The mother-offspring dyad: microbial transmission, immune interactions and allergy development

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The mother–offspring dyad: microbial transmission, immune interactions and allergy development

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Running headline: Perinatal microbial exposures

Abstract

The increasing prevalence of allergy in affluent countries may be caused by reduced intensity and diversity of microbial stimulation, resulting in abnormal postnatal immune maturation. Most studies investigating the underlying immunomodulatory mechanisms have focused on postnatal microbial exposure, for example demonstrating that the gut microbiota differs in composition and diversity during the first months of life in children who later do or do not develop allergic disease. However, it is also becoming increasingly evident that the maternal microbial environment during pregnancy is important in childhood immune programming, and the first microbial encounters may occur already *in utero*. During pregnancy, there is a close immunological interaction between the mother and her offspring, which provides important opportunities for the maternal microbial environment to influence the immune development of the child. In support of this theory, combined pre- and postnatal supplementation seems to be crucial for the preventive effect of probiotics on infant eczema. Here, the influence of microbial and immune interactions within the mother–offspring dyad on childhood allergy development will be discussed. In addition, how perinatal transmission of microbes and immunomodulatory factors from mother to offspring may shape appropriate immune maturation during infancy and beyond, potentially via epigenetic mechanisms, will be examined. Deeper understanding of these interactions between the maternal and offspring microbiome and immunity is needed to identify efficacious preventive measures to combat the allergy epidemic.

Keywords: allergy, immune development, infancy, maternal influences, microbiota, pregnancy.

Introduction

Allergic diseases, including atopic dermatitis, food allergy, allergic rhinitis and allergic asthma, have become a major public health problem in affluent societies, affecting up to one-third of the population [1–3]. These diseases are characterised by inappropriate immune responses to innocuous foreign proteins, i.e. allergens [3]. Atopy is defined as an inherited tendency to produce IgE antibodies to allergens after ordinary exposure, i.e. to become sensitised [3, 4]. Atopic individuals show excessive T helper (Th)2-like responses to allergens, including production of IgE-inducing IL-4 and IL-13 and eosinophilia-enhancing IL-5 [5–8]. During the early phase of the IgE-mediated allergic reaction, allergen crosslinking of IgE antibodies on mast cells triggers release of inflammatory mediators [6–8]. Cytotoxic mediators from eosinophils play an important role in the late-phase reaction, causing chronic inflammation [6–8].

Allergic diseases typically manifest in early childhood, with the so-called allergic march generally beginning with the development of IgE antibodies to food allergens, accompanied by symptoms of atopic dermatitis and food allergy [3, 9, 10]. The IgE reactivity to food allergens such as egg and cow's milk usually declines after infancy when tolerance to these allergens develops [3, 9, 10]. Later in childhood, inhalant allergen sensitisation develops together with symptoms of asthma and allergic rhinoconjunctivitis [3, 9, 10]. Sensitised children with eczema and food allergy are at increased risk of developing airway allergies [3, 9, 10]. Asthma is the most common chronic disease among children, with a major impact on the physiological and psychological well-being of young children [11], as well as on socioeconomic costs due to treatment expenditures, hospital admittance and parental sick leave [1].

Although genetic factors play an important role in individual susceptibility, changes in the genotype cannot explain such a rapid increase in the allergy prevalence [2, 9, 12, 13]. Thus, loss of protective factors or appearance of risk factors in the environment must underlie the increasing prevalence of these diseases since the middle of the last century [2, 9, 12, 13]. Reduced intensity and diversity of microbial stimulation have been proposed as major factors promoting abnormal postnatal immune maturation [2, 9, 12, 13]. As early as 1976, the

Canadian paediatrician John Gerrard and co-workers suggested that allergic disease is the price for relative freedom from diseases caused by viruses, bacteria and helminths [14]. This hypothesis was based on the observation of low allergy prevalence in indigenous populations in northern Canada, where helminth infection and untreated viral and bacterial diseases were common, compared with Caucasian Canadians living in urban environments [14]. It was not until 1989, when the British epidemiologist David Strachan demonstrated an inverse relationship between the risk of hay fever and the number of older siblings [15], that the notion that infections early in life might prevent allergy development was generally considered of interest. 'The hygiene hypothesis' was proposed to describe the association between a high allergy prevalence and reduced infection incidence due to hygienic conditions. However, to emphasise the role of exposure to non-pathogenic beneficial microbes, 'the microbial deprivation hypothesis' has been proposed as a more appropriate term [16]. As other immune-mediated diseases such as type 1 diabetes, multiple sclerosis and Crohn's disease also show rising incidences in affluent countries [12, 17–21], a theory of microbial deprivation syndromes of affluence has been proposed [16]. Although most studies investigating the underlying immunomodulatory mechanisms have focused on postnatal microbial exposure [2, 22–36], it is becoming increasingly evident that the maternal microbial environment during pregnancy is also important in childhood immune programming [9, 12, 13, 37–41]. Here, the influence of microbial and immune interactions within the mother–offspring dyad on childhood allergy development will be discussed, and implications for strategies to reduce the high prevalence of allergy will be considered.

Co-evolutionary interdependency of the microbiome and the immune system

No animal has evolved independently of microbial symbionts [42–44]. Microbes were the pioneers of life and the only life form on Earth for most of its history; in addition, multicellular life arose in a world dominated by prokaryotes [42–44]. Microorganisms have played critical roles in the evolution and functioning of all other organisms [42–44]. Intimate, complex and dynamic interactions between animal hosts and microbes have thus profoundly influenced, and indeed continue to influence, animal evolution [42–46]. Nearly half a billion years of co-evolution with vertebrates has reciprocally shaped the repertoire of the microbial symbionts and the immune system [43, 47]. However, our modern and affluent lifestyle and the declining biodiversity diminish the exposure to microbes with

which we have co-evolved [48–52]. Thus, our establishment of microbial communities differs substantially from that of our ancestors [48–52].

The immune system shapes homeostasis between the host and the microbial symbionts [43, 47, 53, 54]. This allows for a mutualistic partnership, where the microbiota provides digestive and protective advantages to the host in a sheltered environment with abundant nutrition, while pathogenic and invasive behaviour of microbes evokes eliminatory measures [43, 47, 53]. It is likely that our immune system has evolved as much to preserve, protect and promote beneficial microbes as to defend against pathogens [42, 43, 47, 55]. When the adaptive immune system evolved in vertebrates, the capacity to recognise and remember beneficial as well as pathogenic microbes and the ability to both suppress and promote innate inflammatory mechanisms allowed more sophisticated relationships with increasingly complex microbial communities [42, 43, 47, 54–56]. The mammalian intestine is the ecological site with the highest density of bacteria on Earth [57]. Encounters between microbes from this complex ecosystem and immune cells may have profound effects on immune maturation, particularly during critical time windows of developmental programming [12, 13, 38, 39, 58–60].

The first microbial encounters

Contrary to previous assumptions of a 'sterile womb' paradigm, in which the acquisition of bacteria first occurs at birth, recent evidence suggests that the first interactions between the microbiota and the host may be initiated *in utero* [38, 61–68]. Any microbial presence *in utero* was assumed to be a danger for the fetus and intrauterine infection may indeed cause preterm delivery [65, 69]. However, intracellular bacteria have been histologically visualised in the placental basal plate at a similar rate in preterm and term pregnancies without overt infection [69]. The basal plate is the peripheral region of the placenta on the maternal side, in contact with the uterine wall [69]. Furthermore, bacterial DNA has been detected in amniotic fluid [63, 70], placenta [62, 63, 66, 70], umbilical cord blood [71] and meconium [63, 72–74] after 'sterile' term elective caesarean section (CS) deliveries following apparently normal pregnancies without any indication of inflammation or pathology. The microbiota of the meconium, the neonate's first stool sample, shared features with the microbiota detected in

paired amniotic fluid and placental samples collected after term CS deliveries [63]. Moreover, extensive deep sequencing demonstrated a low-abundance but metabolically rich placental microbiome, primarily composed of non-pathogenic commensal bacteria from the Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, Actinobacteria and Fusobacteria phyla, in normal healthy pregnancies at term [62]. Importantly, data obtained by 16S rRNA gene sequencing only demonstrate the presence of microbial DNA, without direct evidence of viable bacteria. Nonetheless, the presence of microbial DNA in the intrauterine compartment suggests that the fetus may be in direct contact with microbial components during gestation [38, 65, 67].

The placental microbiome composition determined in the extensive deep sequencing study most closely resembled the oral microbiome, when compared with the oral, skin, nasal, vaginal and gut microbiomes from non-pregnant controls [62]. Although paired microbiota sampling and characterisation at multiple sites from the same pregnant women, implementing strict validated collection techniques in order to account for potential contamination, would be important for further validation, it has been speculated that the placental microbiome is partially established by haematogenous spread of oral microbiota [38, 62, 65, 67]. Another hypothesis is that maternal bacteria may reach the placenta via the bloodstream after dendritic cell-facilitated translocation across the gut epithelium [38, 61, 65, 67]. Maternal to fetal transfer of labelled *Enterococcus faecium* via the gastrointestinal tract was demonstrated in mice [71], and enhanced translocation of gut bacteria to mesenteric lymph nodes has been demonstrated during pregnancy and lactation in experimental models [38, 65, 67, 75]. In support of an entero-mammary pathway, maternal intestinal microbes have been detected in immune cells circulating in peripheral blood and in breast milk in both lactating mice and humans [75].

Do prenatal microbial exposures affect immune programming?

Direct presentation of maternal bacterial components to the fetus has been recognised as a potential route for immune imprinting [12, 38, 39], as a way to prepare the neonatal immune system to respond appropriately to the much larger inoculum transferred during vaginal delivery [31, 61, 64, 74, 76–85] and breastfeeding [61, 64, 81, 86–88]. In line with this

suggestion, exposure of germ-free mice to bacteria only during pregnancy increased the numbers of monocytes and group 3 innate lymphoid cells in the intestinal mucosa of the offspring [89]. Use of a genetically engineered *Escherichia coli* strain that can persist in the intestine for only 3 days unless continuously supplemented allowed for the transient colonisation (from day 4 to 15 of the 21-day gestation period). It is interesting that the presence of live bacteria *in utero* was not required for the immunomodulatory effects in this model, and transfer of microbial molecules to the offspring during gestation seemed to be facilitated by maternal antibodies [89]. Microbiota-derived metabolites, such as short-chain fatty acids and aryl hydrocarbon receptor ligands, may also exert immunomodulatory effects [41, 89, 90]. Also in support of a role of the prenatal environment in shaping immune development, treatment of maternal mice with lipopolysaccharide [91, 92] or commensals such as *Acinetobacter lwoffii* [93] and *Lactobacillus rhamnosus* [94] during gestation attenuates allergic sensitisation and airway inflammation in the offspring.

Whether prenatal exposures to maternal microbial components also exert immunomodulatory effects in humans is presently not known, but would be in line with allergy intervention studies demonstrating that a combined prenatal and postnatal supplementation seems to be important for the preventive effect of probiotics on infant eczema [37–39, 58, 95] (Table 1). Moreover, maternal exposure to a traditional farm environment during pregnancy confers stronger protection against allergic disease and sensitisation than postnatal exposure alone [40]. Furthermore, maternal antibiotic use during pregnancy has been associated with an increased risk of development of allergic disease [96–98] and asthma [96, 99–102] in childhood (Table 1). Speculatively, more pronounced effects of prenatal microbial exposures on adaptive immune responses in humans as compared with mice may be envisioned, as the immune system matures at a faster rate in humans than in rodents prior to birth [103, 104]. Thus, whereas mature T cells can be detected in human fetal peripheral tissues as early as 10–12 weeks of gestation [105] and circulate in significant numbers by the end of the second trimester [106], they do not fully populate the periphery in mice until after birth [103, 104]. Furthermore, B and T cells appear in Peyer's patches of developing intestinal tissue at gestational day 18.5 in mice [107]; this is much later than in humans [103], with intestinal B and T cells present from 12–14 weeks of gestation [108, 109]. Moreover, functionally active regulatory T cells and regulatory T cell-promoting dendritic cells have also been demonstrated in human mesenteric lymph nodes at this age [110–112].

Of interest, at birth, up to 5–10% of neonatal T cells are differentiated into either memory or effector cells, suggesting activation *in utero* [113]. Furthermore, somatic hypermutations have been observed in the B cell receptor repertoire at gestational week 22 [114]. It is tempting to speculate that fetal immune priming with maternal microbial products could be at least partially responsible for this activation [12, 38, 39] (Table 2).

Microbial transmission from mother to offspring during delivery

Maternal to offspring transmission of microbes is an evolutionarily preserved phenomenon in the animal kingdom, which may play a critical role in evolutionary development by providing a genetically tailored microbiota and optimal mutualism [48, 61]. In addition, the microbial transmission may be accompanied by maternal immunomodifying factors, such as antibodies transferred via placenta and milk (Fig. 1) [41, 54, 115–119]. Vertical transmission of maternal vaginal and gut microbes to the human neonate occurs during vaginal delivery [31, 61, 74, 76–85]. CS delivery, which is performed with increasing rates worldwide and may increase the risk of development of allergy and other immune-mediated diseases [20, 120, 121], thus disrupts these opportunities for the microbiota to be transferred from the mother to her baby [31, 61, 74, 76–85]. The potential for vertical transmission of ancestral microorganisms to the next generation is decreased as well, particularly when horizontal transmission is also diminished for example by antibiotics, antibacterial agents and decreased family size [48–51].

Vaginally delivered infants, but not infants born by CS, share a significantly higher proportion of gut microbiota 16S rRNA gene sequences with their own mother than with other mothers during the first year of life [78, 79, 82]. The importance of maternal gut-derived bacteria in early infant gut colonisation is also supported by the findings of a recent 1-month follow-up study in which CS-delivered neonates were inoculated with maternal vaginal microbes [122]. Thus, the gut microbiota of the infants was not influenced by the 'vaginal seeding' to the same extent as their skin and oral microbiota, as maternal gut-derived bacteria, which are specialised to thrive in this niche, expanded in the stool samples of vaginally delivered but not inoculated CS-delivered neonates [122]. Delivery by CS has been associated with persistent changes in the gut microbiota of children followed for up to

1 [76, 79, 81] and 2 [78, 82] years, and minor differences could be detected in one study even at 7 years of age [123]. The disruptions in infant gut microbial ecology caused by CS delivery include a reduced abundance of the immunomodulatory genus *Bacteroides* [31, 74, 78–85, 124, 125] and a decreased diversity of the Bacteroidetes phylum [78]. In one study in which the authors claimed a limited effect of mode of delivery on the infant microbiota, reduced *Bacteroides* colonisation in CS-delivered infants was in fact demonstrated but not reported [125], in line with the consistent findings in 11 other independent paediatric cohorts [31, 74, 78–85, 124]. Increased colonisation with the opportunistic pathogen *Clostridium difficile*, which expands when gut microbiota niches are vacant [126], has also been reported among infants born by CS in several studies [31, 76, 77].

Impact of maternal immunity and the early infant microbiota on immune and allergy development

The effector functions of the innate and adaptive immune system are not yet fully developed at birth [119, 127]. The capacity to initiate Th1 responses is particularly limited in neonates [12, 119, 127–131]. It is likely that this Th2-skewed state is a consequence of the intrauterine immune milieu during pregnancy [9] and the close immunological interaction between the mother and her offspring [9, 132–134]. The maternal immune system needs to be regulated in order to tolerate the presence of a semi-allogeneic fetus and to prevent Th1-mediated rejection [135]. The fetal–maternal interface is thus characterised by high levels of Th2-like [68, 134, 136, 137] and anti-inflammatory [68, 134, 138, 139] cytokines, as well as enrichment of T regulatory cells [68, 140]. Initially, infants are partially protected by placental transfer of maternal IgG during the third trimester of pregnancy [115, 119], and by secretory IgA in breast milk if breastfed [54]. Maternally derived IgG and IgA antibodies may also have immunomodulatory effects [41, 116–118, 141]. The infant's own adaptive immune capabilities then gradually mature [12, 119, 131], concurrent with the establishment of a gut microbiota of increasing complexity [64, 142].

The neonatal Th2 skewing is even more marked in infants who later develop allergic disease [131, 134, 143, 144], corroborating the notion that the prenatal immune environment can influence allergy development [9, 133]. Prenatal environmental exposures may alter gene

expression via epigenetic mechanisms. In support of this hypothesis, maternal exposure to farms during pregnancy has been associated with increased DNA demethylation of the Foxp3 locus in cord blood cells and enhanced neonatal regulatory T cell function [145]. Furthermore, neonates from farming, as compared with non-farming, families displayed hypermethylation of the promoter regions of the Th2-associated genes *RAD50* and *IL-13*, indicating decreased transcription [146].

Epigenetic regulation by prenatal environmental exposures may provide the offspring with an improved capacity for physiological adaptations to the anticipated postnatal environment [9, 37]. On the other hand, these early changes in developmental trajectory may also influence the predisposition to later disease. It has been speculated that early adaptive epigenetic changes may be more likely to lead to disease if there is 'mismatch' between the anticipated postnatal environment and the actual conditions that are encountered [9, 37]. It is possible that probiotic interventions that are given both pre- and postnatally may decrease the risk of such 'mismatched' responses and induce long-lasting immune modulation [37]. Such mechanisms may partially explain findings from allergy intervention studies demonstrating that probiotic supplementation to the mother during pregnancy, as well as to her baby postnatally, seems to be important for the preventive effect of probiotics on infant eczema [37–39, 58]. Thus, a preventive effect on atopic eczema has been demonstrated by us and by others primarily when probiotics were given both pre- and postnatally [147–155]. By contrast, studies exclusively using postnatal [156–159] or prenatal [160] probiotic supplementation failed to prevent allergic disease. Therefore, it seems that the window of opportunity for intervention begins prior to birth, and probably within the fetal period. However, previous intervention studies started prenatal probiotic supplementation during the last trimester of pregnancy [147–155]. If prenatal microbial exposure is vital for the preventive effect, starting supplementation from the second trimester of pregnancy, when circulating fetal T cells have developed [105, 106], may have a more powerful effect [37, 38], including on asthma development which so far probiotic interventions have failed to prevent [39, 58].

A failure of Th2-silencing during immune system maturation may underlie development of Th2-mediated allergic disease [2, 12, 131, 133, 161]. Appropriate development of regulatory T cell responses [12, 145] and maturation of Th1-like responses [131, 162] are required to

acquire a more balanced immune phenotype during childhood. Furthermore, establishment of adequate mucosal barrier function, e.g. by increasing secretory IgA production during infancy, seems important to counteract allergic responses [60, 163–165]. Thus, low levels of salivary and intestinal secretory IgA are associated with an increased risk of allergic manifestations during early life [163–165], and aberrant IgA responses to the gut microbiota during infancy were recently found to precede asthma and allergy development during the first 7 years of life [117].

Appropriate pre- and postnatal microbial stimulation may be needed to avoid the pathophysiological process leading to allergy [9, 12, 13, 37–40]. In this respect, the gut microbiota is quantitatively the most important source of microbial stimulation and may provide a primary signal for the maturation of a balanced postnatal innate and adaptive immune system [13, 22]. In support of this hypothesis, allergy development is associated with differences in the composition and diversity of the gut microbiota during the first months of life [13, 23–26, 28–34, 36, 166]. Early establishment of a diverse gut microbiota, providing repeated exposure to new bacterial antigens and a consistent immunomodulatory impact, may be more important than the distribution of specific microbial species in shaping normal mucosal and systemic immune maturation [13].

Conclusion

Evidence from intervention trials, epidemiological studies and experimental animal models suggests that perinatal microbial and immune interactions within the mother–offspring dyad influence childhood allergy development. There is a close immunological interaction between the mother and her offspring during pregnancy, and the first microbial encounters may occur already *in utero*. Presentation of maternal bacterial components to the fetus may imprint the developing immune system, preparing it to respond properly to the much larger inoculum transferred during vaginal delivery and breastfeeding. Perinatal mother to offspring transmission of microbes and immunomodulatory factors may shape appropriate immune maturation during infancy and beyond, possibly via epigenetic mechanisms. Efforts to increase our understanding of these interactions between the maternal/offspring microbiomes and immunity are needed to identify efficacious preventive measures to combat the allergy epidemic.

Conflict of interest statement

No conflict of interest was declared.

Fig. 1 Transmission of microbial components from the mother to the fetus during pregnancy may imprint the immune system in preparation for the much larger inoculum transferred during vaginal delivery and breastfeeding. 'Heirloom' microbes received from the mother may be uniquely evolved to the offspring's genotype, increasing the chance for optimal mutualism. Maternal IgG antibodies are transferred to the fetus via the placenta and IgA antibodies are transferred to the infant via breast milk. Modified with permission from Jenmalm MC, Björkstén B. Microbiome and the effect of the immune response. In: Allergy, immunity and tolerance in early childhood: the first steps of the atopic march. Wahn U, Sampson HA, editors. New York: Elsevier, 2016.

Table 1 Intervention trials and epidemiological studies suggesting that prenatal microbial exposures affect allergy development

Probiotic supplementation pre- and postnatally has preventive effects on infant eczema, whereas postnatal probiotic supplementation alone seems to be ineffective	Reviewed in [37–39, 58, 95]
Maternal exposure to a traditional farm environment during pregnancy demonstrates stronger protection against allergy development than postnatal exposure alone	Reviewed in [40]
Maternal antibiotic use during pregnancy is associated with an increased risk of allergy and asthma development	[96–102]

Table 2 Putative mechanisms underlying offspring immunomodulatory effects by maternal microbial exposures during pregnancy	
Bacteria or bacterial components present in amniotic fluid, placenta and cord blood	[62, 63, 66, 70, 71]
Transplacental transfer of maternal IgG-bound bacterial components	[89]
Modulation of maternal immune responses at the fetal–maternal interface, influencing offspring immunity	[9, 93, 132–134]
Microbiota-derived metabolites exerting immunomodulatory effects	[41, 89, 90]

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