Mucin gene expression in intestinal epithelial cells in Crohn’s disease

M-P Buisine, P Desreumaux, E Leteurtre, M-C Copin, J-F Colombel, N Porchet, J-P Aubert

Abstract

Background—Crohn’s disease (CD) is a chronic relapsing inflammatory bowel disease of unknown origin. It is characterised by chronic mucosal ulcerations which affect any part of the intestine but most commonly are found in the ileum and proximal colon.

Aims—Studies were undertaken to provide information regarding cell specific expression of mucin genes in the ileum of patients with CD.

Patients and methods—Expression of mucin genes was analysed in the ileal mucosa of patients with CD and controls by in situ hybridisation and immunohistochemistry.

Results—In healthy ileal mucosa, patients with CD showed a pattern identical to normal controls with main expression of MUC2 and MUC3, lesser expression of MUC1 and MUC4, and no expression of MUC5AC, MUC5B, MUC6, or MUC7. In the involved mucosa, the pattern was somewhat comparable although heterogeneous to that observed in healthy ileal mucosa. Importantly, a particular mucin gene expression pattern was observed in ileal mucosa close to the ulcer margins in ulcer associated cell lineage, with the appearance of MUC5AC and MUC6 mRNAs and peptides, which are normally restricted to the stomach (MUC5AC and MUC6) and duodenum (MUC6), and disappearance of MUC2.

Conclusions—Our results suggest that gel forming mucins (more particularly MUC5AC and MUC6) may have a role in epithelial wound healing after mucosal injury in inflammatory bowel diseases in addition to mucosal protection.

Keywords: mucins; MUC genes; Crohn’s disease; ulcer associated cell lineage

Crohn’s disease (CD) is a chronic relapsing inflammatory bowel disease of unknown origin. It is characterised by chronic mucosal ulcerations which affect any part of the intestine but most commonly are found in the ileum and proximal colon. The intestinal epithelium is covered by a continuous layer of mucus that provides a physical barrier between the underlying epithelium and aggressive agents present in the gastrointestinal tract lumen. Mucus properties are attributed largely to its constituent mucin O-glycoproteins which exhibit high density and viscoelasticity.

To date, eight human epithelial mucin genes have been well characterised: MUC1–4, MUC5AC, MUC5B, and MUC6–7. Additional partial cDNAs have been proposed for MUC8, MUC9, MUC11, and MUC12. Much progress has been made recently in our understanding of the structure of these genes, allowing classification of their products into two categories: membrane anchored mucins and secreted mucins. Membrane anchored mucins consist of the small mucin MUC1 and the two large mucins MUC3 and MUC4. Secreted mucins consist of the small mucin MUC7 and the large gel forming mucins MUC2, MUC5AC, MUC5B, and MUC6 whose genes are clustered on chromosome 11p15.5. Mucins are widely expressed in the gastrointestinal tract in a highly tissue and cell specific manner. Quantitative and qualitative changes in mucins are a feature of inflammatory bowel diseases which may contribute to impaired mucosal integrity. Most of the qualitative changes reported in the literature are related to alterations in the glycosylated portion of mucins. Less is known about the various mucin gene products. In a previous report, using quantitative dot blot analysis, we showed that expression of mucin genes is heterogeneous among patients with CD, with a slight decrease in expression levels in both healthy and involved ileal mucosa. With the aim of providing further information regarding deregulation of expression of mucin genes in CD, we used in situ hybridisation and immunohistochemistry to study expression of MUC1–4, MUC5AC, MUC5B, and MUC6–7 in ileal mucosa of patients with CD and demonstrated that mucin genes (more particularly mucin genes of the 11p15 family) display abnormal expression patterns in the mucosa close to ulcerations. A potential role for mucins in mucosal healing in addition to mucosal protection is discussed.

Patients and methods

PATIENTS AND PROTOCOL

Eleven patients with CD (CD 1–11) (seven females, four males; mean age 29 years, range 18–67) were evaluated for mucin gene expression. The diagnosis of CD was established using defined criteria. Patients had pure ileal involvement or ileocolonic CD. They underwent surgery because of symptomatic stenosis, abscess or fistula, or medical treatment failure.

Abbreviations used in this paper: CD, Crohn’s disease; UACL, ulcer associated cell lineage; TFF, trefoil factor; vWF, von Willebrand factor.
During the surgical procedure, an ileoscopy was systematically performed to assess macroscopically and histologically the integrity of the ileal mucosa 30 cm above the future anastomosis, as previously described. 12 Ileal biopsies were systematically performed at 10 cm and 30 cm above the future anastomosis. Samples were also obtained from surgical specimens in the macroscopically normal mucosa and lesions. To complete the study, additional samples were obtained from surgical specimens from eight patients (CD 12–19) (six females, two males; mean age 31 years, range 20–53) in mucosa close to the ulcer margins.

As controls, ileal biopsy specimens were taken from 14 patients (CT 1–14) (11 females, three males; mean age 38 years, range 17–60) who underwent endoscopy for irritable bowel disease. No endoscopic lesions were found in these patients.

All patients gave informed consent after approval from the ethics committee.

Tissues
Samples were immersed immediately in 4% paraformaldehyde in phosphate buffer or 10% formalin for a minimum of 6–24 hours depending on the sample size and further embedded in paraffin. Sections (3 µm thick) were cut and mounted on gelatine covered slides for in situ hybridisation analysis. Serial sections were mounted on silan covered slides for immunohistochemical and histological analyses. Sections were routinely stained with haematoxylin-eosin-safron and astra blue or trichrome for a first histological analysis.

Histological study
Sections were stained with haematoxylin-eosin and May-Grünwald-Giemsa for histological study. Biopsies were scored for the presence of inflammatory lesions in a standardised way, as previously described. 10 11 This score included features of inflammatory changes such as the intensity of mononuclear and polymorphonuclear cell infiltration in the lamina propria, interaction between inflammatory cells and the epithelium (cryptitis, crypt abscess), features of epithelial cell damage, and structural changes. In addition, goblet cell hyperplasia (increase in number) and increased mucus content were recorded as present or absent. The intensity of the inflammatory changes was graded from 1 to 13 corresponding, respectively, to absent and severe inflammatory changes.

In situ hybridisation
Probes
In situ hybridisation was performed using eight 35S labelled antisense oligonucleotide probes corresponding to each tandem repeat domain of MUC1, MUC2, MUC3, MUC4, MUC5AC, MUC5B, MUC6, and MUC7, as described in previous studies. 14 15

Hybridisation procedure
The hybridisation steps were as described previously. 14 Briefly, tissue sections were deparaffinised, rehydrated, incubated with 2 µg/ml proteinase K (Roche Diagnostics, Meylan, France) for 15 minutes, and fixed again in 4% paraformaldehyde in phosphate buffered saline for 15 minutes. Sections were then immersed in 0.1 M triethanolamine (Sigma, L’Isle d’Abeau Chesnes, France) containing 0.25% acetic anhydride for 10 minutes. Sections were prehybridised in 4× SSPE, 1× Denhardt’s buffer for 45 minutes, and hybridised overnight at 42°C in 20–100 µl of a 4× SSPE solution containing 50% formamide (v/v), 0.1% N-lauroylsarcosine (w/v), 1.2 M sodium phosphate (pH 7.2), 1× Denhardt’s buffer, 3 mg/ml yeast tRNA, 20 mM dithiothreitol, and 7.5×103 dpm/µl of 35S labelled oligonucleotide. After post-hybridisation washes, slides were dipped in LM-1 emulsion (Amersham, Les Ulis, France), developed 1–3 weeks after exposure, and counterstained with methyl green pyronin (Sigma).

The following controls were performed: (i) competition studies by treatment of tissue sections with a large excess of unlabelled oligonucleotide identical to or distinct from the 35S labelled probe; (ii) verification of the absence of background by careful examination of non-epithelial structures (vessels, muscle, and connective tissue); and (iii) tissues from CD patients and controls were tested in parallel under the same conditions.

Scoring
The intensity of the hybridisation signal was scored semiquantitatively as: –, absent; +, weak (visible at magnification ×200); ++, moderate (visible at magnification ×100); ++++, strong (visible at magnification ×40); and ++++, very strong (visible macroscopically).

Immunohistochemistry
Antibodies
Immunohistochemistry was performed using polyclonal antibodies raised against MUC2,16 MUC5AC,17 and MUC5B,17 and a monoclonal antibody raised against MUC6.18

Staining procedure
The staining procedure was conducted using an automated immunostainer (ES, Ventana Medical Systems, Strasbourg, France) and a three step indirect process based on the biotin-streptavidin-peroxidase method. After microwave pretreatment in citrate buffer (pH 6.0) for two 10 minutes cycles, tissue sections were incubated for four minutes with fresh 3% hydrogen peroxide in methanol to block endogenous peroxidase, and for 32 minutes with normal goat serum in phosphate buffered saline to block non-specific binding sites. The sections were then incubated with primary antibodies for 32 minutes at 37°C. Antibodies were used at dilutions of 1/1000 for MUC2, MUC5AC, and MUC5B, and at 1/250 for MUC6. After washing, sections were incubated with the biotinylated secondary goat antirabbit antibody for polyclonal antibodies or rabbit antimouse antibody for the monoclonal antibody for eight minutes at 37°C, with streptavidin-peroxidase conjugate for eight minutes at 37°C, and then developed with diaminobenzidine (Sigma) in 0.03% hydrogen peroxide for 5 minutes.
peroxide. The sections were then routinely counterstained with haematoxylin.

The following controls were performed: negative controls: (i) slides run without the primary antibody; (ii) careful examination of non-epithelial structures (vessels, muscle, and connective tissue); positive controls: inclusion of normal tissues known to express MUC2 (small intestine), MUC5AC (bronchus), MUC5B (bronchus), and MUC6 (antrum) on each automated run.

**Results**

**Histological study**

**Controls**

All endoscopic biopsies performed in macroscopically healthy ileal mucosa from controls were histologically normal (score 0/13).

**Patients with CD**

Ileal biopsies obtained in macroscopically unaffected areas from CD patients were normal (score 0/13) except for one patient (CD 7) with moderate inflammation (score 4/13). A relative increase in the number of surface goblet cells (hyperplasia) or an increase in the amount of mucus content were not apparent in these biopsies.

For the biopsies obtained from ileal lesions of patients with CD, the mean combined structural and inflammatory score was high (10/13, range 7–13). The lesions consisted mainly of an ulcer with adjacent mucosa showing features of inflammation with moderate epithelial damage and structural changes. Goblet cell hyperplasia was noted in four cases. Moreover, ulceration associated cell lineage (UACL) was observed in two cases (n=2/11). UACL was also noted in four samples (n=4/8) taken in mucosa adjacent to the ulcerations. The UACL has been characterised by Wright and coworkers as a specific anatomical structure appearing in close proximity to the ulcerated area. Histologically, the UACL can be divided into three components: the acinar portion, which originates from the bases of adjacent intestinal crypts; the duct, which arises from these acini and grows up the core of an adjacent villus; and the surface cells, which migrate through the duct and replace the indigenous lineages.20 21

**Mucin gene expression**

Data are summarised in tables 1 and 2, and figs 1 and 2.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tissue</th>
<th>Probe</th>
<th>MUC1</th>
<th>MUC2</th>
<th>MUC3</th>
<th>MUC4</th>
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<th>MUC5B</th>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>+++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
</tr>
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<td>Involved ileum</td>
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<td>+++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
</tr>
<tr>
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<td>Involved ileum</td>
<td>-</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>CD 6</td>
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<td>Involved ileum</td>
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<td>+++</td>
<td>++</td>
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<td>-</td>
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<td>+</td>
<td>-</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Labelling intensity: −, absent; +, weak; ++, moderate; ++++, strong; +++++, very strong.

**Table 1** Mucin gene expression in the ileal mucosa of patients with Crohn’s disease (CD) and controls (CT) by in situ hybridisation

U, ulcerations; ND, not determined; UACL, ulcer associated cell lineage.
controls (CT) by immunohistochemistry.

Table 2 Mucin expression in the ileal mucosa of patients with Crohn's disease (CD) and controls (CT) by immunohistochemistry

<table>
<thead>
<tr>
<th>Antibody</th>
<th>MUC2</th>
<th>MUC5AC</th>
<th>MUC5B</th>
<th>MUC6</th>
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<td>Healthy ileum</td>
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<td>−</td>
<td>−</td>
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<td>Involved ileum (close to U)</td>
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</tr>
<tr>
<td>CD 13</td>
<td>Involved ileum (close to U)</td>
<td>+++</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
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<td>−</td>
<td>−</td>
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</tr>
<tr>
<td>CD 18</td>
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<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD 19</td>
<td>Involved ileum (close to U)</td>
<td>+++</td>
<td>−</td>
<td>−</td>
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<tr>
<td>CT 1, 5</td>
<td>Normal ileum</td>
<td>+++</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

*Staining intensity: −, absent; +, weak; ++, moderate; +++, strong.
U, ulcerations; UACL, ulcer associated cell lineage.

MUC5B, MUC6, and MUC7 were not detected in normal ileal mucosa.

Patients with CD

Healthy ileal mucosa. In healthy ileal mucosa in patients with CD, the hybridisation pattern was identical to that observed in normal controls, with main expression of MUC2 and MUC3, lesser expression of MUC1 and MUC4, and no expression of MUC5AC, MUC5B, MUC6, or MUC7 (fig 1A, B).

Involved ileal mucosa. In involved ileal mucosa of patients with CD, the hybridisation pattern was somewhat comparable with that observed in healthy ileal mucosa of the same patients or normal mucosa of controls, regardless of the inflammatory state, with main expression of MUC2 and MUC3, and lesser expression of MUC1 and MUC4. However, the distribution and intensity of the labelling were heterogeneous in a given specimen whatever the probe, with a decrease or an increase in the intensity of the signal depending on the areas examined (fig 1C–E).

Moreover, a particular hybridisation pattern was observed in mucosa adjacent to the ulcerations in the UACL, with appearance of MUC5AC, MUC5B, and MUC6 mRNAs and peptides, and disappearance of MUC2. MUC6 mRNAs and peptides were observed in acinar cells of the new lineage arising from crypts adjacent to the ulcerations and in the lower part of the ducts arising from these acini (figs 1F, 2A, 2B). MUC5AC mRNAs and peptides were observed essentially in epithelial cells of the surface and the upper part of the ducts (figs 1G–I, 2C, 2F). MUC5B mRNAs and peptides were only occasionally detected throughout the UACL (fig 2D). In contrast, MUC2 mRNAs and peptides were not detected in the UACL whereas a strong signal was observed in the surrounding mucosa within goblet cells (figs 1J, 1K, 2E, 2G).

MUC4 mRNAs were detected in surface and duct cells but not in acinar cells (fig 1L). MUC3 mRNAs were observed in all epithelial cells of the lineage although the most intense signal was confined to surface and upper duct cells (fig 1M, 1N). Weak mRNA expression of MUC1 was also detected throughout the UACL (fig 1O).

Overlap between MUC6 and MUC5AC hybridisation patterns was observed in some portions of the ducts. A signal was also detected with the MUC1, MUC3, MUC4, and MUC5B probes in the same duct cells.

MUC7 was not detected in involved ileal mucosa of patients with CD by in situ hybridisation.

Discussion

We have used in situ hybridisation and immunohistochemistry to analyse expression of the mucin genes in the ileum of 19 patients with CD. To our knowledge, the only other study describing cell specific expression of mucin genes in CD was performed by Weiss and colleagues who analysed MUC2 and MUC3 mRNA expression in intestinal mucosa of seven patients and reported a normal hybridisation pattern regardless of whether the mucosa manifested active or quiescent inflammation.

In this study, we showed that the healthy ileal mucosa of patients with CD displayed a normal hybridisation pattern with main expression of MUC2 and MUC3, with MUC2 being expressed in goblet cells on villi and in crypts, and MUC3 in both goblet and absorptive cells essentially on villi. MUC1 and MUC4 were only occasionally detected in normal and healthy ileal mucosa, probably due to the location of the sample (proximal or distal) along the ileum, as suggested previously. Indeed, MUC1 and MUC4 are not seen in the intestine, except in the ileum and colon, and also in duodenal Brunner’s glands for MUC1 only. MUC5AC, MUC5B, MUC6, and MUC7 were never detected in normal or healthy ileal mucosa. These findings are in accordance with previous reports of mucin gene expression in the small intestine.

In the involved ileal mucosa of patients with CD, although the hybridisation pattern was comparable with that observed in healthy ileal mucosa and normal controls with main expression of MUC2 and MUC3 and lesser expression of MUC1 and MUC4, the distribution and intensity of the labelling were heterogeneous depending on the areas examined. This heterogeneity probably reflects typical cytological changes that accompany CD.

More interestingly, we showed that at least six mucin genes, MUC1, MUC3, MUC4, MUC5AC, MUC5B, and MUC6, were expressed in involved ileal mucosa adjacent to ulcerations in the so-called UACL. This lineage can be seen in all diseases of the gastrointestinal tract with chronic mucosal ulceration but most commonly is found in the small intestine in CD and duodenal ulcer disease. In the intestine, it grows out from the base of crypts adjacent to ulcers and ramifies in the lamina propria to form a new gland, finally giving rise to a duct by which glandular secretions are carried to the surface. Epithelial cells from the duct continue their migration onto the villus surface to restore the epithelium.
Figure 1  In situ hybridisation for mucin gene mRNAs in ileal mucosa of patients with Crohn's disease. (A, B) In situ hybridisation for MUC2 (A) and MUC3 (B) mRNAs in healthy ileal mucosa. (A) With the MUC2 probe, labelling was strong and located in the perinuclear region of goblet cells both on villi and in crypts whereas in (B) with the MUC3 probe, labelling was of moderate intensity and located in goblet and absorptive cells on villi (magnification ×200). (C–E) In situ hybridisation for MUC2 (C), MUC3 (D), and MUC4 (E) mRNAs in involved ileal mucosa showing the heterogeneity of the labelling in a given specimen (magnification (C) ×200, (D and E) ×100). (F–O) In situ hybridisation for MUC6 (F), MUC5AC (G–I), MUC2 (J, K), MUC4 (L), MUC3 (M, N), and MUC1 (O) mRNAs in involved ileal mucosa adjacent to ulcerations in the ulcer associated cell lineage (UACL). (F) MUC6 mRNA was observed in newly formed acinar glands of the lineage. (G–I) MUC5AC mRNA was observed in epithelial cells of the upper part of the ducts that have reached the luminal surface and migrate onto the villus surface with the 35S labelled MUC5AC probe (G, I) whereas hybridisation signal was absent with the 35S labelled MUC5AC probe and a large excess of unlabelled MUC5AC probe (H) (negative control). (J, K) MUC2 mRNA was not detected in acinar (J) or surface cells (K) of the new lineage whereas a strong signal was observed in the surrounding goblet cells. (L) A weak signal was observed with the MUC4 probe in epithelial cells of the surface and the ducts. (M, N) A weak signal was observed in epithelial cells of the surface and the ducts with the 35S labelled MUC3 probe (M) whereas hybridisation signal was absent with the 35S labelled MUC3 probe and a large excess of unlabelled MUC3 probe (N) (negative control). (O) A weak signal was observed with the MUC1 probe in epithelial cells of the UACL (magnification (F–I, K–N) ×200, (J) ×100, (O) ×400; all sections were counterstained with methyl green pyronin).
although this lineage has long been regarded as “pyloric” or “Brünner’s gland” metaplasia based on morphological criteria and histochemistry, it is now widely accepted that the UACL is a unique cell lineage which develops de novo and not by metaplasia. The UACL secretes large amounts of neutral mucins in contrast with intestinal goblet cells which secrete acid mucins. We showed that the UACL expressed \( \text{MUC1} \) mRNAs, confirming the finding of a previous immunohistochemical study using antibodies raised against different parts of the mucin core protein (SM3, HMFG1, and HMFG2).\(^2^0\) The UACL also expressed \( \text{MUC3} \) and \( \text{MUC4} \) mRNAs encoding large membrane anchored mucins.

Of the chromosome 11p15 mucin genes encoding gel forming secreted mucins, \( \text{MUC5AC}, \text{MUC6}, \) and to a lesser extent \( \text{MUC5B} \) mRNAs and peptides which are not expressed in normal adult ileum were abnormally expressed in the UACL whereas \( \text{MUC2} \) which is a major mucin gene expressed in normal intestine was not expressed in the UACL. These findings suggest a possible role for at least \( \text{MUC5AC} \) and \( \text{MUC6} \) in wound healing after chronic mucosal ulceration. Moreover, the UACL is a differentiating cell lineage\(^2^0 \) and epithelial cells showed distinct expression patterns of the mucin genes according to their position within the lineage. \( \text{MUC5AC} \) is expressed in epithelial cells of the surface and the upper part of the ducts whereas \( \text{MUC6} \) is expressed in epithelial cells of acinar glands and the deeper part of the ducts. In the normal gastrointestinal tract, \( \text{MUC5AC} \) and \( \text{MUC6} \) are the major mucin genes expressed in adult stomach, where \( \text{MUC5AC} \) is expressed in all epithelial cells of surface and pits and \( \text{MUC6} \) is expressed in mucous neck cells and in cardial and antral glands.\(^1^4 \) \( \text{MUC6} \) is also widely expressed in duodenal Brünner’s glands.\(^1^9 \) Moreover, \( \text{MUC5AC} \) is temporarily expressed in embryonic and fetal intestine.\(^2^3 \) \( \text{MUC5AC} \) is also expressed with \( \text{MUC6} \) and \( \text{MUC5B} \) in embryonic and fetal stomach and duodenum, preceding epithelial cytodifferentiation.\(^1^9 \)\(^2^4 \)\(^2^5 \) The expression pattern of the mucin genes in
the UACL is therefore very similar to that observed in adult stomach and duodenum but more closely resembles that of developing stomach and duodenum, confirming a pr

Mucins are characterised by a large central region composed of tandemly repeated motifs rich in serine and threonine residues (potentially highly O-glycosylated). In gel forming mucins, this region is flanked by cysteine rich domains similar to the D, B, C, and CK (cysteine knot) domains of von Willebrand factor (vWF). D and CK domains are thought to be important for dimer and oligomer formation. Recently, Tomasetto and colleagues have demonstrated direct interaction between murine TFF1 and murine gel forming mucins Muc2 and Muc5ac through their two vWF-like C domains. It is therefore tempting to speculate that each mucin is partnered with one specific TFF. In this context, in the gastrointestinal tract, TFF1 might be mainly associated with MUC5AC, TFF2 with MUC6, and TFF3 with MUC2. Supporting this hypothesis, in vitro combination of TFF3 and gastric mucin (of which major glycoprotein components correspond to MUC5AC and MUC6) has been shown to be less effective than one with colonic mucin (essentially composed of MUC2 glycoproteins). However, the vWF-like C domains are lacking in the carboxy terminal region of MUC6, suggesting that additional sequences in mucins may interact with trefoil factors or that MUC6 does not interact with trefoil factors.

In conclusion, we have shown that the 11p15 mucin gene cluster in a range gel forming mucins display an abnormal expression pattern in patients with CD in the involved ileal mucosa adjacent to ulcerations, with appearance of MUC5AC, MUC6, and MUC3, and disappearance of MUC2. Our findings suggest that gel forming mucins (more particularly MUC5AC and MUC6) may have a role in epithelial wound healing after mucosal injury in inflammatory bowel diseases in addition to mucosal protection and may contribute with trefoil factors to epithelium restitution.

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