GI highlights from the literature

Mairi H McLean, Education editor

BASIC SCIENCE
Red meat consumption, gut microbiota and cardiovascular disease


Numerous studies have highlighted the contribution of the gut microbiota to diseases including cancer, inflammatory conditions such as metabolic disorders and also cardiovascular disease (CVD). Mechanistic studies have shown that the colonic microbiota modulates many host functions including lipid accumulation and inflammation, with dietary influence on microbiome composition becoming ever more apparent. However, there is currently little information on the specific mechanisms through which the gut microbiota exerts its effects and also the influence of specific dietary components especially with reference to red meat consumption which is heavily linked to CVD risk within the developed world. Recent studies have shown that microbial processing of dietary choline produces trimethylamine which is further metabolised to the pro-atherogenic species, trimethylamine-N-oxide (TMAO). This recent study from Cleveland, USA examined the gut microbiota-dependent metabolism of L-carnitine to produce TMAO in both rodent and human studies. Using isotope tracer human clinical studies to examine the effects on CVD risk, they demonstrated a mechanistic link between intestinal microbial metabolism of dietary phosphatidylcholine (lecithin) and L-carnitine, derived predominantly from red meat, and coronary heart disease through the production of a pro-atherosclerotic metabolite. This was attributed to suppression of reverse cholesterol transport by the gut microbiota. The authors demonstrate that bacteria belonging to the Firmicutes phylum (specifically within the Clostridiaceae and Peptostreptococcaceae families) were associated with TMAO production. The study highlights the influence that dietary regimes can have on metabolic functioning of the microbiota and clearly demonstrates that dietary influence can be independent of obesity and obesity-associated disorders; although inflammation associated changes are clearly important in CVD.

Caspase-8; a potential novel future therapeutic target for nonalcoholic steatohepatitis


Due to the increasing incidence of obesity and the metabolic syndrome, chronic liver ailments such as nonalcoholic fatty liver disease (NAFLD) are rapidly increasing in prevalence. Nonalcoholic steatohepatitis (NASH), a progressive form of NAFLD, is characterised by increased fat accumulation, inflammation, and cellular apoptosis in the liver. Furthermore, NASH has been linked as a precursor to end stage liver diseases such as cirrhosis and hepatocellular carcinoma. Currently, the underlying mechanisms associated with NASH initiation and progression is poorly understood leading to limited therapeutic options. In order to address these issues, Hatting and colleagues examined the role of the apoptotic initiator caspase-8 in the methionine and choline-deficient (MCD) diet, a mouse model of NASH. Wildtype (WT) mice fed the MCD diet for 10 weeks displayed characteristic features of NASH, whereas mice with a targeted hepatocyte caspase-8 deletion (casp8Δhep) exhibited a marked decrease in steatosis, hepatic lipid storage, liver injury, and caspase-8 dependent cell death. Hepatic leukocyte infiltration and proinflammatory cytokines TNFα, IFNγ, MCP-1, and IL-6 were also markedly decreased in MCD-fed casp8Δhep mice compared to diet treated WT mice. Enhanced oxidative stress in NASH is associated with increased hepatic fibrosis. WT MCD-fed mice displayed increased superoxide radical production, enhanced oxidative damage, and pronounced fibrosis, which were significantly reduced in MCD-fed casp8Δhep mice by comparison. Interestingly, the authors found caspase-8 may also play a role in fat metabolism. Casp8Δhep MCD-fed mice displayed modulations in genes associated in the uptake, synthesis, oxidation and export of free fatty acids. In summary, the authors were able to identify caspase-8 as a critical driver of NASH pathogenesis in MCD-fed mice. Targeted antagonism of this effector caspase, specifically in the hepatocyte, may serve as an attractive therapeutic strategy for NASH patients in the future.

Targeting specific antigen presenting cell subpopulations as a potential novel therapeutic for IBD


Despite the use of immunosuppressant and biologic therapies, there continues to be a significant cohort of inflammatory bowel disease patients with refractory or relapsing disease or those that can’t tolerate currently available therapies. Therefore, the search for novel treatment strategies continues. For gut homeostasis there is a fine balance between immunogenic tolerance towards commensal microbiota/luminal antigens and an appropriate inflammatory response to pathogenic insult. Lamina propria dendritic cells and resident tissue macrophage play a key role in this process in their capacity as antigen presenting cells (APCs). There are considerable complexities in the phenotype of these cells, with marked heterogeneity. In murine models of colitis, certain populations of APCs such as CD103-CD172a+ dendritic cells are colitogenic via a CD47 dependant mechanism that leads to their accumulation in the murine gut and mesenteric lymph nodes (MLNs). In mice, inhibition of these cells with a CD47-Fc fusion protein can ameliorate colitis. Until now, the importance of these cells in the pathogenesis of human IBD has been unknown. Baba and colleagues assessed APC populations in the colonic mucosa from Crohn’s disease (CD) patients and through sophisticated flow cytometry analysis, identified several phenotypes to be present. Specifically, increased numbers of HLA-DR+CD172a+ cells accumulate in inflamed mucosa and MLNs of CD patients. These were labelled as inflammatory dendritic cells or monocyte derived effector cells. Colonic explant culture revealed that functionally these cells secrete pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF, and when treated with an avidity-human CD47 fusion protein that acts to specifically bind CD172a, this was ameliorated. This was seen in tissue from patients who had previously failed anti-TNF therapy. This novel therapy also impaired the T cell response, specifically Th17 fate. As such, this strategy to selectively inhibit specific APC function in the gastrointestinal (GI) inflamed mucosa warrants further investigation.
**CLINICAL PRACTICE**

**There is no life in MARS!**


The molecular adsorbent recirculating system dialysis (MARS) is an extracorporeal device that removes water and protein bound toxins utilising albumin dialysis. This large, multicentre, randomised trial aimed to study its efficacy in a group of patients with acute-on-chronic liver failure (ACLF) as opposed to standard of care. 195 patients were randomised either to MARS (n=95) or to standard therapy (SMT) (n=94) with 90 and 89 patients remaining in the intention to treat (ITT) analysis and 71 and 85 patients remaining as per protocol analysis (PP). Alcohol and sepsis were the commonest precipitating events in both subgroups. The mean number of MARS sessions was 6.3 with a median time of 6.8 h amounting to 6.3% of the total 28 day study period. The main cause of death was deemed to be multi-organ failure followed by sepsis or uncontrolled GI bleeding. The 28-day transplant free survival was similar in the ITT analysis (60.7% for MARS vs 58.9% for SMT, p=0.79), or in the PP analysis (60% vs 59.2%, p=0.88). There were no differences in the 90-day transplant free survival either (ITT population: 46.1% vs 42.2%, p=0.71; PP population: 44.7% vs 43.7%, p=0.97). In the multivariate logistic analysis, treatment assignment did not affect survival but presence of hepatic encephalopathy, MELD score and rise in bilirubin at day 4 did impact the same. MARS treatment did not alter length of hospital stay or need for mechanical ventilation. The proportion of adverse events was not different between the groups. This negative study has a significant implication for the management of this group of extremely moribund patients. The fact that it took 6 years to complete the study in 19 tertiary academic centres which amounted to less than two patients recruited at each centre every year suggests that it is an extremely difficult study to be replicated and revalidated. Case definition of ACLF will continue to be a bugbear in such studies. The authors have attempted to glean putative changes in bilirubin, creatinine and grade of hepatic encephalopathy as surrogate markers of improvement of organ dysfunction but the fact that MARS does not affect mortality statistics does take the sheen away from these results. Hidden amongst this is the significant cost of this procedure. It has been estimated that the initial intervention costs for MARS is around 14 600 Euros (£12 500). It must be said that this study sounds the death knell for the use of MARS in ACLF and it will take a major ‘mission’ to prove that there is indeed life in MARS.

**Does the use of proton pump inhibitor increase the risk of enteric pathogenic infection?**


Proton pump inhibitors (PPIs) have been reported to increase rates of GI infection as well as non-enteric infection such as pneumonia. However data from Swansea University in the UK suggests that individuals prescribed a PPI probably have a pre-existing increased risk of GI infection prior to PPI prescription. Using *Campylobacter* and *Salmonella* as examples of significant GI infection, Brophy and colleagues analysed data on nearly 2 million patients registered with NHS general practitioners in Wales and compared the incidences of these infections between PPI prescribed and non-PPI prescribed individuals. Furthermore, for individuals prescribed PPI they also analysed rates of infection in the 12-month period prior to index PPI prescription, thus controlling for individual confounding factors by using the same patients as their own controls. Between 1990 and 2010, 358 938 (18.7%) patients were prescribed a PPI. Patients prescribed a PPI were older with a greater frequency of females compared with controls. The PPI patients were more likely to have other factors associated with GI symptoms such as antibiotic use, oral steroid use, NSAID prescription, immunosuppressant medication, bowel surgery, or a diagnosis of arthritis. Rates of *Campylobacter* and *Salmonella* infection were higher after a prescription for PPI compared with rates in the same individual for the period before prescription. However, this increased rate was also observed in the non-PPI group. Patients prescribed a PPI already had a 6.9-fold greater risk for *Campylobacter* infection and a 3.1-fold greater risk for *Salmonella* infection in the 12 months prior to prescription than patients not prescribed a PPI. The authors conclude “there is an association between taking a PPI and GI infection with *Salmonella* or *Campylobacter*. However, this risk is largely owing to differences between those who are prescribed PPIs and those who are not, rather the PPI prescription.”

**Non-GI comorbidities may well explain why the incidence of GI bleeding is not falling**


Despite the widespread use of gastroprotective agents and *Helicobacter pylori* eradication strategies, the incidence of hospital admissions for upper GI haemorrhage (UGIH) remains unchanged in recent years. This is important especially in light of the great interest regarding the provision of out of hours endoscopy serviced in the UK. Crooks and colleagues undertook a case control study to ascertain the effect of comorbidity on the incidence of non-variceal UGIH in the population. Cases were identified via analysis of coding records from primary and secondary care within the NHS in England between 1997 and 2010 and comorbidity was defined using the well validated Charlson Index. Somewhat expectedly, the data revealed that comorbidity had a strong and graded association with non-variceal UGIH with an adjusted OR of 1.43 (95% CI 1.33 to 1.52) for a single comorbidity and 2.26 (95% CI 2.14 to 2.38%) for multiple or severe comorbidity. Perhaps more unexpected was the finding that comorbidity was associated with a far greater proportional population risk for UGIH as compared to NSAID or aspirin intake. Thus gastroprotective strategies may well have limited impact on the population incidence of UGIH and furthermore stakeholders should be aware that the incidence of UGIH is unlikely to fall and very likely to drift upward with an increasing aged and comorbid population.

**Contributors**

Dr Georgina Hold, Dr Walter Baseler, Dr Mairi McLean, Dr Ashis Mukhopadhya, Dr Jonathan MacDonald, Dr Daniel Gaya

**Journals reviewed**


**Competing interests** None.

**Provenance and peer review** Not commissioned; internally peer reviewed.

**To cite** McLean MH. Gut 2013;62:1382–1383.
GI highlights from the literature

Mairi H McLean

*Gut* 2013 62: 1382-1383
doi: 10.1136/gutjnl-2013-305521

Updated information and services can be found at:
http://gut.bmj.com/content/62/9/1382.full.html

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/