IN BRIEF

GUT MICROBIOTA

Fungal dysbiosis associated with colorectal cancer

Despite associations between gut bacterial and viral alterations and colorectal cancer (CRC), the role of the fungal microbiota in CRC remains largely uncharacterized. In a new study, faecal metagenomic sequences from patients with CRC ($n = 184$) or colorectal adenomas ($n = 197$) and healthy controls ($n = 204$) from Hong Kong were analysed. Principal component analysis revealed distinct clusters of patients with CRC or controls, and defined mycobiomes corresponding to early-stage and late-stage CRC. Biomarkers for 14 fungal species enabled the distinction of CRC from controls with an area under the receiver-operating characteristic curve (AUC) of 0.93. Validated AUCs of 0.82 and 0.74 were also obtained for independent cohorts from China and Europe, respectively. Furthermore, ecological analyses revealed synergistic intrafungal and antagonistic bacterial–fungal interactions in colorectal carcinogenesis. Taken together, these findings suggest a role for the gut mycobiota in CRC.

ORIGINAL ARTICLE Coker, O. O. et al. Enteric fungal microbiota dysbiosis and ecological alterations in colorectal cancer. *Gut* https://doi.org/10.1136/gutjnl-2018-317178 (2018)

COLORECTAL CANCER

No risk reduction of colorectal adenoma with aspirin or eicosapentaenoic acid

The chemopreventive efficacy of aspirin and the omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA) for colorectal cancer (CRC) has been tested in a multicentre, placebo-controlled trial. Patients identified at colonoscopy as high-risk for CRC ($n = 709$) from the English Bowel Cancer Screening Programme were randomly allocated to receive daily doses of aspirin, EPA, a combination of both or placebo for 12 months. The primary end point (proportion of patients with any colorectal adenoma) was analysed after 1 year by colonoscopy: no significant differences between the groups were seen. However, evidence from secondary outcomes did show that both aspirin and EPA decreased the recurrence of some adenoma subtypes, measured by adenoma number, suggesting a precision medicine approach to CRC chemoprevention is needed.

ORIGINAL ARTICLE Hull, M. A. et al. Eicosapentaenoic acid and aspirin, alone and in combination, for the prevention of colorectal adenomas (seAFOod Polyp Prevention trial): a multicentre, randomised, double-blind, placebo-controlled, 2 × 2 factorial trial. *Lancet* **392**, 2583–2594 (2018)

INFECTION

Probiotics fail to improve preschool gastroenteritis

Although recommended by some for diarrhoeal diseases, data that support treating children with gastroenteritis using probiotics are limited. Two randomized, placebo-controlled trials have now examined the efficacy of a probiotic to improve outcomes of gastroenteritis among preschool children. A total of 1,857 children aged 3–48 months who presented with gastroenteritis to paediatric departments in North America were enrolled in one of the two trials. They all received a 5-day course of a probiotic containing *Lactobacillus rhamnosus* or placebo, and the primary end point was moderate-to-severe symptoms of gastroenteritis within 14 days, defined using a clinical severity score. In both trials, children that received the probiotic did not have better outcomes than those who received placebo, and no significant differences were found between the groups for secondary outcomes, including duration of diarrhoea or vomiting.

ORIGINAL ARTICLES Schnadower, D. et al. Lactobacillus rhamnosus GG versus placebo for acute gastroenteritis in children. *N. Engl. J. Med.* **379**, 2002–2014 (2018) | Freedman, S. B. et al. Multicenter trial of a combination probiotic for children with gastroenteritis. *N. Engl. J. Med.* **379**, 2015–2026 (2018).

SURGERY

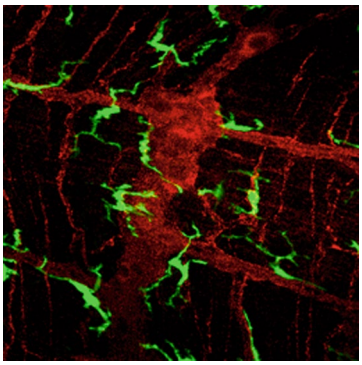
Prucalopride before surgery alleviates postoperative ileus

Preoperative prucalopride treatment alleviates ileus and improves recovery time in patients undergoing abdominal surgery, according to a new study published in *Gut*.

Patients who undergo abdominal surgery temporarily experience impaired gastrointestinal motility. This intestinal response, known as postoperative ileus, is associated with pain and discomfort, prolonged hospitalization and increased costs. Clinical management of postoperative ileus includes the use of prokinetic agents, but these drugs are not very effective.

In the past decade, a number of groups demonstrated that abdominal surgery activates muscularis macrophages and inflames the intestinal muscle layer, leading to impaired contraction and motility. Subsequent preclinical studies showed that inhibiting muscularis macrophage activation, for instance via vagus nerve stimulation (VNS) before surgery, markedly improved ileus. As VNS is an invasive procedure and the protective effects are thought to be mediated through enteric nerves rather than direct interaction with muscularis macrophages, Guy Boeckxstaens and colleagues sought to explore whether direct pharmacological potentiation of these enteric nerves could protect against postoperative ileus.

Using a mouse model and Ca^{2+} imaging, the researchers first confirmed that cholinergic enteric neurons can modulate the activity of muscularis macrophages. Notably, administration of prucalopride, a selective 5-HT4 receptor agonist, mimicked the effect of enteric neuron activation in reducing muscularis macrophage activation. This finding led the investigators to compare prucalopride treatment before or after surgery with sham treatment in a mouse model. Postoperative ileus was improved in mice receiving prucalopride, but only if it was administered before surgery to precondition macrophages.



Credit: Image courtesy of N. Stakenborg

Taking these findings into the clinical setting, the authors designed a placebo-controlled pilot study to compare postoperative ileus outcomes in patients undergoing a pancreaticoduodenectomy. Patients received either prucalopride ($n = 10$; 2 mg prucalopride given 16 hours and 2 hours before surgery) with sham VNS; abdominal VNS ($n = 10$; administered at the start and the end of surgery) with placebo; or sham VNS and placebo ($n = 10$). The primary end point was reduced surgery-induced upregulation of pro-inflammatory gene expression in the intestinal muscle layer. Compared with placebo and sham treatment, surgery-related increases in *IL6*, *IL8* and *CCL2* expression were reduced by prucalopride but not by VNS. In line with these findings, the prucalopride group had the shortest times to removal of the nasogastric tube, reintroduction of solid foods and hospital discharge.

On the basis of these data, the researchers argue that the pharmacological management of postoperative ileus should be adjusted to emphasize preoperative treatment with 5-HT4 receptor agonists. Moreover, a large clinical trial to validate these findings is being initiated.

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ORIGINAL ARTICLE Stakenborg, N. et al. Preoperative administration of the 5-HT4 receptor agonist prucalopride reduces intestinal inflammation and shortens postoperative ileus via cholinergic enteric neurons. *Gut* https://doi.org/10.1136/gutjnl-2018-317263 (2018)