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Mini Review

The Neonatal Microbiome Development

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Abstract

Microbiota (Microbial flora, Microbiome) is the bacteria living both inside and on the human body (a community collectively known as, dwelling in the human microbiome), mostly are friendly, they outnumber the somatic and germ cells of the body by a factor of 10.

This commensal microbial flora enters into an important symbiotic association with the human host beginning with the colonization of the gastrointestinal (GI) tract by the bacteria within half an hour after delivery and continue to develop depending on many factors, this developmental process begins at birth, continues through early age, and remains for life.

This developmental process is actually during vulnerable and sensitive developmental periods has an influence and impact on the structure and function of other organs that last throughout life.

However, although the colonization of microbiota is due to postnatal environmental factors its composition is difficult to change after reaching the adult form.

The microbiota is essential to the proper development of the mucosal and systemic immune systems and in nutrient uptake and metabolism.

Keywords: *Microbiome; Diversity; Hygiene Hypothesis; Mode of Delivery*

Introduction

Over 100 years ago, the hypothesis was that the fetus is born germ free [1]. Accordingly, the placenta and the gut of the developing fetus were considered to be germ free, containing no apparent microbiome. Until recently, the dramatic changes in the fetus and placenta studies showed that the microbiome composition develops during gestation and this has been appreciated and approved [2,3].

In reality, the bacterial presence exists within the feto-placental unit during pregnancy and mainly the last trimester of pregnancy [2,3].Recent work suggests that initial colonization may take place in-utero and continue after birth, while keeping on developing and changing throughout the first 2 years of life, until stabilization to become adult-like [4-6].

Definitions

- Alpha diversity is the diversity of species in sites or habitats at a local scale.
- Beta diversity represents the differences in species composition among sites.
- Gamma diversity is the diversity of the entire landscape [7].

- Taxa are the taxonomic groups of any rank, such as a species, family, or class. Species are regarded as a fundamental unit of biodiversity. By contrast, higher taxa such as genera and families, used as biodiversity metrics and for classification and communication, are not believed to be shaped by shared evolutionary processes in the same way as species [8].
- Pathobionts are members of the normal gut microbiota that may promote disease. These microbes or pathobionts are distinguished from acquired infections. Pathobionts may cause chronic inflammatory diseases [9].

Neonatal microbiome

Neonatal microbiome is the microbial flora of the newborn infant which is acquired prenatally and starts developing as soon as the infant is born. During and hours after birth, various microorganisms from the mother's vagina, skin and environment participate in colonizing the infant gut and skin. The major contributing factor in the type of bacteria is mainly the mode of delivery [10,11]. Other factors such as prematurity, infant diet (breast milk or formula), hygiene, and use of antibiotics will have an effect on the composition of the infant gut microbiome, composition and diversity [11].

There are large swings in composition over time, since gut microbiome development could be regulated by Darwinian dynamics such that microbes that best adapt for the changing conditions of the gut will most likely survive. First come first adhere to intestinal mucosa and contribute to the mucin layer development and tolerance. In reality, the interactions between microbiota with its components and intestinal epithelial cells drive the establishment of homeostasis and tolerance after birth and during the neonatal period towards final microbial adult type [12]. The mucus and epithelial cells of the gastrointestinal tract are the gate keepers which control the bacterial interactions with the host immune system and shape it. Bacteria have their habitat in the outer colonic mucus layer and the combined small intestinal mucus. Antibacterial peptides/proteins limit the bacteria that can reach the epithelium and the Peyer's patches [13].

The bacterial taxa composition and diversity vary with the development of the newborn. The final microbial flora composition determines the path of the future status of the infant health with long-term physiological consequences [4].

Microbiome Development

In the first few weeks of life, the colonization of facultative aerobes reduces the availability of oxygen, which permits the growth of strict anaerobes [14]. Throughout the first year of life, there are compositional changes of the microbial flora in response to diet, environment and host development. Colonization is initially with *Proteobacteria* and *Firmicutes*, followed by a gradual increase in *Actinobacteria* due to the introduction of breast milk [15]. The stability of the microbiota is less in the first months than later in childhood. There are changes in the phylogenetic diversity. The alpha diversity of the infant's gut microbiota gradually increases over time [16]. while the β-diversity is reduced by 12 months of age [17].

By 6 months of age, *Bacteroidetes* dominate while *Proteobacteria* and *Actinobacteria* gradually decline, which may be attributed to the abundance of carbohydrates in solid foods that coincides with weaning [16]. By the end of the first year, the infant gut is dominated by bacteria from the phyla Bacteroides and Firmicutes. The healthy infant gut continues with compositional changes before becoming indistinguishable from adult gut microbiome at age three years [18]. At this stage the pathogens crossing to the lamina propria through the mucosa are recognized and endocytosed by macrophages leading to immune system developing antibodies [19].Malnutrition in young children affects the microbiome diversity and abundance [20].

In case of allergy, atopy and autoimmune status, the microflora looks differently. The antibiotics and other environmental factors eradicate keystone taxa during the critical window of immune development which is the first 100 days [21]. This loss of keystone taxa prevents maturation and differentiation of B and T cells and the Peyer patches. When the keystone taxa return and establishes itself again in the lumen, stasis is reached and microbial functionality returns to normal, but the immature immune system is unable to produce IgA and antimicrobial peptides necessary for prevention of mucosal presentation by the commensal bacteria [21].

In case of infection, antibiotics reduce the diversity in the gut, disrupting hemostasis at the epithelial layer, resulting in reduced mucin, cytokine and AMP production, but this will not affect the immune development. Loss of diversity displaces dominant taxa and enables the blooms of pathobionts and pathogens to pass the permeable gut epithelium increasing the risk for translocation of pathobionts and pathogens and forming an inflammatory gut environment and a permanent compositional change which may lead to chronic infection [22].

The microbiome is an important player in the pathophysiology of a whole spectrum of diseases that affect the normal and critically ill newborn. The microbiome is an organ by itself with many roles in metabolism, development of the immune system and host defense against different pathogens. It is important to note that the collective microbes in a population are referred to as the microbiota and the genetic content as the microbiome [23]. The microbiome (microbial flora) is very sensitive and unstable in the first period of life, especially in premature infants who are admitted to the neonatal intensive care unit where a lot of medications are used such as antibiotics, gastric acid inhibition, different types of feeding, sedatives and opioids [24]. These have immediate and delayed effect on the microbiome; the least of them is severe enough to cause damage in the composition and diversity of the developing microbiome [24].

There are over 150 different microbial species in the gut, which collectively encode more than 100-fold more non-redundant genes than there are in the human genome. The ratio between bacteria and human cells is about 1:1 [25]. Usually in a healthy infant, the intestinal microbiota consists of members of all three domains of life: bacteria, archaea and eukarya, of which the bacterial community is the most abundant and diverse [26,27]. Many of these bacteria in the gut are not cultivated yet. The intestinal microbiota in the growing infant has a critical role in priming the infant immune system. It participates in gut maturation and functions, such as nutrient uptake, metabolism, mucosal barrier defense function, enteric nervous system and motility (brain -gut connections) [25]. Although a full-term infant is born with fully developed digestive tracts, the exogenous stimulation starts as soon as he/she is fed through exposure to dietary antigens, hormones, growth factors, (mainly by breast feeding) and bacteria which is required to elicit proper function throughout life [28].

Breast milk

The important notable difference of breastfed versus formula fed infants microbiome is the predominance of *Bifidobacteria* and *Lactobacilli* in breast fed infants, while formula fed infants harbor more Enterococci and *Enterobacteria* [29]. Human milk modulates bacterial colonization of the gut where the formula fails to do. The human milk microbiome stimulates bacterial growth by (prebiotics) which is especially present in the colostrum and has factors that prevent bacterial growth (antimicrobials) elements. The human milk is bifidogenic and its microbiome consists mainly of *Proteobacteria* and *Firmicutes* [30]. The main group of taxa includes *Staphylococcus, Streptococcus, Serratia, Pseudomonas, Corynebacterium, Ralstonia, Propionibacterium, Sphingomonas and Bradyrhizobiaceae* [31].

The human milk microbiome and diversity changes over time and is dependent on the mother's status and diet [32]. The human milk oligosaccharides, which are sugars consumed by good microbes stimulates and primarily promote the growth of *Bifidobacterium longum subsp. infantis* [33]. In human milk, the antimicrobials that influence the microbes such as the secretory immunoglobulin A, provides antigen-specific protection against microbes that the mother has already encountered [34], and innate immune proteins that they have, such as lactoferrin and lysozyme, harbor bactericidal activity [35]. Milk obtained from mothers of preterm infants had highest concentrations of cytokines and immunoglobulins supporting the importance of breast milk consumption in early life [36].

Mode of delivery is another important factor which has an impact on the microbiome of infants, as the total microbiome (skin, oral mucosa, nasopharyngeal aspirate, and meconium) of vaginally delivered infants resembles the maternal vaginal and intestinal microbiome, while infants delivered by cesarean section have total microbiomes resembling the maternal skin microbiome and the personnel around during delivery and care taking [37]. The microbiomes of vaginally delivered infants consist mostly of Lactobacillus, Prevotella, Atopobium, or Sneathia spp, whereas the microbiome of cesarean section delivered infants contain Staphylococcus spp which has different effect on mucosal reaction of the new born gut [37].

Cesarean section can alter colonization of the microbial flora of the newborn. This is a critical event that influences the development of the physiological processes and the functioning of the immune and neuroendocrine systems, (brain gut axis, with long-lasting effects on the outcome of health). The unhealthy microbial flora (dysbiosis) can promote increased translocation of pathogenic bacterial components from the lumen of the intestine via intestinal mucosa to the lamina propria to the systemic circulation, where they react to activate innate immunity and produce proinflammatory cytokines which result in metabolic inflammation, infection and atopy reaction with abnormal gut function [38]. In this case, the main strategic points of intervention are to reverse the effects of cesarean section delivery. This can be done by improving the environment through different hygienic habits and health practices. Alternatively, the intervention could be by the mother herself during pregnancy through the use of probiotics and/or prebiotics and/or polyunsaturated fatty acids. The newborn who is delivered by cesarean section must be breast fed as soon as possible instead of formula feeding and if breast feeding is not possible infant formulas enriched and improved with probiotics/prebiotics could be provided. Another approach is by using a primitive but interesting procedure where gauze applied at the genital area of the mother to be put on the nose and mouth of the newborn as soon as he/she is delivered (simple fecal transplant) [39,40]. This could be a current modulating therapy to improve the composition of the microbiota and immune neurodevelopmental health of the infant [40].

Conclusion

A healthy microbiota preserves and promotes host well-being and absence of diseases especially in the intestinal tract. Initial colonization with "pioneer bacteria" is enhanced by both bacteria and the Prebiotics "galacto-oligoscharide" of the breast milk and the microbial flora of the mother. These first to come bacteria influence later the microbiota development of the newborn infant and form the basis for health microbiome afterwards. The microbiota will come to resembles the adult type starting by the age of two bifidobacterial count in children always remain more than in adult. The disturbed microbiota succession during early age (first two years) increases the risk in developing infection, atopy and auto immune within inflammation later in life. Intestinal microbial colonization and its function as immune modulator through dietary means is a critical consideration during this period of life.

The healthy human microbiota is metabolically active and provides an important defense mechanism for the host. Deviations in its composition are related to multiple disease states promoting the bifidogenic environment through prebiotic galacto-oligosaccharides and microbes in breast milk and introducing environmental bacteria through contact with the infant. Both the succession of microbial communities during the first years of life and the sequel of these events need to be further clarified.

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