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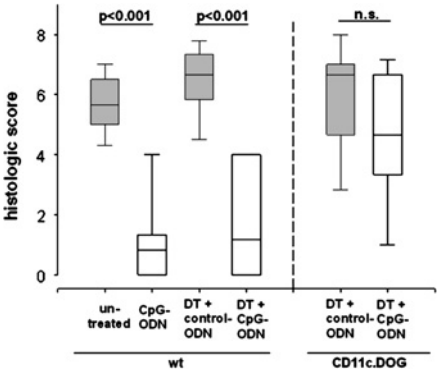
Bacterial DNA motifs and protection against experimental colitis

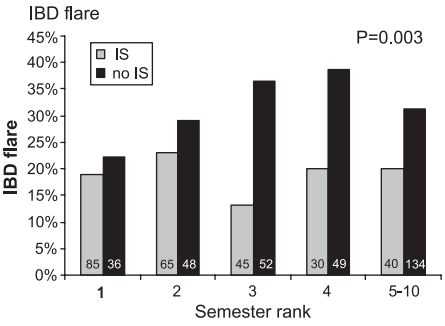
The gut microbiota is critical for gut homeostasis but also in the initiation and perpetuation of chronic intestinal inflammation. The immunosuppressive properties of bacterial DNA are the Oligodeoxynucleotides (ODN) containing cytosineguanosine (CpG) sequence motifs. Prophylactic treatment with CpG-ODN prevents intestinal inflammation but the underlying mechanisms are unknown. In this study, the authors co-incubated total splenic cells or purified selected cell types from Balb/c mice with CpG-ODN for 5 days. They demonstrate that incubation of total splenic cells with CpG-ODN but not of purified CD4+CD62L+ cells reduced the colitogenic potential of transferred T-cells. While CpG-ODN stimulation of co-cultured CD4+CD62L+ and B-cells did not alter the colitogenic potential of T cells, co-incubation of CpG-ODN-stimulated DC and CD4+CD62L+ cells reduced the colitogenic potential of the T cell population. Therefore key mediators of the CpG-ODN-dependent protective effects are CD11c+ dendritic cells. Depletion of these CD11c+ DC abolished the protective CpG-ODN effects. In conclusion, this study shows that the CpG-ODN- protective effects are mediated indirectly by CD4+CD62L+ T cells and CD11c+ DC were identified as key mediators of this protection in experimental colitis. ***See page 1347***.



CD 11c+ DC are critical for colitis-inhibitory properties: Transgenic CD11c/DT receptor mice were depleted of CD11c+ DC and simultaneously treated with CpG-ODN or control-ODN, respectively. Figure shows histolologic scores 8 weeks after transfer.

Co-treatment with immunomodulators in IBD patients on Infliximab maintenance therapy

The anti-TNF antibody Infliximab (IFX) is a very efficacious therapy for patients with Crohn's disease (CD) and ulcerative colitis (UC). The SONIC study showed that in anti-TNF and immunomodulator (IMM)-naïve patients, combination therapy of IFX with azathioprine had better remission rates than IFX monotherapy. In contrast, a previous study not in IMM-naïve patients, suggested that IMMs could safely be stopped after 6 months while continuing patients on IFX monotherapy. In the current study, the authors assessed if co-treatment with IMMs is really useful in IBD patients on scheduled IFX infusions. A total of 121 consecutive IBD patients (23 UC, 98 CD) treated with IFX and IMMs for at least 6 months were analysed regarding IBD activity where semesters with IMMs (n=265) and without IMMs (n=319) were compared. IBD flares, perianal complications and switch to Adalimumab were less frequent in semesters with than in those without IMMs (respectively 19.3 vs 32.0%, p=0.003; 4.1 vs 11.8%, p=0.03; 1.1 vs 5.3%, p=0.006). In multivariate analysis, concomitant IMMs were associated with a decreased risk of IBD flare (OR 0.52; 95% CI [0.35 to 0.79]). The authors conclude that co-treatment with IMMs during IFX maintenance is the preferred treatment option, although risk/benefit profile needs to be carefully assessed. ***See page 1363***.



Proportion of semesters with IBD flare according IMM co-treatment and stratified by semester rank.

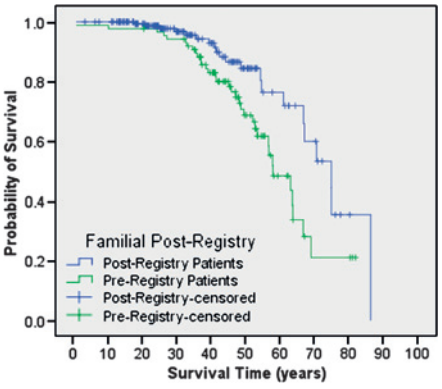
Lung metastases and colorectal cancer

The lung is known to be the most common extra-abdominal site of metastases from CRC. However, the real frequency for both synchronous and metachronous lung metastases is not known. Mitry *et al* studied all cases of lung metastases from colorectal cancer registered in the Burgundy digestive cancer registry between 1976 and 2005. They estimated trends in the incidence of synchronous colorectal cancer lung metastases and used a Cox model to analyse the risk of developing a metachronous metastasis. Multivariate analyses were performed using a relative survival model with proportional hazard applied to the net survival by interval. They showed that the incidence of synchronous lung metastases increased over time, whereas the incidence of metachronous lung metastases remained stable. Lung metastases were more frequent in rectal cancer than in colon cancer. In multivariate analysis, the RR of death for the 1996–2005 period was about one fifth of that for the 1976–1985 period. Compared to colon cancer, rectal cancers had a higher risk of developing lung metastases and may thus benefit from a specific surveillance strategy. ***See page 1383***.

The impact of screening and genetic registration on mortality and colorectal cancer incidence in familial adenomatous polyposis

Regular screening of patients at risk of familial adenomatous polyposis (FAP), improves prognosis. Polyposis Registries have been established to coordinate screening programmes. Mallinson *et al* assessed the effect of screening and of the formation of the Registry on survival, incidence of CRC and age at onset of CRC, in FAP patients in Manchester. Patients were categorised according to their mode of presentation; screening or

symptomatic, and survival time from birth was calculated for each patient (n=353). The effect of the formation of the Registry was assessed by comparing survival times from birth for patients diagnosed in the 20 years before the establishment of the Registry, to patients diagnosed in the 20 years since the formation of the Registry (n=273). Survival was increased from 57.8 years to 70.4 years ($p<0.001$) by screening, and from 58.1 years to 69.6 years ($p=0.007$) following establishment of the Polyposis Registry. The incidence of CRC was reduced from 43.5% to 3.8% by screening, and from 28.7% to 14.0% following establishment of the Polyposis Registry. The benefits demonstrated clearly call for the implementation of Polyposis Registries in areas currently lacking. ***See page 1378***.

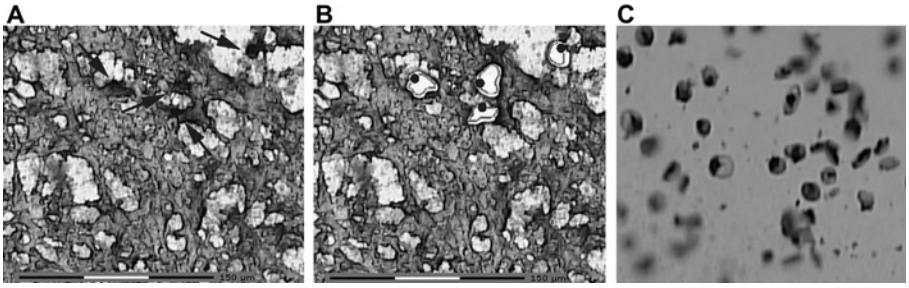


Kaplan–Meier survival curve to show the cumulative survival of familial adenomatous polyposis (FAP) patients who were diagnosed in the 20 years before the formation of the Polyposis Registry and those patients diagnosed in the 20 years since the formation of the Registry ($\chi^2=7.36$, 1 df, $p=0.007$, log rank test).

HCV infection of the brain and cognitive dysfunction

Patients with chronic HCV infection frequently suffer from cognitive and mood disorders. The pathogenesis of these clinically important conditions remains to be elucidated.

Recently, penetration of the hepatitis C virus into the central nervous system and replication in brain macrophages has been demonstrated. In their exciting article Laskus and co-workers investigate whether this is related to activation of proinflammatory pathways. They used postmortem brain specimens from patients with chronic HCV and from pts with liver disease not related to HCV as controls. Interestingly, levels of proinflammatory cytokines and chemokines were clearly higher in macrophages of brain and microglia of HCV pts. This profile was observed in the CD 68 positive cells from HCV-infected patients and was dependent on the HCV status of the CD 68 positive cells. These findings provide exciting novel molecular evidence for immune activation in the central nervous system by HCV. If this is indeed related to cognitive disorders and depression in patients with chronic HCV infection an ultimate clinical consequence may be targeting HCV in the brain. ***See page 1394***.



Laser Capture Microscopy (LCM) separation of CD68+ cells from brain tissue. (A) frontal cortex sections from patient 2 stained with monoclonal antibodies against CD68 (subsequently harvested cells are marked by arrows); (B) the same sections after the positively staining cells were removed; (C) LCM separated cells. The size of the bar corresponds to 150 μm.