Deficiency for mannan-binding lectin is associated with antibodies to *Saccharomyces cerevisiae* in patients with Crohn's disease and their relatives

Mannan-binding lectin (MBL) is a member of the collectin family and is an important component of the innate immune response. Three different MBL alleles in coding exon 1 (point mutations in codons 52, 54 and 57) result in low serum levels of MBL.¹ Earlier, we described cellular and humoral immune reactivity of a subgroup of patients with Crohn's disease to mannans, a cell wall antigen of yeasts.² The humoral immune response in these patients is commonly known as antibodies to *Saccharomyces cerevisiae* (ASCA). In a previous paper, we found considerably more patients with Crohn's disease with low MBL serum levels to be ASCA positive than in the subgroup with high MBL levels. The homozygotic or compound heterozygotic mutations in the exon were associated with the development of ASCA in patients with Crohn's disease.³

This is in contrast with the data reported in this journal by another group that found an increased prevalence of ASCA in patients with MBL mutations in exon 1, which however, did not reach significance in their large independent cohort of patients with Crohn's disease.⁴ In this paper, we confirmed in another cohort that patients with low serum MBL or MBL deficiency were considerably more often ASCA positive as compared with patients with normal levels of MBL. Low MBL levels (defined as <500 ng/ml) were found in 30 of 52 (58%) patients with Crohn's disease; 26 (87%) of these patients were ASCA positive. By contrast, only 9 (41%) patients with normal MBL levels were ASCA positive ($p < 0.001$, Fisher's, exact test; fig 1). There are several possible explanations for the observed differences found in comparison to the above-mentioned report⁴: (1) the method of the ASCA test that was used; (2) the genetic difference due to the geographically different origins of the populations; and (3) a bias towards a population of patients

with Crohn's disease with a more severe disease course seen at the University Hospital of Bern, Switzerland. To extend our study and to evaluate the relationship between MBL deficiency and generation of ASCA, the second part of our study focused on the ASCA and the MBL status of the healthy family members of patients with Crohn's disease. A total of 158 family members of 53 patients agreed to provide clinical data and blood samples. ASCA were found in 38 of 158 (24%) family members. A similar prevalence was observed in previously published papers.³⁻⁷ All 46 (29%) family members had low MBL levels (<500 ng/ml). This population was analysed for its ASCA status; 23 (50%) family members were ASCA positive and 23 were ASCA negative (fig 1). This was in contrast with 112 family members with normal MBL levels; among those, 15 (13%) were ASCA positive and 97 were ASCA negative ($p < 0.001$). In 16 family members, MBL mutations leading to MBL deficiency were found (B/B, four relatives; D/D, three relatives; and nine compound heterozygotic people). Further, seven patients were genotyped as either LXPA/LYPD or LXPA/LYPB and had a MBL concentration <100 ng/ml. Relatives with mutations leading to MBL deficiency had a significantly greater prevalence of ASCA compared with the 135 relatives with normal MBL values ($p = 0.018$, χ^2 test). Thus, our analyses clearly show an association of ASCA positivity with MBL deficiency in patients with Crohn's disease and also in their healthy family members.

Therefore, our paper provides further evidence that genetically altered MBL levels in patients with Crohn's disease and their relatives could be, at least partly, responsible for the enhanced immune reactivity to yeast antigens seen in a subgroup of these patients and their relatives. However, other factors also contribute to the development of this unusual immune reaction, as there are MBL-deficient healthy people who are ASCA negative.

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Molecular comparison of dominant microbiota associated with injured versus healthy mucosa in ulcerative colitis

Ulcerative colitis is an inflammatory bowel disease (IBD) characterised by a chronic inflammation of the colorectal mucosa. The role of the gut microbiota in triggering or maintenance of the mucosal inflammation is strongly suspected.¹ We may postulate that a localised dysbiosis could explain the localisation of the lesions. Many of the recent studies have been made possible by the development of culture-independent techniques, which identify bacteria on the basis of comparisons of the nucleic acid sequence of rRNA molecules. Temporal temperature-gradient gel electrophoresis (TTGE) showed that in healthy people dominant microbiota associated with colonic mucosa is similar from the caecum to the rectum.² This has also been observed in Crohn's disease,³ and the dominant microbiota associated with ulcerated mucosa did not differ markedly from the microbiota associated with non-ulcerated mucosa.³

The aim of this study was to compare the dominant microbiota associated with injured colonic mucosa versus healthy colonic mucosa, using TTGE in patients with active ulcerative colitis.

Ten patients with active ulcerative colitis were studied, after informed consent was obtained. Three patients had a proctitis and seven had a left-sided colitis. None of them had received antibiotics or sulfasalazine within the previous 3 months. Four patients were receiving corticosteroids, four mesalazine and three azathioprine. Colonoscopy was performed during ulcerative colitis flare-ups. Colonic or rectal biopsy samples were collected from both injured and healthy mucosa in each patient

Figure 1 Incidence of antibodies to *Saccharomyces cerevisiae* (ASCA) in patients (black) and in healthy relatives (white) depends on the serum mannan-binding lectin (MBL) level. ASCA and MBL levels were measured by ELISA. ASCA was significantly more prevalent in people with low MBL values ($p < 0.001$ for patients and $p < 0.001$ for relatives) than in people with normal MBL levels.