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Original Article

Correlation analysis of survivin, ING4, CXCL8 and VEGF expression in prostate cancer tissue

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Abstract: Objective: This study aimed to investigate the expression of Survivin, inhibitor of growth 4 (ING4), CXC chemokine ligand 8 (CXCL8), vascular endothelial growth factor (VEGF), and the correlation between Survivin, ING4, CXCL8 and VEGF in prostate cancer (PCa) tissues. Methods: From January 2019 to December 2019, 51 patients from Chengwu People's Hospital and The First People's Hospital of Taian, with PCa were selected as the PCa group and 47 patients with benign prostatic hyperplasia (BPH) were included as the BPH group. The expression of Survivin, ING4, CXCL8 and VEGF in both groups and among patients with different clinical stages in the PCa group were compared, and the correlation between Survivin, ING4, CXCL8 and VEGF expression in PCa tissues was analyzed. Results: Survivin, ING4, CXCL8, and VEGF expression differed significantly between the two groups (P<0.05). The Survivin positive expression rate, CXCL8 positive expression rate, and VEGF positive expression rate in the PCa group were significantly higher than those in the BPH group (P<0.05), and ING4 positive expression rate in the PCa group was significantly lower than that in the BPH group (P<0.05). Survivin positive expression rate, CXCL8 positive expression rate, and VEGF positive expression rate were significantly higher in PCa patients with stage III+IV than those of stage I+II (P<0.05), and ING4 positive expression rate in PCa patients in stage III+IV was significantly lower than that in stage I+II (P<0.05). Kendall's tau-b analysis, VEGF was positively correlated with Survivin and CXCL8 (P<0.05) and negatively correlated with ING4 (P<0.05) in PCa tissues. Conclusion: Survivin, CXCL8, and VEGF were highly expressed and ING4 was lowly expressed in PCa tissues, which was correlated with clinical stage; additionally, Survivin, ING4, CXCL8, and VEGF played a synergistic role with each other in the development and progression of PCa.

Keywords: Prostate cancer, survivin, growth inhibitory factor, CXC chemokine ligand 8, vascular endothelial growth factor

Introduction

Prostate cancer (PCa) is a malignant tumor of the male urological system. An autopsy study of men over 50 years found that the incidence of PCa was about 10% to 45%, and increased with age [1, 2]. Early PCa has no obvious clinical symptoms. Only when the tumor tissue grows to a certain size, there will be a sense of urethral pressure and abnormal urination since part of the urethra passes through the prostate tissue. A small number of patients go to the clinic only when they feel pain during urination or have hematuria, and by this time, the patients have reached the advanced stage of PCa and will develop back pain, negatively impacting the prognosis.

The pathogenesis of PCa is complex and its occurrence is related to diet, environment, genetics, and the regulation of multiple genes [3]. Survivin is an apoptosis suppressor, and high expression of Survivin inhibits apoptosis induced by apoptosis-associated proteins such as p53, Bax, and chemotherapeutic agents, and also directly inhibits the release of cytochrome C in mitochondria. It has been shown that Survivin is highly expressed in a variety of malignant tumors, which is associated with tumor prognosis and it may be a potential tumor

marker [4, 5]. Inhibitor of growth 4 (ING4) is absent or lowly expressed in a variety of tumor cells and may play a key part in tumorigenesis as well as tumor development. Studies have shown that ING4 inhibits tumor neovascularization in breast and colon cancers [6, 7]. CXC chemokine ligand 8 (CXCL8) belongs to the CXC chemotactic family with a molecular weight of 8 KD. It is produced mainly in peripheral inflammatory cells as well as cancer cells; it promotes angiogenesis and mitosis, and is expressed in malignant tumors such as bronchogenic, hepatocellular, and lung cancers. Compared to cancer cells with low CXCL8 expression, cancer cells with high CXCL8 expression have a higher ability to infiltrate as well as metastasize, indicating that CXCL8 is closely related to tumorigenesis, migration, and invasion, affecting patient prognosis [8]. Tumorigenesis and invasion are related to blood vessels in the surrounding tissues, so the survival of blood vessels is closely related to tumorigenesis. Vascular endothelial growth factor (VEGF) can play a regulatory role in vascular endothelial cells, which can enhance the permeability of blood vessels and promote the generation of new capillary networks as well as tumor cells, and is associated with tumor angiogenesis [9].

Tumor metastasis and recurrence make clinical treatment more difficult, but the mechanisms of tumor metastasis and recurrence are not yet fully understood. Evidence has shown that solid tumors with a diameter of more than 2 mm rely exclusively on nutrients provided by blood vessels for their growth, suggesting that blood vessels play a vital role in tumor metastasis and invasion [10]. Survivin is a potential tumor marker, ING4 and CXCL8 are related to the prognosis of patients with malignant tumors, and VEGF is a promoter of the formation of tumor blood vessels, but there are few studies on the combined effects of these indicators. This study investigated Survivin, ING4, CXCL8 and VEGF in PCa tissues, and the correlation between Survivin, ING4, CXCL8, and VEGF, aiming to provide an auxiliary reference for PCa diagnosis, treatment, and prognostic assessment.

Materials and methods

Baseline data

From January 2019 to December 2019, this study included 51 patients with PCa as the PCa group, and 47 patients with benign prostatic hyperplasia (BPH) as the BPH group, all patients were from Chengwu People's Hospital and The First People's Hospital of Taian. Inclusion criteria for PCa patients: (i) postoperative pathological examination confirmed the diagnosis of PCa; (ii) all patients received transurethral resection of the prostate (TURP) or surgical resection, and they had no contraindications to surgery. Inclusion criteria for patients with BPH: (i) patients were confirmed by pathological diagnosis after TURP or puncture examination; (ii) no contraindication to TURP. Exclusion criteria: (i) those who did not receive other targeted treatment before surgery; (ii) those who had previous prostate surgery; (iii) those who had rectal examination of the prostate 1 week before collection of specimens; (iv) those who had undergone surgical castration; (v) those who had long-term use of androgenic drugs. This study was approved by the Ethics Committee of Chengwu People's Hospital and The First People's Hospital of Taian. The research subjects and their families were informed of the study and signed a fully-informed consent form.

Methods

Fifty-one specimens by TURP or surgical resection and 47 specimens by TURP or puncture were collected. The Survivin, ING4, CXCL8 and VEGF levels were detected using the streptavidin-peroxidase conjugated method. The biopsy specimens were fixed with 10% formalin, dehydrated with different concentrations of ethanol, and then embedded in paraffin, cut into sections with a thickness of 4 μm. After dewaxing, hydration and antigen retrieval, specimens were treated with rabbit anti-human Survivin polyclonal antibody, rabbit anti-human ING4 polyclonal antibody, rabbit anti-human CXCL8 polyclonal antibody, and rabbit anti-human VEGF polyclonal antibody, color development with DAB, hematoxylin counterstain, and differentiation with hydrochloric acid-alcohol solution, dehydration and mounting. Results criteria [11]: 5-10 high-powered fields were randomly selected for observation, with 100 cells as one field. The positive cell rate of 5%, 5%-24%, 25%-49%, >50% was scored as 0 points, 1 point, 2 points, and 3 points, respectively. According to the coloring intensity, 1 point, 2 points, 3 points were respectively recorded for light yellow, yellow, and brown. If the product of the two scores was 0, it was negative (-); 1-3

Table 1. Comparison of baseline information ($\bar{x}\pm s$; n, %)

Group	Number of cases	Age (years)	Body weight (kg)	Height (cm)	Diabetes	Hypertension	Coronary heart disease
PCa group	51	63.95±6.43	57.36±6.59	162.26±11.47	16 (31.37)	39 (76.47)	24 (47.06)
BPH group	47	64.63±7.24	55.36±7.31	159.49±10.41	18 (38.30)	38 (80.85)	19 (40.43)
t		0.492	1.424	1.248	0.518	0.279	0.437
P		0.624	0.158	0.215	0.472	0.598	0.509

Table 2. Comparison of Survivin, ING4, CXCL8, and VEGF expression between the two groups (n, %)

Indicator	Number of cases	Survivin positive expression rate	ING4 positive expression rate	CXCL8 positive expression rate	VEGF positive expression rate
PCa group	51	42 (82.35)	25 (49.02)	49 (96.08)	44 (86.27)
BPH group	47	0 (0.00)	44 (93.62)	0 (0.00)	15 (31.91)
χ^2		-	23.349	-	30.167
P		<0.001*	<0.001	<0.001*	<0.001

Note: **P*-value by the fisher exact probability method test.

points were weakly positive (+), 4-6 points were moderately positive (++), and 7-9 points were strong positive (+++). The positive rate = (total number of cases-negative cases)/total number of cases × 100%.

Observation indicators

The Survivin, ING4, CXCL8, and VEGF expression in the PCa group, BPH group, and their expression in patients with different clinical stages (stage I+II and stage III+IV) of the PCa patients were analyzed to explore the correlation between Survivin, ING4, CXCL8, and with VEGF in PCa tissues.

Statistical methods

All data were processed by SPSS 22.0 statistical software. All statistical graphics were processed by Graphpad Prism V8 software. Count data (n, %) were examined by χ^2 test, rank sum test, or fisher's exact probability method test. Measurement data ($\bar{x}\pm s$) were tested with independent samples t test. Correlation analysis was performed using Kendall's tau-b analysis. Statistically significant differences were expressed as $P<0.05$.

Results

Baseline data

The baseline data did not differ significantly between the two groups ($P>0.05$), which were comparable (**Table 1**).

Survivin, ING4, CXCL8, and VEGF expression in both groups

The expression of Survivin, ING4, CXCL8 and VEGF differed significantly between the two groups ($P<0.001$). The positive expression of Survivin, CXCL8 and VEGF in the PCa group was 82.35%, 96.08% and 86.27%, respectively, significantly higher than 0.00%, 0.00% and 31.91% in the BPH group ($P<0.001$), and the positive expression of ING4 in the PCa group was 49.02%, significantly lower than 93.62% in the BPH group ($P<0.001$) (**Table 2** and **Figures 1-4**).

The survivin, ING4, CXCL8, VEGF expression in patients with different clinical stages

Survivin, CXCL8, and VEGF positive expression rates in stage III+IV were 89.74%, 100.00%, and 94.87%, respectively, significantly higher than 58.33%, 83.33%, and 58.33% in stage I+II ($P=0.013$, 0.009, 0.001). The ING4 positive expression rate in stage III+IV (35.90%) was significantly lower than that in stage I+II (91.67%) ($P=0.001$) (**Table 3**).

Correlation of VEGF with survivin, ING4, and CXCL8 expression in PCa tissues

Kendall's tau-b analysis found that VEGF expression was positively correlated with Survivin and CXCL8 expression (r=0.712, 0.507, $P<0.001$) and negatively correlated with ING4 expression (r=-0.407, $P=0.004$) in PCa tissues (**Table 4**).

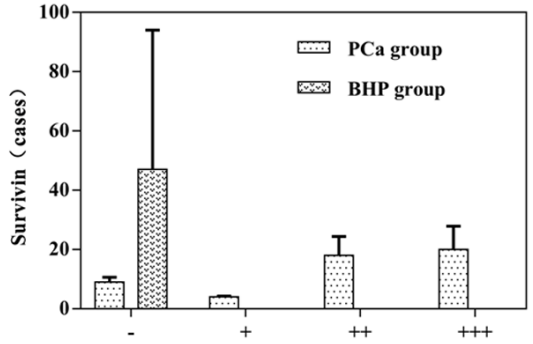

Figure 1. The expression of Survivin. The cases of Survivin (-), (+), (++) and (+++) were 9, 4, 18 and 20 in the PCa group, respectively, and the case of Survivin (-) was 47 cases in the BPH group.

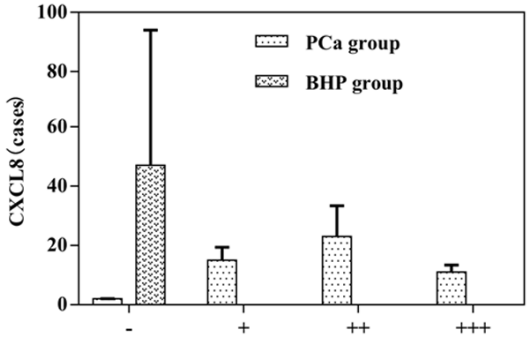

Figure 3. CXCL8 expression in both groups. The cases of CXCL8 (-), (+), (++) and (+++) were 2, 15, 23 and 11 in the PCa group, respectively, and the case of CXCL8 (-) was 47 in the BPH group.

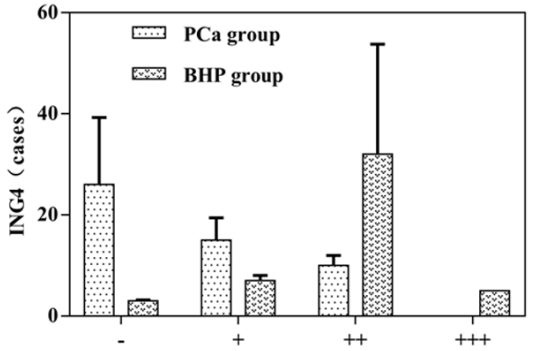

Figure 2. ING4 expression in both groups. The cases of ING4 (-), (+) and (++) were 26, 15 and 10 in the PCa group, respectively, and the cases of ING4 (-), (+), (++) and (+++) were 3, 7, 32 and 5 in the BPH group, respectively.

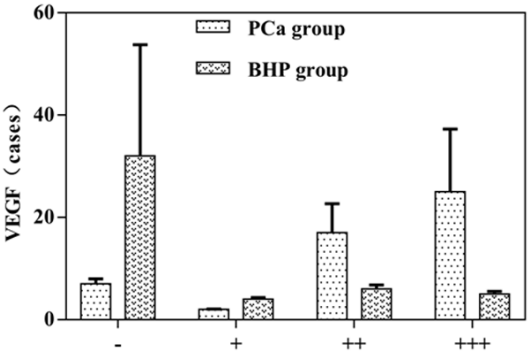

Figure 4. VEGF expression in both groups. The cases of VEGF (-), (+), (++) and (+++) were 7, 2, 17 and 25 in the PCa group, respectively, and the cases of VEGF (-), (+), (++) and (+++) were 32, 4, 6 and 5 in the BPH group, respectively.

Discussion

In tumor tissues, Survivin inhibits the normal process of apoptosis, and the higher the expression of Survivin in tumor tissues, the more the apoptosis of cancer cells is inhibited, the tumor becomes more aggressive, and the neighboring tissues become more susceptible to malignant cell invasion, and finally tumor metastasis occurs, shortening the survival time of patients resulting in a poor prognosis [12, 13]. It has been shown that inhibition of malignant cell apoptosis by Survivin is closely related to distant metastasis of PCa [14]. In this study, the Survivin positive expression rate in the PCa group was significantly higher than that in BPH group, and Survivin positive expression rate in stages III+IV was significantly higher than that in stages I+II, suggesting that Survivin plays an important part in the onset and development of PCa.

ING4 is mainly expressed in the nucleus of normal tissue cells, while its expression is significantly lower in tumors such as lung cancer, head and neck squamous cell carcinoma, and glioblastoma, and is negatively correlated with cancer risk and staging [15, 16]. Some studies have reported that ING4 has a strong oncogenic effect in colorectal, hepatocellular, and gastric and renal cancers [17, 18]. ING4 plays a key role in the normal differentiation of prostate cells, and its absent or low expression may cause abnormal differentiation of prostate cells, leading to the development of PCa. In this study, the positive expression rate of ING4 in the PCa group (49.02% vs. 93.62%) was significantly lower than that in the BPH group, and the

Table 3. Comparison of Survivin, ING4, CXCL8, and VEGF expression in different clinical stages in the PCa group (n, %)

Clinical stage	Number of cases	Survivin		ING4		CXCL8		VEGF	
		Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
I+II stage	12	5 (41.67)	7 (58.33)	1 (8.33)	11 (91.67)	2 (16.673)	10 (83.33)	5 (41.67)	7 (58.33)
III+IV stage	39	4 (10.26)	35 (89.74)	25 (64.10)	14 (35.90)	0 (0.00)	39 (100)	2 (5.13)	37 (94.87)
χ^2		6.23		11.421		6.765		10.346	
P		0.013		0.001		0.009		0.001	

Table 4. Correlation analysis of VEGF with Survivin, ING4, and CXCL8 expression in PCa tissues

VEGF	Number of cases	Survivin		ING4		CXCL8	
		Negative	Positive	Negative	Positive	Negative	Positive
Negative	7	6 (85.71)	1 (14.29)	0 (0.00)	7 (100)	2 (28.57)	5 (71.43)
Positive	44	3 (6.82)	41 (93.18)	26 (59.09)	18 (40.91)	0 (0.00)	44 (100.00)
r		0.712		-0.407		0.507	
P		<0.001		0.004		<0.001	

positive expression rate of ING4 in stages III+IV (35.90% vs. 91.67%) was significantly lower than that in stages I+II, suggesting that ING4 has an oncogenic role in PCa development and progression, and its low expression is correlated with tumor metastasis as well as invasion.

CXCL8 can be used as a prognostic indicator for tumors such as breast cancer and head and neck squamous carcinoma [19, 20]. CXCL8 contributes to the generation of new capillaries, providing nutrients and oxygen to prostate tumor tissues to promote the occurrence of hematogeneous metastasis, which allows further proliferation of PCa tissues, affecting PCa prognosis. It has been shown that CXCL8 can upregulate the expression of chemokine receptor 7 (CXCR7), thus promoting the growth and the proliferation of PCa cells [21, 22]. In this study, CXCL8 positive expression rate in the PCa group (96.08% vs. 0.00%) was significantly higher than that in the BPH group and was also higher in stages III+IV (100.00% vs. 83.33%) than in stages I+II, suggesting that CXCL8 is involved in the occurrence and development of PCa.

Tumor growth and infiltration involve physiological processes such as abnormal proliferation, angiogenesis, and stromal degradation, which are closely related to neovascularization [23, 24]. Metastasis and invasion of solid tumors are dependent on nutrients provided by blood vessels [25]. VEGF is an angiogenesis-promoting factor, and studies have shown that VEGF is highly expressed in malignant tumors such as bladder and colorectal cancers, and it is more highly expressed in higher clinical stages, suggesting that VEGF is involved in tumorigenesis, development, and metastasis [26, 27]. In this study, the VEGF positive expression rate in the PCa group (86.27% vs. 31.91%) was significantly higher than that in the BPH group, and was also higher in stages III+IV (94.87% vs. 58.33%) than in stages I+II, suggesting that VEGF weights in the onset and the development of PCa and may be related to the activation of the VEGF promoter by androgens in PCa tissues, leading to elevated VEGF expression. In this study, VEGF was positively correlated with Survivin and CXCL8 and negatively correlated with ING4 in PCa tissue by Kendall's tau-b analysis, suggesting that Survivin, ING4, CXCL8 and VEGF play a synergistic role with each other in the development and progression of PCa.

In summary, Survivin, CXCL8, and VEGF were highly expressed in PCa tissues, and the higher the clinical stage, the higher their positive expression rate, suggesting that high expression of Survivin, CXCL8, and VEGF is related to tumorigenesis and development. ING4 is lowly expressed in PCa tissues, and the higher the clinical stage, the higher the positive expression rate, indicating that ING4 has a tumor suppressor effect in the occurrence and development of PCa. VEGF is positively correlated with Survivin and CXCL8, and negatively correlated with ING4, indicating that Survivin, ING4, CXCL8 and VEGF play a synergistic role in the

occurrence and development of PCa. Simultaneous detection of Survivin, ING4, CXCL8, VEGF expression can provide a new reference for the diagnosis, treatment and prognosis of PCa. However, this study is a retrospective analysis, the selection may be biased, and the study sample is relatively small. Therefore, further studies are needed to verify the experimental results through other research methods, such as prospective studies with larger samples.

Disclosure of conflict of interest

None.

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