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Original Article

β-arrestin1 over-expression is associated with an unfavorable prognosis in lung adenocarcinomas and correlated with vascular endothelial growth factor

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Abstract: The aim of this study was to examine β-arrestin1 expression in patients with lung adenocarcinoma (ADC) and explore the relationship of β-arrestin1 protein with clinicopathologic factors, vascular endothelial growth factor (VEGF) and prognosis. A total of 105 surgically resected lung adenocarcinoma patients were recruited for the study. The expression of β-arrestin1 and VEGF were determined by immunohistochemistry (IHC). The score measuring the β-arrestin1 and VEGF were calculated by combining the percentage of positive cells and the intensity of staining. Kaplan-Meier method and multivariable Cox proportional hazards regression analyses were used to examine the relationship between β-arrestin1 and survival. The results demonstrated that a notably higher level of β-arrestin1 expression was found in lung ADC tissues. We also found that an elevated nuclear B-arrestin1 correlates with higher intratumoral VEGF (P = 0.007). β-arrestin 1 over-expression indicated a poor 5-year overall survival (P = 0.016), and the Cox regression model confirmed that β-arrestin1 over-expression were independent prognostic factor for tumor progression (P = 0.027) and unfavorable overall survival (P = 0.015). We conclude that β-arrestin1 had a high expression in ADC and β-arrestin1 may be a promising biomarker to identify individuals with poor prognosis for patients with ADC.

Keywords: β-arrestin1, VEGF, lung adenocarcinoma, prognosis

Introduction

Lung cancer is one of the most prevalent malignancies and the leading cause of cancer-related death worldwide. Recently, adenocarcinoma became the predominant histological form of lung cancer [1]. To improve the clinical outcome of patients with lung adenocarcinoma (ADC), effective novel therapies are warranted and angiogenesis is an attractive target [2]. Searching for novel and validated biomarkers correlated with the clinical and prognostic characteristics is important for diagnosis and treatment.

Beta-arrestins (consisting of β-arrestin1 and β-arrestin2) are cytosolic proteins, initially known merely as negative regulators of GPCRs [3]. The new roles of β-arrestins, serve as scaffolds and adapters, in receptor endocytosis and signal transduction have been discovered [4]. Recent evidence suggests that receptor-activation-dependent signal regulatory processes such as endocytosis may also be directly involved in the signaling functions and serve as an important pathway to transmit signals from the cell membrane to the cytoplasm and the nucleus [5, 6].

In recent years, more and more attention was paid to the role of β-arrestin1 in the tumor. In a human colorectal carcinoma cell line, β-arrestin1 mediated c-Src activation was found to be necessary for the transactivation of the growth factor receptor EGFR and downstream AKT activation in vitro [7]. β-arrestin1 regulates breast cancer cell survival during hypoxia through a novel interaction with the transcription factor, HIF-1 [8]. Transgenic over-expression of β-arrestin1 leads to rapid tumor pro-

gression and increased angiogenesis in mice [9]. In addition, the secreted VEGF concentration in plasma was evidently increased in β-arrestin1 transgenic mice after tumor cell injection, indicating that there was some correction between β-arrestin1 expression and tumor angiogenesis.

In the present study, we detected the expression of β-arrestin1 and VEGF by immunohistochemistry with the objective of examining the correlation between them and revealing their effects on prognosis.

Materials and methods

Clinical characteristics of the patients

Primary tumor samples were randomly obtained from 105 patients who underwent complete surgical resection for ADC in Shandong Provincial Hospital Affiliated to Shandong University between March 2006 and December 2008. The inclusion criteria also included absence of cancer within the 5 years before surgery, and no treatment with chemotherapy or radiotherapy before surgery. Clinical and pathological features (including age, sex, smoking history, pathologic stage, tumor stage, lymph node metastasis, differentiation and surgical procedure) were abstracted from the patients' charts. Tumors pathological stage were classified by TNM staging system according to the AJCC 2010 [10].

A total of 105 patients were followed up until death or the last day of follow-up (Aug 15, 2014). The overall survival (OS) was defined as the time from the date of surgery to the last date of follow-up for patients who remained alive, or to the date of death. Progression-free survival (PFS) was defined as the time from the date of surgery to the date of recurrence recognition, death, or to the end of observation. The study protocol was approved by the ethics committee of Provincial Hospital Affiliated to Shandong University. Written informed consent was obtained from each patient. Reported recommendations for tumor marker prognostic studies (REMARK) criteria were followed throughout the study [11].

Immunohistochemical staining of β-arrestin1 and VEGF

Immunohistochemical staining was performed on formalin-fixed paraffin-embedded tissue sections with anti-beta-arrestin1 (E274, rabbit monoclonal; Ab-32099, Abcam), anti-VEGF (A-20, rabbit polyclonal, Santa Cruz) diluted at 1:100, 1:100 respectively. The immunohistochemical procedures were performed using serial sections from the same paraffin-embedded blocks by previously described methods [12, 13]. Briefly, formalin-fixed paraffin-embedded tissue was cut in 4-μm sections and mounted on poly-L-lysine-coated slides. Sections were deparaffinized with turpentine oil and rehydrated through a graded series of ethanol. After endogenous peroxidase activity was quenched with 3% H_2O_2 for 15 minutes. Antigen retrieval was conducted with triethanolamine-ethylene diamine tetraacetic acid (Tris-EDTA) (1 mM, pH = 9.0) for 30 minutes. Nonspecific binding sites were blocked with 7% goat serum in Phosphate Buffer Solution (PBS, pH = 7.4) for 30 minutes. Sections were incubated with primary antibody for overnight at 4°C. After a rinse with PBS, sections were incubated with the streptavidin-biotin-peroxidase complex (Histostain SP kit, ZYMED, San Diego, USA). Finally, sections were developed with 3,3-Diaminobenzidine (DAB), lightly counterstained with hematoxylin to visualize the nuclei and mounted with neutral balsam. For negative controls, sections were incubated with PBS instead of the primary antibodies.

Evaluation of immunostaining

Specimens were evaluated by two independent observers (C.Q. and CL.Z.) who were unaware of the clinical features and outcomes of patients. Evaluation of the cell staining reaction was performed in accordance with the following immunoreactive score (IRS), a reproducible semiquantitative method, proposed by Remmele and Stegner [14] with slight modification as follows: IRS = SI (staining intensity) × PP (percentage of positive cells). SI was determined as 0, negative; 1, weak; 2, moderate; and 3, strong. PP was defined as 0, negative; 1, 1-20% positive cells; 2, 21-50% positive cells; 3, 51-80% positive cells; 4, 81-100% positive cells. Ten visual fields from different areas of each specimen were chosen at random for the IRS evaluation and the average IRS was calculated as final value [15].

The cutoff point for high and low expression that was statistically significant with respect to overall survival was set using the X-tile software program (The Rimm Lab at Yale University;

Table 1. Correlation of clinicopathologic variables of ADC with β-arr1 and VEGF

Characteristic	Total	β-arrestin1			VEGF		
		Positive	Negative	*P*	Positive	Negative	*P*
Age (year)							
≥60	56	37	19	0.674	44	12	0.052
<60	49	35	14		30	19	
Sex							
Male	51	38	13	0.216	38	13	0.401
Female	54	34	20		36	18	
Smoking							
No	61	41	20	0.724	39	22	0.084
Yes	44	31	13		35	9	
Pathological stage							
I	56	38	18	0.973	39	17	0.228
II	22	15	7		13	9	
IIIa	27	19	8		22	5	
Tumor status							
T1	41	26	15	0.239	27	14	0.458
T2	56	42	14		40	16	
T3-4	8	4	4		7	1	
Nodal status							
0	61	43	18	0.750	43	18	0.197
1	18	11	7		10	8	
2	26	18	8		21	5	
Differentiation							
Poor	25	17	8	0.983	18	7	0.902
Moderate	68	47	21		47	21	
Well	12	8	4		9	3	
Surgical procedure							
Pneumonectomy	7	4	3	0.394	7	0	0.101
Lobectomy	90	64	26		60	30	
Wedge	8	4	4		7	1	

http://www.tissuearray.org/rimmlab) as described previously [16]. The degree of β-arrestin1 and VEGF staining was quantified using a two-level grading system, and staining scores were defined as follows: 0-3, low expression, and 4-12, high expression.

Statistical analysis

The expression of each marker was dichotomized into low and high according to the cutoff value of the semi-quantitative expression score. The Fisher's exact test was used to assess the association between β-arrestin1 expression and VEGF, and the correlations between β-arrestin1 or VEGF expression and clinical pathological parameters. The Kaplan-Meier method was used to assess the associations between each marker expression and patients' outcomes. Multivariate analyses using Cox's proportional hazards regression models were performed to determine factors that were independently associated with OS and PFS. The Mann-Whitney U test was used to assess the association between β-arrestin1 expression and VEGF expression. For all tests, a two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed by employing SPSS 17.0 software package (SPSS Inc, Chicago, IL).

Results

Clinicopathologic variables

The main clinicopathologic characteristics of patients are shown in **Table 1**. A total of 105 patients with completely resected pathologic stage I-IIIa ADC were included in this study. The median age was 60 (range, 30-83) years, with 51 males and 54 females. In terms of the distribution of pathological stage, 56 patients were at stage I, 22 were at stage II, and 44 patients were at stage IIIa. There were 44 patients encountered positive lymph node metastasis, 58 patients experienced cancer relapse. Median follow-up time was 39 months (range, 4-88 months).

Relationship between β-arrestin1, VEGF expression and clinicopathological factors

The relationships between β-arrestin1, VEGF and clinicopathological factors are listed in **Table 1**. We detected the expression of β-arrestin1 in 105 ADC patients. There were 72 cases (68.6%) patients with high expression

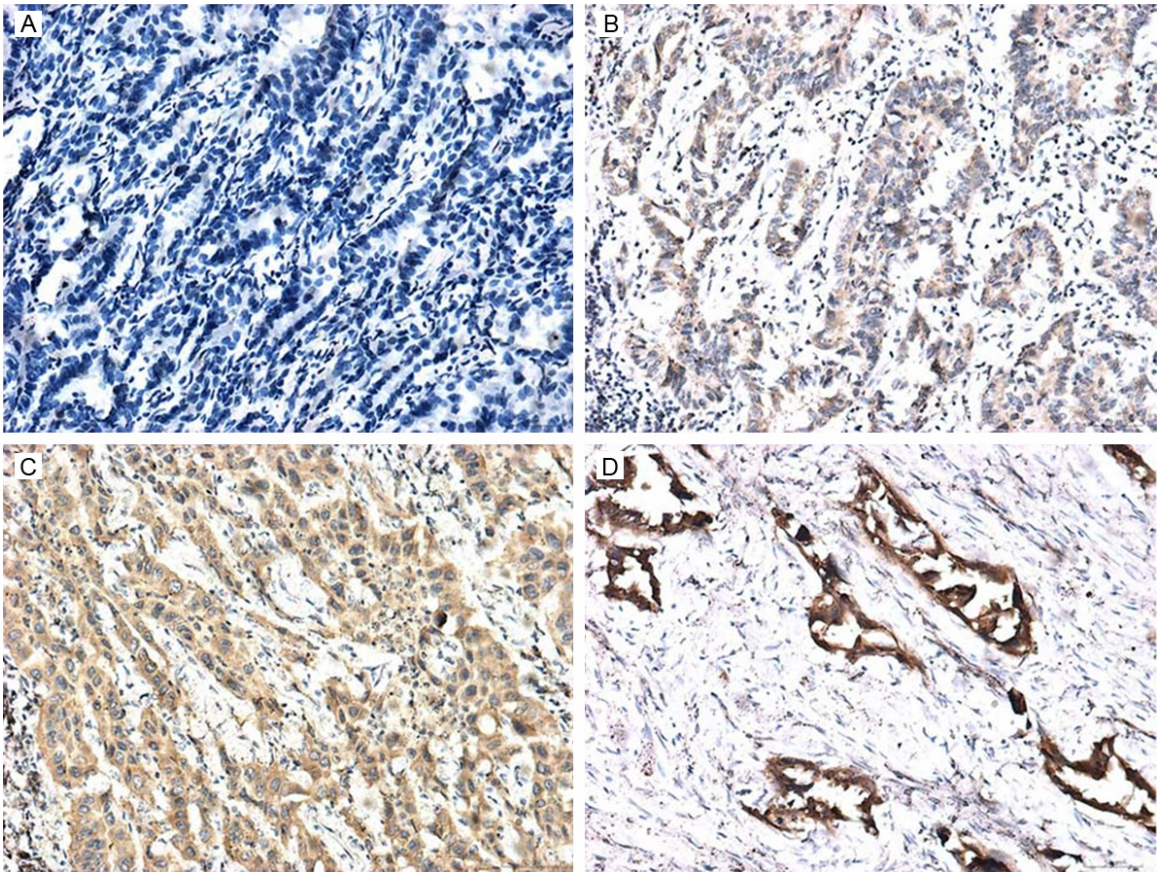

Figure1. Representative examples of β-arrestin1 immunohistochemistry in the lung adenocarcinomas tissues. (A) negative, (B) weak, (C) moderate, and (D) strong cytoplasmic and nuclear staining (×20, original magnification).

and 33 cases (31.4%) with low expression. As shown in **Figure 1**, positive staining was mainly localized in the cytoplasm, and diffuse nuclear staining of β-arrestin1 protein at various intensities was also observed (**Figure 1B-D**). There was no significant relationship between the β-arrestin1 expression and patient age, sex, smoking, tumor stage, or differentiation ($P > 0.05$).

For VEGF expression, 74 cases (70.5%) were high expression and 31 cases (29.5%) were low expression. No significant associations between the VEGF expression and any clinicopathological factors were observed ($P > 0.05$). Positive staining was mainly localized in the cytoplasm of cancer cells. The observed typical IHC staining shapes for VEGF expression in ADC are shown in **Figure 2**.

Univariate and multivariate survival analysis

Results of univariate analysis of overall survival are shown in **Table 2**. There were no significant differences in overall survival in terms of age ($P = 0.224$), sex ($P = 0.460$), smoking status ($P = 0.384$) or VEGF expression ($P = 0.129$). The univariate analysis demonstrated that tumor status ($P = 0.007$), nodal status ($P = 0.001$), stage ($P < 0.001$), differentiation ($P = 0.042$) and β-arrestin1 expression ($P = 0.016$) were significantly associated with OS. Similarly, the tumor status, nodal status, stage, and differentiation separately predicted high risk of disease progression ($P = 0.005$, $P < 0.001$, $P < 0.001$ and $P = 0.030$; **Table 3**). While the age, sex, smoking status, β-arrestin1 and VEGF expression weren't correlated with progression-free survival.

Of the 105 patients, 45 (42.9%) cases died within 5 years after operation, and tumor relapse developed during follow-up in 58 (55.2%) patients. Kaplan-Meier analysis demonstrated that patients with high expression of β-arrestin1 have a poorer prognosis than did those in low β-arrestin1 expression group, and has a correlation with overall survival ($P = 0.016$, **Figure 3A**), but there was no statistically significant correlation with progression-free

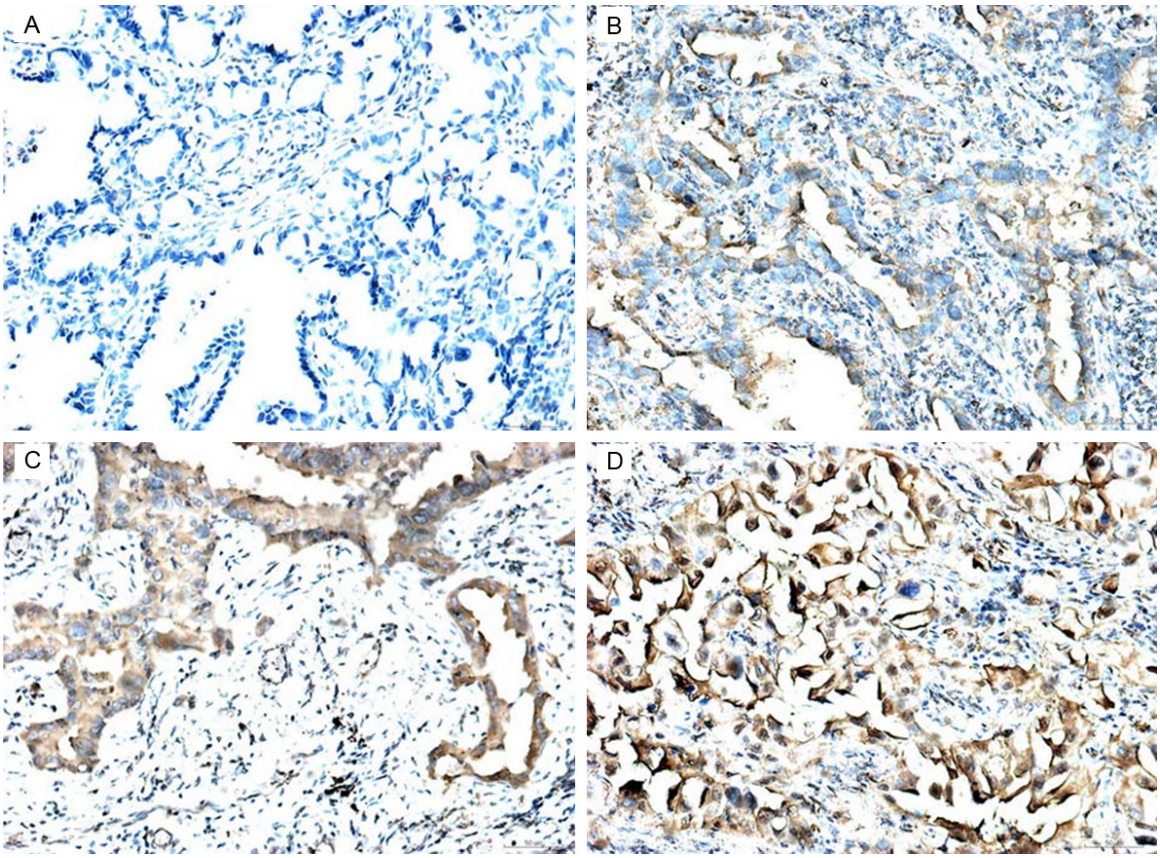

Figure 2. Representative examples of VEGF immunohistochemistry in the lung adenocarcinomas tissues. (A) negative, (B) weak, (C) moderate, and (D) strong staining of tumor cells (×20, original magnification).

Table 2. Univariate and multivariate analyses for overall survival

		OS Univariate analysis	OS Multivariate analysis		
Variable		*P* value (log-rank test)	95.0% confidence interval	Exp (B)	*P* value
Age (≥60 and <60)		0.224	0.444-1.816	0.898	0.765
Sex (male *vs.* female)		0.460	0.256-3.058	0.885	0.846
Smoking(yes *vs.* no)		0.384	0.135-1.728	0.483	0.263
Tumor status	T1	0.007		1.000	
	T2		0.081-1.323	0.327	0.117
	T3-4		0.094-1.086	0.320	0.068
Nodal status	N0	0.001		1.000	
	N1		0.138-46.049	2.522	0.533
	N2		0.161-19.161	1.755	0.645
Stage	I	<0.001		1.000	
	II		0.006-2.907	0.137	0.202
	IIIa		0.050-7.961	0.631	0.722
Differentiation	Poor	0.042		1.000	
	Moderate		0.469-12.372	2.410	0.292
	Well		0.386-7.957	1.754	0.467
β-arrestin1 (high *vs.* low)		0.016	1.266-9.291	3.430	0.015
VEGF (high *vs.* low)		0.129	0.599-3.101	1.363	0.460

Table 3. Univariate and multivariate analyses for progression -free survival

		PFS Univariate analysis	PFS Multivariate analysis		
Variable		*P* value(log-rank test)	95.0% confidence interval	Exp (B)	*P* value
Age (≥60 and <60)		0.159	0.462-1.849	0.924	0.824
Sex (male *vs.* female)		0.548	0.347-3.857	1.157	0.812
Smoking (yes *vs.* no)		0.490	0.181-2.232	0.635	0.479
Tumor status	T1	0.005		1.000	
	T2		0.080-1.191	0.308	0.088
	T3-4		0.116-1.252	0.381	0.112
Nodal status	N0	<0.001		1.000	
	N1		0.161-39.938	2.537	0.500
	N2		0.134-13.807	1.359	0.795
Stage	I	<0.001		1.000	
	II		0.009-3.154	0.171	0.235
	IIIa		0.071-10.476	0.864	0.909
Differentiation	Poor	0.030		1.000	
	Moderate		0.492-12.817	2.512	0.268
	Well		0.414-8.544	1.880	0.414
β-arrestin1 (high *vs.* low)		0.056	1.132-7.787	2.969	0.027
VEGF (high *vs.* low)		0.262	0.537-2.680	1.199	0.658

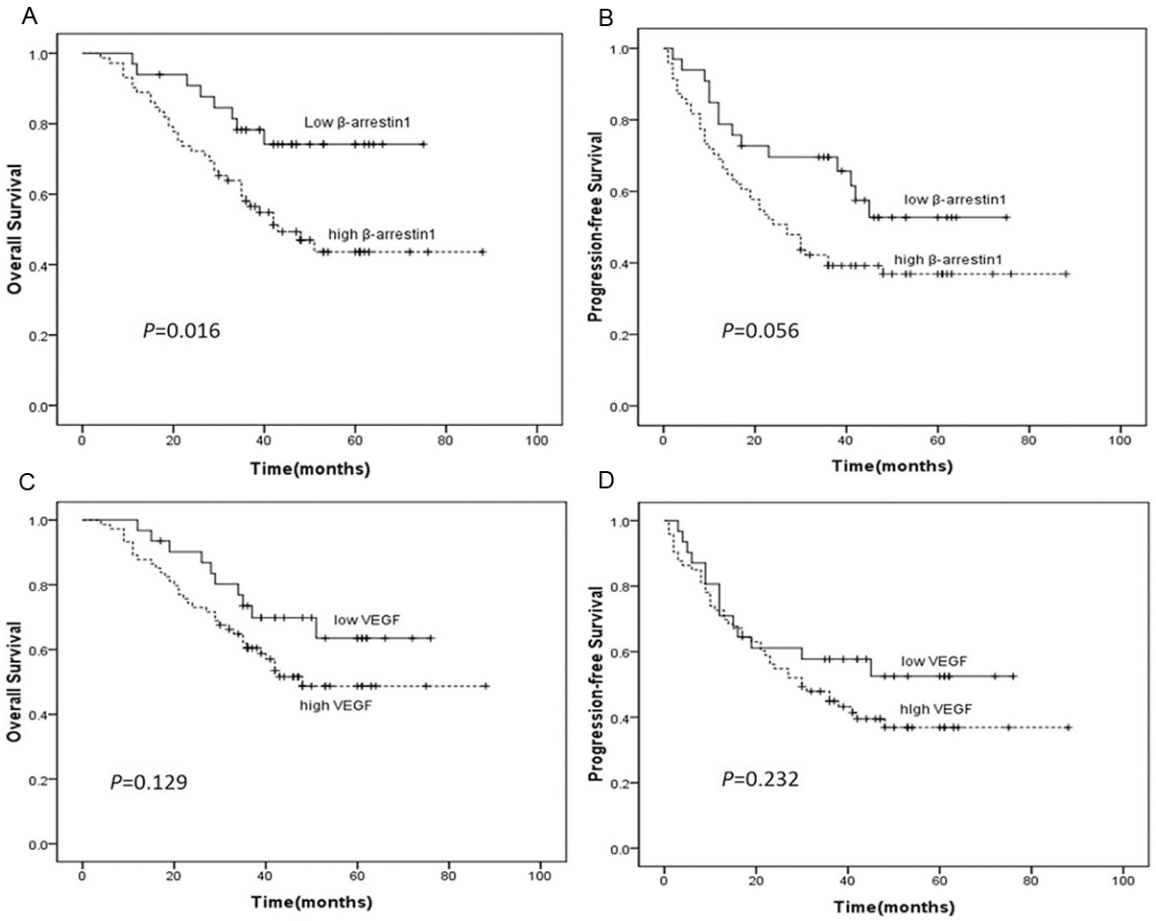

Figure 3. Kaplan-Meier curves of overall survival and progression-free survival stratified according to the β-arrestin1 (A, B) and VEGF expression (C, D).

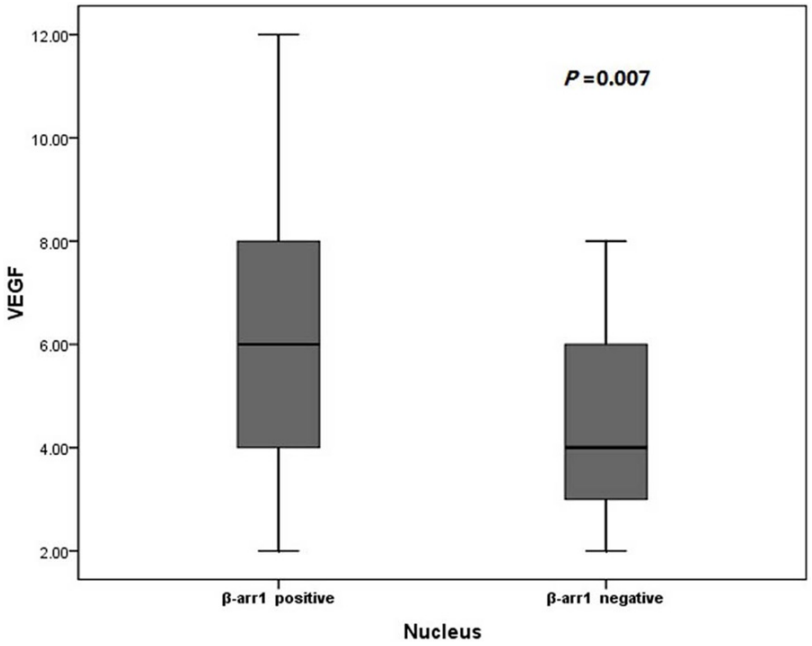

Figure 4. Intratumoral vascular endothelial growth factor (VEGF) in relation to β-arrestin1 protein immunoreactivity. Mann-Whitney U test demonstrated that tumors with β-arrestin1 nuclear positive expression showed significantly higher intratumoral VEGF than tumors with β-arrestin1 nuclear negative expression (*P* = 0.007).

Table 4. Survival differences stratified by low VEGF and high VEGF in patients with or without β-arrestin1 overexpression

	β-arrestin1 positive			β-arrestin1 negative		
5-year survival	VEGF high	VEGF low	*P*	VEGF high	VEGF low	*P*
Overall	30 (53.6%)	7 (43.8%)	0.267	5 (27.8%)	3 (20.0%)	0.717
Disease-free	36 (64.3%)	8 (50.0%)	0.375	8 (44.4%)	6 (40.0%)	0.949

survival (*P* = 0.056, **Figure 3B**). There was no significant association between VEGF expression and overall survival (*P* = 0.129, **Figure 3C**) and progression-free survival (*P* = 0. 232, **Figure 3D**).

Multivariate analysis using Cox regression model indicated that β-arrestin1 high expression may serve as independent prognostic factors for overall survival (*P* = 0.015, **Table 2**) and progression-free survival (*P* = 0.027, **Table 3**). While VEGF over-expression weren't independent prognostic factors for overall survival (*P* = 0.460, **Table 2**) and progression-free survival (P = 0.658, **Table 3**).

Interactions of molecular markers

To explore the correlation of β-arrestin1 with VEGF, the further statistical analysis demonstrated that there was significantly more VEGF in tumors with β-arrestin1 nuclear positive expression than that in those with β-arrestin1 protein nuclear negative expression (*P* = 0.007, **Figure 4**).

In addition, we also examined the survival differences of patients stratified by low VEGF and high VEGF according to β-arrestin1 protein expression status. For patients without β-arrestin1 overexpression, we didn't detected a highly significant differences on overall survival and progression-free survival, respectively, in patients with high VEGF compared with patients with low VEGF (*P* = 0.717 for OS and *P* = 0.949 for PFS, **Table 4**). And there were no significant differences in survival between low-VEGF group and high-VEGF group for patients with β-arrestin1 over-expression (*P* = 0.267 for OS and *P* = 0.375 for PFS, **Table 4**).

Discussion

Increasing evidence showed that β-arrestins involved in several cancer-related signals and processes via a range of receptor subtypes [17]. Moreover, elevated β-arrestin mRNA levels have been observed in cancerous tumors and tumorigenic cancer cell lines [18]. Previous studies demonstrated that β-arrestin1 protein levels were significantly higher in invasive ductal carcinoma samples [19] and malignant prostate tissue [20]. Elevated β-arrestin1 expression correlated with high risk stratification in acute lymphoblastic leukemia [21] and linked to poor prognosis in gastric [22]. However, few studies have investigated the expression and significance of β-arrestin1 in lung ADC, especially for the prognosis of lung ADC.

In the present study, we showed that β-arrestin1 expression was common in lung ADC tissues. Survival analysis demonstrated that high

β-arrestin1 expression significantly predicted decreased overall 5-year survival and higher recurrence rate. Further analysis using the Cox regression model confirmed that β-arrestin1 high expression was an independent and significantly prognostic factor in predicting progression-free survival for lung ADC patients.

β-arrestins were previously known as cytosolic signaling regulatory and scaffold proteins [23]. Recent studies revealed that β-arrestins were able to shuttle between the cytoplasm and the nucleus as a cytoplasm-nucleus messenger [5, 23], and β-arrestin1 was present in both the nucleus and the cytoplasm at steady state [24, 25]. Few studies have addressed the mechanistic role of β-arrestins in promoting nuclear transcription [23]. A recent study showed that β-arrestin1 mediates metastatic growth of breast cancer cells by facilitating HIF-1-dependent VEGF [8], which suggested that β-arrestins may have an important, yet unknown function in the nucleus, most likely, to regulate gene transcription through a novel mechanism.

We have found that that an elevated nuclear β-arrestin1 correlates with higher intratumoral VEGF, a key regulator of tumor angiogenesis, supporting the hypothesis that β-arrestin1 translocated to the nucleus to facilitate VEGF gene expression which plays an crucial role in lung ADC tumorigenesis [8]. Although multiple growth factors have been shown to regulate angiogenesis and vascular development [26], little is known about the complex regulation mechanism of gene expression and translation. Our results highlight the potential role of nuclear β-arrestin1 in tumor angiogenesis.

The ability of β-arrestin1 to translocate to the nucleus, and directly bind and regulate the activity of transcription factors involved in tumor growth and survival, validates future studies on determining the potential of inhibiting β-arrestins proteins as therapeutic targets [27]. It was recently reported that the rapid xenograft tumor progression in β-arrestin1 transgenic mice is due to enhanced MMP9 activity, VEGF secretion, and subsequent increase in tumor angiogenesis [9]. In addition, the secreted VEGF concentration in plasma was evidently increased in β-arrestin1 transgenic mice after tumor cell injection, indicating that tumor angiogenesis is more abundant in β-arrestin1 transgenic mice [9].

Taken together, our data support the assumption that β-arrestins1 protein high expression is common in lung ADC and its nuclear expression significantly correlated with vascular endothelial growth factor. Moreover, β-arrestins1 high expression is an independent prognostic factor for lung AD patients, which provide information for future researches targeting β-arrestin1 signaling pathways.

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Disclosure of conflict of interest

None.

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