Digest

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Seven-microRNA signature and prediction of gastric cancer survival

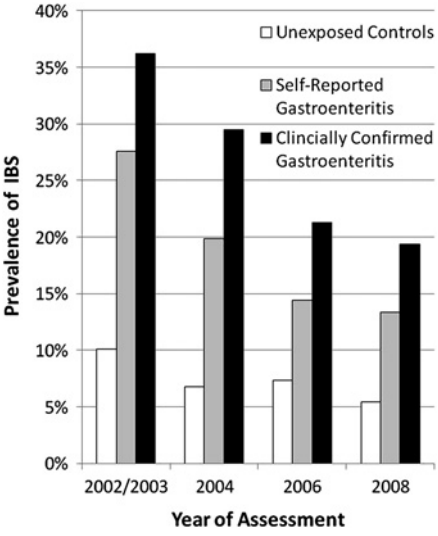
MicroRNAs are a wide class of small, non-coding RNAs that negatively regulate protein expression at the post-transcriptional level. MicroRNAs regulate the expression of hundreds of their target genes, thereby controlling a wide range of biological functions such as cellular proliferation, differentiation and apoptosis. Disruption of the physiological expression patterns of micro-RNAs is associated with several examples of human tumorigenesis. In this study by Li *et al* microRNA expression profile was analysed by real-time RT-PCR in 100 patients with gastric cancer, and Cox proportional hazard regression and risk-score analysis were used to identify a stage-independent set of seven-microRNA signatures. This microRNA signature was further validated in an independent cohort of 60 patients. Multivariate analysis showed that the risk signature was an independent predictor of overall survival (HR=3.046; 95% CI 1.246 to 7.445, p=0.015) and relapse-free survival (HR=3.337; 95% CI 1.298 to 8.580, p=0.012) (figure). This prognostic signature could be applicable to future decisions about treatment. ***See page 579***.

Levofloxacin or clarithromycin for first- or second- line *H pylori* regimens

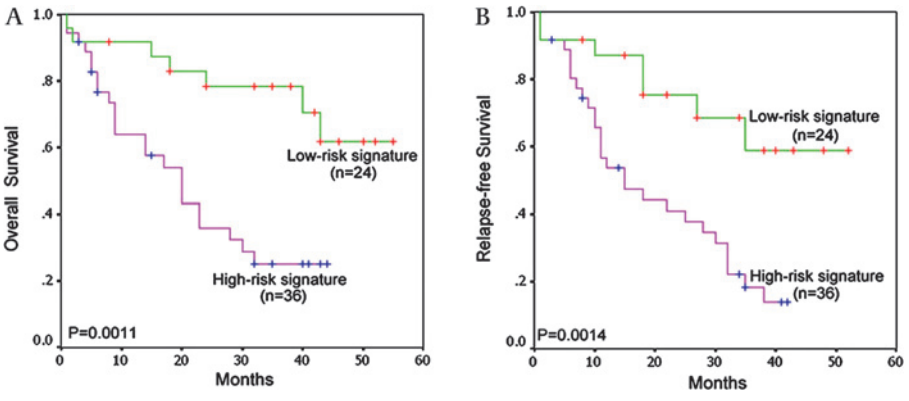
Which antibiotic is better to use first: levofloxacin (LAL) or clarithromycin (CAL)? This question was answered by Wu *et al* in a randomised comparative trial with crossover design. Eligible patients were randomised to receive LAL (750 mg every day), amoxicillin (1000 mg twice a day) and lansoprazole (30 mg twice a day) for 7 days, OR CAL (500 mg twice a day), amoxicillin (1000 mg twice a day) and lansoprazole (30 mg twice a day) for 7 days. Patients with positive [^{13}C]urea breath test after treatment were re-treated with a rescue regimen in a crossover manner for 10 days. In the intention-to-treat (ITT) analysis, the CAL regimen achieved a higher eradication rate than LAL (74.2% and 83.7%, p=0.015). For the second-line treatment, the eradication rate of LAL and CAL were 76.9% and 60% (p=0.154) in ITT analysis. The overall eradication rate of CAL followed by a LAL regimen was better than the reverse sequence (93% vs 85.3%, p=0.01). The authors conclude that using CAL as initial treatment and LAL for rescue is a better strategy overall. ***See page 572.***

Long-term prognosis of post-infectious IBS

Acute gastroenteritis is a known risk factor for irritable bowel syndrome (IBS). The pathogenesis of postinfectious irritable bowel syndrome (PI-IBS) is, however, poorly understood. With prolonged follow-up, most patients will eventually improve. In this study, the authors report the 8-year outcome of PI-IBS in the Walkerton cohort, a cohort of people from the community outbreak of acute gastroenteritis related to municipal water contamination in May 2000 in Walkerton, Canada. Of the 4561 participants, 2451 returned for their 8-year assessment and 1166 were eligible for the PI-IBS study cohort (688 women, mean age 46.2 years). The prevalence of IBS declined from 28.3% after 2–3 years to 15.4% after 8 years (figure), but remained significantly increased compared with controls who did not have acute gastroenteritis (OR=3.12; 95% CI 1.99 to 5.04). Independent risk factors for PI-IBS at 8 years included female gender, younger age, prior anxiety/depression and fever or weight loss during the acute enteric illness. The authors conclude that acute gastroenteritis can trigger IBS symptoms that persist for at least 8 years. Characteristics of the host and the acute enteric illness can predict the long-term risk of PI-IBS. ***See page 605.***



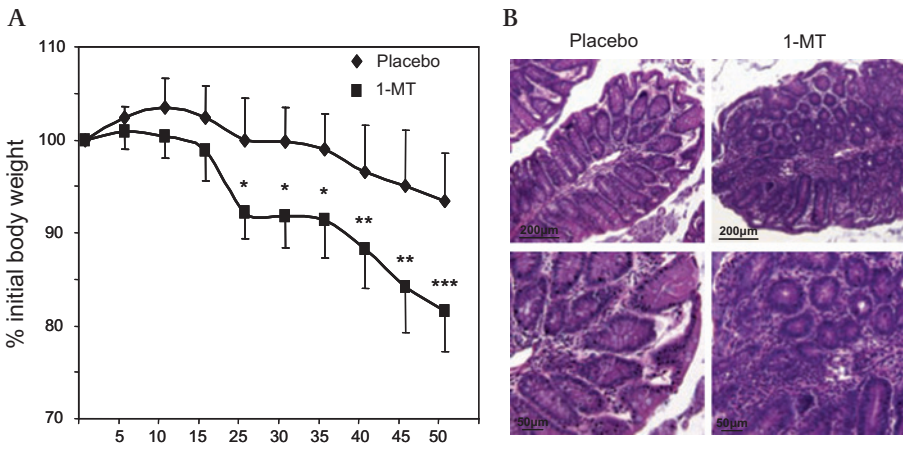
Prevalence of IBS by Rome I criteria.



Kaplan–Meier estimates of overall survival and relapse-free survival according to the seven-microRNA signature.

Indoleamine dioxygenase expression in intestinal dendritic cells and oral tolerance

CD103+ dendritic cells (DCs) from the lamina propria and the mesenteric lymph nodes preferentially drive CD4+Foxp3+ T-regulatory cells. Indoleamine 2,3-dioxygenase (IDO) is an enzyme involved in tryptophan catabolism that is expressed by DCs and has immunosuppressive effects. Activation of IDO has detrimental effects on T-cell proliferation through tryptophan deprivation and via induction



IDO inhibition by 1-methyl-＞dl-tryptophan (1-MT) worsens disease in a T-cell-transfer colitis model. (A) Variation in body weight; (B) the H&E staining of the colon compared with placebo.

of Treg cells. In this study, the authors investigated the expression and role of IDO in the tolerogenic properties of intestinal DCs. They demonstrate in their experiments that IDO is expressed primarily by CD11c+CD103+ DCs in the gut both in humans and in mouse. IDO was involved in the ability of CD103+ DCs to drive Foxp3+ Treg cell development and IDO activity was required for the establishment of oral tolerance. Blocking of IDO worsened T-cell-mediated and DSS colitis. Therefore, they conclude that IDO expression in intestinal DCs is important for the regulation of intestinal immune homoeostasis by keeping the balance between Foxp3+ Tregs and Th1/Th17 effector cells in the lamina propria and may represent a possible therapeutic target for gut disorders. ***See page 595.***

Hepatology

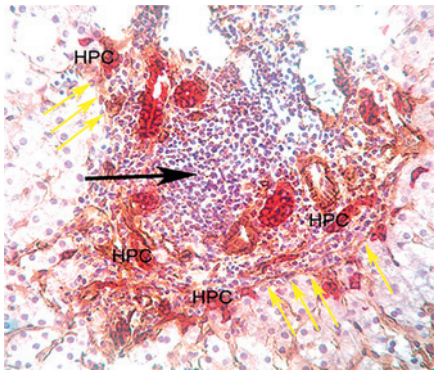
Focus on liver progenitor cells

A typical hepatic structure for progenitor cells in mice and men

In severe liver injury hepatic progenitor cells can be activated and may contribute to liver regeneration. The existence of liver stem cells, initially termed oval cells, has been known for about 50 years, but only recently has there been major progress in understanding their origin and role. The paper by Stuart Forbes and his group is a major step forward by describing important morphological and functional features of liver progenitor cells. In rodent models as well as in liver tissue of patients with chronic viral hepatitis they were able to characterise a stereotypical progenitor cell niche. This niche is composed of macrophages, myofibroblasts and endothelial cells and a laminin matrix. Interaction of progenitor cells with this laminin matrix seems to be pivotal for gene expression and cellular differentiation. Further characterisation of these minute liver repair units may enable us to influence regeneration and fibrosis of the liver. ***See page 645.***

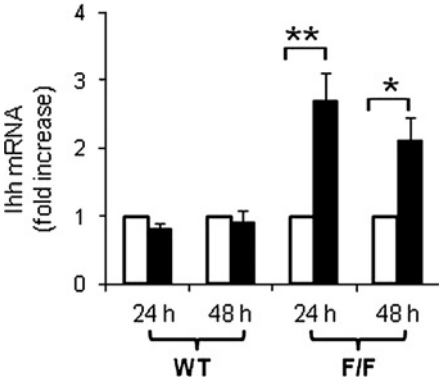
How dying hepatocytes promote liver regeneration

Hedgehog signalling is important for wound healing and during development. In the normal liver Hedgehog activity is low, but increases markedly in various types of liver disease. The exciting study



Hepatic progenitor cell niche in a patient with chronic hepatitis C.

by Anna Mae Diehl and her group provides a novel mechanism linking hepatocyte death to regenerating pathways resulting in repair of liver injury and in fibrosis. Using hepatocytes, animal models and human tissue, they establish a remarkable sequence: hepatocytes undergoing apoptosis produce Hedgehog ligands which recruit liver progenitor cells, but also myofibroblasts. Thus, dying hepatocytes stimulate liver regeneration and at the same time induce fibrosis. Interfering with Hedgehog signalling thus might be a promising approach to influencing the development of liver cirrhosis or even hepatocellular carcinoma. ***See page 655.***



Hepatocyte apoptosis promotes Hedgehog signalling or IgG.