

p27

Expression of p27 Protein in Adenoma and Adenocarcinoma of the Colorectum

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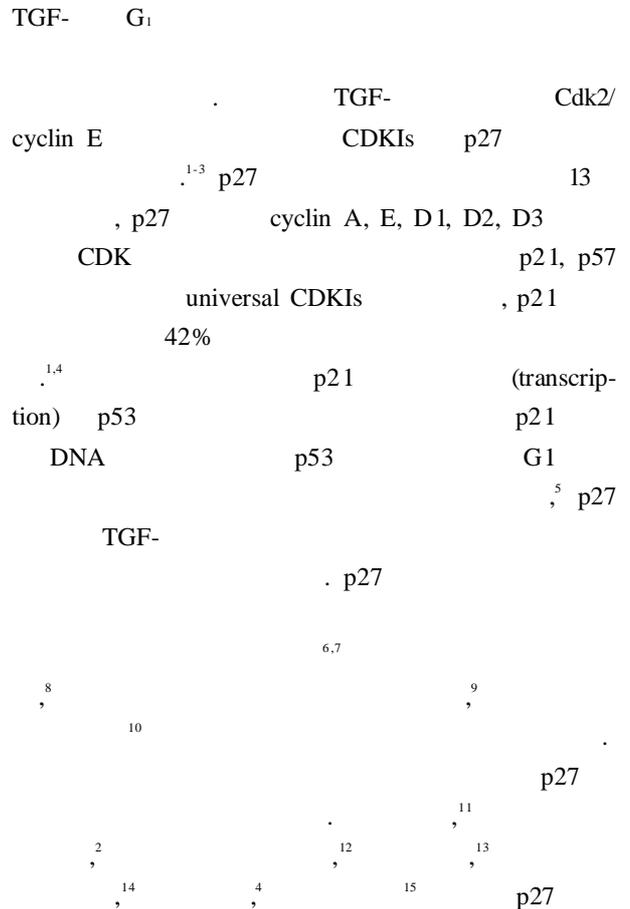
Purpose: The cyclin-dependent kinase inhibitor protein is a negative regulator of the cell division its degradation is required for entry into the S phase of p27^{KIP1} protein expression has been reported to be associated with aggressive behavior in a variety of epithelial and lymphoid origin. The purpose of this study was to determine the expression of p27 protein in adenoma and adenocarcinoma of the colorectum and to assess the prognostic significance.

Methods: We performed immunohistochemical staining for expression of p27 protein in adenomas (20 cases) and adenocarcinomas (30 cases) of the colorectum. The data on p27 protein labeling index (LI, mean ± standard deviation) were analyzed in association with clinicopathologic parameters.

Results: p27 protein LI of normal mucosa (10 cases), adenoma, and adenocarcinoma were 93.3 ± 4.5, 65.4 ± 17.2 and 28.2 ± 14.5, respectively (p < 0.0001). p27 protein expression of well differentiated adenocarcinoma was slightly lower than those of moderately and/or poorly differentiated adenocarcinoma, but did not show any significant difference among these groups (p = 0.19). Also p27 protein expression did not show any significant relationship to other parameters such as age, invasion depth, and operative status.

Conclusions: The results suggested that reduced expression of p27 protein may play an important role in the malignant transformation process of colorectal carcinoma.
Korean Soc Coloproctol 2001;17:251-258

Key Words: p27, Colorectal adenoma, Colorectal adenocarcinoma, p27,



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가 . 1998 5 4 , 8.8% 4 , 8.7% 4 20,21 de novo 18-20 p27 () , p27 p27 1) 1997 1 1998 12 가 HE 가 (20 , 30) (10) 2) (1) : , , , , (2) : 가 5 (×400) . p27 LI (7) , (4) (9) , (4) (4) , (22) , (4) 가 (3) :

4 μm p27 1 Microprobe Detection System avidin-biotin-peroxidase complex 4 μm xylene HistoClear (National diagnostics; Manvill, NJ.) 1 : 3 1 7 60°C Automation buffer (Biomed, Foster city, CA) , 10 mM citrate (pH 6.0) mi-crowave oven 20 Endo/Blocker (Biomed, Foster city, CA) 40°C 2 Automation buffer Tissue conditioner (Dako, Carpinteria, LA) 40°C 3 1 : 50 p27 (Santa Cruz) 40°C 12 Automation buffer . Biotin 2 (Dako, Carpinteria, LA) 8 Auto-mation buffer 가 peroxidase enhancer (Biomed, Foster city, CA) 8 . Chromogen , 2% hydrogen peroxide , chromogen buffer 5 ml 40°C 10 crystal mount

(4) 가: 1999 Ohtani 13 1998 Kawana 12

$$p27 \text{ LI } (\%) = \frac{\text{No of positive tumor cell nuclei of the any intensity}}{\text{No of overall tumor cell nuclei seen in 5 HPF } (\times 400)} \times 100$$

(5) Student's t-test ANOVA

1) (Table 1)

28 78 (58.6)
 가 14 , 가 6
 31 80 (58.4) , 가 13
 , 가 17 4 ,
 22 4 .

(2/3) 9 , (S)
 11 10 가 .

Table 1. Summary of clinicopathologic features

Factors	No. of patients (%)
Age (yrs, mean ±SD)	58.6 ± 13.5
Gender	
Adenoma (n=20)	
Male	14 (70)
Female	6 (30)
Atypia	
Mild	7 (35)
Moderate	9 (45)
Severe	4 (20)
Adenocarcinoma (n=30)	
Age (yrs, mean ±SD)	58.4 ± 12.7
Gender	
Male	13 (43)
Female	17 (57)
Localization	
Right	9 (23)
Left	11 (37)
Rectum	10 (33)
Histologic grade	
Well	4 (13)
Moderately	22 (73)
Poorly	4 (13)
Modified Dukes' stage	
Stage A	1 (3)
Stage B	15 (47)
Stage C	13 (40)
Stage D	1 (3)

modified Dukes' stage stage A 1 , stage B 15 , stage C 13 stage D가 1 가 .

2) p27 (Table 2)

(1) , p27 (Fig. 1) 10 p27 LI 89 98.7% (93.3±4.5%)

p27 (Fig. 2) 20 p27 LI 40 94.8% (65.4±17.5%)

p27 30 p27 LI 7.6 63.5% (28.2 ± 14.5%)

Table 2. Distribution of p27 expression by clinicopathologic factors of adenocarcinoma of the colorectum

Factor	No. of patients	p27 LI (%)	
		Mean ±SD	P value
Total No	30	28.2 ± 14.5	
Age (yrs)*			P=0.1182
< 60	13	23.4 ± 10.4	
60	17	31.8 ± 16.4	
Gender*			P=0.03
Male	13	34.7 ± 16.3	
Female	17	23.2 ± 11.1	
Location [†]			P=0.01
Right	9	16.5 ± 5.2	
Left	11	28.9 ± 13.9	
Rectum	10	33.5 ± 13.5	
Histologic type [†]			P=0.19
Well	4	40.4 ± 9.7	
Moderately	22	26.3 ± 15.0	
Poorly	4	26.0 ± 11.8	
LN metastasis*			P=0.69
Negative	16	27.1 ± 12.7	
Positive	14	29.3 ± 16.8	
Invasion depth*			P=0.29
Muscularis propria	9	25.1 ± 12.8	
Extramural	19	31.3 ± 14.9	

*P value by Student's t-test; [†] P value by ANOVA.

도는 주변림프구와 비교하여 비교적 약한 양성반응을 보였고 비균질성 소견을 보였으며(Fig. 3A) 주로 핵막을 따라 염색반응을 보였다(Fig. 3B). 정상 대장 점막, 선종과 선암종에서의 p27 단백 발현의 정도는 통계학적으로 유의성있는 차이를 보였다($P < 0.0001$, Fig. 4).

(2) 선종의 이형성정도와 p27 단백 발현과의 관계: 경도의 이형성을 지닌 선종 7예의 p27 단백 LI는 40~94.8% ($72.9 \pm 17.4\%$), 중등도 이형성 선종을 지닌 선

종 9예의 p27 단백 LI는 41.5~86.3% ($61.0 \pm 17.0\%$), 심한 이형성을 보이는 선종 4예의 p27 단백 LI는 46.6~78.4% ($56.4 \pm 15.0\%$)로 나타났으며 통계학적 처리를 하였을 때 유의한 차이는 없었다($P = 0.2125$).

(3) 선암종에서 환자의 나이와 p27 단백 발현과의 관계: 환자의 나이를 60세를 기준으로 하여 나누었을 때 60세 미만인 군이 13예로서 이들의 p27 단백 LI는 $23.4 \pm 10.4\%$, 60세 이상인 군이 17예로서 p27 단백 LI는 $31.8 \pm 16.4\%$ 였으며 두 군간에 통계학적인 차

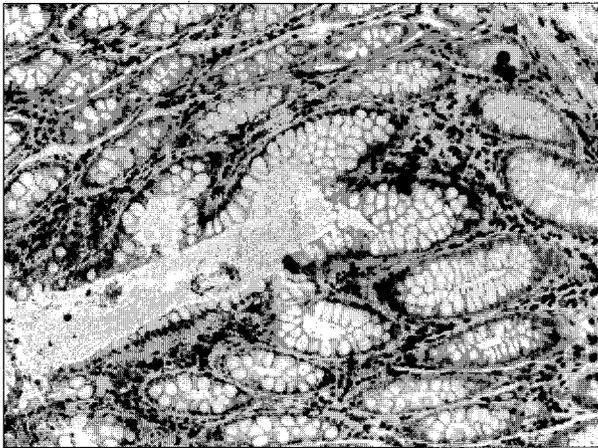


Fig. 1. Immunohistochemical staining of p27 protein in normal mucosa of the colon. p27 protein expression was localized exclusively in the nuclei and staining intensity was similar to intensity of surrounding lymphocytes ($\times 100$).



Fig. 2. Immunohistochemical staining of p27 protein in adenoma of the colon. p27 protein expression was localized exclusively on the nuclei ($\times 100$).

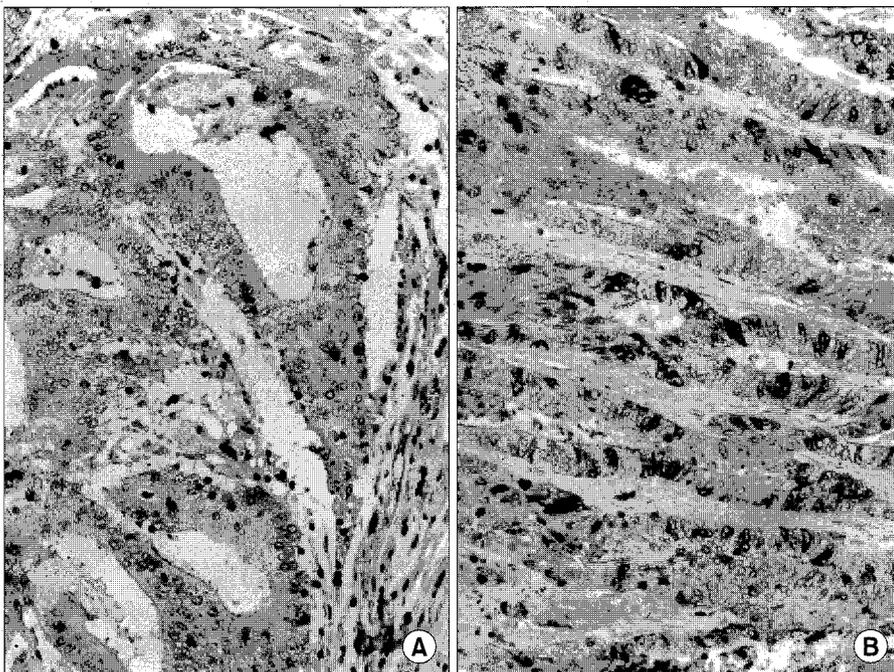


Fig. 3. Immunohistochemical staining of p27 protein in adenocarcinoma of the colon. (A) Adenocarcinoma showed cytoplasmic staining in addition to nuclear staining, which was weak and heterogenous ($\times 100$). (B) In this case, tumor cells express p27 protein in cytoplasmic and perinuclear area ($\times 100$).

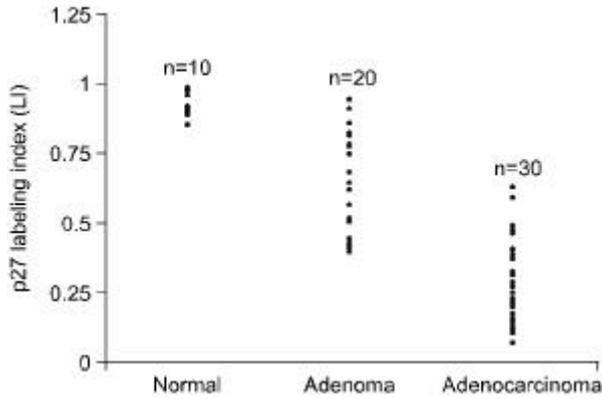


Fig. 4. Comparison of p27 labeling index (LI) of normal mucosa, adenoma, and adenocarcinoma of the colon (P < 0.0001, by ANOVA test).

(P=0.1182).

(4) p27
 : 가 13 p27 LI 34.7 ± 16.3%,
 가 17 p27 LI 23.2 ± 11.1% (P=0.03).

(5) p27
 : , p27
 LI 16.5 ± 5.2%, 28.9 ± 13.9%,
 p27 LI 33.5 ± 13.5%

p27 (P=0.01).

(6) p27
 : 4 p27 LI 40.4 ± 9.7%,
 22 p27 LI 26.3 ± 15.0%,
 4 p27 LI 26.0 ± 11.8%

ANOVA p27 (P=0.19).

(7) p27 : (muscularis propria, Dukes' stage B₁+C₁)
 (extramural, Dukes' stage B₂+C₂)
 9 p27 LI 25.1 ± 12.8%,
 19 p27 LI 31.3 ± 14.9% (P=0.29).

G₁ (checkpoints) 가 START (DNA re-
 striction point) 가 , 가
 16
 , cyclin
 가 CDKIs
 가 cyclin-CDK
 16,17
 G₁ S Rb
 가 , Rb
 S - E2F
 가 Rb
 18
 cyclin cyclin-CDK
 . CDK4 CDK6 cyclin D1, D2,
 D3 G₁ pRb
 , CDK2 cyclin E
 G₁ pRb
 19,20
 CDKIs가 cyclin-CDK
 .
 CDKIs가 p15^{Ink4b},
 p16^{Ink4a}, p18^{Ink4c} p19^{Ink4d} Ink4
 p21^{Waf1, Cip1, Sdi1}, p27^{Kip1} p57^{Kip2}
 Cip/Kip . Cip/Kip cyclin A, E, D1, D2,
 D3 CDK
 universal CDKIs ! p27 TGF-
 cyclin-CDK ,¹⁻³ p27
 ubiquitin-proteasome
 .²¹ p27
 -
 p27 p27
 가 .²² pRb가
 cyclin D p16 p16
 가 , 가 p27
 cyclin D-CDK4/6
 p27 cyclin-CDK2
 23

Gillett²⁴ (proliferative activity) p27 가
 p27 가
 , S-phase fraction (SPF) Singh²⁵ Barrett
 (ER) p27 mRNA (subcellular localization) p27 mRNA가 가
 p27 (50%
 CDK4/6 cyclin D1) p27 ubi-
 p27 pRb p27 quitin-proteasome (posttranslational mechanism)
 p27 Pal- 26% p27
 mqvist⁴ (, ,) p27 LI 가 , p27
 , Ki-67 LI 가
 p27
 (LI 50%) (LI 50%)
) p27
 (P=0.026). 10 p27 LI 89 98.7% (93.9±
 4.5%)
 p27
 p27
 LI가 ,
 (P=0.19), (, ,) p27
 p27 LI가 (P=0.03). ± 17.5%) 20 p27 LI 40 94.8% (65.4
 p27 p27
 가 p27 7.6 63.5% (28.2± 14.5%) 30 p27 LI
 . Palmqvist⁴ , p27
 p27 LI (P < 0.0001).
 Palmqvist 가
 p27 LI가 p27
 (P=0.01).

p27

p27

가

p27

p27

p27

p27

가

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