anti-TNF-α alone is effective. Clinical improvement with Infliximab has been reported in two cases of proteinuria due to secondary amyloidosis in Crohn's disease. However, they did not show the significant improvement in proteinuria and anatomopathological parameters observed in our patient.

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The stomach periglandular fibroblast sheath: all present and correct

We were interested in the paper by Mutoh and colleagues[1] showing the development of epithelial intestinal metaplasia and mesenchymal proliferation in human stomach resections and Cdx2 transgenic mice. The authors used α smooth muscle actin (α-SMA) staining to mark periglandular fibroblasts and failed to show any α-SMA positive cells surrounding the en face glands of normal mouse and human stomach mucosa. In metaplastic tissue however, the periglandular fibroblast sheath was easily discernible, and the authors concluded that the fibroblast sheath was generated from the intestinal submucosa, possibly through expression of Cdx2.

Mesenchymal cells such as intestinal subepithelial myofibroblasts (ISEMF) are widely distributed. They are important coordinating cells that possess significant influence on their environment by virtue of their receptor profile and the signals they produce. Characteristically, ISEMF form a protective fenestrated sheath around the stem cell compartment, creating the stem cell niche—the optimal microenvironment for stem cells to give rise to differentiated progeny.[2] The stem cell niche is situated in the isthmus/neck region of the gastric gland. ISEMF regulate stem cell behaviour via paracrine secretion of growth factors and cytokines, and perform vital functions in the growth, differentiation, and development of the embryological stomach. They participate in

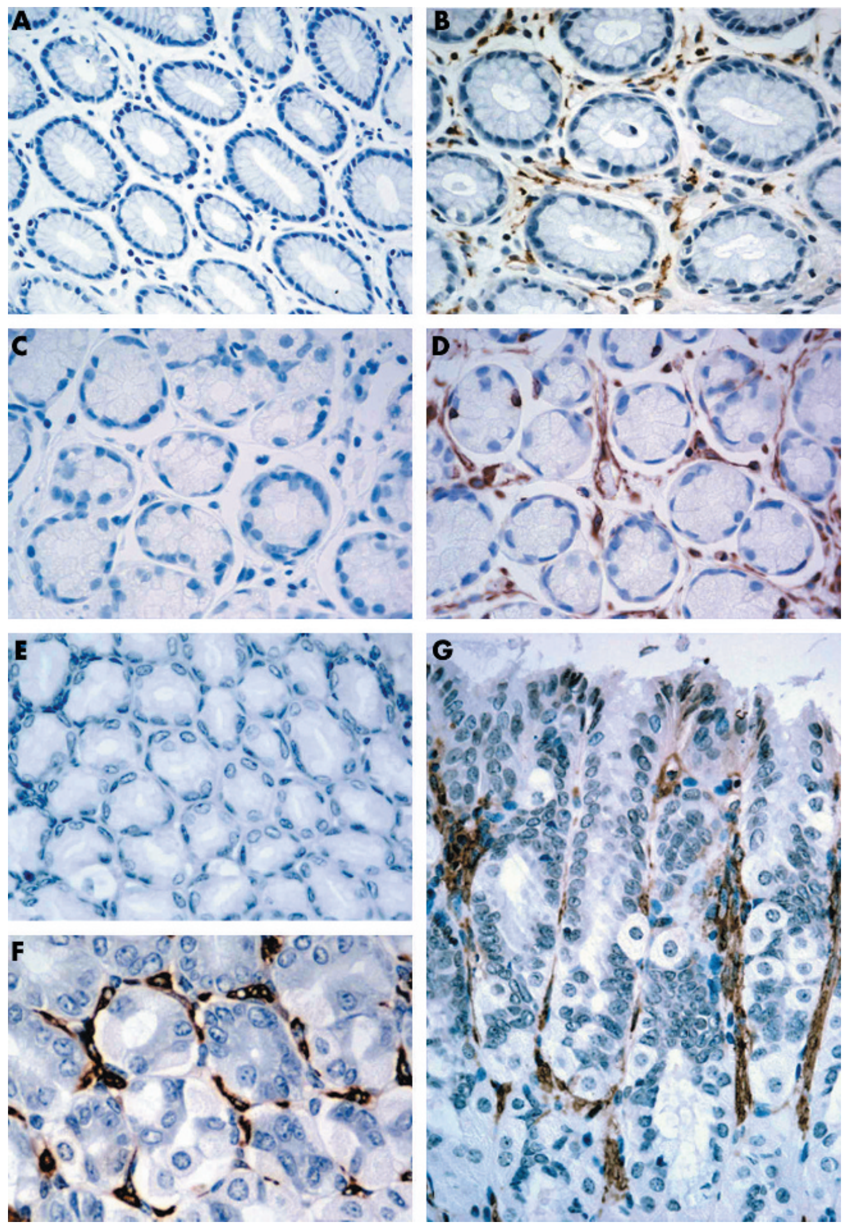

Figure 1 The normal stomach periglandular fibroblast sheath (PGFS). (A) Human α smooth muscle actin (α-SMA) control. (C) Human vimentin control. Normal human gastric glands counterstained with haematoxylin (40× magnification). (B) α-SMA immunostaining. (D) Vimentin immunostaining. Normal human gastric glands with surrounding PGFS (brown stain) embracing the epithelial cells of the gastric glands (40× magnification). (E) Mouse α-SMA control. Normal mouse gastric glands counterstained with haematoxylin (40× magnification). (F, G) α-SMA immunostaining. Normal mouse gastric glands in en face (F) and cross sectional (G) orientation showing the close association of the PGFS (brown stain) surrounding and enveloping the normal stomach glands (60× magnification).

mucosal wound healing and the response to inflammatory stimuli in the adult gastrointestinal tract.[3] As these are vital homeostatic roles, it seems unlikely that the periglandular fibroblast sheath is only generated in abnormal metaplastic tissue. We immunostained for ISEMF in paraffin embedded normal mouse and human stomach specimens. To identify ISEMF, we stained for α-SMA in three mouse gastric specimens, and α-SMA and vimentin in six sets of human gastric biopsies. Sections for vimentin staining underwent 10 minutes of microwave treatment in citrate buffer for antigen retrieval. Immunostaining was completed using the same antibodies and methods described in detail by Direkze and colleagues.[5] Antibody binding was detected by 1,3-diaminobenzidine (DAB; Sigma, St Louis, Missouri, USA). ISEMF were identified on the basis of their morphology and positive immunoreactivity for α-SMA in mouse tissue, and α-SMA and vimentin in human tissue. They were clearly and consistently seen surrounding the stomach glands in normal mouse and human stomach sections, both in the en face and cross sectional plane (see fig 1). There was little variation in staining intensity from sample to sample in the three mouse and six human subjects studied.

ISEMF are involved in the response to damage or disease in the stomach. After epithelial injury, ISEMF contraction limits the exposed area of the wound while secreted growth factors such as transforming growth factors α and β, epidermal growth factor, and fibroblast growth factor promote epithelial cell migration and proliferation.[3] In intestinal-type gastric cancer, myofibroblasts appear not only at the edge of the tumour, contributing to a desmoplastic reaction, but also within the tumour stroma.[4] The presence of increased inter-tubular reticulin, the histological hallmark of increased extracellular matrix deposition, is regarded as among the first signs of chronic atrophic gastritis, and likely to be caused by elevated numbers or activity of ISEMF. The source of these cells is very interesting—it is more likely that these cells are recruited from circulating precursor cells rather than being generated by metaplastic mucosa. Direkze *et al* have shown a large contribution of bone marrow donor derived myofibroblasts, making up to 64% of the periglandular fibroblast sheath in mouse stomach after total body irradiation and bone marrow transplant,[5] and Nakayama *et al* hypothesise that engraftment is responsible for myofibroblast presence in tumours.[4] The mechanisms initiating this engraftment are unclear but it may relate to the release of growth factors, such as transforming growth factor β,[6] released from inflammatory cells and the existing periglandular fibroblast sheath in response to gastritis induced damage.

We conclude that the periglandular myofibroblast sheath in normal stomach is very much a reality and likely to be pivotal in modulating epithelial cell behaviour.

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Anti-*saccharomyces cerevisiae* antibodies (ASCA) in coeliac disease

We read with great interest the paper by Israeli and colleagues (*Gut* 2005;**54**:1232–6) assessing the presence of anti-*Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear antineutrophil cytoplasmic antibodies (pANCA) before the occurrence of overt clinical manifestations in patients with Crohn's disease (CD) and ulcerative colitis (UC). They found that ASCA were present in 31% of CD patients before clinical diagnosis (but not in UC patients or controls), and that pANCA were detectable in two (25%) of eight UC patients before clinical manifestations but not in 24 matched controls. These observations led the authors to conclude that ASCA and pANCA may predict the development of inflammatory bowel disease long before its clinical onset.

We have recently published our experience on the prevalence and behaviour of ASCA and pANCA in adult and paediatric coeliac disease patients.[1] Sixty two (59%) of 105 coeliac patients had IgA and/or IgG ASCA (Quanta Lite ASCA IgG and IgA assay; Inova Diagnostics, San Diego, California, USA) at diagnosis while only one patient (0.9%) had pANCA. No significant correlation was found between ASCA positivity and severity of small intestinal mucosal damage. Moreover, after a gluten free diet (mean 14.4 (2.7) months), 93% of revaluated coeliac patients lost IgA ASCA whereas 83% maintained IgG ASCA reactivity.

Interestingly, seven (six women; median age 26 (range 18–33) years) of the 62 coeliac patients with IgA and/or IgG ASCA were diagnosed before developing any clinical symptoms as they were screened as first degree relatives of coeliac patients. All had antitissue transglutaminase antibodies (tTG), antiendomysial antibodies (EmA), the HLA DQ2/DQ8 haplotype, and a histological picture on small intestinal biopsy showing an increased number of intraepithelial lymphocytes in five and mild villous flattening in two (grade 1 and grade 3a, respectively, according to Marsh's classification modified by Oberhuber).

In this type of patient, known as having "potential" and "silent" coeliac disease, respectively, positivity for the serological markers (EmA and tTG) together with the typical HLA predisposing genotype (DQ2 or DQ8) allows accidental diagnosis of gluten enteropathy when clinical manifestations are still lacking.[2 3]

Our observation indicates that in asymptomatic patients, ASCA positivity is not only predictive of CD but may also be associated with "potential/silent" coeliac disease. Increased permeability in the small bowel of coeliac patients seems to be an early event, preceding the development of more severe mucosal damage.[4 5] Similar to asymptomatic CD patients, the altered permeability of the small bowel towards yeast antigens could account for the occurrence of ASCA from a very early stage of the disease in asymptomatic coeliac patients, as suggested by our five coeliac patients with minimally abnormal mucosal architecture. The "altered permeability" hypothesis should be investigated further to explain the frequent detection of ASCA in other autoimmune disorders, such as primary biliary cirrhosis and primary sclerosing cholangitis.[6]

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