

## Gut Microbiota: What We Could Do, Not Just Use ‘Young Healthy Poo’ for Drugs?

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### Introduction

The faeces were used as ‘drugs’ for years. If patients occasionally have taken overdose antibiotics, doctors just give them faeces from whom they live with to help rebuild their gut microbiomes. As the technologies developed, we know gut microbiomes have changed if being obesity [1], being sick [2] or being ageing [3], so researchers tried to make faeces ‘drugs’ from thin, healthy and young individuals [4]. It’s prospective and shows great benefits if this idea works in the near future, however, in this review, we’d like to discuss some other essential questions in this area.

### Culture System

#### Gut microbes culture

From microscopical view, for now just parts of gut microbiomes could be cultured *in vitro* [5]. However, new culturing approaches, like microbial culturomics [6], were introduced recently and doubling the number of culturable species. As more and more experimental parameters could be modulated artificially and smoothly, more and more bacterias could become culturable in the near future. At least two areas could from get benefits this. One is drug or antibiotics developments. For instance, culturable *B. adolescentis* is helpful in drug development targeting Th17 cells [7]. The other one is improving the *in vitro* bacteria-host cell model, which is more easily and tightly manipulated than *in vivo* animal models.

#### Mono-associated mice

Mice associated with a single or a limited number of bacterial species, or so called mono-associated mouse model, have been used for decades [8,9]. This model has previously been developed to define the taxonomy and functions of a single bacteria, but for now it is also an crucial tool to analyze the microbiota-host relationships in the gut. Geva-Zatorsky and his colleagues have recently showed a comprehensive immunomodulatory role of gut microbiota using selected 53 different mono-associated mice and observed a bunch of uncharacterized bacteria-host interactions [10]. The next step might be focusing on this two aspects: one is what is the molecular mechanisms when a certain bacteria was introduced to mice, and the other is why these immune responses happens and what happens after the initial immune response.

#### Gut resident cells

Except for microbiomes, there are also various kinds of cells residing in the gut, like neurons in the nervous system [11] and lymphocytes and myeloid cells in the immune system [12,13]. Most of

these primary cells or cell lines could be isolated and cultured in monolayers, and it would be a simplified bacteria-host system if supplied with bacterias. However it is far from enough, Yissachar et al. recently built an organ culture system using the mouse intestine, which might try the best to keep hosts’ components complete and alive, and also make some essential factors controllable [14]. Of note, mouse intestines from different disease models could also be used as the culture systems, which much broadens this system’s applications.

### Cross Talks

From macroscopical view, gut microbiota might also be regarded as an indivisible whole, and tightly coordinated with immune system, metabolic system and nervous system, which might take at least three more reviews to discuss. Very recently, Lefrançois et al. showed that the megakaryocytic cells circulated in the lung and produced approximately half of the total platelet using 2-photon intravital microscopy [15], which leads us to look back forward to think over some fundamental questions, from the origins of fetus microbiota, the evolutions, the changes to the regulations of adult microbiota.

Increasing evidences suggest that gut microbiota have already been set up before birth [16], but still some gaps left. First, at which period of pregnancy the microbiota is seeded? Second, is the proces that bacterias get through maternal-fetal interface selectively or unselectively and what is the regulative networks? Third, does the fetus’s immune system and nervous system coevolve with microbiota and how?

Certain bacterial species could promote or induce certain immune cells. For example, Th17 cells accumulate in the gut and take its role as the safeguards there by secreting cytokines like IL-17 and IL-22, and inducing some antimicrobial peptides and tight junction proteins from intestinal epithelial cells [17-19]. Both segmented filamentous bacteria (SFB) from mice’s gut [20-22] and *B. adolescentis* from human’ [23] could induce T Helper 17 cells (Th17). Not surprisingly, gut microbiota-derived products, such as short-chain fatty acids (SCFAs), adenosine triphosphate (ATP) and various cytokines could also regulate the immune cells and immune response directly or indirectly [23]. For instance, excessive production and accumulation of SCFAs such as acetic acid, propionic acid and butyric acid, cause the increased luminal carbohydrates malabsorption and poor gastrointestinal motility, and ultimately might lead to the necrotizing enterocolitis, especially premature infants, whose immune systems are not fully established. Various immune cells are involved in this process and most of them have receptors for SCFAs, but which is particularly responsible for this is poorly discussed. On the other hand, IgA is the crucial host immune effector to modulate microbiota back [23]. However, we know much less about how certain immune cells control

or regulate gut microbiota, by phagocytosis or by secreted cytokines or something else? Moreover, it is still lack of whole pictures that the gut microbiota triggers comprehensive immune responses while the immune systems trim gut microbiota as a feedback.

To sum up, the research on microbiota has dramatically advanced these years, but still numerous issues need to be elucidated. One aspect is to further improve the technologies, and the other is some basal questions to be proposed and clarified, from molecular, signaling pathway to organ levels.

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