expression, designated the BM CK7/20 pattern, has been demonstrated to be both sensitive and specific to Barrett's oesphagus and may be used as an objective marker of BM.[7] This pattern shows superficial CK20 staining and strong CK7 staining of both superficial and deep glands and can be used to distinguish BM from intestinal metaplasia of the stomach which, although can be histologically indistinguishable, has a different pattern of cytokeratin expression, is associated with *Helicobacter pylori* infection, and is not associated with an increased risk of malignancy.[8]

The Barrett's CK7/20 pattern has been demonstrated in both long and short segment BM. The paper by Couvelard *et al* confirms the presence of a Barrett's CK7/20 pattern and demonstrates that the same CK7/20 pattern holds true for ultrashort segment BM.[4] The authors further suggest that these findings may be useful to improve endoscopic surveillance strategies to specifically target those at increased risk of BM and its complications. Ultrashort BM is however an area surrounded by controversy. It is defined as intestinal metaplasia found at the gastro-oesophageal junction arising in either very short tongues of columnar mucosa or in eccentric or normal appearing squamocolumnar junctions (SCJs). It has been reported that the prevalence of this may be up to 43% in unselected patients undergoing routine endoscopy. The nature of metaplasia in eccentric or normal SCJs remains unknown. This has prompted much debate as to the risk (if any) of dysplasia or indeed cancer in this group and the appropriateness of endoscopic surveillance. Furthermore, if we are to regard this lesion in a similar way to short and long segment Barrett's and it is found in up to 43% of normal appearing SCJs, should we be performing screening biopsies of these patients? Certainly this does not seem to be a plausible option.

Perhaps it is in the understanding of the biology of BM where cytokeratins have already made a potentially useful contribution. Specifically, rearrangements in the composition of lateral cell-cell adhesion junctions, the desmosomes, have been recently reported in BM.[9] These alterations in adhesion complexes while being associated with concomitant changes in cytokeratins are also important in releasing gamma catenin, a known oncogene involved in T cell factor/leucocyte enhancing factor transcription.[10]

In conclusion, greater understanding of the processes involved in the development and progression of BM is crucial if we are to develop strategies to intervene at an earlier stage in the metaplasia-dysplasia-carcinoma sequence and alter the outcome of oesophageal adenocarcinomas. Cytokeratins are undoubtedly of great scientific importance but caution should be observed in areas where clinical risk has not been already established.

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Monocytes or T cells in Crohn's disease: does IL-16 allow both to play at that game?

Interleukin (IL)-16 was first described in 1982 under the name "lymphocyte chemoattractant factor".[1] Since its cloning in 1994,[2] the complex structure and biological function of this cytokine has been extensively explored. In 1999, the IL-16 gene was localised to chromosome 15q26.3[3] but the role of genetic variants of this gene have yet to be explored in human disease.

IL-16 can be produced by a variety of inflammatory cells, including mast cells, eosinophils, mononuclear phagocytes, and CD4+ and CD8+ T cells.[4] IL-16 is expressed as an 80 kDa precursor molecule,[5] which is processed to active IL-16 by caspase 3.[6]

Most interestingly, the main receptor for IL-16 appears to be the CD4 molecule (which identifies T helper cells but is also present on monocytes and other phagocytes). It is assumed that interaction with the CD4 molecule is the main event in induction of most IL-16 mediated biological effects although other receptors and co-receptors may exist. The main biological function of IL-16 appears to be recruitment of CD4+ T cells. In addition, IL-16 induces the production of proinflammatory cytokines (that is, tumour necrosis factor, IL-1β, IL-6, and IL-15 by monocytes)[7] and can regulate RAG gene expression in CD4+ B cells. The mechanisms of signal transduction of IL-16 are still unclear but appear to involve tyrosine kinases (that is, p56lck) in T cells, the stress activated protein kinases (SAPK) pathway, and activation of the p38 mitogen activated protein kinase (MAPK).[8 9]

Not surprisingly, IL-16 is implicated in the pathophysiology of chronic immune diseases, including allergen induced bronchial asthma, rheumatoid arthritis,[10] and Crohn's disease.[11 12] It has been found to be elevated in both Crohn's disease and ulcerative colitis where a positive correlation between disease activity and IL-16 expression has been found.[12] Expression of IL-16 was also upregulated in an animal model of chronic intestinal inflammation and blocking IL-16 activity ameliorates TNBS colitis.[11]

In this issue of *Gut*, Middel and colleagues[13] analysed the contribution of IL-16 to the pathophysiology of inflammatory bowel disease in an elegant study using a variety of

molecular techniques (see page 795). They found that increased production of IL-16 is particularly important in the pathophysiology of the inflammatory lesions in Crohn's disease in comparison with ulcerative colitis. A strong relationship between increased expression of IL-16 in T cells/mast cells and numbers of CD4+ T cells was found. Discrete accumulation of mast cells as well as increased numbers of eosinophils have frequently been seen by pathologists although their contribution to pathophysiology was unexplained until now. The role of these cells in the pathophysiology of Crohn's disease is now explained as important contributors of IL-16.

Recently, three studies have independently identified mutations in the NOD2 gene on chromosome 16q as a primary cause of Crohn's disease in a subset (up to 25%) of patients.[14–16] NOD2 is only expressed by monocytes/macrophages and its role in other phagocytes is presently unclear. However, it is not expressed in lymphocytes or epithelial cells. It is currently hypothesised that a mutation in the NOD2 gene impacts the handling of bacterial pathogens by monocytes by alteration in the lipopolysaccharide/NOD2 induced activation of nuclear factor kappa B (NFκB). It is thought that this constitutive defect predisposes patients with Crohn's disease to chronic inflammation, which may be triggered by the commensal flora.

The argument can be made that T cells and hence IL-16 may only play a secondary role in the disease process. The study presented by Middle *et al* links activation of phagocytes in the pathophysiology of Crohn's disease to strong evidence of a T cell contribution to disease pathophysiology. Increased activation of mononuclear phagocytes that results in the release of proinflammatory cytokines and also IL-16 is directly associated with CD4+ T cell recruitment. As first reports showed increased activation of p38 MAPK in Crohn's disease,[17] which may result in increased levels of IL-16, additional molecular data provided by Middle *et al* strongly supports this interpretation.

IL-16 may be an interesting target to interrupt the loop between mononuclear phagocytes and T cell activation. An important question will be whether mast cells, eosinophils, and other phagocytes also express genes of the NOD2 family. As expression of IL-16 is most likely controlled by NFκB, this cytokine may be a central player in linking the different aspects of Crohn's disease pathophysiology.

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Sodium in preascitic cirrhosis: please pass the salt

The relationship between sodium retention, hyperactivity of the neurohumoral vasoactive systems, and ascites formation in cirrhosis is intriguing and still remains a subject of interest and debate. According to the most widely accepted theory, the so-called peripheral arteriolar vasodilatation hypothesis of sodium retention and ascites formation in cirrhosis, the predominant mechanism in the pathogenesis of these abnormalities is the presence of persistent systemic arterial vasodilation leading to arterial hypotension, low peripheral resistance, high cardiac output, and decreased effective arterial blood volume.[1] These circulatory abnormalities are detected by arterial and cardiopulmonary baroreceptors which in turn initiate the homeostatic activation of the endogenous neurohumoral systems aimed at maintaining arterial pressure within normal or near normal levels. In the kidneys however homeostatic activation of the vasoactive and sodium retaining systems promotes tubular sodium reabsorption and sodium retention.[1] Because the splanchnic vasculature is a major site of arteriolar vasodilatation in cirrhosis, it is not surprising that extravasation of the fluid retained by the kidneys occurs mainly in this compartment, leading to the formation of ascites.

The renin-angiotensin-aldosterone (RAAS) and sympathetic nervous (SNS) systems, together with atrial natriuretic peptide (ANP), are the main endogenous neurohumoral systems involved in sodium homeostasis. The RAAS is one of the most extensively investigated endogenous vasoactive systems in cirrhosis because it is markedly activated in patients with sodium retention.[2 3] Plasma renin activity and plasma aldosterone levels closely correlate with urinary sodium excretion and in many decompensated cirrhotic patients they reach extraordinarily high values, with levels being higher in patients with marked sodium retention.[2 3] The SNS is another key factor involved in the pathogenesis of sodium retention and ascites formation in cirrhosis. In fact, noradrenaline concentrations are consistently found to be increased in patients with sodium retention and ascites.[2 3] On the other hand, endogenous natriuretic substances such