GI highlights from the literature

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BASIC SCIENCE

Atlas of colonic CD8+ T cells in UC

Corridoni D, Antanaviciute A, Gupta T, *et al*. Single-cell atlas of colonic CD8+ T cells in ulcerative colitis. *Nat Med* 2020;26:1480–90.

The aetiology of UC remains unclear but the immune system undoubtedly has a central role in the pathogenesis. The colonic mucosa lamina propria contains an abundance of tissue resident CD8+ T cells. Their transcriptional regulation, effector function and how they dynamically remodel to influence inflammation in IBD remain poorly characterised.

This study profiled CD8+ T cells from three healthy volunteers and compared these with patients with UC using single drop, single cell RNA sequencing. They then linked this with T cell receptor analysis to help define functional relationships and crosstalk with epithelial cell subtypes. They used various techniques to study CD8+ T cells to include gene expression data and gene ontology enrichment analysis followed by area under the receiver operating characteristic curve analysis.

The key findings of this paper highlighted extensive heterogeneity in CD8+ T cell composition, including expanded effector and posteffector terminally differentiated CD8+ T cells. Furthermore, they found that UC-associated CD8+ effector T cells can trigger tissue destruction and produce tumour necrosis factor (TNF)-α. Furthermore, the posteffector cells acquire innate signatures to adopt regulatory functions that may mitigate excessive inflammation. Other key findings included observations that interleukin-26+ (*IL-26*+) CD8+ cells demonstrated features of chronic stimulation displaying a colitis-specific ETS variant transcription factor 7 transcriptional network that limits inflammation through inhibition of ETS proto-oncogene 1 (*ETS1*)-controlled genes. The authors summarised that an imbalance between granzyme K+ TNF+ effectors and immunoregulatory *IL-26*++ may facilitate tissue destruction that manifests as UC. They demonstrated that *IL-26* attenuates the severity of colitis when tested in a rodent model but this would require more exploration in IBD human populations.

IFN signalling preserves the stemness of intestinal stem cells

Sato T, Ishikawa S, Asano J *et al*. Regulated IFN signalling preserves the stemness of intestinal stem cells by restricting differentiation into secretory-cell lineages. *Nat Cell Biol* 2020;22:919–26. doi: 10.1038/s41556-020-0545-5.

Type I interferons (IFNs) are produced in response to bacteria and viruses and IFN-induced gene expression is negatively controlled through production of interferon regulatory factor-2 (*IRF2*). The intestinal crypt produces low-level IFNs in homoeostatic conditions and the authors hypothesised that *IRF2* may play a role in stem cell homoeostasis in the intestine. They showed that *IRF2* is expressed widely in the intestinal epithelium including stem cells and Paneth cells. Knocking out *IRF2* had no effect on intestinal morphology and proliferation dynamics. However, when *IRF2*−/− mice were subjected to 5-fluorouracil, a known inducer of mucositis and stem cell toxin, the regenerative response was profoundly compromised in comparison to controls. The number of crypts and stem cell gene expression were significantly reduced but there was no change in the amount of apoptosis. Interestingly, in homoeostatic *IRF2*−/− mice the number of stem cells remained similar to wild type mice, but lineage tracing potential was unaffected, however, *IRF2*−/− stem cells were unable to form organoids. This suggested that while cell differentiation was unaffected there, stem cell regeneration was significantly reduced. This was confirmed by chronic exposure to known inducers of IFNs (PolyI:C and lymphocytic viruses). Interestingly, a prime observation was an increase in the number of Paneth cells and activation of secretory cell-specific gene expression. Together, these data show an important role for IFNs in stem cell homoeostasis by preserving stem cell number, acting as a brake to limit the numbers of Paneth cells in the intestinal crypt.

Microbiome and health implications for ethnic minorities

Keohane D, Ghosh T, Jeffery I *et al*. Microbiome and health implications for ethnic minorities after enforced lifestyle changes. *Nat Med* 2020;26:1089–95. doi: 10.1038/s41591-020-0963-8.

Modern or 'Western' lifestyles have been associated with an increased risk of chronic non-communicable diseases. This is known to be part modulated by the gut microbiota. Studies of ethnic minorities and particularly non-industrialised communities give an opportunity to study 'ancestral' or 'pre-westernised' microbiomes. To date, the majority of such studies have relied on transcontinental comparisons of different societies. Keohane *et al* investigated the gut microbiome of Irish travellers, an ethnically distinct but genetically similar subpopulation of Ireland. Shotgun metagenomics was performed on 118 Irish travellers and compared against publicly available data sets comprising local Irish controls and a collection of global international controls. The faecal microbiomes of Irish travellers was distinct from the non-traveller Irish population and when compared with the global population occupied an intermediate position between industrialised and non-industrialised populations. Retention of a non-industrialised-like microbiome was linked with identifiable features of the ancient traveller lifestyle, whereas adoption of new housing conditions, lower sibling counts and lower animal ownership rates were associated with an industrialised-like microbiome. Functional profiling further revealed travellers with an industrialised-like microbiome had an increased predicted capacity for degrading animal-derived carbohydrates and mucin, depleted expression of butyrate pathways and increased trimethylamine production compared with non-industrialised-like counterparts. These changes have been previously associated with an increased risk of chronic disorders of industrialised societies. These findings highlight the need to understand how the gut microbiome changes with modernisation. It also raises public health concerns in relation to ethnic minorities who are effectively being pressured to change their lifestyle.

CLINICAL PRACTICE

Cytosponge-trefoil factor 3 testing may identify patients at increased risk of Barrett's oesophagus in primary care

Fitzgerald R, di Pietro M, O'Donovan M *et al*. Cytosponge-trefoil factor 3 vs usual care to identify Barrett's oesophagus in a primary care setting: a multicentre, pragmatic, randomised controlled trial. *Lancet* 2020;396:333–44. doi: 10.1016/S0140-6736(20)31099-0.

Fitzgerald *et al* report a primary care study of Cytosponge-trefoil factor 3 (TFF3) testing for patients over 50 years old who had received acid-suppressant therapy for at least 6 months. One hundred and nine GP practices in England participated. Patients were randomised either to receive standard care including lifestyle advice, symptomatic treatment and referral for endoscopy depending on the severity of their

symptoms, or invitation to swallow a Cytosponge device for cytological examination and TFF3 immunohistochemistry. Cytosponge tests were administered by general practice or Clinical Research Network nurses. Participants with positive Cytosponge-TFF3 tests were invited for upper GI endoscopy.

The primary end point was to establish whether Cytosponge-TFF3 testing increased the Barrett's oesophagus (BO) diagnostic yield. Within the standard-care group, 13 of 6388 patients were diagnosed with BO, while 140 of 6834 patients in the Cytosponge-TFF3 group were diagnosed; an adjusted rate ratio of 10.6 (95% CI 6.0 to 18.8, p<0.0001).

Of the patients with positive Cytosponge-TFF3 tests, eight were diagnosed with dysplastic BO (n=4) or stage I oesophagogastric cancer (n=4), all of which were treated with curative intent. In contrast, these lesions were not diagnosed in the standard care group. During the study follow-up period, three patients in the standard care group presented with cancer, of which two had palliative disease at diagnosis and died during follow-up.

Further work is needed to quantify how Cytosponge-TFF3 testing would impact the delivery of healthcare; however, this study suggests that introduction of Cytosponge-TFF3 testing could improve the detection of BO, enabling timely intervention for dysplasia and early cancer.

Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy in predicted severe acute gallstone pancreatitis

Schepers N, Hallensleben N, Besselink M *et al*. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy vs conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. *Lancet* 2020;396:167–76.

The role of endoscopic retrograde cholangiopancreatography (ERCP) in patients with acute pancreatitis is not certain. Previous trials show some reduction in complications of acute pancreatitis but are not easily compared.

Schepers *et al* performed a large, multicentre, randomised trial comparing urgent early ERCP with biliary sphincterotomy with conservative treatment in patients with predicted severe acute gallstone pancreatitis. Two hundred and thirty-two individuals were randomised with the median time to ERCP from presentation of 20 hours. The primary end point was mortality or major complications and secondary end points were the need for, and length of, intensive care admission, length of hospital stay, readmission, quality of life and costs. There was no difference in the primary outcome between the ERCP group (38%) and conservative management groups (44%, p=0.37). The ERCP group was less likely to have cholangitis (2% vs 10%, p=0.01) and recurrent gallstone pancreatitis (0% vs 9%, p=0.001) compared with conservative management. There were some limitations of this study in that the biliary cannulation rate in the ERCP group was only 81% compared with 91% in those requiring ERCP in the conservative group. Defining cholangitis during an episode of acute pancreatitis is challenging and the study employed quite strict criteria. Similarly, patients were enrolled using a predictive scoring system, which will have meant that some did not endure a severe attack. However, this study shows that in patients with predicted acute severe gallstone pancreatitis, urgent ERCP with biliary sphincterotomy should be reserved for those with cholangitis meaning two-thirds of patients would have avoided ERCP and potential complications.

COVID-19 and liver transplant: lessons from Spain

Colmenero J, Rodríguez-Perálvarez M, Salcedo M, *et al*. Epidemiological pattern, incidence and outcomes of COVID-19 in liver transplant patients. *J Hepatol* 2020;S0168-8278:30521–3. doi: 10.1016/j.jhep.2020.07.040.

Liver transplant patients on long-term immunosuppression are extremely vulnerable in the midst of the COVID-19 pandemic. This study reports a prospective, nationwide assessment of outcomes of COVID-19 infection in liver transplant recipients during the Spanish outbreak from 28 February to 7 April 2020. A total of 111 patients were infected with a large proportion requiring admission (96 (86.5%)) and 12 patients were admitted to the intensive care unit (10.8%). Respiratory support was necessary in 22 patients (19.8%). Treatment protocols varied among treating physicians, with hydroxychloroquine and/or azithromycin and antiviral therapy with lopinavir/ritonavir or remdesivir commonly used.

During the time period, 146 690 persons were diagnosed with COVID-19 in Spain (cumulative incidence 311.93 cases/10^5 inhabitants) as opposed to 111 cases of COVID-19 among 13 255 liver transplant patients (cumulative incidence 837.41 cases/10^5 patients), with a standardised incidence ratio of 191.22 (95% CI 190.28 to 192.16). The mortality rate was 18%, but was lower than the matched general population (standardised mortality ratio=95.5; 95% CI 94.2 to 96.8). On the multivariate analysis, baseline immunosuppression containing mycophenolate was an independent predictor of severe COVID-19 (relative risk =3.94; 95% CI 1.59 to 9.74; p=0.003), particularly at doses higher than 1000 mg/day (p=0.003), but not with calcineurin inhibitors like ciclosporine. Beneficial effects of dexamethasone in severe COVID-19 have been recently documented, suggesting that immunosuppression could ameliorate the 'cytokine storm'. The putative antiviral effect of ciclosporine against coronaviruses has been documented and it would be worth looking at this effect in larger cohorts. What is clear is that the cytostatic effect of high-dose mycophenolate on lymphocytes is associated with deleterious outcomes in COVID-19 infection.

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JOURNALS REVIEWED

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