

Highlights from this issue

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Luminal GI

Obesity and risk of oesophageal and gastric adenocarcinoma

The incidence of oesophageal adenocarcinoma (EAC) has increased rapidly over the past 40 years, and is the most rapidly increasing cancer in the western world. Epidemiological evidence suggests that obesity, as measured by BMI, may be a major risk factor but few studies have specifically examined body fat distribution, in particular measures of abdominal obesity (waist circumference and waist-hip ratio (WHR)). In this excellent paper, O'Doherty *et al* examined the relation between overall (BMI) and abdominal obesity with EAC using the large prospective NIH-AARP cohort. Cox proportional hazards regression was used to examine these associations among 218 854 participants. They also assessed these associations with adjacent adenocarcinomas of the gastric cardia and gastric non-cardia. Overall obesity (BMI) was associated with a higher risk of EAC and gastric cardia adenocarcinoma, whereas abdominal obesity, as measured by waist circumference and WHR was associated with an increased EAC risk. Waist circumference was also related to an increased risk of gastric cardia adenocarcinoma, but no association with WHR was observed. The positive association between WHR and EAC risk persisted in patients with normal BMI (18.5 to <25 kg/m²). These findings suggest that interventions to reduce the prevalence of obesity may help to prevent adenocarcinomas of the oesophagus and gastric cardia (*see page 1261*).

Post-menopausal hormone replacement appears to prevent some types of colon cancers but not others

Postmenopausal hormone (PMH) therapy likely reduces the risk of colorectal cancer (CRC), although there is still some controversy over this. Limsui and colleagues have evaluated the association between PMH therapy and incident CRC, including the incidence of the molecular subtypes of CRC, which include chromosomal unstable (CIN or MSS) CRC, microsatellite unstable CRC, and CpG Island Methylator Phenotype (CIMP) CRC. They assessed this association in a large population-based study and found

that PMH therapy was inversely associated with incident CRC overall (RR=0.82; 95% CI 0.72 to 0.93), with a significantly lower risk for MSS tumours (RR=0.75; 95% CI 0.60 to 0.94), and borderline significantly lower risks for CIMP-negative (RR=0.79; 95% CI 0.63 to 1.01). Their findings suggest that PMH therapy may prevent certain types of CRC but not others, which has implications for chemoprevention strategies for CRC (*see page 1299*).

Another way that APC mutations promote colorectal cancer

The role of the enzyme cyclooxygenase 2 (COX-2) in CRC formation is well known. The overexpression of COX-2 leads to increased prostaglandin E2 (PGE2) which promotes the formation of colon adenomas and cancer. Drugs that suppress COX-2, like aspirin, are effective chemoprevention agents for CRC. Recently, it

was shown that an enzyme that suppresses PGE2 production, 15-prostaglandin dehydrogenase (15-PGDH) is suppressed in many CRCs, which promotes the formation of these tumours. The loss of 15-PGDH is believed to promote CRC formation through increased PGE2 levels, just like increased COX-2 does, but the mechanism of suppressing 15-PGDH has not been determined to date. Now, the research team led by Chris Paraskeva show that a signalling pathway induced by mutations in the APC gene, the Wnt/ β -catenin pathway, is responsible for suppressing 15-PGDH (figure 1). This effect appears to precede the effects of increased COX-2 on PGE2 in colon tumours. These results provide additional support for ongoing efforts to develop targeted agents that can suppress the Wnt/ β -catenin pathway for use in preventing and treating colorectal neoplasms (*see page 1306*).

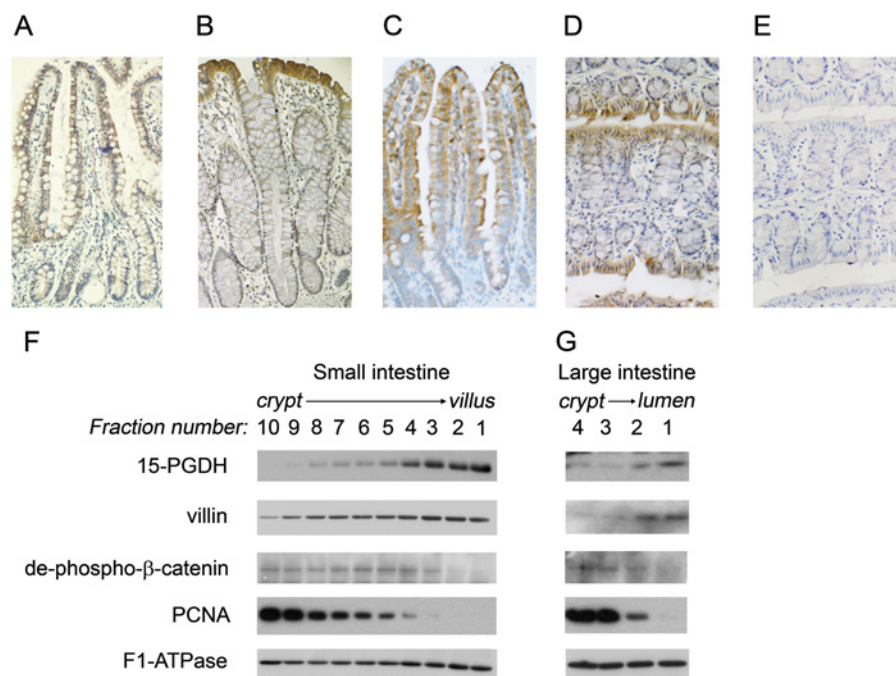


Figure 1 (A–E) Inverse correlation of 15-PGDH expression with β -catenin in normal intestinal epithelia. (A–E) 15-PGDH expression in intestinal epithelium. Immunohistochemical staining of A, human small intestine; B, human large intestine; C, murine small intestine; D and E, murine large intestine. A–D are stained for 15-PGDH and show highest expression in the differentiated luminal epithelium where β -catenin activity is established as being low.³¹ (E) Negative control (no primary antibody). (F, G) High 15-PGDH expression and low active β -catenin in the differentiated epithelial compartment.

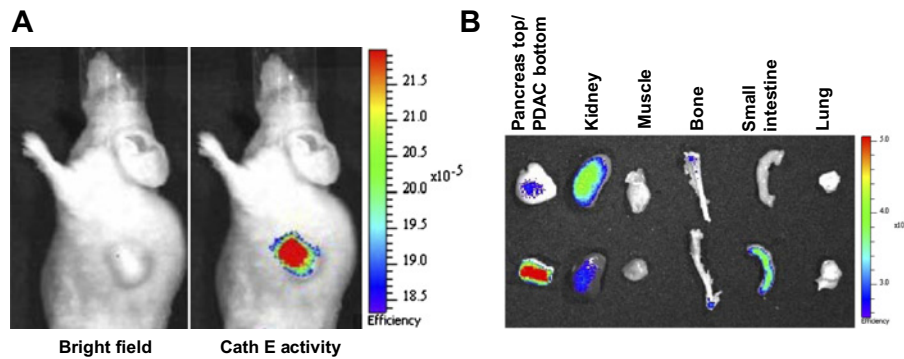


Figure 2 Cath E activity can be detected efficiently in human pancreatic cancer xenografts in mouse. (A) Representative in-vivo image of human pancreatic cancer primary patient tumour grafts in mice showing brightfield (left) and fluorescence (Cath E activity) (right) signal at tumour location ($n=4$). (B) Representative ex vivo image of mouse orthotopic tumour formed from cells (MDA PATC-3) isolated from human pancreatic cancer tumour grafts (A) showing fluorescence signal from pancreas with tumour (bottom) compared with a pancreas without a tumour (top) as well as kidney, muscle, bone, small intestine and lung ($n=3$).

Detection of pancreatic neoplasia by Cathepsin E activity in mouse models: hope for the future

Pancreatic cancer retains the worst prognosis of all major cancers highlighting the urgent need to identify molecular biomarkers that would enable early detection. In this issue of *Gut*, Cruz-Monserrate *et al* report their studies on Cathepsin E (Cath E). Cath E is an intracellular aspartic protease that belongs to the pepsin family of proteases which in normal physiology is expressed primarily in immune cells but is not expressed in normal healthy pancreas. It is however present in precursor lesions such as pancreatic intraepithelial neoplasia (PanIN) and nearly all pancreatic ductal adenocarcinoma (PDAC). The authors

investigated the utility of Cath E to act as an imageable biomarker for PDAC and tested the usefulness of a Cath E-activatable imaging probe to selectively detect pancreas containing PanIN lesions and PDAC. Pancreas from normal, chronic pancreatitis and PDAC patients was assessed for Cath E expression by quantitative real-time PCR and immunohistochemistry. Human PDAC xenografts and genetically engineered mouse models (GEMM) of PDAC were injected with a Cath E activity selective fluorescent probe and imaged using an optical imaging system. The elevated Cath E expression in PanIN and pancreatic tumours allowed in-vivo detection of human PDAC xenografts and imaging of pancreas with PanIN and

PDAC tumours in GEMM (see figure 2). These results support the usefulness of Cath E activity as a potential molecular target for PDAC and early detection imaging (see page 1315).

Hepatology

Liver cells augment the effects of RNA interference (RNAi) treatment

RNA interference (RNAi), a sequence-specific inhibition of gene expression, is an important mechanism of defence against viral pathogens, for example in plants. It is caused by small interfering RNA (siRNA) spreading from cell to cell. RNAi has been used as a novel approach to fight viral infections presently being investigated in numerous clinical trials.

This exciting study from Rotterdam (see page 1330) shows that both human liver cell lines and mouse livers exchange siRNA including endogenous microRNA and delivered siRNA targeting HCV or the viral receptor CD81. Interestingly, RNAi transmission was independent of cell-cell contact and mediated by exosomes. Importantly, inhibition of viral replication exceeded the percentage of transduced cells. Extension of RNAi to non-transduced cells may account for inhibition of HCV replication by 58% at a transduction efficiency of only 45%. These findings have important implications for RNAi-based therapies against HCV or other liver diseases. Hepatic transfer of gene silencing to non-transduced cells could help to overcome the problem of suboptimal vector transduction.