INFLAMMATORY BOWEL DISEASE

Altered colonic glycoprotein expression in unaffected monozygotic twins of inflammatory bowel disease patients

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Background and aims: Previous chromatographic analysis of colonic mucins from monozygotic twins with inflammatory bowel disease (IBD) suggested a genetic mucin alteration in ulcerative colitis (UC). This study explores this further by assessing mucosal expression of the oncofetal carbohydrate antigen TF (galactose β1, 3 *N*-acetylgalactosamine α-), among the same IBD twins.
Materials and methods: Formalin fixed paraffin embedded rectal biopsies were studied from 22 monozygotic twin pairs with IBD. These included eight UC twin pairs and 14 Crohn's disease (CD) twin pairs, with six pairs concordant for disease and 16 unaffected twin siblings. Closely adjacent sections were assessed by peanut lectin histochemistry for TF expression and immunohistochemically for nuclear factor κB (NFκB) activation with investigators blinded to the diagnosis.
Results: Unaffected twins were almost all TF positive (15/16) compared with 5/29 histologically normal controls ($p<0.0001$). Unaffected UC (7/8) and CD twins (8/8) were similarly TF positive. TF positivity was confined mainly to the superficial epithelium and absent from the stem cell compartment of the lower crypts, suggesting that glycosylation changes are acquired rather than genetically determined. Activated NFκB was present in the surface epithelium of mucosal biopsies from 13/14 unaffected IBD twins but in only 6/22 histologically normal controls ($p=0.0004$). All 22 affected IBD twins were TF positive and 18 were positive for activated NFκB.
Conclusions: Altered mucosal glycosylation in unaffected identical twins of IBD patients was confirmed in this study. This occurred in both UC and CD twins. The changes are probably acquired rather than congenital and may reflect ''preinflammatory'' NFκB activation.

It is a plausible hypothesis that ulcerative colitis (UC) might, at least in part, be a consequence of a defect in the colonic mucus barrier.[1 2] Evidence in support of this came from studies showing selective depletion in a subgroup of mucus glycoproteins, as defined by ion exchange chromatography.[1] Although there were some uncertainties about the interpretation of the ion exchange chromatography,[3 4] it had already been shown that mucins from UC colon samples had relatively short oligosaccharide side chains[5] and more detailed analysis confirmed the presence of altered mucus glycoprotein glycosylation in inflammatory bowel disease.[6–8] Subsequent studies showed increased expression of the oncofetal Thomsen-Friedenreich (TF) carbohydrate antigen (galactose β1,3 *N* acetyl galactosamine α-)[6 9] and reduced mucin sulphation.[10 11]

The biological significance of altered mucosal glycosylation in the pathogenesis of inflammatory bowel disease (IBD) is unclear. Abnormal expression of specific carbohydrate epitopes by epithelial cell mucins may allow interactions with luminal lectins of microbial or dietary origin.[12] These changes may promote alterations to the mucosa associated bacterial flora or allow dietary lectins to promote a hyperproliferative epithelial response.[13–15]

The finding that the selective defect in a mucin fraction defined by ion exchange chromatography was frequently shared by healthy monozygotic twin siblings of patients with UC suggested a possible genetic basis for this mucin abnormality.[16] We have further examined glycosylation abnormalities in the original cohort of IBD twins using histochemical techniques that allow assessment of mucosal localisation of glycosylation changes.

MATERIALS AND METHODS

Monozygotic twins

The original cohort of monozygotic twins with IBD was identified by matching the Swedish Twin Registry with the Swedish hospital discharge register, and consisted of 80 monozygotic or dizygotic twin pairs.[17]

The present study utilised formalin fixed paraffin embedded rectal biopsies from 22 monozygotic twin pairs with IBD. Six of the pairs, four with Crohn's disease (CD) and two with UC, were concordant for disease. Rectal biopsies were available from all 16 unaffected twin siblings, eight twins having a sibling with UC and eight having a sibling with CD, and from 22 of 28 affected twins. Affected twins were in clinical and endoscopic remission at the time of rectal biopsy.[17] Unaffected twin siblings had no past history of IBD and had a normal rectal mucosa macro- and microscopically. They had remained healthy for a mean of 21.4 (range 8–40) years after diagnosis of their sibling with UC and for a mean of 14.9 (range 7–31) years after diagnosis of their sibling with CD.

Control subjects

Rectal biopsies from controls with a normal mucosa ($n = 19$) were obtained from the archive of the Pathology Department, Royal Liverpool University Hospital, UK. These were patients who had undergone colonoscopy or flexible sigmoidoscopy

Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; NFκB, nuclear factor κB; TF, Thomsen-Friedenreich; PNA, peanut lectin

for investigation of colonic symptoms with a final diagnosis of irritable bowel syndrome (n = 12) or unexplained rectal bleeding, presumed haemorrhoidal (n = 7), and who had macroscopically and microscopically normal colonic mucosa. Additional rectal biopsy samples were obtained as positive control tissues from Liverpool UC patients (n = 20). Subsequently, additional Swedish control samples were obtained from individuals with normal mucosa (irritable bowel syndrome, n = 10), UC patients (n = 11), and colon cancer (n = 3). This allowed for exclusion of any histochemical alterations that might have resulted from differences in fixation or processing of tissue prepared in Liverpool and Örebro. All mucosal samples had been fixed in 10% neutral buffered formal saline.

Peanut lectin histochemistry

Expression of TF antigen was determined using lectin histochemistry employing peroxidase conjugated peanut lectin (PNA peroxidase; Sigma, St Louis, Missouri, USA).[9] Briefly, sections were dewaxed, rehydrated through graded alcohols, and endogenous peroxidase activity quenched with 3% hydrogen peroxide in methanol. Sections were then incubated at room temperature for one hour with PNA peroxidase (1 in 200 dilution of stock solution, final concentration 5 μg/ml in phosphate buffered saline). After washing in phosphate buffered saline, bound lectin conjugate was visualised using diaminobenzidine.

Immunohistochemistry for activated nuclear factor κB (NFκB)

Immunohistochemistry for activated NFκB was performed using a monoclonal antibody (MAB3026; Chemicon Europe, Chandlers Ford, UK) directed against an epitope of the NFκB, p65 subunit, that is only revealed following release from IκB during the activation process.[18] Following antigen retrieval by microwaving in citrate buffer, pH 6.0, and blocking of endogenous peroxidase, biotin, and protein interactions, sections were incubated with the primary antibody at a concentration of 2.5 μg/ml overnight at 4℃. Sections were then incubated with biotinylated rabbit antimouse Fab_2 secondary antibody (Dakocytomation, Ely, UK) followed by streptavidin biotin peroxidase complexes, (Dakocytomation) both for 30 minutes at room temperature, and visualised with diaminobenzidene.

For both staining techniques, all Swedish twin and control and Liverpool control slides were stained together.

Histological assessment

Sections were scored simultaneously by two observers: KB and JMR for TF, and FC and JMR for NFκB, both blinded to patient diagnosis, who reached an agreed score that was then reconfirmed by the third observer, still blinded. For PNA histochemistry, sections were designated as having either positive or negative staining and were also scored semiquantitatively (graded 0–3). Histochemistry for activated NFκB was graded (0–3) for surface epithelium. Staining of activated NFκB within inflammatory cells was noted in control UC and cancer sections but not included in the final analysis as the hypothesis under assessment was whether NFκB activation within surface epithelial cells could be a marker of inflammatory changes that could have led to acquired alterations in epithelial glycosylation.

Statistical analysis

Comparison of proportions of positively stained sections between the patient groups were made using Fisher's exact test and between histochemical scores by the Mann-Whitney U test. Correlation between gradings for PNA histochemistry and for NFκB immunohistochemistry on adjacent samples from the same subjects was made using the Spearman rank correlation test. All analyses were two tailed with a p value of <0.05 regarded as significant.

Ethics approval

Ethics approval for the Swedish biopsies was given by the Ethics Committee of Örebro County and for study of the Liverpool tissue samples by the Liverpool Adult Research Ethics Committee.

RESULTS

Positive staining for TF antigen was an invariable finding among the 22 affected monozygotic twins with IBD (table 1, fig 1), irrespective of whether the patient had UC or CD. Staining was generally localised to the supranuclear region plus a variable degree of staining of the glycocalyx and of surface secretory material. A similarly high prevalence of PNA positivity (15/16) was observed among unaffected twin siblings of IBD patients (fig 1A, B). In comparison, only five of 29 healthy controls ($p<0.0001$, 5/19 Liverpool controls and 0/10 Örebro controls) had evidence of PNA positivity within rectal mucosa, with staining exclusively confined to the supranuclear cytoplasmic region. Median TF score was also significantly higher in unaffected twins (median score 2 on 0–3 scale) compared with healthy control subjects (median score 0; $p<0.0001$).

Evidence of NFκB activation (fig 2) was seen in the surface epithelium of 13/14 (two not done) unaffected IBD twins. Activated NFκB was also seen in some histologically normal controls but less frequently (6/22; $p = 0.0004$), and at lower intensity (median score on a scale of 0–3, 0 for controls and 2 for healthy IBD twins; $p = 0.0002$).

There was a strong correlation across all samples analysed between PNA grading and NFκB grading in biopsies from the same subject (Rho = 0.43, $p<0.0001$). One identical twin, who did not have clinical or histological IBD at the time of biopsy for this study, has subsequently developed UC and primary

Table 1 Expression of Thomsen Friedenreich (TF) carbohydrate antigen and activated nuclear factor κB (NFκB) by surface epithelium of twin and control rectal mucosal biopsies

	TF expression			Activated NFκB		
	n	Positive (n)	Median score	n	Positive (n)	Median score
Affected UC twins	8	8	2	8	5	1
Unaffected UC twins	8	7	1.5	7	6	2
Affected CD twins	14	14	2	14	13	2
Unaffected CD twins	8	8	2	7	7	1
Normal mucosa controls	29	5	0	22	6	0
UC controls	31	24	1	24	13	1
Cancer controls	3	3	1	3	3	2

UC, ulcerative colitis; CD, Crohn's disease.

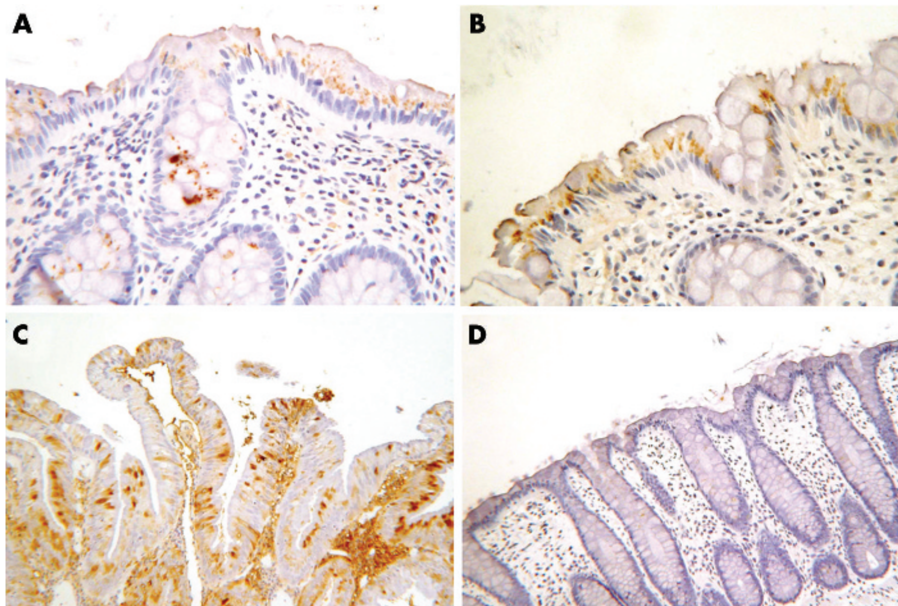

Figure 1 Rectal mucosal expression of Thomsen Friedenreich (TF) antigen (galactose β1,3 N acetyl galactosamine α-) using peanut lectin (PNA) histochemistry. Supranuclear staining is seen in a subject in remission from ulcerative colitis (A) and in their healthy (unaffected) monozygotic twin sibling (B). Strong TF expression is also seen in colorectal cancer control tissue (C) but negative staining in a control subject with irritable bowel syndrome (D).

sclerosing cholangitis. Biopsies from this individual were scored 2+ for both PNA and activated NFκB in this study.

DISCUSSION

In this study, almost all of the unaffected twins possessed the same colonic mucosal glycosylation abnormality as their genetically identical twins who were affected by IBD. The altered glycosylation was seen equally in UC and CD twins. It was predominantly seen in the surface epithelium whereas genetic changes in glycosylation would be expected to originate from the stem cell compartment and therefore to affect whole crypts, as for example is seen with mutations identifiable using *Dolichos biflorus* lectin[19] or mild periodic acid Schiff[20] staining techniques.

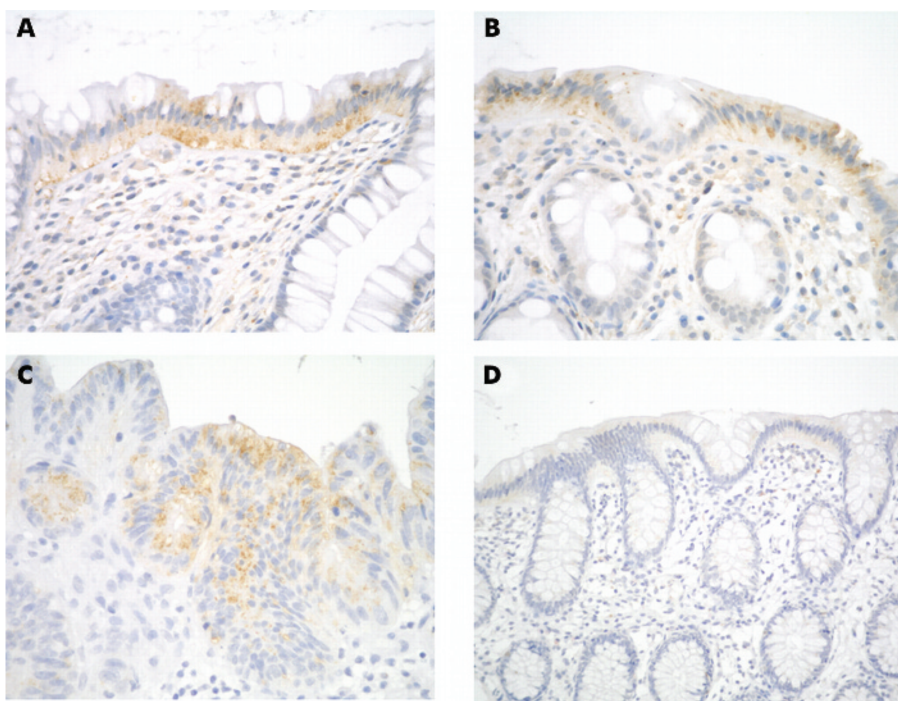

Figure 2 Rectal mucosal expression of activated nuclear factor κB (NFκB) using immunohistochemistry. Activated NFκB is seen, predominantly within the cytoplasm, of a subject in remission from ulcerative colitis (A) and in their healthy (unaffected) monozygotic twin sibling (B). Expression of activated NFκB is also seen in colorectal cancer control tissue (C) but negative staining in a control subject with irritable bowel syndrome (D). These examples are illustrative and are not from the same cases as in fig 1 but a strong correlation ($p<0.0001$) was seen between activated NFκB immunostaining and peanut lectin staining in samples from the same subjects.

Mucosal glycosylation changes can be seen not only in UC and CD but even in diverticulitis[21] and presumably can be acquired as a consequence of inflammation. Careful inspection of the mucosal biopsies from unaffected twins showed no increase in inflammatory cells within the crypt or surface epithelium, or within the lamina propria. Subsequent immunostaining did, however, show that activated NFκB could be identified in all but one of the unaffected IBD identical twins and there was a strong correlation across all samples studied between PNA positivity and evidence of NFκB activation. Although inflammatory cells within the lamina propria were often seen to express activated NFκB in IBD tissue samples, as reported by others,[22] epithelial NFκB activation in the unaffected monozygotic twins was largely confined to the surface, implying that it may have occurred as a result of interaction between the surface epithelium and some intraluminal component(s). Candidates for such components could include bacteria or bacterial products,[23] or even immunoglobulin, shown previously to be adherent to the luminal aspect of the surface epithelium in UC.[24] One would then have to postulate that some additional trigger would still be required to induce clinically and histologically significant inflammation.

Increased mucosal expression of oncofetal carbohydrate antigens has been reported previously, not only in both UC and CD[9] but also in colorectal cancer and adenoma and hyperplastic colonic polyps.[25] Its mechanism has been best studied in cancer where the glycosylation abnormalities have been shown to correlate poorly with Golgi glycosyltransferase activity.[26] Similar changes can however be induced in well differentiated goblet cell lines by agents such as bafilomycin which prevent the normal Golgi acidification by blocking its proton pump.[27] This has been shown to disrupt the normal Golgi organisation leading to relocalisation of glycosyltransferases. In the normal situation, proteins undergo progressive glycosylation as they pass from the cis to trans Golgi. When the Golgi organisation is disrupted, the protein acceptor no longer meets each appropriate glycosyltransferase in the appropriate sequence to ensure normal glycosylation. Such disruption has been shown to occur in human colorectal cancer[28] and is a plausible explanation for the poor correlation between glycosylation changes and glycosyltransferase activity. It is not yet clear whether similar Golgi disruption occurs in inflamed epithelia but tumour necrosis factor α has been shown to cause significant changes in glycosylation in vitro.[29]

The glycosylation changes seen in this study, as in others using lectin histochemistry to assess glycosylation in IBD, are not confined to goblet cell mucins but are seen in the Golgi (supranuclear) region of non-goblet epithelial cells, particularly in the surface epithelium. The question follows as to how the current study fits with demonstration of altered mucus chromatography in unaffected UC, but not CD, identical twins.[16] The latter study depended on ion exchange chromatography performed with a discontinuous salt gradient to separate mucin fractions by charge. There are some difficulties in the interpretation of this technique. Firstly, the discontinuous salt gradient tends to produce as many fractions as there are steps in the gradient.[3] Moreover, the same technique when applied previously to rodent mucin resulted in most of the colonic mucin, which is predominantly acidic as a result of sialylation and/or sulfation, eluting in the same fraction that was subsequently shown to be depleted in UC.[30] When a continuous salt gradient was used for ion exchange chromatography in a subsequent study of UC and control mucin, most of the mucin eluted with relatively high salt as before but with no significant difference found between inactive UC and control.[4] Mucus glycoproteins are notoriously difficult to purify free from contaminating glycoproteins and proteoglycans and it seems plausible that the apparent selective depletion of a mucin fraction (fraction IV) seen in UC and UC twins in fact represents overall mucus depletion. This is nevertheless important and again would be compatible with subclinical inflammation in the unaffected twins as the goblet cell depletion that occurs in UC is probably driven by inflammation. Lack of any ion exchange chromatographic abnormality in CD would then be a reflection of the well established lack of goblet cell depletion seen in this condition, even in the presence of inflammation, a phenomenon that could be a result of neutrophil dysfunction.[31]

In conclusion, changes in mucosal glycosylation occur strikingly commonly in the unaffected identical twins of individuals with CD and UC. These changes seem to be acquired rather than a consequence of inherited abnormalities in glycosylation. They probably reflect subclinical ''preinflammatory'' changes in the surface epithelium that result from interaction with intraluminal factors in genetically predisposed individuals.

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EDITOR'S QUIZ: GI SNAPSHOT

Answer

From question on page 932

Computed tomography scan demonstrated a duodenal mass intussuscepting into the jejunum causing obstruction. The scan showed a dilated duodenum and due to the retroperitoneal fixation of the duodenum, the intussusception appeared as two separate masses at the genu inferius (A in fig 1) and duodenojejunal junction (B in fig 1). The classic radiological presentation of intussusception is the coiled spring appearance; this was poorly visible in the duodenum because it was fixed to the retroperitoneum. As a result, while the leading edge of the intussusception was found at the duodenojejunal junction, part of the intussusception remained above the junction of the first and second part of the duodenum (the genu inferius) often resulting in the appearance of two separated masses.

The patient underwent surgery and the intussusception was reduced. A pancreas preserving duodenectomy (PSD) with resection of the proximal jejunum was then performed. She made an uneventful recovery. Pathology revealed a malignant change in a villous adenoma (fig 2). Despite a strong familial adenomatous polyposis (FAP) family history, no family member had undergone duodenal surveillance.

Duodenal cancer is the leading cause of cancer related death in patients with FAP who have undergone colectomy. Most patients will develop adenomatous duodenal polyps yet only 5% progress to cancer. In order to predict outcome, Spigelman stratified duodenal disease based on number, size, and histopathology. Intervention is recommended in patients with stage IV disease where 36% will develop carcinoma. Intervention for FAP patients with duodenal polyposis has ranged from endoscopic ablation to

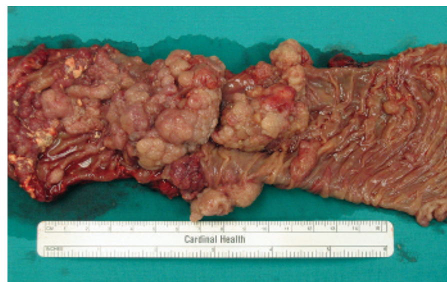

Figure 2 The specimen following a pancreas sparing duodenectomy demonstrating the large villous adenoma.

pancreaticoduodenectomy. Local therapy is associated with recurrences rates of up to 100% and does not alter disease progression. Pancreaticoduodenectomy or PSD both offer definitive therapy in preventing duodenal carcinoma. PSD has been used infrequently for the management of FAP although it offers the potential advantage of preserving the normal pancreas without additional morbidity.

Our patient demonstrated the rare finding of a duodenal intussusception—there are only a few case reports in the literature. More importantly, the case emphasises the fact that all FAP patients should be entered into an upper gastrointestinal surveillance programme.

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