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E-cadherin expression is homogeneously reduced in adenoma from patients with familial adenomatous polyposis: an immunohistochemical study of E-cadherin, β-catenin and cyclooxygenase-2 expression

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Abstract *Background and aims:* The adenomatous polyposis coli (APC) protein plays a crucial role in the regulation of β-catenin, which is linked to the cell adhesion molecule E-cadherin. Furthermore, β-catenin and cyclooxygenase-2 (COX-2) are both involved in the activation of nuclear transcription factors inducing cell proliferation. Germline mutations in the APC gene are the cause of familial adenomatous polyposis (FAP). To characterise the expression pattern of these proteins in FAP in comparison with sporadic adenomas, we studied 18 FAP-associated adenomas, 16 sporadic adenomas and seven normal colonic controls. *Methods:* E-cadherin, β-catenin, COX-2 expression and the proliferative index (Ki67) were assessed by immunohistochemistry (index of expressing cells / total number of cells) in adenomatous mucosa, adjacent non-neoplastic tissue and normal colonic controls. *Results:* E-cadherin expression was significantly and homogeneously reduced in FAP adenomas (24%; 95%CI 16–32; sporadic adenomas 61%; 38–84; normal controls 98%; 96–100). Membraneous β-catenin expression was significantly reduced in both FAP (30%; 11–49) and sporadic (42%; 19–65) adenomas (normal controls 96%; 88–104), whereas marked nuclear staining occurred in sporadic, but not in FAP adenomas. Stromal COX-2 expression and the proliferative index were increased only in sporadic adenomas (sporadic adenomas: COX-2 12%; 7–17, Ki67 24%; 15–33, FAP adenomas: COX-2 8%; 5–11, Ki67 5%; 2–9, normal controls: COX-2 4%; 2–7, Ki67 6%; 1–11). *Conclusion:* Proteins involved in cell adhesion and cell proliferation, especially E-cadherin, are expressed differently in FAP and sporadic adenoma, pointing to possible differences in the molecular pathways to adenoma.

Keywords Adenomatous polyposis coli · Beta-catenin · Cell adhesion molecules · Colonic neoplasms · Cyclooxygenase-2 (COX-2) · Immunohistochemistry

Introduction

Familial adenomatous polyposis (FAP) is caused by germline mutations in the adenomatous polyposis coli (APC) gene, which leads to the development of hundreds of colorectal adenomas. The crucial role of the APC gene for the regulation of cellular proliferation and differentiation was evaluated by Kinzler and Vogelstein in their genetic model of colorectal carcinogenesis [1]. APC interacts with β-catenin. This protein plays a pivotal role in cell proliferation and cell adhesion pathways. On the one hand, it is linked to E-cadherin, the key protein for cell-cell-adhesion in adherens junctions. E-cadherin is anchored to the cytoskeleton: the cytoplasmic tail of E-cadherin binds to β-catenin, which binds to α-catenin, which—in turn—interacts with actin filaments [2] and β-

catenin. The interruption of the E-cadherin mediated cell adhesion is associated with invasiveness of tumour cells [3]. On the other hand, β-catenin is a key regulator of cellular proliferation. The level of free cytosolic β-catenin is regulated under the influence of the Wnt proteins by a protein degradation complex containing APC. Unbound cytosolic β-catenin can translocate to the nucleus and bind to proteins of the lymphocyte enhancer factor (LEF) / T cell factor (TCF) protein family [4]. Their target genes, e.g. cyclin D1 and the peroxisome proliferator-activated receptor δ(PPARδ) gene [5, 6, 7], are involved in cell cycle control. In colorectal tumours this pathway is activated by two alternative mechanisms: either the interaction between APC and β-catenin is compromised due to a mutation of the APC gene or β-catenin expression is increased due to a mutation in the β-catenin gene (CTNNB1) itself [8].

Recently, alternative pathways to colorectal neoplasia have been described: in contrast to classical sporadic adenomas, alterations of APC do not appear to be an early event in the development of so called serrated adenomas. Instead, resistance to apoptosis and a defective DNA repair are the postulated hallmarks of this pathway (reviewed in [9]).

Weak or absent expression of E-cadherin, together with nuclear β-catenin expression and increased COX-2 expression, has repeatedly been noted in sporadic colo-rectal carcinoma as well as in other gastrointestinal neoplasms [10]. In order to further elucidate the role of these proteins in familial as well as sporadic adenoma formation, we studied the expression of E-cadherin, β-catenin, COX-2 and the proliferation marker Ki67 in biopsies taken from adenomatous and non-adenomatous mucosa of patients with FAP and sporadic adenoma in comparison with normal controls.

Methods

Patients

Eighteen adenomas taken from 18 patients with FAP during colonic surgery or colonoscopy were included in this study (mean age at diagnosis due to symptoms was 30.7 years, range 16–44 years). The diagnosis of FAP was based on the presence of more than 100 colonic adenomatous polyps (n=8), less than 100 adenomatous polyps together with an identified germline mutation in the APC gene (n=8), or colonic adenomatous polyps in combination with a positive familial history (n=2). Overall, germline mutations were known in 13/18 (72%) patients (Table 1). Sixteen adenomas from patients without FAP (single adenoma in elderly patients, mean age 62.1 years, range 52–84 years) and biopsies from seven patients without colorectal

Table 1 Clinical data and identified germline mutations of the studied FAP patients. Age at onset refers to the age when the first symptoms occurred, except for the patients marked (†), in whom the disease was diagnosed during a surveillance program. All identified mutations lead to a truncated APC protein and have been published previously [12]. *F* female, *M* male

Gender	Age at onset	>100 adenomas at diagnosis	Germline mutation
M	44	No	Large deletion
F	18	Yes	Large deletion
F	42	Yes	Not known
F	43	Yes	Not known
M	32†	No	Not known
F	16	Yes	Not known
M	16†	No	Not known
M	19	Yes	Codon 283
M	29	No	Codon 283
M	20	Yes	Codon 1061
F	34	Yes	Codon 1069
F	17†	No	Codon 1156
M	20	Yes	Codon 1309
F	9†	No	Codon 1309
F	13†	No	Codon 1309
M	11†	No	Codon 1309
M	25	No	Codon 1541
M	32	No	Codon 1548

neoplasia (mean age 51.1 years, range 22–92 years) served as controls. The clinical data of the adenomas studied are summarised in Table 2. The study was approved by the Bonn University ethics committee in accordance with the Helsinki declaration of 1975, revised 1983. Each patient had given informed consent.

Genetic studies

Genomic DNA was isolated from peripheral blood lymphocytes using standard salting out techniques [11]. Screening for germline mutations was performed by nonradioactive single-strand confor-mation analysis (SSCP) and heteroduplex analysis with genomic DNA as described previously [12]. Alternatively, total RNA was extracted from EDTA blood samples with TRIZOL (Invitrogen, Karlsruhe, Germany) according to the manufacturer's protocol, and a protein truncation test (PTT) was performed using previously described primers [13]. Sequencing of aberrant PCR fragments was done with Sequenase version 2.0 (Amersham Biosciences, Frei-burg, Germany) in the presence of ^{35}S-dATP, or by semiautomatic cycle sequencing with BigDye chain terminators on an ABI 377 sequencer (Perkin Elmer, Weiterstadt, Germany).

Immunohistochemistry

Paraffin-embedded tissue was cut into 6-µm sections. Slides for E-cadherin, β-catenin and Ki67 staining were processed in citrate buffer (pH 6.0) in a microwave oven for 30 min to enhance antigen retrieval. Immunohistochemical staining was carried out with the avidin-biotin-peroxidase-complex method using 3-amino-9-ethyl-

Table 2 Clinical and pathological characteristics of the adenomas studied

	FAP adenomas	Sporadic adenomas
Age of patients (years ± SD)	30.7±10.5	62.1±16.34
Proportion of tubular adenomas (%)	82.4	75
Size of adenomas in millimetres (mean ± SD)	7.1±5.3	13.6±14.53
Proportion of adenomas with severe dysplasia (%)	5.6	6.7

carbazole as substrate [14]. The following murine monoclonal antibodies were applied as primary antibodies: E-cadherin (clone 36, cat. no. C20820, Transduction Laboratories, Lexington, USA) diluted 1:40, β-catenin (clone 14, cat. no. C19220, Transduction Laboratories) diluted 1:160, Ki67 (clone Ki-S5, cat. no. 1742345, Roche Diagnostics, Mannheim, Germany) diluted 1:80 and COX-2 (cat. no. C22420, Transduction Laboratories) diluted 1:160.

For semiquantitative evaluation of protein expression, we identified the region of the slide with the predominant expression pattern and chose three crypts. Whenever possible, only orthogonally cut crypts were considered to ensure that only complete crypts were counted and no bias towards superficial or basal crypt cells occurred. The cells expressing the antigen in a typical fashion (E-cadherin/β-catenin: membraneous staining, COX-2: cytoplasmic staining, Ki67: nuclear staining) were counted under a microscope. The ratio of antigen-positive cells to the total number of counted cells was determined. To quantify COX-2 expression in stroma cells, three stroma areas, each limited by two crypts, were evaluated. The stained cells were counted in a high power field at a 400× magnification. Thereafter, the ratio of stained cells to the total number of counted cells was calculated. The evaluation was done by two independent observers (MJ, FG), who were not informed of the group allocation

of the specimens. In the rare case of differences between the results of the two observers, the specimens were reevaluated by the two observers together and consensus was obtained.

Statistical analysis

Expression ratios in FAP-associated adenoma, sporadic adenoma and normal controls were compared by the Mann-Whitney U test for unpaired samples. All calculations were done with the SPSS software package (SPSS, Chicago, USA). Results are given as means and 95% confidence intervals. A p value <0.05 was considered to indicate statistical significance.

Results

When conventional criteria for the classification of adenoma were applied to the adenomas of our two groups of patients, the groups differed only in the size of the
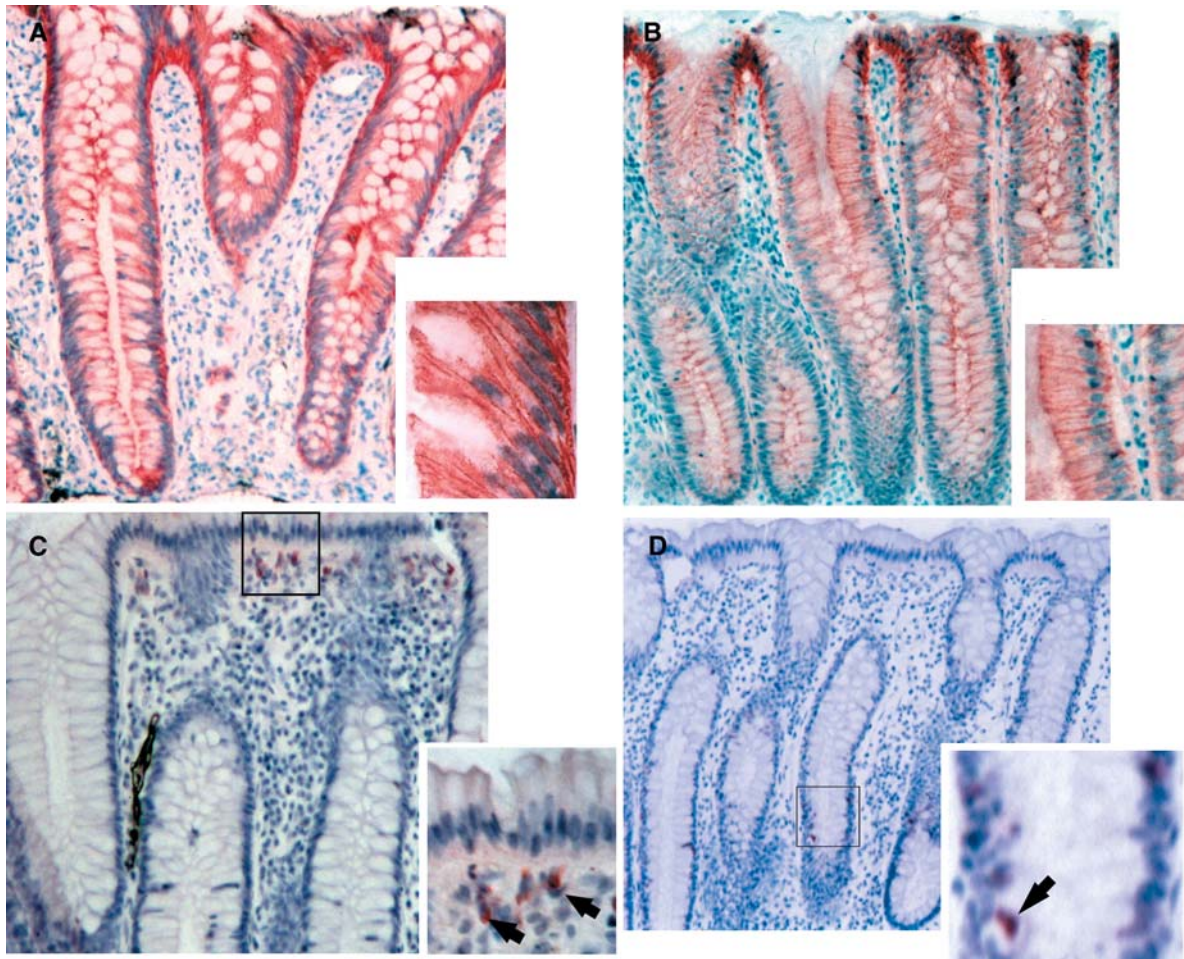

Fig. 1A–D Protein expression in mucosa of normal controls. **A** Membraneous E-cadherin expression in all epithelial cells. **B** Membraneous β-catenin expression in all crypt cells. **C** Scarce COX-2 expression in stromal cells. Detail of the region marked in the overview by a *black box*. Cytoplasmic expression of COX-2 protein (*small arrows*). **D** Seldom Ki67 expression in normal mucosa. The detail is taken from the region which is marked in the overview by a *black box*. Nuclear staining of Ki67 (*small arrow*) (magnification: Overview 200×, detail: 400×)

Table 3 Protein expression of E-cadherin, β-catenin, Ki67 and COX-2 for 18 FAP associated and 16 sporadic adenomas (percent of cells with typical expression). Under each adenoma group, the mean value of the percentage of crypt cells with typical expression is noted (±95% CI). At the end of the table, the mean number of cells counted per biopsy is indicated

Patient	E-cadherin		β-catenin		Ki67		COX-2	
	Adenomas	Normal mucosa	Adenomas	Normal mucosa	Adenomas	Normal mucosa	Adenomas	Normal mucosa
FAP								
1	2	79	9	1	7	1	5	2
2	14	14	8	3	3	02	10	9
3	20	21	22	3	1	0	11	1
4	6	21	0	100	2	0	6	4
5	44	39	63	9	10	0	2	3
6	31	95	24	32	3	4	5	9
7	10	100	18	100	5	4	15	8
8	32	100	22	25	1	0	5	0
9	16	100	100	98	9	0	12	5
10	11	26	3	0	27	0	25	0
11	53	95	30	29	6	0	1	0
12	11	80	70	100	1	1	16	10
13	52	100	57	77	7	4	3	0
14	13	24	30	5	1	3	4	6
15	9	100	22	24	2	0	3	2
16	27	42	13	2	1	4	8	10
17	31	85	16	10	2	0	5	8
18	45	32	35	25	0	0	4	10
Mean	24%[*][x]	64%[§][*]	30%[*]	39%[*]	5%[x]	1%[§][*]	8%	5%
±SD	(±0.081)	(±0.187)	(±0.186)	(±0.304)	(±0.035)	(±0.014)	(±0.030)	(±0.026)
Sporadic								
1	9	92	2	86	40	2	19	10
2	40	98	28	2	18	1	4	3
3	20	6	30	83	49	0	2	1
4	36	100	2	23	9	0	18	8
5	100	43	87	25	0	8	14	10
6	92	77	60	55	13	0	7	4
7	95	97	84	33	36	0	9	4
8	68	61	19	1	57	4	0	0
9	9	100	84	1	28	2	16	4
10	99	95	87	5	45	1	21	8
11	99	63	96	100	33	1	4	0
12	91	100	9	100	20	5	17	0
13	100	100	12	45	35	0	15	0
14	17	26	20	27	5	1	18	10
15	90	72	9	16	9	1	12	5
16	13	13	35	12	5	1	8	6
Mean	61%[*][x]	71%	42%[*]	38%[*]	24%[*]	2%[§][*]	12%[*]	5%[§]
±SD	(±0.233)	(±0.194)	(±0.228)	(±0.223)	(±0.092)	(±0.019)	(±0.052)	(±0.035)
Controls	-	98% (±0.022)	-	96% (±0.079)	-	6% (±0.049)	-	4% (±0.033)
Number of cells counted per biopsy								
Mean	492	370	438	337	564	340	559	431
SD	183	207	194	187	287	171	334	315

Statistical significance is symbolised as follows:
[x] Significant between adenoma groups ($p < 0.05$)
[§] Significant between normal and adenomatous mucosa in the same patient group ($p < 0.05$)
[*] Significant compared with normal controls ($p < 0.05$)

adenomas (Table 2). In normal mucosa, membraneous expression of E-cadherin and β-catenin was found in almost every colonic epithelial cell (Fig.1A, B). COX-2 expression was absent in epithelial cells but occasionally noted in stromal cells beneath the epithelial layer (Fig.1C). The percentage of proliferating cells as assessed by Ki67 expression was rather low (6%, Fig.1D). Table 3 summarises the semiquantitative data of all studied proteins.

In FAP patients, a marked reduction of E-cadherin expression was noted in the epithelial cells of adenomatous mucosa (Fig. 2). As can be seen in the semiquantitative evaluation (Table 3), E-cadherin expression in sporadic adenoma was reduced to a lesser but still
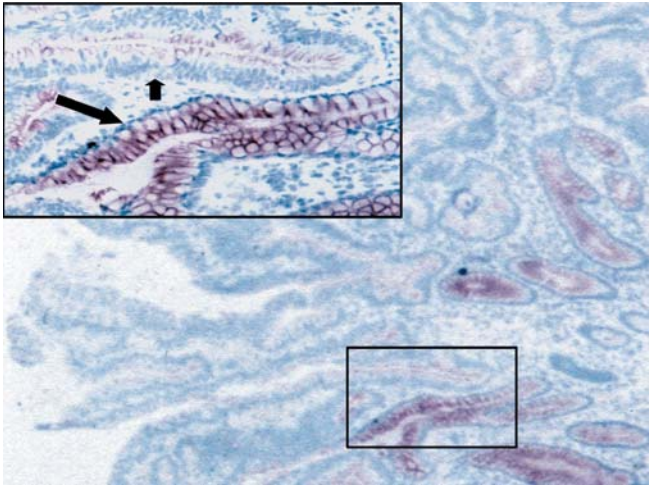
Fig. 2 E-cadherin expression in mucosa of an FAP patient: normal membraneous expression in non-neoplastic regions, lost expression in adenomatous glands. This fact is presented in detail (normal mucosa: *large arrow,* adenomatous mucosa: *small arrow*). The region of the detail is marked by a *black box* (magnification: overview 40×, insert 200×)

significant extent. The normal mucosa adjacent to FAP-associated adenomas showed a moderate reduction in the number of cells positive for E-cadherin. This lower E-cadherin expression was comparable to the reduction found in sporadic adenoma. The numbers of E-cadherin positive cells were lower in both groups of patients with adenoma than in normal controls.

In adenomatous mucosa of patients with sporadic and FAP-associated adenoma, membraneous β-catenin expression was reduced to a variable extent (Fig. 3A). Instead, cytoplasmic and nuclear β-catenin immunoreactivity was detected (Fig. 3B, C, Table 4).

Epithelial cell proliferation and stromal COX-2 expression in adenomatous mucosa of FAP patients did not reveal significant differences compared with normal controls. In contrast, both were markedly increased in sporadic adenoma (Figs. 4A and 5). It is noteworthy, however, that in adenomatous mucosa of both sporadic and FAP-associated adenoma, COX-2 expressing cells could be detected not only in stromal cells but also in epithelial cells (Fig. 4B).

Discussion

The key result of this study is the highly significant and homogeneous reduction of E-cadherin expression in FAP-associated adenomas.

While the considerable heterogeneity with respect to E-cadherin expression in sporadic adenomas is compatible with previous findings [15, 16], the uniform reduction of E-cadherin expression in FAP-associated adenoma was unexpected. Reduction of E-cadherin expression is usually considered a late event in the process of gastrointestinal carcinogenesis. In sporadic colorectal carcinoma and
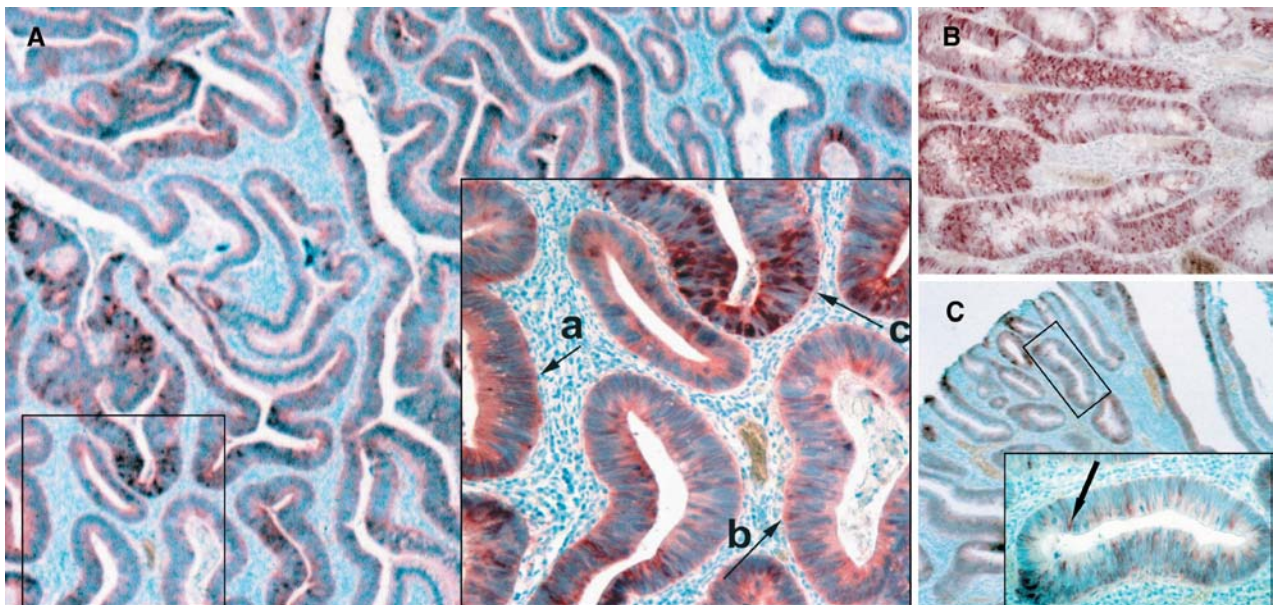

Fig. 3A–C β-catenin expression. **A** Reduction of membraneous expression (insert, *arrow a*) and appearance of cytoplasmic (insert, *arrow b*) and nuclear (insert, *arrow c*) β-catenin expression in a sporadic adenoma (magnification: overview 40×, insert 400×). **B** Widespread nuclear expression in a sporadic adenoma (magnification 200×). **C** Marked cytoplasmic expression (detail: *arrow*) in an adenoma of an FAP patient (magnification: overview 40×, insert 400×)
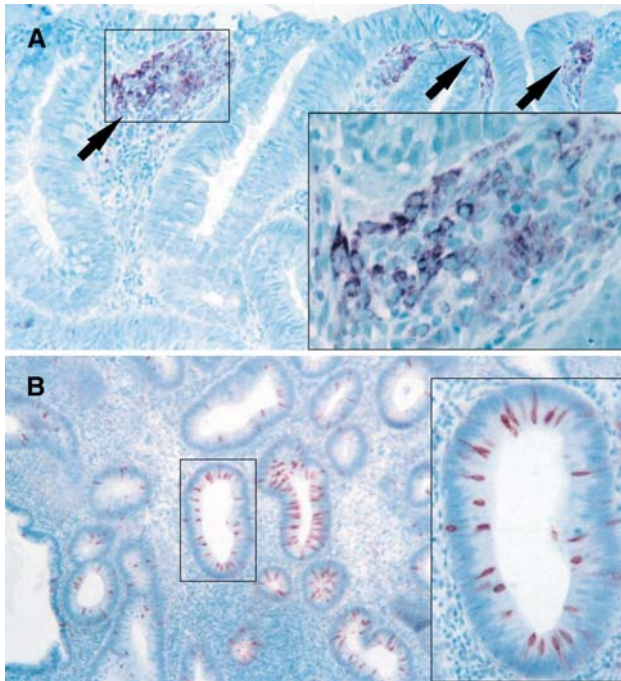
Fig. 4A, B COX-2 expression. **A** Increased stromal COX-2 expression in a sporadic adenoma. Note the subepithelial localisation of the protein in the adenoma (*arrows*). Detail: documentation of the cytoplasmic expression in the region marked in the overview by a *black box* (magnification: overview 40×, insert 400×). **B** Epithelial COX-2 expression in an FAP-associated adenoma. The box marked crypt is presented in detail to demonstrate cytoplasmic expression (magnification: overview 40×, insert 400×)
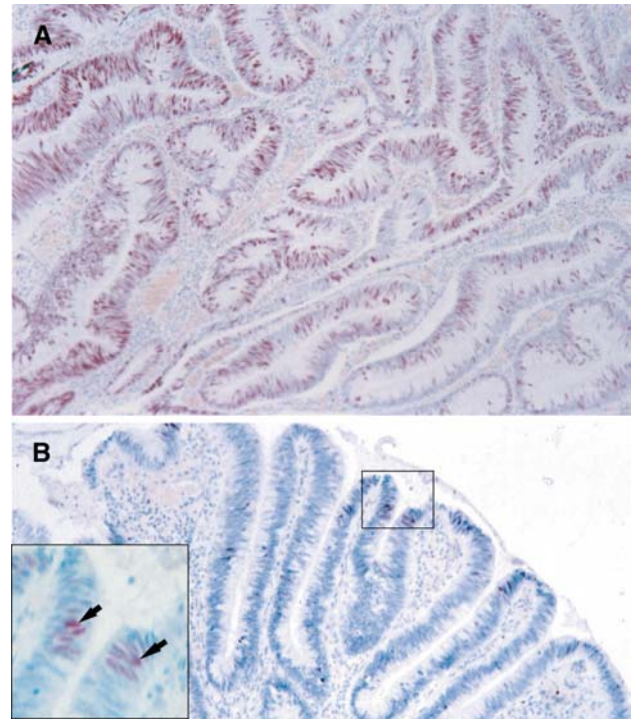

Fig. 5A, B Ki67 expression. **A** Widespread nuclear expression in crypts of a sporadic adenoma representing the increased proliferative index (magnification: 200×). **B** Seldom Ki67 expression in an FAP-associated adenoma. Detail: nuclear localisation of the protein (*arrows*) (magnification: overview 100×, insert 400×)

Table 4 Mean value of the percentage of crypt cells with atypical β-catenin expression (±95% CI) in FAP and sporadic adenomas

	Cytoplasmic	Nuclear
FAP	0% (±0.01))	3% (±0.09)
Sporadic	13% (±0.22)	2% (±0.05)

cholangiocellular carcinoma, for example, the proportion of tumours showing reduced E-cadherin expression was higher in less-differentiated carcinomas than in well-differentiated tumours [10, 17]. Due to this fact, one might suggest that the differences between the adenoma groups could be due to different sizes. The 16 sporadic adenomas were almost twice as large as the FAP-associated adenomas. However, the difference in E-cadherin expression cannot be explained by different adenoma size since large adenomas should represent a more advanced stage of dedifferentiation [18] with less E-cadherin expression. The opposite was observed in our study.

In contrast to our results, previous studies showed considerable abnormal β-catenin expression [19] and abnormal β-catenin expression in concert with preserved membraneous E-cadherin expression [20] in FAP-associated adenomas. In both studies, only clinically characterised patients with a classical FAP phenotype were included. In our study, in most of the patients a APC germline mutation was identified, and patients with an atypical phenotype were also included. El-Bahrawy et al. reported a general overexpression of E-cadherin and β-catenin as a result of abnormal protein expression in addition to a preserved membraneous protein localisation. This unusual expression pattern has not been observed before. In addition, these data have to be questioned since an increased cellular pool of unbound β-catenin is thought to induce proliferation but there is evidence that FAP adenomas are more due to decreased apoptosis than to increased proliferation (see below). Unfortunately, El-Bahrawy's group did not provide data on cell proliferation. Cell culture data on the interaction between E-cadherin and β-catenin indicate that abnormal β-catenin localisation in the cytoplasm disturbs E-cadherin function and may also shift the expression pattern of E-cadherin from membraneous to cytoplasmic [21]. But the reduction of E-cadherin in our FAP group can not be explained by this mechanism, because we did not observe significant cytoplasmic β-catenin and E-cadherin expression in FAP

adenomas. We do not believe that the differences between our study and others' work concerning β-catenin expression is due to methodological issues since our data on β-catenin expression in sporadic adenoma were in line with previous studies [22]. Mutations in the APC gene can lead to accumulation of β-catenin in the cytosol and translocation of β-catenin to the nucleus [23, 24]. In agreement with this concept we found nuclear expression of β-catenin in 50% of the sporadic adenomas.

The observed proliferative activity in our samples is well compatible with our β-catenin data. FAP adenomas showed proliferation rates equal to normal controls in line with the rare observation of nuclear β-catenin expression in FAP adenomas. Normal epithelial proliferation rates were also reported in the MIN mouse, a murine model for FAP. On the other hand, apoptosis was decreased in this animal model [25] and in human tissue [26]. Thus, the initial adenoma formation in FAP may be the result of decreased apoptosis rather than increased proliferation.

The more heterogeneous alteration of the expression of E-cadherin and β-catenin in sporadic adenoma may reflect the greater genetic heterogeneity of sporadic adenoma. In particular, sporadic adenoma may have additional lesions in the Wnt-pathway or may have mutations in the β-catenin (CNTTB) gene itself, postulated by cell culture data [8, 27].

COX-2 overexpression was demonstrated in patients with sporadic colorectal carcinoma and adenoma [28, 29]. Indeed, we found an increased COX-2 expression in sporadic adenoma. However, COX-2 expression was predominantly found in stroma cells directly beneath the epithelial layer rather than in epithelial cells. This expression pattern suggests a paracrine mechanism for the released COX-2 products such as prostaglandins, as already proposed by previous authors [28]. In contrast, COX-2 expression in colorectal carcinoma was observed primarily in epithelial cells. In a subset of our sporadic and FAP related adenomas, we also observed epithelial COX-2 expression.

Despite the small study population—FAP is a rare disease—we found highly significant differences between FAP and non-FAP adenomas, especially with respect to the expression of E-cadherin. The mechanism of this differences remains to be elucidated. Our results may be an additional indicator that FAP is not simply an inherited version of colorectal neoplasia but a distinct neoplasia.

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