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Maternal helminth infections and the shaping of offspring immunity

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Abstract

Helminth infections leave a long lasting immunological footprint on their hosts. Clinical studies have provided first evidence that maternal helminth infections can result in an altered immune profile in their offspring which can potentially shape how they respond to conditions throughout life. This can relate to changes in offspring induction of immune responses against other diseases. However, if these changes result in actual changes in offspring ability to control disease is unclear. Our understanding of which immune mechanisms are altered and how they are changed is limited. In this review, we highlight what we know from human and mouse studies about this important context of helminth exposure. Moreover, we discuss how mechanisms such as antibody transfer, antigen exposure, maternal cell uptake, chimerism and epigenetics are all likely to be functional contributors to the striking changes that are seen in offspring born or nursed by helminth exposed mothers.

Introduction

Maternal transfer of immunity both *in utero* and *via* nursing provides critical sources of early life immune education and protection from disease. This maternally acquired protection from infection is typically associated with a passive transfer to offspring of maternal innate opsonins and antibody which provide a transient, but critical, early life protection from infection.[1, 2] This protection provides high levels of effective but often temporary immunity to dangerous infections such as non-typhoid Salmonella *spp.* in infants. Protection is typically lost when maternally derived antibodies are degraded.[3]

Nursing, independently of *in utero* derived protection, provides an important defence to offspring against both infectious and non-infectious diseases.[4, 5] Again, this is primarily associated with transfer of maternally derived antibody[6], although other immunogenic

components of breast milk such as cytokines and non-inherited antigens also influence offspring immunity [7]. Epidemiological and experimental evidence suggests maternal immune transfer via nursing may also provide long lasting pathogen-specific protection from infection.[8] Maintenance of maternally transferred products *via* breastmilk is however widely considered to be temporary, although the indirect effects of such transferred protection can be longer lasting.[9] Nevertheless, the mechanisms underlying any such long-term protection are not well defined and contributions and maintenance of maternal components in offspring is not completely understood.

Maternal exposure to micro-organisms, be they either pathogens or components of the microbiome, can directly affect foetal health through transplacental transmission (i.e. viruses, bacteria or protozoans)[10] and/or impact on offspring immunity.[11] Parasitic helminth infections are also an important cause of infection and disease,[12] they normally do not cross the placenta in humans, whereas transplacental larvae migration is common for some species such as *Toxocara canis* infection in dogs.[13] While mostly chronic and clinically unapparent, helminths still leave a profound immunological footprint on a host.[14] These infections are extremely common and accepted as inducing immune regulatory as well as pathological effects on host immunity.[15, 16] In this review, we will focus our attention on human infections with helminth and present the current body of knowledge of how maternal helminth infection can affect the immune system of the offspring in the long term, nurtured by experimental work in the laboratory mouse.

Effect of helminth infection on maternal health and birth outcome

That maternal helminth infections influence the relationship between the mother and the foetus is supported by epidemiological data that associates helminth infection with altered fecundity and birth intervals.[17] Helminth infections before and during pregnancy could potentially alter maternal and child/offspring health in a number of ways. This could be *via* exacerbating the effects of maternal malnutrition and anemia[18], potentially increasing the risks of complications during and after pregnancy, such as low-birth weight (LBW) and increased offspring risk of certain non-infectious and infectious diseases later in life.[19, 20] Maternal immune-suppression and physiological stress during pregnancy may also place the mother at an increased risk of carrying higher parasite burdens or of the infections being more likely to cause immune pathology.[21-23] Studies addressing if maternal anaemia resulting from helminth infection influences offspring health, such as incidence or extent of

LBW or childhood anaemia, are however inconclusive.[24, 25] Heavy hookworm infections can lead to maternal anaemia which can be reversed by deworming and use of iron supplements.[26, 27] However, studies in Uganda and Peru also addressing birth outcomes failed to find deworming to have any major influence on birth outcome.[22, 28]

An underworked possible significance of helminth infections may also be found in the context that pregnancy is inherently a period where type 2 immunity predominates; the same immune response enhanced during most helminth infections. It may be that effects from maternal helminth infections could extend or enhance this period of type 2 immunity which might be hypothesized (in theory) as having benefits for successful pregnancy.

Successful pregnancy requires the maternal endometrium to accept invasion and infiltration of the semi-allogenic foetus. This “antigenic-exposure” typically induces a type 1 immune response, i.e. with an interferon (IFN)-γ biased response. For the maternal immune system to accept the foetus as an allograft and not destroy it by mounting this type 1 cytotoxic response, the maternal-foetal interface suppresses potential maternal inflammatory responses.[29] This can be achieved by production of type 2 cytokines by the placenta which counterbalance the potential pro-inflammatory effects of type 1 cytokines. Such a pro-inflammatory type 1 response involving cytokines like IFN-γ and TNFα could have a range of negative effects on foetal survival, such as promoting expression of the pro-apoptotic transmembrane protein Fas and predispose trophoblast cells to apoptosis. Regulatory cytokines (such as IL-10), suppress these type 1 immune effects and allied cytotoxic events such as activation of NK cells, thereby promoting successful implantation and maintenance of the trophoblast.[30, 31] The importance of a strong type 2 immune environment has also been supported by studies in mice showing that foeto-placental tissue spontaneously secretes type 2 and regulatory cytokines which maintains a type 2-biased cytokine production greater than that of restimulated maternal splenic cells.[32, 33] Thus a normal pregnancy depends on a type 2-biased environment to avoid loss of the trophoblast. This regulatory immune imbalance that protects the foetus *in utero* is passed onto the foetus itself and is maintained into the neonatal period.[29] Thus, reports of helminth infections promoting fecundity and age of first pregnancy could be explained in part by such an effect, in the case of exposure to *Ascaris lumbricoides*.[17] However, the same study also presented converse associations in the case of hookworm infections. Irrespective, understanding how helminth infections may influence the fertility and the progression of pregnancy in the setting of foetal allograft survival are justified.

Evidence from human studies that maternal helminth infection influences infant immunity

While the effect of helminth infections on the mother is unclear, the implications for infant immunity from a maternal helminth infection are better understood. Children whose mothers have been infected with helminths during pregnancy can exhibit populations of B and T cells responsive to helminth antigens[34-37] or B cells class switched to secrete IgE and IgG4.[38] The potential effects of this *in utero* sensitization is likely to be broad and not restricted to homologous influence on subsequent infant helminth infection. Indeed, the effect of maternal exposure to filarial nematodes such as *Wuchereria bancrofti* may be to impair the ability of children to control a subsequent infection.[36]

Vaccine efficacy in infants born to schistosome or filarial-infected mothers has also been reported to be impaired.[39, 40] In both studies maternal helminth exposure relates to reduced levels of protective IgG against a range of important pathogens such as *Haemophilus influenzae type B* and Diptheria.[40] Infection with the filarial nematode *Mansonella perstans* during pregnancy has also been associated with changes in children's responses to vaccination against mycobacterial antigens and tetanus toxoid.[41] Importantly, albendazole treatment of hookworm infected mothers reduced IL-5 and IL-13 production to tetanus toxoid indicating that hookworm infections may impair tetanus vaccine efficacy.[42] Therefore, maternal exposure to helminths does appear to lead to a genuine reduction in IgG responses after vaccination. Underlying, this bias to type 2-dominated responses in offspring after maternal helminth infection may be a reduction of the type 1 immune responses usually observed in non-endemic populations to these pathogens. In addition, helminth induced immune regulation (for example raised IL-10) may also suppress vaccine efficacy e.g. by impairing antigen presentation. If these changes to antibody responses to vaccination result in an actual increased risk of reduced protection is much less clear.

The effects of maternal helminth infection do not appear to be restricted to vaccine efficacy. It is well established that helminth infections can associate with protecting children from atopic disease.[43] Insights from birth cohort studies in Uganda suggest that this protection may be acquired, at least in part, prenatally. Here, treating mothers with albendazole during pregnancy increased risk of eczema in their children.[44] While host adapted helminth

infections appear to provide some levels of protection against allergy, exposure to zoonotic helminth infections such as *Toxocara* spp. can be a risk factor for atopic disease. Epidemiological data shows this risk can also be associated with parental exposure to these parasites.[45]

These few examples illustrate how maternal helminth infections have been associated with altered child health. However, we do not fully understand the range of mechanisms through which maternal helminth infections can influence offspring ability to control either a helminth infection or another heterologous immune challenge. The following sections comment on mechanistic insights gathered from experimental work in the laboratory mouse model and are summarized in Figure 1.

Maternal helminth infection and offspring immunity: lessons from the laboratory mouse

To identify the potential mechanisms underlying the clinical observations related to maternal helminth exposure is difficult to achieve in clinical studies. Instead careful application of experimental animal models is likely to provide the key insights of how maternal exposure may actually alter infant immunity. Currently our experimental understanding of how maternal helminth infections alters offspring immunity is limited. However, data that does exist provides some important insights. For example, maternal infection with the nematode *Heligmosomoides polygyrus* provides high levels of nursing acquired-antibody mediated protection to offspring against this infection.[46] Similarly, infection during gestation of mice with *Schistosoma mansoni* also transfers protective immunity to offspring, although the mechanisms by which this occurs are not currently understood.[47]

In addition to the transfer of immunity against helminth infection, animal models have also been applied to understand the effects of helminth infection on unrelated diseases.[48] Recent work has shown that maternal helminth infections have striking bystander effects; driving both susceptibility to and protection from allergy depending on the progression of, in this case, maternal infection with *S. mansoni.*[49] It is likely that this effect is mediated by a number of mechanisms. While cytokine mediated exacerbation was implicated after maternal *S. mansoni* infection,[49] more recent work identified epigenetic changes to offspring T cells which could play an important role in the maternal effects on offspring immunity.[50]

As the immune system is constantly reshaped upon antigenic stimuli, the maternal interface (which is rich in immune components) during gestation and/or nursing adapts to antigenic challenge and subsequently influences maturation of offspring immunity. Pre-clinical mouse studies have shown that a number of non-exclusive mechanisms contribute to how maternal helminth infection affects offspring immunity. Among those mechanisms passive antibody transfer is the most comprehensively understood and highly relevant in the first weeks of life when the immune system is not fully mature and unable to mount effective antigen-specific responses.[51] However, antibody transfer is not the sole mechanism by which maternal immunity is transferred to the offspring. Transfer of cytokines[52], antigens[53], changes in offspring microbiota[54], transfer of maternal cells[9] or non-inherited maternal antigens (NIMAs)[55] as well as inherited or non-inherited epigenetic modifications[50] in offspring are all influenced by our mother and shape our immune system pre- and postnatally. How helminth infections influence these effects represents a significantly underworked component of our understanding of the host helminth relationship. In the remainder of the review we address components of maternal transfer of protection which we feel are particularly important and pertinent to helminth infections.

Passive transfer of antibody

The mechanisms of passive maternal transfer of antibodies to the offspring vary between species and occurs *via* the placenta or breast milk. Whereas immunoglobulin transfer in humans (or rabbits) occurs mainly *via* the placenta, others are exclusively *via* mammary secretions (cows, pigs) and some animals transfer *via* both (mice, dogs).[56] An important physiological factor which influences the quality and quantity of antibody transfer *in utero* is the extent of invasion into the uterus by placental trophoblast cells of foetal origin that directly determines the immune tolerance of the foetus by the mother as well as the extent of permeability of the foetus to maternal blood.[57] Species including cows, pigs or horses have a non-invasive epitheliochorial placenta that does not allow passive antibody transfer to the foetus.[57] These offspring therefore exclusively rely on colostrum and milk ingestion by the neonate for effective passive immunity.[58] In contrast, the particularly invasive haemochorial structure of human or mouse placenta results in a direct contact of trophoblast cells with maternal blood, enabling passive transfer of immunoglobulins during gestation.[57] It is important to note that while human and mouse placenta share an invasive haemochorial structure, murine placenta is not as efficient for *in utero* antibody transfer as that from human.[58] Therefore, the mouse must be considered as a useful but not perfect model of the

human placenta. The consequence of such evolution is that human neonates are born with high concentration of plasma IgG of maternal origin and mouse milk contains high IgG concentrations. Interestingly, in contrast to cow colostrum (IgG), the major immunoglobulin in human milk is IgA which has consequences on the role of colostrum since the transfer of IgA targets protection of the infant's gastrointestinal tract and supports oral tolerance mechanisms.[59] Indeed, IgG transfer in humans is concluded prior to birth *via* the bloodstream although continues *via* the milk in mice. This is therefore another aspect that has to be considered when translating pre-clinical findings to a clinical setting.

Interesting data from Harris and colleagues showed that immune protection from mothers infected with the nematode *H. polygyrus* could be transferred *via* nursed IgGs into neonates.[51] Moreover, parenteral administration of IgG antibodies also conferred protection *via* natural Fc receptor-mediated retrotransportation to the intestinal lumen.[51] But all antibody isotypes were not equal in their effector functions. Indeed, secretory IgA (sIgA) were rather involved in limiting penetration of commensal microbiota, together with Tregs, to prevent immune stimulation in the intestinal mucosa. In consequence, an active suppression of intestinal $CD4^+$ T cells occurred postnatally in homeostatic conditions which could contribute to prevent auto-reactivity possibly by sustaining a broad TCR repertoire.[51, 60] If this passive antibody mediated effect applies to all helminth species also needs to be considered. For example the allied laboratory helminth model *Nippostrongylus brasiliensis* has been shown to be largely refractory to antibody mediated immunity.[61]

Cytokine and antigen transfer

Antigens, some cytokines and even parasite infection can be transferred to the foetus *via* the placenta[11, 62] and to neonates by breastfeeding.[63] However, the contribution of such transfer during helminth infection to the development of the offspring immune system remains poorly investigated. In dogs, *T. canis* can be transmitted to the foetus by reactivating during gestation from larvae having halted their migration and crossing the placenta of the infected female dog as well as *via* the nursing milk. *Ancylostoma* spp. are normally soil-transmitted helminths but the transmammary route has also been described.[64] Thus, worm infection can directly be transferred to the foetus or neonates but most of maternal helminth infection are not directly transferred to the offspring. Up to now evidence of schistosome-egg-derived as

well as filarial antigens in the cord blood, breast milk and placentas of infected women and their newborns was provided by several studies.[65-69] Further studies investigating possible effects of such transferred antigens have demonstrated firstly stimulatory effects on human trophoblast cells and placental inflammation leading to IL-6, IL-8 and MIP-1alpha secretion,[70-72] secondly that sensitization had occurred in terms of measurable antigen-specific T cells responses in cord blood mononuclear cells (CBMCs)[73] as well as activation of B cells[66] and thirdly protection against reinfection.[74] In general, maternal schistosomiasis leads to a more activated status of the innate as well as adaptive cell compartments of CBMCs,[75] whereas filariasis during pregnancy seems to lead to tolerance with rather increased susceptibility of the offspring to develop filariasis during childhood indicating a certain longevity of the maternally imprint.[68, 76] In addition, immunomodulatory properties of helminth antigens could eventually suppress innate immune responses to TLR ligands as shown *in vitro*[77, 78] and induce de novo expansion of Treg cells *in vivo*[79, 80].

The effects of *S. mansoni* infection during gestation on the mother and on the susceptibility of the offspring to *S. mansoni* has been investigated more thoroughly in the mouse model. Here *in utero* exposure to *S. mansoni* attenuated the pathogenesis of schistosomiasis in adult age[47], potentially through antigenic transfer to the fetus and neonates and subsequent sensitization[65, 81, 82]. However, using cross-fostering experiments, breastfeeding from *S. mansoni* infected mothers provided a better control of chronic hepatic disease. Whether such observation involves transfer of antigens and/or other mediators has not been defined[83]. In addition to the impact on helminth immunity in offspring, maternal exposure to helminth infection also alters the immune response against heterologous antigens. Schistosomiasis is characterized by various stages of infection that are dominated by different cytokine responses. In BALB/c mice, IFN-γ dominates the early response before appearance of parasitic eggs in the vasculature which shifts the response towards type 2 cytokine production (IL-4, IL-5 and IL-13). During the resolution phase, IL-10 dominates and downregulates the type 2 immune response. A recent report has appreciated that *S. mansoni* infection of female mice transferred antigen-independent but IFN-γ dependent protection against allergic airway inflammation to their offspring if mated during the first weeks of infection.[49] In addition, this study also showed that maternal schistosomiasis led to differential gene expression profiles and cytokine responses in the placenta depending on the infection phase. The potential for offspring to have what can only be maternally acquired helminth associated responses has also been demonstrated in a number of human studies. For example children whose mothers were infected with *Ascaris lumbricoides* during pregnancy exhibit populations of lymphocytes responsive to *Ascaris* antigens.[34] If such

effects are mediated by transfer of maternal cytokines or antigens is less clear and but both are plausible and do occur in other disease settings. Importantly, we know that helminth immune-modulatory molecules as well helminth induced host derived molecules can impart dramatic systemic effects on the host; this provides ample justification for investigating their likely role in a transgenerational setting.[84, 85]

Maternal cell transfer and microchimerism

Pregnancy requires high levels of immune tolerance to allow the foetus to develop[86], this effect is widely conserved across mammalian species.[87] Helminth infections while characterized by strong type 2 immune responses also typically have an allied regulatory T cell response. This effect underlies many of the bystander protective effects of helminth infections on autoimmune diseases.[88] Importantly this characteristic of helminth infections also promotes tolerance of allogenic tissue. For example, *N. brasiliensis* infected mice show enhanced maintenance of kidney allograft.[89] Moreover, the precise mechanisms by which this effect is mediated may well be common to enhanced acceptance of skin grafts in mice treated with the *Heligmosomoides polygyrus* secreted TGF-beta orthologue.[84] These tolerogenic effects on the immune system are not understood at all in the context of maternal helminth immunity but could have significant implications for the offspring immune system.

This potential promotion of the tolerogenic environment between the mother and foetus/neonate has parallels with the immune basis for promotion of acceptance of maternal cells by offspring *via* microchimerism. Here vertically transferred cells of maternal origin provide non-inherited maternal antigen (NIMA) experience to the foetus and these cells can persist in individuals at very low levels throughout postnatal development and even until adulthood.[90] Although it remains uncertain whether the microchimerism created by such transfer results in specific functions by the transferred maternal cells, tolerance of NIMAs mainly results from the differentiation of NIMAs-specific T cells into Tregs.[55, 91] Thus, it is suggested that both exposure to NIMAs during gestation and *via* nursing are necessary for tolerance of the non-self antigens of maternal origin [92]. But Tregs might not be the only cell-mediated mechanism for tolerogenic responses against NIMAs. Non-cytopathic strains of bovine viral diarrhoea virus (BVDV), a pestivirus of the *Flaviridae* family can cause lifelong persistent viral infection and shedding in the newborn calves. This phenomenon occurs when BVDV is transmitted from mothers to the foetus during the developmental phase of the

immune system (<150 days of gestation), resulting in immune tolerance of viral antigens.[93-96] In addition, a recent report demonstrated that vertical transmission of hepatitis B virus results in chronic infection alongside macrophage-mediated exhaustion of $CD8^+$ T cells expressing high levels of PD-1.[97, 98] Thus, transfer of non-inherited antigens to the foetus *via* the haemochorial placenta can occur and benefit from mechanisms of immune tolerance at the foeto-maternal interface to persist in the offspring. Colostrum and milk have also been shown to contain significant amounts of immune cells such as macrophages, granulocytes or lymphocytes. Although not fully conclusive, early reports suggested that maternal immune cell transfer to the offspring could occur and potentially lead to long term persistence.[99-104] As acidification of the stomach only occurs (in rodents) from approximately 14 days post birth, prior to this the stomach has relatively neutral pH of 6 with acidification only occurring at weaning.[105] It is therefore feasible that cells in breast milk could survive and cross the epithelium during this permissive window. In support of this delay in the onset of stomach acidification promoting cell transfer *via* nursing is presented in recent cross-fostering study in MHC-matched or MHC-mismatched conditions in mice. This study identified GFP^+ leukocytes of maternal milk origin accumulated in Peyer's patches up to 18 days after birth.[106] Here, the majority of milk leukocytes were $CD11b^+$ and $Gr1^+$ myeloid cells. About 70% of transferred cells located to the Peyer's patches were the local T lymphocytes expressed high levels of CCR9 and $\alpha_4\beta_7$ integrin and in addition displayed increased susceptibility to *ex vivo* restimulation. The percentage of these maternal T cells in the Peyer's patches remained however very low and became undetectable by day 28. Whether true immunological memory can be transferred from the mother to the offspring remains to be adequately addressed. Thus, although the maternal-neonatal interface *via* placenta and nursing favours bilateral cell transfer and long-term immune tolerance, it remains uncertain whether transfer of maternal lymphocytes to the offspring can truly impact the neonate immune system and if helminth exposure can alter this effect.

Epigenetic effects

Recent findings have shown that prenatal exposure to LPS, IFN-γ or bacteria could dampen offspring susceptibility to allergic asthma[107, 108]. More in-depth analysis of the epigenetic state of Th1- and Th2-related transcription factors demonstrated changes in the H3 histone acetylation as well as methylation status which correlated to the functional observations of suppressed allergic Th2 immune responses in offspring.[109] Notably, reversing these epigenetic changes by administering a DNA methyltransferase (DNMT) inhibitor *in vivo* ameliorated the allergic phenotype.[109] Interestingly, mating female mice during the first 5

weeks of *S. mansoni* infection was shown to transfer protection against allergic airway inflammation to the offspring via IFN-γ which predominates in this acute phase of infection. However, when offspring were derived by *in vitro*-fertilized oocytes from infected females during the acute phase and were subsequently embryo-transferred into healthy females, suppression of ovalbumin-induced allergic responses was lost. Thus, acute maternal schistosome infection most likely do not affect epigenetic marks on the gametes.[49] In addition, the bystander protective effects against ovalbumin-induced airway allergy was also observed during the long-term regulatory phase of infection with *S. mansoni.*[49] Klar and colleagues observed a T helper cell intrinsic block of Th2 differentiation from naive $CD4^+$ T cells in offspring born of these long-term *S. mansoni* infected mothers,[50] which correlated with reduced histone acetylation pattern of Th2 promotor regions. As it stands, these correlative observations still lack evidence of causality and more in-depth analyses are needed to decipher the dynamics of such epigenetic changes alongside their role in other immune response such as vaccines and bacterial or viral infections besides allergies.

Concluding remark

The huge global significance of helminth exposure therefore has an important influence on the immunological relationship between mother and child but also in terms of general maternal health and fecundity. Helminth infections are unique in that they remain active over many years and modulate host responses in subtle and as yet, still undiscovered ways. Indeed, the mechanisms by which helminth infections influence host and maternal relationships remains incomplete but could be elicited through numerous routes: placenta, colostrum, epigenetics. Moreover, deciphering those components of immunology and relating them to those discovered in other parasitic infections during pregnancy is becoming an important field. The layers of complexity deepen further when one additionally takes into consideration the likelihood of multiple helminth infections and furthermore, how helminth-mediated maternal responses could be shifted upon co-infections with other parasites such as malaria. In essence, these transgenerational immunological relationships have genuine importance for our understanding of how early life events influence life-long ability to control a variety of diseases.

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Figures.

Figure 1. Diagram summarizing the current knowledge and main hypotheses on how maternal infection with helminths can shape offspring immunity. Placental and mammary routes are presented as well as potential germline transmission. Adult nematodes or *S. mansoni* worms are depicted. Murine placenta is represented on the left: maternal trophoblast giant cells, spongiotrophoblast and labyrinth are represented in blue.[110] Murine mammary gland at puberty is represented on the right: epithelial cap (brown), luminal epithelial (purple), myoepithelial (red), and epithelial body (blue) cells are shown as described.[111]