NSCLC patients by IHC. Of the 196 cancer tissue samples, there were 94 (48%) specimens with positive expression of KPNA2. With respect to clinicopathological features, the expression of KPNA2 correlat-

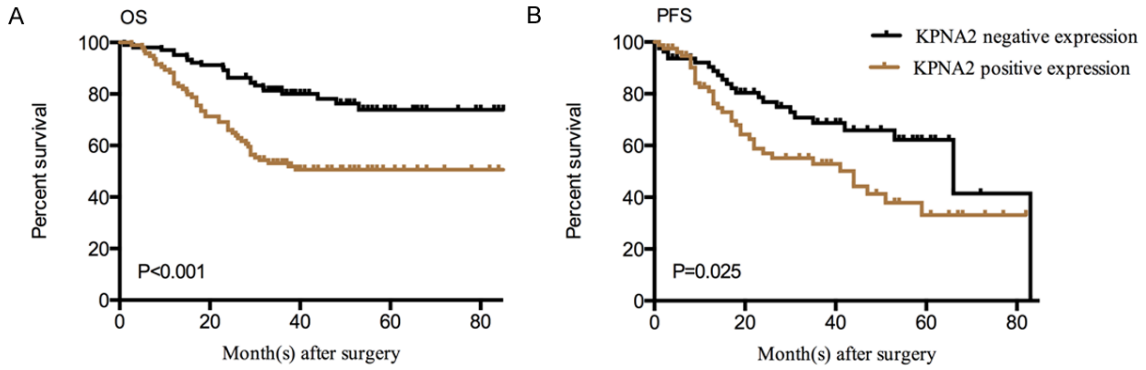

Figure 3. The prognostic significance of KPNA2 expression in resected NSCLC patients. The survival analysis showed that overall survival of patients with KPNA2 positive expression was significantly shorter than that of patients with KPNA2 negative expression (log-rank test P<0.001, A), Moreover, the difference significantly exist in the progress-free survival (PFS) (P=0.025, B).

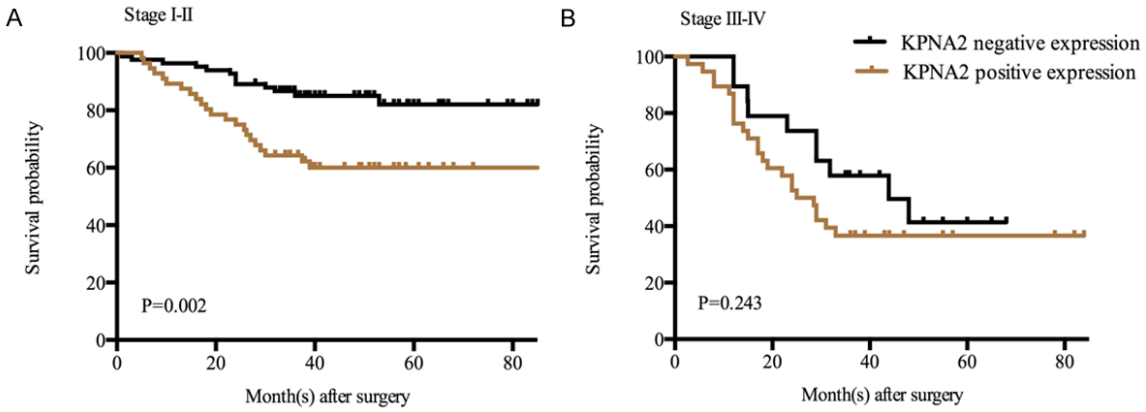

Figure 4. Kaplan-Meier for patients' overall survival was stratified by KPNA2-positive and KPNA2-negative expression in patients staged I-II (P=0.002, A) and staged III-IV (P=0.243, B).

ed with gender, smoking, histological type, differentiation, T-stage, lymph node metastasis, and TNM stage, respectively. Overexpression of KPNA2 was associated with the progression of lung cancer. Based on our results, KPNA2 expression was an independent prognostic factor for poor survival in resected NSCLC patients on both univariate analysis and multivariate analysis. Patients with KPNA2 positive expression were more likely to be recurrence or progression. Furthermore, we found that NSCLC patients staged I-II with KPNA2 positive expression had a poorer overall survival.

Karyopherin α-2 (KPNA2) is a member of the Karyopherin-α family, consists of 529 amino acids and weighs about 58 kDa [19]. KPNA2 gene with 11 exons spanning approximately 10 Kb on chromosome 17q23-q24 [27], is a part of a karyopherin heterodimer, directly binds to the nuclear localization signal (NLS) of proteins and functions as an adaptor [11, 12]. Several studies have linked KPNA2 to cancer [19], and several researches has demonstrated that KPNA2 interacted with several proteins in cancer, for example, Zannini, L., et al. reported that Karyopherin-alpha 2 protein interacts with cell-cycle regulator Chk2 and contributes to its nuclear import [28], and may promote NF-κB activation via facilitating P65 nuclear transportation in osteoarthritis [29], and regulated the process of OCT4 nuclear transportation [18, 30]. Tseng, S.F. et al. strongly suggest that an interaction with KPNA2 contributes to nuclear localization and multiple tumor suppression functions of the NBS1 complex [31].

Moreover, KPNA2 is overexpressed in multiple cancers [14-17, 32-34]. In our study, the expres-

Table 2. The Univariate and multivariate analysis of 196 lung cancer patients

Variable	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (>60/≤60)	1.439	0.894-2.316	0.134			
Gender (female/male)	0.514	0.286-0.924	*0.026**	0.982	0.459-2.102	0.962
Smoking status (Yes/No)	2.001	1.225-3.293	*0.006**	1.626	0.983-2.692	0.058
Histology (ADC/SCC)	0.83	0.560-1.231	0.354			
Differentiation (Moderate to well/poor)	0.576	0.354-0.938	*0.026**	0.828	0.493-1.391	0.476
VPI status (Absent vs. present)	0.802	0.631-1.020	0.072			
Lymph node metastasis (Yes/No)	2.458	1.528-3.956	*<0.001**	1.424	0.736-2.754	0.294
TNM stage (III-IV/I-II)	1.051	1.029-1.074	*<0.001**	1.039	1.015-1.063	*0.001**
KPNA2 expression (positive/negative)	2.669	1.617-4.407	*<0.001**	2.012	1.183-3.423	*0.010**

ADC, Adenocarcinoma; SCC, Squamous cell carcinoma; VPI: visceral plural invasion; *statistically significant.

sion of KPNA2 in cancer tissue appears to be predominantly nuclear, which is accordance to the previous studies [16, 26]. The observed expression of KPNA2 in lung cancer tissues are markedly elevated compared to normal tissue, KPNA2 could potentially participate in carcinogenesis. And the positive expression of KPNA2 was significantly association with differentiation, and more likely to be present with adenocarcinoma, those are accordance to the previous studies in lung cancer [20, 21]. Furthermore, our study suggested that overexpression of KPNA2 was associated with poor differentiation, higher T stage, lymph node metastasis, advanced stage (staged III-IV), the association between KPNA2 expression and tumor stage indicates that KPNA2 overexpression may involve in lung cancer progression.

The aberrant expression of KPNA2 has been demonstrated to correlate with a worse survival for the patients with small hepatocellular carcinoma [13], gastric adenocarcinoma [14], esophageal squamous cell carcinoma [15], breast cancer [16], colorectal cancer [17], and bladder cancer [18]. These results suggested that KPNA2 expression was more likely to play an important role in the progression and metastasis of cancer. Importantly, several studies have established KPNA2 to be an independent prognostic factor [14, 17, 35]. In our study, the difference in overall survival (OS) and progress free survival (PFS) between the positive and negative KPNA2 expression groups was significant. Furthermore, the present results showed that positive KPNA2 expression was significantly correlated with survival in patients staged I-II, rather than patients staged III-IV. Based on our results, KPNA2 expression was an independent prognostic factor for poor survival in resected NSCLC patients on both univariate analysis and multivariate analysis. Our results corroborate those of previous studies. Thus, KPNA2 may be a potential prognostic marker and therapeutic target for NSCLC patients, especially for early-staged lung cancer patients.

With respect to lung cancer, previous research has suggested that high levels of KPNA2 could also be detected in lung cancer patient serum, and significantly higher serum KPNA2 in NSCLC patients than in healthy controls, and knockdown of KPNA2 inhibited the migration ability and viability of lung cancer cells [21]. However, our present study has just established only by the IHC observation. Further studies are required to research the mechanism of how KPNA2 contribute to carcinogenesis and tumor progress in lung cancer.

In summary, we demonstrated that KPNA2 play an important role in progression and prognosis of lung cancer. KPNA2 may be a potential prognostic marker and therapeutic target for NSCLC patients. Further investigation with a large cohort is necessary to further demonstrate the role of KPNA2 in the development and progression of lung cancer.

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Disclosure of conflict of interest

None.

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References

[1] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115-32.

[2] Travis WD. Pathology of lung cancer. Clin Chest Med 2011; 32: 669-92.

[3] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65: 5-29.

[4] Hill R, Cautain B, de Pedro N and Link W. Targeting nucleocytoplasmic transport in cancer therapy. Oncotarget 2014; 5: 11-28.

[5] Weis K. Regulating access to the genome: nucleocytoplasmic transport throughout the cell cycle. Cell 2003; 112: 441-51.

[6] Ferrando-May E. Nucleocytoplasmic transport in apoptosis. Cell Death Differ 2005; 12: 1263-76.

[7] Kihlmark M, Rustum C, Eriksson C, Beckman M, Iverfeldt K, Hallberg E. Correlation between nucleocytoplasmic transport and caspase-3-dependent dismantling of nuclear pores during apoptosis. Exp Cell Res 2004; 293: 346-56.

[8] Thomas M, Zielke B, Reuter N and Stamminger T. Methods to study the nucleocytoplasmic transport of macromolecules with respect to their impact on the regulation of human cytomegalovirus gene expression. Methods Mol Biol 2014; 1119: 197-216.

[9] Tu LC and Musser SM. Single molecule studies of nucleocytoplasmic transport. Biochim Biophys Acta 2011; 1813: 1607-18.

[10] Dickmanns A, Kehlenbach RH and Fahrenkrog B. Nuclear pore complexes and nucleocytoplasmic transport: from structure to function to disease. Int Rev Cell Mol Biol 2015; 320: 171-233.

[11] Goldfarb DS, Corbett AH, Mason DA, Harreman MT, Adam SA. Importin alpha: a multipurpose nuclear-transport receptor. Trends Cell Biol 2004; 14: 505-14.

[12] Stewart M. Molecular mechanism of the nuclear protein import cycle. Nat Rev Mol Cell Biol 2007; 8: 195-208.

[13] Jiang P, Tang Y, He L, Tang H, Liang M, Mai C, Hu L, Hong J. Aberrant expression of nuclear KPNA2 is correlated with early recurrence and poor prognosis in patients with small hepatocellular carcinoma after hepatectomy. Med Oncol 2014; 31: 131.

[14] Li C, Ji L, Ding ZY, Zhang QD, Huang GR. Overexpression of KPNA2 correlates with poor prognosis in patients with gastric adenocarcinoma. Tumour Biol 2013; 34: 1021-6.

[15] Sakai M, Sohda M, Miyazaki T, Suzuki S, Sano A, Tanaka N, Inose T, Nakajima M, Kato H, Kuwano H. Significance of karyopherin-{alpha} 2 (KPNA2) expression in esophageal squamous cell carcinoma. Anticancer Res 2010; 30: 851-6.

[16] Alshareeda AT, Negm OH, Green AR, Nolan CC, Tighe P, Albarakati N, Sultana R, Madhusudan S, Ellis IO, Rakha EA. KPNA2 is a nuclear export protein that contributes to aberrant localisation of key proteins and poor prognosis of breast cancer. Br J Cancer 2015; 112: 1929-37.

[17] Takada T, Tsutsumi S, Takahashi R, Ohsone K, Tatsuki H, Suto T, Kato T, Fujii T, Yokobori T, Kuwano H. KPNA2 over-expression is a potential marker of prognosis and therapeutic sensitivity in colorectal cancer patients. J Surg Oncol 2016; 113: 213-7.

[18] Zhou J, Dong D, Cheng R, Wang Y, Jiang S, Zhu Y, Fan L, Mao X, Gui Y, Li Z, Li X, Shi B. Aberrant expression of KPNA2 is associated with a poor prognosis and contributes to OCT4 nuclear transportation in bladder cancer. Oncotarget 2016; 7: 72767-72776.

[19] Christiansen A and Dyrskjot L. The functional role of the novel biomarker karyopherin alpha 2 (KPNA2) in cancer. Cancer Lett 2013; 331: 18-23.

[20] Li XL, Jia LL, Shi MM, Li X, Li ZH, Li HF, Wang EH, Jia XS. Downregulation of KPNA2 in non-small-cell lung cancer is associated with Oct4 expression. J Transl Med 2013; 11: 232.

[21] Wang CI, Wang CL, Wang CW, Chen CD, Wu CC, Liang Y, Tsai YH, Chang YS, Yu JS, Yu CJ. Importin subunit alpha-2 is identified as a potential biomarker for non-small cell lung cancer by integration of the cancer cell secretome and tissue transcriptome. Int J Cancer 2011; 128: 2364-72.

[22] Zakowski MF. Cytology nomenclature and 2015 world health organization classification of lung cancer. Cancer Cytopathol 2016; 124: 81-8.

[23] Edge SB and Compton CC. The American Joint committee on cancer: the 7th edition of the

AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17: 1471-4.
[24] Zhao S, Qiu ZX, Zhang L and Li WM. Prognostic values of ERK1/2 and p-ERK1/2 expressions for poor survival in non-small cell lung cancer. Tumour Biol 2015; 36: 4143-50.
[25] Carlini MJ, Roitman P, Nuñez M, Pallotta MG, Boggio G, Smith D, Salatino M, Joffé ED, Rabinovich GA, Puricelli LI. Clinical relevance of galectin-1 expression in non-small cell lung cancer patients. Lung Cancer 2014; 84: 73-8.
[26] Grupp K, Habermann M, Sirma H, Simon R, Steurer S, Hube-Magg C, Prien K, Burkhardt L, Jedrzejewska K, Salomon G, Heinzer H, Wilczak W, Kluth M, Izbicki JR, Sauter G, Minner S, Schlomm T, Tsourlakis MC. High nuclear karyopherin alpha 2 expression is a strong and independent predictor of biochemical recurrence in prostate cancer patients treated by radical prostatectomy. Mod Pathol 2014; 27: 96-106.
[27] Dorr SN, Schlicker MN and Hansmann IN. Genomic structure of karyopherin alpha2 (KPNA2) within a low-copy repeat on chromosome 17q23-q24 and mutation analysis in patients with russell-silver syndrome. Hum Genet 2001; 109: 479-86.
[28] Zannini L, Lecis D, Lisanti S, Benetti R, Buscemi G, Schneider C, Delia D. Karyopherin-alpha2 protein interacts with Chk2 and contributes to its nuclear import. J Biol Chem 2003; 278: 42346-51.
[29] Tao R, Xu X, Sun C, Wang Y, Wang S, Liu Z, Zhai L, Cheng H, Xiao M, Zhang D. KPNA2 interacts with P65 to modulate catabolic events in osteoarthritis. Exp Mol Pathol 2015; 99: 245-52.
[30] Li X, Sun L and Jin Y. Identification of karyopherin-alpha 2 as an Oct4 associated protein. J Genet Genomics 2008; 35: 723-8.
[31] Tseng SF, Chang CY, Wu KJ, Teng SC. Importin KPNA2 is required for proper nuclear localization and multiple functions of NBS1. J Biol Chem 2005; 280: 39594-600.
[32] Zhang Y, Zhang M, Yu F, Lu S, Sun H, Tang H, Peng Z. Karyopherin alpha 2 is a novel prognostic marker and a potential therapeutic target for colon cancer. J Exp Clin Cancer Res 2015; 34: 145.
[33] Ma S and Zhao X. KPNA2 is a promising biomarker candidate for esophageal squamous cell carcinoma and correlates with cell proliferation. Oncol Rep 2014; 32: 1631-7.
[34] Ikenberg K, Valtcheva N, Brandt S, Zhong Q, Wong CE, Noske A, Rechsteiner M, Rueschoff JH, Caduff R, Dellas A, Obermann E, Fink D, Fuchs T, Krek W, Moch H, Frew IJ, Wild PJ. KPNA2 is overexpressed in human and mouse endometrial cancers and promotes cellular proliferation. J Pathol 2014; 234: 239-52.
[35] Erben PB, Brunner K, Hecht M, Haderlein M, Büttner-Herold M, Agaimy A, Fietkau R, Hartmann A, Distel LV. Low cytoplasmic and nuclear KPNA2 expression in radiotherapy-treated head and neck squamous cell cancer is associated with an adverse outcome. Int J Clin Exp Pathol 2015; 8: 15814-24.