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Tracking microbiota fibre breakdown to treat NASH

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Tracking the journey of inulin, a soluble dietary fibre, reveals its fate and transformation by the gut microbiota to alleviate liver disease in mice.

Dietary fibres are complex carbohydrates that nourish the gut microbiota and help shape host–microbe symbiosis. They cannot be fully degraded by human digestive enzymes, ensuring their availability for anaerobic fermentative bacteria in the large intestine. In return, commensal bacteria can produce beneficial fibre-derived metabolites that help regulate intestinal transit and reduce the risk of metabolic disease. However, the mechanisms that underlie this exchange of favours are likely influenced by the specific fibre type and the responsiveness of the host's gut microbiota to these dietary components. Indeed, the extent to which the gut microbiota contributes to the health benefits of dietary fibres is under debate, largely due to our limited knowledge of the mediating factors and mechanisms. Some human intervention trials with dietary fibre report improvements, for example, in type 2 diabetes. These are linked to increases in fibre-fermenting bacteria[1]. However, others report improvements in the host metabolic phenotype (for example, reductions in body weight and systemic inflammation) without induction of major changes to the gut microbiome, suggesting that the microbiota does not mediate the observed beneficial metabolic effects[2].

Writing in *Nature Microbiology*, Wei et al. report a mechanism by which inulin, a soluble fibre fermented by our gut microbiota, ameliorates non-alcoholic steatohepatitis (NASH). NASH is a liver disease that is characterized by inflammation and fat accumulation, and it is frequently associated with obesity and type 2 diabetes[3]. Gut microbiome alterations contribute to NASH. Microbiome-modulating strategies, such as inulin intake, could thus help prevent disease progression[3,4]. The authors employed an elegant strategy that combined stable-isotope probing, shotgun metagenomics and metabolomics to reveal that the gut commensal *Parabacteroides distasonis* uses inulin to produce pentadecanoic acid — an odd-chain saturated fatty acid that alleviates NASH in different mouse models (Fig. 1).

The authors first compared the effects of two different fibre types in their mouse models of NASH — a soluble fibre (inulin) and an insoluble fibre (cellulose) — which are used differently by gut microbes. They found that inulin was more effective than cellulose in protecting against NASH, specifically through the attenuation of hepatic steatosis and fibrosis and the dampening of inflammation and oxidative stress. To identify the best inulin consumers in the gut microbiota and those responsible for these benefits, the authors tracked the incorporation of ^{13}C-labelled inulin into bacterial DNA using metagenome sequencing. The bulk of the ^{13}C-labelled species were *Bacteroides* (80%) and *Parabacteroides* (10%). Consistent with these findings, *Bacteroides* levels are frequently increased in response to dietary fibre in humans, which

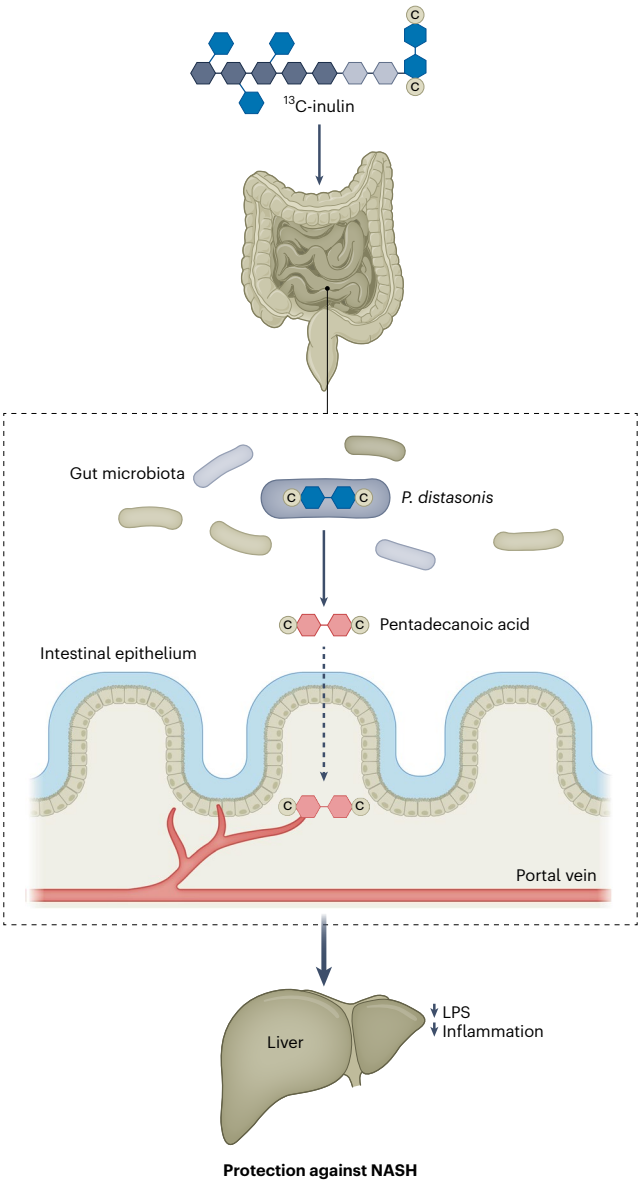

Fig. 1 | *P. distasonis* uses inulin to produce pentadecanoic acid and ameliorate NASH in mice. Stable-isotope probing was used to track the transformation of inulin by the gut microbiota, specifically *P. distasonis*, into pentadecanoic acid in the intestine. Downstream metabolites, including pentadecanoic acid, could then be tracked to the liver via the portal vein — also known as the gut–liver axis. Administration of inulin, *P. distasonis* or pentadecanoic acid demonstrated a protective effect against NASH, contributing to the restoration of gut barrier function and decreased hepatic inflammation. LPS, lipopolysaccharide.

is likely due to their diverse repertoire of fibre-degrading machinery. Recent work has also shown that inulin administration to mice can increase the levels of *Parabacteroides*[5]. However, direct evidence of fibre utilization by these gut microbes had not been provided until now[3].

To test the role of these bacteria in NASH amelioration, the authors fed mice the top three species enriched by ^{13}C-labelled inulin: *Bacteroides uniformis, Bacteroides acidifaciens* or *P. distasonis*. Although *Bacteroides* dominated the ^{13}C-labelled fraction of microbes, it was *P. distasonis* that showed the greatest potential to reduce hepatic steatosis and inflammation in their mouse model of NASH. This complements a recent study showing that oral administration of *P. distasonis* reduces weight gain, hyperglycaemia and hepatic steatosis in murine models of obesity[6].

Using untargeted metabolomics, inulin fermentation was found to generate a distinct faecal metabolome signature in NASH mice compared with control mice given cellulose[3]. Labelled metabolites were also found in the colonic tissue, portal vein serum and liver tissues of the inulin-fed group but not of the cellulose-fed group, indicating that inulin breakdown products are absorbed and transported via the gut–liver axis. Further analysis of metabolomics data revealed ^{13}C labelling of fatty acids, nucleotides and vitamins. This suggests that gut microbes can use inulin for the biosynthesis of a wide range of metabolites that can be exploited by both bacteria and host. Of these, pentadecanoic acid was enriched in the faeces and portal vein (the key link between the intestine and the liver) of mice. Interestingly, pentadecanoic acid was previously used as a marker of inulin intake in clinical trials[7], supporting the potential translation of this research to humans. Importantly, Wei et al. confirmed that *P. distasonis* produces pentadecanoic acid in vitro and in germ-free mice[3].

To complete the causality loop, the authors showed that treatments with inulin, *P. distasonis* or pentadecanoic acid were all protective against NASH in their murine models. These treatments restored gut barrier function and limited the translocation of bacterial-derived products from the gut to circulation — features that are characteristic of this disorder[8]. Indeed, earlier work attributed the beneficial effects of *P. distasonis* in animal models of obesity to its metabolic capacity. Specifically, its ability to produce succinate and transform primary bile acids into secondary bile acids[6]. The study by Wei et al. adds to growing evidence that supports a role for gut-bacteria-produced metabolites in improving diet-related diseases[2].

The findings reported by Wei et al. elegantly show how a dietary fibre is metabolized by a specific bacterial species, producing a metabolite that functions as a gatekeeper of the intestinal barrier[3]. In humans, however, these effects may depend on many more variables than those studied in rodent models. For example, the inulin-metabolizing capacity of each individual's microbiome[9], as well as other lifestyle and endogenous factors (diet, exercise, medication, comorbidities and so on)[10]. Challenges remain in translating these findings into real solutions. Nonetheless, this study exemplifies the value of tracking host–microbe nutrient flows to design microbiota-targeted diets that drive the desired microbial functions and treat metabolic diseases with increasing prevalence, such as NASH.

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Competing interests

The authors declare no competing interests.