Digest

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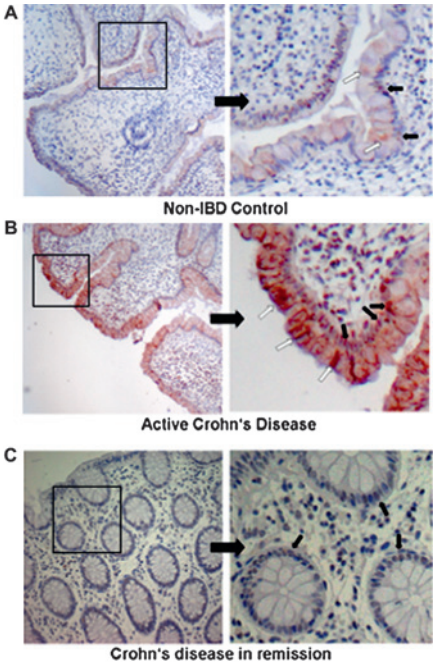
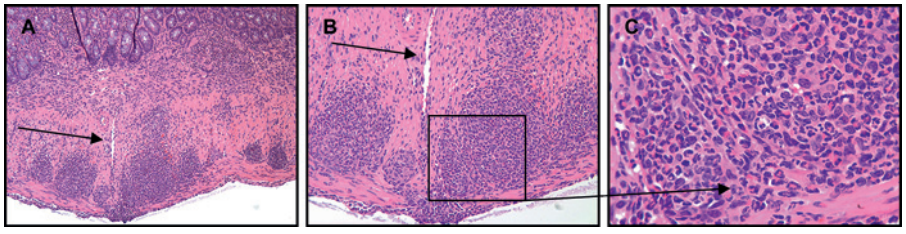
SHIP deficiency causes Crohn's disease-like ileitis

Inflammatory bowel disease is characterised by changes in intestinal epithelial cell integrity and immune regulation. SHIP controls the homeostasis of immunoregulatory myeloid and T lymphoid cells. In this study, the authors determined if SHIP plays a role in control of immune tolerance in the gut mucosa. They studied SHIP deficient mice and their respective wild-type (WT) littermates. To determine if SHIP is needed for intestinal epithelial barrier integrity or mucosal immunoregulation, SHIP-deficient hosts were reconstituted with WT haematopoietic cell grafts, and WT hosts with SHIP-deficient haematopoietic grafts including whole splenocytes, purified T cells or NK cells. The results of these experiments show that SHIP-deficient mice develop segmental, transmural pyogranulomatous ilietis resembling the changes observed in Crohn's disease (see figure). WT Bone marrow reconstitution of SHIP-/- hosts corrected ileitis and reconstitution with SHIP-/- splenocytes transferred ileitis to WT hosts. They conclude that SHIP plays a pivotal role in immune function in the intestine and that further study in IBD is required. Also, SHIP-deficient ileitis results from a local deficit in mucosal T cell immunity that promotes a damaging granulocyte-monocyte inflammation of the distal ileum. ***See page 177***.



Expression of PTPN2 in intestinal biopsies from controls (A), active CD (B) and CD in remission (C).



CD -like ileitis of SHIP-deficient mice with transmural inflammatory cell infiltrations, bowel wall thickening and stricture formation. Arrows show fissures that penetrate into and ended blindly within the tunica muscularis.

PTPN2 regulates TNFalpha-effects

The Crohn's disease susceptibility gene Protein tyrosine phosphatase N2 (PTPN2), regulates IFNγ-induced signalling and epithelial barrier function in intestinal epithelial cells (IEC). The authors here investigated whether PTPN2 is also regulated by TNFα and if PTPN2 controls TNFα-induced signalling and effects in IEC. They used T84 IECs and performed Western blotting (protein), RT-PCR (mRNA), ELISA (cytokines) and immunohistochemistry. PTPN2 knock-down was induced by siRNA. They demonstrate that TNFα led to an increase in PTPN2 mRNA as well as protein levels and caused cytoplasmic accumulation of PTPN2. Biopsies from patients with active CD showed strong PTPN2 staining in the epithelium, whereas CD in remission had PTPN2 levels similar to non-IBD controls (see figure). PTPN2 expression in UC was lower than in active CD. Samples from CD patients responding to anti-TNF treatment also showed PTPN2 levels that were similar to those in control patients. Pharmacological inhibition of NFκB by BMS-345541 prevented the TNFα-induced increase in PTPN2. The findings suggest a possible mechanism of how PTPN2 dysfunction could contribute to the onset of chronic intestinal inflammation, as seen in Crohn's disease. ***See page 189***.

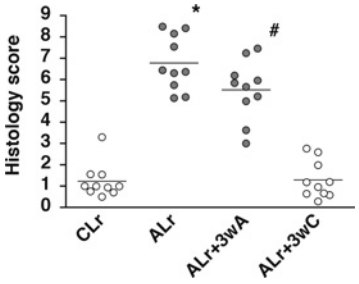
Concurrent drug use and the risk of perforated colonic diverticular disease

Perforated diverticular disease is an important surgical emergency with a high mortality and increasing incidence. The role of concurrent drug use in diverticular perforation is not clear. In this study, Humes *et al* determined if current or ever use of a corticosteroid, opiate analgesic, NSAID, aspirin, cyclooxygenase-2 inhibitors (coxibs), calcium channel blocker or statin was associated with diverticular perforation. They used a large administrative primary care database from the UK to identify cases of perforation (899) and compare them with the general population (8980). They found that current use of opiate analgesics and oral corticosteroids was associated with a two- and three-fold increase in the risk of diverticular perforation, respectively. Current use of calcium antagonists and aspirin had no effect while use of statins reduced risk by 54%. The authors suggest that clinicians should avoid prescribing opiates and corticosteroids to patients with diverticular disease, where possible. ***See page 219***.

Alcohol abstinence and regression of LPS-induced pancreatic injury

Is alcoholic pancreatitis reversible? It is well established that alcohol and lipopolysaccharide (LPS) lead to pancreatic injury (including fibrosis) in rats. Pancreatic stellate cells (PSCs) are the main effectors of pancreatic fibrosis. In this interesting study, Vonlaufen *et al* studied rats that had been fed isocaloric Lieber-DeCarli liquid diets ± alcohol for 10 weeks and were

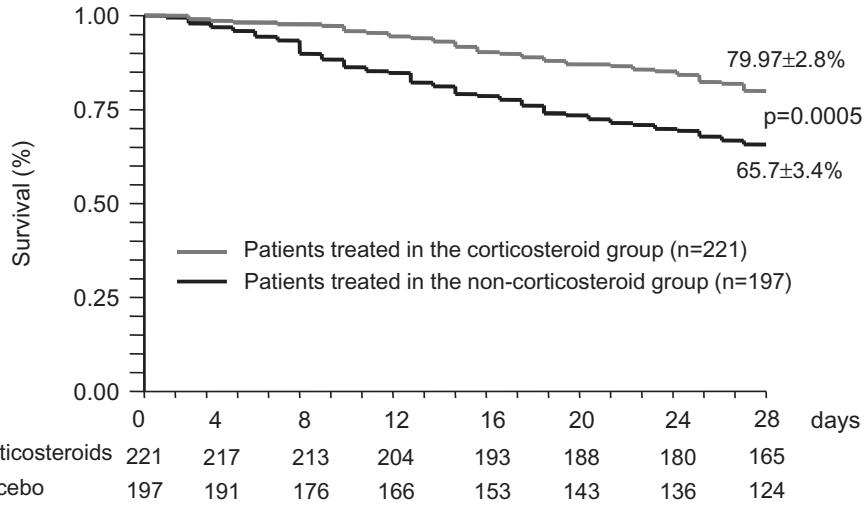
challenged with LPS (3 mg/kg/week for 3 weeks) and then either switched to control diet or maintained on an alcohol diet for 3 days, 7 days or 3 weeks. Pancreatic sections were assessed for acute tissue injury, fibrosis, PSC apoptosis and activation. Alcohol continuation after established pancreatitis perpetuated the disease while alcohol withdrawal led to regression of pancreatic lesions (including fibrosis, see figure). Alcohol and LPS inhibited PSC apoptosis in vitro. Extrapolating the findings to humans suggests that alcohol abstinence can lead to regression of pancreatic injury and should be encouraged. Proapoptotic agents promoting PSC apoptosis may be a useful therapeutic approach in chronic alcoholic pancreatitis. ***See page 238***.



Morphometric assessment of the effect of alcohol continuation/withdrawal for 3 weeks on established pancreatitis. CLr = control diet-fed rats receiving repeated LPS injections; ALr = alcohol-fed rats receiving repeated LPS injections; ALr+3wA = alcohol-fed rats receiving repeated LPS injections followed by 3 weeks of alcohol diet; ALr+3wC = alcohol-fed rats receiving repeated LPS injections followed by 3 weeks of control diet.

Treating alcoholic hepatitis—new cut-off values for the Lille score

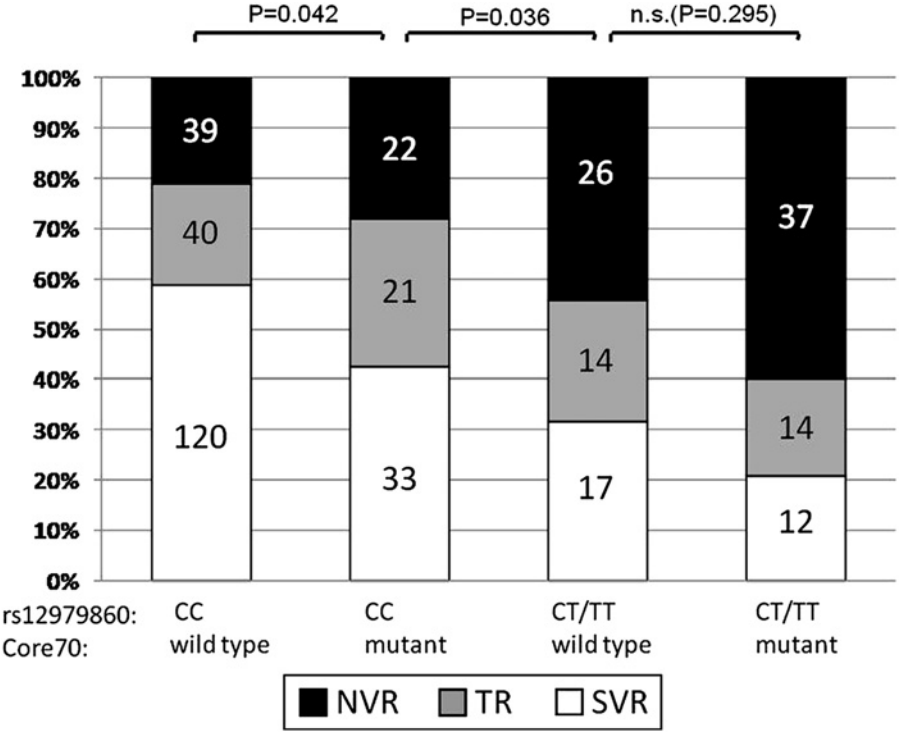
The efficacy of corticosteroids in improving survival in alcoholic hepatitis has been controversially discussed. However, now it is widely accepted that patients with severe alcoholic hepatitis benefit from steroid treatment. This important meta-analysis combines individual patient data of five large randomised trials on the effects of corticosteroids including the two most recent trials employing enteral nutrition and an antioxidative cocktail, respectively in the control groups. It confirms the survival benefit for corticosteroid treatment. More importantly, the Lille score was revisited which uses mainly the change of serum bilirubin after 7 days to predict 28 day survival. By defining two new cut-off values (see figure) Mathurin and colleagues define two subgroups of patients who benefit clearly from steroid treatment. In contrast patients with a score above 0.56 at 7 days of treatment are very unlikely to improve and should be considered for alternative therapies. ***See page 255***.



Probability of 28-day survival according to the new Lille score categories.

Viral and host genetics independently affect response to HCV treatment

Several recent studies have demonstrated a marked effect of *IL28B* polymorphisms in patients with chronic hepatitis C virus infection on the response to combination therapy with interferon and ribavirin. The role of *viral* polymorphisms for treatment response has been controversially discussed. This important study from Japan analyzes both viral and host genetic factors in a group of more than 800 HCV patients. Host, but also viral polymorphisms, independently predicted sustained virological response (see figure). These findings suggest that host and viral genetics influence treatment outcome through different mechanisms and have important implications for future trials of HCV treatment. ***See page 261***.



Cumulative effect of HCV polymorphisms on response to therapy.