Infant Gut Microbiota

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Evidence is accumulating which shows that maternal transmission of microbes to the infant gut occurs prenatally, in utero. However, the first big wave of microbial colonization occurs after birth. Gut microbial dysbiosis in infant increase the risk of subsequent asthma through a number of perinatal factors such as diet, delivery mode, antibiotic exposure, maternal asthma during pregnancy and pre-gestational body mass index.

Nutrition plays a fundamental role as a potent modifiable factor influencing the human gut microbiota composition, which provides new insights into therapeutic strategies aimed at manipulating the gut microbiota through dietary modification. There is very little evidence to date linking maternal dietary patterns during pregnancy with alterations in the infant gut microbiota. The effect of maternal dietary nutrient intake causes alterations in breast milk microbiota composition. There is however a paucity of human data examining the effects and underlying mechanisms of maternal diet on the infant gut microbiota shaping through the alteration of milk microbiota composition. Further long-term cohort studies are needed where the effect of maternal nutrition during pregnancy and lactation on the infant gut microbiota composition are studied in further detail in context of asthma development and may provide useful insights into potential mechanisms that could potentially reduce the risk of asthma.

Keywords: Infant ; Gut microbiota ; Maternal nutrition ; Pregnancy ; Lactation

1. Definition

Research has amply demonstrated that early life dysbiosis of the gut microbiota influences the propensity to develop asthma. The influence of maternal nutrition on infant gut microbiota is therefore of growing interest. However, a handful of prospective studies have examined the role of maternal dietary patterns during pregnancy in influencing the infant gut microbiota but did not assess whether this resulted in an increased risk of asthma later in life. The mechanisms involved in the process are also, thus far, poorly documented. There have also been few studies examining the effect of maternal dietary nutrient intake during lactation on the milk microbiota, the effect on the infant gut microbiota and, furthermore, the consequences for asthma development remain largely unknown.

2. Introduction

Asthma is considered one of the most widespread chronic respiratory diseases of childhood, with hospitalization rates reportedly having increased for children under the age of 5 years over the last two decades [1]. The body of evidence around asthma development in young children suggests that genetic predisposition [2][3][4], environmental exposures [2][5] as well as the gut microbiome [6][7][8][9] have a strong influence.

The maternal gut microbiota promotes the microbiota colonization of the infant gut prior to birth in utero, after delivery and then through breastfeeding [10][11][12]. Gut microbial colonization during early life represents a critical window of offspring immune system development [13]. According to the sterile womb paradigm, the gut microbiota are transferred from mother to infant prior to or during delivery and breastfeeding via a vertical pathway, and from the environment after delivery via a horizontal pathway [14][15]. Early-life microbial dysbiosis of the gut has been linked to an increased risk of asthma in the first years of life [16][17][18]. Such a link is significantly modified by the mode of birth delivery, antibiotic exposure and maternal body mass index (BMI), asthma and stress [6][16][18][19][20][21][22][23]. However, pre- and postnatal pet exposure may influence the infant gut microbiota and the development of their immune systems, with a subsequent reduced risk of asthma [24].

The maternal diet has been found to be a significant factor that influences the gut microbiota and potentially the development of asthma in offspring [25]. There is apparently an additional value obtained from animal models in understanding the mechanisms by which maternal dietary patterns during pregnancy influence asthma development in offspring via the maternal gut microbiota and their metabolites [21][26][27]. However, our understanding of the

aforementioned mechanisms is incomplete and further long-term studies in humans are needed. In addition, the mechanisms by which maternal dietary patterns and breast milk microbiota alter the offspring gut microbiota, which may in turn underlie asthma, remain underdeveloped. Indeed, the protective role of breastfeeding against asthma in childhood is still a controversial matter. This controversy arises because there are inconsistent results from previous studies [19][28]. Recently, the modulation of gut microbiota composition by probiotics and prebiotics during pregnancy and lactation has been proposed as a potential dietary strategy to reduce the risk of asthma in offspring. Despite evidence of alterations in maternal gut bacteria, a systematic review and meta-analysis of a randomized controlled trial (RCT) reported no benefit of probiotic supplements during pregnancy and early life for asthma or wheeze prevention in children [29]. Because of the low certainty of the evidence, the World Allergy Organization panel suggests not recommending prebiotic supplementation in both pregnant and lactating women for the prevention of asthma and allergic diseases in children [30].

The maternal gut microbiota progressively changes throughout pregnancy and significantly determines what is transmitted to the offspring and how the offspring gut microbiota eventually develops [31]. Diet is considered a major driver of the maternal gut microbiota changes [31] and therefore, in human studies, maternal dietary intake in gestation is associated with alterations in the offspring gut microbiota as well [32][33][34]. In particular, the type of dietary fat in the diet of pregnant mothers can negatively affect the trajectory of the offspring microbiota. It has been found that a high-fat maternal diet during gestation is associated with lower levels of the genera Bacteroides in the offspring gut [32].

Breastfeeding has a significant effect on the alterations in the gut microbiota following birth either by infant exposure to milk microbiota or by breast milk factors interacting with the maternal and infant gut microbiota such as human milk oligosaccharides (HMOs) [35]. The composition and diversity of breast milk microbiota are influenced by several maternal factors such as mode of delivery, gestational age, lactation stage, maternal BMI, mode of feeding and antibiotic exposure [36][37][38][39][40][41][42][43][44][45]. A few compelling studies have been undertaken which do indeed demonstrate that maternal dietary nutrient intake strongly influences breast milk microbiota. Further studies are needed to understand how maternal nutrition during pregnancy and lactation alter the infant gut microbiota, and whether this interaction increases the risk of asthma.

3. Gut Microbiota in Early Life and Its Relationship with Asthma Development

The first large wave of microbes to colonize the gut occurs following birth and the gut continues to acquire microbes during the transition between infancy and early childhood [12]. The early gut microbial colonization plays a significant role in the maturation of the metabolic, endocrine and immune systems [46]. The gut microbiota during the first three years of life has taxonomic and functional compositions different to that in adults, and the gut of some infant may exhibit lower microbial diversity than in others [47]. Following birth, the gut microbiota is predominantly colonized by Enterobacteriaceae and Staphylococcus genera [11]. During breastfeeding, the gut microbiota are dominated by Bifidobacterium genera which have the ability to metabolize HMOs [11][48]. HMOs are soluble complex carbohydrates and are thought to play a crucial role in increasing the abundance of Bifidobacteria which protect against pathogenic infection and alter bacteria-host interactions [42][49][50]. The time of weaning, the initiation of solid foods results in the establishment of microorganisms, represented by the genera Bacteroidetes and Firmicutes [11][51], species known to disassemble complex plant-derived polysaccharides [52]. The introduction of food items with protein and fiber contents (e.g., rye bread, meat, cheese, animal fat) increased the relative abundance of *Ruminococcaceae* and *Lachnospiraceae* spp. in the infant gut [53]. By around three years of age, the gut microbiota are colonized by microbial-enriched genes, most belong to the genera Prevotella, Veillonella, Ruminococcus, Clostridium, Bacteroides and Firmicutes, species involved in carbohydrate metabolism, xenobiotic degradation and vitamin B synthesis [11][47].

There is strong evidence that early-life gut microbial exposure plays a significant role in the development of childhood asthma [17]. The link between the early life dysbiosis of the gut microbiota and the subsequent development of asthma has been well-established in large-cohort studies [16][17][18]. It has also become clear through findings from epidemiological studies and reviews that this link is conceivably influenced by a wide range of perinatal factors. These findings suggest that maternal asthma during pregnancy [18][23], pre-gestational BMI [23], delivery mode (vaginal, cesarean) [6][16][19][20], breastfeeding mothers with a history of atopic conditions [19], maternal stress [19][22] and antibiotic exposure [6][19][21] are considered the main modifiers of the infant gut microbiota contributing to the development of asthma.

Maternal diet has also been considered a key factor that influences asthma development in offspring through the maternal gut microbiota and its metabolites' modulating effects [25]. There are substantial animal mechanistic studies, which demonstrate that diet and microbial exposure during pregnancy influence asthma development in offspring [26]. However, our understanding at this point is still incomplete in human studies. Evidence in animal models demonstrates that the gut

microbiome transferred through the placenta produces diverse metabolites, which act as significant mediators of fetal immune development [21]. Short-chain fatty acids (SCFAs), propionate, acetate and butyrate, are the main metabolites generated by the microbial fermentation of complex plant carbohydrates derived from microbiota-accessible carbohydrates (MACs), which represent the major energy sources for gut bacteria [21][27]. SCFAs influence T lymphocytes and dendritic cells through their binding to protein-coupled receptors and the direct inhibition of histone deacetylase, thereby promoting the differentiation of helperT cells (Th1, Th2). The Th2 asthmatic phenotype plays a pivotal role in increasing eosinophils, Immunoglobulin E (IgE) production, and the production of inflammatory cytokines. These cytokines enhance the allergic immune system and increase the risk of asthma in offspring [21][26]. Changes in dietary patterns during pregnancy may affect the microbial composition and diversity in the gut as well as the production of SCFAs [21]. A low-MAC diet is found to decrease bacterial diversity and SCFA production, which may hinder the functioning of regulatory T cells and lead to inhibited immunoglobulin A and G (IgA, IgG) production [27]. Data from human research has shown that a high maternal fiber intake during late pregnancy increases acetate (but not propionate or butyrate) levels in serum, which leads to a reduced risk of coughing and wheezing symptoms in the offspring's first year of life [54].

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