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Review

Impact of early gut microbiota on immune and metabolic development and function

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SUMMARY

Microbial colonization of the infant intestine occurs in the first two years of life. Symbiotic host and microbe interactions are critical for host metabolic and immune development. Emerging evidence indicates that early microbiota colonization may influence the occurrence of metabolic and immune diseases. Further understanding of the importance of environmental factors, including fetal microbial exposure, diet, delivery mode, pre- and probiotic consumption, and antibiotic use on immune and metabolic programming will provide new opportunities for the development of therapeutic and prophylactic measures to improve infant health and reduce the risk of disease in post-infancy years.

1. Introduction

Development of the infant gut microbiota is a dynamic process that begins prenatally and continues during the first two to three years of life. Host genetics and environmental factors, including gestational age, mode of delivery, diet, antibiotic use, maternal weight gain, and stress shape the colonization process [1–3]. Data from germ-free (GF) animal studies have shown that gut microbiota and the host do not simply co-exist, but rather form a mutualistic relationship. Interactions between the commensal bacteria and the host in the early postnatal period are important for host metabolism, and development of healthy gastrointestinal, immunological, and neural systems [4]. Reduced microbial diversity and dysbiosis (aberrations in the microbiota) are linked with a number of gastrointestinal and systemic disorders in childhood and later in life, including necrotizing enterocolitis (NEC), inflammatory bowel diseases (IBD), eczema, asthma, obesity and autism [1,5,6]. This review summarizes the main factors that influence the development of infant gut microbiota and highlights the role of early microbiota on host immune and metabolic functions and consequent health outcomes (Fig. 1).

2. Factors influencing the microbiota in infancy

Establishment of the human gut microbiota is a complex process and involves stepwise succession [7]. The bacteria that first colonize the infant gastrointestinal tract are facultative anaerobes, including staphylococcus, streptococcus, enterococcus, and Enterobacteriaceae [7]. These bacteria decrease the oxidation potential, thereby creating anaerobic conditions favorable for the growth of obligate anaerobes, such as bifidobacterium, bacteroides, clostridium and eubacterium [7]. The microbiota composition within the first year of life is characterized by low diversity, high instability, and high interindividual variations [7–9]. By two to three years of age, the microbiota of infants becomes stable and more diverse, and an adult-like microbiota is established, with the phyla Firmicutes and Bacteroidetes predominating [9,10]. Summarized in the next section are the factors that influence microbial colonization in infants.

2.1. Prenatal period

2.1.1. Host genetics

Support for a role of host genetics on the gut microbiota comes from the studies of monozygotic and dizygotic twin pairs. For example, when the fecal microbiota profiles of identical twin pairs, fraternal twin pairs, and unrelated individuals were compared, the microbiota similarity was greatest between identical twin pairs, intermediate between fraternal twin pairs, and lowest between unrelated individuals [11]. More recently, the gut microbiota of a healthy dichorionic triplet set (a pair of monozygotic twins and a

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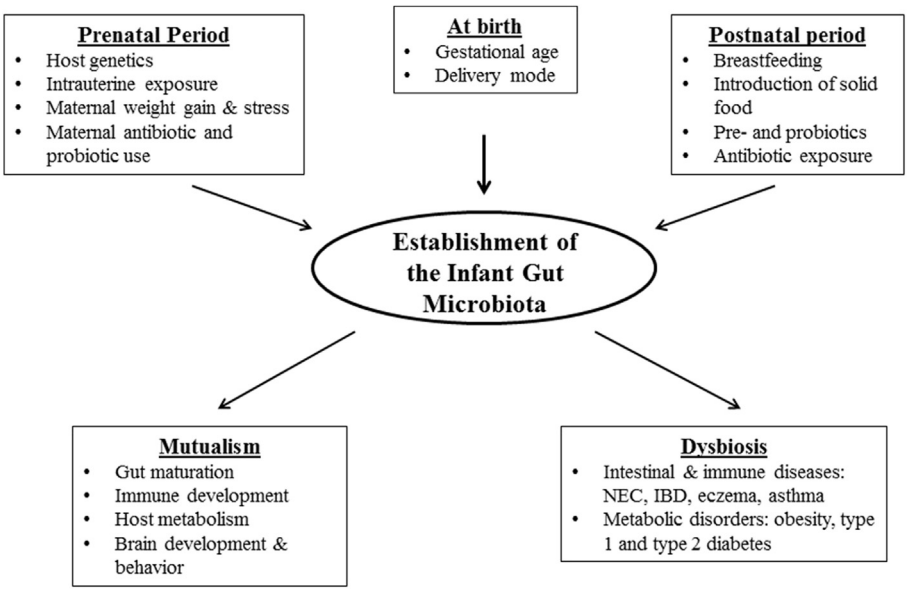

Fig. 1. Main factors influencing the development of infant gut microbiota and host–microbiota interaction in early life. IBD, inflammatory bowel diseases; NEC, necrotizing enterocolitis.

fraternal sibling) was studied. At one month, the fecal microbial composition of the monozygotic pair shared a similar microbiota that was distinct to the fraternal sibling. By month 12, the monozygotic pair was no longer separated from the fraternal twin. These findings demonstrate that host genetics influences gut microbiota composition even when prenatal and early life environments are controlled for [12]. To identify which components of the human gut microbiota are heritable, Goodrich and co-workers compared the fecal microbiota of 416 twin pairs. They reported that the abundances of many microbial taxa were influenced by host genetics, with the family Christensenellaceae being the most heritable taxon [13].

2.1.2. Intrauterine exposure

The intestinal tract of a fetus has been considered to be sterile and microbial colonization to be initiated when the infant is exposed to the microbes from the mother or surrounding environment during birth [7]. However, the presence of bacterial isolates and/or DNA in amniotic fluid and fetal membranes, umbilical cord blood, placenta, and meconium of healthy mothers and infants suggests that colonization may begin prenatally [1]. Although it is difficult to rule out the possiblity of bacterial contamination when samples containing low microbial biomass (such as meconium and intrauterine samples) are studied using high-throughput sequencing [14], animal experiments suggest that maternal gut microbiota may be transmitted from the pregnant mother to the fetus. Jiménez and co-workers orally inoculated pregnant mice with a genetically labelled *Enterococcus faecium* strain, which was found in amniotic fluid and meconium of the pups from inoculated mothers after cesarean delivery (CD). However, the labelled bacteria were not detected in the pups of non-inoculated control mice [15,16].

2.1.3. Maternal probiotic and antibiotic use

Adminstration of the probiotic *Lactobacillus rhamnosus* GG (LGG) to mothers during late pregnancy has been shown to increase the prevalence of *Bifidobacterium longum* group in three-month-old infants at high risk of allergy [17]. Maternal antibiotic treatment during late pregnancy and/or while breastfeeding has been associated with lower proportions of bacteroides and atopobium cluster in infants of aged six weeks [18]. In a more recent study, Aloisio and co-workers studied the effect of intrapartum antibiotic prophylaxis (IAP; antibiotic use on the mother during labor) against group B streptococcus on the bacterial colonization of vaginally delivered newborns; they reported that IAP significantly reduced the counts of bifidobacterium in seven-day-old infants in comparison with infants whose mother did not receive the treatment [19].

2.1.4. Maternal weight gain and stress

Lower abundances of the bacteroides–prevotella group at one month and higher abundances of the *Clostridium histolyticum* group at six months of age were observed in infants born to the mothers with excessive weight gain during pregnancy compared to infants of mothers with recommended weight gain [2]. Zijlmans and co-workers found that infants of mothers with high cumulative stress during pregnancy had a significantly higher proportion of Proteobacteria and lower relative abundances of lactic acid bacteria and Actinobacteria compared to controls infants [3]. The mechanisms whereby maternal weight gain and stress influence the microbiota require further study, but suggest that clinicians should holistically consider pregnancy-related factors that could influence infant microbiome development.

2.2. At birth

2.2.1. Delivery mode

By comparison with vaginal delivery (VD), CD deprives neonates of exposure to maternal vaginal and fecal microbiota, alters infant microbial composition, and reduces diversity during first days, months or years of life [20–22]. Within the first 24 h of birth, the fecal microbiota of VD infants resembled that of their mother's vaginal microbiota, with *Lactobacillus*, *Prevotella*, and *Atopobium* spp. being predominating, whereas the microbiota of infants born by CD were more similar to that of mother's skin, dominated by *Staphylococcus*, *Corynebacterium* and *Propionibacterium* spp. [20]. At one month of age, infants delivered by CD had lower numbers of bifidobacterium and *Bacteroides fragilis* group and were more often colonized with *Clostridium difficile* compared to VD infants [21].

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