Highlights from this issue

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LUMINAL GI

Bringing precision medicine to the clinic

Substantial advances in the treatment of certain cancer types have been made in the last 10 years as the result of the development of targeted therapies, which are treatments directed at specific molecular alterations detected in these cancers. For targeted therapies to be successful, the tumours need to be characterised at the molecular level to determine if they will be sensitive to the therapy. This is particularly important because cancers vary significantly with regards to the molecular alterations they carry. So, a major challenge in the use of targeted therapies is matching therapies to tumours. Paterson and colleagues have now conducted a study to determine whether receptor tyrosine kinases are good targets for the treatment of gastro-oesophageal cancers. They used receptor tyrosine kinase arrays to identify promising candidates and then tested the efficacy of these therapies in pre-clinical model systems. They found that the MAPK (mitogen activated protein kinase) pathway was the most frequently activated pathway in gastro-oesophageal cancer and that it became more frequently activated as the tumours progressed. Most importantly, tumours with activated MAPK pathways were sensitive to inhibitors of this pathway. These results demonstrate that for molecularly heterogeneous cancers, target selection can be individualised using applications such as receptor tyrosine kinase (RTK) arrays ***(see page 1415)***.

Immune phenotypes of irritable bowel syndrome

Irritable bowel syndrome (IBS) patient subgroups have altered immune profiles but this immune activation has been controversial, with numerous contrasting reports. In this issue of Gut, Hughes *et al* studied the circulating immune profile in subclasses of IBS patients and how altered immune function specifically interacts with sensory pathways to give rise to symptoms of pain. Peripheral blood mononuclear cell (PBMC) supernatants from 20 diarrhoea predominant IBS (D-IBS) patients, 15 constipation predominant IBS (C-IBS) patients and 36 healthy subjects were applied to mouse colonic sensory nerves and the effects on mechanosensitivity were assessed. The authors found that the proinflammatory cytokines TNF-α, IL-1β and IL-6 were increased in PBMC supernatants from D-IBS patients, their receptors were expressed on colonic afferent endings, they sensitised colonic afferents to mechanical stimuli and they correlated with symptoms of pain (see figure 1). These findings suggest that distinct patterns of immune dysfunction and interaction with sensory pathways occur in different IBS patient groups through different intracellular pathways. The results indicate IBS patient subgroups would potentially benefit from selective targeting of the immune system ***(see page 1456)***.

The epidemic of gastro-oesophageal cancer

Over the last 20–30 years there has been a dramatic rise in the incidence of oesophageal cancer in western countries but the cause of this increase remains unclear. In this issue of Gut, Edgren *et al* carefully characterised the incident cases of oesophageal adenocarcinoma from population-based cancer registries in Australia, Europe, North America, and Asia. They found a consistent dramatic increase in incidence with an observed or estimated start in the rise in incidence between 1960 and 1990. Notably, the start time varied significantly between countries. Furthermore, the average annual increase ranged from 3.5% in Scotland to 8.1% in Hawaii. Their results suggest that the epidemic appears to be caused by some exposure that was first introduced around 1950 and should inform future studies that seek to determine the factors responsible for the increased incidence of oesophageal cancer ***(see page 1406)***.

Gata6 and pancreatic development

Gata6 is a transcription factor which is mainly involved in endocrine pancreas development. *GATA6* haploinsufficient de novo mutations are associated with pancreatic agenesis in humans. In this outstanding piece of work from Martinelli *et al*, the effects of Gata6 inactivation on pancreas development and function were analysed. Gata6 was deleted in all epithelial cells in the murine pancreas at the onset of its development. Acinar proliferation, apoptosis, differentiation and exocrine functions were assessed using RT-qPCR, chromatin immunoprecipitation, immunohistochemistry and enzyme assays. The authors found that Gata6 is not required for the formation of the exocrine or endocrine pancreas but it is

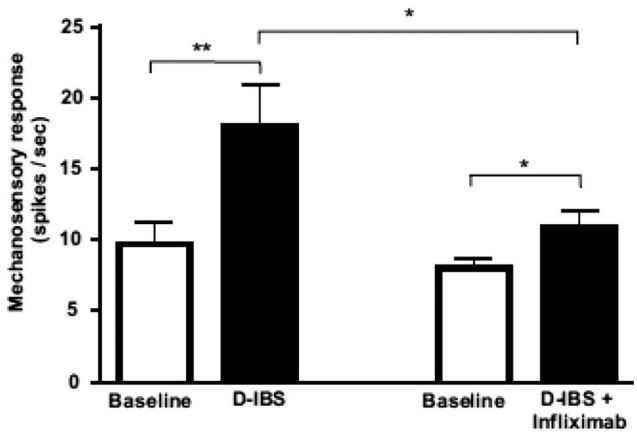

Figure 1 TNF-α is the primary mediator of colonic afferent mechanical hypersensitivity caused by immune products from diarrhoea predominant IBS (D-IBS) patients. Incubation of D-IBS PBMC supernatants with infliximab (1.5 mM) substantially reduced their ability to induce colonic afferent mechanical sensitisation (N=4, n=6) compared with D-IBS supernatants alone (N=5, n=6); however, a residual hypersensitive effect remains. All data expressed as Mean±SEM. *p<0.05, **p<0.01.

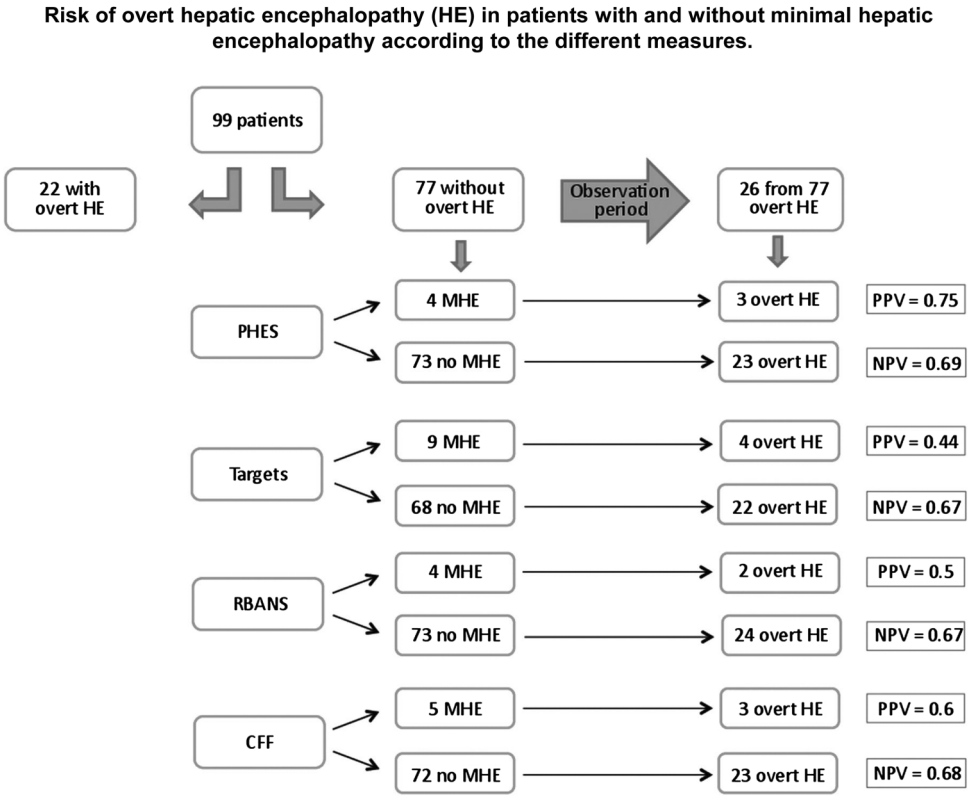

Figure 2 Risk of overt hepatic encephalopathy (HE) in patients with and without minimal hepatic encephalopathy according to the different measures. CFF, critical flicker frequency; PHES, psychometric hepatic encephalopathy score; RBANS, repeatable battery for the assessment of neuropsychological status; MHE, minimal hepatic encephalopathy; NPV, negative predictive value; PPV, positive predictive value.

essential for normal maturation of acinar cells (full expression of digestive enzymes and normal cell polarity). Gata6 is also required for the maintenance of the acinar compartment in the adult pancreas in the absence of damage. Gata6 inactivation favours acinar-to-ductal metaplasia and fat replacement of the pancreas, including epithelial-adipocyte transdifferentiation. However, no evidence of exocrine insufficiency was observed. The results have a translational relevance as in humans, *GATA6* genetic variation may contribute to the development of diseases of the exocrine pancreas ***(see page 1481)***.

HEPATOLOGY

Diagnosis of minimal hepatic encephalopathy (MHE) remains a challenge

Several psychometric tests and neurophysiological methods have been developed to diagnose hepatic encephalopathy in patients with cirrhosis of the liver. There is an on-going discussion about the best method to diagnose encephalopathy, in particular MHE. This interesting study from Hannover ***(see page 1497)*** shows that tests are influenced by age or by comorbidities such as diabetes mellitus or renal failure. Moreover it investigates the predictive values of several tests in patients without overt encephalopathy to develop clinical hepatic encephalopathy later on (figure 2). This study highlights the problems of psychometric tests to diagnose MHE. Please also read the insightful commentary by Peter Ferenci ***(see page 1394)***.

ENDOSCOPY

Follow-up after endoscopic resection of early gastric cancer

There are several ways to endoscopically resect early gastric cancer; the most promising with regards to oncologic completeness is endoscopic submucosal dissection (ESD), although at the cost of increased complication rates. This large retrospective Japanese series from the homeland of ESD shows that 20% of synchronous cancers in the proximal stomach are initially missed and that the annual incidence rate of metachronous cancers is 3.5%. Under the conditions of the strict Japanese endoscopic follow-up regimen every 6 months, the vast majority of these metachronous lesions were treatable endoscopically. It is however not known whether these results can be extrapolated to Western countries where initial retrospective enquiries showed much lower complete resection rates and also higher complication rates. A randomised trial is still urgently required before recommendations about the clinical application of ESD for early gastroc cancer at least in low-incidence countries can be made and based on evidence ***(see page 1425)***.

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