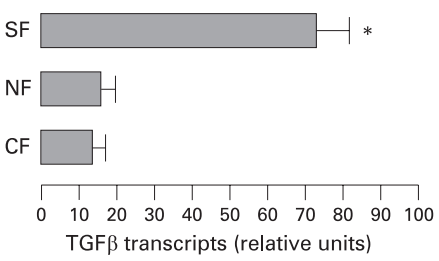
Digest

Robin Spiller and Magnus Simren, *editor and deputy editor*

Imbalance between deposition of extracellular matrix and its degradation in Crohn's strictures

Fibrosis in inflammatory bowel disease is believed to be due to an excess deposition of extracellular matrix (ECM) by myofibroblasts and an impairment of the matrix degrading metalloproteinases (MMPs). Transforming growth factor-β (TGFβ) stimulates ECM synthesis and the level of MMPs are reduced by tissue inhibitors of metalloproteinase (TIMPs). This study examined uninflamed mucosa from 25 patients with Crohn's disease (CD) with strictures and compared this with tissue from 18 patients with CD without stricturing. TGFβ was over expressed in myofibroblasts from mucosa overlying strictures (see fig). Binding of TGF activates the Smad proteins, phosphorylating Smad 2 and 3 whose action on gene transcription is inhibited by Smad 6 and 7. The authors showed an increase in phosphorylated Smad 2 and 3 from mucosa above the stricture and a decrease in the inhibitory Smad 6 and 7. There was also a reduction in mucosal MMP-12 and an increase in the inhibitor TIMP-1. Isolated myofibroblasts from strictures showed increased TGFβ transcription and produced more phosphorylated Smad 2 and 3. Thus, the mucosa overlying fibrosis in CD appears to have a reduced capacity to degrade extracellular matrix but how this relates to events in the deeper layers where scarring occurs remains to be determined. ***See page 777***



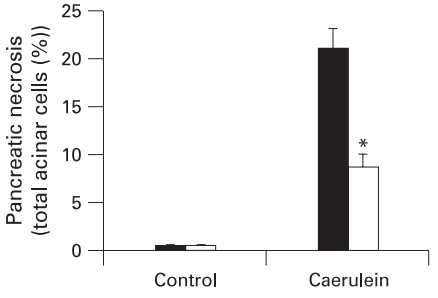
Transforming growth factor-β (TGFβ) transcripts from uninflamed mucosa overlying strictures (SF) and non-strictured areas (NF) compared with control subjects (CF) $p<0.01$.

Common protective alleles in coeliac disease and ulcerative colitis

While over 30 genes have been associated with CD, far fewer are known for ulcerative colitis (UC). Recent interest has focused on the interleukin *(IL) 2/IL21* locus on chromosome 4q27, which is associated with coeliac disease, type I diabetes, Graves disease, systemic sclerosis and rheumatoid arthritis. This study analysed the four most strongly associated single nucleotide polymorphisms (SNPs) in *IL2/IL21*, recently found to be associated with coeliac disease. The first phase of the study used 1590 patients with inflammatory bowel disease (IBD) (813 with UC) from The Netherlands and these findings were replicated in the North American IBD Genetics Consortium (2387 cases, 1733 with UC) and again in an Italian IBD cohort with 648 patients with UC. All four SNPs showed an association with IBD, which was particularly strong for the cases with UC (see fig). The strength of association was weaker in CD. The *IL2/IL21* locus is the fifth locus that has been associated with both UC and coeliac disease, suggesting that a common set of biological pathways leads to the two conditions. ***See page 799***

Toll-like receptor 4 is pro-inflammatory during acute pancreatitis

Acute pancreatitis is accompanied by substantial morbidity and mortality and infection of the inflamed pancreas and surrounding tissue is one of the main determinants of a poor prognosis. Mechanisms involved in the progression of acute pancreatitis are not well known. Toll-like receptors (TLRs) recognise products of microbial metabolism and play an important role in the innate immune response and activation of TLR4 results in a proinflammatory response. Sharif and colleagues evaluated the role of TLR4 and its co-receptor CD14 in the progression and severity of caerulein- and L-arginin-induced acute pancreatitis in mice by studying wild-type and knockout mice. In a series of experiments it was demonstrated that the severity of pancreatitis was ameliorated in mice that lack TLR4 (see fig) or CD14 compared with wild-type mice. Moreover, it was also shown that TLR4 in pancreatitis was activated in the absence of lipopolysaccharide (LPS) or bacteria, implicating that TLR4 has a pro-inflammatory role in the progression of pancreatitis independent of LPS. These findings implicate an important role for TLR4 in the progression of acute pancreatitis, which opens new therapeutic possibilities for this serious disease. ***See page 813***



Effects of toll-like receptor (TLR) 4 deficiency of caerulein-induced pancreatitis (black bars: wild-type mice; white bars: $TLR4^{-/-}$ mice).

Association between the four single nucleotide polymorphisms (SNP) studied and ulcerative colitis (UC) showing significant reduction of the minor allele frequency in UC

			Dutch UC: 813 cases, 929 controls			
SNP	A1	A2	MAF controls	MAF cases	p Value	OR (95%CI)
rs13151961	G	A	0.19	0.14	**0.00003**	0.67 (0.56 to 0.81)
rs13119723	G	A	0.16	0.12	**0.00038**	0.71 (0.58 to 0.86)
rs6840978	T	C	0.22	0.16	**0.00001**	0.68 (0.57 to 0.81)

MAF, minor allele frequency.

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Serum biomarkers of severe non-alcoholic fatty liver disease

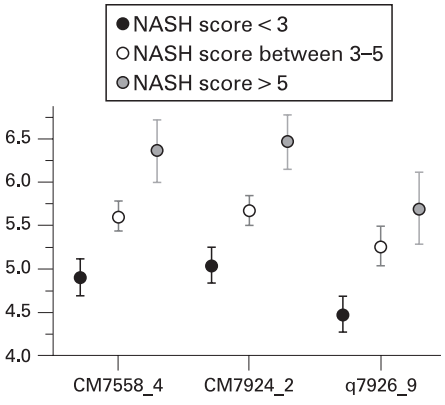
Non-alcoholic fatty liver disease (NAFLD) is an increasing problem worldwide as the prevalence of obesity is steadily increasing. Today, liver biopsy is needed in order to find obese patients with risk factors for progression to severe liver disease, ie steatosis and non-alcoholic steatohepatitis. Less invasive diagnostic strategies to predict risk for progression to severe liver disease are needed. In this issue of *Gut*, Trak-Smayra and co-authors show the potential clinical usefulness of proteomics for this purpose. In obese patients, serum protein levels were detected before and after bariatric surgery and the patients were grouped according to the severity of liver injury (biopsy obtained during surgery). Serum protein profiles identified three peaks (identified as double charged ions of α- and β-haemoglobin subunits) with significantly different intensity according to the severity of liver disease (see fig). Moreover, the levels returned to normal after bariatric surgery. It was also demonstrated that these parameters were unrelated to liver function tests or metabolic parameters, implicating that they may serve as biomarkers of the severity of liver damage, which holds promise for the future. ***See page 825***

Early detection of malignant transformation in patients with cirrhosis by plasma proteasome

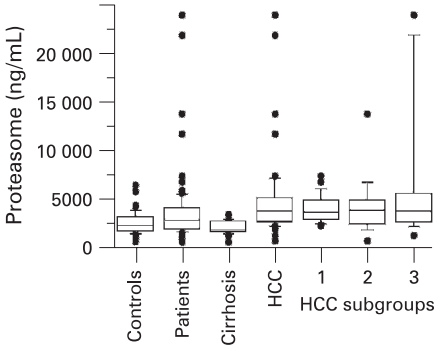
Proteasomes are barrel-shaped intracellular structures responsible for degrading proteins, which play a critical role in cell cycle regulation and are increased in a range of neoplasms, including solid tumours and leukaemias. This study examines plasma proteasome (PP) levels in 83 patients with cirrhosis, 50 of whom had hepatocellular carcinoma (HCC) and 40 healthy controls. Proteasome levels were elevated in patients with HCC (see fig). Those with tumour were subgrouped according to the tumour bulk; subgroup 1 = one nodule < 3cm, subgroup 2 = tumour 3–5 cm in diameter or >3 nodules < 3cm in diameter and subgroup 3 = tumour mass greater than subgroup 2. Proteasome levels were equally elevated in all three groups. Receiver-operating curves were constructed for both plasma proteasome and α-fetoprotein (AFP) for diagnosing HCC and the area under the curve (AUC) for PP at 0.88 was better than for AFP (AUC = 0.75). Sensitivity of PP was 81.9% and specificity 97%, while AFP sensitivity was inferior at 68.7% and specificity 54.5%. PP did especially well in the low tumour mass with sensitivity of 76%. Increased proteasome appears a crucial step in malignant transformation and could be both a biomarker for diagnosis and a possible therapeutic target. ***See page 833***

Visceral fat increases the risk of recurrence of hepatocellular carcinoma in NASH patients

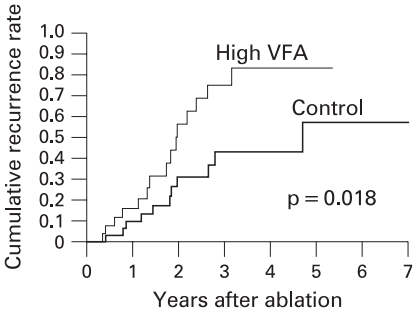
HCC is one of the main causes of cancer death worldwide and this usually develops in patients with severe chronic liver disease. Recently, obesity has been reported to be a risk factor of HCC development in patients with chronic liver disease other than non-alcoholic steatohepatitis (NASH). Ohki and co-workers included patients with HCC and suspected NASH. All the patients were treated with percutaneous radiofrequency ablation and the visceral fat area was determined with CT image analysis. It was demonstrated that visceral fat, together with age, were independent risk factors for recurrence of HCC after curative treatment (see fig). The next step now would be to see whether reduction of fat could decrease the risk for HCC recurrence, which would be a major step ahead. However, significant weight reduction in patients who are overweight is not an easy task… ***See page 839***



Mean peak intensities of selected peaks of the serum protein profile according to non-alcoholic steatohepatitis (NASH) severity score.



Plasma proteasome in controls, all patients, those with cirrhosis and hepatocellular carcinoma (HCC). HCC divided into subgroups according to size showed no difference in levels.



The cumulative recurrence rates of hepatocellular carcinoma in the high "visceral fat area" (VFA) vs control subjects.

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