MICROBIOME

To grow, or not to grow

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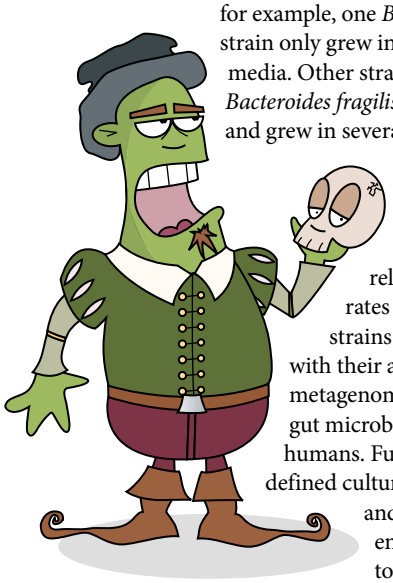
The gut microbiota inhabits a complex environment and is exposed to various compounds that are ingested or produced by the host or the microbiota itself. Unravelling how different molecules influence the growth of individual members of the microbiota is challenging owing to a lack of systematic screens. In two new studies, Typas and colleagues studied the growth of representative isolates from the gut microbiota in different media and in the presence of drugs.

So far, most studies used complex media with chemically poorly characterized components to culture the gut microbiota. This makes elucidating the metabolic requirements and capabilities of different gut bacteria difficult. Therefore, Bork, Typas, Patil and colleagues tested the growth of 96 gut bacterial strains from 72 phylogenetically diverse species in 15 defined media and four rich, undefined media. 76 strains grew in at least one defined medium. Many strains showed fastidiousness; for example, one *Bifidobacterium* strain only grew in the four rich media. Other strains, such as *Bacteroides fragilis*, were generalists and grew in several defined media. Interestingly, the authors could identify media for which the relative growth rates of the different strains correlated with their abundance in metagenome data from the gut microbiome of healthy humans. Furthermore, the defined culture conditions and growth rates enabled the authors to test the influence of short-chain fatty acids (SCFA) and mucin, which are abundant components of the gut environment, on growth. More species than previously identified could degrade mucin, which indicates that these species might colonize the mucus layer and influence the intestinal barrier. Interestingly, SCFAs inhibited the growth of 14 species and enhanced the growth of only one species. This might be due to SCFA toxicity, an effect that might have hindered previous attempts to culture some gut microbiota in media that contained these metabolites. The defined media and the insights into the growth requirements of different strains helped the authors to improve metabolic models and provide a valuable resource for future culture-dependent studies.



Credit: Philip Patenall/Macmillan Publishers Limited

In the second study, which is an example of such a culture-dependent study, Zeller, Patil, Bork, Typas and colleagues tested the influence of 1,197 drugs, which contained compounds that represent all main drug classes used to treat humans, on the growth of 40 representative strains isolated from the human gut microbiota. As expected, more than three quarters of the antibiotics inhibited at least one bacterial strain. Some of the antibiotics that showed no effect are inactive under anaerobic conditions or specifically target mycobacteria. More than half of antimicrobials that target eukaryotes or viruses also inhibited bacteria. Notably, 24% of the drugs that had human targets also reduced bacterial growth. Most of these drugs only inhibited a few bacterial strains, which makes them candidates for narrow-spectrum microbiota modulators. However, 20% of the human-targeted growth inhibitors had a broad spectrum and inhibited at least one-quarter of the strains. Therefore, these drugs could be explored as novel antibiotics. Interestingly, the authors found overlapping resistance mechanisms to antibiotics and human-targeted growth inhibitors, which suggests that unrelated medications might promote antibiotic resistance. Antimetabolites, which are used to treat cancer and for immunosuppression, were particularly prone to inhibit bacterial growth. Many of these drugs have targets that are conserved between bacteria and humans and, therefore, are expected to affect both. Antipsychotics also were over-represented in the hits, and the authors speculated that effects on the microbiota might contribute to their mechanism of action. Notably, the drug effects observed in this study were in agreement with the limited metagenomic patient microbiome data that takes drug intake into account and with known antibiotic-like side effects of human-targeted drugs.

These two large screens provide a detailed insight into the growth characteristics of the gut microbiota and how different nutrients, metabolites and ingested compounds influence individual species. Such detailed knowledge is essential to decipher the interactions and functions of the gut microbiota.

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ORIGINAL ARTICLES Tramontano, M., Andrejev, S. et al. Nutritional preferences of human gut bacteria reveal their metabolic idiosyncrasies. *Nat. Microbiol.* https://doi.org/10.1038/s41564-018-0123-9 (2018) | Maier L., Pruteanu, M., Kuhn, M. et al. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature* https://doi.org/10.1038/nature25979 (2018)