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장형 위암에서, pS2, c-MYC, beta-catenin, APC 단백을 포함한 APC유전자경로의 역할

장희경

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APC pathway including beta-catenin, c-MYC, and pS2 protein in intestinal type of Stomach Cancer

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Abstract

Background: A proposal that in normal colorectal epithelial cells, the adenomatous polyposis coli gene (APC) might modulate directly c-MYC transcription through beta-catenin/Tcf-4 was reported in 1998. It was reported that intestinal trefoil factor (TTF) which is the same family of pS as a gastric - specific tumor suppressor gene is related to beta-catenin. **Method and Material**: To elucidate the applicability of APC pathway in stomach and relationship between this pathway and pS2, the expressions of pS2, c-MYC, and beta-catenin proteins wereevaluated by immunohistochemically in 30 cases of intestinal carcinoma of stomach which is morphologically close to colon cancer. **Restults**: *Their immunoreactivities were 56.7% for pS2, 43.3% for c-MYC, and 86.7% for beta-catenin proteins,* respectively. Interestingly, positive staining of beta-catenin showed heterogenous pattern according to the depth of invasion. Tumor cells in the invading or infiltrating edges showed strong positivity, while thetumor cells in mucosa showed loss of the expression even ib the same tumors. **Conclusion**: This results suggest that in intestinal carcinoma of stomach, beta-catenin involves in the tumor cell migration and invasion not as cell adhesion molecule but as tumor-suppressor molecule forming complex with APC. In addition, the expressions of c-MYC and pS2 was not correlated with the function of adhesion molecule of beta-catenin

Key words : APC gene, beta-catenin, pS2, gastric canc

INTRODUCTION

The APC(adenomatous polyposis coli) gene product has been known as a blocker of cell cycle progression from G1 to S in fibroblasts and initiating apoptosis in a colon cancer cell line and having a role in regulating cell migration [1,2]. But it has not yet been shown how each of these proposed activities contributes to the function of APC as a tumor suppressor [2]. Beta-catenin forms a complex with the APC protein, which then binds T cell factor-4 (Tcf-4), raised the possibility that signaling through beta-catenin may contribute to human cancers [3,4]This pathway was well documented in colon cancer by Vogelstein [1,2], however is not yet well-documented in gastric cancer. Beta-catenin also has been well-known as involving in cell adhesion with E-cadherin [4]. The c-MYC oncogene is

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identified as a target gene in this signaling pathway [3]. pS2 is essential for the normal differentiation of antral and pyloric gastric mucosa [5-7]and is assumed to have many functions as a gastric - specific tumor suppressor gene [5.8].Recently there was a report that intestinal trefoil factor (TFF3) which is the same family of pS2, enhances tumor cell migration through modulation of thyrosine phosphorylation of beta-catenin [6]. These proteins might be tissue or cell-specificitt. Therefore APC signalling pathway including, beta-catenin and c-MYC or pS2 can be suggested in intestinal carcinoma of stomach, morphologically close to colon cancer.

MATERIALS AND METHODS

The materials were 30 cases of intestinal carcinoma of the stomach submitted to the department of Pathology following gastrectomy. The immunohistochemical stainings for pS2, c-MYC, and beta-catenin proteins were performed on the 10% buffered formalin-fixed paraffin embedded tumor and nonneoplastic tissues using antigen retrieval system.

RESULTS AND CONCLUSIONS

The number of cases showing positive reaction to pS2, c-MYC, and beta-catenin were 17(56.7%), 13(43.3%), and 26(86.7%), respectively (Table 1,2). The staining of beta-catenin showed membraneous, cytoplasmic, and intranuclear patterns. In mucosal or surface carcinoma, membraneous and cytoplasmic patterns were predomiant and showed almost even distribution in tumor mass(Fig.1). Interestingly, the invasive tumors arising fromthe mucosa showed positive staining of beta-catenin in the invading or infiltrating edges of tumor cells, while the mucosal tumor cells showed loss of the expression of beta-catenin in the same tumors. These findings can indicate that in intestinal carcinoma of stomach beta-catenin involves in the tumor cell migration and invasion as tumor-suppressor molecule forming complex with APC than as. cell adhesion molecule. c-MYC and pS2 showed no specific distribution of staining compared to beta-catenin (Table 3).

Table 1. Expressions of beta-catenin, c-myc, and pS2 in 30 cases of intestinal type of gastric carcinoma

No.	Expression of antibodies		
	Beta-catenin	c-MYC	pS2
1	+	-	-
2	+	-	+
3	-	-	-
4	+	-	-
5	+	-	-
6	-	-	+
7	+	-	+
8	+	+	+
9	+	-	+
10	+	-	+
11	+	-	-
12	+	+	-
13	+	+	+
14	+	+	+
15	+	+	-
16	+	+	+
17	+	-	+
18	+	+	-
19	+	+	+
20	+	-	-
21	-	+	+
22	+	+	-
23	+	+	+
24	-	+	-
25	+	+	+
26	+	-	+
27	+	-	+
28	+	-	+
29	+	-	-
30	+	-	-
total positive	26(86.7%)	13(43.3%)	17(56.7%)

Table 2. Heterogenous Expression of beta-catenin according to invasion depth.

No	depth of invasion	expression of beta-catenin mucosa	extramucosal invading edge
1	mucosa	+	
2	submucosa	-	+
3	subserosa	-	
4	mucosa	+	
5	mucosa	+	
6	proper muscle	-	-
7	submucosa	-	+
8	proper muscle	-	+
9	subserosa	-	+
10	proper muscle	-	+
11	mucosa	+	
12	proper muscle	-	+
13	submucosa	+	++
14	proper muscle	-	+
15	mucosa	+	
16	submucosa	-	+
17	submucosa	-	+
18	mucosa	+	
19	submucosa	-	+
20	submucosa	-	+
21	mucosa	-	
22	mucosa	+	
23	submucosa	-	+
24	muscle	-	-
25	mucosa	+	
26	mucosa	+	
27	mucosa	+	
28	mucosa	+	
29	muscle		+
30	submucosa	-	+

(p>0.05)

Table 3. The relationships between APC and c-MYC, β -catenin, ,pS2 proteins and depth of invasion.

	APC	c-MYC	bcatenin	pS2	Depth
APC	1				
c-MYC	-0.0053	1			
bcatenin	0.216386	-0.25065	1		
pS2	0.256219	0.107018	0.31201	1	
Depth	-0.25081	0.037518	-0.27668	-0.1112	1

p=0.0053 between APC and c-MYC.
P=0.037 between c-MYC and depth of invasion.
p>0.05 among the other variables.

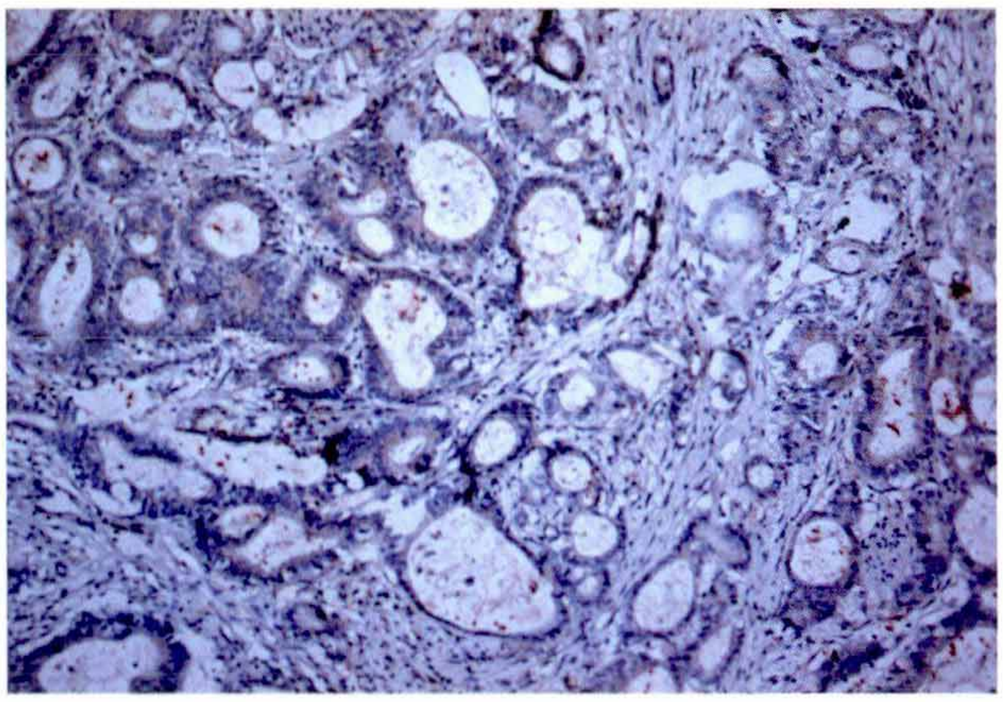

Fig.1.1: The positive immunoreactivity of pS2 in intestinal type of gastric cancer

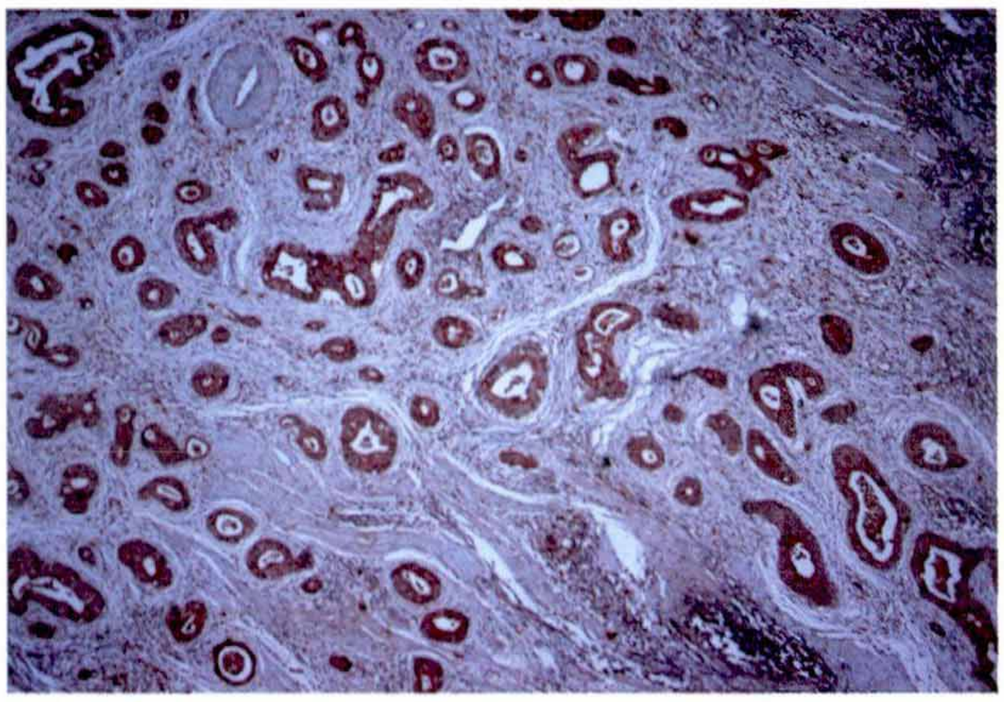

Fig.1.2: The positive immunoreactivity of c-MYC in intestinal type of gastric cancer

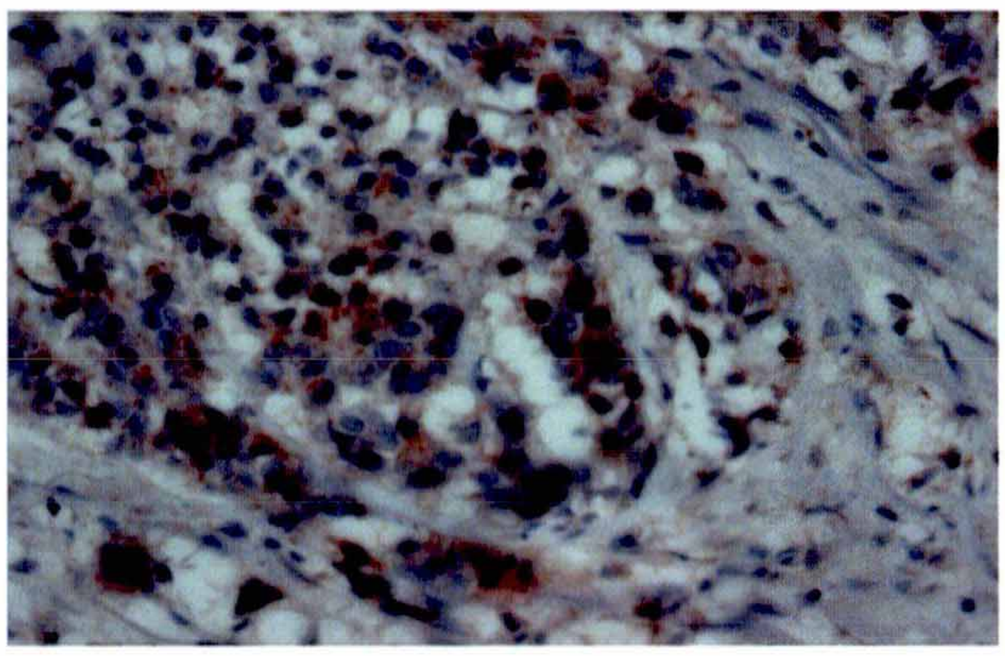

Fig.1.3: The immunoreactivity of beta-catenin with intranuclear staining in intestinal type of gastric cance

DISCUSSION

Vogelstein2) proposed in 1998that in normal colorectal epithelial cells, the adenomatous polyposis coli gene (APC) might modulate directly c-MYC transcription through beta-catenin/Tcf-4. Recently there was a report that intestinal trefoil factor (TTF), which is the same family of pS as a gastric - specific tumor suppressor gene [(5)], is related to beta-catenin [(6)]. On the basis of above speculations, the author attempted to elucidate the applicability of APC pathway in stomach and relationship between this pathway and pS2, the expressions of pS2, c-MYC, and beta-catenin proteins was e evaluated by immunohistochemically in 30 cases of intestinal carcinoma of stomach which is morphologically similar to colon cancer. APC gene product has been known as a blocker of cell cycle progression from G1 to S in fibroblasts and initiating apoptosis in a colon cancer cell line and having a role in regulating cell migration[(1-4)]. -catenin :forms a complex with the APC protein which then binds Tcf-4. Vogelsteinraised the possibility that signaling through beta-catenin may contribute to colon cancer, c-MYC oncogene was identified as a target gene in this signaling pathway [(1-4)]. pS2 gene is essential for the normal differentiation of antral and pyloric gastric mucosa and is assumed as a gastric - specific tumor suppressor gene, however it enhances tumor cell migration through modulation of thyrosine phosphorylation of beta-catenin [(6-8)]. In this study, the immunoreactivities of gastric cancerwere 56.7% for pS2, 43.3% for c-MYC, and 86.7% for beta-catenin proteins. Interestingly, positive staining of beta-catenin showed heterogenous pattern according to the depth of invasion. In other words, tumor cells ofthe invading or infiltrating edges shows strong positivity, while the tumor cells in mucosa showed loss of the expression even in the same tumors. This mean that the expressions of c-MYC and pS2 are not correlated with the function of adhesion molecule of beta-catenin. These findings indicate that in intestinal carcinoma of stomach beta-catenin involves in the tumor cell migration and invasion not as cell adhesion molecule but as tumor-suppressor molecule by forming complex with APC. But the relationship among c-MYC, beta-catenin, and pS2 is unclear yet in the APC pathway in intestinal carcinoma of stomach. It should be considered that every protein may be tissue or cell-specificity Functionally, so the same or similsr application of APC pathway during colon cancer development in gastric cancer should be careful. To verify and clarify these results further study including molecular genetics will be warrented with larger scales.

Conclusions

Inactivation of APC gene involves more than two thirds of intestinal type of gastric carcinomas and has inverse relationship between APC and c-MYC. However, the relationship among -catenin and pS2 is unclear yet in the APC pathway in intestinal carcinoma of stomach. These resultssuggested that the APC gene pathway might cannot be applied or might have different targets in the development of intestinal carcinoma of stomach.

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국문요약

배경 : 1998년 가족성대장용종증 환자의 비종양성 상피세포에서 APC유전자가 beta-catenin/Tcf-4 유전자를 통한 c-MYC 유전자를 직접 조정한다는 가설이 보고되었다. pS2가 속하는 intestinal trefoil factor(TTF)가 beta-catenin가 관련되는 위-특이 종양억제 유전자일 것일라는 보고도 있었다. 따라서 위암발생에 있어서도 대장암 발생과 같이 beta-catenin, c-MYC과 관련된 APC 경로가 적용될 수 있는 지 또, pS2를 이 경로에 포함시킬 수 있는지를 조사하고자 하였다. **대상 및 방법** : 대장암과 형태학적으로 유사한 장형 위암을 30례의 포르말린에 고정되고 파라핀에 포매된 위암조직과 주위 조직을 대상으로 면역 염색을 실시하였다. **결과** : pS2의 면역 염색결과는 56.7%, c-MYC는 43.3%, beta-catenin은 86.7%의 양성율을 나태내었다. 특히, beta-catenin은 종양의 침윤 상태에 따라 다양한 면역 염색 반응을 보였다. 종양이 침윤하는 가장 깊은 부분인 최전면부에서는 강한 양성 반응을 보이는 반면, 그위의 점막에 있는 종양에서는 발현되지 않았다. **결론** : 위암중 장형암은 대장암에서와 같은 APC 경로의 이상변형으로 암이 발생한다는 가설은 아직은 과학적 근거는 부복한 것으로 생각되나, beta-catenin은 세포질의 단백이 핵내로 이동하여 암화 과정에 관여하는 것과 동시에 종양이 침윤하는 최전면부에서는 세포간 부착 단백으로서의 성질을 소실하여 종양이 세포외 기질로 침윤하도록 한다고 생각된다.