

• CLINICAL RESEARCH •

Expression of p57^{kip2}, Rb protein and PCNA and their relationships with clinicopathology in human pancreatic cancer

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Received: 2002-07-23 **Accepted:** 2002-08-23

Abstract

AIM: To investigate the effects of inhibiting factor of cell cycle regulation p57^{kip2}, retinoblastoma protein (Rb protein) and proliferating cell nuclear antigen (PCNA) in the genesis and progression of human pancreatic cancer.

METHODS: The expression of p57^{kip2}, Rb protein and PCNA in tumor tissues and adjacent tissues of 32 patients with pancreatic cancer was detected with SP immunohistochemical technique.

RESULTS: p57^{kip2} protein positive-expression rate in tumor tissues of pancreatic cancer was 46.9 %, which was lower than that in adjacent pancreatic tissues (75.0 %) ($\chi^2=5.317$, $P<0.05$), p57^{kip2} protein positive-expression correlated significantly with tumor cell differentiation (well-differentiation versus moderate or low-differentiation, $P<0.05$) but did not correlate significantly with lymph node metastasis (lymph node metastasis versus non-lymph node metastasis, $P>0.05$); Rb gene protein positive-expression rate in tumor tissues was 50.0 %, which was also lower than that in adjacent pancreatic tissues (78.1 %) ($\chi^2=5.497$, $P<0.05$); PCNA positive-expression rate was 71.9 %, being higher than that in adjacent pancreatic tissues (43.8 %) ($\chi^2=5.189$, $P<0.05$), PCNA positive-expression also correlated significantly with tumor cell differentiation and lymph node metastasis (well-differentiation versus moderate or low-differentiation, lymph node metastasis versus non-lymph node metastasis, $P<0.05$). Rb protein positive-expression rate in the tumor tissues of p57^{kip2} protein positive-expression group was 53.3 %; and Rb protein positive-expression rate in the tumor tissues of p57^{kip2} protein negative-expression group was 47.1 %. There was no significant relationship between the two groups ($r=0.16507$, $P>0.05$).

CONCLUSION: The decreased expression of p57^{kip2}, Rb protein or over-expression of PCNA protein might contribute to the genesis or progression of pancreatic cancer, p57^{kip2}, Rb protein and PCNA may play an important role in genesis and progression of pancreatic cancer.

Yue H, Na YL, Feng XL, Ma SR, Song FL, Yang B. Expression of p57^{kip2}, Rb protein and PCNA and their relationships with clinicopathology in human pancreatic cancer. *World J Gastroenterol* 2003; 9(2): 377-380

<http://www.wjgnet.com/1007-9327/9/377.htm>

INTRODUCTION

The abnormality of mammalian cell cycle regulation is an important cause of cell over-proliferation and oncogenesis^[1]. Orderly progression of the cell cycle is controlled by a family of cyclins and cyclin-dependent kinase (CDKs) which are restrictively counterbalanced by CDK inhibitors(CDKIs)^[2].

Two distinct families of CDKIs, the INK4 and CIP/KIP families which regulate the the activity of the cyclin-CDK complexes, have been described^[3]. The CIP/KIP family, including p21, p27 and p57 proteins, harbors homologous CDK binding domains or fuction of cyclin-CDK complexes and makes cell cycle to arrest in G₁ phase. Retinoblastoma protein (Rb protein) is one of the tumor suppressor proteins and affects the progression of G₁ phase of cell cycle. The expression of proliferating cell nuclear antigen (PCNA) is obviously associated with cell proliferation. The relationships between p57^{kip2} protein and pancreatic cancer has not been reported in China. In this study, the expression of p57^{kip2}, Rb and PCNA protein in the tissues of pancreatic cancer were detected with immunohistochemical technique to investigate the effects of inhibiting proteins of cell cycle regulation p57^{kip2}, Rb protein and PCNA in the genesis and progression of human pancreatic cancer.

MATERIALS AND METHODS

Patients and tumor samples

Thirty-two specimens of primary human pancreatic cancer collected at pancreatic resection performed in the Hepatobiliary Department of General Hospital of Shenyang Military Region and the First Clinical College, China Medical University were studied. Of the patients, 20 (62.5 %) were male and 12 (37.5 %) were female. The mean age was 59.5 years (range, 26-72 years). Nineteen (59.4 %) were well-differentiated pancreatic cancer, thirteen (40.6 %) were moderate or low-differentiated pancreatic cancer. Twelve (37.5 %) had lymph node metastasis. All the patients were confirmed by clinicopathological diagnosis. Tumor tissues and adjacent tissues were obtained from the thirty-two specimens of primary human pancreatic cancer and were fixed in 100 mL/L buffered formalin, processed routinely and embedded in paraffin. In each case, all available hematoxylin and eosin-stained sections were reviewed, and representative blocks were chosen for further studies.

Immunohistochemical study

Four micrometer-thick sections from the formalin-fixed paraffin-embedded tissues were placed on the poly-L-lysine-coated slide for immunohistochemistry. The expression of p57^{kip2}, Rb protein and PCNA were assessed by SP immunohistochemical method using an anti-human p57^{kip2} monoclonal antibody (57P06), anti-human Rb protein monoclonal antibody (1F8), anti-human PCNA monoclonal antibody (PC10) and UltraSensitive™ S-P kit (kit-9720). The deparaffinized sections were boiled in the EDTA buffer at high temprature and high pressure for antigen retrieval and incubated with each antibody at 4 °C overnight. Immunohistochemical staining for these proteins was then performed according to the UltraSensitive™ S-P kit manual.

All the reagents were supplied by Maixin-Bio Co. Fuzhou, China. The cells with brown-yellow granules in the nuclei or cytoplasm were taken as positive cells. Five hundred cells on each slide were counted. The slides were distinguished as negative (-), positive (+), strong positive (++) and strongest positive (+++) when the count of positive cells were less than 10 %, ranging from 10-25 %, ranged from 25-50 %, and more than 50 % respectively for p57^{kip2} and Rb proteins. The slides were distinguished as negative (-), and positive (+) when the count of positive cells were less than 50 % and exceeded 50 % for PCNA respectively.

Statistical analysis

The Chi-square test and Fisher exact test of SAS system statistical software (Release 6.12) were adopted. $P < 0.05$ was considered as the significant level.

RESULTS

Expression of p57^{kip2} protein

p57^{kip2} protein was located in the nuclei or cytoplasm of normal pancreatic cells and positive pancreatic cancer cells with brown-yellow granules (Figure 1). p57^{kip2} protein positive-expression rate in tumor tissues of pancreatic cancer was 46.9 %, which was lower than that (75.0 %) in adjacent pancreatic tissues ($\chi^2 = 5.317$, $P < 0.05$, Table 1). p57^{kip2} protein positive-expression rate in the moderate or low differentiated group was 23.1 %, being lower than that (63.2 %) in the well differentiated group ($\chi^2 = 4.979$, $P < 0.05$, Table 1). p57^{kip2} protein positive-expression rate in the lymph node metastasis group was 25.0 %, which was lower than that (60.0 %) in the non-lymph node metastasis group ($P > 0.05$, Table 1).

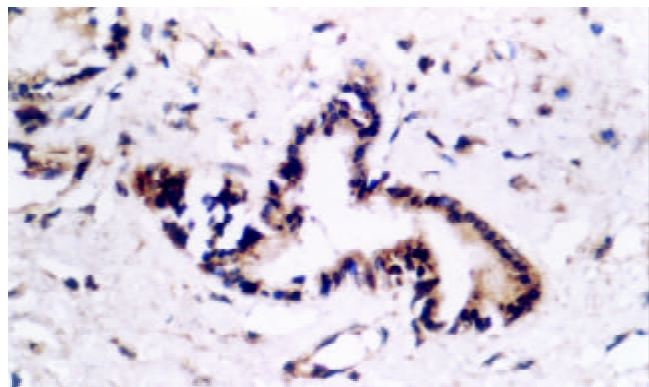


Figure 1 Expression of p57^{kip2} in tumor tissues of pancreatic cancer. SP×400.

Table 1 Expression of p57^{kip2} protein in pancreatic cancer tissues

Characteristics	p57 ^{kip2} protein expression				Rate (%)
	-	+	++	+++	
Tumor tissues	17	11	3	1	46.9 ^a
Adjacent tissues	8	13	6	5	75.0 ^a
Well-differentiated	7	9	2	1	63.2 ^b
Moderate or low-differentiated	10	2	1	0	23.1 ^b
Lymph node metastasis	9	2	1	0	25.0 ^c
Non- lymph node metastasis	8	9	2	1	60.0 ^c

^a $P < 0.05$, ^b $P < 0.05$, ^c $P > 0.05$.

Expression of Rb protein

Rb protein was located in the nuclei or cytoplasm of normal pancreatic cells and positive pancreatic cancer cells with brown-

yellow granules (Figure 2). Rb protein positive-expression rate in tumor tissues of pancreatic cancer was 50.0 %, which was lower than that (78.1 %) in adjacent pancreatic tissues ($\chi^2 = 5.497$, $P < 0.05$, Table 2). Rb protein positive-expression rate in the moderate or low differentiated group of pancreatic cancer was 46.2 %, being lower than that (52.6 %) in the well differentiation ($P > 0.05$, Table 2). Rb protein positive-expression rate in the lymph node metastasis group was 33.3 %, which was lower than that (60.0 %) in the non-lymph node metastasis group ($P > 0.05$, Table 2).

Table 2 Expression of Rb protein in pancreatic cancer tissues

Characteristics	Rb protein expression				Rate(%)
	-	+	++	+++	
Tumor tissues	16	10	2	4	50.0 ^a
Adjacent tissues	7	12	8	5	78.1 ^a
Well differentiated	9	4	2	4	52.6 ^b
Moderate or low-differentiated	7	6	0	0	46.2 ^b
Lymph node metastasis	8	3	1	0	33.3 ^c
Non- lymph node metastasis	8	7	1	4	60.0 ^c

^a $P < 0.05$, ^b $P > 0.05$, ^c $P > 0.05$.

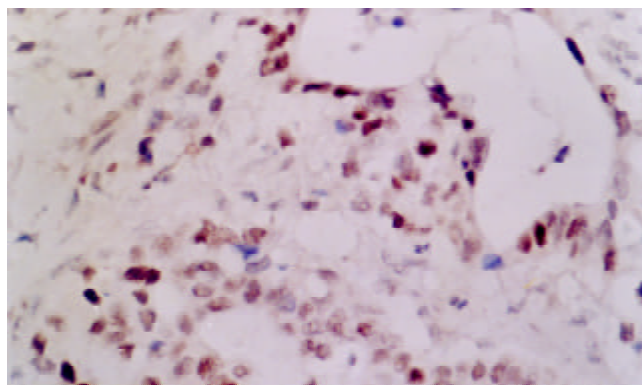


Figure 2 Expression of Rb protein in tumor tissue of pancreatic cancer. SP×400.

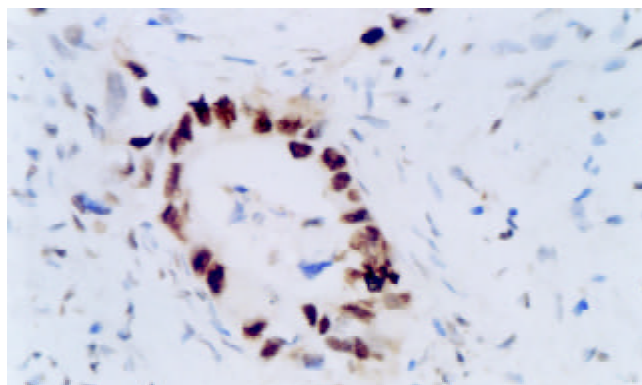


Figure 3 Expression of PCNA protein of tumor tissue in pancreatic cancer. SP×400.

Expression of PCNA protein

PCNA protein was located in the nuclei of normal pancreatic cells and positive pancreatic cancer cells with brown-yellow granules (Figure 3). PCNA protein positive-expression rate in tumor tissues of pancreatic cancer was 71.9 %, which was higher than that (43.8 %) in adjacent pancreatic tissues ($\chi^2 = 5.189$, $P < 0.05$, Table 3). PCNA protein positive-expression rate in the moderate or low differentiated group of pancreatic cancer was

92.3 %, which was higher than that (57.9 %) in the well differentiated group ($\chi^2=4.522$, $P<0.05$, Table 3). PCNA protein positive-expression rate in the lymph node metastasis group of pancreatic cancer was 100.0 %, which was higher than that (55.0 %) in the non-lymph node metastasis group ($\chi^2=7.513$, $P<0.05$, Table 3).

Table 3 Expression of PCNA protein in pancreatic cancer tissues

Characteristics	PCNA protein expression		
	-	+	Rate (%)
Tumor tissue	9	23	71.9 ^a
Adjacent tissue	18	14	43.8 ^a
Well-differentiation	8	11	57.9 ^b
Moderate or low-differentiation	1	12	92.3 ^b
Lymph node metastasis	0	12	100.0 ^c
Non- Lymph node metastasis	9	11	55.0 ^c

^a $P<0.05$, ^b $P<0.05$, ^c $P<0.05$.

Relationships of expression between p57^{kip2} and Rb protein

Rb protein positive-expression rate in the tumor tissues of p57^{kip2} protein positive-expression group was 53.3 %; and Rb protein positive-expression rate in the tumor tissues of p57^{kip2} protein negative-expression group was 47.1 %. There was no significant relationships between the two groups ($r=0.16507$, $P>0.05$, Table 4).

Table 4 Relationships between p57^{kip2} and Rb protein in pancreatic cancer

p57 ^{kip2}	Rb -expression				Rate(%)
	-	+	++	+++	
-	9	6	0	2	47.1
+	6	3	1	1	53.3
++	1	1	0	1	
+++		0	0	1	0

DISCUSSION

The question on cell cycle regulation is a hot issue of oncological research at present. The studies in recent years showed G1 phase regulation was a complex procedures which multiple cell factors took part in and abnormality of cell cycle regulation significantly correlated with the genesis and progression of tumors^[4-7]. p57^{kip2} gene was located in chromosome 11p15.5, and p57^{kip2} protein was a cell cycle inhibitor with molecular weight of 57kD which was included in the CIP/KIP family and similar to p21, p27 protein in functions^[8,9]. Lee *et al*^[10] suggested that the tumor suppressor mechanism of p57^{kip2} protein may be integrated with cyclin-CDK complexes and made cell cycle to arrest in the G₁ phase. Kondon *et al*^[11] considered that paternal alleles of p57^{kip2} were imprinted, maternal alleles of p57^{kip2} were expressed in the normal status, Loss of imprinting and imprinting mistakes of p57^{kip2} led to decrease at level of gene expression in the tumors. Matsumoto *et al*^[12] reported that p57^{kip2} protein positive-expression rate was 43.3±3.2 % with immunohistochemical technique in 92 patients with esophageal squamous cell carcinoma. The author considered that this was the first immunohistochemical study to characterize p57^{kip2} expression in non-neoplastic esophageal epithelium and esophageal squamous cell carcinoma in the year 2000. From then on, a few of studies about p57^{kip2} protein expression in human colorectal carcinoma, epithelial ovarian tumor, hepatocellular

carcinoma, neoplastic thyroid tissues, extrahepatic bile duct carcinoma and intrahepatic cholangiocellular carcinoma have been reported^[13-20], but the relationship between p57^{kip2} protein expression and pancreatic carcinoma was less reported^[21]. In this study, We found that p57^{kip2} protein positive-expression rate in tumor tissues of pancreatic cancer was significantly lower than that in adjacent tissues; the worse cancer cell differentiated, the lower expression of p57^{kip2} in tumor tissue was, and there was no correlation between the reduced expression of p57^{kip2} and lymph node metastasis. The results suggested that reduced expression of p57^{kip2} correlated with genesis and malignant degree of pancreatic cancer. Rb gene was the first isolated and detected tumor suppressor gene, and was an important factor in regulating system of G₁ phase as well. Inactivity of Rb protein was associated with liver carcinoma, small cell lung carcinoma, gastric cancer and pancreatic cancer apart from retinoblastoma^[22-25]. The results in this study showed Rb protein positive-expression rate in tumor tissues was significantly lower than that in adjacent tissues, which suggested reduced expression or loss of p57^{kip2} protein correlated with genesis of pancreatic cancer. The lower expression of p57^{kip2} protein decreased, the higher malignant degree and lymph node metastasis increased, but there was no significant difference between two groups possibly because of the limited cases of pancreatic cancer. PCNA was δ -assistant factor of DNA synthetase, took part in DNA biological synthesis and regulated cell cycle and cell proliferation by tetramer with cyclin, CDK and p21. Over-expression of PCNA was associated with a variety of tumors of digestive system^[26-35]. The results in this study showed PCNA protein positive-expression rate in tumor tissues was higher than that in adjacent tissues of pancreatic cancer, PCNA protein positive-expression rate in the moderate or low differentiated group was higher than that in the well differentiated group. PCNA protein positive-expression rate in the lymph node metastasis group was higher than that in the non-lymph node metastasis group. these suggested that over-expression of PCNA was associated with the genesis and progression of pancreatic cancer, and malignant proliferating status of pancreatic cancer determined by expression of PCNA was of an practical value. our results suggested that cell proliferative activity was high for the negative or reduced expression of p57^{kip2} and Rb protein, furthermore, p57^{kip2}, Rb protein played a suppressor role in cell proliferation. There was no significant difference in Rb protein positive-expression rate between p57^{kip2} positive-expression group and p57^{kip2} negative-expression group, suggesting there was no significant correlation in tumor suppression between p57^{kip2} protein and Rb protein.

In summary, our findings in p57^{kip2}, Rb and PCNA expression at the protein level suggested that loss of p57^{kip2}, Rb protein expression or over-expression of PCNA protein may contribute to the genesis or progression of pancreatic cancer, p57^{kip2}, Rb and PCNA proteins might play a regulating role in different pathways of cell cycle.

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Edited by Ma JY