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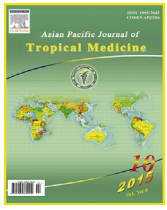

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Expression of serum Dickkopf-1 in gastric cancer patients

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ABSTRACT

Objective: To explore the expression and clinical significance of DKK-1 protein in patients with gastric cancers.

Methods: Enzyme linked immuno sorbent assay was used to detect expressions of serum DKK-1 protein in 90 cases of gastric cancers, 50 cases of gastric benign disease and 40 healthy cases. The dynamic change in serum DKK-1 protein of gastric cancer patients who accepted radical operation for a month was also observed.

Results: The expression of serum DKK-1 protein in gastric cancer groups was significantly higher than that in gastric benign group's ($P < 0.01$) and in health control ($P < 0.01$). Serum DKK-1 level was increased gradually along with the progress of the disease. Serum DKK-1 levels were significantly higher in patients at TNM staging III and IV than patients at TNM staging I and II. Level of serum DKK-1 was related to microvascular invasion, differentiation degree and infiltration depth. Level of serum DKK-1 was significantly reduced in patients after radical surgery ($P < 0.01$).

Conclusions: The expression of serum DKK-1 protein in gastric cancer patients is increased. Level of serum DKK-1 is related to TNM staging, microvascular invasion, differentiation degree and infiltration depth. DKK-1 detection can be used as a reference index in monitoring gastric cancer progress and biological behavior.

1. Introduction

Wnt signaling pathway mediates various cellular biological processes, such as proliferation, apoptosis, differentiation, movement, *etc*. The abnormality in such processes always leads to tumor. Dickkopf-1 (DKK-1) is an important regulatory factor of Wnt signaling pathway [1]. DDK-1 is one of secretory proteins, and is expressed in many tumor tissues and blood. It is reported that DKK-1 are overexpressed in peripheral blood of patients with gastric cancer, liver cancer, rectal cancer, lung cancer, *etc* [2]. In this study, we analyzed the correlation between DKK-1 and clinicopathological feature of gastric cancer, and compare DKK-1 with alpha fetal protein (AFP) and CA19-9 to explore the significance of DKK-1.

2. Material and methods

2.1. General data

A total of 90 gastric cancer patients admitted from January 2013 to April 2015 were selected, aged 29–67 years old, with median age as 55 years old. According to TNM staging for gastric cancer of UICC in 2010, there were 12 cases at staging I, 28 cases at staging II, 30 cases at staging III, and 20 cases at staging IV. They included 65 cases with radical surgery, and 25 cases with palliative surgery. All patients had no chemotherapy or radiotherapy, and were of normal liver and renal function. Another 50 patients with benign tumor (benign tumor group) and 40 healthy subjects (control group) were also selected. Out of 50 benign tumor patients, there were 27 cases with gastric ulcer and 23 cases with chronic gastritis, aged 24–68 years old, with median age as 52 years old. And the median age of control group was 52 years old (26–62 years old). There was no significant difference in age among three groups ($P > 0.05$).

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2.2. Sample collection

All subjects had no treatment. Five *milliliter* venous blood was extracted at 8 AM under fasting. Then the blood was centifugated. The supernate was drawn, and preserved under liquid nitrogen at −70 °C.

2.3. Reagent and method

DKK-1 mouse-anti-human monoclonal antibody assay kit was purchased from R&D System, and Elx800 Auto ELISA detecter was from BIO-TEK. DKK-1 was detected by ELISA.

2.4. Statistical analysis

All data were analyzed by SPSS19.0, and expressed as mean ± SD. They were analyzed by t test. And it was considered as significant difference as $P < 0.05$.

3. Results

3.1. DKK-1 level of gastric cancer, benign tumor and normal subjects

The DKK-1 level of gastric tumor patients was (6.52 ± 1.49) ng/mL, and was significantly higher than that of benign group [(5.23 ± 1.41) ng/mL] and control group [(5.13 ± 1.35) ng/mL] ($P < 0.05$).

3.2. DKK-1 level of patients at difference staging

As the progressing of tumor, DKK-1 level was increased in gastric cancer patients. There was no significant difference between staging I and II ($P > 0.05$), while the difference was significant between staging III, IV and staging I, II ($P < 0.05$) (Table 1).

3.3. DKK-1 level after radical surgery

DKK-1 of 65 cases with radical surgery was (6.53 ± 1.51) ng/mL before surgery. It was decreased to (5.75 ± 1.44) ng/mL, with significant difference ($t = 3.0139$, $P = 0.0031$). There was no significant difference between the level of gastric cancer patients 1 month after surgery and benign group ($P > 0.05$), and the difference was significant as compared with control group ($P < 0.05$).

3.4. Correlation between DKK-1 and clinicopathological features

There was no significant difference in DKK-1 between patients with focus >4 cm and patients with focus ≤4 cm ($P > 0.05$). But the difference among patients with different differentiation, infiltration and microvascular transfer was significant ($P < 0.05$) (Table 2).

Table 1
DKK-1 level of patients at difference staging.

TNM staging	n	DKK-1 level (ng/mL)
Staging I	12	6.17 ± 1.33△*
Staging II	28	6.28 ± 1.40△*
Staging III	30	6.56 ± 1.52
Staging IV	20	6.81 ± 1.53

△compared with staging III, $P < 0.05$; *compared with staging IV, $P < 0.05$.

Table 2
Correlation between DKK-1 and clinicopathological features.

Clinicopathological features	n	DKK-1 level (ng/mL)	t	P
Tumor size				
>4 cm	42	6.72 ± 1.56	1.264 5	0.209 4
≤4 cm	48	6.32 ± 1.44		
Differentiation				
Good	33	6.03 ± 1.50	2.233 7	0.028 0
Bad	57	6.82 ± 1.68		
Infiltration				
T1–T2	39	5.98 ± 1.40	2.671 7	0.009 0
T3–T4	51	6.88 ± 1.71		
Microvascular transfer				
Yes	34	6.85 ± 1.72	2.480 0	0.015 0
No	56	6.02 ± 1.42		

4. Discussion

DKK-1 is a member of DKK gene family. It is comprised of one signal peptide sequence and two districts with abundant cysteine. The molecule weight is 35 kD. DKK-1 is the key secretory factor of microenvironment mediation, and the function is different in different microenvironment and different structure [3]. Therefore, DKK-1 has different function in different tumor. It has negative regulatory effect on Wnt signaling pathway in colon cancer and gastric cancer [4,5]. While, it shows potential oncogene effect in liver, lung and esophageal cancer [6,7]. It is reported that DKK-1 is expressed in various tumor tissues and serum of cancer patients. There is correlation between DKK-1 level in serum and in tumor tissues. The level is increased as tumor progressing. Besides, DKK-1 is closely correlated with vessel infiltration and development of liver cancer [8]. The increased DKK-1 indicates shorter survival time. Kemik *et al* [9] found that DKK-1 has potential correlation with differentiation, infiltration, lymphatic metastasis and TNM staging in study of 150 rectal cancer cases.

Lee *et al* [10] found that DKK-1 level is significant higher in gastric cancer patients, indicating that DKK-1 is a possible serum marker of gastric cancer. In this study, we detected DKK-1 in 90 gastric cancer cases, and it showed that DKK-1 in serum of gastric cancer patients were significantly higher than that of benign group and control group. Then we analyzed the relationship between DKK-1 and TNM staging, and found that DKK-1 level was increased as progressing, especial in patients with microvascular transfer, which is similar to Lee *et al* [10]. DKK-1 detection may be helpful in clinical staging, increased DKK-1 level indicates progressive stage. It also shows that DKK-1 after surgery is significantly decreased ($P < 0.05$), which testifies that DKK-1 is related with development of gastric cancer. Foreign researches show that DKK-1 has no relationship with age or gender. However, there are different reports on the relationship of DKK-1 with tumor size, histological type, infiltration depth and transfer. In our study, we found that tumor size has no effect on DKK-1, but the difference is significant in patients with different differentiation degree, infiltration depth and microvascular transfer ($P < 0.05$).

In conclusion, DKK-1 level of gastric cancer patients is higher than that of normal persons, and is related with tumor

invasion, transfer, *etc*. The increased DKK-1 is also related with TNM staging. So detection of DKK-1 is valuable in judging progress and prognosis of gastric cancer. It also can be used as an index for postoperation monitoring and follow-up.

Conflict of interest statement

We declare that we have no conflict of interest.

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