Transition from Infant to Adult Gut Microbiota

Ekaterina Avershina, PhD, and Knut Rudi, PhD
Norwegian University of Life Sciences
Chemistry, Biotechnology and Food Science
Oslo, Norway
knut.rudi@nmbu.no

Abstract

Gut microbiota (GM) plays a pivotal role in our health by modulating physiologic, metabolic, and immune processes and by maintaining gut homeostasis. Timely transition from an infant- to an adult- like state of the GM is particularly important for proper immune and metabolic development. We have, therefore, applied a population ecology approach to determine how gut bacteria are recruited from infancy to adulthood. Our results suggest that the direct mother-to-child transmission of gut bacteria is relatively low, and that there is a constant recruitment of gut bacteria, with a switch from infant- to adult- like gut microbiota during the second year of life. The switch seems to be partly controlled by bacterial-bacterial interactions. We, therefore, propose a model for the transition from an infant- to adult-like gut microbiota, advocating the importance of the aforementioned bacterial interactions. Understanding the infant-to-adult gut microbiota transition could have a major implication for our general knowledge on the establishment of the human gut microbiota.

Glossary of Abbreviations
GM: Gut Microbiota

Key Words
Infant
Gut Microbiota
Recruitment

Introduction

The human gut is inhabited by more than 100 trillion commensal microbes that live in a mutualistic symbiosis with our body.[1] The GM plays an important role in promoting our health by participating in pathogen protection and modulation of physiologic, metabolic, and immunological processes.[2] Disruption of the GM leads to an increased risk of developing a number of gastrointestinal conditions, such as inflammatory bowel diseases, diabetes, and obesity, diseases that are increasing in industrialized countries.[3]

It has recently become evident that the species richness of the human gut microbiota has been fivefold to tenfold overestimated, and consequently the knowledge about transmission patterns was highly biased.[4,5] A common perception among scientists today is that commensal bacteria are transmitted from mother to child during or shortly after birth. However, our recent data from human studies using refined models for species richness estimation indicate that adult-associated microbiota colonization takes place at a later stage, between 1 and 2 years of age, and that the phylotypes found in the children's microbiota overlap with that of the general adult population rather than of the mother.[6]

Gut Microbiota Transmission

Our hypothesis is that adult-associated intestinal microorganisms are not directly transmitted from mothers at birth but are recruited from the adult population at a later stage[6,7] through forms capable of survival in ambient air, such as spores. In support of our hypothesis, it has been found that a major portion of the bacteria colonizing the human adult gut are actually spore-formers and that spores represent a frequent vector for transmission of adult-like gut bacteria.[8] The establishment of the GM, therefore, can be considered as a successive process in which parts of the microbiota are inherited directly from the mother and parts from the environment and/or from the adult population.[9] The important question following these observations is which mechanisms bacteria use for the transmission and establishment in the gut.

Recruitment of Gut Bacteria from a Common Pool

Assuming there is a later stage random colonization by adult-associated bacteria from the environment, one would expect a very high diversity of potential colonizers. However, only around 100 to 200 bacterial species actually colonize the gut of each adult individual, and therefore, it seems evident that there must be restrictions on which bacteria are allowed to colonize. We have previously hypothesized that the number of bacteria that can colonize the gut can be restricted through the positive host selection.[5] It also was shown 20 years ago that the main gut colonizer was able to induce production of host-derived nutrients upon its colonization.[10] However, this positive selection still fails to explain the late transition from infant- to adult-like gut microbiota. We believe that a clue to the late transition could be mother's milk oligosaccharide selection of *Bifidobacteria*,[11] which constitute more than 60% of the microbiota composition at the age of 4 months, representing a potential diversity bottleneck.[12]

Shaping of Gut Microbiota Composition by Bacterial-Bacterial Interactions

Not only host selection but also bacterial-bacterial interactions are important determinants for controlling the colonization of the adult gut. We recently described a keystone role of

Bifidobacterium breve in controlling the transition from an infant- to an adult-like gut microbiota.[6] The gatekeeping *B. breve* particularly was associated with the restriction of certain adult-associated *Clostridial* species. *Clostridia* represent one of the most predominant groups of bacteria in the adult gut and are remarkably important for the intestinal physiology and for immune system functioning, with specific species being universally distributed among humans.[13] Although they have anaerobic requirements for growth, *Clostridia* can persist in the environment in the dormant and highly resistant spore morphotype.[8] Despite their indisputable importance, there is limited knowledge on how *Clostridia* are transmitted among humans, how they are established in the intestine, which factors influence their colonization, and which *Clostridial* species are beneficial.[14] The discovery of *Bifidobacteria*-driven control of *Clostridial* colonization opens the potential for modulating the microbiota during the so-called "window of opportunity" in infancy, which is tightly associated with health maintenance.[2]

Model for the Transition from an Infant- to an Adult-Like State of the Gut Microbiota

We believe that bacterial-bacterial interactions contribute to controlling the transition from an infant- to an adult-like gut microbiota through a limited number of keystone gatekeeping bacteria,[6] which, promoted by indirect host selection, hold back adult-associated bacteria until selection drops down. This hypothesis is outlined in Figure 1, and it represents a fundamentally new concept in understanding the mechanisms for colonization of the human gut.

Based on recent research, we know that the gatekeeping bacteria belong to *Bifidobacteria*, and we also have indications that they are host selected through mothers milk.[6] More data, however, is needed to identify the gatekeeping bacteria at the strain level and to characterize their role and functional potential.

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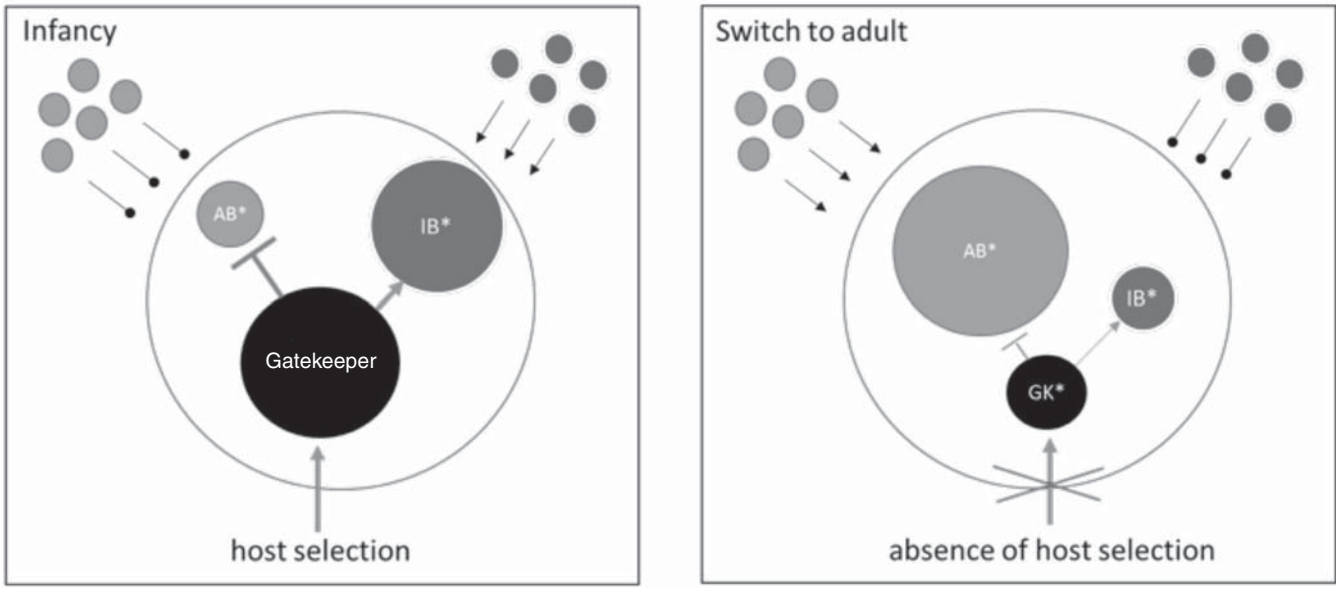

Figure 1. Gatekeeper hypothesis. In infancy, gatekeeping bacteria are selected via mother's milk that regulate which bacteria will be allowed to establish themselves in the gut. With cessation of breast milk, gatekeeping bacteria drop in numbers, and those bacteria that were kept aside can now colonize the gut.
*AB – adult-associated bacteria; IB – infant-associated bacteria; GK – gate-keeping bacteria

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