Interferon-inducible Gene Family 1-8U Expression in Colitis-associated Colon Cancer and Severely Inflamed Mucosa in Ulcerative Colitis

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ABSTRACT

Persistent severe inflammation in colonic mucosa is thought to cause the development of colon cancer in patients with ulcerative colitis (UC). However, predisposing genetic abnormalities have not been identified in this sequence. Using differential display PCR, we isolated cDNA fragments corresponding to mRNAs that were differentially expressed in colitis-associated cancer tissues and mucosa with mild inflammation in the colon of five UC patients. This molecular screening approach identified 60 cDNA fragments, and we sequenced 34 fragments. One cDNA fragment, which is identical to IFN-inducible gene family 1-8U, was strongly expressed in all five UC-associated cancers. 1-8U was also expressed in sporadic colon cancer tissues and colon cancer cell lines, but not in normal mucosa. This gene was strongly expressed in severely inflamed colonic mucosa of UC without colitis-associated colon cancer, although 1-8U expression was not related to the extent and duration of the disease. However, 1-8U was expressed in the colonic mucosa of all patients with chronic, continuously severe inflammation. These results indicated that IFN-inducible gene family 1-8U expression in inflamed colonic mucosa might be used as a preferential marker of colitis-associated colon cancer in UC.

INTRODUCTION

The risk for colorectal carcinoma increases considerably in patients with chronic UC after 10 years. Dysplasia in UC mucosa is thought to be a precursor of carcinoma and an indication for colectomy (1–3). Molecular mechanisms underlying UC-associated neoplasms have been studied for years, but understanding of these mechanisms remains incomplete. It is likely that an accumulation of multiple gene mutations leads to dysplasia and cancer in UC in a manner similar to that of sporadic colon malignancy. However, biological features differ between UC-associated cancer and sporadic colorectal cancer. Mutations in the APC gene and ras proto-oncogenes are not consistently present in UC-associated cancer, in contrast to sporadic colorectal cancer resulting from the adenoma–cancer sequence pathway (4–8). Conversely, p53 mutation is a frequent occurrence in early dysplastic UC lesions, whereas p53 mutation is rare in early dysplastic adenomas (9, 10). Moreover, the time interval between UC-associated dysplasia and cancer is short compared to that between sporadic adenoma and carcinoma (8). Patients with dysplasia or cancer in UC are younger than those with sporadic colorectal cancer. These results indicate that destroyed molecular mechanisms might underlie UC-associated cancer, although conclusive evidence is limited.

Findings in patients with chronic UC are paralleled in animal models, the cotton top tamarin, a new world monkey that spontaneously develops an idiopathic colitis with histopathological similarity in human UC. In this model, adenocarcinoma develops frequently (50%) in association with chronic colitis (11–14). HLA-B27 transgenic rats (15), Gαi2-deficient mice (16), and dominant negative N-cadherin mice (17) that express chronic colitis also develop associated colonic adenoma or adenocarcinoma. In both UC patients and animal models, persistent severe inflammation in the colonic mucosa is thought to cause the development of colorectal cancer. However, molecular biological mechanisms of carcinogenesis due to colonic inflammation have not yet been identified.

The DD-PCR using arbitrary primers may be used to identify changes in gene expression (18). Candidate oncopgenes and tumor suppressor genes have been isolated using this method (19, 20). Using DD-PCR, we isolated cDNA fragments corresponding to mRNAs that are differentially expressed in mucosa with UC-associated cancer and mild inflammation, and we sequenced those fragments. In the present study, we show evidence that the IFN-inducible gene family 1-8U is expressed not only in UC-associated cancer tissues, but also in severely inflamed colonic mucosa of UC. Our results indicated that IFN-inducible gene family 1-8U expression in inflamed colonic mucosa may be used as a preferential marker of colitis-associated colon cancer in UC.

MATERIALS AND METHODS

Tissue Samples. Tissue samples were obtained at surgery from five patients with UC who developed colonic adenocarcinoma. Clinical features of UC in patients with UC-associated colon cancer are shown in Table 1. Inflamed colonic mucosa was obtained from 14 UC patients without colon cancer at surgery and endoscopically. We defined the quantification of inflammation in UC mucosa according to the widely accepted histopathological classification by Mats (21). Based on Mats’s classification, we defined mild inflammation as inflammation < grade 3, and severe inflammation was defined as inflammation = grade 4–5. The clinical type of UC patients included 4 chronic continuous and 10 relapsing-remitting type. Eight patients were in active stage, and six were in remission. Duration of the disease was less than 5 years in seven patients and more than 5 years in seven patients.

mRNA DD-PCR. Total cellular RNA was isolated by RNeasy B (Tel-Test, Inc., Friendswood, TX), and 0.2 µg of the respective DNA-free RNAs was reverse transcribed with Moloney murine leukemia virus reverse transcriptase using three different pools of oligodeoxynucleotide acid-anchored 3′ primers (RNA image; GenHunter Co., Brookline, MA). The RT reaction was amplified in the presence of [32P]dATP in a PCR protocol. PCR reactions were carried out with 2 µM HT11M primer, 2 µM arbitrary primer (see below), 25 µM dNTP, 10x reaction buffer, 0.3 unit of Taq DNA polymerase (Perkin-Elmer Corp., Foster City, CA). Reactions were performed at 94°C for 60 s and then at 94°C for 30 s, 40°C for 120 s, and 72°C for 30 s for a total of 40 cycles. PCR products were displayed on standard sequence gels. Bands representing potentially differentially expressed mRNAs were excised from the gel and
eluted in distilled water. cDNA PCR products were then amplified by using the same primers. The following 3′ and 5′ primers were used for RT and DD:

(a) HT11A, 5′-AAGCTTTCGGGTAA-3′; (b) HT11C, 5′-AACGCTTCTCCACCT-3′; and (c) HT11G, 5′-AAGCTTCTCCACCT-3′. Randomly selected 5′ primers for DD were as follows: (a) AP-9, 5′-AACGCTTCATTCCCG-3′; (b) AP-10, 5′-AACGCTTCACCGTA-3′; (c) AP-11, 5′-AACGCTTCGGTAAA-3′; (d) AP-12, 5′-AACGCTTATGTC-3′; (e) AP-13, 5′-AACGCTTGGCACT-3′; (f) AP-14, 5′-AACGCTTGGACCT-3′; (g) AP-15, 5′-AACGCTTCAGCAAC-3′; and (h) AP-16, 5′-AACGCTTACAGGCC-3′.

**Northern Blot Analysis.** Ten μg of the indicated total RNA extracted from tissue samples were electrophoresed on a 1.2% formaldehyde agarose gel and transferred to a positively charged nylon membrane (Hybond N+; Amersham, Buckinghamshire, United Kingdom). Equivalent sample loading was confirmed by ethidium bromide staining and visualization of 28S rRNA bands and by the mRNA levels of GAPDH. Labeling of DNA probes by [α-32P]dCTP was carried out using DNA Labeling Beads (Ready To Go; Amersham), and positively charged nylon membranes were hybridized with radiolabeled probe in Rapid-Hyb Buffer (Amersham).

**Subcloning, DNA Sequencing, and Homology Search of cDNA Fragments.** The cDNA fragments were reamplified and subcloned into the TA cloning vector (Invitrogen, Carlsbad, CA). These fragments were sequenced with the ABI PRISM Dye Terminator Cycle Sequencing Ready Reaction Kit (Perkin-Elmer Corp.) using ~21M13 primers. All sequences of cDNA fragments were compared to the National Center for Biotechnology Information GenBank database using the BLAST algorithm.

**Cell Lines.** The human colon carcinoma cell lines HT29, Caco-2, and WiDr were obtained from the American Type Culture Collection (Rockville, MD), and ACM and CW2 were kindly provided by Dr. M. Mitsuhashi (Tokyo Women’s Medical College, Tokyo, Japan). Human cervical cancer cell line HeLa was kindly provided by Dr. K. Toda (Kitasato Institute Hospital, Tokyo, Japan).

**RT-PCR of IFN-inducible Gene Family 1-8U.** Total RNA was isolated from endoscopically obtained specimens and by surgical resections using RNazol (Cinna/Biotech Laboratory, Houston, TX). Two μg of total RNA were incubated at 70°C for 10 min and reverse transcribed in the presence of DTT, and Superscript reverse transcriptase (Life Technologies, Inc., Rockville, MD). The RT reaction was performed at 42°C for 50 min, 90°C for 5 min, and 37°C for 20 min after the addition of RNase H (Life Technologies, Inc.). PCR reactions were carried out with an equal amount of cDNA, 2 μM dNTP, 0.3 unit of Taq DNA polymerase (Perkin-Elmer Corp.), and 0.1 M dNTP, and Superscript reverse transcriptase (Life Technologies, Inc., Rockville, MD). The RT reaction was performed at 42°C for 50 min, 90°C for 5 min, and 37°C for 20 min after the addition of RNase H (Life Technologies, Inc.). PCR reactions were carried out with an equal amount of cDNA, 2 μM dNTP and 0.3 unit of Taq DNA polymerase (Perkin-Elmer Corp.). Reactions were performed at 94°C for 60 s and then at 94°C for 30 s, 40°C for 120 s, and 72°C for 30 s for a total of 30 cycles. PCR products were displayed on 1.6% agarose gels and stained with ethidium bromide. GAPDH was used as an internal control. The following 3′ and 5′ primers of DD40 (predicted size of the product was 97 bp) and GAPDH (predicted size of the product was 440 bp) were used for PCRs: (a) 3′ primer of DD40, 5′-GTGCACCTTATGGAACCG-3′; (b) 5′ primer of DD40, 5′-CTCCACACTCACTCCCTGG-3′; (c) 3′ primer of GAPDH, 5′-CGACGCTCTGCTTCCACCT-3′; and (d) 5′ primer of GAPDH, 5′-TCATCTCCGCCCTCTGCT-3′. All specific primers synthesized by the phosphoramide method using a DNA synthesizer (model 392 PCR-MATA; Applied Biosystems, Inc., Foster City, CA) were purchased from Sawady (Tokyo, Japan).

**Isolation of Colon Epithelial Cell and Mucosal Lymphocytes.** Human colonic epithelial cells were isolated from resected specimens as described previously (22). Briefly, surgical samples of colonic mucosa were dissected free from underlying musculature and washed in CMF-HBSS. Tissues were then treated with 1 mM DTT (Sigma Chemical Co., St. Louis, MO) in CMF-HBSS for 15 min at 22°C. After washing three times with CMF-HBSS, the tissue pieces were incubated in CMF-HBSS containing 1 mg/ml dispase (Boehringer Mannheim Biochemicals, Indianapolis, IN) for 30 min at 37°C. During this treatment, epithelial cells and intraepithelial lymphocytes were released from the tissues. Disperse treatment was repeated once. The cell suspensions resulting from dispase treatments were washed twice, pelleted, and resuspended in 3 ml of 100% Percoll (Pharmacia Biotech, Piscataway, NJ). Three-ml layers of 60%, 40%, and 30% Percoll were layered successively on top before centrifugation at 1500 rpm for 30 min at 4°C. Cells at the top 0–30% layer interface contained epithelial cells. The purity of the epithelial cells was confirmed by flow cytometric analysis using antihuman intestinal epithelial cell mAb B9 and antilymphocyte mAbs against CD3 and CD20. B9 (IgG1) was kindly provided by Prof. L. Mayer (Mount Sinai Medical Center, New York, NY; Ref. 23) and was biotinylated in our laboratory. Cells in this preparation method contained >95% pure epithelial cells, as reported previously (24). Cells were washed three times in RPMI 1640, and viability was determined by trypan blue exclusion.

Colonic LPLs were also isolated from colonic mucosa. After treatment with 0.5 mM DTT, the tissue was washed and incubated twice with stirring for 60 min at 37°C in CMF-HBSS containing 0.75 mM EDTA to remove epithelial cells. The supernatant was decanted, and the remaining tissue was incubated with stirring at 37°C in 5% CO2 in RPMI 1640 containing antibiotics, 10% FCS, 0.02% collagenase (CLSPA; Worthington Biochemical Co., Freehold, NJ), and 0.01% DNase I (DP; Worthington Biochemical Co.) for 18 h. The crude cell suspension was filtered through 50-μm stainless mesh and then washed. After resuspension in 100% FCS, the cell suspension was separated over Ficoll-Hypaque. The lymphoid cell suspension was washed and resuspended in a complete medium.

**RESULTS**

**DD of mRNA Expression between Colitis-associated Cancer and Mucosa with Mild Inflammation in the Same UC Patients.** Using mRNA DD-PCR, we assessed the patterns of gene expression in colitis-associated cancer tissues and mucosa with mild inflammation in the same UC patients. We used eight different 5′ primers in combination with three sets of 3′ primer pools for the reaction. Combinations of the forward primers AP9–16 and the reverse HT11M primers HT11A, HT11G, and HT11C produced strikingly different patterns when used in our DD-PCRs.

**Subcloning and Sequencing of cDNA Fragments Corresponding to Differentially Expressed mRNAs.** We identified 60 cDNA fragments corresponding to mRNAs differentially expressed in mucosa with colitis-associated cancer and with mild inflammation from all five UC patients using all of the primer combinations. These fragments were then excised and subjected to reamplification using the same sets of primers. We subcloned 34 fragments and sequenced them. Approximately 100–500 bp of nucleotide sequences were obtained from these fragments and compared to the National Center for Biotechnology Information GenBank database using the BLAST algorithm. Among them, 19 cDNA fragments were more strongly expressed in UC-associated cancer tissues than in mucosa with mild inflammation. These fragments were considered as candidate cancer-related genes. Only two fragments, DD2 and DD40, were highly (>95%) homologous to known cDNA sequences. Northern blot analysis demonstrated that expression of DD2, which was completely homologous to human tyrosine phosphatase, was slightly different between UC-associated cancer and mildly inflamed mucosa. In contrast, DD40 was expressed quite strongly in UC-associated cancer tissues. We identified the nucleotide sequence of DD40, and this 114-bp cDNA fragment, including the polyadenylic acid site, was completely homologous to the partial sequence of IFN-inducible gene family 1-8U.

**Expression of IFN-inducible Gene Family 1-8U in Colon Cancer Tissues.** In three samples from five UC-associated colon cancer patients, IFN-inducible gene family 1-8U mRNA was strongly ex-

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**Table 1 Clinical features of UC in patients with UC-associated colon cancer**

<table>
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<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Clinical type</th>
<th>Duration (yr)</th>
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<td>5</td>
<td>25</td>
<td>Relapsing-remitting</td>
<td>12</td>
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</tr>
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</table>

**Expression of IFN-inducible Gene Family 1-8U in Colon Cancer Tissues.** In three samples from five UC-associated colon cancer patients, IFN-inducible gene family 1-8U mRNA was strongly expressed.
pressed in UC-associated cancer tissues rather than in mildly inflamed tissues by Northern blot analysis (Fig. 1A). In two other samples, a Northern blot could not be done. However, PCR revealed that 1-8U was also more strongly expressed in UC-associated cancer tissue than in inflamed mucosa in those patients (Fig. 1B).

To assess whether high expression of this gene was specific for UC-associated colon cancers, we examined IFN-inducible gene family 1-8U expression in 10 sporadic colorectal cancers. As shown in Fig. 2, 1-8U mRNA was also expressed in all 10 sporadic colorectal cancer tissues. To clarify the expression of this gene in colonic epithelial cells, we examined its expression in some colon cancer cell lines. 1-8U was expressed in cancer cell lines, including colon cancer cell lines HT29, CW2, and ACM (Fig. 3A), and its expression was increased by IFN-α stimulation (data not shown).

In contrast, 1-8U was not expressed in normal colonic mucosa from 10 healthy volunteers (Fig. 3B).

Expression of IFN-inducible Gene Family 1-8U in Inflamed Colonic Mucosa of UC. We then assessed the expression of IFN-inducible gene family 1-8U in inflamed colonic mucosa of UC patients without colon cancer. To determine the cellular source of 1-8U, we first isolated colonic epithelial cells and LPLs from the colonic mucosa of the patients. As shown in Fig. 4, this gene was strongly expressed in freshly isolated colonic epithelial cells. In contrast, this gene was not strongly expressed in freshly isolated LPLs, even from severely inflamed mucosa. This result indicated that we could assess the mRNA expression of 1-8U in colonic epithelial cells by using mRNA from colonic mucosa.

Interestingly, this gene was strongly expressed in severely inflamed colonic mucosa of UC patients without colitis-associated colon cancer (Fig. 5). Expression of 1-8U was quite strong in all eight patients with severe colonic inflammation (Table 2). In contrast, expression of 1-8U was weak or negligible in four of six patients in the remission stage with very mild colonic inflammation. This gene expression was not related to the extent and duration of the disease. However, 1-8U was expressed in the colonic mucosa of all four patients with chronic, continuously severe inflammation.

Fig. 1. A, expression of 1-8U mRNA in macroscopically normal mucosa (N), mildly inflamed colon mucosa (I), and UC-associated cancer tissue (T) of patients 3–5. The predicted size of 1-8U mRNA was 0.8 kb. For the internal standard, GAPDH was used as a housekeeping gene. B, RT-PCR demonstrating 1-8U mRNA expression in UC-associated cancer tissues rather than in mildly inflamed colonic mucosa in patients 1 and 2. The predicted size of RT-PCR products of 1-8U was 97 bp.

Fig. 2. Expression of 1-8U mRNA in sporadic colon cancer tissues. Ten representative samples of 1-8U mRNA expression in normal colon mucosa (N) and colon cancer tissues (T) from the same patients are shown.

Fig. 3. A, expression of 1-8U mRNA in cancer cell lines. The human colon carcinoma cell lines HT29, Caco2, ACM, WiDr, and CW2 were used. A human cervical cancer cell line, HeLa, was also used. B, expression of 1-8U mRNA in normal colon mucosa from healthy volunteers. Six representative samples of 1-8U mRNA expression in normal colon mucosa are shown. HeLa was used as a positive control.

Fig. 4. Expression of 1-8U mRNA in freshly isolated colonic epithelial cells (Epithelial cell) and LPLs from severely inflamed colonic mucosa of a UC patient. Ethidium bromide staining of the PCR products by DD40 primers is shown.

Fig. 5. Expression of 1-8U mRNA in severely inflamed colonic mucosa and in remission stage mucosa from UC patients without colitis-associated colon cancer. Three representative samples of severely inflamed colonic mucosa and four samples of 1-8U mRNA expression in remission stage mucosa from UC patients were shown. HeLa was used as a positive control.
**DISCUSSION**

Previous molecular and epidemiological studies suggest that tumorigenesis in UC differs from sporadic colon cancer and that chronic inflammation likely plays a role in the former but not the latter (9, 10, 25, 26). To clarify the mechanism of carcinogenesis from chronic inflammation in colonic mucosa, we tried to isolate cDNA fragments corresponding to mRNAs that are differentially expressed between UC-associated cancer tissue and inflamed mucosa. We isolated 60 cDNA fragments from all five samples. Nineteen of 34 sequenced DNA fragments were strongly expressed in UC-associated colon cancer. Two of these fragments were highly homologous to known cDNA sequences. Only DD40 was definitively overexpressed in UC-associated cancer. Therefore, we focused on the nucleotide sequence of this DD40 fragment. The DD40 fragment was identical to the partial sequence of human IFN-inducible gene family 1-8U that are highly induced by both type I (α and β) and II (γ) IFN. IFN-inducible gene family 1-8U was originally cloned from a human lymphoid cell cDNA library (27). 1-8U was expressed in HeLa cell line, and this expression was enhanced by IFN-α treatment. Human 1-8U gene-transfected Chinese hamster ovary cells are highly responsive to IFN-α. This gene has the IFN stimulation regulatory element in its promoter region that is the binding site of IFN stimulated gene factor 3 and the IFN regulatory factor family, and transcription of this gene is thought to be regulated by INF signal transduction (27). However, the function of IFN-inducible gene 1-8U in IFN systems is still unknown.

Interestingly, 1-8U was strongly expressed in both UC-associated cancer and sporadic colon cancer tissues. In contrast, 1-8U was not expressed in normal colon mucosa. Consistent with these findings, a recent study reported that IFN-inducible gene family 1-8U and 1-8D were strongly expressed in colon primary tumors and in some colon cancer cell lines, but not in normal colon mucosa by serial analysis of gene expression (28), suggesting that 1-8U may be a colon cancer-associated gene.

Importantly, this colon cancer-associated gene, 1-8U, was strongly expressed in severely inflamed mucosa of UC. Expression of 1-8U was weak or negligible in UC patients with very mild colonic inflammation. In contrast, expression of 1-8U was quite strong in the patients with severe colonic inflammation. To confirm the purity of colonic epithelial cells isolated from mucosa of biopsied specimens, we have performed flow cytometric analysis by using an antihuman intestinal epithelial cell-specific mAb, not just by using lymphocyte-specific mAbs. Cells in our preparation method contained >95% pure epithelial cells (24). Moreover, our recent experiments using epithelial cells with high B9 expression isolated from our epithelial preparations demonstrated that those cells strongly expressed 1-8U in mucosal tissues with active UC. Therefore, we are quite sure of the purity of epithelial cells. Our results indicated that 1-8U expression in LPLs was quite weak and was not comparable to that in purified epithelial cells. Although we cannot completely negate contamination by LPLs in our epithelial cell preparations, we are sure that the main cellular source of 1-8U expression in the UC mucosa was epithelial cells. These issues are supported by the fact that 1-8U expression in LPLs from some active UC patients was not demonstrated. In contrast to the situation regarding epithelial cells, LPLs isolated from mucosal biopsied specimens contained up to 10% B9-positive colonic epithelial cells in our preparation method.

Interestingly, this gene was expressed in colonic mucosa from all patients with chronic, continuously severe inflammation. Therefore, this gene expression may be related to the severity of the disease. This gene expression was not correlated with duration of the disease. Long-term persistent inflammation in colonic mucosa has been thought to cause the development of colon cancer in patients with UC (1–3). A recent study demonstrated that UC patients with chronic continuously severe inflammation developed colitis-associated colon cancer in shorter periods of time than previously reported. In these patients, colitis-associated colon cancer developed in severely inflamed colonic mucosa. It has been considered that the risk of UC-associated colon cancer depends only on the duration of the disease. Our results suggest that the severity of inflammation may also be important in the tumorigenesis of UC. Therefore, long-term persistent expression of 1-8U in the colonic mucosa might be used as a marker that is preferentially expressed in UC-associated colon cancer.

Production and expression of a variety of inflammatory cytokines are increased in severely inflamed colonic mucosa of UC, and colonic epithelial cells in severely inflamed colonic mucosa of UC are exposed to several kinds of IFNs. Therefore, it is quite reasonable that the IFN-inducible gene family is strongly expressed in severely inflamed mucosa, but not in normal colonic mucosa. In contrast, the molecular mechanism for induction of 1-8U gene expression and function of the expressed gene in colitis-associated cancer tissues in UC remains unclear. How does increased IFN expression as a result of severe inflammation affect carcinogenesis in UC? Although the function of IFN-inducible gene 1-8U remains unclear, recent studies demonstrated that some IFN-inducible genes and proteins are overexpressed in cancer tissues. p27 was overexpressed in breast carcinoma (29), and a new glycoprotein that cross-reacts with carcinoembryonic antigen was reported to be up-regulated by IFN-γ (30). Therefore, IFN-inducible genes such as p27, the new glycoprotein, and 1-8U that are overexpressed in cancer tissues may be cancer-related genes. IFN-inducible genes mediate several kinds of functional roles. IFN-inducible genes such as double-stranded RNA-dependent protein kinase exert an antiviral and antiproliferative effect (31). IFN-inducible protein p202 binds retinoblastoma protein and inhibits cell growth (32). IFN-inducible protein IP-10 is an antitumor agent that promotes damage in established tumor vasculature and induces tissue necrosis in human Burkitt lymphoma (33). Therefore, 1-8U expression in severely inflamed mucosa and colitis-associated cancer tissues in UC may also be important in protection against the proliferation of inflammation-mediated cells and tumor cells. Although it is not defined whether 1-8U act as antitumor gene or carcinogenic gene, our study indicates that expression of this gene in colonic mucosa may be a useful marker in the identification of the high-risk group of UC-associated colon cancer.

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**Table 2** Relationship between 1-8U expression in the colonic mucosa and clinical features in UC patients without cancer

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*Unpublished observation.

5 T. Hibi and T. Hisamatsu, unpublished observation.
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