

-catenin

The Pattern of -Catenin Expression in Adenomas and Carcinomas of the Gallbladder

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Purpose: -catenin is a key regulator of the cadherin-mediated cell adhesion system and also plays a role as a transcription regulating factor. Nuclear expression and mutation of -catenin have been identified in some benign and malignant tumors, and over expression of -catenin indicates an oncogenic potential. This study was designed to clarify the role of -catenin in the histogenesis of gallbladder carcinoma.

Methods: In benign hyperplastic lesions, adenomas, and carcinomas of the gallbladder, intracellular expression of -catenin was investigated by immunohistochemical stainings. Cyclin D1 and Ki-67 were also examined.

Results: All of the hyperplastic lesions showed membranous expression of -catenin. Adenomas and polypoid carcinomas showed significantly higher incidence of cytoplasmic and nuclear expression of -catenin than hyperplastic lesions and infiltrative carcinomas (P < 0.01). Loss of -catenin expression was frequently noticed in infiltrative and poorly differentiated carcinomas. Nuclear expression of -catenin in carcinomas had unique pathologic characteristics, including polypoid growing, well differentiated tubular type, and early stage. Cytoplasmic and nuclear expression of -catenin showed good correlations with cyclin-D1 expression (P < 0.05). The Ki-67 index was significantly higher in infiltrative carcinomas than in adenomas or polypoid carcinomas (P < 0.05).

Conclusion: Our results suggest that -catenin as a molecular marker may play a role in the carcinogenesis of the adenoma-carcinoma sequence of polypoid carcinomas.

Infiltrative carcinomas, however, may have different mechanisms. (J Korean Surg Soc 2002;63:138-145)

Key Words: -catenin, Adenoma, Carcinoma, Gallbladder

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(carcinogenesis) (1-4)
 가 5 (4)
 가 가 (5)
 (dysplasia) (adenoma) 가 가 (infiltrative) (polypoid)
 가 (6)
 가 (7-13)
 -catenin E-cadherin, -catenin (adherence junction)
 가 (13-16)
 -catenin (17-23)
 (24) (25,26) (27) (28)

(Infiltrative, I) (polypoid, P)

(tubular type) (papillary type)

(well differentiated, Tub 1), (moderately differentiated, Tub 2), (poorly differentiated, Tub 3)

(36)

(tumour in situ, Tis), (lamina propria) T1, T2, T3

(37)

3) -catenin, cyclin D1, Ki-67

(intestinal metaplasia), (6) -catenin

-catenin

-catenin

-catenin

-catenin

Ki-67 cyclin-D1

1)

1996 1 2001 1 4 17 11 22 77 53.1±

15.8

2)

10%

Hematoxylin-Eosin

(tubular type) (papillary type)

(intestinal type) (pyloric

type) (36)

(polypoid, P)

(Infiltrative, I)

(tubular type) (papillary type)

(well differentiated, Tub 1), (moderately differentiated, Tub 2), (poorly differentiated, Tub 3)

(36)

(tumour in situ, Tis), (lamina propria) T1, T2, T3

(37)

3) -catenin, cyclin D1, Ki-67

4 mm

60°C 1

100% xylene 10 2 , 90%, 85%, 80%, 70%, 60%, 50%

-catenin

가 9 : 1 10

peroxidase

1% zinc sulfate (Sigma Chemical Co., St. Louis, MO)가

10 mM citrate (pH 6.0)

microwave 5 3 가

0.5% (Dako, Carpinteria, CA, USA)

Tris-buffered saline (TBS) 30

mouse anti-human -catenin (1 : 300, Tansduction Laboratories, Lexington, KY) 4°C

0.1%

Tween 20 (Bio-Rad Laboratories, Hercules, CA)

TBS 10 3 , goat bio-

tinylated anti-mouse IgG (Dako, Carpinteria, CA)

30 . TBS 3

horse reddish peroxidase (HRP)-conjugated streptavidin (Dako, Carpinteria, CA) 30 TBS 3

0.05% DAB (3,3-diaminobenzidine, Sigma Chemical Co., St. Louis, MO)/0.01% H₂O₂가 TBS 10 , Mayer's Hematoxylin -catenin

TBS

가

-catenin
 (membranous pattern),
 (nuclear pattern)
 (cytoplas-
 mic pattern),
 Cyclin D1
 5%
 (negative)
 (positive), 5%
 5%
 Ki-67
 (Ki-67 labelling index)
 Cyclin-D1 (mouse anti-human anti-cyclin D1, 1 : 100, Zymed
 Laboratories, South San Francisco, CA)
 Ki-67 (mouse anti-
 human anti-Ki-67, 1 : 30, Immunotech, Marsheilles, France)
 -catenin
 -catenin

Table 1. Pathologic characteristics of hyperplastic lesions, adenomas, and carcinomas of the gallbladder

Case	Sex	Age	Group	Gross*	Histology [†]	pT [‡]	-catenin expression [§]		
							M	C	N
C06	M	59	Carcinoma	I	Tub2	T2	+	+	-
C13	F	61	Carcinoma	I	Tub2	T2	-	-	-
C01	F	73	Carcinoma	I	Tub3	T3	-	-	-
C10	F	67	Carcinoma	I	AS	T3	-	-	-
C17	M	56	Carcinoma	I	Tub2	T3	+	+	-
C02	M	54	Carcinoma	P	Tub 1	T1	+	+	+
C05	F	58	Carcinoma	P	Pap	T2	+	-	-
C11	F	65	Carcinoma	P	Tub 1	T1	+	+	-
C12	F	23	Carcinoma	P	Tub2	T2	+	-	-
C03	F	60	Carcinoma	P	Tub 1	Tis	+	+	+
C04	F	60	Carcinoma	P	Tub 1	Tis	+	+	+
C07	M	43	Carcinoma	P	Tub 1	Tis	+	+	+
C08	M	72	Carcinoma	P	Pap	Tis	+	-	-
C09	F	36	Carcinoma	P	Tub 1	Tis	+	+	+
C14	F	22	Carcinoma	P	Tub 1	Tis	+	+	-
C15	F	50	Carcinoma	P	Tub 1	Tis	+	+	+
C16	F	75	Carcinoma	P	Tub 1	Tis	+	+	+
A01	F	48	Adenoma		Pyloric		+	+	+
A02	F	59	Adenoma		Pyloric		+	+	+
A03	M	24	Adenoma		Pyloric		+	+	+
A04	F	51	Adenoma		Pyloric		+	+	+
B01	F	44	Hyperplasia				+	-	-
B02	M	77	Hyperplasia				+	-	-
B03	M	29	Hyperplasia				+	-	-
B04	F	59	Hyperplasia				+	-	-
B05	M	69	Hyperplasia				+	-	-
B06	M	48	Hyperplasia				+	-	-
B07	F	42	Hyperplasia				+	-	-
B08	F	79	Hyperplasia				+	-	-
B09	F	48	Hyperplasia				+	-	-
B10	M	66	Hyperplasia				+	-	-

*P = polypoid; I = infiltrative. [†] Tub 1 = well differentiated; Tub2 = moderately differentiated; Tub3 = poorly differentiated; AS = adeno-squamous; Pap = papillary. [‡] Tis = tumor in situ; T1 = tumor invading lamina propria or muscle layer; T2 = tumor invading perimuscular connective tissue; T3 = tumor perforates serosa or directly invades into one adjacent organ. [§] M = membranous; C = cytoplasmic; N = nuclear.

Ki-67, , cyclin D1
 . chi-square test
 P 0.05

(adenomatous lesion)
 10,
 2 , 2
 8 , 가 3 , 가 2
 가
 (dysplastic lesion) 가 2

1)

Table 1

4 ,
 12
 5 , 14
 2 , 1
 1 11 가 ,
 12

T1 T2 가 2
 (Tis) .
 T2 가 2 , T3 3
 (Table 1).
 10 -catenin
 1 (Table 1, Fig. 1A).
 4 , -catenin

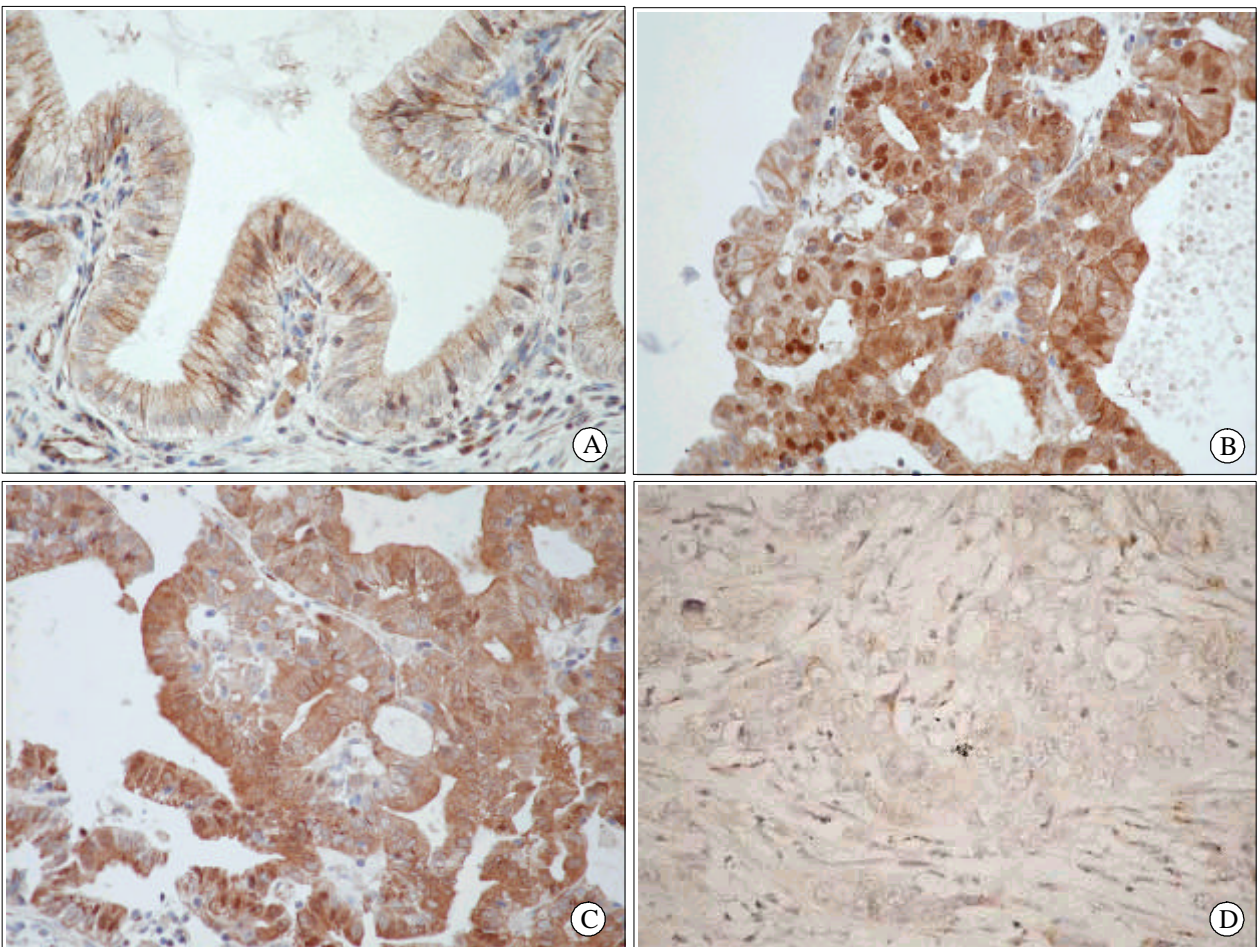


Fig. 1. -catenin expression in hyperplastic mucosa (A), gallbladder adenoma (B), polypoid adenocarcinoma (C), and infiltrative adenocarcinoma (D) by immunohistochemical staining ($\times 400$). Note clear membranous expression pattern along the epithelial cell membrane in hyperplastic mucosa. But adenoma and polypoid adenocarcinoma disclosing prominent cytoplasmic and nuclear expression pattern. Expression is markedly decreased in infiltrative adenocarcinoma.

Table 2. Correlation between β -catenin expression and pathologic variables in carcinomas of the gallbladder

Variables*	β -catenin expression [†] (%)			P-value
	M	C	N	
Growth pattern				
Polypoid (n=12)	12 (100)	9 (75)	7 (58)	0.002
Infiltrative (n=5)	2 (40)	2 (40)	0 (0)	
Histologic type				
Tubular (n=14)	12 (86)	11 (79)	7 (50)	0.002
Papillary (n=2)	2 (100)	0 (0)	0 (0)	
Adenosquamous (n=1)	0 (0)	0 (0)	0 (0)	
Differentiation grade				
Well (n=9)	9 (100)	9 (100)	7 (78)	0.002
Moderately (n=4)	3 (75)	2 (50)	0 (0)	
Poorly (n=1)	0 (0)	0 (0)	0 (0)	
Depth of invasion				
Tis (n=8)	8 (100)	7 (88)	6 (75)	0.003
T1 (n=2)	2 (100)	2 (100)	1 (50)	
T2 (n=4)	3 (75)	1 (25)	0 (0)	
T3 (n=3)	1 (33)	1 (33)	0 (0)	

*Tis = tumor in situ; T1 = tumor invading lamina propria or muscle layer; T2 = tumor invading perimuscular connective tissue; T3 = tumor perforates serosa or directly invades into one adjacent organ. [†] M = membranous; C = cytoplasmic; N = nuclear.

Table 3. Expressions of β -catenin, cyclin D1, and Ki-67 in hyperplastic lesions, adenomas, and carcinomas of the gallbladder

β -catenin expression	Hyperplasia (n=10)	Adenoma (n=4)	Carcinoma	
			Polypoid (n=12)	Infiltrative (n=5)
Membranous	10 (100%)	4 (100%)	12 (100%)	2 (40%)*
Cytoplasmic	0 (0%)	4 (100%) [†]	9 (75%) [‡]	2 (40%)
Nuclear	0 (0%)	4 (100%) [§]	7 (58%)	0 (0%)
Cyclin D1	0 (0%)	4 (100%) [¶]	9 (75%)**	2 (50%)
Ki-67 Index	2.9±0.9	4.2±0.8	6.7±1.7 ^{††}	11.3±1.0 ^{‡‡}

*Compared with hyperplasia, P=0.032; [†] Compared with hyperplasia, P=0.004 and infiltrative carcinoma, P=0.007; [‡] Compared with hyperplasia, P=0.037; [§] compared with hyperplasia (P=0.004) and invasive carcinoma (P=0.007); compared with hyperplasia, P=0.007 and infiltrative carcinoma, P=0.009; [¶] compared with hyperplasia, P=0.004 and infiltrative carcinoma, P=0.042; **compared with hyperplasia, P=0.007 and infiltrative carcinoma, P=0.038; ^{††} Compared with hyperplasia, P=0.012; ^{‡‡} Compared with hyperplasia, P=0.028 and adenoma, P=0.031.

Fig. 1B)(P=0.001) 가
(P=0.765).
-catenin
가 (Table 1, 9 (9/12, 75%) -catenin 7 (7/12, 58%)
(Table 1, 2, Fig. 1C).
-catenin 2
3 -catenin
1 (Table 1, 2, Fig. 1D).
가 (P=0.002),
-catenin
(Table 2)(P=0.035).
-catenin 2
가 (Table 2).
가 9 7 (78%)가 -catenin
100%,
50% 1 -catenin
가 -catenin
가 (Table 2)(P=0.002). Tis
T1 6 (6/8, 75%) 1 (1/2,
50%) -catenin T2, T3
Tis T1
88% 100% T2, T3 25%, 33%
-catenin

(Table 2)(P=0.003).

2) Cyclin D1 *Ki-67*

cyclin D1 가

5% 10 가

100%, 75%, 50% cyclin (P=0.042)

(Table 3). -catenin

cyclin D1 (P=0.043).

Ki-67 가 (P=0.028) (0.031) *Ki-67* 6 (86%)가 -catenin 가 (13) 7

-catenin cyclin-D1 (P=0.981).

-catenin 7 가

-catenin 1

-catenin -

-catenin E-cadherin, α -catenin

(1-4)

(17) 가 -catenin

(1) 가 가

(7-13) 가 가

가 (6) 가 가 가 (13)

가 -catenin

(5) -catenin

가 -catenin -catenin/TCF/LEF

(6, 13) matrilysin (matrix metalloproteinase, MMP) 가

(33,34)

(11) 5 2 가 -catenin 가 가 -

catenin 가 (34) -catenin

86%가 Tis , -

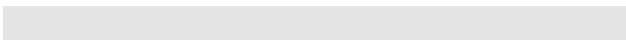
catenin -catenin

가 (12) *K-ras, p16,*

가 -catenin *p53, APC, DCC, DPC4, mismatch repair gene* (7-12)

K-ras, p53, -catenin

가 (7,11,13)
 가
 .APC
 .(I) APC
 -catenin/TCF/LEF
 ,
 -catenin
 가 , -catenin
 TCF, LEF
 가 (29) -catenin
 -catenin (23)
 APC 가 -
 catenin 가
 (29)
 catenin 가 -
 Yanagisawa (13) -catenin
 62.5%, 50.0%
 catenin 가 ,
 -catenin 가 -catenin
 Cyclin D1
 -catenin/TCF/LEF cyclin D1 가
 -catenin cyclin D1
 가 (27,32) -catenin
 catenin cyclin D1
 Ki-67
 -catenin cyclin
 D1
 가 -catenin
 cyclin D1 가
 catenin , -catenin 가
 cyclin D1 , Ki-67 가
 가
 -catenin
 가



-catenin
 ,
 -
 .
 catenin 가
 .

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