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REVIEW

Transfer of maternal immunity and programming of the newborn immune system

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Abstract As placental mammals, the pregnant women and the fetus have intense and prolonged interactions during gestation. There is increasing evidence that multiple molecular as well as cellular components originating in pregnant women are transferred to the fetus. The transfer of maternal antibodies has long been recognized as a central component of newborn immunity against pathogens. More recent studies indicate that inflammatory mediators, micronutrients, microbial products and maternal cells are transferred in utero and influence the fetal immune system. Together, these multiple signals are likely to form a complex network of interactions that program the neonatal immune system and tune its homeostatic regulation. Maternal disorders, in particular infectious diseases, modify these signals and may thereby alter immunity in early life. Understanding maternal programming of the newborn immune system could provide a basis for interventions promoting child health.

Keywords Fetal immune system · Pregnancy · Maternal antibodies · Inflammation · Infectious diseases · Microchimerism

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Introduction

As placental mammals, the pregnant women and the fetus have intense and prolonged interactions during gestation. There is increasing evidence that multiple molecular as well as cellular components originating in pregnant women are transferred to the fetus. The most studied of these components are maternal antibodies that provide the newborn with essential early life protection against infectious pathogens prior to childhood vaccination [1]. Less studied are inflammatory signals that are involved in healthy pregnancy and that can be amplified by maternal infections. Innate and adaptive immune responses in the neonate are also influenced by maternal diet and micronutrients. Increasing evidence indicate that the maternal microbiome and its components provide key signals for the development of the immune system in utero and after birth. Maternal cells are also transferred across the placenta and may promote reproductive fitness across generations by inducing tolerance to non-self tissue antigens. Together, these multiple signals are likely to form a complex network of interactions that provide passive immunity to the newborn, program the neonatal immune system, and tune its homeostatic regulation [2]. Maternal disorders, in particular infectious diseases, modify these signals and may thereby alter immunity in early life. These alterations could have a direct impact on infant health and possibly longer-term consequences through adulthood.

Transfer of maternal antibodies

The transfer of maternal antibodies provides the newborn with passive immunity against pathogens that are prevalent in the community. If maternal antibody levels are too low for optimal protection during the first months of life, they can be boosted by maternal immunization against specific pathogens affecting

the young infant [3]. Maternal immunization against tetanus, pertussis, and influenza has been used successfully in many populations and could be used to protect against additional pathogens, including group B streptococcus and respiratory syncytial virus [4, 5]. Transfer of maternal antibodies occurs in utero, predominantly across the placenta, and after birth through breast milk [1, 6]. Although it was recognized more than a hundred years ago by Paul Ehrlich [7], the mechanisms that govern the transfer of maternal antibodies have yet to be fully elucidated. Further research into these mechanisms should improve our understanding of immunity in early life and will help the development of optimal immunization strategies.

At birth, IgG are the dominant isotype detected in the serum, with low levels of IgM, IgE, or IgA [1]. Studies suggest that maternal IgE are transferred to the fetus as IgG/IgE complexes [8]. Fetal IgG levels increase slowly during the first and second trimesters of pregnancy, and the most important increase is observed during the third trimester of pregnancy. In term neonates, IgG level is close to 1000 g/dL and about 125% of the level in maternal serum, indicating active transfer [1, 9, 10]. The major point of transfer of maternal IgG is through the placenta, where maternal and fetal vasculatures come in close contact. While smaller substances can diffuse through the placenta, IgG must be actively transported, with the aid of the neonatal Fc receptor (FcRn) [11]. The efficiency of maternal IgG transfer is dependent on their subclass; of the four subclasses of human IgG, there is preferential transfer of IgG1, followed by IgG4, and IgG3 with slightly lower abundance, and low IgG2 transfer, though the molecular basis of this hierarchy has not been fully elucidated [6, 12]. IgG transfer is also influenced by their antigen specificity [13]. Overall, protein-antigen-specific IgG are transferred more efficiently than polysaccharide-specific IgG, a fact that is probably related to the low transfer of IgG2. However, diverse protein or polysaccharide antigens are transferred at different rates, and the basis for this difference is unknown. Among the factors that could be involved is IgG glycosylation. IgG are glycoproteins and carry N-glycans on Asn297 of each heavy chain Fc fragment. The structure of these glycans influences the interactions between IgG and Fc receptors as well as those between IgG and complement and thereby modulates their effector functions [14]. The galactosylation and sialylation of IgG increase during pregnancy, a profile that is associated with lower inflammatory potential [15]. There is some evidence for an impact of maternal IgG glycosylation on their transfer, with higher galactosylation, bisection, and sialylation detected in newborns as compared to mothers [16]. However, recent studies suggest that these differences in glycosylation may affect Fab rather than Fc fragments of maternal IgG [16, 17]. The functional consequences of maternal IgG glycosylation on their effector functions once transferred to the newborn are unknown.

The placenta as site of transfer

The placenta forms primarily from fetal tissue that, over the course of pregnancy, invades the uterus to construct the crucial interface between maternal and fetal vasculatures [6, 18]. Maternal IgG encounter several parts of the placental anatomy and must cross two layers of tissue: the syncytiotrophoblast layer and the fetal endothelium (Fig. 1). The antibodies must also traverse the stroma between these two tissues [6, 18]. It is important to note that mice and other rodents differ from humans, not only in that their major route of transfer of IgG is breast milk, but also that transfer occurs across membranes of the inverted yolk sac, not the placenta, which has slightly different morphology [6]. The mechanisms of IgG transfer are thought to be similar, but it is an important caveat to comparing mouse and human data.

FcRn-mediated transfer across the placenta

FcRn, a MHC-class receptor, is the primary receptor that mediates the transfer of IgG [11]. FcRn has a high affinity for monomeric IgG and minimal affinity for complexed IgG [6, 19]. The five known alleles of FcRn do not affect the transfer efficiency or subclass distribution of IgG [20]. FcRn, which arose via duplication of the MHC locus, retains the structure of MHC with the peptide-binding groove occluded, and associates with β2 microglobulin [11]. It binds the constant region of IgG, at the CH2-CH3 interface, and does not induce structural change of the antibody [11]. Although this point is still debated, FcRn appears to bind in a 2:1 stoichiometry the majority of the time, with one receptor dominating the binding interaction and the second providing stability [11]. FcRn binds IgG with high affinity only at acidic but not at the physiological pH [11]. Within the placenta, syncytiotrophoblasts take up fluid from maternal blood by pinocytosis into vesicles that mature into endosomes [1, 9]. Acidification occurs within the endosome and allows membrane-bound FcRn to bind IgG and to prevent its degradation [11]. The endosome is then re-directed to the basal surface of the cell, in a yet unknown process, where FcRn deposits IgG into the neutral pH of the stroma [11]. Some studies suggest that FcRn is slightly influenced by glycosylation, with aglycosylated antibodies binding with less affinity than highly sialylated species, but this is not supported by other studies [19, 21].

Transfer across the villious stroma and fetal endothelium

While it is broadly clear how IgG moves through the syncytiotrophoblast layer, the mechanism by which it moves through the villious stroma and eventually the fetal endothelium is less well understood. Within the stroma, IgG encounter connective tissue and Hofbauer cells [6, 9]. Hofbauer cells are fetal macrophages that can interact with IgG through multiple Fc

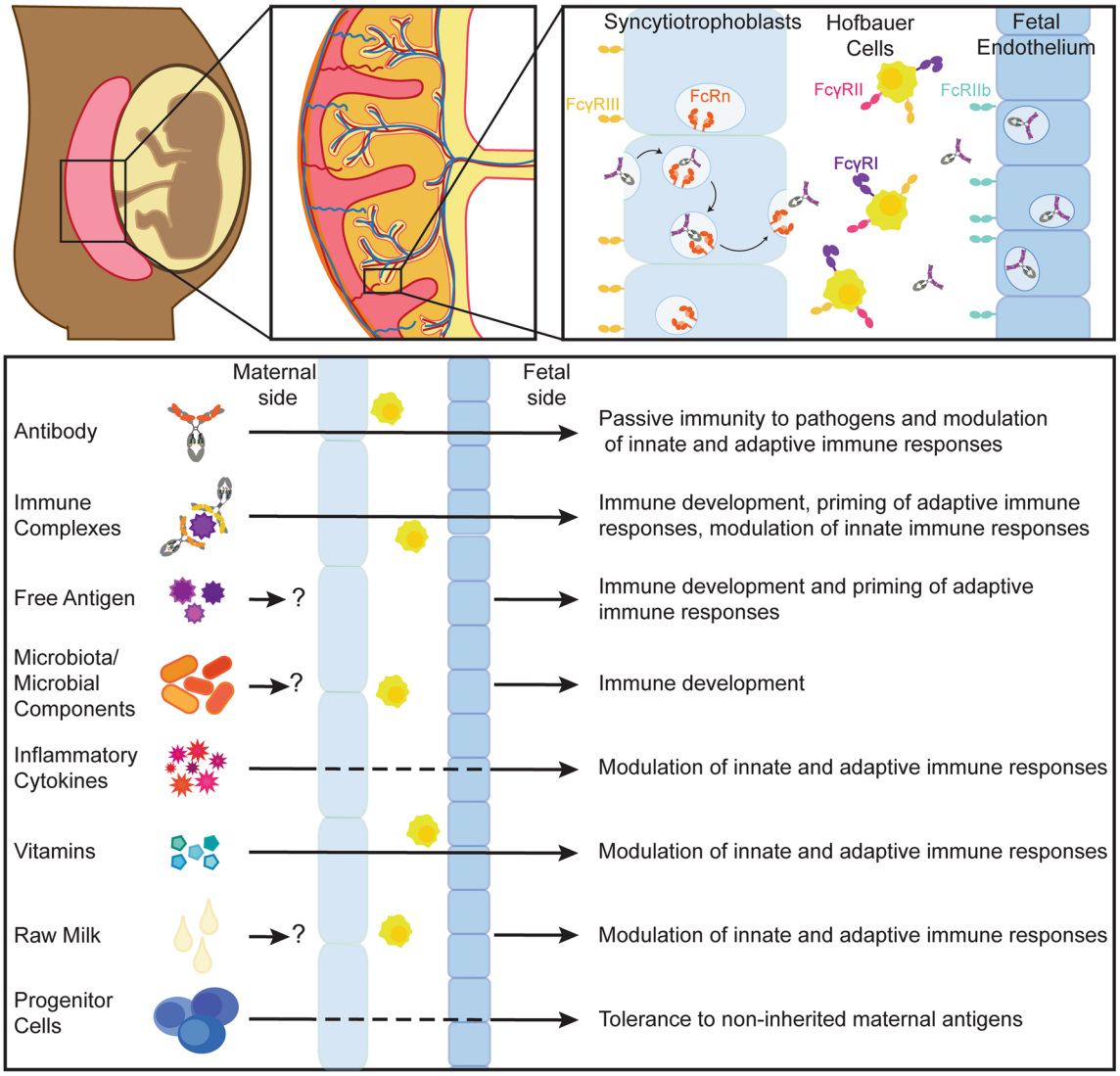

Fig. 1 Transplacental transfer of molecular and cellular components of maternal origin. Multiple components originating in the pregnant women are transferred across the placenta and influence the fetal immune system. Upper panel: maternal IgG are actively transported across syncytiotrophoblasts by the neonatal Fc receptor (FcRn). The mechanisms underlying the transfer of IgG across the placental stroma and fetal endothelium are not fully defined but probably involve other Fc-gamma (Fcγ) receptors expressed by Hofbauer cells and endothelial cells. Lower panel: maternal antibodies provide protection to the young infant against infectious pathogens and may modulate innate and adaptive immune responses. Microbial components, free and/or complexed to maternal IgG, promote immune development and prime fetal adaptive immune responses. Inflammatory cytokines and nutrients modulate fetal innate and adaptive immune responses. Maternal cells induce fetal regulatory T cell responses to non-inherited alloantigens and may thereby promote reproductive fitness

receptors [9]. It is thought that one of the functions of the Hofbauer cells is immune surveillance via adsorption of paternal antigen immune complexes [1, 22]. Hofbauer cells and the entire stroma show diffuse accumulation of IgG, indicating that not all maternal IgG successfully cross the placenta [22]. The next, and final, barrier is the fetal endothelium. This layer forms a tight barrier that is impermeable to trans-junctional transfer [1, 22]. As FcRn is not expressed on the fetal endothelium, IgG must rely on one or several other receptors to transit across this layer [1]. One candidate is FcγRIIb2, an Fc-receptor expressed by fetal endothelial cells of the capillaries and terminal villi but not on other endothelia [23]. Interestingly, fetal endothelial cells solely express the b2 isoform of FcγRIIb2, an isoform that is associated with internalization [24]. Furthermore, fetal endothelial cells contain abundant vesicles, distinct from endosomes or caveloae, that contain FcγRIIb and stain brightly for IgG [22]. These vesicles or tubular structures that contain IgG can be found originating at the cell surface and fuse or extend along the apical/basal axis [25]. Direct evidence for a role of FcγRIIb in the transfer of IgG was obtained in an in vitro model system [25]. However, FcγRIIb2 has no affinity for monomeric IgG and has a high affinity for IgG3 [24, 26]. As FcRn has a much lower affinity for this isotype, the moderate transfer efficiency of IgG3 across the placenta may be the result of the combined

affinities of the two receptors [16, 26]. FcγRIIb2 is not expressed by the mouse yolk sac endothelium, and FcγRIIb2 knock-out fetal mice have a near-normal serum IgG concentration [27]. The relevance of this observation to the transfer of human IgG is debated since the architecture of the yolk sac and the mouse placenta vasculatures are different from those of the human placenta [6, 27].

Transfer through breast milk and amniotic fluid

While placental transfer of IgG is the major mechanism of transfer of antibodies in humans, transfer also occurs before birth via amniotic fluid and after birth via breast milk [28, 29]. Transfer through amniotic fluid involves cellular pinocytosis, diffusion, and absorption of IgG across the fetal gut [6, 30]. During lactation, lymphocytes of the gut associated lymphoid tissue migrate to the mammary glands where they secrete antibodies, primarily IgA and IgM, that are transported by the polymeric immunoglobulin receptor across mammary epithelial cells [31]. It is thought that maternal antibodies protect infants in different manners. By binding toxins, bacteria, and macromolecules in the gut, they serve an immunosuppressive role and prevent inflammation induced by oral antigens as well as shaping the composition of the gut flora [31–33].

Antibody transfer and disease

The transfer of maternal antibodies can be affected by maternal diseases. In particular, chronic maternal infections are associated with reduced transfer of IgG across the placenta. HIV infection and placental malaria have been the most studied, but other infections may have an impact as well [9, 34]. The mechanisms underlying this reduced transfer are not fully elucidated. The hypergammaglobulinemia induced by chronic infections is considered to play an important role by saturating the placental FcRn [34, 35]. Indeed, maternal IgG levels above 15 g/L are associated with reduced transfer ratios [9]. However, the impact of maternal hypergammaglobulinemia appears to vary between IgG of different specificities and subclasses, suggesting that other mechanisms are involved [36].

On the other hand, maternal antibodies can have pathogenic roles in the fetus and young infant. Extant antibodies against dengue virus can dramatically worsen infection and cause dengue hemorrhagic fever through a phenomenon called antibody-dependent enhancement of infection (ADE) [35]. When high levels of maternal IgG against dengue are transferred, the infant is protected against infection and disease. However, when maternal IgG levels decline over the first months of life, infants lose protection and are at risk of ADE mediated by non-protective levels of IgG [35]. This mechanism may also play a role in fetal infection with Zika virus, as maternal dengue IgG transferred to the fetus could contribute to pathology [37].

Transfer of maternal IgG can also cause disease when directed against paternal antigens, for example red blood cell antigens or platelet antigens can cause thrombocytopenia and fetal brain hemorrhage or fetal hemolytic disease [9, 38, 39]. Removal of antibodies to paternal antigens is thought to be one of the functions of Hofbauer cells [1, 22]. Interestingly, the severity of fetal cytopenia is correlated with the glycosylation of maternal IgG rather than with their levels, supporting the importance of the functional regulation of maternal antibodies through their glycosylation profile [38, 39].

Impact of maternal IgG on infant vaccine responses

Although maternal antibodies can worsen the outcome of some infections with pathogens like dengue virus, their primary role is to attenuate the severity of infections and promote the survival of young infants. It has been proposed that this attenuation also allows the infant immune system to be primed and acquire specific immunological memory against pathogens, thereby promoting natural vaccination [40]. Maternal antibodies also attenuate the response to a number of vaccines administered during infancy [41]. The magnitude of this effect varies between vaccines, and the basis for this variability is not fully understood [42]. Maternal IgG markedly interfere with infant measle immunization. Intriguingly, studies suggest that neutralizing antibody titers are more affected than ELISA titers, suggesting an interference with the avidity maturation of vaccine-induced infant IgG [43, 44]. Although the potential impact of maternal antibodies on the memory response to infant vaccines has not been systematically studied, studies suggest no inhibition of responses to booster immunization [45]. Masking of vaccine-antigen epitopes has long been considered as the central mechanism of maternal antibody interference [41]. Recent studies suggested a mechanism of inhibition of infant B cell responses involving the crosslinking of the inhibitory receptor FcγRIIb by maternal IgG: vaccine-antigen complexes [46]. As maternal immunization is becoming increasingly used as a strategy to protect young infants, the integration of maternal and infant immunization is an important challenge to address [3]. Typically, maternal immunization against pertussis lowers infant morbidity and mortality caused by whooping cough, but it also reduces the antibody response to infant pertussis immunization [4, 47–49]. Although the clinical significance of this blunting has not been assessed, further research on the impact of maternal antibodies on the acquisition of infant immune responses is likely to help the control of infectious pathogens in early life.

Transfer of inflammatory mediators

Studies indicate that inflammatory responses in pregnant women generate signals that modulate immune responses in the newborn. Under physiological conditions, increased plasma levels of inflammatory cytokines are detected during the second and third trimesters of pregnancy [50]. At term, similar levels of inflammatory cytokines are detected in maternal and cord blood following elective cesarean section, suggesting co-regulation [51]. Higher levels of IL-6 were detected in cord blood plasma following labor as compared to elective cesarean section, supporting a role of inflammatory mediators in the induction of labor [52].

Animal models indicate that inflammation induced by microbial products during pregnancy impact inflammatory responses in the newborn. Lipopolysaccharide (LPS) injection of dams reduced pro-inflammatory cytokine responses to LPS in the pup, suggesting transplacental induction of LPS tolerance [53]. The mediators involved in this process are unclear. Placental perfusion studies indicate that cytokines do not cross the placenta and some data suggest that the placenta is a source of inflammatory cytokines [52, 54, 55].

Maternal antibodies may play an important role in the regulation of inflammatory responses in the newborn. As indicated above, maternal IgG acquire glycosylation profiles that are generally associated with reduced inflammatory responses and could thereby limit potentially deleterious inflammation when the newborn and young infant are exposed to microbes [15].

Chronic maternal infections are commonly associated with increased levels of pro- and anti-inflammatory cytokine levels in cord blood, independent of pathogen transmission [56]. In newborns of HIV-infected mothers, who are not themselves infected with HIV (called HIV-exposed uninfected (HEU)), high levels of inflammatory mediators are detected in cord blood [57]. Increased inflammatory responses could have important clinical consequences after birth and participate in the increased susceptibility of HEU infants to severe infections [58]. Inflammation induced in the newborn by chronic maternal infections may also promote immunity to unrelated pathogens and vaccines [56]. Newborns of mothers with chronic hepatitis B virus (HBV) infection have an increased capacity to produce the Th1 polarizing cytokine IL-12 and to respond in vitro to unrelated pathogens as compared to HBV-unexposed newborns [59]. It was suggested that this phenomenon is related to the acquisition of innate immunological memory or trained immunity [60]. Trained immunity involves epigenetic reprogramming of innate immune cells and could play a central role in the defense against pathogens in early life [61]. Identifying the maternal signals that could train innate immune responses in the newborn and modify their capacity to respond to infectious pathogens after birth is likely to have a profound influence on the way infectious diseases affecting young infants could be prevented in the future.

Maternal diet and nutrients

There is increasing evidence that nutrients and maternal diet during pregnancy affect the newborn immune system. As reviewed elsewhere, maternal deficiency of certain micronutrients impacts immune development and functions [62]. For example, vitamin D, a direct regulator of antimicrobial innate and adaptive immune responses, promotes the production of anti-microbial peptides by monocytes in cord blood. The potential impact of vitamin D supplementation during pregnancy has been evaluated, but clinical trials were not conclusive [63]. Gestational fish oil supplementation may affect immune responses in the newborn. Fish oil supplementation during pregnancy was associated with reduced levels of plasma IL-13 in cord blood and a lower production of pro-inflammatory leukotriene by cord blood of newborns at high risk of atopy [64, 65]. Consumption of unprocessed cow milk during pregnancy is associated with reduced risk of allergic disorders and respiratory infections in childhood [66, 67]. The mechanism underlying this effect has not been fully elucidated. Exposure of pregnant women to raw milk was associated with increased number and function of cord blood regulatory T cells and with decreased Th2 responses to allergens [68]. These observations support an early life origin for allergic disorders and the potential to develop targeted preventive interventions.

Transfer of maternal cells

Cells of maternal and fetal origins cross the placenta and establish microchimerism in the fetus and pregnant women [69]. Maternal immune tolerance to fetal cells is fundamental to successful pregnancy. Studies indicate that the fetus also acquires immunological tolerance to non-inherited maternal tissue antigens (NIMA). NIMA preferentially induce the differentiation of regulatory CD4 T (Treg) cells in the fetus [70]. Mouse studies indicate that these Treg cells persist until adulthood. NIMA-specific Tregs acquired in early life persist in the genital tract of female mice [71]. If adult female mice mate with males expressing antigens common to the NIMA, fetuses are protected by the long-lived Treg from immune-mediated wasting. This process could play an important role in reproductive fitness. Evidence for this process is not available in humans, but a similar mechanism may underlie the better survival of organ transplants when the sibling providing the graft expresses maternal antigens not inherited by the recipient [69]. Multiple mechanisms are probably involved in the expansion of fetal Tregs in response to NIMA and potentially to other antigens to which the fetus is exposed. Fetal hematopoietic stem cells (HSC) have been shown to preferentially give rise to Tregs as compared to adult HSCs [72]. In addition, fetal

dendritic cells were recently shown to strongly promote the differentiation of Tregs [73].

Transfer of antigens

There is accumulating evidence that non-infectious microbial antigens and allergens can cross the placenta. Most of this evidence comes from studies indicating in utero sensitization of the fetal immune system to antigens that pregnant women have been exposed to. In endemic areas, maternal parasitic infections have been associated with the induction of antigen-specific adaptive immune responses in the fetus. Cord blood CD4 T lymphocytes from Kenyan newborns commonly produce cytokines in response to helminth antigens whereas no responses are detected in newborns in the U.S.A. [74]. In utero sensitization of both T and B lymphocytes can be detected in uninfected newborns born to mothers who are chronically infected with *Schistosoma mansoni* or *Schistosoma haematobium* (reviewed in [56]). Similar observations have been made in newborns of mothers infected with *Ascaris lumbricoides* or *Plasmodium falciparum* [75–77]. Both Th1 and Th2 type cytokine responses as well as IL-10 responses can be detected in exposed newborns, supporting the notion that fetal CD4 T cells can acquire diverse functional profiles in humans [78]. Direct evidence for the transfer of microbial antigens comes from the detection of *Plasmodium falciparum* merozoite surface protein 1 or *Wuchereria bancrofti* antigens in the cord blood of newborns of infected women [79, 80]. Interestingly, an ex vivo model of placental perfusion indicated that antigen transfer is dependent on the presence of maternal antibodies, indicating the transport of immune complexes and suggesting a role for maternal immunity in this process [79]. Studies suggest that in utero sensitization to microbial antigens affects the immune response to homologous pathogens after birth (reviewed in [56]). For example, Kenyan newborns exposed to maternal *Wuchereria bancrofti* infection who did not display detectable cord blood T cell responses, and called tolerant, were at higher risk of postnatal infection than immune sensitized newborns [74]. Interestingly, in utero induced immunity appeared to last through childhood.

There is also increasing evidence that the fetus can be sensitized to vaccine antigens to which the mother has been exposed during pregnancy. Historical studies report tetanus toxoid-specific IgM in some newborns of mothers immunized during pregnancy [81]. As IgM do not cross the placenta, this observation suggests sensitization of fetal B lymphocytes. Follow-up studies indicated that detection of IgM in cord blood was more common when women had been immunized during the third as compared to the first or second trimesters of pregnancy [82]. Detection of vaccine-specific IgM in cord blood has also been reported following maternal influenza immunization [83, 84]. Direct evidence of fetal T cell priming comes from the detection of influenza HA-specific T cells using HLA-peptide multimers [84]. Whether pertussis immunization during pregnancy sensitizes the fetal immune system is unknown. And the potential implications of in utero sensitization on postnatal responses to homologous vaccines and protective immunity remain to be determined.

Studies suggest that the fetus can also be sensitized to allergens. Allergen-specific IgE can be detected in cord blood, but, as indicated above, this could be predominantly maternal IgE transported across the placenta as IgE/IgG complexes [8]. However, house-dust-mite allergen has been detected in amniotic fluid and cord blood and could therefore be recognized by B and T cells [85]. Some studies report proliferative responses of cord blood cells to allergens, but this point remains controversial [86, 87].

Transfer of maternal microbiota

The maternal microbiota is transferred at birth to the newborn and has a marked impact on immune development and functions later in life [88]. Recent studies indicate that such impact also occurs before birth through fetal exposure to components of the maternal microbiota, although the transfer of microbiota per se before birth has not been demonstrated yet. The composition of the maternal microbiota changes during pregnancy, and animal studies suggest that these changes participate in the physiological modifications of metabolism and innate immune responses observed in pregnant women [89] (reviewed in [90]). Studies analyzing the gut and genital microbiota in pregnant women suggest that the placenta could host a specific microbiome that may influence the immune homeostasis of the fetus [91]. Strong evidence for the role of the gut microbiota in the development of the fetal immune system comes from studies of germ-free pregnant mice transiently colonized with a genetically hobbled *Escheria coli* strain that show an impact on the proportions of the pup's intestinal innate immune cell birth [92]. Interestingly, part of the process was dependent on maternal antibodies, suggesting that microbial components cross the placenta complexed with IgG. Future studies will hopefully determine the potential impact of other microbes or microbe combinations on the development of the immune system in early life. The impact of the maternal microbiome suggests that interventions modifying its composition may have beneficial effects on the offspring. For example, supplementation of pregnant women with probiotics was associated with increased levels of IFN-γ in cord blood and increased levels of transforming growth factor beta 1 and IgA in breast milk [93]. On the other hand, maternal supplementation with oligosaccharides promoting the growth of bifidobacteriae had no impact on neonatal immune parameters [94].

Concluding remarks

Multiple molecular and cellular components of maternal origin are transferred across the placenta, provide passive immunity but also influence the fetal immune system, and thereby program postnatal immune responses. The transfer of maternal antibodies has long been recognized as a central component of newborn immunity against pathogens. More recent studies indicate that maternal antibodies may carry microbial antigens across the placenta and thereby influence pathogen-specific immunity and immune development. The impact of pregnancy on maternal IgG glycosylation may provide an additional layer of immune modulation in the newborn. These effects are probably part of complex networks of interactions involving inflammatory signals as well as nutrients originating in the pregnant women. The integration of these complex networks will be required to elucidate the immunological and clinical consequences of the maternal programming of the newborn immune system. The comparison of healthy and complicated pregnancies could provide important opportunities to identify key pathways affecting immunity in early life. Ultimately, the identification of these pathways could provide a basis for new or improved interventions targeting the pregnant women or the newborn for the promotion of child health.

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