論文の内容の要旨

Universality of commensal microbiota and its mathematical interpretation
(常在細菌叢の普遍的性質と、その数理的解釈)

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Introduction

It is known that the host body sites are colonized by numbers of microbes to form normal microbiota. The number of the microbial cells is estimated to be ~10 times greater than the total number of our somatic cells [1]. The normal microbiota is profoundly related to host physiologies, particularly various diseases such as obesity [2][3], inflammatory bowel diseases (IBD) [4][5], cancer [6], periodontal diseases [7], and pancreatic diseases [8].

A lot of large-scale metagenomic studies on normal gut and oral microbiota have been recently advanced, however, it has been largely limited for elucidating universal features and rules for shaping normal microbiota structure. Focusing on the intestinal and salivary microbial community in humans and mice, here I clarified the conditions in which relative species abundance distributions vary and further demonstrated that such distributions can be generated under spatially heterogeneous proliferation of microbes into their nutrient source.

Results and Discussion

Discovery of the robust bacterial population distribution

I used fecal samples from 104 healthy Japanese adults for the analysis [8]. I obtained high-quality 2,500 reads of the V1-V2 sequences in 16S ribosomal RNA gene from each gut microbiome sample, and classified the microbiota data into two distinct enterotype clusters [9] based on the microbial composition (Fig. 1A). From each cluster, I calculated the cumulative relative abundance distributions (CRADs) with the OTU level abundance of microbes (Fig. 1B). The CRADs of two cluster samples followed the same distribution. In addition, these CRADs showed a long-tailed structure with the microbial abundance, which was well approximated by a power law function with power exponent (β) of 0.71 with an exponential decrease particularly in high abundant fractions of species. These results suggested the existence of a hitherto unknown universal rule which produces characteristic CRADs independent of enterotypes determined by the microbial composition. Such robustness of CRADs independent of inter-individual variability was also observed in fecal microbiota of mice. Furthermore, I also observed little change in the CRADs of the gut microbiota under the dietary intervention conditions in mice and humans, respectively. More interestingly, this robust trait of CRAD was also observed in several diseases such as Type 2 diabetes, inflammatory bowel disease

(IBD), and multiple sclerosis (MS) of which the gut microbiota exhibited microbial dysbiosis. These findings suggested the existence of a hitherto unknown universal rule which produces characteristic

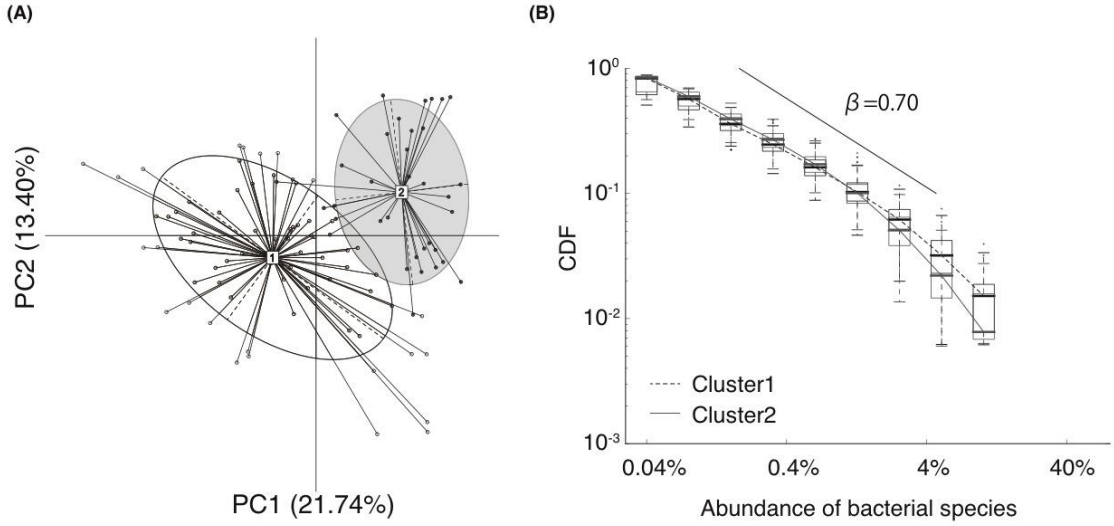

Fig. 1. Robust CRADs on 104 healthy Japanese gut microbiota. (A) Enterotype analysis of 104 healthy Japanese individuals based on genus abundance using R (http://enterotype.embl.de). (B) CRADs of each enterotype.

CRADs independent of changes in the species members.

I further investigated on the CRADs of human salivary microbiota. By collecting human salivary samples from 6 healthy subjects with 4-hour interval for 3 days, I found a highly regulated circadian oscillation in the microbial and genetic composition. The CRADs of salivary microbiota was approximated by a power law with $\beta = 0.8$ commonly in all the 6 subjects. Though the maximum degree of compositional variation generated by circadian oscillation was comparable to the inter-individual compositional diversity, the CRADs were also independent of daily compositional variation.

Shift of CRADs

To examine the cases in which the slopes of CRADs shift, we collected the contents of the large and small intestines to obtain 16S V1-V2 sequences of the microbiome from six SPF mice (Fig. 2A). I found that β in the CRADs of the microbiota from some parts of the small intestine was estimated to be about 0.4, and that from the cecum was about 0.8 with the largest value in the all six mice (Fig. 2B). The microbiota of the small intestine with small β values tended to be composed of small numbers of OTUs, while those of cecum with large β tended to be composed of large numbers of OTUs (Fig. 2C). Similar CRADs shift was also observed in human infant feces samples. 13 feces samples of 0-year old infants were collected and studied based on V1-V2 sequence data of the 16S rRNA gene. Most of the

CRADs of the infant samples showed the slopes with β=0.35-0.4, which is similar to the CRAD of the microbiota in mice small intestines.

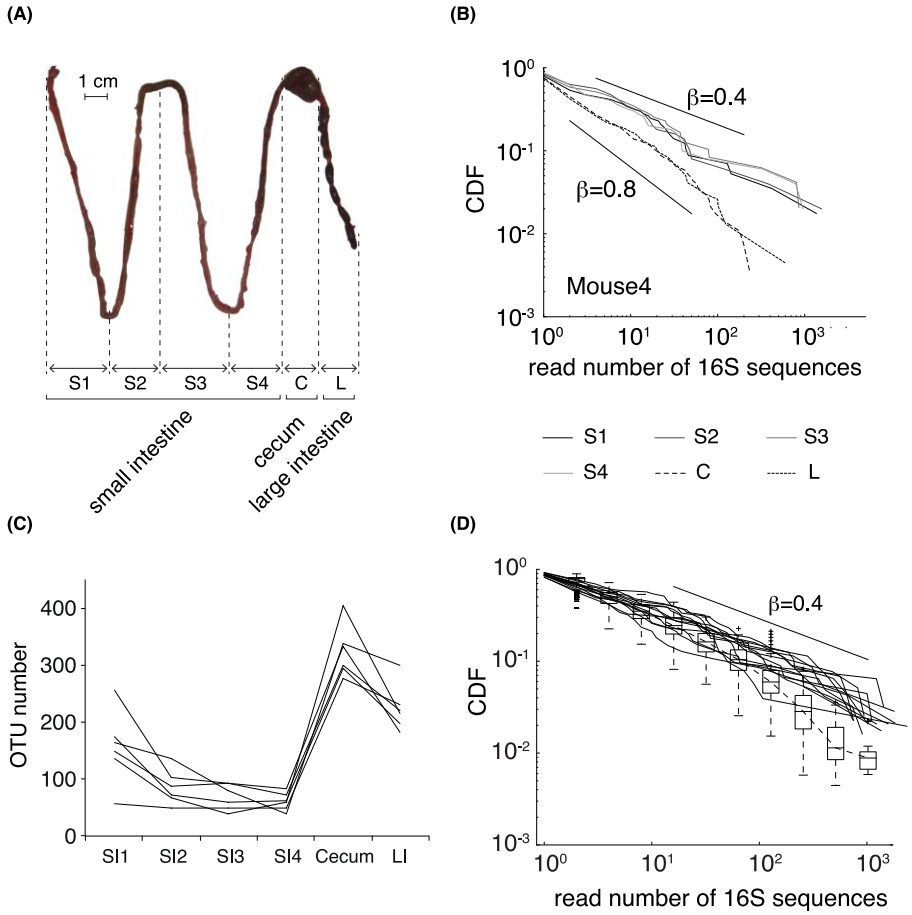

Fig. 2. CRAD shift of mice intestine and human infants. (A) Dissected sections of mice gut. (B) CRADs of each dissected section of mouse intestine. (C) Observed species number of each dissected section of mouse gut. (D) CRADs of Gut microbiota of a human infant.

Simulation of CRADs shift

To examine the mechanisms of shaping gut microbiota causing the CRAD shift, I introduced a 3-dimentional territory invading model under the assumption of spatial competitive proliferation by congregated bacteria into the nutrients (Fig. 3A). Basically I assumed the neutral condition of initial state and growth rate of each species and interactions. The CRADs and the resulting species number of the 104 Japanese samples were well reproduced by the simulation with p=0.9985. On the other hand, the simulation with p=1.0 reproduced the shallow slope observed in the human infant CRADs (Fig. 3B). Comparing the data of mouse intestinal contents, the simulation using p=1 also reproduced the shallow slope of the small intestinal contents (Fig. 3C). The simulation with p=0.9975 matched with the steep slope of the cecum contents. These variations in p indicate that more bacterial species participate in the competitive proliferation in the adult gut or mice cecum than in the infant gut or

mice small intestine, as more bacterial species reside. The present simulation indicates that such mixing and participation of forthcoming bacteria to the competitive proliferation into the nutrient for resources is a primary factor for determining CRADs.

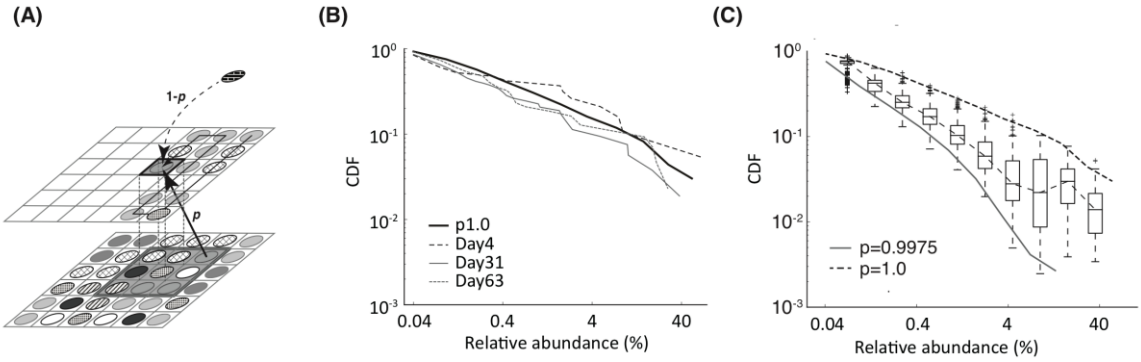

Fig. 3. Reproduction of CRADs by mathematical simulation. (A) Concept of the mathematical model. (B) Simulation of CRADs of infant and adult human feces samples. (C) Simulation of CRADs of mice intestinal contents samples.

Conclusion and Perspectives

I observed robust cumulative relative abundance distributions (CRADs) characteristic to the normal microbiota of humans and mice, and found that CRADs are generally approximated by power law functions. Based on the simulation under various conditions, CRADs may be derived from competitively proliferation adjoining to the nutrient sources distributed non-uniformly. The progress of mathematical models for human microbiota based on their ecological trait will lead to improved prediction and control of human microbiota structure.

References

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