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POINT OF VIEW

Future prospect of faecal microbiota transplantation as a potential therapy in asthma

Y. Kang[a,b,*], Y. Cai[a,c]

[a] *Medical School, Kunming University of Science and Technology, Kunming, Yunnan, China*
[b] *Genetics and Pharmacogenomics Laboratory, Kunming University of Science and Technology, Kunming, Yunnan, China*
[c] *Pathogen Biology Laboratory, Kunming University of Science and Technology, Kunming, Yunnan, China*

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Abstract There is convincing evidence from both human and animal studies suggesting that the gut microbiota plays an important role in regulating immune responses associated with the development of asthma. Certain intestinal microbial strains have been demonstrated to suppress or impair immune responsiveness in asthma experimental models, suggesting that specific species among gut commensal microbiota may play either a morbific or phylactic role in the progression of asthma. Evidence to date suggests that the intestinal microbiota represent fertile targets for prevention or management of asthma. The faecal microbiota transplantation (FMT) is a rather straightforward therapy that manipulates the human gastrointestinal (GI) microbiota, by which a healthy donor microbiota is transferred into an existing but disturbed microbial ecosystem. The FMT may therefore represent a therapeutic approach for asthma treatment in the foreseeable future. At present, FMT therapy for asthma is very limited and should be actively studied. Considerable efforts are needed to increase our knowledge in the field of FMT therapy for asthma. In this review, we aimed to provide several insights into the development of FMT therapy for asthma.

Asthma is estimated to affect approximately 300 million individuals worldwide, incurs significant health care expenditure,[1,2] and is one of the most common chronic diseases. Given increases in disease prevalence over the last several decades, it is predicted that the number of individuals affected worldwide will increase by 100 million people by 2025.[3] Asthma is classically associated with hyperactivation of the T helper 2 (Th2) arm of adaptive immunity. However, the aetiology of asthma remains elusive. Some studies on genetic predisposition to asthma have implicated genes, such as *ADAM-33*, *HLA-G*, *KCNIP4*.[4–6] Estimates of inheritability suggest that genetic factors are only partially responsible for the risk of developing asthma.[7] This means that environmental factors must also play a significant role. Gut microbial triggers as an important environmental factor have been implicated in asthma.[8] The largest and earliest

* Corresponding author.
E-mail address: 657151276@qq.com (Y. Kang).

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source of microbial exposure in human subjects comes from the intestinal tract. The gut contains a large and diverse population of microbes which are collectively termed as the gut microbiota. It contains approximately 10^{14}, and consists of 6–10 major phyla and 3000–5000 species, weighting 1–2 kg.[9] The amount of microbial luminal cells is 10-fold more than eukaryotic cells of living beings.[10] It is estimated that the microbiota genome has 150-fold more genes than the host genome.[11] The microbial metagenome can provide a huge genetic diversity susceptible to convey a large number of functions. In addition, gut microbiota is, quantitatively, the most important postnatal source of microbial stimulation of the immune system.[12] At present, a growing body of evidence has demonstrated that gut microbiota play an important role in promoting and maintaining a balanced immune response in early life.[13] Hence disruption of this process early on in life at a time of dynamic changes[14] in the infant's gut might have long-term health effects. Asthma often begins in early childhood, when the gut microbiota is primarily developed.[7] The accumulating evidence has shed light on the association of dysbiosis of gut microbiota with asthma in animal models and in human subjects.[8] Especially, certain gut microbial strains have been shown to inhibit or attenuate immune responses associated with chronic inflammation.[15] Although still a relatively nascent field of research, evidence to date suggests that the gut microbiome may represent fertile targets for prevention or management of allergic asthma. Faecal microbiota transplantation (FMT) may therefore represent a therapeutic approach for asthma treatment.

Faecal microbiota transplantation is a rather straightforward therapy that manipulates the human gastrointestinal (GI) microbiota, by which a healthy donor microbiota is transferred into an existing but disturbed microbial ecosystem.[16] The administration of faeces for therapeutic purposes was first described more than 1500 years ago by Ge Hong.[17] Afterward, in the sixteenth century, Li Shizhen treated several gastrointestinal symptoms, such as diarrhoea, constipation, vomiting or pain, by faecal products. FMT came to the attention of mainstream medical science only in the late 1950s: in 1958, Eiseman, a surgeon from Colorado, successfully treated four patients with pseudomembranous colitis using faecal enemas.[18] Specially, FMT has emerged as a highly effective treatment for recurrent *Clostridium difficile* infection. Thus, FMT have been encouraged to cure *C. difficile* infections worldwide, especially in Western Countries. The recent advancement in our understanding of gut microbiota has given a solid pathophysiological background to FMT. Accounting our microbial flora as a bodily organ[19] let the interpretation of FMT change from being considered a mere injection of faeces to becoming a true organ transplantation. Such a conceptual transition has led FMT to being used in the treatment of several diseases associated with the disruption of gut microbiota, such as obesity, diabetes, inflammatory bowel disease (IBD), metabolic syndrome, irritable bowel syndrome, anorexia nervosa, autoimmune diseases, multiple sclerosis, cancer, neuropsychiatric disorders, and cardiovascular diseases.[15] Over the past decades, compelling rationale has been provided for oral administration of probiotics/prebiotics as adjunctive therapies in asthma.[20] The emergence of promising experimental studies has led to several clinical trials of probiotics (live bacteria given orally that allow for intestinal colonisation) in human subjects with asthma.[21] Faecal microbiota transplantation may be more effective than probiotics in the restoration of altered gut microbiota, since a faecal infusion overcomes the intrinsic quantitative gap of probiotics (oral probiotic doses are usually more than three orders of magnitude lower than the 100 trillion native micro-organisms of the large bowel). In addition, the administration of faecal flora establishes a durable alteration of the recipient's gut microbiota,[22] while probiotics are able to colonise the gut lumen only for a temporary period.[23] Although the exact mechanism whereby transplanted stool is protective to patients is unknown, FMT probably restores a patient's altered intestinal microbiota to restore colonisation resistance. In assessing a transplant recipient's faecal microbiota pre- and post-FMT, even 33 days after FMT, careful RNA gene sequencing showed that the patient's stool was strikingly similar to the donor stool after transplant suggesting that the donor's stool had helped restore a healthy colonic microbiome.[24]

In conclusion, FMT represents a possible therapeutic for improving asthma. However, the available data in this field remain limited, and the relevant scientific work has only just begun; especially, at present, new technologies have allowed the attempt to a systematic intestinal bacterial flora study, giving more realistic information about its composition and its pathological variance. Furthermore, recent technological developments permit the identification of microbes and their products using culture-independent molecular detection techniques. Thus, FMT may be considered a potentially useful therapy for asthma in the future. FMT therapy for asthma should be actively studied. A lot of research needs to be done in the future. Firstly, in order to better use FMT to treat asthma, an in-depth understanding of the mechanism of action between gut microbiota and host is needed. Secondly, it will also be important to determine how FMT changes the composition of the gut microbiota (restores bacterial flora) and how relevant this is to asthma. The alteration of gut microbiome and health status should be careful analysed/investigated in pre- and post-FMT treatment among asthma patients. The emergence of promising experimental studies will lead to several clinical trials of FMT in human subjects with asthma. There is increasing uptake and acceptance for the therapeutic use of FMT, partially due to its perception as a 'natural' treatment, and its relatively inexpensive implementation.[25] Excitingly, the introduction of gut microbiota into consideration will bring breakthroughs in the research and treatment of asthma in the foreseeable future. Future research could lead to the development of FMT that can improve asthma by restoring the intestinal microbiota.

Ethical disclosures

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this investigation.

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Conflict of interest

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