Highlights from this issue

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Emad El-Omar, Alexander Gerbes, William Grady, Thomas Rösch, *Editor and Deputy Editors*

LUMINAL

Insights into ways to treat diarrhoea

In the setting of diarrhoea, the colon often secretes substantial amounts of water, secondary chloride (Cl^-) and/or potassium (K^+). This ion secretion occurs via Cl^- (CFTR) and K^+ (BK) channels, which are generally assumed to be co-located in the colonocyte apical membrane, although their exact cellular sites are not known. Linley and his co-workers have now identified the location of these channels in the colon epithelium. They found two types of crypt cells with regards to these ion channels with goblet cells having one particular type of channel (BK) and the other colonocytes expressing CFTR. Thus, in the colon, Cl^- secretion originates from colonocytes expressing apical CFTR, whereas K^+ secretion is derived from a smaller population of goblet cells expressing apical BK channels. Their findings will help direct the development of anti-diarrheal drugs.

A promising target for colorectal cancer treatment

Colorectal cancer (CRC) is a major global killer. Consequently, efforts are being made to determine the molecular alterations present in CRC in order to find better ways to treat these tumours. LIM kinase 2 (LIMK2) is a kinase that promotes tumour cell invasion and metastasis. This led Olson and colleagues to determine how LIMK2 expression is associated with CRC progression and patient outcome. They used a novel approach to conduct this analysis by employing genetically-modified Drosophila and mice to determine how LIMK2 deletion affects gastrointestinal stem cell (SC) regulation and tumour development. They found that LIMK2 expression was reduced in intestinal tumours of cancer-prone mice, as well as in human cancers. Importantly, they found reduced LIMK2 expression and substrate phosphorylation were associated with shorter patient survival. Their studies suggest there is selective pressure for reduced LIMK2 expression in CRC to relieve negative constraints imposed upon gastrointestinal SCs.

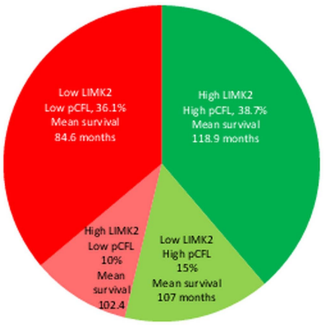

Figure 2 Association of LIMK2 expression and cofilin phosphorylation (pCFL) with patient outcomes. Distribution of outcomes for all combinations of High and Low LIMK2 and pCFL.

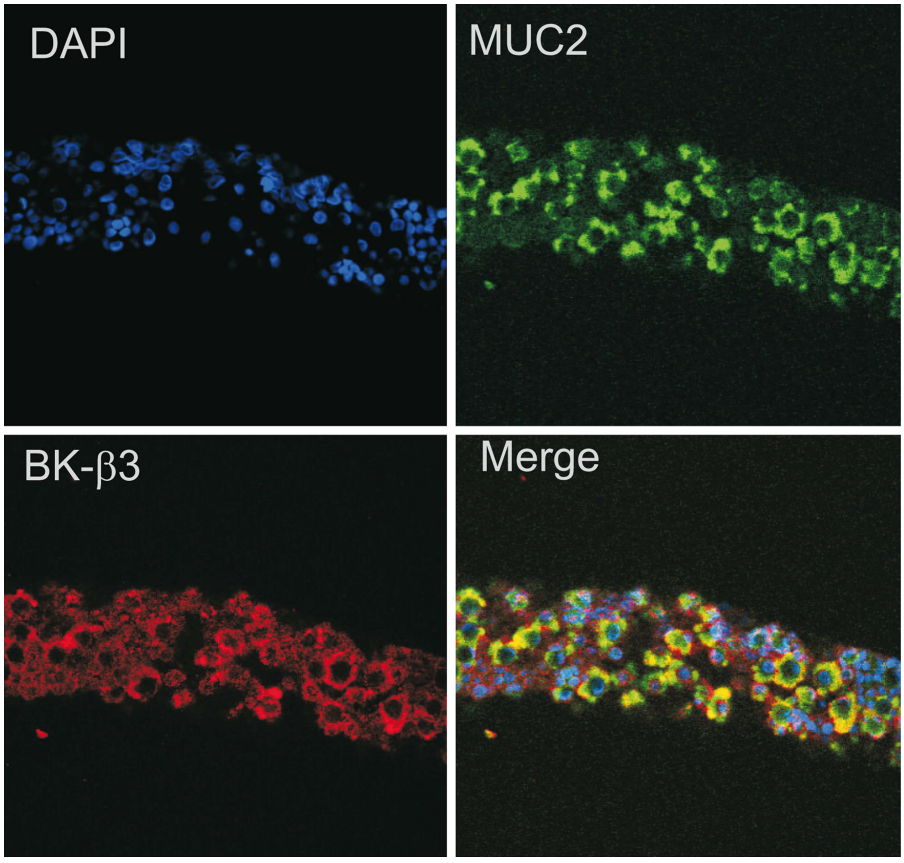

Figure 1 BK channel β3-subunit co-localizes with the goblet cell marker MUC2. Confocal images of the mid-third region of a single, isolated human colonic crypt. (Goblet cells were stained with MUC2 antibody with DAPI nuclear counterstain). The BK channel β3-subunit protein was localised to goblet cells. The merged image shows overlap of MUC2 antibody and BK channel β3-subunit antibody in the yellow areas.

ENDOSCOPY

Faecal immunochemical testing plus risk factors: a better filter for screening colonoscopy

Faecal immunochemical testing (FIT) is increasingly used in CRC screening but has a low sensitivity rate for detecting advanced neoplasia. In this study from the Netherlands, Stegeman et al explored the value of combining risk stratification, based on established risk factors for advanced neoplasia, with the FIT result for allocating screenees to colonoscopy. They used data from the colonoscopy arm of a Dutch screening study which compared colonoscopy with CT colonography (n=1112) and where subjects had also completed a risk factor questionnaire and delivered a FIT. Smoking and positive family history of CRC were independently associated with a higher risk of advanced neoplasia/adenomas and were thus used for a clinical risk score in addition to

positive FIT assessment in the same cohort. Adding risk based stratification increases the accuracy of FIT-based CRC screening and could be used in pre-selection for colonoscopy in CRC screening programmes.

Is it time to resect and discard small colonic polyps?

The adenoma detection rate is considered a key parameter of competent colonoscopy. Inevitably, more polyps, especially smaller ones, are being detected. The histologic analysis of these polyps is costly, so endoscopists have been thinking about resecting all polyps and discarding the small ones (mostly <5 mm, some also think <1 cm). Follow-up intervals (10 years for small hyperplastic and 5 years for small adenomatous polyps) would then be determined by the endoscopic features and differential diagnosis between these two entities. This has been called the DISCARD strategy. In this issue of Gut, Schachschal et al report on a large German private practice based screening study that prospectively assessed whether the high accuracy for endoscopic polyp diagnosis as reported by reference centres can be reproduced in routine screening colonoscopy. They show that accuracy rates of endoscopic polyp differentiation are still insufficient for daily routine. Better training and perhaps also endoscope and image capture technology may help in the future, but this would have to be shown in well-designed studies.

HEPATOLOGY

HCV infection—a surprising role of liver natural killer cells

An important role of natural killer (NK) cells in controlling viral infections is well known. However, it remains to be clarified how intrahepatic NK cell populations influence HCV pathogenesis and treatment. This interesting study from the UK (***see page 515***) provides surprising insights employing repeated liver sampling of the same patients during interferon treatment. The authors identify NKp46 as markedly activated hepatic NK cell population in HCV patients. Paradoxically, increased NKp46 is associated with Interferon treatment failure (figure 3). This opens the intriguing option to target Nkp46 in the treatment of HCV. See also commentary on this paper.

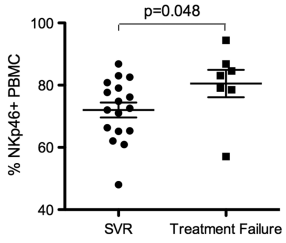

Figure 3 Patients clearing HCV upon Interferon treatment (SVR) exhibit lower expression of NKp46 before treatment than patients failing treatment.

Patients with both HCV and HBV infection benefit from HCV treatment

Patients with HCV/HBV dual infection have a two- to three-fold higher risk of developing hepatocellular carcinoma (HCC) than patients with either infection alone. Response rates to combined antiviral treatment are similar in dual infected and in HCV only infected patients. This retrospective study from Taiwan (***see page 506***) with an impressive number of patients shows that antiviral treatment reduces HCC incidence, liver-related and overall mortality in dually infected patients. Therefore treatment is strongly suggested despite increased incidence of side effects. See also commentary on this paper.