

# Highlights from this issue

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## Luminal GI

### *Helicobacter pylori* eradication and/or celecoxib for gastric cancer prevention: two is not better than one

Eradication of *H. pylori* is known to slow down or even reverse premalignant gastric lesions. COX-2 over-expression may be an important step in *H. pylori* associated gastric carcinogenesis. Although several studies have shown that long-term use of aspirin or non-aspirin NSAIDs can prevent the development of GC, no randomised study of selective COX-2 inhibitor, such as celecoxib, on GC prevention or its precursors has yet been reported. In this issue of Gut Wong *et al* evaluated the effect of celecoxib alone and combined with *H. pylori* eradication on the evolution of precancerous gastric lesions. They conducted a randomised, placebo controlled trial in Linqu County, Shandong Province, China, an area with a very high incidence of gastric cancer. This population-based intervention trial revealed that celecoxib treatment or *H. pylori* eradication alone had beneficial effects on the regression of advanced gastric lesions. Curiously however, no favourable effects were seen for *H. pylori* eradication followed by celecoxib treatment (see table 1). (see page 812).

### Probiotics protect small bowel epithelium against radiation damage

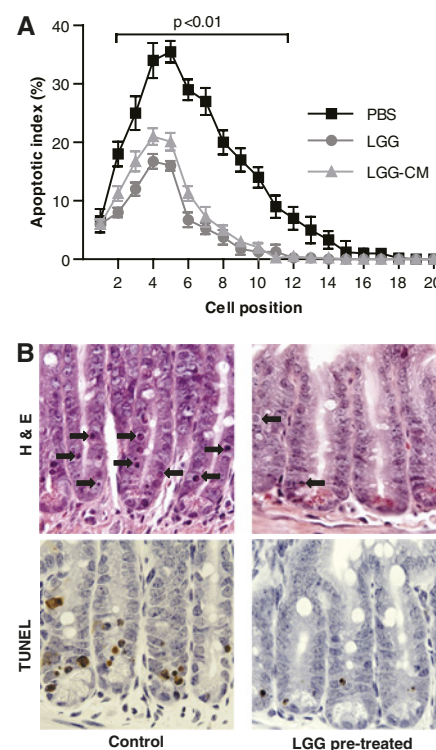
The small intestinal epithelium is highly sensitive to radiation and frequently suffers serious injury during radiation therapy and environmental overexposure. In this excellent study from the US,

Ciorba *et al* examined probiotic bacteria as potential radioprotective agents in the intestine. 8-week-old C57BL/6 wild-type or knockout mice were administered probiotic by gavage for 3 days before 12 Gy whole body radiation. The intestine was evaluated for cell-positional apoptosis (6 h) and crypt survival (84 h). Orally administered *Lactobacillus rhamnosus* GG (LGG) probiotic and its conditioned medium protected the murine small intestinal epithelium from radiation injury (see figure 1). This radioprotection is dependent on MyD88, TLR-2 and COX-2 and occurs without significantly altering the bacterial family composition of the small intestine. The authors raise the possibility that LGG, other probiotic bacteria, or probiotic-derived products may be useful as a prophylactic strategy to limit intestinal injury to humans during radiation therapy. (see page 829).

### Location, location, location—What do we know about colon cancers that occur on the right side of the colon versus the left side of the colon?

The anatomic location of colorectal cancer in the colon is believed to affect the pathogenesis of the tumour. Thus, colorectal cancer is often thought of as being either right-sided or left-sided. The frequency of certain mutations, such as *BRAF V600E* mutations, and of microsatellite instability varies between tumours found on the right and left side of the colon supporting the concept that the right and left colon have fundamental differences when it comes to colorectal

cancer. It is not clear if this transition from right to left colon is abrupt or gradual. Yamauchi have addressed this question in this issue of Gut. They have studied 1443 colorectal cancers from two US nationwide prospective cohort studies and found that there was a gradual shift in many of the molecular features in the tumours when going from right to left in



**Figure 1** Radiation-induced epithelial apoptosis is suppressed by *Lactobacillus rhamnosus* GG (LGG) and LGG conditioned medium (LGG-CM). C57/B6 mice (8–10-weeks-old) received gavage with phosphate-buffered saline (PBS) (control), LGG ( $5 \times 10^7$ ) or LGG-CM for 3 days before exposure to 12 Gy of whole body  $\gamma$  radiation. (A) Cell position distribution of apoptotic epithelial cells was determined on H&E and TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling). Stained slides in 100 proximal jejunal half-crypt sections per mouse ( $n=6$ /group) and expressed as the apoptotic index. The apoptotic index was significantly lower in mice pretreated with LGG or LGG-CM versus control ( $p<0.01$  at all cell positions 3–12). This protected region included the putative stem cell domain (position 4–5). (B) Representative images from the jejunum are shown with arrows pointing to apoptotic cells (200 $\times$ ).

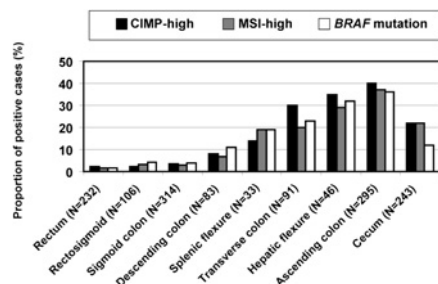
**Table 1** Regression and progression of histopathology by different treatment arms\*

Group	No change n	Regression n	OR (95% CI)*
Intention-to-treat analysis			
Placebo	78	99	1.00
Anti-Hp+celecoxib	59	114	1.50 (0.97 to 2.32)
Anti-Hp+placebo	55	126	1.80 (1.16 to 22.78)
Celecoxib+placebo	61	120	1.55 (1.01 to 22.38)
Per-protocol analysis			
Placebo†	67	82	1.00
Anti-Hp+celecoxib‡	47	84	1.48 (0.91 to 2.40)
Anti-Hp+placebo‡	36	96	2.19 (1.32 to 3.64)
Celecoxib+placebo‡	49	102	1.72 (1.07 to 2.76)

\*ORs and 95% CIs were calculated by logistic regression and adjusted for age, sex, smoking and drinking status.

†The participants who remained *H. pylori* positive.

‡The participants in whom *H. pylori* was eradicated (negative by carbon-13 urea breath test after 45 days).

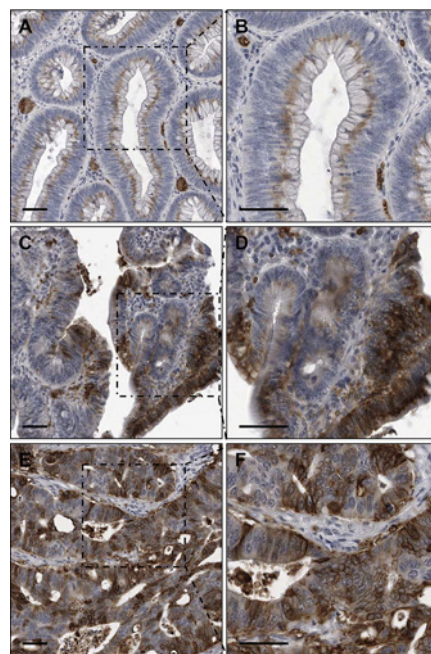


**Figure 2** Frequencies of CIMP-high, MSI-high, and BRAF mutation in colorectal cancer along bowel subsites. The frequencies of these molecular features increase gradually from the rectum to the ascending colon. CIMP, CpG island methylator phenotype; MSI, microsatellite instability.

the colon. Their results challenge the common conception of discrete molecular features of right versus left-sided colorectal cancers, which has implications for translational and epidemiology research figure 2. (*see page 847*).

### New markers for aggressive colon adenomas?

The early detection of colon adenomas at high risk of progression to cancer and of early stage colorectal cancer (CRC) is an effective approach to reduce CRC mortality rates. However, our current screening methods rely on the histological assessment of the adenomas, which cannot precisely tell which adenomas are likely to progress and which ones will remain adenomas. Precise markers for high-risk adenomas could be used to personalise screening programs and develop new screening methods. De Wit *et al* conducted a proteomic based screen of colorectal neoplasms and found increased protein expression in high-risk adenomas and CRCs compared to low-risk adenomas for the glucose transporter type 1 (GLUT1; gene symbol *SLC2A*) and prion protein (PrPC; gene symbol *PRNP*;  $p < 0.005$ ). They showed that GLUT1 and PrPC, as well as 42 other cell surface candidate biomarkers for adenoma-to-carcinoma progression could



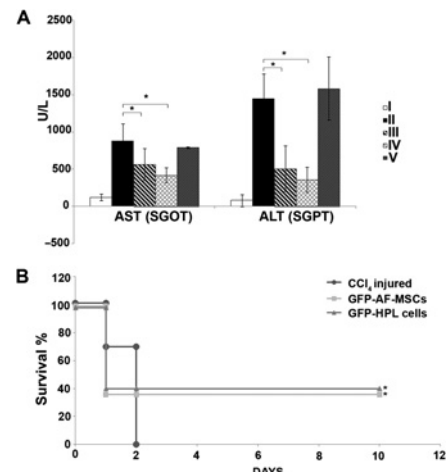
**Figure 3** GLUT1 immunohistochemical staining of colon adenomas and carcinomas. TMAs containing a series of colon adenomas and carcinomas were stained for GLUT1 by immunohistochemistry. Representative examples show that GLUT1 staining of epithelial cells in adenomas (A, B) was less intense than in high-risk adenomas (C, D) and carcinomas (E, F). GLUT1 staining was present in the cytoplasm and at the plasma membrane of the epithelial cells. Scale bars indicate 50  $\mu$ m.

potentially serve as targets for emerging molecular imaging modalities like optical imaging and be accurate markers for high-risk adenomas figure 3. (*see page 855*).

## Hepatology

### Cell-based therapies for acute liver failure—a novel approach

Liver transplantation is the ultimate treatment for acute liver failure. However, the decision to list a patient for high-urgency transplantation is difficult because of the uncertainty about spontaneous recovery, the need of lifetime immunosuppression and 1-year mortality probabilities around 30%. Therefore cell-



**Figure 4** Hepatic function after GFP-AF-MSC, HPL or HL cell transplantation. (A) Biochemical analysis for estimating the concentrations of AST (SGOT) and ALT (SGPT) in blood serum. Group I: non-injured mice that did not undergo transplantation, Group II: injured mice that did not undergo transplantation, Group III: injured mice that received GFP-AF-MSCs, Group IV: injured mice that received GFP-HPL cells and Group V: injured mice that received GFP-HL cells. (B) Treatment with GFP-AF-MSCs or GFP-HPL cells significantly prolonged the survival of the mice received lethal dose of  $\text{CCl}_4$  in contrast to non-treated animals.

based approaches have been proposed in order to support liver function and to improve hepatic regeneration. This study from Greece (*see page 894*) suggests the use of human amniotic fluid mesenchymal stem cells and hepatic progenitor-like cells which have the advantage of low immunogenic profiles. In a mouse model of acute liver failure a single intravenous dose of either cell type reduced liver injury and improved survival (figure 4A,B). Interestingly, secretion of cytokines such as IL-10 from the transplanted cells seemed to be crucial for these effects. However, only 6% of the amniotic fluid mesenchymal cells could be used for further expansion and for storage. Moreover, the superiority of these cells over previously described cell models remains to be shown.