

Highlights from this issue

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Emad El-Omar, Alexander Gerbes and William Grady, *Editor and Deputy Editors*

Helicobacter pylori DNA may attenuate experimental colitis

IBD patients have a lower prevalence of *H pylori* infection compared with the rest of the population but the clinical relevance of this finding has always been intriguing. In this issue of Gut, Kao *et al* shed some light on this puzzle. Their work shows that *H pylori* DNA, which is shed into the distal intestinal track, is capable of unique immunoregulatory properties. In-vitro experiments revealed the inability of *H pylori* DNA to stimulate type I IFN or interleukin-12 production from mouse or human dendritic cells. *H pylori* DNA was also able to suppress *Escherichia coli* DNA production of type I IFN and IL-12. Most fascinatingly, the administration of *H pylori* DNA before the induction of DSS colitis significantly ameliorated the severity of colitis compared with *E coli* DNA or vehicle control in both an acute and chronic model. Finally, the systemic levels of type I IFN were found to be lower in *H pylori*-colonised patients than non-colonised controls (figure 1). The authors conclude by suggesting that asymptomatic *H pylori* colonisation may be of value in protecting against conditions such as IBD (see page 1479).

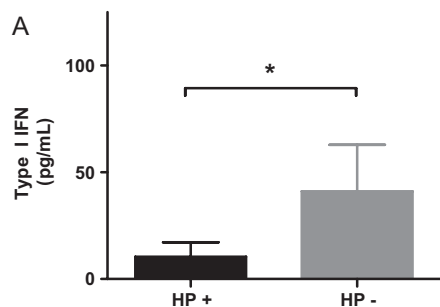


Figure 1 *H pylori*-colonised patients have lower systemic levels of type I IFN.

Cryptic genetic gluten intolerance responds to gluten free diet

The presence of both serum and intestinal mucosa antitransglutaminase (anti-TG2) antibodies are predictive of coeliac disease even in the absence of intestinal damage. In this study, Not *et al* investigated

whether mucosal antibodies represent an early stage of gluten intolerance even in the absence of intestinal damage and serum anti-TG2 antibodies. They studied 22 relatives of patients with coeliac disease genetically predisposed to gluten intolerance but in whom none of the usual diagnostic markers is present. The presence of IgA anti-TG2 antibodies in the intestine was studied by creating phage-antibody libraries against TG-2. They showed that the presence of mucosal anti-TG2 antibodies is significantly related to the presence of gluten-dependent symptoms and to serum levels of intestinal fatty acid-binding protein, a marker of early enterocyte damage. Many of these subjects had both extraintestinal (eg, anaemia, elbow arthritis, pancytopenia) and intestinal (eg, explosive diarrhoea, severe constipation) symptoms that were resolved on a gluten-free diet while the anti-TG2 antibodies had disappeared in the majority of cases (figure 2). See page 1487

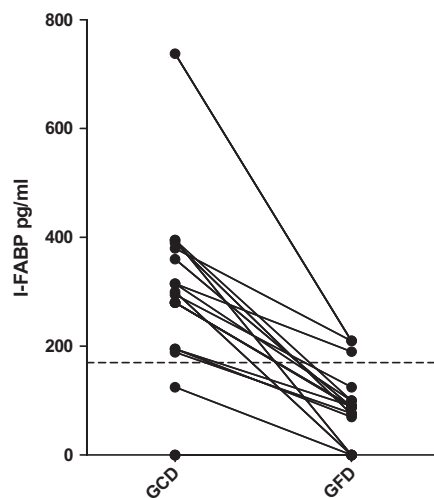


Figure 2 Serum concentration of intestinal fatty acid-binding protein (I-FABP), at the beginning of the study and after 1 year of diet in the 19 relatives who completed the clinical trial.

Is 5 years the right interval for post-polypectomy colonoscopy surveillance?

Individuals with colon adenomas are known to be at increased risk of forming subsequent polyps and therefore require

more frequent surveillance intervals than those without polyps. However, it is not clear which people with polyps will benefit the most from frequent colonoscopic exams. Chung and colleagues now present a study assessing the 5-year incidence of advanced neoplasms in individuals with a history of adenomas and identify risk factors that associate with increased or decreased risk of metachronous polyps. They conducted a prospective study of surveillance colonoscopy after screening colonoscopy on 3803 asymptomatic Koreans and analysed the outcomes in three different risk groups: normal (no baseline adenoma), low-risk (1–2 adenomas <10 mm) and high-risk (an advanced adenoma or >3 adenomas) groups. The low-risk group did not show an increased risk for subsequent advanced adenoma, however, the high-risk group showed a significantly higher 5-year rate (12.2% vs 2%) and early recurrence rate (figure 3). These results suggest that the surveillance interval for low-risk patients could be extended beyond 5 years saving resources for those people at highest risk for recurrent colon polyps, who appear to need colonoscopy every 3 years (see page 1537).

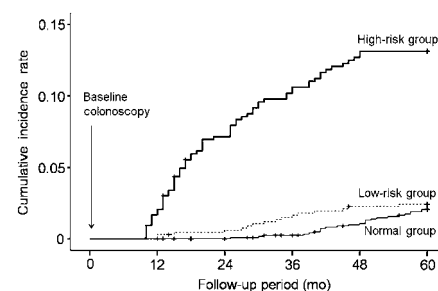


Figure 3 Cumulative incidence of advanced adenoma according to the baseline risk categories.

Turbo-charging chemotherapy for colorectal cancer (CRC)

Insights into the molecular biology of CRC promise to lead to more effective treatment for this common cause of cancer-related deaths. The aberrant methylation of genes is one mechanism

through which cancers silence tumour suppressor genes. These methylated genes can be reactivated by drugs that reverse epigenetic alterations, and drugs with these effects represent a class of promising agents for cancer chemotherapy. ‘Statins’ are cholesterol-lowering drugs with an excellent safety profile and are associated with a reduced incidence of various cancers including CRC. Interestingly statins appear to act by activating tumour suppressive bone morphogenetic protein (BMP) signalling in CRC, increasing expression of BMP2. In this issue of Gut, Kodach *et al* demonstrate that BMP2 is silenced by promoter hypermethylation and that treatment with lovastatin downregulates DNA methyltransferase activity, leading to BMP2 promoter demethylation and to increased expression of BMP2 as well as other genes methylated in CRC (figure 4). Perhaps most importantly, simvastatin sensitised colon cancer cells to the effects of 5-fluorouracil, perhaps through upregulating BMP signalling, which can alter the ‘stem-like’ state of CRC cells. These results suggest statins may be able to be re-purposed as cancer chemotherapy agents for CRC (*see page 1544*).

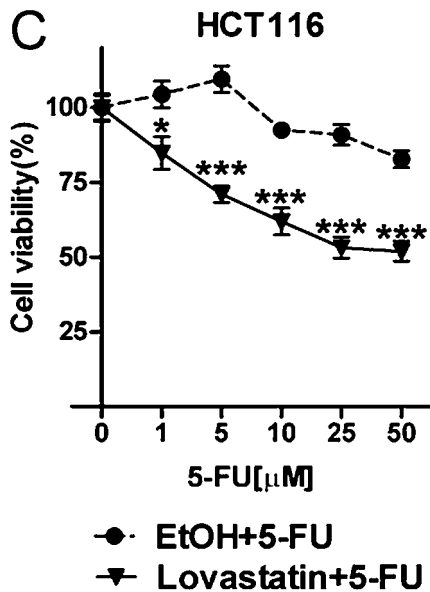


Figure 4 After 5 days of treatment with lovastatin or EtOH and 1 day of no treatment, cells were treated with different concentrations of 5-fluorouracil (5-FU), and the MTT assay was performed. Values are expressed as a percentage of living cells relative to the control with control values set at 100%.

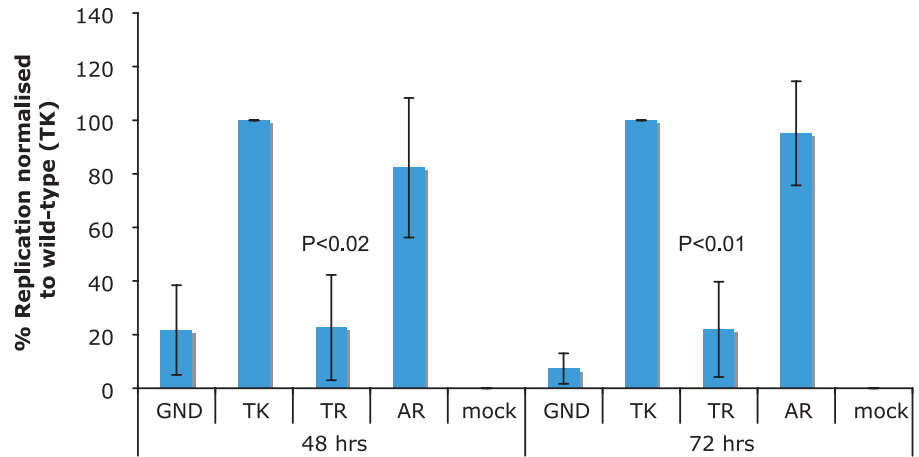


Figure 5 The percentage replication efficiency of mutants compared to wild-type (TK). Representative time course of mutants TR and AR compared with wild-type (TK) and the negative mutant (GND) at 48 and 72 h.

Hepatology

Interesting news for HCV immunobiology

The reasons why T cells fail to control HCV viraemia remain a critical issue. This interesting study used samples from a group of Irish women who were infected with HCV in 1977 from a single source, namely through contaminated anti-D immunoglobulin. With this unique set of genetic information the authors tried to elucidate the mechanisms of viral clearance linked with HLA-A03. They found that a single escape mutation is accompanied by a marked impairment of viral fitness which may be rescued by a mutation at a second covariant site (figure 5). These results may have important implications for HCV vaccine studies (*see page 1563*).

p38 MAP kinase: a novel therapeutic target for hepatic encephalopathy

Neuroinflammation has been considered as a key element in hepatic encephalopathy. However, treatment with anti-inflammatory drugs such as ibuprofen is accompanied by side effects, mainly renal dysfunction. This important study from Valencia assessed the potential of p38 inhibition in a rat model of hepatic encephalopathy. Using SB 239063, a second generation inhibitor of p38 they achieved reduction of neuroinflammation (figure 6), restoration of learning ability and of motor coordination (figure 7).

Interestingly, this was not accompanied by impairment of renal function. Novel compounds inhibiting p38 have entered phase 1 and phase 2 trials for inflammatory diseases and may soon be tested for treatment of hepatic encephalopathy (*see page 1572*).

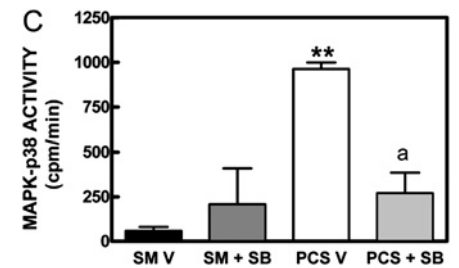


Figure 6 p38 activity in the cerebral cortex is increased in rats with portacaval shunts (PCS) compared to sham controls (SM). The p38 inhibitor SB significantly attenuates p38 activation.

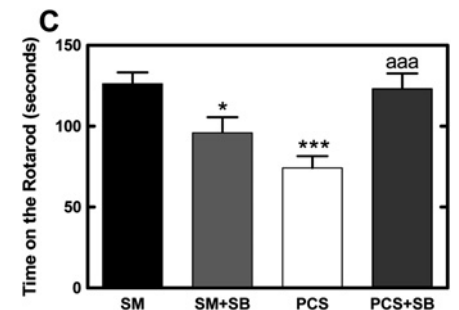


Figure 7 Treatment with SB restores motor coordination in portacaval shunt rats.