Inherent maternal type 2 immunity

Inherent maternal Type 2 Immunity: consequences for maternal and offspring health

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Abstract

An inherent elevation in type 2 immunity is a feature of maternal and offspring immune systems. This has diverse implications for maternal and offspring biology including influencing success of pregnancy, offspring immune development and maternal and offspring ability to control infection and diseases such as allergies. In this review we provide a broad insight into how this immunological feature of pregnancy and early life impacts both maternal and offspring biology. We also suggest how understanding of this axis of immune influence is and may be utilised to improve maternal and offspring health.

Introduction

A major advance in our understanding of immune system development is that immunological challenges during early-life shape adult immunity. Early-life exposures result in the long-term programming of the immune system with accumulating evidence showing important contributions via this axis in protection from infection, immune tolerance and optimal physiological function. This balancing influence on inflammation, tolerance and immune homeostasis can last until adulthood influencing our ability to control infection, allergies, autoimmunity, mental illnesses and regulate our metabolism.

Pregnancy, obviously, plays a central role in influencing early-life immune programming. Foetal immune responses are significantly shaped *in utero*. This influence extends beyond birth with neonatal immunity receiving further direction via lactation. These *in utero* and lactation influences on offspring immune programming can both enhance and mitigate future susceptibility to infection, vaccination, allergies, autoimmune disease [1-3], and behavior and the development of mental illnesses [4, 5] .

An important immunological signature during pregnancy and early life influencing these phenotypes is the presence of a Type 2 immune bias in both mothers and neonates [6]. The precise roles of this type 2 immune environment are not fully understood. However, the broad influence on maternal and offspring biology is apparent in existing literature.

A more comprehensive understanding of the mechanisms and factors influenced by the maternal/early life type 2 immune bias in foetal and neonatal immune programming will help to predict how individuals will respond in adult life and develop public health guidance and policies. Maternal/early life type 2 immune bias also needs to be considered when developing treatments that therapeutically programme early-life immune development to prevent immune-mediated disease or promote resistance to infection. This review explores the role of Type 2 immunity in pregnancy, it's influences on foetal and neonatal immune programming, as well as the knowledge gaps that need to be filled to start developing therapies and diagnoses.

Type 2 immunity in pregnancy

Fundamentally a successful pregnancy requires the maternal endometrium to accept invasion and infiltration of the semi-allogenic foetus. This “antigenic-exposure” would typically be expected to induce a type 1 immune response, i.e. with an interferon (IFN)-γ biased response that would drive a cytotoxic response against the foetus. Therefore, for the maternal immune system to accept the foetus as an allograft and not destroy it by mounting a type 1 cytotoxic response, the maternal-foetal interface needs to suppress/regulate potential maternal inflammatory responses [7]. Production of type 2 cytokines by the placenta is one mechanism which can dampen potential pro-inflammatory effects of the type 1 cytokines which would promote foetus rejection. Maternal type 2 immunity is not an overarching requirement for successful pregnancy; animals lacking key type 2 cytokines and/or receptors can breed [8]. Instead, other mechanisms are likely to act in concert with type 2 maternal immunity to optimize survival and appropriate development of the blastocyst through to foetus. For example, elevated Fas Ligand (FasL) expression on trophoblast cells may promote foetal immune privilege by inducing apoptosis of potential cytotoxic immune cells such as NK cells and CD8 T cells [9]. Production of regulatory cytokines (such as IL-10) could also suppress potential type 1 immune effects and allied cytotoxic events, such as activation of NK cells, to promote successful implantation and maintenance of the trophoblast [10, 11].

The maternal type 2 immune environment is none the less prominent. Pre-clinical studies demonstrate foetus-placental tissue spontaneously secreting type 2 and regulatory cytokines and to maintain a type 2-biased cytokine production greater than that of restimulated maternal splenic cells [12, 13]. Moreover, defined functions for (for example) IL-4 and IL-10 are beginning to be identified. Here both IL4 and IL-10 have been shown to promote optimal interactions between decidual immune cells (DICs) and trophoblasts by supporting appropriate function of T-cell immunoglobulin mucin-3 (Tim-3) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), both of which are essential for optimal placental development and protection against foetal loss [14].Therefore, a normal pregnancy’s type 2-biased environment contributes to protecting the trophoblast at the onset of gestation.

Later in pregnancy the type 2 environment has also been identified as a correlate of protection from important maternal pathologies, such as spontaneous abortion, hypertension-and subsequent risk of endometriosis [15]. For example recurrent abortion has been shown to associate with reduced IL-4 and IL-10 production by decidual $CD4^+$ T cells[16, 17]. A number of clinical studies have also identified reductions in IL-4 and IL-10 in women with hypertension and endometriosis [18, 19]. Subsequent preclinical studies are demonstrating that both IL-4 and IL-10 contribute to this immune-pathology. Here in studies using loss of function of IL-4/IL-10 enhanced maternal hypertension has been clearly demonstrated[20, 21] and treatment with IL-4/IL-10 protects against placental ischaemic induced maternal hypertension [22]. In each of these disease settings it appears that risk of pathology or protection from pathology is a result of respective reduction or promotion of both IL-4 and IL-10.

Related findings have been found addressing expression of IL-4 and IL-13 signalling on the placenta. Here signalling via IL-4Ra has a significant anti-inflammatory effect in response to LPS challenge [23]. IL-33, an important early initiator of Type 2 immunity and its receptor ST2 are also enriched at the maternal fetal interface. Using IL-33-/- rats, this presence of IL-33 at the placental interface has been shown to also provide protection against LPS induced fetal restricted growth and failure of pregnancy [24]. Therefore, type 2 immunity at the maternal-foetal interface provides a significant level of protection against bacterial infection induced inflammation causing failure of pregnancy.

Together, our current understanding of raised maternal type 2 immunity points to it being an important component for protecting both the foetus *in* utero and directing appropriate

development of foetus. Moreover, this type 2 immunity also contributes to protection of the mother from common causes of pathology associated with pregnancy, such as hypertension. It is intriguing to speculate that reports of type 2 driving infections by helminths promoting fecundity and age of first pregnancy may be explained in part by such effects, in the case of exposure to *Ascaris lumbricoides* [25]. However, the same study also presented converse associations in the case of hookworm infections. Irrespective, understanding how helminth infection induced immunity may influence fertility and progression of pregnancy in the setting of foetal allograft survival are justified and would be fascinating.

Consequences/Outcomes for offspring:

Maternal type 2 immunity contributes to offspring immunity at birth and later in life. Again, the consequences/outcomes for offspring of maternal type 2 immunity, while appreciated, is incompletely understood. However, insights into offspring risk of allergy [26] and susceptibility to helminth infections related to maternal immunity [27] clearly support inherent maternal type 2 immunity being likely to exert effects on offspring immunity .

Irrespective of this relatively limited current lack of insight we do know that communication between mother and child *in utero* and during breast feeding has profound effects on subsequent offspring immunity. For example, maternal transfer of immunity can provide direct protection from infection via (for example) transfer of antibodies [28] or mothers cells [27]. Maternal immunity can also reprogramme offspring immunity, either sensitising (increasing) or tolerising (reducing) immune responses [3, 29, 30]. These mechanisms are discussed in more detail in subsequent sections.

To what extent inherent maternal type 2 immune competency drives many phenotypes reported to date is unclear. Much of what we understand is framed in the context of maternal disease, such as infection with helminths or allergic inflammation [31, 32] which promote enhanced type 2 immunity in the mother. Helminth infection and allergy associated type 2 immunity are very well defined. The host response is often initiated by epithelial stress resulting from direct interaction with the helminth or allergen. This results in release of alarmins (such as IL-25, IL-33 and TSLP) from epithelial cells. These alarmins initiate the type 2 immune cascade by activating ILC2 responses and directing myeloid cell phenotypes. These effects lead to a range of epithelial responses such a mucus secretion, smooth muscle cell hypercontractility and the development Th2 CD4 T cell immunity and promotion of B cell IgE secretion [33].

Early life type 2 immunity induced independently of an external challenge is not widely reported. However, neonatal IL-33 has been shown to be induced very early after birth in response to the airway epithelial stress that results from initial lung inflation [34]. This leads to promotion of a type 2 lung environment which may be lost post weaning. A consequence of this early life type 2 lung environment may be increased susceptibility to pulmonary bacterial infection such as *Streptococcus pneumonia,* driven by altered alveolar macrophage function. This finding shows that inherent early life Type 2 immunity has a striking influence on immunity and suggests an influence from raised maternal type 2 immunity as well.

Maternal/early life type-2 immune polarisation is also likely to influence efficacy of maternal/ early life vaccinations. Early life Type-2 immune influence on vaccine responses is incompletely understood and may be context dependent. For example, IL-4 has been shown to promote neonatal antiviral antibody responses [35]. Conversely, blockade of IL-4 enhanced efficacy of vaccination against oxycodone [36]. If manipulation of maternal immunity contributes to these effects is not currently known.

Human and animal studies also show that maternal helminth infections (which would promote Type 2 immunity in their own right) transfer a maternal CD4 T cell dependent protection from helminth infection to offspring [27]. Additionally, helminth infections during pregnancy can impair control of unrelated infections. This includes reduced induction of MtB/BCG-specific

IFNg responses [37, 38] and increased risk of maternal transfer of HIV to children [39] in mothers infected with helminths.

Mechanisms of offspring immune programming

Elucidating the mechanisms by which immune communication occurs between the mother and baby is a key step in understanding how maternal immunity influences the development of their offspring's immune system. The passage of immune components, antigens, and cells from mother to baby can take place in utero via transplacental transfer and neonatally via breast feeding. To be able to predict how an individual will respond to immune challenges in the future, and potentially be able intervene with therapies, we need to understand how these interactions sensitise or tolerise the offspring to particular immune challenges, and be able to link them to future predisposition to infections, allergies, and other immune diseases.

Antigen transfer and priming of foetal and neonatal immunity

Helminth antigens and allergens have been identified in the cord blood of children born to infected or allergen-exposed mothers indicating *in utero* transfer of Ag [40-42], and T and B cell responses to helminth antigens and allergens can been detected in cord blood [38, 41, 43-50]. Similarly, allergens and helminth antigens can be detected in breast milk [42, 51-53]. Thus, offspring are exposed, and can become primed towards, a similar antigenic landscape as their mothers, setting the potential for antigen-specific sensitisation or tolerization that could affect future immunity.

A key question in regard to allergies is whether offspring become sensitised to allergens *in utero* or via breast milk so predisposing them to type 2 responses and allergic inflammation towards those allergens. Induction of Allergic Airway Inflammation (AAI) in mothers can result in increased AAI responses to those allergens in their offspring [54-56], and the presence of allergens in breast milk alone can be sufficient to induce allergic responses in offspring [57, 58]. In a model of maternal house dust mite AAI, offspring showed increased AAI responses to house dust mite allergens but not to *Aspergillus fumigatus* extract, indicating antigen-specific sensitisation [56]. Thus, maternal allergic inflammation can sensitise offspring towards allergens to which the mother is exposed. However, in humans, the strength of allergen-specific recall responses in cord blood does not correlate with subsequent susceptibility to allergies [47, 49, 50], and non-atopic individuals can show higher recall responses than atopic individuals ([47, 48, 59]. Similarly, allergen-avoidance guidance during pregnancy and lactation has had no detectable impact on subsequent allergy levels, suggesting that maternal allergen exposure is a not a key determinant [60-63]). Thus, whilst offspring can be sensitised to allergens *in utero* and through breast feeding, the resulting impact on their future predisposition to allergies is unclear.

Foetal and neonatal immune responses tend to favour regulatory rather than inflammatory response [1], suggesting that antigen-exposure may preferentially result in tolerance rather than sensitisation. They produce IL-10 rather than inflammatory cytokines [64, 65], and their T cell responses are biased towards tolerance with the generation of regulatory DC and $Foxp3^+$ regulatory T (Treg) cells in conjunction with TGF-β [66-69]. In line with this, maternal exposure to oral antigens, in a way that can induce oral tolerance, results in reduced offspring responsiveness to immunisation or AAI indicating development of antigen-specific tolerance in the offspring [69-71]. Interestingly, exposure of mothers to antigens by immunisation [72], epicutaneous sensitisation [73], or in models of AAI [51, 74-76], can also result in the reduced type 2 responses to those allergens in the offspring with amelioration of AAI. Thus, the induction of an inflammatory type 2 immune response in the mother can still prime the offspring towards tolerance, consistent with the regulatory nature of neonatal immunity. The induction

of tolerance in the offspring is related to the transfer of antigens and/or antibodies *in utero* [75] or via breast milk [51, 69-71, 73, 74, 76]. Whilst these results imply the development of antigen-specific tolerance in the offspring, only a few studies have formally demonstrated that tolerance did not extend to third-party antigens [51, 72]. Despite the evidence for tolerance induction in animal models, evidence in humans that exposure to allergens via breast milk is protective against subsequent development of allergies is mixed. There is some evidence that breast feeding associates with reduced eczma, asthma, food allergies [52, 77, 78], but this is not consistent and likely context dependent [62, 78, 79].

Foetal and neonatal immune regulation parallels that observed during helminth infections, which also potently elicit Foxp3$^+$ Tregs, Th2 cell tolerance, TGF-β and IL-10 [33]. The immune regulatory biases of the foetus, combined with those of maternal helminth infection, could reinforce the development of tolerance in offspring. It is not surprising then that children born to filarial infected mothers show lower proliferative and cytokine responses to filarial antigens compared to children born to non-infected mothers [80, 81]. As their responses to mitogen and non-helminth Ag were unaffected this suggests the induction of antigen-specific suppression in the offspring, which is consistent with the ability of helminths to down-regulate or tolerise Th2 cells [82-84]. Children born to filarial infected mothers also have higher levels of CD4$^+$CD25^{hi} T cells in their cord blood [40], indicative of preferential *in utero* priming of Treg responses. In turn, maternal filariasis during pregnancy associates with offspring being more susceptible to subsequent filarial infection [80, 85-88]. The evidence that immunological tolerance relates to increased susceptibility was provided by Malhotra *et al.,* who showed that human maternal infection with filarial nematodes results in two distinct outcomes for cord blood T cells [87]. Half the children became sensitised and had active filarial-specific Th2 responses in their cord blood, whilst other half were unresponsive to filarial antigens and were classed as tolerised. Tolerised children showed increased susceptibility to subsequent filarial infection compared to sensitised children, or children born to uninfected mothers.

Although antigen-specific sensitisation or tolerization can occur *in utero* or through breast feeding, there is also evidence for programming of fetal and neonatal immunity independently of the mothers' antigen exposure. Murine models demonstrate that maternal AAI, or breast milk from an allergic mother, can enhance allergic inflammation in offspring in an antigen-independent fashion [89-92]. Initiation of allergic contact dermatitis in the mother can also result in enhanced AAI to a third-party antigen in the offspring, indicating transfer of allergy predisposition that is independent of both the antigen and tissue site [93]. Similarly, breast milk HMOs can condition DC's to promote Treg generation [94], presumably favouring tolerance to a range of different antigens. Maternal helminth infections can suppress offspring immunity to third-party allergens [95, 96], and can alter responses to third-party vaccinations [37, 97], indicating the transfer of antigen-non-specific immune modulation. Thus, foetal and neonatal immune programming occurs via a combination or antigen-dependent and antigen-independent mechanisms.

Cytokines

The type 2 immune bias that develops in pregnancy is believed to extend into neonates, and type 1 cytokines in cord blood tend to be found at lower levels than in adults [98]. There is evidence that the type 2 to type 1 balance in the mother during pregnancy, and in the child at birth, determines the child's predisposition to allergies. Children from mothers with stronger type 2 responses, or weaker type 1 responses, are more likely to develop allergies. Children who develop wheeze were found to be born to mothers with lower levels of blood IFN-γ and TNF-α during pregnancy, whilst the mothers' of atopic children had lower IFN-γ to IL-4 ratios during their first trimester [99]. Studies investigating cytokine responses in cord blood found that children who later developed atopic dermatitis had reduced frequencies of T cells producing IFN-γ and/or increased percentages of Th2 cells [100, 101]. Similarly, IFN-γ

production by cord blood cells was lower in children who subsequently developed allergies, atopy, or positive skin prick tests [102, 103].

Importantly, external influences on the mother are able to influence the offspring's type 2 to type 1 balance, and in murine models the induction of allergic inflammation in mothers during pregnancy results in impaired Th1 responses in the offspring and increased cutaneous hypersensitivity [91], or accelerated IgE responses following immunisation [92]. Maternal AAI during pregnancy was found to increase offspring susceptibility to AAI, and this effect could be negated by antibody-mediated neutralisation of IL-4 in allergen exposed mothers, demonstrating that excessive type 2 responses in the mother during pregnancy make the offspring more susceptible to allergic inflammation [89]. Heightened offspring allergy is not always related solely to the maternal IL-4Rα Type 2 immune axis. Overexpression of maternal IL-5 can also drive enhanced offspring asthmatic pathology [26]. In contrast, exposing pregnant mice to Th1 stimuli such as LPS or CpG [55, 104, 105], or giving IFN-γ [106], increased Th1 responses in the offspring and protected against AAI. Although protection was limited to decreased cellular infiltration and did not impact airway hyper-responsiveness to methylcholine. Supporting evidence is seen in humans where maternal farm exposure, often used as a surrogate measure for exposure to Type 1 driving microbes and their products, was found to associate with lower Th2 cytokine production by cord blood cells, as well as increased cord blood Treg cell frequencies and suppressive ability [107]. In the murine models, the enhanced allergic inflammation in offspring from allergic mothers was antigen-independent [89, 91, 92], and protection from AAI mediated by raw cow's milk was associated decreased histone acetylation at Th2 cytokine genes, indicating epigenetic effects [108]. Similarly, cord blood cells of children born to farm-exposed mothers show differential methylation of type 2 associated genes [109]. This indicates that early perturbations in the mother's type 1/type 2 balance can increase an offspring's type 2 bias and thus predisposition to allergies in an antigen non-specific fashion, possibly relating to epigenetic changes in type 1 and type 2 - associated genes.

Maternal TGF-β plays a key role in neonatal programming for immune tolerance, and transfer of oral-tolerance from the mother to their offspring positively correlates with TGF-β levels in breast milk [69]. The antigen-specific immune tolerance observed in offspring born to mothers undergoing AAI was abrogated by neutralising maternal TGF-β, and was dependent upon the offspring's Tregs [51]. This indicates that TGF-β in the breast milk elicited a Treg response towards the co-transferred antigens. An intriguing question is why allergic responses in the mother favour a Th2 bias in the offspring and increased susceptibility to allergic inflammation in some contexts, whilst favouring TGF-β and tolerance in other contexts. The induction of Tregs in mouse models does also have parallels in humans. Cord blood from children with allergic mothers tend to have reduced Treg cell proportions, and the Tregs showed reduced suppressive ability [100, 103], suggesting that impaired Treg priming contributes to increased allergy susceptibility. In contrast, the reduced incidence of allergies seen in children born to farm-exposed mothers associated with an increased proportion of cord blood Tregs [107], as well as an altered type 1 to type 2 balance.

Helminths stimulate chronic Type 2 immune responses, as well as host immune regulatory responses such as TGF-β. Thus, helminth infections during pregnancy have the potential to exacerbate offspring allergy by increasing the type 2/type 1 ratio, or ameliorate offspring allergy by favouring the induction of tolerance. A good illustration of this comes from murine infection with the trematode *S. mansoni*. *S. mansoni* infection follows three phases; an acute phased consisting of mixed Th1/Th2 responses, a Th2 phase dominated by a strong egg-induced Th2 response, followed by an immune regulatory phase. Pregnancies during the Th2 phase increased the offspring's responses to AAI, whilst pregnancies during the acute Th1/Th2 phase reduced offspring susceptibility to AAI [95]. The protection mediated during acute phase infection was abrogated in IFN-$\gamma^{-/-}$ mice, indicating that maternal helminth infection can influence the type 1 to type 2 balance of the offspring so altering their

predisposition to allergies. Pregnancies timed during the immune regulatory phase of infection, when egg-induced Th2 responses are downregulated via multiple immune pathways, also resulted in reduced AAI in the offspring. Whilst the mechanisms induced during the regulatory stage were not investigated in this study, it does suggest that helminth-induced regulatory can also influence offspring immune development. There is also evidence of human maternal helminth infections both protecting against and enhancing allergic predisposition. Maternal hookworm infection associates with reduced eczema incidence [110], and maternal geohelminth infection was found to be protective against atopy (skin prick test), particularly if reinforced by early-life helminth infection [96]. In contrast, in non-atopic children, maternal *T. trichiura* infection positively associated with wheeze in children that did not subsequently become infected, and high *A. lumbricoides* infection loads positively correlated with increased airways inflammation [96].

Passive transfer of antibodies

Alongside protecting infants from infections, passive transfer of maternal antibodies can also tolerise offspring to antigens to which the mother has been exposed and subsequently ameliorate their allergic inflammatory responses. Antibody-mediated tolerance can occur by the transfer of antibody-antigen complexes to the offspring in utero or in breast milk via the offspring's neonatal IgG FcR [74-76, 111]. These Ab-Ag complexes can directly down-regulate the offspring's B cell responses and IgE production by upregulating and cross-linking the inhibitory FcγRIIb on neonatal B cells [111]. Alternatively, the transfer of Ab-Ag complexes can also stimulate fetal and neonatal DC to differentiate T cells towards a $Foxp3^+$ Treg cells, with protection from allergic inflammation being dependent upon Tregs [75, 76]. The induction of Tregs was independent of the FcγRIIb [76], indicating that there are at least two different mechanisms by which Ab-Ag complexes can protect against allergic inflammation. The induction of $Foxp3^+$ Tregs by Ab-Ag complexes was also independent of TGF-β [76], whilst the TGF-β mediated induction of Tregs to free Ag in breast milk was independent of B cells [51], indicating at least two distinct mechanisms by which maternal exposure to allergens can induce protective Treg responses in their offspring.

Other immune regulatory milk components

Breast milk contains a complex array of components, including immunomodulators such as Human Milk Oligosaccharides (HMOs), extracellular vesicles (EV) and microRNAs (miRNA), and fatty acids [30]. Whilst the functions of many of these are yet to be elucidated, there is evidence that they can regulate the offspring's development of Type 2 immunity.

HMOs are the third most abundant constituent of human breast milk, and can influence neonatal immune development and barrier formation by direct interactions with immune and epithelial cells or indirectly through the regulation of microbiota [112]. Dysregulation of the epithelial barrier resulting in the release of the alarmins IL-33, IL-25, and TSLP can result in the generation of type 2 immune responses and allergic inflammation. Thus, HMOs could potentially protect against future allergies by stimulating epithelial cell maturation and barrier formation [112]. Exposure of human monocyte-derived DCs to HMOs *in vitro* causes them to develop a semi-mature state and promote the generation of Treg cells [94]. This suggests another pathway by which breast milk may favour the generation of immune tolerance to antigens, such as allergens, to which offspring are exposed in early life. There is also evidence that HMOs can directly downregulate Type 2 immune responses, as injection of HMOs into adult mice can inhibit allergic Type 2 responses, reducing allergy symptoms, IgE levels, and mast cell degranulation [113, 114]. Thus, HMOs may limit the magnitude of Type 2 responses in offspring whilst breast feeding, although it is not known whether these effects would be longer-lasting. Direct evidence that HMOs can influence the development of allergic

inflammation is limited. However, the presence of individual, or groups of, HMOs in breast milk both positively and negatively correlate with offsprings' future allergic status suggesting that they do play a role [115-119].

Maternal EVs and miRNAs are detectable in breast milk, and include miRNAs associated with the regulation of immune cell function [120-123]. *In vitro* studies show that EVs are resistant to digestion and can be taken up by epithelial cells with their contents intact [124], indicating that maternal EVs could communicate with the offspring's cells. Whilst the *in vivo* functions of breast milk EVs and miRNAs are unknown, exosomes isolated from milk can inhibit cytokine production, and favour Foxp3^{+} Treg development, from human PBMC *in vitro* [120]. MicroRNAs play an important role in regulating allergic inflammation [125], and based on surface phenotype, there is evidence that milk EV populations differ between sensitised and non-sensitised mothers and also between offspring that become sensitised or not [121]. Thus, transfer of EVs and miRNA may be another avenue by which the mother regulates offspring immune development, and could alter offspring predisposition to allergies. It is argued that small RNAs and extracellular vesicles are a mechanism for cross-species communication [126]. Helminth parasites are known to secrete EV and small RNAs that can downmodulate the hosts Type 2 immune responses [127], and small RNAs are one method helminth parasites use to manipulate their host [126]. Interestingly, bamboo miRNAs can be transferred from Giant Panda mothers to their offspring [128], indicating the potential for cross-species transfer of miRNA via breast milk. Thus, it is feasible that helminth parasites can manipulate neonatal immune development through the transfer of small RNAs, and is a potential mechanism by which maternal helminth infection can alter offspring susceptibility to infections, allergies, and vaccinations.

Movement of cells between mother and offspring: Microchimerism

Cellular exchange between mothers and offspring (Microchimerism: MC) has been recognised as a potentially important transgenerational relationship for some time; observations relating to fetal cell movement to mother can probably be traced to the late 19th century [129]. It is now well demonstrated that both fetomaternal (fMC) and maternofetal microchimersim (mMC) have important influences on both maternal and offspring health, this is comprehensively reviewed elsewhere e.g: [130, 131]. The effects of MC are driven by cells which occur at very low frequencies mMC, for example, is reported to occur at rates of between 1 in 10^{-5} to 1 in 10^{-7} offspring cells. This discrete nature of MC hampers deep insight into how discrete immune influences may promote or impair the level of fMC or mMC [131]. To the best of our knowledge, it not known how maternal type 2 immunity influences fMC or mMC. mMC has however been reported to occur at lower rates in asthmatic children, risk of maternal asthma was independent of MC [132]. Additionally, transfer of maternal immune cells to offspring via breast feeding has been shown to be strikingly reduced in offspring nursed on IL-4Ra-/- mothers [133]. This small number of existing studies addressing scenarios where maternal type 2 immunity may influence MC incidence does justify further focused work addressing this discrete axis of immune influence.

Microbiota

The composition of the maternal microbiome has significant and wide-ranging influence on offspring immunity [134]. Disruption of maternal microbiota, with (for example) non-absorbed antibiotic treatment of mother's changes offspring microbiota and immunity [135]. Moreover, maternal microbiota can be clearly influenced by an enhanced type 2 environment, such as a helminth infection and this maternal influence can also alter offspring microbiota and immunity [136]. A consequence of disruption of maternal microbiome in mice can also be increased

severity of ovalbumin induced allergy [137]. Studies addressing maternal microbiome and allergy have also demonstrated enrichment in the mother for bacteria that produce short chain fatty acids (SCFA) that protect against offspring allergy [132]. What a maternal type 2 immune bias may contribute to changes in microbial diversity that will alter risk of offspring allergy is not understood. However, in other non-infectious disease settings it has been reported that mothers with IBD can display a normalised microbiota and reduced pathology in second and third trimesters and this may associate with enhanced maternal Type 2 immunity [138].

Future

We know that maternal influences impact offspring immune development both transiently and more permanently. Studies are also revealing lasting impacts of this transfer of immunity on offspring type 2 immunity, and susceptibility to infection and diseases such as allergies. However, we do not currently fully understand the contexts and factors that determine whether the offspring favours immune sensitisation versus tolerance. For example, the lack of clear correlations between breast feeding and allergic outcomes suggests the involvement of an array of factors, and as yet we have only identified a few mechanisms by which foetal and neonatal immune programming occurs. These mechanisms have only been studied in isolation, and so we don't know which are dominant. We also don't know to what extent the presence or absence of type 2 immune responses influences the various mechanisms of offspring sensitisation and tolerance (summarised in Fig 1). If we can further elucidate the factors that determine whether maternal influences lead to tolerance versus sensitisation then there is the potential to begin to predict a child's future risk from infection and immune diseases. This could allow the identification of maternal risk factors, and of children that are at higher risk from infections and allergies in later life. Identification of risk factors could help the development of health policies and guidance related to pregnancy, such as exposure to allergies and anti-helminth treatments. Pregnancy-related immune therapies to reprogramme offspring immune development are a feature of medicine already in the form of maternal vaccination. However, targeting other arms of maternal immunity to influence maternal and offspring health is also a possibility for the future.

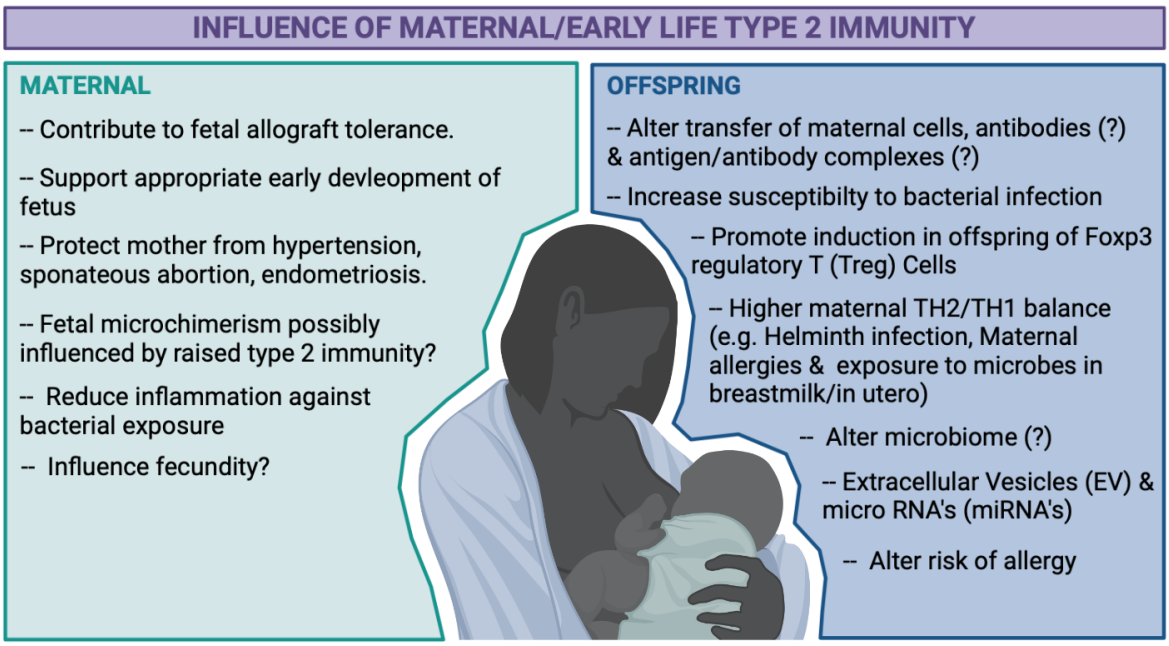

Fig 1: Summary of identified and potential influences of maternal and offspring type 2 immune bias on immunity.

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