Digest

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Decoy receptor 3 promotes inflammation in Crohn's disease

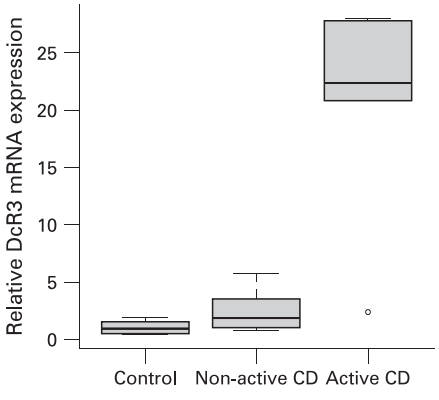
Epithelial barrier dysfunction and apoptosis resistance of immune cells have been proposed to contribute to the chronic inflammation seen in patients with inflammatory bowel disease. The soluble decoy receptor 3 (DcR3) inhibits death ligand-induced apoptosis. In the study by Funke and co-writers in this issue of *Gut*, the authors demonstrate that DcR3 is over-expressed in patients with Crohn's disease (CD), both in the epithelial layer of ileum (see fig) and in serum. Moreover, this was seen both at active and non-active sites within the gut and present in patients with active and non-active disease. Furthermore, they could also demonstrate that DcR3 over-expression was associated with activation of nuclear factor kappa B (NF-κB), which is of interest because a deregulated activation of NF-κB-dependent pro-survival signalling pathways may be involved in malignant transformation of enterocytes. The increased DcR3 expression was also found to protect against death ligand-induced apoptosis of intestinal epithelial cells and lamina propria T cells. Taken together, this data supports the involvement of DcR3 in the pathogenesis of CD, where it likely promotes inflammation and may also be involved in carcinogenesis. ***See page 483***

Importance of KITENIN in control of invasiveness of colorectal cancers

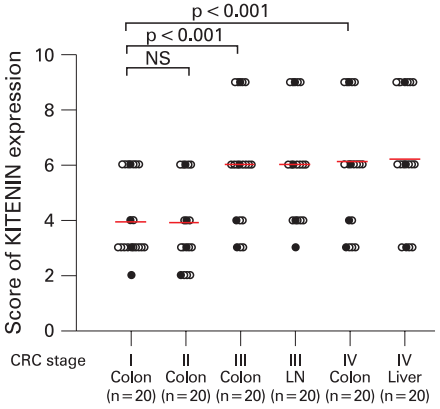
The invasiveness of colorectal cancers (CRCs) depends, amongst other factors, on complex changes in the actin cytoskeleton, mediated via the planar cell polarity (PCP) cascade. One of the proteins involved, Dishevelled (Dvl), controls cell membrane protrusions during cell migration. This study by Kho and co-authors, focuses on the interaction between Dvl and KITENIN, a novel metastasis promoting protein in CRC. Overexpression of KITENIN in rat cell lines accelerated migration as assessed by a wound healing model, an effect which could be blocked by mitogen-activated protein kinase and phosphatidylinositol 3-kinase (PI3) antagonists. KITENIN also increased the activation of AP-1, a transcription factor that regulates cells motility. Using small interfering RNAs, they were able to show that knockdown of Dvl isoforms and protein kinase (PK) Cδ prevented this KITENIN action. The conclusions were that KITENIN acted as a scaffold facilitating Dvl/ PKCδ interaction. The significance of these findings is seen in the figure showing that KITENIN expression steadily increased as tumour stage increased. ***See page 509***

T8reg: a novel regulatory T lymphocyte subset associated with CRC progression

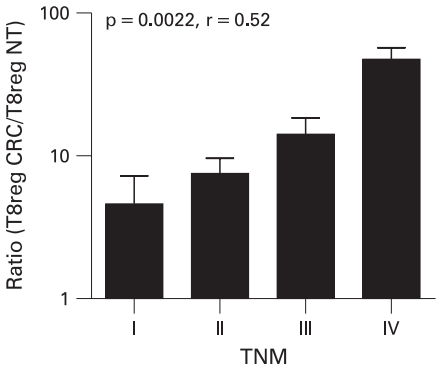
Although immune surveillance can limit tumour growth, tumours have ways of perverting this control. Thus, infiltration of CRC with immune cells can be associated with good prognosis but this depends on the specific immunocyte type. More specifically, infiltration by a subset of lymphocytes T4reg, which downregulate the immune response, is known to be associated with poor outcome in ovarian cancer. The study by Chaput and colleagues investigated the role of T8regs, a related T cell subset, in 32 patients with CRC. They found numbers of T8regs were increased in peripheral blood and more markedly in CRC tissue when compared with normal colonic tissue. This increase was correlated strongly with tumour stage (see fig). T8regs were found in only 36% of normal colonic tissue but 96% of CRC tissue. By isolating T8regs from tumour tissue the authors were able to show that they were immunosuppressive, reducing T cell proliferation and their production of interleukin (IL) 2 and INFγ. T8regs appear to be generated locally under the influence of IL6 and TGFβ1, both of which might be targeted to help overcome the local immune impairment in CRC. ***See page 520***



In human ileal epithelium higher expression of decoy receptor 3 (DcR3) occurred in active Crohn's disease (CD) vs control ($p<0.001$) and non-active CD vs control ($p<0.05$).



Score of KITENIN increases as tumour stage advances.



Increased numbers of T8regs in colorectal cancer compared with normal tissue correlates with advanced tumour stage.

Population-based screening for CRC: practical experience from the first three rounds in Scotland

As many nations embark on colorectal screening of their populations, this study is of particular interest because it provides data on how these programmes will evolve, with important resource and cost implications. All those aged 50–69 years resident in three Scottish NHS Board areas (304 245 individuals) were invited to take part, with a second invitation letter after 6 weeks for non-responders. Uptake of the invitation remained steady at around 55% and response to the invitation actually rose from the initial 44% to 55% (see table). Males were less likely to take part. Predictably, those in socially deprived areas were also under represented. Positivity rates fell as expected from 2.07% in the first round to 1.16% in the third. This may in part be due to the decision in the third round not to test further those with an initial weak positive whose second test was negative. Paradoxically, the percentage of cancers detected that were stage A actually fell from the first to third round from 49% to 36%, respectively. However, 30% of recorded cancers presented between screening, indicating that there is still plenty of room for further improvements. ***See page 530***

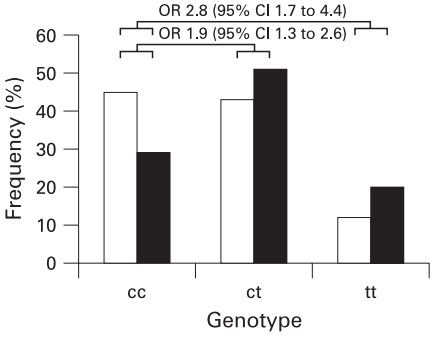
Uptake of screening and positivity rates expressed as percent

	First round	Second round	Third round
Uptake			
Total	55.0	53.0	55.3
Males	50.4	48.7	51.0
Females	59.5	57.1	59.6
Response to first kit	43.8	51.5	53.7
Non-responders in all previous rounds	–	13.8	13.9
Responders in any previous round	–	85.4	85.2
Positivity rate			
Total	2.07	1.90	1.16
Males	2.83	2.56	1.52
Females	1.44	1.36	0.86
Non-responders in all previous rounds	–	2.56	1.58
Responders in any previous round	–	1.88	1.10

The differences between males and females in all rounds and in both parameters were statistically significant at the $p<0.001$ level and the decline of the positivity rate was statistically significant at the $p<0.01$ level (χ^2 test).

Genetic predisposition to intrahepatic cholestasis of pregnancy

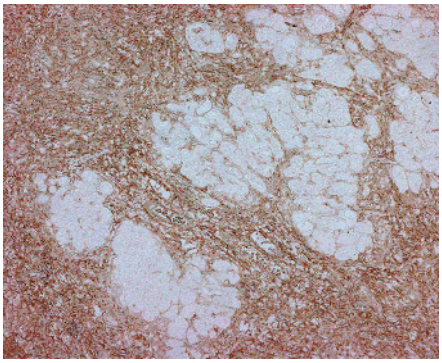
Intrahepatic cholestasis of pregnancy (ICP) affects 0.7% of pregnancies in the UK. It causes maternal pruritus and increases the risk of fetal distress, premature delivery and intrauterine death. Recent studies have provided insights into genetic predisposition to ICP. In this collaborative European study including a group of 333 patients with ICP, mutations in *ABCB11*, a gene that encodes the bile salt export pump (BSEP), were investigated. The authors also genotyped V444A polymorphism, which possibly affects BSEP expression. Heterozygosity for common *ABCB11* mutations (E297G, D482G and N591S) was seen in seven patients. Moreover, V444A polymorphism was found to be associated with ICP (OR 1.7), where CC homozygotes were more likely to have ICP than TT homozygotes (OR 2.8) (see fig). The authors also performed additional structural analyses and these suggested that two of the mutations destabilise the protein folding of BSEP, which is a potential molecular explanation for the dysfunction. This data suggests a relatively minor role for common mutant alleles of BSEP in the pathology of ICP but also suggests that V444A polymorphism is a significant risk factor for ICP. ***See page 537***



Genotype frequencies in cases (white bars) and controls (black bars) for the V444A variant.

Fibrinogen is of importance in pancreatic diseases

Pancreatic stellate cells are thought to be involved in the development of fibrosis in chronic pancreatitis (CP) and to be responsible for the dense stroma associated with pancreatic cancer (PC) (“desmoplastic reaction”). Fibrinogen is overexpressed in CP and PC and, in order to evaluate its role in the pathogenesis, the effect of fibrinogen on cell function in PSCs was investigated in the study by Masamune and colleagues. Fibrinogen was expressed in the fibrotic areas of pancreas (see fig) and stimulated several cell functions in human PSCs, like enhancing the production of pro-inflammatory cytokines, proangiogenic factors, collagen production and activated signal transduction pathways. Moreover, these effects were found to be integrin-dependent and the fibrinogen induced cytokine production could be abolished by an NF-κB antagonist and partially blocked by mitogen-activated protein kinase inhibitors. This study has provided important new knowledge about the pathophysiology of chronic pancreatitis and pancreatic cancer. Further studies are now needed to establish the important role for fibrinogen in these diseases. Hopefully, this could lead to more rational treatment approaches for these patients. ***See page 550***



Fibrinogen expression in the stromal tissue of a patient with chronic pancreatitis.