Highlights from this issue

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Luminal GI

Host genetics of Irritable bowel syndrome: more clues towards inflammation and infection

Irritable bowel syndrome (IBS) shows a familial tendency but studying host genetic factors in this condition is fraught with difficulty due to vaguely defined phenotypes. One in five of IBS begins with an acute gastroenteritis; this is defined as post-infectious IBS (PI-IBS). Given the similarity between PI-IBS and diarrhoea-predominant IBS (IBS-D), Swan *et al* hypothesised that IBS-D would be characterised by a genetic tendency to overreact to infectious or inflammatory insults and to show persistent immune activation. In order to test this hypothesis, the authors carried out two studies: in the first, they assessed gene expression analysis in rectal biopsies and peripheral blood mononuclear cell cytokine production in healthy volunteers, patients 6 months after *Campylobacter jejuni* infection, IBS-D and IBS with constipation (IBS-C) patients. In part 2, polymorphisms in genes whose expression was altered in Part 1 were assessed in 179 HV, 179 IBS-D, 122 IBS-C and 41 PI-IBS. Mucosal expression of CCL11, CCL13, TNFSF15 and Calpain 8 was increased while NR1D1, GPR161 and GABRE was decreased in IBS. Similar patterns were seen after infection with *Campylobacter jejuni*. Polymorphisms in *TNFSF15*, previously linked to Crohn's disease, were associated with IBS with diarrhoea. Polymorphisms in *TNFA* were also associated with post-infective IBS. The findings confirm a genetic tendency to a proinflammatory state in IBS and encourage the search for biomarkers to direct the use of anti-inflammatory treatments (see page 985).

A modified gluten challenge test for coeliac disease

Gluten challenge is used clinically in cases where coeliac disease is indeterminate and in evaluation of new therapeutic agents. Classical gluten challenge requires consuming 10 g of gluten per day for 8 weeks, but is poorly tolerated. Little is known regarding early changes which occur in adults with coeliac disease

undergoing gluten challenge. In this unique study from the USA, Leffler *et al* set out to test a new and simple gluten challenge protocol in 20 adults with biopsy-proven coeliac disease. The authors found that a 14 day GC at ≥ 3 g of gluten/day induced histological and serological changes in the majority of adults with coeliac disease. These data suggest that gluten challenge done for coeliac disease diagnosis may be abbreviated in many patients improving tolerability (see figure 1). They also permit accurate design of clinical trials and indicate that many individuals will meet coeliac diagnostic criteria after a 2-week gluten challenge (see page 996).

Identifying the cells that give rise to colorectal cancer

Studies in mice have identified a number of cell surface proteins that appear to be stem cell markers for intestinal epithelial cells, including, Wnt/Tcf, Lgr5, Ascl2 and Bmi1. These proteins have been proposed to identify cancer stem cells, and Ascl2 and Lgr5 may indicate whether a signalling pathway commonly deregulated in colon cancer, the Wnt signalling pathway, is activated. However, it has been unclear whether any of these are relevant to humans, which led Jubb and colleagues to assess the expression of these putative stem cell markers in human colorectal adenocarcinomas (figure 2). They found

that two of the markers, *ASCL2* and *LGR5*, are commonly expressed in human colorectal cancer and that other candidate stem cell markers are not as clearly relevant to human colon cancer. Their results suggest that *LGR5* and *ASCL2* may be useful for identifying human colorectal cancer derived predominately from intestinal crypt stem cells and that have deregulated Wnt signalling. Moreover, as Lgr5 is a transmembrane protein, it is a potential target for therapeutic intervention in this subset of cancers (see page 1012).

Assessing quality of care requires attention to detail

The abdominoperineal excision (APE) rate is a widely studied quality-of-care indicator in rectal cancer surgery. However, it is not clear if it is accurate if not properly adjusted for confounding factors. Penninckx *et al* have now evaluated variability in the APE rate between medical centres participating in PROCARE, a Belgian improvement initiative before and after adjustment for these confounding factors. They analysed data from the care of 3197 patients who underwent elective, radical resection for invasive rectal adenocarcinoma between January 2006 and March 2011 at 59 centres. The overall APE rate was 21.1% (19.7–22.5% 95% CI). Significant variation of the APE rate was observed before and after risk

Figure 1 Proposed modified gluten challenge algorithm.

Figure 2 A–B. Bright field (upper) and dark field (lower) in situ hybridisation for Ascl2 (A, score 2), Lgr5 (B, score 2), hybridisation is indicated by silver grain deposition against a haematoxylin and eosin stain.

Figure 3 Antiviral effects of NS5A replication complex inhibitor combinations with either an NS3 protease inhibitor or an NS5B inhibitor in mice infected with HCV genotype 1b. Each of the four mice were treated with 10 mg/kg of BMS-788329 and either 75 mg/kg twice daily of BMS-605339 (A) or 100 mg/kg of BMS-821095 (B) for four weeks (closed circles).

Hepatology

Predicting response of different genotypes to novel anti HCV drugs

Direct-acting antiviral drugs offer a major advance towards effective treatment of chronic viral hepatitis C and may allow for excellent response rates without the side effects of interferon-based therapy (see Welsch C, Jesudian A, Zeuzem S, *et al.* New direct-acting antiviral agents for the treatment of hepatitis C virus infection and perspectives. GUT 2012;61(Suppl 1): i36–i46.). This interesting study from Japan (page 1055) used a humanised mouse model to investigate the therapeutic effects of various combinations of antiviral agents on human hepatocytes infected with different hepatitis C virus genotypes. The combination of an NS5a inhibitor with different inhibitor classes cleared HCV genotype 1b (figure 3), but not genotype 2 infections. Presently, these results seem to be confirmed in on-going clinical trials. The present paper is an excellent example of translational research. It shows that combinations of new orally administered antiviral drugs can offer interferon-free treatment of viral hepatitis C—however, not any combination and not for every genotype (see page 1055).

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adjustment ($p < 0.0001$). Importantly, they found adjustment for confounding factors as well as merging Hartmann

with APE rates were important for the accurate assessment of performance between centres (see page 1005).