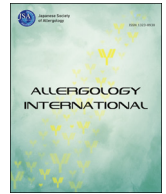




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Invited review article

## Development of the gut microbiota in infancy and its impact on health in later life



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GI, gastrointestinal; IBD, inflammatory bowel disease; SCFA, short chain fatty acids; Treg, regulatory T; Th, helper T; Ig, immune globulin; HMO, oligosaccharides in human milk; GOS, galactooligosaccharide; IL, interleukin; FA, fatty acids; SFB, segmented filamentous bacteria; Foxp3, Forkhead box P3; tTreg, Treg in the thymus; pTreg, Treg in the periphery; ATP, adenosine triphosphate

## ABSTRACT

Gut microbial ecology and function are dynamic in infancy, but are stabilized in childhood. The ‘new friends’ have a great impact on the development of the digestive tract and host immune system. In the first year of life, especially, the gut microbiota dramatically changes through interactions with the developing immune system in the gut. The process of establishing the gut microbiota is affected by various environmental factors, with the potential to be a main determinant of life-long health. In this review, we summarize recent findings regarding gut microbiota establishment, including the importance of various factors related to the development of the immune system and allergic diseases later in life.

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## Introduction

Several hundred bacterial species and a total of  $10^{14}$  cells colonize the human gastrointestinal (GI) tract in a mutualistic relationship with the host and its immune system.<sup>1,2</sup> A healthy gut microbiota is stable and serves various useful functions such as metabolizing barely digestible polysaccharides,<sup>3,4</sup> detoxifying toxic products,<sup>5</sup> serving as a barrier against pathogens,<sup>6,7</sup> and aiding in the development of the host immune system.<sup>8</sup> However, it has become clear through recent studies that dysbiosis, in which the symbiotic relationship between the host and gut microbiota is altered, is associated with various diseases, including inflammatory

bowel disease (IBD),<sup>9</sup> irritable bowel syndrome,<sup>10</sup> obesity,<sup>11–14</sup> allergy,<sup>15</sup> autoimmune disease, and brain disorders.<sup>16</sup>

Although intestinal bacterial colonization begins when a fetus is in the lower uterus, an infant's gut microbiota is established after birth. The establishment of a stable gut microbiota generally accompanies two big transitions in infancy. The first transition occurs soon after birth, during lactation, and results in dominance of the gut microbiota by *Bifidobacterium*. The second transition occurs during the weaning period, with the introduction of solid foods and continuation of breast milk feeding,<sup>17–21</sup> and results in the establishment of an adult-type complex microbiome dominated by the phyla *Bacteroidetes* and *Firmicutes*. These alterations continue until three years of age<sup>22</sup> and, subsequently, humans acquire stable gut microbiotas maintained in well-balanced host-microbiota symbiotic states called “Enterotypes”. Enterotypes are classified into three types that are dominated by *Bacteroides*, *Prevotella*, and other *Firmicutes*.<sup>23</sup> The early establishment of gut microbiota is affected

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by several factors such as delivery mode (cesarean delivery vs. vaginal delivery), breast milk vs. formula feeding, antibiotic usage, and timing of the introduction of solid foods and cessation of milk feeding.<sup>24</sup> In addition, intestinal bacterial colonization has profound effects on the development and physiology of the host immune system in early life and affects health and disease in later life. In particular, colonization with intestinal bacteria is necessary for normal immune system development, as indicated by the loss of immune function in germ-free mice.<sup>25–27</sup> A number of previous studies have shown that intestinal bacteria and their metabolites, including short chain fatty acids (SCFA), play an important role in the proliferation and differentiation of T cells, such as regulatory T (Treg) and helper T (Th) cells, and B cells such as immune globulin (Ig) A- or IgG-secreting B cells.<sup>28</sup>

Therefore, development of the gut microbiota in infancy occurs during a ‘critical window,’ and a disturbance in this process may cause immune diseases such as food allergies, atopic dermatitis, and asthma.<sup>29</sup> To elucidate this association, a large number of studies on microbiotas and microbial ecology, as well as work in animal models and epidemiological surveys, have been conducted. The recent increase in access to next-generation sequencers has allowed researchers to gain deep insight into intestinal ecosystems at the molecular level. On the other hand, hygiene hypothesis has been introduced into gut microbiology to correlate changes in life style with marked increase in childhood allergy in the past half century. This review aims to provide an overview of the recent advances in research on infant gut microbiotas and health and disease, including childhood allergies.

### GI tract microbiotas *in utero*

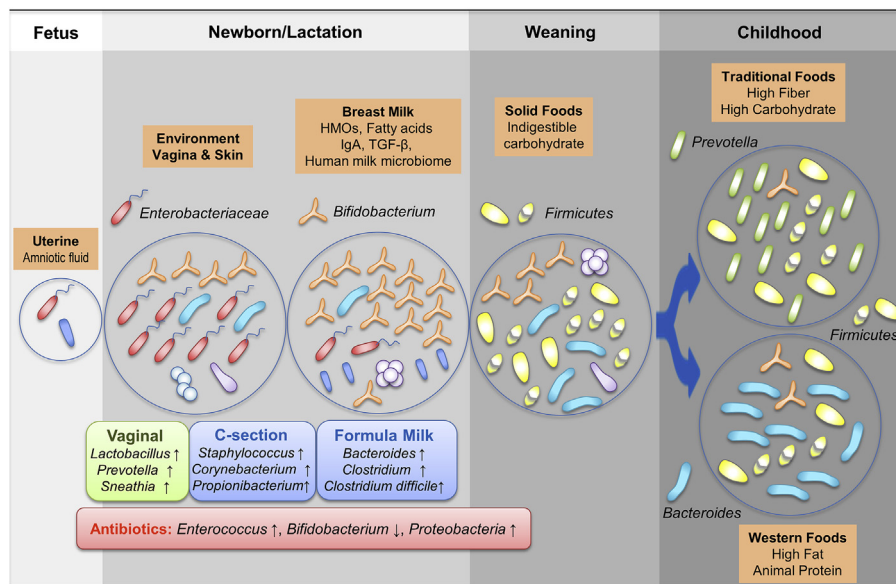
The GI tract has traditionally been considered sterile until it is colonized by microorganisms residing in the environment at birth. However, recent studies have revealed the presence of microorganisms in amniotic fluid,<sup>30–32</sup> fetal membranes,<sup>33</sup> umbilical cords, placentas,<sup>34</sup> and meconium.<sup>35–37</sup> Gosalbes *et al.*<sup>37</sup> showed that meconium microbiotas could be classified into two types: the first is less diverse and dominated by bacteria in the family Enterobacteriaceae, and the other is more diverse and dominated by bacteria

in the phylum *Firmicutes*, especially lactic acid bacteria. These microbial communities differ from the microbiotas of the vagina, feces, or skin of a pregnant women, but resemble the microbiota of the amniotic fluid, suggesting that microbes in the meconium originate from the uterus of the mother. A fetus’s GI tract appeared to be colonized by bacteria through amniotic fluid that was swallowed. Further, the type of microbiota in the meconium was associated with maternal factors such as history of allergies and could have consequences for childhood health.

Experimental work with mice has demonstrated efflux of bacteria from a mother’s gut to that of her fetus.<sup>38</sup> Pregnant mice were orally inoculated with a genetically labeled *Enterococcus faecium* strain that was previously isolated from the breast milk of a healthy woman. The strain was detected in the amniotic fluid of the inoculated animals. This suggests that bacteria might be transferred from the oral cavity to the uterus, possibly via the blood stream. Oral bacteria are known to reach the uterus via the blood stream, particularly in periodontal disease.<sup>39</sup> This route is also supported by the findings of Aagaard *et al.* and others, which has shown that the genetic and taxonomic composition of the placental microbiota closely resemble those of the oral cavity.

### Compositional and functional development of the gut microbiota during infancy (Fig. 1)

After birth, the gut microbiota of a newborn is transiently dominated by *Enterobacteriaceae* and *Staphylococcus*.<sup>40</sup> Thereafter, an infant’s gut microbiota is dominated by *Bifidobacterium* and some lactic acid bacteria.<sup>18</sup> *Bifidobacterium*-dominated microbiota, called “Bifidus flora,” is maintained until the introduction of solid food.<sup>41,42</sup> After weaning, Bifidus flora is outcompeted by adult-type microorganisms, represented mainly by bacteria in the genera *Bacteroides*, *Prevotella*, *Ruminococcus*, *Clostridium*, and *Veillonella*, which colonize an infant’s intestines.<sup>41</sup> Eventually, by about three years of age, a typical adult-like gut microbiota is established.<sup>22</sup> The functions of the gut microbiota also change greatly before and after the introduction of weaning foods. The functional repertoire of an infant’s microbiota changes during the first year of life, as the early microbiota before weaning is enriched in bacteria with genes that



**Fig. 1.** Fetal-to-childhood gut microbiota colonization and important factors affecting this process. Establishment of the gut microbiota may begin *in utero* and be affected by dynamic shifts in early life. Diversity of the gut microbiota increases with age until it becomes a stable adult microbiota. This process of establishing the gut microbiota is affected by various factors such as delivery mode, methods of milk feeding, the introduction of solid foods, and foods consumed daily in childhood.

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