Ulcerative colitis specific cytotoxic IgG-autoantibodies against colonic epithelial cancer cells

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SUMMARY Serum antibodies cytotoxic to the colon cancer cell line RPMI 4788 were studied in 42 patients with ulcerative colitis, 61 patients with Crohn's disease, 27 patients with other inflammatory diseases (disease-controls) and 22 healthy controls. Cytotoxicity of antibodies towards RPMI 4788 was studied by means of a chromium release assay using peripheral blood mononuclear leucocytes of healthy subjects as effector cells. Using a four hour antibody dependent cell mediated cytotoxicity assay sera from 29% of ulcerative colitis patients contained antibodies cytotoxic for the target, while only 3% of the Crohn's patients and 6% of the disease controls and non of the healthy controls were positive. When an 18 hour assay was applied, however, not only 40% of ulcerative colitis patients, but also 14% of Crohn's patients and 21% of disease controls were found positive. The reactive antibody in the four hour assay was mainly of the IgG class, which points to a classical antibody dependent cell mediated cytotoxicity mechanism. In the 18 hour cytotoxic assay IgG and particularly IgM antibodies were found to be reactive. This suggests that in the latter case other cellular cytotoxic mechanism might be involved. There was a significant inverse correlation between the appearance of the ulcerative colitis restricted IgG-anticolon epithelial cell antibodies (four hour assay) and the disease activity (p<0.01). Absorption studies showed that the reactive antigen is not specific for ulcerative colitis colonic tissue, but is similarly found in Crohn's bowel tissue, and to a lower extent in normal bowel, liver and kidney. The reactive antigen, however, could not be detected in brain and lymphoblastoid cells.

About 25 years ago Broberger and Perlmann described haemagglutinating serum antibodies to antigens extracted from human colonic tissue1 as well as antibodies reacting with colonic antigen in situ in patients with ulcerative colitis (UC). These antibodies were shown to be autoantibodies.2 While the autoantibodies which were detected by means of immunofluorescence studies on human colon tissue seemed specific for UC, antibodies to germ free rat colon tissue were also found in sera of patients with Crohn's disease (CD) in a comparable frequency and even in disease – controls (review in 8). Early in vitro studies were unable to reveal a complement dependent cytotoxicity of these anticolon antibodies when human fetal colonic cells were used as target.39 Thus, these antibodies were repeatedly considered rather as an epiphenomenon than as of any potential pathogenic relevance.10

In 1981, Nagai and Das11 showed an antibody cytotoxic to the human colon cancer cell line RPMI 4788 in UC sera by mediating an antibody dependent cell mediated cytotoxicity (ADCC) like activity against this colon cancer cell. The reported restriction of this cytotoxic anticolon antibody as well as of the reactive antigen11 to UC led to the hypothesis that this autoantibody antigen system might play an important autoimmune pathogenic role in colonic cell destruction in UC.11

These intriguing perspectives prompted our investigations on cytotoxic serum antibodies to colon tissue antigens in chronic inflammatory bowel diseases (IBD), on the nature of the antibodies, and the tissue distribution of the reactive antigen.
Methods

Patients and controls
In all instances informed consent was obtained before testing.

IBD patients
The diagnosis of UC or CD was confirmed histologically in all of the 42 UC patients and the 61 CD patients. In UC disease activity (UCAI) was arbitrarily scored using the Crohn's disease activity index with the following modifications: In variable X 4 of the CDAI, the symptoms of anal fissure, abscess or fistula were replaced by 'blood in the faeces'. In variable X 6, sedimentation rate of 30 mm in the first hour was used instead of 'abdominal mass'. Eleven of the UC patients had proctosigmoiditis, nine suffered from left sided colitis and 16 from universal colitis. In the CD patients, the disease was restricted to the ileum in 16 cases, to the small bowel as well as the colon in 33 cases and the colon in seven cases.

Controls
Twenty seven patients with inflammatory diseases other than IBD were also tested. This group of disease controls (group D) consisted of six patients with systemic lupus erythematosus (SLE), five patients with rheumatoid arthritis (RA) or ankylosing spondylitis, five patients with inflammatory bowel diseases other than IBD (diverticulitis, salmonellosis, shigellosis), four patients with renal disease, two patients with cirrhosis of the liver and one patient, each with irritable bowel disease, cholangitis, lymphosarcoma, AIDS, and dermatomyositis. In addition, sera of 22 healthy controls (group N) were tested.

Serum samples
Serum samples were obtained by venous puncture. Blood was centrifuged within 30 minutes after bleeding. Sera were stored at -80°C in small aliquots.

Leucocyte separation
In all assays peripheral blood mononuclear leucocytes (PBML) obtained by Ficoll Isopaque density gradient centrifugation were used. Peripheral blood mononuclear leucocytes were resuspended to a concentration of 5×10^6 cells/ml in culture medium (CM) consisting of RPMI 1640 (GIBCO, Grand Island, NY) plus HEPES (25 mM) supplemented with penicillin (10 U/ml), streptomycin (100 μg/ml), gentamycin (50 μg/ml), fungizone (0·25 μg/ml), L-glutamine (2 mM) and 20% heat inactivated fetal calf serum (FCS). The viability in all suspensions was greater than 95% when tested by trypan blue dye exclusion.

Cytotoxicity tests
Antibody dependent cell mediated cytotoxicity (ADCC)
The technique used in determining the ADCC activity was essentially that described by Auer and Ziemer with minor modifications. In brief, the established human colon cancer cell line RPMI 4788 which was kindly supplied by Drs W Beeken and J Krawitt, Medical College of Vermont, Burlington, Vermont, USA, and the HeLa-cell line were used as target cells. The HLA phenotype of the RPMI 4788 cells and the HeLa-cells included HLA-A2 and HLA-A28. The target cells RPMI 4788 were used 96 hours after splitting, at which time lysability was found to be optimal (see results). An equal volume of target cell suspension (20×10^6 viable cells/ml) was mixed with 0·1 ml Na25CrO4 (spec activ 200 Ci/mmol Na25CrO4 in 0·9% sodium chloride, New England Nuclear, Boston, Mass, USA). After incubation for 60 minutes at 37°C in a 5% CO2/95% air atmosphere with frequent agitation, chromium uptake was stopped by addition of cold FCS. Thereafter cells were washed twice in CM supplemented with 10% heat inactivated FCS. Cells were resuspended at a concentration of 1×10^6 viable cells/ml in CM. As positive serum control for the RPMI 4788 and HeLa-cells an alloantiserum to the HLA-A2 and HLA-A28 determinants was used. It was applied in the ADCC assay at an optimal dilution of 10^-1 in PBS supplemented with 5% inactivated FCS, according to the results of serum dilution experiments using PBML of normal subjects as effector cells.

Effector cells were prepared from heparinised peripheral blood, as described above. The effector lymphocytes were resuspended at a concentration of 5×10^6 viable cells/ml in CM supplemented with 10% FCS.

Cytotoxicity tests were done in round bottom microtitre plates (Greiner Plastik, Nürtingen, FRG). Triplicate cultures were used throughout. To each experimental well (E) 5×10^5 target cells in 50 μl and 50 μl of heat inactivated anti-HLA-antiserum as

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<th>UCAI</th>
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<td>Total</td>
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*% specific lysis >4%. χ² test with maximum likelihood probability. p=0·015.
positive controls or of the sera of various patients and controls were added. Wells for ‘total release’ (T), ‘spontaneous release’ (S) and ‘spontaneous cytotoxicity’ (SCMC) received target cells and FCS instead of the anti-HLA-antiserum or the sera. Wells for ‘serum control’ received target cells and the sera to be tested. After 60 minutes incubation of the mixture at 37°C, 100 μl of the effector cell suspension containing 5×10^6 cells were added to the ‘experimental wells’ (E) and the ‘spontaneous cytotoxicity’ wells (SCMC). The wells for ‘total release’ (T) received 100 μl Triton X 100 (10% in PBS), the ‘spontaneous release’ wells (S) and the ‘serum control’ wells received 100 μl CM. After four hour incubation at 37°C the plates were centrifuged at 4°C at 500 g for 10 minutes. Half of the total volume was removed from each well and counted for ^51Cr release. (R) as a measure of the cytotoxic activity was calculated according to the following formula:

\[ R (%) = \frac{E \text{ (cpm)} - SCMC \text{ (cpm)}}{T \text{ (cpm)} - S \text{ (cpm)}} \times 100 \]

For the 18 hour assay the same experimental set up was applied, except that the complete mixtures of effector cells, sera and target cells and the controls, respectively, were incubated for 18 hours.

In very few instances ^51Cr release values of the serum controls were higher than that of spontaneous release, which indicated unspecific cytotoxicity. Therefore, the results of such sera were discarded.

**Separation of the Immunoglobulin Classes G, M, and A**

The sera were chromatographically separated by application of the FPLC system (Pharmacia, Sweden). The major three immunoglobulin classes were fractioned from 1-2 ml serum by Mono Q column as an anion exchanger.\(^1\) The fractionation was achieved by a step gradient of phosphate buffer (0-025 M, pH 6-7-0-3 M, pH 6-5, total volume 40 ml). IgG-enriched fractions contained 60 to 65% IgG of the total protein. These fractions were depleted of IgM (<0-008 g/l) as well as IgA (<0-008 g/dl). IgM enriched fractions contained 5 to 10% IgM of the total protein and were free of IgG (<0-008 g/l) and IgA (<0-011 g/l); IgA enriched fractions contained 5 to 10% IgA of the total protein and were free of IgG (<0-011 g/l) and IgM (<0-008 g/l). Using the Millipore ultrafiltration units (Millipore, Mass, USA) the Ig-fractions were concentrated to an extent that the concentration of the enriched Ig was comparable to the concentration of the corresponding immunoglobulin in the original serum, unless otherwise stated.

**Absorption Studies**

The absorption of sera with human tissue, colon cancer cells and lymphoblastoid cells was done according to Nagai and Das\(^2\) with minor modifications. Tissues of colon and ileum from UC-, CD-, and colon cancer patients (in the latter case only uninvolved areas of the tissue were used) were obtained from fresh surgical specimens, while liver, kidney and brain tissue were obtained from autopsy specimens.

Mucosal bowel tissue was separated from serosa and muscle layer. Mucosa or the tissues of other organs were minced into pieces and homogenised eight times for 10 seconds on ice by Ultra Turrax (OKA Staufen, RFG). These homogenates were mixed with an equal volume of cold 0-01 M PBS (v/w) containing 2 mM phenylmethylsulfonylfluoride (PMSF) as protease inhibitor and were washed three times. The pellet obtained by the last centrifugation at 1250 g for 4°C was mixed with an equal volume of serum and incubated at 4°C under permanent shaking for one hour. Absorbed sera were recovered from the homogenates by centrifugation at 1250 g for 30 minutes at 4°C.

In the same manner sera were absorbed with colon cancer cells (RPMI 4788) and lymphoblastoid cells (LIK). To avoid cell damage the cells were washed three times at 500 g and finally packed at 800 g. After incubation the cells were centrifuged at 1000 g for 30 minutes to regain the serum. To exclude unspecific absorption on plastic material or unspecific loss of cytotoxic activity similar aliquotes of serum were treated in the same manner without absorbing tissue cells.

**Statistical Analysis**

Results are given as mean (standard error) of the mean (±1 SEM), unless otherwise stated. All statistical evaluations were done using a TR 440 Computer (Institute for Applied Mathematics, University of Würzburg). Correlation studies were done using Spearmen’s correlation test or the exact test of Fisher including the Yates-correction. All tests were two-tailed.

**Results**

**Methodological Considerations**

In order to find optimal conditions for the evaluation of cytotoxic antibodies kinetic studies were performed on the lysability of the target cells. For that purpose sera of UC patients which proved to be cytolytic against RPMI 4788 in preliminary experiments and the control serum (anti-HLA-A2 and -A28 serum) were tested against RPMI 4788 cells at various intervals after splitting of the target cell.
cultures. Lysability in both the four hour and 18 hour assay was found optimal four days after splitting of the RPMI 4788 target cells. For the HeLa cells optimal lysability by the control serum was found on day two after splitting. Therefore, all further cytotoxicity experiments were carried out under these optimal conditions of the two target cells.

PREVALENCE OF CYTOTOXIC ANTIBODIES
Sera of patients with UC, CD, other inflammatory diseases like SLE, RA, ankylosing spondylitis and cirrhosis etc (group D) and normal controls (group N) were tested against RPMI 4788 cells, using PBML of healthy blood donors as effector cells. The results obtained by means of the four hour cytotoxic assay

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**Fig. 1**  Per cent specific lysis against the colonic epithelial cancer cells RPMI 4788 of sera of patients with UC or CD, of patients with other inflammatory diseases (D) and of healthy controls (N). Cytotoxicity was evaluated in an antibody dependent cell mediated cytotoxicity assay. A specific lysis of 4% has arbitrarily been considered 'positive'. (a) % specific lysis after four hours incubation. (b) % specific lysis after 18 hours incubation.
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are summarised in Fig. 1a. Positive results – that is, cytotoxicity of 4% specific lysis, were observed in 13 (29%) of UC sera. Only two sera from Crohn's patients (3%) and two sera of group D (6%; both patients suffered from active SLE), were positive (Fig. 1a). None of the normal controls showed any cytotoxicity. In contrast, when incubation was done for 18 hours, not only 40% of UC, but also 14% of CD patients and 21% of D patients were positive, while normals remained negative throughout (Fig. 1b).

In the four hour assay HeLa cells were lysed by only two of 21 UC sera (7%), none out of 20 CD sera and three of 10 normal sera. Five of these 21 UC sera lysed the RPMI 4788 target. Only one of these five sera was cytotoxic also towards the HeLa target, while the second UC serum cytotoxic against HeLa cells did not lyse RPMI 4788 cells.

IMMUNOGLOBULIN CLASSES OF CYTOTOXIC ANTIBODIES

Figure 2 illustrates the results obtained by serum fractions from high titre UC-sera which have been enriched for one of the three main Ig-fractions and depleted of the other two by means of FPLC (see methods).

In the four hour assay (Fig. 2; UC1, UC2) cytotoxicity was primarily exerted by the IgG fraction when used in the same Ig-concentration as that in the original serum. IgM poorly, and IgA never mediated any cytotoxicity in the four hour assay. When highly enriched immunoglobulin concentrations were applied (three to four-fold higher concentrated than in the original serum) not only the IgG-mediated cytolyis increased significantly, but also some IgM-dependent cytotoxicity could be observed in the four hour assay (Fig. 2; UC2b, UC3, CD). In the 18 hour assay, however, cytolsis was mainly mediated by the IgM fractions. Time kinetics of the concentrated Ig-fractions made obvious that the IgM-dependent cytolyis increased considerably during the 14 hour incubation period following the first four hours incubation (UC2b, UC3, CD), while the IgG fractions had reached their peak cytotoxicity already after four hours and did not increase further. The IgG-mediated cytotoxicity rather became even lower in some instances with ongoing incubation (UC3). This latter effect is caused by the time dependent rise of the SCMC (UC2, UC3, UC4), which had always to be subtracted from the total cytotoxicity to obtain the antibody dependent cell mediated cytotoxicity.

Fig. 2  Cytotoxic activity of sera and their immunoglobulin fractions against the colonic epithelial cancer cell line RPMI 4788. IgG-fraction: This immunoglobulin fraction has been enriched for IgG and depleted of measurable IgM and IgA. SCMC: Spontaneous cell mediated cytotoxicity. UC1 and UC2a: The immunoglobulin fractions have been applied in concentrations comparable to the immunoglobulin concentrations in original sera. UC2b, UC3, UC4 and CD: Immunoglobulin fractions have been applied in three to four-fold higher concentrations than in the original serum. ▲: Cytotoxicity of the original, unseparated serum.
RELATIONSHIP TO CLINICAL PARAMETERS

In patients with UC there was a significant inverse correlation between the disease activity as evaluated by the UCAI (see methods) and the appearance of UC restricted cytotoxic IgG-anticolon cancer cell antibodies (Table). When 'positive' UC sera were evaluated in the 18 hour assay, however, no such correlation became evident. Patients with total colitis contained more often UC restricted cytotoxic IgG-anticolon antibodies (seven of 16; 44%) than patients with left sided colitis (two of nine; 22%) or proctosigmoiditis (two of 11; 18%). The difference failed to reach statistical significance.

STUDIES ON THE REACTIVE ANTIGEN(S)

By extensive absorption studies we hoped to get information on the distribution of the reactive antigen(s) (a) in various segments of the bowel, (b) in bowel tissue of various disease groups, and (c) in tissues other than the bowel. Samples of high titre UC sera were subjected to absorption with homogenates from bowel mucosa of patients with UC or CD, or with homogenates from uninvolved areas of mucosa from colon cancer specimens. Furthermore, tissue homogenates from organs other than bowel mucosa, and a lymphoblastoid cell line (LIK) were used for absorptions. These absorbed serum samples were then tested against RPMI 4788. As expected UC colon tissue absorbed completely the cytotoxic activity, both in the four hour and 18 hour assay. As Figure 3 shows, however, one absorption step with bowel tissue from CD patients colon as well as ileum, also abolished the cytotoxic activity of the sera. Absorption with normal ileal and colonic tissue from colon cancer patients (Fig. 3) or with RPMI 4788 (Fig. 4) had a consistent absorbing effect on the cytotoxic activity in the four hour assay, while these tissues hardly showed an absorbing effect in the 18 hour assay (not shown). Under these latter experimental conditions, one absorption step with RPMI 4788 hardly removed cytotoxic activity, which was abolished after repeated absorption with these cells. Also absorption with kidney and liver considerably decreased the cytotoxic activity in both assays, while one absorption step with brain or with the lymphoblastoid LIK-line had virtually no effect on the cytotoxic activity (Fig. 4). Even with repeated absorption these latter tissues did not alter the cytotoxic activity towards RPMI 4788.

Discussion

This study showed that specifically in UC sera of about one third of patients contain antibodies which direct a cell mediated cytotoxicity against the human colon cancer cell line RPMI 4788 in a four hour assay and that mainly IgG-antibodies mediate this UC specific cytotoxicity. Sera of patients with CD, other inflammatory diseases or normal controls barely exerted such an activity. HeLa-cells, which were used as control target, were not lysed by 'positive' UC-sera (cytotoxic to RPMI 4788) with one exception, as vice versa most sera cytotoxic towards HeLa did not exert lytic activity against RPMI 4788. Similar results have been reported by Nagai and Das. 31

As second important finding, which has not been reported so far, we observed a similar cytotoxicity of UC-sera against the cell line RPMI 4788 in an 18 hour assay. This 18 hour cytotoxicity has, however, also been found in patients with CD and in patients with inflammatory diseases other than IBD. Thus, it was
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not as strongly restricted to UC as the four hour cytotoxicity. In contrast with the four hour cytotoxicity, which was primarily mediated by IgG, the 18 hour cytotoxicity assay was mainly conferred by IgM.

Thus, the cytotoxic antibodies towards colonic epithelial cells detected in the four hour and 18 hour assay do not only show a different prevalence in the various disease groups, but in addition, they belong to different immunoglobin classes. Although ADCC might also be mediated through IgA-antibodies, we could not observe any cytotoxicity in the IgA enriched and the IgG as well as IgM depleted serum fractions. Nagai and Das have also found the cytotoxicity against RPMI 4788 in the IgG class of the UC serum. These authors, however, did not evaluate other Ig fractions.

It is unclear at present, whether the restriction of cytotoxic IgG-anticolon cellular antibody detected in the four hour assay to UC might be the result of an UC restricted immunological capability to switch from IgM to IgG production of these cytotoxic antibody, or, whether this might have to do with the observation, that in UC-sera the IgG 1-subtype predominates. IgG 1 is particularly apt to mediate ADCC.

Unlike a previous report of a positive correlation between the appearance of UC restricted cytotoxic IgG serum anticolon antibodies and disease activity in UC, we observed an inverse correlation. This discrepancy of the findings might be in part caused by differences in assessing the disease activity of patients with UC. The ulcerative colitis activity index (UCAI) used in the present study, however, has been successfully applied in elaborating the influence of disease activity both on ConA-generated, irradiated T-suppressor cells to suppress the proliferation of autologous lymphocytes, stimulated by PHA, PWM or mixed lymphocyte culture and on the spontaneous T-suppressor cell activity to suppress PHA and ConA stimulated lymphocyte proliferation. Whether this inverse correlation between disease activity and the appearance of circulating cytotoxic IgG-anticolon antibodies might be the result of the binding of the antibody to bowel tissue during active disease remains speculative at present.

As a fourth finding, our extensive absorption studies revealed that the reactive antigen(s) of the UC-restricted cytotoxic IgG-anticolon-epithelial antibody is present both in UC colon and in ileal as well as colonic tissue of patients with CD, and even in normal liver, kidney, ileum and – although to a lower extent – colon. This contrasts with the previous report of Nagai and Das, that the reactive antigen of the UC specific cytotoxic antibody is specific for UC colonic tissue. Because absorptions neither with brain tissue nor with the lymphoblastoid cell line LIK had any influence on the cytotoxic activity, the absorptions with ‘positive’ tissues are not unspecific, but reflect the true distribution of the reactive antigen(s). Although the absorption results in the four hour and 18 hour assay seem at first glance comparable, the absorptions with normal bowel tissues, particularly ileal tissue, and with RPMI 4788 cells, however, differed considerably in the two assays. Thus, the question arises whether besides different immunoglobin classes also different antigen-antibody systems are reacting in the two assays. This cannot be conclusively answered as yet. In any case, the reactive antigen(s) of the cytotoxic IgG-anticolon antibodies of the four hour assay is by no means specific for ulcerative colitis as has previously been reported, and not even restricted to the intestine. Yet, this finding does not necessarily exclude a possible pathogenic relevance of these antibodies, because it is unclear as yet, whether the reactive antigen observed in ileum, liver and kidney tissue is similarly expressed at the cell surface of these tissues and thus accessible to the antibodies as it is with colon cells, or whether it might be hidden in the cytoplasm.

Using different techniques various ‘anticolon’-antibodies have been reported in sera of patients with IBD in the past. The relation of the cytotoxic antibodies reported here to the circulating ‘anticolon’-antibodies, actually antigoblet cell antibodies, reported earlier by Broberger and Perlmann and others is of particular interest. Heterogeneity seems to exist among these long-known ‘anticolon’-antibodies, and interestingly, none of the UC sera cytotoxic to RPMI 4788 contained these ‘anticolon’-antibodies which react with goblet cells of human fetal colonic tissue (Auer and Stöcker, unpublished observation).

Hibi et al suggested that in UC-sera cytotoxic antibodies to rat colonic epithelial cells and cold reactive lymphocytotoxic antibodies are interrelated. The UC specific cytotoxic IgG-antibody against human colon epithelial cells described here is, however, not simply comparable with the findings of Hibi et al with rat tissue. First, lymphocytophhilic antibodies are found in equal incidence in UC and CD and are not restricted to UC as is the cytotoxic IgG antibody described here. Second, the lymphocytotoxic toxin is an antibody of the IgM class, whereas the UC specific cytotoxic anticolon epithelial cell antibody mainly belongs to the IgG class. Third, the lymphoblastoid cell line LIK did not absorb the cytotoxic IgG-anticolon antibody. Fourth, as Hibi et al did not take into account the SCM C in calculating the ‘ADCC’, there is no formal proof that the reported cytotoxicity against rat colon epithelial cells is indeed antibody mediated.
Shorter et al\textsuperscript{28} had shown that sera from patients with IBD transferred an \textit{in vitro} cytotoxicity against homologous colonic epithelial cells on peripheral blood mononuclear leucocytes of normal subjects. Similar to our findings after 18 hour incubation, this anticolon cytotoxicity was equally found in UC and CD \textsuperscript{29} and a cytophilic IgM antibody has been postulated to mediate this cell-mediated cytotoxicity.\textsuperscript{22} These two observations distinguish the cytotoxic serum anticolon antibodies of Shorter \textit{et al} clearly from the cytotoxic anticolon epithelial cell IgG antibody observed in our four hour assay.

Specifically in UC, tissue bound IgG antibodies have been shown on the basement membrane and the basal area of the colonic epithelial cells by means of immunoperoxidase technique.\textsuperscript{29} Furthermore, colon tissue bound IgG antibodies could be eluted from colonic tissue of patients with UC, but not from colonic tissue of patients with CD or colonic cancer.\textsuperscript{28} The reactive antigen of these colonic tissue bound antibodies is a normal colonic tissue protein antigen of 40 Kd which has been reported to be present in colonic, but not in ileal tissue.\textsuperscript{27,28} Although the UC specific circulating cytotoxic IgG antibodies towards colonic epithelial cells detected in the four hour assay seem therefore to react with an antigen different from 40 Kd-antigen, they nevertheless might bind to colonic tissue \textit{in vivo}. This and a potential pathogenetic role, however, remain to be established.

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References

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