Digest

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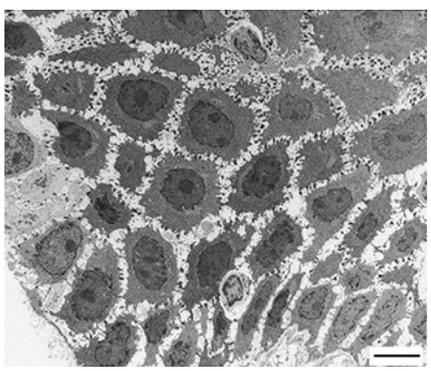
Robin Spiller and Severine Vermeire, *editor and deputy editor*

Exposure of human oesophageal mucosa to intraluminal acid induces dilation of intercellular spaces

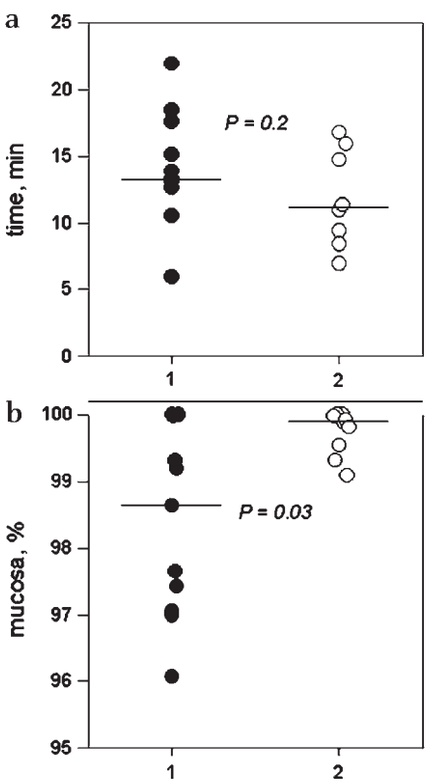
Patients with non-erosive oesophageal reflux disease (NERD) have dilation of intercellular spaces (DIS), which may allow intraluminal acid access to acid-sensitive nerves within the oesophageal wall and hence symptoms. Animal studies show that DIS can be induced by intraluminal acid. The current study examined whether DIS could be experimentally induced in healthy subjects by infusing solutions to mimic acidic and weakly acidic reflux. 14 healthy volunteers had oesophageal biopsies, 3 and 13 cm proximal to the oesophagogastric junction before and after 30 minutes infusion of saline at pH 7.2, 5.5, 2.0 with pepsin +/− 2 mmol glycocolic acid. Gross histology was unchanged but electron microscopy showed DIS after pH 5.5 and 2.0 solutions (see figure). Adding bile to acid pepsin did not increase DIS. DIS was seen not only in the acid exposed distal oesophagus but also proximally where no acid reached. Interestingly despite DIS the healthy subjects did not experience pain suggesting other factors including up regulation of acid sensitive receptors (TRVP-1) are necessary to induce symptoms. *See page 164*



Electron micrographs showing dilated intercellular spaces (DIS) in oesophageal mucosa after exposure to pH 2.0 perfusate.

Randomised controlled trial on the impact of constructive feedback on training in gastrointestinal endoscopy

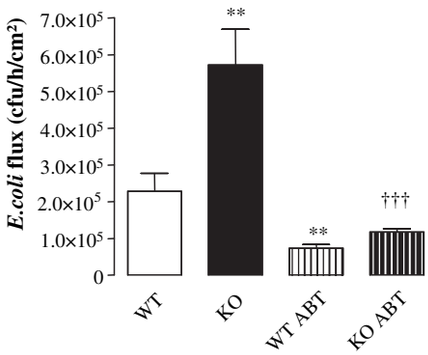
Virtual-reality (VR) computer simulators have been used to enhance the traditional endoscopy teaching. As there are no data on the impact of external feedback on acquisition of endoscopic skills, the present study assessed the impact of external feedback on the learning curves on a VR colonoscopy simulator. A total of 22 trainees, without colonoscopy experience, were randomised to a group which received structured feedback provided by an experienced supervisor and a controlled group. All participants performed 15 repetitions of task 3 from the Introduction colonoscopy module of the Accu Touch Endoscopy simulator. The proficiency levels were based on the performance of 8 experienced colonoscopists. Results show that there were no perforations in the feedback group versus 7 in the non-feedback group. Subjects in the feedback group reached expert proficiency levels in percentage of mucosa visualised and time to reach the cecum significantly faster compared with the control group. The authors conclude that concurrent feedback given by supervisor has an advantage in acquisition of basic colonoscopy skills and achieving of proficiency level as compared to independent training. *See page 181*



Learning curves for feedback group (white circles), non-feedback group (black circles) and experts (black triangles) for a) total procedure time, b) percentage of mucosa visualised.

Nod2 regulates host response towards microflora by modulating T-cell function and epithelial permeability

NOD2/CARD15 mutations are associated with susceptibility to Crohn's disease and Graft-Versus-Host Disease, two diseases which have dysfunctions of Peyer's patches (PP). In both disorders, the intestinal barrier is disrupted as shown by an excessive gut permeability of macromolecules and bacteria. However, the link between Nod2 deficiency and the mucosal abnormalities observed in CD or GVHD has not been fully explored. In the present study, the authors show that anti-CD4+ and anti-IFNγ monoclonal antibodies abrogate this phenotype of increased permeability and bacterial translocation. These results demonstrate that immune T cells influence the epithelial functions. Interestingly, all parameters normalised after intake of antibiotics, suggesting influence of the gut microflora in the cross talk between immune cells and epithelial functions. Most likely this occurs through the Toll like receptor pathway as TLR2 and TLR4 expression were increased in Nod2−/− mice and TLR2 and TLR4 agonists induced an increased transcellular permeability in Nod2+/+ mice. Muramyldipeptide, a Nod2 agonist was able to reverse this phenomenon. *See page 207*

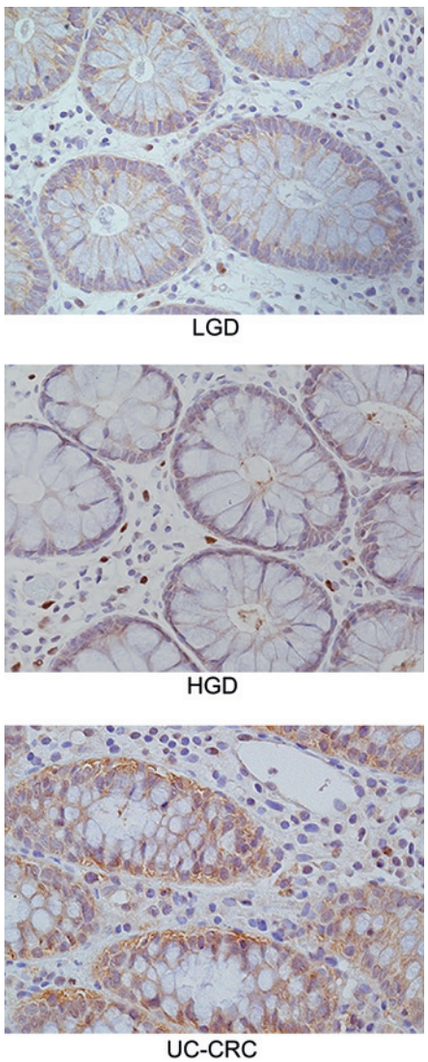


Bacterial translocation of E coli through PP formations is increased in NOD2−/− mice

Expression of IL-6 / STAT3 / SOCS3 in ulcerative colitis and UC-related carcinogenesis

IL-6 stimulates survival, proliferation and progression to cancer of intestinal epithelial cells via activation of STAT3 as shown in mouse models. In the present study, the authors investigated expression of

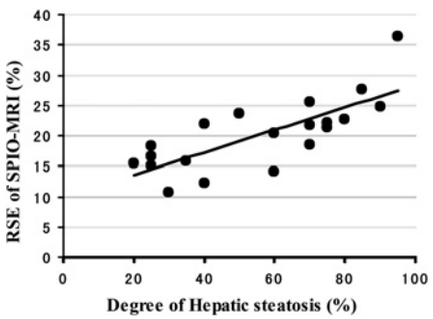
IL-6/p-STAT3 and SOCS3 in biopsies from patients with ulcerative colitis (UC), and in UC related-colorectal cancer (CRC) progression (low-grade dysplasia , UC with high-grade dysplasia and UC with CRC. The results show that patients with active UC have significantly more IL-6 and p-STAT3 positive epithelial cells than inactive UC and controls. SOCS3-positive cells were significantly increased in colonic epithelium of inactive and active UC compared with controls. In dysplasia and cancer, significantly more epithelial cells expressed IL-6 and p-STAT3 compared with controls (72.7% and 0% respectively for IL-6 and 54.5% and 11.1% respectively for p-STAT3; both $p<0.05$), whereas the proportion of SOCS3-positive cells in this progression reduced (low grade dysplasia 33.3%; high grade 14.3%; UC-CRC 9.1%). In addition, methylation of the SOCS3 gene was detected in epithelial cells from UC-CRC biopsies. This study therefore concludes that IL-6/p-STAT3 is important in patients with inflammation-induced CRC and that absence of SOCS3 seems critical for CRC progression. *See page 227*



Immunohistochemical staining of SOCS3 in colonic biopsies from UC, patients with LGD, HGD and CRC.

Non-alcoholic fatty liver disease (NAFLD) impairs human Kupfer cell function

Animal and human data show increased endotoxaemia in NAFLD which could be due to impaired clearance of endotoxin by the diseased liver. The current study assessed Kupfer cell function from the uptake of superparamagnetic iron oxide (SPIO) particles measured by MRI. SPIO's paramagnetic nature quenches signal intensity on T2 weighted images and impairment of SPIO uptake leads to a higher relative signal enhancement (RSE). The authors studied 26 NAFLD patients and combined this with a detailed histological study of rats fed a methionine and choline deficient (MCD) diet to induce NAFLD. These rats showed higher RSE indicating less uptake of the superparamagnetic iron oxide. There was also a reduction in the uptake of fluorescent beads confirming impairment of Kupfer cell function. Neither rats nor patients showed any reduction in Kupfer cell numbers. In patients, there was a similar impairment of Kupfer cell function shown with a strong correlation between the RSE and degree of hepatic steatosis (see figure). This may be important since impaired Kupfer cell function could lead to increased exposure to gut bacterial products leading to increased production of inflammatory cytokines such as TNF-α, which is thought to be an important 'second hit' in the pathogenesis of NAFLD. *See page 258*



Hepatic steatosis correlates with reduced uptake of SPIO and reduced quenching of signal hence a higher relative signal enhancement of the MRI signal in NAFLD patients after SPIO injection.

Genetic predictors of liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD)

NAFLD is an increasingly important cause of cirrhosis and hepatocellular carcinoma worldwide. Peripheral insulin resistance causes increased delivery of free fatty acids to hepatocytes causing oxidative stress. Genetic factors influence insulin resistance and two single nucleotide polymorphisms (SNPs), the plasma cell membrane glycoprotein-1 (PC-1) Lys121Gln SNP and the insulin receptor substrate 1(IRS-1) Gly972Arg SNP inhibit the effectiveness of insulin signalling and have been associated with increased risk of insulin resistance and diabetes. The present study examined the link between these polymorphisms and liver damage in 702 NAFLD patients from the UK and Italy, comparing them with 310 Italian blood donor controls without liver disease. Although there were only borderline differences in the SNPs frequency between NAFLD and controls, the two polymorphic alleles were significantly associated with an increased risk of developing fibrosis with an adjusted odds ratio of 2.9 for those possessing both alleles (see table). Insulin acts via the insulin receptor to activate a kinase AKT leading to decreased glucose production. In a small subgroup of patients, AKT activity as assessed by phosphorylation was decreased in those who were positive for the defined SNPs with about a one-third reduction. The authors conclude that evaluation of genotype may identify those at increased risk and thus influence management. *See page 267*

Results of multivariate analysis of clinical and genetic factors predicting fibrosis score >1. Those having both PC1/ENPP1 121 Gln and IRS1 972Arg alleles had an increased adjusted OR of 2.9

	Adjusted OR	
	OR (95% CI)	**p Value**
Age years	1.06 (1.04 to 1.08)	<0.0001
ALT, UI/ml	1.009 (1.004 to 1.012)	<0.0001
BMI, kg/m^2	1.11 (1.07 to 1.16)	<0.0001
Glucose, mg/dl	1.008 (1.004 to 1.12)	<0.0001
Ferritin, ng/ml	1.001 (1 to 1.002)	0.05
ENPP1, 121Gln+, IRS1 972Arg+	2.92 (1.55 to 5.72)	0.001
ENPP1 121Gln+, IRS1 972Arg−	1.30 (1.01 to 1.67)	0.03
IRS-1 972Arg+	1.57 (1.12 to 2.23)	0.01

Model χ^2 172.3, $p<0.0001$.
ALT, alanine aminotransferase; BMI, body mass index; ENPP1, ectoenzyme nucleotide pyrophosphate phosphodiesterase 1; IRS-1, insulin receptor substrate-1; NAFLD, non-alcoholic fatty liver disease.