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Original Article

Correlation between the activation of PI3K/Akt/mTOR signaling pathway and the clinical prognosis in patients with cervical cancer

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Abstract: Objective: To investigate the correlation between the activation of PI3K/Akt/mTOR signaling pathway and the clinical prognosis in cervical cancer patients. Methods: One hundred cervical cancer patients who underwent the surgery at our hospital from June 2006 to December 2008 were enrolled in this study. The expression levels of PI3K, p-Akt and p-mTOR in carcinoma and paracarcinoma tissues were analyzed by immunohistochemical staining, and their correlations with the clinical prognosis were evaluated via Kaplan-Meier method and Cox regression analysis. Results: In the carcinoma tissues, there were 36 (36%) cases with positive PI3K expression, 33 (33%) with positive p-Akt expression, and 29 (29%) with positive p-mTOR expression. While no expression of PI3K, p-Akt and p-mTOR was detected in the paracarcinoma tissues. Results of Kaplan-Meier analysis indicated that patients with positive PI3K, p-Akt and p-mTOR expressions presented an obviously shorter overall survival (OS) than those with negative expressions (all $P<0.05$). Patients with positive p-Akt and p-mTOR expressions presented an evidently shorter disease-free survival (DFS) than those with negative expressions (both $P<0.05$). Multivariate Cox regression analysis also showed that the positive expression levels of PI3K, pAkt and p-mTOR were independent risk factors for poor clinical prognosis in patients with cervical cancer. Conclusion: The activation of PI3K/Akt/mTOR signaling pathway may be a promising molecular marker for prognosis prediction in patients with cervical cancer.

Keywords: PI3K, Akt, mTOR, cervical cancer, prognosis

Introduction

Cervical cancer, one of most common malignant tumor in women [1-3], as the 5-year survival of patients with cervical cancer reached 50%-90% [4, 5]. A study showed that the exact mechanism underlying the occurrence and development of cervical cancer might be related to the activation of several oncogenes, the mutation of tumor-suppressive genes as well as the over-expression of anti-apoptotic genes [6].

In the previous researches, the PI3K/Akt/mTOR signaling pathway was excessively activated in several human tumors, such as squamous cell carcinomas, to involve in the regulation of cell proliferation, differentiation and metabolism as well as the process of tumor development, metastasis and drug resistance [7]. PI3K is an important member of the phospholipid kinase family with both lipid kinase activity and protein kinase activity, and is responsible for the transduction of growth factors and the stimuli from the cell membrane to the cytoplasm [8].

Akt is the direct downstream target protein of PI3K. Phosphorylated Akt (p-Akt), the active form of Akt, can induce cell malignant transformation [9]. It was reported that p-Akt played an important role in the progression of non-small cell lung cancer, while in breast cancer and ovarian cancer, p-Akt was participated in the cell adhesion, movement, invasion and metastasis [10]. These findings were also confirmed in cervical cancer, which showed that the activation of Akt was closely related to the occurrence of cervical cancer [11].

As for mTOR, an atypical serine/threonine kinase, is the downstream molecular of Akt. Phosphylated mTOR (p-mTOR) contributes to the synthesis of ribosomal S6 kinase and eukaryotic initiation factor 4E-binding protein,

Table 1. The clinicopathological characteristics of the patients

Characteristics	Patients (n=100)
Age (year)	
≤30	21/21.0%
>30	79/79.0%
Tumor size (n/%)	
≤4 cm	69/69.0%
>4 cm	31/31.0%
Pelvic lymph node metastasis (n/%)	
No	69/69.0%
Yes	31/31.0%
Clinical stage (n/%)	
Ia	12/12.0%
Ib	60/60.0%
IIa	28/28.0%
Pathological type (n/%)	
Squamous cell carcinoma	81/81.0%
Adenocarcinoma	19/19.0%
Depth of invasion (n/%)	
≥1/2	38/38.0%
<1/2	62/62.0%

which can further regulate cell growth and differentiation [12, 13]. The overexpression and activation of mTOR can be observed in a variety of tumors, including ovarian cancer, prostate cancer, myeloma, breast cancer, pancreatic cancer, lung cancer, etc. [14].

So far, few studies have reported the relationship between PI3K/Akt/mTOR signaling pathway and clinical prognosis in cervical cancer. Therefore, in this study, we detected the expression levels of PI3K, p-Akt, p-mTOR in cervical cancer and analyzed the correlation between their expressions and the clinical prognosis in cervical cancer patients to clarify the role of PI3K/Akt/mTOR signaling transduction pathway in the development of cervical cancer.

Methods and materials

Participants

A total of 100 patients with early cervical cancer who underwent radical surgery in our hospital from June 2006 to December 2008 were enrolled in this study. This study was approved by the Hospital Ethics Committee, and all the patients have provided the informed consent prior to the start of the study.

Inclusion criteria: Patients who were pathologically diagnosed with early cervical cancer; patients underwent radical surgery. Exclusion criteria: All the patients who had distant metastasis were excluded by the examination of chest and abdominal CT scan and enhanced pelvic CT scan before operation.

Immunohistochemical staining

The cervical cancer tissues and paracarcnoma tissues were fixed, paraffin-embedded, and sliced (4 um). After antigen retrieval and blocking, the slices were incubated with anti-human monoclonal antibody PI3K (1:500, Abcam, USA), anti-human monoclonal antibody p-Akt (1:500, Abcam, USA) and rabbit anti-human polyclonal antibody p-mTOR (1:300, Abcam, USA) at 37°C for 1 h. Then the slices were washed and incubated with horse radish peroxidase (HRP)-conjugated secondary antibody (1:1,000, Abcam, USA) at 37°C for 30 min, and then stained with DAB and hematoxylin.

The positive expression of PI3K, p-Akt and p-mTOR protein were observed and analyzed by two pathological physicians. The number of positive cells in 100 tumor cells was counted under light microscope (400X) in 5 non-overlapped fields. The ratio of positive cells was scored from 0 to 4 as follows: the positive rate <5%, score 0; the positive rate 5-25%, score 1; the positive rate 26-50%, score 2; the positive rate 51-75%, score 3; the positive rate >75%, score 4. The intensity of staining was scored from 0 to 3 as follows: no staining, score 0; light brown, score 1; moderate brown, score 2; strong brown, score 3. Cases with both ratio of positive cells ≥5% and scores of the staining intensity ≥1 were considered positive [15].

Treatment

All patients underwent surgical treatment. Patients at stage Ia underwent extensive hysterectomy; patients at stage Ib~IIa with tumor size less than 4 cm underwent hysterectomy and pelvic lymphadenectomy; patients at stage Ib~IIa with tumor size over 4 cm underwent extensive hysterectomy and pelvic lymphadenectomy followed by neoadjuvant chemotherapy (paclitaxel 135 mg/m^2 and cisplatin 75 mg/m^2, 21 days per course) with an interval of 2-4 weeks. The postoperative radiotherapy with a dose of 40-45 Gy (completed in 4-6 weeks),

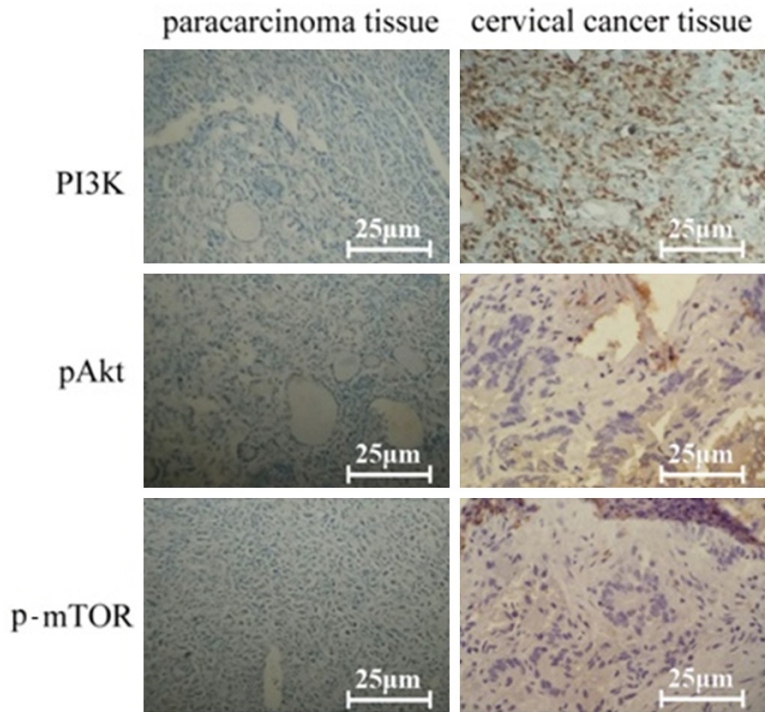

Figure 1. The expression levels of PI3K, p-Akt and p-mTOR. PI3K, p-Akt and p-mTOR were mainly expressed in the cytoplasm of cervical cancer cells, but no expression of PI3K, p-Akt and p-mTOR was detected in paracarcinoma tissues (400X). The cancer tissues and the pararcarcinoma tissues were collected from the same patient.

combined with chemotherapy (cisplatin 40 mg/m^2, once a week, completed in 5-6 weeks) was performed when the pathological examination showed one of the following conditions: the invasive depth >1/2 muscular layer, pelvic lymph node metastasis, surgical margin with carcinoma. And patients at high risk were given additional intracavitary radiotherapy for vaginal stump at a dose of 5-6 Gy for 2-4 times.

Follow-up

All the patients were followed up by telephone or outpatient visit every 3 months for the first year, and every 6 months thereafter. The overall survival (OS) was defined as the time from surgery to any cause of death or follow-up deadline. Disease free survival (DFS) was defined as the time from surgery to disease progression (tumor recurrence and metastasis, or a new tumor) or death from a tumor.

Information collection

Clinicopathological characteristics including age, tumor size, pathological type, clinical stage (according to FIGO standard), lymph node metastasis and depth of invasion were collected. The OS and DFS were recorded.

Statistical analysis

Data analyses were performed by using SPSS 19.0 statistical package, and the impacts of PI3K, p-Akt and p-mTOR expressions on survival (OS and DFS) were analyzed by Log-rank test. Multivariate Cox regression was used to analyze the correlation between the expression levels of PI3K, p-Akt and p-mTOR and the clinical prognosis (OS and DFS) in cervical cancer patients. $P<0.05$ was considered to be statistically significant.

Results

Clinicopathological characteristics

In this study, the average age of all the patients at the time receiving surgery was 43.60±15.31 years old. There were 12 (12.0%) patients at stage Ia, 60 (60.0%) at stage Ib, and 28 (28.0%) at stage IIa. For tumor size, there were 69 (69%) cases with a tumor size less than 4 cm, 31 (31%) with tumor size over 4 cm. For pathological types, there were 81 (81%) cases with squamous cell carcinoma and 19 (19%) cases with adenocarcinoma. For pelvic lymph node metastasis, there were 69 (69%) cases without lymph node metastasis, and 31 (31.0%) with lymph node metastasis. For the depth of invasion, there were 62 (62.0%) cases with invasion <1/2 muscular layer, and 38 (38.0%) with invasion >1/2 muscular layer (**Table 1**).

The expression levels of PI3K, p-Akt and p-mTOR

In our study, the positive expression ratio of PI3K, p-Akt and p-mTOR were 36%, 33% and 29%, respectively. All of these positive expressions were detected in the cytoplasm of tumor cells while none was detected in paracarcinoma tissues (**Figure 1**).

Table 2. The correlation between PI3K expression and clinicopathological characteristics

Characteristics	PI3K		χ^2	*P* value
	Positive (n=36)	Negative (n=64)		
Age (year)			0.54	0.46
≤30	9	12		
>30	27	52		
Tumor size (n/%)			3.51	0.06
≤4 cm	29	40		
>4 cm	7	24		
Pelvic lymph node metastasis (n/%)			2.03	0.15
No	28	41		
Yes	8	23		
Clinical stage (n/%)			3.29	0.19
Ia	7	5		
Ib	21	39		
IIa	8	20		
Pathological type (n/%)			0.20	0.66
Squamous cell carcinoma	30	51		
Adenocarcinoma	6	13		
Depth of invasion (n/%)			0.51	0.47
≥1/2	12	26		
<1/2	24	38		

Table 3. The correlation between p-AKt expression and clinicopathological characteristics

Characteristics	p-Akt		χ^2	*P* value
	Positive (n=33)	Negative (n=67)		
Age (year)			0.31	0.58
≤30	8	13		
>30	25	54		
Tumor size (n/%)			0.01	0.92
≤4 cm	23	46		
>4 cm	10	21		
Pelvic lymph node metastasis (n/%)			0.13	0.72
No	22	47		
Yes	11	20		
Clinical stage (n/%)			2.38	0.30
Ia	6	6		
Ib	20	40		
IIa	7	21		
Pathological type (n/%)			3.14	0.08
Squamous cell carcinoma	30	51		
Adenocarcinoma	3	16		
Depth of invasion (n/%)			0.46	0.50
≥1/2	11	27		
<1/2	22	40		

Correlation between PI3K, p-Akt and p-mTOR expressions and clinicopathological characteristics

The patients were divided into two groups (Positive vs. Negative) according to the expression levels of PI3K, p-Akt and p-mTOR respectively. The correlation between the expression levels of PI3K, p-Akt and p-mTOR and clinicopathological characteristics were analyzed, respectively, and results showed that there was no correlation between them (all P >0.05, **Tables 2-4**).

Survival analysis

All the patients were followed up for 18 months to 109 months, with an average of (67.95±24.57) months. During the follow-up, 26 patients died and 12 patients relapsed, which yielded an OS of (90.71±3.21) months, and a DFS of (95.86±2.75) months.

Survival analysis showed that the OS in patients with positive PI3K, p-Akt, p-mTOR expressions were respectively significantly lower than those with negative expressions (P=0.04, P<0.01, P<0.01). Additionally, the DFS in patients with positive p-Akt, p-mTOR expressions were respectively shorter than those with negative expressions (P=0.00, P=0.00), however, there was no evidently differences in DFS of patients with positive or negative PI3K expression (P=0.41). See **Table 5**.

Correlation between the expression levels of PI3K, p-Akt and p-mTOR and clinical prognosis in cervical cancer

As shown in **Table 6**, multivariate Cox regression analysis showed that the positive expressions of PI3K, p-Akt and p-mTOR were independent risk factors for poor postoperative prognosis in patients with cervical cancer. The expres-

Table 4. The correlation between p-mTOR expression and clinicopathological characteristics

Characteristics	p-mTOR		χ^2	*P* value
	Positive (n=29)	Negative (n=71)		
Age (year)			1.07	0.30
≤30	8	13		
>30	21	58		
Tumor size (n/%)			0.23	0.63
≤4 cm	19	50		
>4 cm	10	21		
Pelvic lymph node metastasis (n/%)			0.00	0.99
No	20	49		
Yes	9	22		
Clinical stage (n/%)			0.87	0.65
Ia	3	9		
Ib	16	44		
IIa	10	18		
Pathological type (n/%)			0.08	0.78
Squamous cell carcinoma	23	58		
Adenocarcinoma	6	13		
Depth of invasion (n/%)			0.21	0.64
≥1/2	10	28		
<1/2	19	43		

Table 5. Survival analysis

	Positive	Negative	Log-rank	P
PI3K				
OS (month)	82.06±5.97	94.09±3.21	4.21	0.04
DFS (month)	85.21±4.45	96.58±3.35	0.69	0.41
p-Akt				
OS (month)	70.73±6.22	99.11±2.50	23.11	<0.01
DFS (month)	73.16±6.17	102.31±2.09	16.05	0.00
p-mTOR				
OS (month)	76.76±7.41	95.17±2.71	9.57	<0.01
DFS (month)	67.19±5.88	102.45±2.00	18.83	0.00

sions of PI3K, p-Akt and p-mTOR were all negatively correlated with the OS in patients after surgery. In addition, the expression of p-Akt and p-mTOR were negatively correlated with postoperative DFS in patients with cervical cancer.

Discussion

Cervical cancer is a common gynecologic malignant tumor, which seriously endangers women's life and health. In China, the incidence of cervical cancer has increased significantly in recent years, moreover, the patients tend to be younger. Among the various factors that participate in the development of cervical cancer, the activation and inactivation of several genes are most concerned. Recent study found that many oncogenes and tumor suppressor genes were involved in the process of cell growth, proliferation, differentiation and signal transduction, among which, abnormal signal transduction was thought to play a vital role in the tumor development [16]. Reportedly, PI3K/Akt/mTOR signaling pathway is one of the most closely related signal transduction pathways regulating cell bio-behaviors, including cell proliferation, apoptosis and differentiation [17]. In the meanwhile, a study also reported that PI3K/Akt/mTOR signaling pathway had important physiological functions on regulating cell cycle, protein synthesis, and cell energy metabolism via a variety of ways [18]. Therefore, the abnormal activation of PI3K/Akt/mTOR signaling pathway might not only lead to malignant transformation, but also result in tumor cell migration and adhesion, angiogenesis and degradation of extracellular matrix [19].

In the previous study, Zhang et al. reported that the expression level of PI3K in cervical cancer tissues was significantly higher than that in normal cervical tissue [20], which was consisted with our conclusion as the positive expression level of PI3K in cervical cancer specimens was significantly higher than that in paracarcinoma tissues, indicating that PI3K was correlated with the occurrence of cervical cancer. In addition, our study showed that the OS in patients with positive PI3K expression was significantly shorter than those with negative expression, and multivariate Cox regression analysis also showed that PI3K was an independent risk factor associated with the OS in patients with cervical cancer. All these results suggested that PI3K was closely related with the development and prog-

Table 6. Correlation between the expression levels of PI3K, p-Akt and p-mTOR and clinical prognosis in cervical cancer

	OS		DFS	
	HR (95% CI)	P	HR (95% CI)	P
PI3K (Positive vs. Negative)	0.216 (0.081-0.930)	0.03	0.966 (0.389-1.690)	0.09
p-Akt (Positive vs. Negative)	0.128 (0.066-0.776)	<0.01	0.161 (0.031-0.416)	<0.01
p-mTOR (Positive vs. Negative)	0.108 (0.059-0.701)	0.01	0.120 (0.061-0.399)	<0.01

nosis of cervical cancer, which may be due to the fact that PI3K expression could promote the proliferation and survival of cancer cells, leading to tumor recurrence and metastasis.

In addition, our results showed that the positivity of p-Akt expression in cervical cancer tissues was 33%, which was significantly higher than that in paracarcinoma tissues, suggesting that the activation of Akt was closely related to the occurrence of cervical cancer. Previous studies showed that the activation of Akt occurred in many human tumors, including breast cancer, gastric cancer, colon cancer, pancreatic cancer, prostate cancer, and played a role in tumor resistance to chemotherapy and radiotherapy, indicating that the inhibition of Akt activation may be a promising target in the treatment of cancer [10, 21]. A retrospective analysis with 27 patients suffered locally advanced cervical squamous cell carcinoma showed that there was a negative correlation between the p-Akt expression and the sensitivity of tumor cells to radiotherapy, and the prognosis was better in patients with low expression level of p-Akt [22]. Our study also showed that the OS and DFS in patients with positive p-Akt expression were significantly lower than those with negative expression. In addition, Cox regression analysis showed that the p-Akt expression level was negatively associated with the OS and DFS, and was an independent risk factor associated with prognosis of cervical cancer, which was consistent with previous study.

Moreover, the activation and overexpression of mTOR was found in many solid tumor tissues as well, which was closely related to cell growth and differentiation [11]. In the current study, we found that the positivity of p-mTOR expression in cervical carcinoma tissues was 29%, which was significantly higher than those in paracarcinoma tissues, and further analysis showed that the OS and DFS in cervical cancer patients with positive p-mTOR expression were significantly shorter than those negative to p-mTOR expression. And multivariate Cox regression analysis showed that mTOR was negatively correlated the OS and DFS, indicating that the activation of mTOR was also closely related with the occurrence and development of cervical cancer. Previous study has shown that the inhibition of mTOR activation can down regulate cell proliferation by PI3K/Akt pathway and block cell cycle and tumor growth [23]. All these results suggested that mTOR inhibitors had the potential to become a new anti-tumor drug. For example, rapamycin, a specific inhibitor of mTOR, has been proved that it could enhance the sensitivity of glioblastoma in the radiotherapy treatment.

However, there were some limitations in study. Firstly, the samples size in this study was small, which may cause some statistical bias. Secondly, due to the low positive expression ratio of PI3K, p-Akt and p-mTOR, the association between the double and triple positive expressions of these signaling molecules and the clinical prognosis cannot be further analyzed. Thirdly, this study was conducted at the histological level, thus, more work is needed to be done at both cellular and molecular levels.

In conclusion, the abnormal activation of P13K/Akt/mTOR signaling pathway was closely related to the occurrence and development of cervical cancer, therefore, P13K, Akt, mTOR might be used as the promising molecular markers for prognosis prediction.

Disclosure of conflict of interest

None.

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