Research round-up

Highlights from microbe studies. By Liam Drew

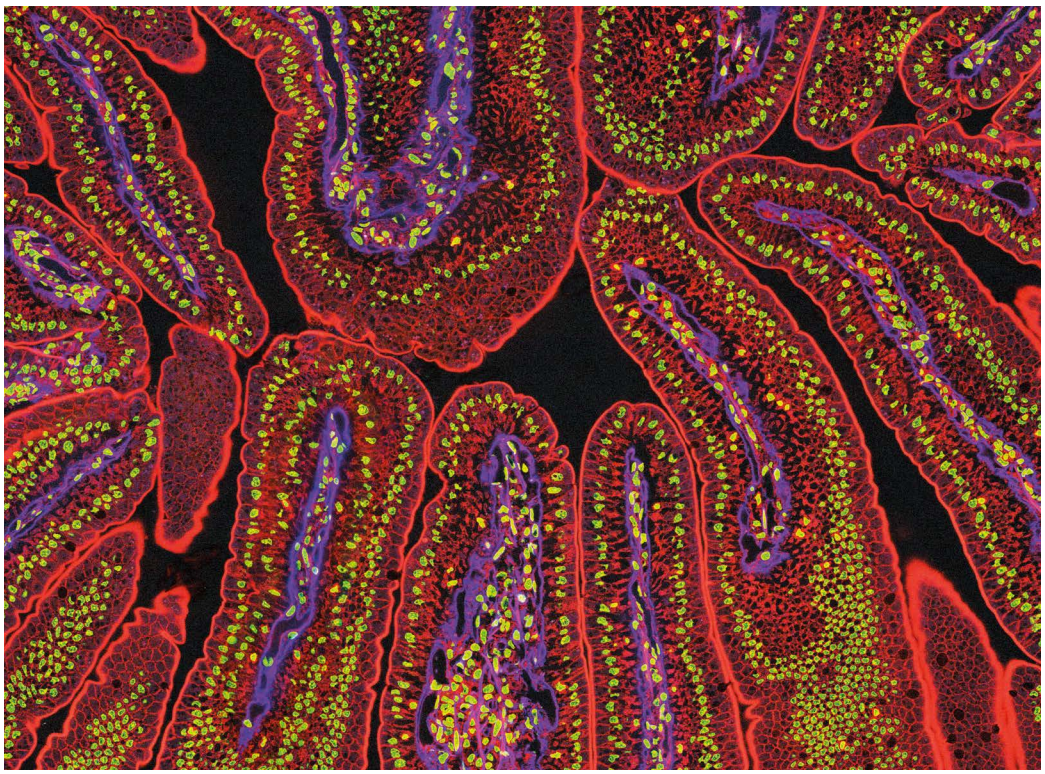
The gut's link to mental health

A study of a pair of 1,000-strong cohorts has strengthened the link between the community of microorganisms that live in the gut and mental health.

Jeroen Raes at the Catholic University of Leuven, Belgium, and his team initially looked for links between the microbiome and depression and quality of life in participants in the Belgian Flemish Gut Flora Project. In this cohort, the team showed that two bacterial species were positively correlated with self-reported high quality of life, whereas a third was most abundant in people reporting low quality of life. A subsequent analysis that categorized people as having one of four types of microbiome found that people with depression more often had a type associated with low overall bacterial abundance. Using published genetic characterizations of gut-bacterial metabolic pathways, the team also showed around 50 routes by which various intestinal microbes can produce neuroactive metabolites. Among the pathways, it found an association between higher quality of life and the presence of bacteria that produce a metabolite of the neurotransmitter dopamine.

The study frames hypotheses for future work to investigate whether the microbiome can affect mental health — and, if so, whether this happens through altered dopamine signalling.

Nature Microbiol. **4**, 623–632 (2019)



THOMAS DEERINCK, NCMIR/SPL

Villi of the small intestine are home to gut microbes.

The key to faecal transplantation

A follow-up analysis of a landmark clinical trial of faecal microbiota transplantation (FMT) for ulcerative colitis might have identified bacterial species that could help to treat this form of inflammatory bowel disease. In a 2017 trial, 27% of people with ulcerative colitis entered full remission after receiving FMT — a success, but a partial one.

Now, Nadeem Kaakoush at the University of New South Wales in Sydney, Australia, and his colleagues report on detailed analyses that link remission to features of the recipients' intestinal microbiomes before and after treatment, and also to the bacterial composition of donor stool.

People whose disease went into remission had greater overall microbiota diversity both pre- and post-FMT. But following treatment, remission was associated with the enrichment of two species of bacteria: *Eubacterium hallii* and *Roseburia inulinivorans*. These microbes are thought to boost production of short-chain fatty acids (SFCAs) and the breakdown of starch. Indeed, the guts of people in remission showed an increase in SCFA production.

The likelihood of successful treatment also correlated with the bacterial content of donated stool. Remission was more likely if the stool had high levels of *Bacteroides* species, whereas *Streptococcus* species were more common in samples that did not induce remission.

The results could allow rational selection of both donors and recipients of FMT for ulcerative colitis, and might make it possible for physicians to use particular bacterial strains to enhance responses or treat ulcerative colitis.

Gastroenterology **156**, 1440–1454 (2019)

Microbe boosts metabolic health

According to a clinical trial, a daily dose of the bacterium *Akkermansia muciniphila* might treat metabolic syndrome — a condition that predisposes individuals to type 2 diabetes and serious cardiovascular disease, and that is marked by obesity, high blood pressure, and raised levels of blood sugar, fats and cholesterol. *A. muciniphila* is abundant in the guts of lean people and

its prevalence decreases with obesity. In a proof-of-principle study, Belgian researchers gave people who were insulin-resistant and overweight or obese a preparation of either live or pasteurized *A. muciniphila*, or a placebo, daily for three months.

Both the live and pasteurized bacteria had beneficial effects. Pasteurized *A. muciniphila* in particular lowered circulating insulin and total cholesterol levels and decreased insulin resistance. The microbes also reduced white blood cell counts, an indication that there was less overall inflammation. It is unclear why dead bacteria were more effective, but the results suggest that the bacteria's metabolites or cell-wall fragments might be therapeutically active.

Patrice Cani at the Catholic University of Louvain, Louvain-la-Neuve, Belgium, and his team note the study was small, with only about ten people per group, and neither abdominal fat nor body mass index were reduced. They are now looking at the effects of individual molecules in mice and are planning a larger trial of pasteurized *A. muciniphila* in humans.

Nature Med. **25**, 1096–1103 (2019)

Bacterial effect on disease pathways

Investigations of links between the gut microbiome and specific diseases tend to have a causality problem: it's unclear whether an altered microbiome contributes to the disease or whether the disease alters the collection of microbes. But a team of researchers led by Serena Sanna and Cisca Wijmenga at the University of Groningen in the Netherlands and Mark McCarthy at the University of Oxford, UK, have addressed this issue using an analytical approach called Mendelian randomization — in which genetic variants are treated as manipulations that define experimental groups — to show that the microbiome can cause metabolic dysfunction. The team also suggested a mechanism by which this occurs: changes in microbial production of short-chain fatty acids (SCFAs).

The metabolic health of nearly 1,000 people in the Netherlands was found to correlate with the presence of certain bacteria and bacterial metabolic pathways. Most notably, higher faecal levels of butyrate — an SCFA produced by gut microbes — predicted better insulin responses. The study also showed that participants' genes partially predict the level of butyrate production in people's guts, and microbiome structure more broadly — a finding confirmed in a different group of more than 4,000 individuals.

Then came the test of causality. If altered insulin sensitivity changes the microbiome (rather than the microbiome disrupting insulin physiology), all genetic factors known to influence insulin sensitivity should also predict a person's butyrate production. But they did not. This suggests that genes associated with both microbiome structure and insulin responses influence gut microbiomes, which in turn disrupt insulin signalling.

The team also found that genetic variants elevating faecal levels of another bacteria-derived SCFA, propionate, increase the risk of type 2 diabetes. These findings pave the way for more personalized treatments of metabolic disease.

Nature Genet. **51**, 600–605 (2019)

Childbirth and the microbiome

A person's gut microbiome is seeded in early life according to the bacteria they are exposed to and how successfully these microbes colonize the intestines. Research, led by Trevor Lawley at the Wellcome Sanger Centre in Hinxton, UK, and Nigel Field at University College London, shows that a caesarean-section birth radically affects newborns' microbiomes, and that infants born this way are often host to opportunistic hospital bacteria.

Looking at 596 healthy babies shortly after birth and again at 8–10 months old, the researchers showed that when babies were 4 days old, the microbiomes of those delivered by c-section were markedly different from those of babies born vaginally. And although the microbiomes of c-section infants gradually shifted closer to those of vaginally born babies over the first three weeks of life, significant differences persisted into infancy.

One of the most pronounced differences in the microbiomes of c-section babies was a low abundance of *Bacteroides*. Levels of bacteria commonly found in hospitals in the microbiomes of c-section newborns did decrease sharply in the months after birth, but those organisms were still slightly more common than in vaginally born babies at around eight months. The authors attributed the differences to infants born by c-section having less exposure to the maternal microbiome during birth. But the study also found that when mothers who gave birth vaginally were given prenatal, prophylactic antibiotics — which are also given to nearly all women who have c-sections — their babies' microbiomes were also low in *Bacteroides* bacteria.

Both c-section delivery and antibiotic exposure have been implicated in the development of childhood allergies. Although the study does not provide direct evidence that an altered microbiome is the mechanistic link between these events and illness, it does raise the question of whether a drastically different initial gut microbiome has long-term consequences.

Nature **574**, 117–121 (2019)

Weight loss without microbial gains

French scientists have examined the microbiomes of people with severe obesity, and how the communities of microbes changed after bariatric surgery. The research, by Karine Clément at Sorbonne University, Paris, and her co-workers, showed that most people who are severely obese have impoverished gut microbiomes — and that post-surgical weight loss and improved metabolic health were not accompanied by a full recovery of microbial diversity.

Microbiomes were analysed by quantifying the overall genomic diversity and measuring the serum levels of microbiome-associated metabolites before and after surgery. Three-quarters of participants had low microbial gene richness — compared with 20–40% of people who were moderately obese. When the authors looked for correlations between metabolites and microbiome structure, they found nine metabolites were affected by changes to the microbiome.

Bariatric surgery — either a gastric band or a bypass — increased microbial diversity by 25–40%, but, on average, levels remained lower than those of people of a healthy weight. This held true one year after surgery, when weight loss was maximal. In some people, the comparative lack of diversity persisted five years after surgery.

The study suggests that applying strategies to correct the gut dysbiosis associated with severe obesity, alongside surgery, could further improve metabolic function.

Gut **68**, 70–82 (2019)

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