South Asian and European colitics show characteristic differences in colonic mucus glycoprotein type and turnover

C S J Probert, B F Warren, T Perry, E H Mackay, J F Mayberry, A P Corfield

Abstract

South Asians in Britain have a high incidence of ulcerative colitis and a low incidence of colorectal cancer. The pattern of mucus production in 12 South Asian and 16 European colitics and a control group of 19 South Asians was studied. Three types of mucin were identified after organ culture of colonic biopsy specimens with a dual label of [3H]-glucosamine and sodium [35S]-sulphate: type A had a high [35S]:[3H] ratio and high incorporation ([3H] dpm/μg DNA >500); type B had a low ratio and high incorporation; and type C had low incorporation but with either high (C1) or low (C2) ratios. European colitic mucins show a significant reduction in the level of sulphation detected by mucin histochemistry with high iron diamine/Alcian blue staining, together with predominantly type B or C2 mucins (low sulphation). South Asian colitics showed histochemically normal patterns of high sulphation and largely type A and C1 mucins (high sulphation). There was no correlation of mucin type with disease activity index in either ethnic group. The appearance of apparently normal mucin in patients with ulcerative colitis may be a useful marker for the identification of a subgroup at low risk of colorectal cancer.

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Keywords: ulcerative colitis, mucus glycoprotein type, South Asian, European.

Ulcerative colitis is a chronic inflammatory disorder of the large bowel, associated with bloody diarrhoea and an increased risk of developing colorectal carcinoma, which occurs in approximately 0·1% of the European population. 

Recent epidemiological studies have shown that South Asians in Britain— that is, those people whose families originated in India, Pakistan, or Sri Lanka, and particularly Hindus— have a greater incidence of ulcerative colitis than Europeans. 

Colorectal carcinoma, however, seems to be relatively uncommon in South Asians, both in Britain and South Asia. 

The mucins produced and secreted by normal colon mucosal cells are rich in sulphate and sialic acids. In man these sialic acids are characteristically O-acetylated. 

Both sulphation and sialic acid O-acetylation are related to the rate of mucin degradation by enteric bacterial enzymes underlining the importance of these characteristic structural features in normal colonic mucin.

Changes in the metabolism of colonic mucous glycoproteins have been implicated in ulcerative colitis. Histological studies have identified goblet cell depletion and a reduction in staining for sulphated mucin in goblet cell vesicles associated with ulcerative colitis. 

Biochemical analysis of the mucins by metabolic labelling has confirmed the loss of sulphation and also suggested that alteration in the turnover of the secreted mucin fraction may be an important factor in the disease. 

A further post-translational modification, sialic acid O-acetyl ester formation, is known to vary within the normal population and with ethnic background. Such O-acetylation may be modified in ulcerative colitis and is lost in cancer.

This study aimed, firstly, to assess whether the sulphation and O-acetylation of mucins in South Asian colitics were linked with their increased susceptibility for ulcerative colitis when compared with European colitics, and secondly, to determine the value of mucin analysis in the identification of mild and severe disease, thus improving detection of high risk patients.

Methods

PATIENTS

Fifty four South Asians from the Leicestershire database were contacted by post and asked to take part; 11 accepted. Sixteen Europeans attending outpatient clinics in Leicester and Gloucester and a further South Asian from Gloucester agreed to take part in the study. All had established ulcerative colitis of at least 6 months’ duration. The disease activity, scored as noted below, ranged from inactive to severely active. Biopsy specimens from 19 normal South Asian controls were obtained from Leicester; the biopsy specimens were taken during clinical investigation for diarrhoea and had been found to be normal.

MATERIALS

Radioactive materials [3H]-glucosamine (740 GBq/mmol) and sodium [35S]-sulphate (2·04 GBq/mmol) were obtained from Amersham International plc, Amersham, UK. Cell culture products were purchased from Gibco Ltd, Edinburgh, Scotland. Sepharose CL 2B and
South Asian and European colitics show characteristic differences in colonic mucus glycoprotein type and turnover

HiSafe 3 were products of Pharmacia/LKB, Milton Keynes, UK. Hoechst dye 33258 was purchased from Hoeffer Scientific, Oxford, UK. Coomassie Protein assay reagent was obtained from Pierce and Warinr, Chester, UK. Chondroitinase ABC was obtained from Boehringer Mannheim, Lewes, UK. Hyaluronidase, heparinase types II and III from Flavobacterium heparinum, guanidine hydrochloride, caesium chloride, and other analytical grade biochemicals were obtained from the Sigma Chemical Co Ltd, Poole, UK.

METHODS

Tissue

Paired rectal mucosal biopsy specimens were obtained at rigid sigmoidoscopy. One was maintained at room temperature during transport to the laboratory, before incubation at 37°C. It was dissected to separate the mucosal layer from the muscularis mucosae. The other was submitted for histology.

Histology

All mucosal biopsy specimens were fixed in 10% buffered formalin, processed routinely, and sectioned at 2 µm. Specimens were stained with haematoxylin and eosin, high iron diamine/Alician blue and mild periodic acid Schiff (PAS) with and without saponification. High iron diamine/Alician blue staining was carried out using fresh 60% ferric chloride solution. Staining was performed in large batches and a standard control block was used each time. This comprised normal jejunum, gastric body, and right colon with known staining patterns.33 This method stains sulphated mucus dark brown and non-sulphated sialemucin pale blue. The pattern of staining in the goblet cell mucin, the glycoalkys, and in secreted mucin was studied. The mild PAS method stains 7–9 O-acetylated sialemucins.9 11 12 34 Saponification was performed using 0·1 M potassium hydroxide for 30 minutes at 20°C. The presence of 7–9 O-acetylation is indicated by an increase in staining intensity after saponification, and is present in most people in all races studied.30 35 The absence of O-acetylation results in no increased staining intensity after saponification.7 12 36 The sections were scored on a scale of 0–4 according to staining intensity and numbers of crypts stained. Biopsy specimens from one South Asian and two European patients were too small to assess histologically.

Diagnostic histological criteria for ulcerative colitis

A biopsy diagnosis of ulcerative colitis was made if the large bowel mucosa had branched and shortened crypts with diffuse chronic inflammation in the lamina propria were seen. Active disease was signified by the presence of neutrophils and consequent mucus depletion. Activity was scored on the Bristol histological disease activity index for ulcerative colitis33 as shown in Table I.

TABLE 1 Bristol histological disease activity index for ulcerative colitis. The features used to determine the overall score of disease activity in ulcerative colitis patients are divided into acute and chronic inflammation as described.33 The highest possible score is 4 (acute) × 2 (chronic) = 6 overall

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>Acute</th>
<th>Chronic</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>PMN in lamina propria</td>
<td>1</td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td>PMN in crypt wall</td>
<td>2</td>
<td>Severe</td>
<td>2</td>
</tr>
<tr>
<td>Crypt abscesses</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crypt destruction</td>
<td>4</td>
<td></td>
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<tr>
<td>Maximum</td>
<td>4</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Overall maximum sum= 6</td>
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</table>

PMN = polymorphonuclear cells.

Organ culture

Organ culture was carried out as described before.37 Briefly, dissected mucosal tissue was cut into squares of approximately 3 mm². The squares were placed on lens tissue over a stainless steel supporting grid to allow easy collection of any secreted, adherent mucus gel formed around the tissue squares during culture. Up to six tissue squares were incubated per dish with the radioactive precursors 370 kBq [3H]-glucosamine and 925 kBq sodium [35S]-sulphate for each dish. After 24 hours at 37°C, the medium was removed; the tissue was washed with 1 ml of phosphate buffered saline (PBS) containing 1 mM phenyl methyl sulphonyl fluoride, 5 mM EDTA, 10 mM benzidine hydrochloride, 0·1 mg/ml soybean trypsin inhibitor, and 10 mM N-ethylmaleimide (PBS-protease inhibitor buffer); and any adherent surface mucus was separated from the squares, using forceps if necessary. The tissue squares were removed and the lens tissue was carefully washed in the same buffer to collect additional adherent mucus. The medium and PBS washings were combined and dialysed against distilled water at 4°C (secreted fraction containing soluble and adherent mucus). Tissue was homogenised in 1 ml of PBS-protease inhibitors; an aliquot (20 µl) was taken for DNA determination and the remainder was centrifuged to yield the cellular soluble fraction and the total membranes.

Gel filtration

Aliquots of the secreted fraction (2 ml) and cellular soluble fraction (0·8 ml) for all culture incubations were separated on Sepharose CL 2B, and fractions were collected as described.33 The [35S] and [3H] contents of all fractions were measured and the high molecular weight peak eluting at the Vo was quantified and pooled.

Density gradient centrifugation

Density gradient centrifugation was carried out by the method of Carlstedt et al.38 Radio-labelled high molecular weight Vo samples containing at least 10 000 cpm of [35S]-sulphate were dissolved in PBS/4M guanidine hydrochloride, the density was adjusted to
TABLE II

<table>
<thead>
<tr>
<th>Patient no</th>
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<th>Glycocalyx Score</th>
<th>Secreted Score</th>
<th>Score (HDAI)</th>
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<td>+++</td>
<td>+++</td>
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</tbody>
</table>

Staining was carried out as in the methods. The results are expressed on a scale of 0 to +++ for HID and AB staining methods. The score for the histological disease activity index (HDAI) was determined as detailed in Table I.

Enzyme digests

Digestion with chondroitinase ABC at a concentration of 5 units/ml was with the dual labelled mucin fractions from Sepharose CL 2B in 250 mM Tris/HCl, 176 mM sodium acetate, 250 mM NaCl pH 8.0 at 37°C for 15 hours. Samples containing dual labelled mucin were incubated with testicular hyaluronidase, 200 units, in 0.1 M NaCl, 0.05 mg/ml bovine serum albumin, 0.1 M sodium acetate pH 5.2 in a final volume of 300 µl at 37°C for 6 hours. Additional enzyme was added at 2 hours and 4 hours. A mixture of heparinase and heparitinase (0.01 units of each enzyme) was incubated with dual labelled mucin in 10 mM calcium acetate, 100 mM sodium acetate pH 7.0 for 4 hours in a total volume of 250 µl. Pronase digestion of the Sepharose purified mucin at 1 mg/ml enzyme in 20 mM Tris/HCl, 10 mM calcium chloride pH 8.0 was for 24 hours at 37°C. The products of enzyme digestion were analysed by Sepharose CL 2B chromatography.

Other methods

DNA was measured in aliquots of biopsy homogenate after extraction into the aqueous layer of phenol:chloroform:isooamyl alcohol saturated with 0.01 M Tris, 1 mM EDTA, pH 8.0 (Sigma, Poole, UK). The DNA content of the extracts was measured with a fluorometric dye-binding assay, Hoechst 33258 (Hoeffer Technical Bulletin #119, 1992). Protein was measured using the Pierce Coomassie Protein assay, a dye binding assay, and was standardised using bovine serum albumin.

Radioactivity was measured in Hisafe 3 scintillation fluid on an LS 1410 scintillation counter (LKB Wallace) using an [35S][3H] dual label programme for dpm calculation.

STATISTICAL METHOD

Statistical analysis of the disease groups was carried out using the Mann-Whitney U test.

RESULTS

DISEASE ACTIVITY

The histological disease activity index score in most cases was mild to moderate with three giving a score of 5 and one of 6. The median activity score for South Asians was 2 (with an IQR of 1–3) and that for Europeans was 1 (IQR 1–4). There was no significant difference between the two disease groups analysed by the Mann-Whitney U test.

HISTOLOGY

All patients, in both South Asian and European groups, had histological features of ulcerative colitis. High iron diamine/Alcian blue staining showed an excess of sulphated mucin in the Asian colitics irrespective of their disease severity (Table II). European patients with more active colitis had increased amounts of non-sulphated sialomucin, while this was less pronounced in inactive disease (Table II). Seventeen of the 19 South Asian controls were normal, one had minor mucosal prolapse syndrome, and one had melanosis coli. This group showed strong staining with the high iron diamine/Alcian blue stain, indicating high sulphation as typically seen in normal human colonic tissue where no separation on a basis of race was made.

In the South Asian normal control group, 16 (84%) subjects had increased staining with mild PAS after saponification, indicating high 7–9 O-acetylation in these individuals. Ten Asian (91%) and 13 Europeans (93%) subjects with colitis showed this high acetylation pattern.

ANALYSIS OF THE MUCIN FRACTION ISOLATED AFTER ORGAN CULTURE

Analysis of the [35S]:[3H] ratio for the isolated mucin fractions gives an indication of the composition and type of mucin. Any variation in this ratio will indicate a change in mucin composition. The turnover of the mucin during the experiment is given by the amount of [35S] or [3H] incorporated into the isolated mucin relative to DNA or protein, as a measure of the size of the biopsy specimen. This is only a measure of mucin synthesised during the experiment and is not an absolute value for total mucin.

The soluble fraction from the medium and washings (secreted) and homogenate (cellular) was separated by gel filtration on Sepharose CL 2B (Fig I) to give the high molecular weight Vo pool, which contains the mucins.
The pooled Vo secreted and cellular mucin fractions from South Asian and European colitics patients were further analysed to confirm their mucin properties. Samples run on CsCl density gradients showed that more than 90% of the radioactive activity sedimated at densities between 1.35 and 1.45 g/ml, typical of colonic mucins (data not shown).

Digestion of the pooled Vo fractions with proteoglycan degrading enzymes or hyaluronidase resulted in less than 7% conversion to low molecular weight material in all cases when assessed by rechromatography on Sepharose CL 2B (data not shown). This was not significantly different from controls incubated under the same conditions without enzyme. Digestion with pronase resulted in a reduction in molecular weight to partially included peaks on Sepharose CL 2B. Low molecular weight material accounted for less than 5% of the total radioactivity recovered and was not significantly different from samples incubated in buffer without pronase.

**MUCIN LABELLING IN SOUTH ASIAN AND EUROPEAN COLITIS GROUPS**

Analysis of the elution profiles on Sepharose CL 2B showed three different patterns of Vo labelled mucin material, based on high or low [3H]-glucosamine incorporation (dpm/µg DNA >500) and a high or low ([35S]:[3H]) ratio (<0.7) as follows:

*Type A* – where high incorporation was observed with a ratio of [35S]:[3H] close to or more than 1.0, typical for normal mucin (Fig 1A).

*Type B* – a pattern with high incorporation, but with a low [35S]:[3H] ratio, low sulphation (Fig 1B).

*Type C* – a profile where low incorporation ([3H] dpm/µg DNA <500) was found with high (C1) or low (C2) [35S]:[3H] ratios (Fig 1C).

Distribution of the mucin types between patients is shown in Figure 2. The same patterns were observed if [35S]-glucosamine incorporation relative to protein was used ([3H] dpm/µg protein <30). All of the biopsy incubations showed incorporation of the label into glycoproteins excluded or included on Sepharose CL 2B, or both (Fig 1), suggesting that the biopsy specimens were variable. This is important for the type C pattern (Fig 1C) where little or no mucin synthesis (excluded, Vo peak) was found. Specimens which showed no incorporation into material fractionated on Sepharose CL 2B were excluded from this study. Further assays for biopsy viability were not carried out.

With regard to cellular mucins, type A occurred mainly in South Asians, while type B was found exclusively in Europeans. In secreted mucins, however, the distribution was less obvious, with a type C mucin pattern being the most frequent (Fig 2).
The ratio of $[^{35}S]$ to $[^{3}H]$ was greater than 0·7 for the cellular mucin fractions in all (100%) South Asians compared with only 2 (13%) Europeans, $p<0.0001$ (Table II). In contrast, the secreted fraction showed only 5 (42%) Asians and 3 (20%) Europeans with a ratio of 0·7 or higher. The ratio for secreted $v$ cells mucin was significantly different within the South Asian group but not in the Europeans.

The turnover of labelled mucin relative to total biopsy DNA showed higher $[^{35}S]$ incorporation in both secreted and cellular mucin from Asian patients relative to Europeans; this was significantly different in the cellular mucin ($p=0.01$, Table III). Secreted mucin $[^{3}H]$-glucosamine incorporation was higher in the South Asian group but this was reversed for the cellular mucin; neither of these differences was significant. The very high values of $[^{3}H]$-glucosamine incorporation found for secreted mucin in two South Asians and one European were responsible for large interquartile ranges (Table III). Only one of these corresponded with high disease activity. Results expressed relative to the amount of protein instead of DNA showed the same pattern (Table III), indicating that the DNA contribution of inflammatory cells does not seem to influence the results.

The $[^{35}S]$ and $[^{3}H]$ content of mucins samples isolated from organ culture are expressed relative to the total biopsy DNA and protein, as a measure of turnover and the ratio of each isotope in the product. Results are given as the median and interquartile range (IQR). The statistical significance of differences between the groups was calculated using the Mann-Whitney U test and $p$ values derived from this test.

Comparison of the $[^{35}S]$: $[^{3}H]$ ratio in secreted and cellular mucins with disease activity showed no correlation (Fig 3). The cellular mucin showed a significant difference between South Asians and Europeans ($p=0.0005$, Fig 3A). Indeed, ratio values above 0·7 were found in only three Europeans compared with all of the South Asian patients. Furthermore, ratios higher than 0·7 were present in secreted mucin from 42% of the South Asians but only 13% of the Europeans. The difference between these two groups did not reach statistical significance.

**Discussion**

We report here differences in the structure of colonic mucins in South Asian and European ulcerative colitis patient groups. These patients are otherwise comparable, as determined by histological criteria routinely used to characterize the disease. Epidemiological studies suggest, however, that South Asians with colitis have a more benign form because their mortality remains low and they have a significantly lower resection rate.1,3,9 The reduction in mucin sulphation reported in ulcerative colitis16,17,25–27 is uncommon in South Asians compared with Europeans, irrespective of disease activity.

We have detected three labelling patterns for metabolically labelled mucin formed in organ cultures with $[^{3}H]$-glucosamine and $[^{35}S]$-sulphate and separated by gel filtration (Fig 1). A high $[^{35}S]$: $[^{3}H]$ ratio has previously been shown to be characteristic for normal colonic tissue16,17,25–27 and a reduction in this ratio occurs in colitic groups – although the ethnic origin of patients has not usually been identified. In addition, this study also identifies a further pattern of low turnover common to both South Asian and European groups and present in both secreted and cellular mucins (type C, Fig 1). These patients all showed incorporation into lower molecular weight glycoproteins, suggesting that the biopsy specimens are still viable, but further analysis of this group is required to confirm its reproducibility. The type C group contains both high and low $[^{35}S]$: $[^{3}H]$ ratios. Most striking is the cellular mucin in the South Asian group

**Figure 3: Comparison of the disease activity score with the mucin $[^{35}S]$: $[^{3}H]$ ratio. The ratio of dual labelled mucin isolated from organ culture is shown relative to the disease score for each patient in terms of cellular mucin, and secreted mucin (South Asian patients □, n=12; European patients ■, n=11). Three patients were excluded as biopsy specimens were not adequate for disease activity determination. Retention of mucin sulphation in South Asian colitics was significantly greater than for European colitics for cellular mucin, $p<0.0005$.**
which contains only high sulphate types A and C1. The variation detected using metabolic labelling is supported by mucin histochemistry with the high iron diamine/Alician blue stain for sulphomucins, which shows a retention of the normal sulphation pattern predominating in the South Asian colitis group. This was similar to the pattern found in the South Asian control group.

The results show that the pattern of mucin synthesised in colitis patients differs between ethnic groups. Comparison of these groups with normal controls has only been possible histologically because of the difficulty in obtaining normal south Asian controls for culture experiments. The controls for the European group and the colitis patients reported earlier25 26 showed less interpatient variability than that found in this study. These were peroperative surgical specimens and may reflect the change in advanced disease or an influence of bowel preparation for surgery. The South Asian and European patients in this study were a heterogeneous group attending outpatient clinics with no special bowel preparation and reflected the whole spectrum of disease activity.

The patterns of labelling suggests several properties of the mucins formed in the organ culture system used. The difference in $^{35S}/[\text{H}]$ ratio between secreted and cellular mucins from one individual may indicate the existence of more than one type of mucin present in the mucosal cells. The secretion of one of these mucin types and the retention of others could account for difference in the ratio, but the ratios found for secreted and cellular mucins do not support this interpretation. On the other hand, the reduction in the ratio may be due to a loss of sulphate or a change in mucin glycosylation, or both. N-Acetylglucosamine, N-acetylglactosamine, and sialic acids, which are the major monosaccharide components of colonic mucins, are all formed and incorporated into mucins from the radioactive precursor $[^{3}H]$-glucosamine. Thus, changes in the individual contents of these monosaccharides may lead to differences in the overall incorporation of $[^{3}H]$ found in the isolated mucin fraction.

The total mucin content of fractions isolated from cultures has proved difficult to quantify accurately and metabolic labelling gives a measure of mucin turnover within the duration of the experiment and not absolute values for total secreted material. The demonstration of the mucin nature of the material eluted at the exclusion limit of the Sepharose CL.2B column is therefore an important part of this study. Density gradient centrifugation confirms that >90% of the isolated fraction has a buoyant density typical of mucins and shows no contaminating low glycosylated material, which would also be labelled by this technique. Proteolytic cleavage of the mucin fraction yields only high molecular weight material consistent with the formation of subunit structures and not small glycopeptides. Finally, the product is not broken down by any of the proteoglycan or hyaluronan degrading enzymes, thus eliminating the possibility of co-purification of these molecules after organ culture.

The group of patients showing low turnover type C1/C2 mucin comprised 50% of both secreted and cellular mucin in South Asians and 73% and 27% of secreted and cellular for Europeans, and is thus a significant proportion of all mucin produced by colitics. Low mucin turnover in these experiments represents a lower level of incorporation of label into the completed mucin within the time course of the experiment. If metabolic incorporation and mucin storage was occurring the cellular mucin would show higher labelling relative to the secreted mucin. This is not found, and the results suggest that there is a generally reduced synthesis of mucin in these cases. As this is in apparent conflict with the clinical observations of increased mucus in colitis, further study is required to measure the absolute amount of mucin produced under these conditions.

The reduction in mucin sialic acid O-acetylation previously described for human colonic mucin8 9 21 31 was found in only three of all patients analysed (two South Asians and one European). Sixteen per cent of normal South Asian controls were non-O-acetylators. This reflects proportions reported previously for normal and ulcerative colitis patients11 30 35 and may be related to the disease but represent a genetically determined phenotype.

South Asians have a high incidence of ulcerative colitis and yet are at low risk of severe colitis and colorectal cancer. This study shows that the mucin sulphation and sialic acid O-acetylation patterns of South Asian colitics are similar to normal controls and differ from European colitics. In general, the pattern of normal mucin sulphation in colitis patients correlates with mild disease, while sulphate depletion is more common in those with severe colitis. We suggest that mucin studies may help to identify high risk patients in the future.

Some of the data presented in this paper have been presented in abstract form (Probert CSJ, Warren BF, Mayberry JF, Corfield AP. Mucin sulphation in South Asians with ulcerative colitis may be normal. J Pathol 1993; 168: 24A).


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