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Commentary

Development of an alternative animal model to investigate host-microbe interactions

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In this article of *EBioMedicine*, Lleal et al. characterise a rat model of colitis to investigate the role of the gut microbiota, the indigenous microbes in the gastrointestinal tract, in colitis [1]. The authors demonstrate two concepts that aid this line of investigation: 1) they establish an alternative model to mice to study inflammatory bowel disease (IBD), and 2) establish efficacy of a single administration of faecal microbiota transplantation (FMT) from a human source in their model, showing that it attenuates disease. They therefore present an alternative animal model for studying host-microbe interactions that may better model the human microbiota.

IBD is a complex gastrointestinal condition defined by chronic inflammation that includes Crohn's Disease (CD) and Ulcerative Colitis (UC). Although direct aetiology is unknown, disruption of the gut microbiota likely plays a key role. Both alterations to the microbiota structure and overall loss of microbial diversity have been observed in patients with IBD [2], prompting interest in developing microbial therapeutics to cure or alleviate symptoms. One such treatment, fecal microbiota transplantation (FMT), has been used to treat IBD, particularly UC, with some success [3,4]. FMT has been highly effective against infections caused by the healthcare-associated bacterium, *Clostridioides (Clostridium) difficile*, acting to restore colonization resistance against the pathogen.

Despite success in using FMT to treat CDI, there has been limited success in using FMT for other gastrointestinal conditions such as IBD and non-gastrointestinal conditions like metabolic syndrome or autism [5]. Reasons for this include disease complexity, issues in donor matching, or selection of target microbes, which have not been clearly delineated for each condition. Additionally, the long-term consequences of FMT are unknown, and compatibility of the recipient and donor microbiota may be important. It is likely that FMT is not a one-size-fits-all treatment, thus impacting individuals differently depending on the condition being treated. Recent studies in humans have attempted to characterize how FMT functions by tracking colonization of microbes or restored functions. Variable colonization following FMT has been observed for certain patient populations [6,7]. Although strain colonization has not been conducted in patients with IBD, where ongoing inflammation may further complicate FMT efficacy, it has been suggested that donor selection plays a role in successful outcome in patients with IBD [4].

Animal models provide the ability to design interventions not possible in human studies that test specific hypotheses. A common method of modeling animals in a more human context includes "humanising" the microbiota of animals, where human microbiota from different patients can be transplanted into germ-free animals. Mice with humanised microbiota from patients with IBD, for instance, have been demonstrated to harbor increased intestinal Th17 and decreased regulatory T cells that exacerbate colitis [8]. One limitation with these studies is the difference between mouse and human microbiota; while the microbiota at a broad taxonomic level may be interchangeable, studies have demonstrated strain-level and functional differences between the microbiota of mice and humans, such as differences in their bile acid capability [9].

The availability of an animal model that more strongly reflects human microbiota is a welcome addition to the field, and Lleal et al. present a case for inclusion of other animals to study human microbes. The authors demonstrate that transplantation of human faecal material was increased and more sustained in rats compared to mice. They then go on to use these "humanised" rats in a model

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of colitis, reflective of IBD. Rats subsequently treated with FMT from human donors faired significantly better than untreated rats, exhibiting not only changes in their microbiota reflective of the human donor material, but also demonstrating decreased inflammation and histopathology.

Questions still remain about the superiority of a rat model to study host-microbe interactions. The availability of ample comparative data and different genetic backgrounds continue to make mice an attractive model. As the authors mention, the current study used 16S rRNA gene sequencing to compare the microbiota, which is not sufficient to establish strain- or gene-level differences. Additionally, only one mouse population was used in this study. It is known that even mice from the same genetic background can harbor variable microbiota depending on the source, potentially impacting study outcome [10]. Studies that compare mouse populations and focus on differences at the gene or functional level would strengthen rat vs. human microbiota comparisons. Finally, the authors did not compare disease outcome of FMT from rats or mice in their rat model. It is possible that using the host's own source of FMT would attenuate colitis even further, providing a parallel control of FMT where the host and microbes are "matched" to ascertain if this is important.

Going forward, it is necessary to recognize that conclusions from one disease system, and perhaps microbiota, are not necessarily interchangeable with another. For there to be success with FMT and related therapies, both models and human studies are required to identify targeted microbial functions as well as determine treatment efficacy, safety, and long-term consequences. The current study provides a useful model and perspective that may aid these lines of inquiry.

Author's contribution

AMS reviewed the article and related literature, interpreted results, and wrote the commentary.

Declaration of Competing Interest

Dr. Seekatz has nothing to disclose.

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