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The Hygiene Hypothesis Revisited: Role of Materno-Fetal Interactions

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Abstract For 20 years, the hygiene hypothesis has dominated attempts to explain the increasing prevalence of allergic disease. A causal link between maternal innate immune response during pregnancy and disease protection in the offspring was recently demonstrated. Central to this was a systemically diffused signal that downregulated Toll-like receptor expression in placental tissues. Herein we develop the hypothesis that maternal systemic regulatory mechanisms operational during pregnancy could impact allergic disease risk of the offspring, depending on the type of inflammatory response from which they originate. Classic microbial-derived, mild, subacute inflammation provides a protective signal, whereas allergic inflammation provides a negative one. Mild, subacute inflammation of pregnant women leads to systemically diffused signals manifest in the gestation-associated tissues and by the fetus and newborn as a dampened inflammatory response. The converse is true if the mother has allergic inflammation during pregnancy. In both cases, these impact on development of the airways and of balanced immune function at birth and in early postnatal life. Thus, we seem to be at the dawn of a new incarnation of the hygiene hypothesis in which the pregnant woman's inflammatory response is crucial to determining the child's likelihood of developing allergic disease.

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Introduction

A large of body of epidemiologic data highlights the detrimental effects of maternal allergy on allergy and allergic disease development in the offspring. The mechanisms underlying this association are not well-understood but must operate during pregnancy and the immediate postpartum period. More recently, the prospect that the maternal immune response during pregnancy might also confer protection against disease development has been suggested [1••, 2]. The positive or negative impact of the maternal inflammatory response, be it classic microbial-driven inflammation or allergic inflammation, respectively, likely reflects systemically acting mediators released from inflamed maternal tissues that exert their effect at the materno-fetal interface. Understanding the relationship between the maternal immune response to various inflammatory stimuli, the gestation-associated cell and cytokine microenvironment, and development of the fetal immune system therefore is critical.

The Innate Immune Response

Much of the interest in the contribution of innate immunity to the initiation and even maintenance of allergy and allergic disease stems from the hygiene hypothesis (discussed in more detail below). The innate immune response is the first line of host defense against infection and other signals of danger. The pattern-recognition strategy of the

receptors that contribute to innate immunity is based on the detection of a limited set of conserved molecular patterns that are unique to the microbial world. The targets of pattern recognition, called *pathogen-associated molecular patterns*, signal to the host the presence of infection [3]. Pattern-recognition receptors form a number of families, including the well-known Toll-like receptor (TLR) family. TLRs signal inflammatory responses to lipopolysaccharide, lipoprotein, flagellin, and other bacterial and viral products. Lesser-known families include retinoic acid–inducible gene-1–like receptors, which signal responses to RNA viruses; NOD-like receptors, which are cytoplasmic receptors for bacterial products; and C-type lectin receptors, which are responsive to fungal products such as β-glucan [4•]. Pattern-recognition receptors are expressed by cells involved in innate immunity and enable recognition of invading microbes and initiation of antimicrobial activity characterized by production of pro- and anti-inflammatory mediators. The innate immune system does not operate in isolation, and recent years have been witness to a growing appreciation of the interaction between the innate and adaptive immune response.

Brief History of the Hygiene Hypothesis

More than 20 years have passed since the inverse association between family size and birth order and the risk of developing allergy and allergic disease was first highlighted [5]. This observation led to the formulation of the *hygiene hypothesis*, which has remained a prominent candidate to explain the increasing prevalence of allergic diseases such as eczema, food allergy, hay fever, and asthma. Although the basic tenet has remained much the same—that the host response to foreign antigens has changed as a consequence of alterations in the nature, timing, or dose of microbial signals received postnatally or even prenatally—our understanding of the mechanism(s) that might underlie this association have changed in pace with developments in the wider field of immunology. Initially, the immunologic mechanism postulated to underpin the hygiene hypothesis was the downregulation of development of T-helper type 2 (Th2)-skewed immunologic memory against allergens as a consequence of the ability of infectious organisms to favor Th1 reactivity. The current incarnation of the hypothesis relates to the role of the innate immune response in controlling immunoregulatory mechanisms and suggests that microbial signals of noninfectious origin regulate the induction and expression of immune responsiveness in early life. As a consequence, deficiencies in this signalling underlie the increasing prevalence of allergic (and other) diseases.

The hygiene hypothesis has at its foundation the so-called sibling effect—that the prevalence of allergic disease is lower in children from larger families. Notably, although the effect of family size was seen for both the number of older and younger siblings, the protective effect was stronger for older siblings [5]. This highlights a shortcoming of the birth order and allergic outcomes literature: authors variably relate their outcome measures to birth order, number of siblings, family size, number of older siblings, number of younger siblings, number of brothers, and even just having an older brother. However, family size may be an indirect measure of some as-yet-undetermined biologically relevant factor(s) that increases with family size and in other environments associated with a low prevalence of allergic disease [6].

Initially, the focus of epidemiologic and laboratory-based studies related to the hygiene hypothesis was the postnatal period. This was based on the postulate that older siblings transmit infections to younger siblings earlier in life, providing protection against the development of allergic disease. This progressed into consideration of a broad range of environmental sources that provide or modify patterns of microbial exposure in infancy, particularly those that might have changed during the second half of the 20th century. This list includes the use of day care, vaccinations, and antibiotics. Transitions in the ongoing evolution of the hygiene hypothesis are summarized in Table 1. Most attention has been on the child, especially in the first 2 years of life. However, other more pregnancy/maternally focused formulations of the hygiene hypothesis have to a much lesser extent also been considered: 1) the maternal microbial burden changes with each pregnancy that results in a live birth (with each successive child increasing this burden) [7]; 2) hormonal and other changes in each pregnancy differentially affect the mother's own allergic disease [8]; 3) maternal reactivity against paternal HLA antigens increases with each pregnancy and impacts on the responses of her immune system to each successive offspring, assuming the father, and therefore the HLA to which the mother responds, remains the same; and 4) pregnancy has a long-term effect on general immune function of women. Any associated changes in maternal immune function during pregnancy are postulated to impact on the developing fetal immune system, with downstream consequences for the development of allergic disease. There is, however, a paucity of studies that consider these alternative, non–mutually exclusive mechanisms. The need for a better understanding of the pregnant woman's interaction with nonpathogenic inflammatory stimuli has been highlighted by a recently published study exploring the mechanism whereby maternal prenatal exposure to a farming environment confers protection against development of allergy and allergic disease [1••, 2].

Table 1 The four major transitions in the ongoing evolutionary process of the hygiene hypothesis since its inception in 1989

HH generation	Data	Interpretation	Key references
HH Mark 1	Children with multiple older siblings display reduced risk of allergic disease	Shared infections among children within large families attenuate atopy risk	[5]
HH Mark 2	Slow postnatal Th1 maturation elevates Th2-dependent atopy risk	Signals from gut bacterial commensals protect against atopic disease by controlling Th1/Th2 balance; severe respiratory viral infections promote development of atopic asthma	[59]
	Gut microbiota drives normal maturation of Th1 competence		[60]
	Gut colonization patterns in early infancy modulate atopy risk		[60–62]
	Severe respiratory infections in infancy increase atopic asthma risk		[63, 64]
HH Mark 3	Prevalence of autoimmune disease starts to show comparable increases	The problem involves overall immunoregulation, T-regulatory and/or dendritic cell malfunction?	[65, 66]
HH Mark 4	Prenatal maternal microbial exposures also attenuate disease risk in offspring	The "trajectory" of postnatal immune function development is partially set in utero	[1••, 23, 67, 68]

HH hygiene hypothesis; *Th* T-helper cell

The Farming Environment

The benefits of an early childhood spent on a farm have been demonstrated in many countries and include a reduction in atopic sensitization/skin prick test reactivity, hay fever, asthma, and wheeze but less often eczema in children [9–12]. The benefits of farming seem to relate to the presence of livestock, especially barns and stables, and the consumption of unpasteurized milk or farm butter. Full-time farming offers the greatest protection, with lifelong exposure conferring protection into adulthood [12, 13]. The reproducibility of the protective effect of farming has led to attempts to define the critical component in this environment. Elevated levels of bacterial endotoxins and other microbial products such as mold glucans and fungal extracellular polysaccharides are a feature of farming households, barns, and stables [14, 15]. During feeding in the winter months, pollen levels inside barns exceed those typically measured outdoors during the pollen season [16]. Several studies have identified farm-derived bacterial species with potential allergy protective effects. Microorganisms identified to date include *Bacillus licheniformis* (spores), *Acinetobacter lwoffi*, and *Lactococcus lactis*. All these have been shown to favor Th1 responses in human adult peripheral blood mononuclear cells in vitro and to alleviate the symptoms of allergic airways disease such as eosinophilia and goblet cell hyperplasia in animal models [17–19].

The observation that prenatal exposure of the mother to the farm environment is crucial to the protective effect has led to studies of the impact of such exposure on immune function of the newborn. These studies used umbilical cord blood to reveal increased number and function of natural regulatory T cells in newborns of farm-exposed mothers [20•] and increased mitogen-stimulated interferon (IFN)-γ and tumor necrosis factor (TNF)-α, but not interleukin (IL)-5, IL-10, and IL-12, by cord blood mononuclear cells from newborns of farm-exposed mothers [21•]. In the latter study, maternal contact with different animal species and barns and the consumption of farm-produced butter during pregnancy enhanced IFN-γ and TNF-α production at birth. Longer-term impact on the immune function of the child is suggested by the observation that the children of farmers have elevated gene expression of key receptors involved in innate immune signalling, such as CD14, TLR2, and TLR4, compared with children of nonfarmers [22]. As each additional farm species to which the mother was exposed during pregnancy increased the expression of these receptors by the child, it is probable that these expression patterns are programmed during fetal development [23].

Given the emerging importance of maternal prenatal exposures from both epidemiologic and experimental studies, a murine model was established to identify possible mechanisms underlying this [1••]. Maternal intranasal exposure to *A. lwoffi* protected the offspring against the development of experimental allergic asthma, with reduced eosinophils, goblet cells, and mucin but no change in specific IgE. There was evidence of local airways and systemic inflammation in the mothers, including rapid elevation of IL-6 in the circulation and increased expression of various TLRs and proinflammatory cytokines in the lungs. In contrast, TLR expression in placental tissues was downregulated, an effect that could be mimicked by exposing in vitro placental cell cultures to IL-6. If the mother's ability to mount an inflammatory response was abrogated by knocking out multiple TLRs (TLR2, TLR3, TLR4, TLR7, and TLR9 in this case), the asthma protective effect in the progeny was lost. This study is the first to establish a causal link between maternal prenatal exposure, the maternal innate immune response, and disease protec-

tion in the offspring; further studies are required in similar models as well as in humans.

The systemic diffusion of maternally derived signals that exert tissue-specific effects within the uteroplacental unit warrants further investigation. As most pregnant women do not have the good fortune of living and working on a farm, the impact of other microbial exposures such as endotoxins and mold glucans that are present in many homes should be considered. However, this phenomenon provides a potential common pathway for exerting a negative or positive effect on disease risk in the offspring in association with maternal health status.

Allergy as a Systemic Disease

Most of the data from ex vivo analysis of tissue biopsies after natural allergen exposure or in vivo allergen challenge, as well as peripheral blood and animal studies support a common systemic pathway linking the affected tissue site to the bone marrow via the blood. Nasal and lung biopsies from those with allergic airways disease contain more dendritic cells (DCs) than biopsies from those without disease, and seasonal fluctuations have been documented [24, 25]. This increase in DC numbers in affected tissues is matched by a decrease in blood DCs within 3 h of inhaled allergen challenge, which is sustained for at least 24 h [26]. During acute, severe atopic asthma exacerbations, the numbers of bone marrow–derived myeloid cells (monocytes and DCs) bearing the high-affinity IgE receptor (FcεRI) increase 10- to12-fold [27]. Moreover, expression of FcεRI on Langerhans cells in the uninvolved skin of not only those with active atopic dermatitis but also those with active asthma or active rhinitis provides further support for systemic regulatory mechanisms operative during active allergic disease [28]. Similarly, both upper and lower allergic airways disease are characterized by eosinophilic and basophilic inflammation, reflecting a systemically active process whereby progenitor cells are recruited from the bone marrow to allergically inflamed tissue via the blood [29].

Maternal systemic regulatory mechanisms related to mild subclinical inflammation or active allergic disease during pregnancy could have two potential effects: 1) systemically released mediators could cross the placenta and impact on fetal bone marrow; and 2) cells, especially myeloid cells (eg, monocytes and DCs), released into the maternal circulation from the maternal bone marrow in response to systemically acting mediators could populate the maternally derived tissues, namely the decidua, at the materno-fetal interface. In support of the first possibility, a correlation between maternal and fetal eotaxin has been observed [30], and cord blood eotaxin is significantly elevated in pregnancies complicated by asthma [31]. The ability of eotaxin and other mediators to traverse the placenta should be explored. Secondary to this, several studies highlight that differences in the relative abundance and/or phenotype of eosinophil/basophil progenitors or DC subsets at birth (umbilical cord blood) can be related to maternal atopic status or to disease in childhood [32–34]. Surprisingly little is known about how maternal tissue–specific and/or systemic inflammation impacts on the gestation-associated tissues or the fetus. As the systemically diffused signals of interest originate from the mother, any attempt to study the maternal inflammatory cascade during pregnancy must take into account the changes in immune function that characterize normal pregnancy.

Maternal Immune Response During Pregnancy

Although there are examples of impaired responses to infectious agents in pregnant women, the concept of immune suppression during pregnancy has been superseded by one of active maternal immunologic tolerance of fetal cells. Many immunologic mechanisms to explain this have been postulated and reviewed extensively elsewhere. In the context of the above discussion, consideration of changes in the innate immune response and inflammation are of greatest importance (although this does not preclude other pathways). It is also worth noting that a number of discrete but interacting compartments need to be considered: the embryonically derived placenta, the embryonically derived amnion and chorion that form the placental/fetal membranes, the maternally derived decidua (lining of uterus/endometrium of pregnancy), amniotic fluid, the fetus itself, and systemic maternal immune function. Mammary gland development and breast milk could also fit under this umbrella. Temporal differences in activity within these different compartments also need to be taken into account (eg, implantation vs parturition). However, for the purposes of this overview, the site of contact between maternal and fetal cells is of particular importance, with two main sites of interaction to consider: that between maternal decidua and trophoblast in the nonplacental bed and that between syncytiotrophoblast on the surface of placental villi and cells in the maternal circulation (Table 2) [35].

Table 2 Two pathways by which maternally derived, systemically diffused inflammatory signature might impact on the fetus

1.	Systemically released mediators cross the placenta and impact on the fetal bone marrow.
2.	Cells that efflux from the maternal bone marrow in response to systemically released mediators take up residence in the decidua or occupy the intervillous blood space.

Well-controlled inflammation has a physiologic role in implantation, the maintenance of pregnancy, and parturition, and aberrantly regulated inflammation contributes to adverse outcomes in fertility as well as pregnancy. The systemic inflammatory response is heightened in pregnant women [36, 37]; this includes increased white blood cell count and increased levels of C-reactive protein and other acute-phase proteins [38], and these tend to increase during gestation. The enhanced systemic inflammatory response during pregnancy is postulated to be driven by placenta-derived particulate debris and/or soluble products that enter the maternal circulation [35]. These placenta-derived microparticles can be found attached to circulating monocytes and free in the circulation from the second and increasing into the third trimester. Placental microparticles isolated in vitro from the placenta can induce an inflammatory response in nonpregnant women [36]. Given the increasing interest in endogenous danger-associated molecular patterns [39], it is feasible that additional stimuli of the low-grade systemic inflammation that characterizes healthy pregnancy will be revealed. However, whereas the human placenta expresses TLR1 through TLR10 [40], little is known about how the expression and/or function of TLRs and other pattern-recognition receptors either systemically or within gestation-associated tissues might be modulated by maternal inflammatory activity during pregnancy.

Those who study allergy and allergic disease are familiar with the notion of Th1 and Th2 and the prototypic patterns of cytokine production that define these phenotypes. Despite the lack of convincing data from humans and the observation that mice lacking expression of the main Th2 cytokines IL-4, IL-5, IL-9, and IL-13 (ie, quadruple knockouts) do not have fertility problems, even during allogeneic pregnancy [41], the concept that a Th2-biased immune response prevails during pregnancy has dominated the immunology literature for many years. Initial investigations of the Th1/Th2 balance in pregnancy focused on T cells themselves, but the materno-fetal interface itself is relatively devoid of T cells, and the paradigm evolved to encompass type 1 and type 2 cytokines irrespective of their cell source. These can include natural killer cells and the gestation-associated tissues themselves [35, 42]. However, an appreciation of the temporal and spatial variation in the balance between type 1 and type 2 responses depending on the tissue site and stage of pregnancy has emerged. Other T-cell subsets, namely regulatory T cells and Th17 cells, are also of interest, and it has been suggested that homeostasis between regulatory and proinflammatory $CD4^+$ T-cell subsets may be pivotal for maternal immune tolerance to fetal antigen [43].

Impact of Maternal Allergy on Immune Function During Pregnancy

Despite the well-known relationship between maternal allergy and increased allergic disease risk in the offspring, little is known about how pregnancy impacts on the maternal allergic response. The possibility that active allergic disease during pregnancy impacts on the phenotype and function of maternal cells that reside at the materno-fetal interface has not been studied extensively. Understanding how the allergic response might change during pregnancy is critical if we are to elucidate how maternal disease impacts on fetal immune system development. A Th2-biased response to allergen seems to be retained in pregnancy: 1) pollen allergic women with detectable pollen-specific IgE have a Th2-skewed response to pollen allergens (Timothy grass/birch) [44]; and 2) allergen-specific and mitogen-induced IFN-γ decreases during pregnancy in atopic and nonatopic women, whereas allergen-specific IL-13 declines in nonatopic women only [45]. The relative blood eosinophilia that characterizes allergy also occurs in asthmatic pregnant women despite an apparent decline in eosinophil numbers during pregnancy [46]. Maternal allergy modifies alloresponses by the mother, which may impact on the cytokine milieu at the materno-fetal interface and thereby fetal immune development [47, 48]. Pregnancy is well-documented to affect the course of maternal asthma, and maternal asthma in turn increases the risk of adverse pregnancy outcomes and affects fetal growth and survival. There is a great deal of interest in how pregnancy-derived factors might impact on epithelial cells in the mother's own airways.

The downstream implications of the above observations are unclear but do highlight that a different maternal environment is provided by allergic and/or asthmatic women compared with nonallergic/nonasthmatic women. Few studies have directly examined the materno-fetal interface in relation to maternal allergy/allergic disease. Decidual cytokine (IL-4, IL-5, IL-10, IL-13, or IFN-γ) production does not differ in allergic versus nonallergic women. However, a significant positive correlation between IFN-γ production by decidual mononuclear cells and that by umbilical cord blood mononuclear cells was found [49]. Notably, reduced IFN-γ production at birth has been repeatedly, although not always, associated with maternal/family history of allergic disease and/or allergic disease outcomes in infancy. Maternal moderate or severe asthma has been associated with changes in placental vascular function and placental histomorphology as early as 18 weeks of gestation and in placental cytokine gene expression at term [50, 51]. These changes were postulated to affect inflammatory and thereby angiogenic pathways in the placenta.

Positive and Negative Impact of Maternal Inflammatory Response During Pregnancy

From the above observations, the hypothesis that maternal systemic regulatory mechanisms operational during pregnancy could have a positive or negative impact on allergic disease risk in the offspring emerges. Central to this are maternal myeloid cells released from the bone marrow in response to systemically distributed activation signals emanating from site(s) of maternal inflammation, similar to the mechanism described in viral-induced asthma exacerbations [27]. In addition to trafficking to the inflamed tissue from which the signal is transmitted, these cells might traffic to the materno-fetal interface [2]. The decidua is the main site of maternal cells that are in intimate contact with fetally derived cells. Macrophages and DCs are scattered throughout the decidua. In contrast, the healthy decidua is relatively devoid of other myeloid populations, namely granulocytes, and lymphoid cells. Decidual macrophages and DCs are postulated to have a role in tissue remodelling and angiogenesis during placental invasion and an immunoregulatory role in the pregnant uterus.

Macrophages make up about 30% of decidual leukocytes in the first and second trimester, and although numbers decline in the third trimester, macrophages still make up about 20% of decidual cells [52]. First trimester decidual macrophages have a gene expression profile reminiscent of alternatively activated macrophages, suggesting an immunosuppressive phenotype [43]. Chemokines produced by the gestation-associated tissues have been postulated to have a role in recruiting monocytes to the decidua, where local environmental factors drive polarization to alternatively activated macrophages. IL-4 and IL-13 favor the development of alternatively activated macrophages [53], although in the one study that attempted to identify the uteroplacental environment that might drive the development of decidual macrophages, IL-4 and/or IL-13 were not considered [54]. Decidual cells secrete a host of cytokines, including IL-1, IL-4, IL-5, IL-10, IL-13, IFN-γ, TNF-α, and transforming growth factor-β [42, 49], and are also responsive to IL-4 [42].

During the first trimester, the abundance of myeloid DCs is greater than in peripheral blood, whereas the abundance of plasmacytoid DCs is less than in peripheral blood [55]. Decidual DCs can stimulate a mixed lymphocyte reaction, but this is reduced compared with blood DCs [56], and there are fewer IL-12p70–producing DCs in the decidual than in the blood DC population [55]. Furthermore, co-culture of decidual myeloid DCs with naïve T cells favors Th2 responses, which are abolished by addition of endogenous IL-12 [57]. In a murine model, DCs at the materno-fetal interface are prevented from migrating to the draining lymph nodes for at least the first half of pregnancy [58]. This is postulated to minimize exposure of maternal immunogenic T cells to fetal/placental antigen; the mechanism of this defect is unknown but might include anti-inflammatory cytokines produced at this site.

In the above, the focus has been on maternal myeloid cells in the decidua. However, the other site of contact between maternal and fetal cells is that between the mother's circulating leukocytes and trophoblast—either intact trophoblast as the surface of chorionic villi, or systemically with placental trophoblast debris [35]. There are practical challenges to studying the maternal leukocytes in the intervillous space, but such studies would be worthwhile to pursue.

Conclusions

In Fig. 1, we have attempted to provide a scheme that draws together the potential effects of persistent, mild, subclinical inflammation versus allergic inflammation in the mother on the tissues at the materno-fetal interface itself as well as the fetus, and subsequently the newborn. In the scheme shown, we posit that a persistent state of mild subclinical inflammation during pregnancy that lacks a dominant Th2 signature, which from an evolutionary perspective was probably the norm in climatically temperate environments, triggers a maternally derived "protective" response. This response takes the form of a dampening of

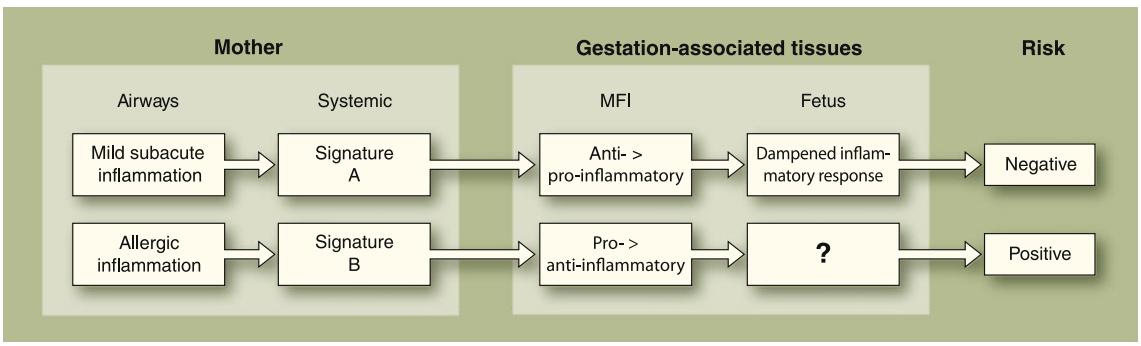

Fig. 1 The systemically distributed inflammatory signature of pregnancy differs with classical versus allergic airways inflammation. This imparts a message at the materno-fetal interface (MFI) that alters the pro- versus anti-inflammatory balance at this site, modifying fetal immune development, and thereby allergy and allergic disease risk

mechanisms/pathways operative in tissues at the materno-fetal interface that may lead to excessive local inflammation in that sensitive microenvironment. Excessive inflammation at the materno-fetal interface would be detrimental to the development of fetal tissues, including the airways, and may also have a negative impact on the maturation of balanced immune function within the fetus. The mother's own low-grade systemic inflammatory response typical of healthy pregnancy would also prime her for a rapid response to any danger signals, such as microbial stimuli, but also paternally derived HLA. An overzealous response to such stimuli would potentially lead to premature delivery of the baby and the associated morbidity and mortality of preterm birth. We propose that this risk is counterbalanced by the dampening of inflammatory mechanisms at the materno-fetal interface, which would serve to attenuate any such responses by the gestation-associated tissues themselves or by the fetus. Such a mechanism would, as a consequence, also help set the "tonus" of immune function within the immune system of the offspring at the time of birth, and hence contribute to the subsequent trajectory of postnatal maturation of immune competence.

The contrasting pattern in Fig. 1, in which the mother experiences ongoing allergic inflammation during pregnancy, might instead mimic (in an evolutionary sense) the tropical environment in which parasitic infestation poses a major threat to the mother, fetus, and newborn alike. In such a situation, it seems logical that selective enhancement or priming of parasite-antagonistic Th2 immunity during immune development in the offspring would carry a survival advantage. However, translocating the latter to a parasite-free environment might "open the allergy floodgates" as the relatively Th2-polarized immune system of such offspring mistakenly turns its attention toward nonparasitic antigens.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. •• Conrad ML, Ferstl R, Teich R, et al.: Maternal TLR signaling is required for prenatal asthma protection by the nonpathogenic microbe Acinetobacter lwoffii F78. J Exp Med 2009, 206:2869–2877. *This is the first evidence linking exposure to an organism identified in the farming environment to maternal exposure during pregnancy and protection of the progeny against the development of allergic airways inflammation; a role for TLR expression in the placenta is suggested*.
2. Holt PG, Strickland DH: Soothing signals: transplacental transmission of resistance to asthma and allergy. J Exp Med 2009, 206:2861–2864.
3. Janeway CA Jr, Medzhitov R: Innate immune recognition. Annu Rev Immunol 2002, 20:197–216.
4. • Takeuchi O, Akira S: Pattern recognition receptors and inflammation. Cell 2010, 140:805–820. *This is a comprehensive and recent review of the different families of pattern-recognition receptors*.
5. Strachan DP: Hay fever, hygiene, and household size. BMJ 1989, 299:1259–1260.
6. Strachan DP: Family size, infection and atopy: the first decade of the "hygiene hypothesis." Thorax 2000, 55(Suppl 1):S2–S10.
7. Hersoug LG: A reformulation of the hygiene hypothesis: maternal infectious diseases confer protection against asthma in the infant. Med Hypotheses 2006, 67:717–720.
8. Rangaraj S, Doull I: Hormones not hygiene? Birth order and atopy. Clin Exp Allergy 2003, 33:277–278.
9. Braun-Fahrlander C, Gassner M, Grize L, et al.: Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. SCARPOL team. Swiss Study on Childhood Allergy and Respiratory Symptoms With Respect to Air Pollution. Clin Exp Allergy 1999, 29:28–34.
10. Klintberg B, Berglund N, Lilja G, et al.: Fewer allergic respiratory disorders among farmers' children in a closed birth cohort from Sweden. Eur Respir J 2001, 17:1151–1157.
11. Riedler J, Eder W, Oberfeld G, et al.: Austrian children living on a farm have less hay fever, asthma and allergic sensitization. Clin Exp Allergy 2000, 30:194–200.
12. Von Ehrenstein OS, Von Mutius E, Illi S, et al.: Reduced risk of hay fever and asthma among children of farmers. Clin Exp Allergy 2000, 30:187–193.
13. Douwes J, Travier N, Huang K, et al.: Lifelong farm exposure may strongly reduce the risk of asthma in adults. Allergy 2007, 62:1158–1165.
14. Perkin MR, Strachan DP: Which aspects of the farming lifestyle explain the inverse association with childhood allergy? J Allergy Clin Immunol 2006, 117:1374–1381.
15. Schram D, Doekes G, Boeve M, et al.: Bacterial and fungal components in house dust of farm children, Rudolf Steiner school children and reference children—the PARSIFAL study. Allergy 2005, 60:611–618.
16. Sudre B, Vacheyrou M, Braun-Fahrlander C, et al.: High levels of grass pollen inside European dairy farms: a role for the allergy-protective effects of environment? Allergy 2009, 64:1068–1073.
17. Debarry J, Garn H, Hanuszkiewicz A, et al.: Acinetobacter lwoffii and Lactococcus lactis strains isolated from farm cowsheds possess strong allergy-protective properties. J Allergy Clin Immunol 2007, 119:1514–1521.
18. Vogel K, Blumer N, Korthals M, et al.: Animal shed Bacillus licheniformis spores possess allergy-protective as well as inflammatory properties. J Allergy Clin Immunol 2008, 122:307–312.
19. Debarry J, Hanuszkiewicz A, Stein K, et al.: The allergy-protective properties of Acinetobacter lwoffii F78 are imparted by its lipopolysaccharide. Allergy 2010, 65:690–697.
20. • Schaub B, Liu J, Hoppler S, et al.: Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. J Allergy Clin Immunol 2009, 123:774.e5–782.e5. *This article explores potential mechanisms of the beneficial effect of the farming environment and suggests a role for natural regulatory T cells*.
21. • Pfefferle PI, Buchele G, Blumer N, et al.: Cord blood cytokines are modulated by maternal farming activities and consumption of farm dairy products during pregnancy: the PASTURE study. J Allergy Clin Immunol 2010, 125:108.e1-3–115.e1-3. *This article explores impact of the farming environment on cytokine responses at birth*.

22. Lauener RP, Birchler T, Adamski J, et al.: Expression of CD14 and Toll-like receptor 2 in farmers' and non-farmers' children. Lancet 2002, 360:465–466.
23. Ege MJ, Bieli C, Frei R, et al.: Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children. J Allergy Clin Immunol 2006, 117:817–823.
24. Robays LJ, Maes T, Lebecque S, et al.: Chemokine receptor CCR2 but not CCR5 or CCR6 mediates the increase in pulmonary dendritic cells during allergic airway inflammation. J Immunol 2007, 178:5305–5311.
25. Till SJ, Jacobson MR, O'Brien F, et al.: Recruitment of CD1a+ Langerhans cells to the nasal mucosa in seasonal allergic rhinitis and effects of topical corticosteroid therapy. Allergy 2001, 56:126–131.
26. Upham JW, Denburg JA, O'Byrne PM: Rapid response of circulating myeloid dendritic cells to inhaled allergen in asthmatic subjects. Clin Exp Allergy 2002, 32:818–823.
27. Subrata LS, Bizzintino J, Mamessier E, et al.: Interactions between innate antiviral and atopic immunoinflammatory pathways precipitate and sustain asthma exacerbations in children. J Immunol 2009, 183:2793–2800.
28. Semper AE, Heron K, Woollard AC, et al.: Surface expression of Fc epsilon RI on Langerhans' cells of clinically uninvolved skin is associated with disease activity in atopic dermatitis, allergic asthma, and rhinitis. J Allergy Clin Immunol 2003, 112:411–419.
29. Denburg JA, Keith PK: Eosinophil progenitors in airway diseases: clinical implications. Chest 2008, 134:1037–1043.
30. Rastogi D, Wang C, Lendor C, et al.: T-helper type 2 polarization among asthmatics during and following pregnancy. Clin Exp Allergy 2006, 36:892–898.
31. Osei-Kumah A, Smith R, Clifton VL: Maternal and cord plasma cytokine and chemokine profile in pregnancies complicated by asthma. Cytokine 2008, 43:187–193.
32. Fernandes R, Kusel M, Cyr M, et al.: Cord blood hemopoietic progenitor profiles predict acute respiratory symptoms in infancy. Pediatr Allergy Immunol 2008, 19:239–247.
33. Upham JW, Hayes LM, Lundahl J, et al.: Reduced expression of hemopoietic cytokine receptors on cord blood progenitor cells in neonates at risk for atopy. J Allergy Clin Immunol 1999, 104:370–375.
34. Upham JW, Zhang G, Rate A, et al.: Plasmacytoid dendritic cells during infancy are inversely associated with childhood respiratory tract infections and wheezing. J Allergy Clin Immunol 2009, 124:707.e2–713.e2.
35. Sargent IL, Borzychowski AM, Redman CW: NK cells and human pregnancy—an inflammatory view. Trends Immunol 2006, 27:399–404.
36. Germain SJ, Sacks GP, Sooranna SR, et al.: Systemic inflammatory priming in normal pregnancy and preeclampsia: the role of circulating syncytiotrophoblast microparticles. J Immunol 2007, 178:5949–5956.
37. Zhao J, Lei Z, Liu Y, et al.: Human pregnancy up-regulates Tim-3 in innate immune cells for systemic immunity. J Immunol 2009, 182:6618–6624.
38. Miller EM: Changes in serum immunity during pregnancy. Am J Hum Biol 2009, 21:401–403.
39. Lotze MT, Zeh HJ, Rubartelli A, et al.: The grateful dead: damage-associated molecular pattern molecules and reduction/oxidation regulate immunity. Immunol Rev 2007, 220:60–81.
40. Patni S, Wynen LP, Seager AL, et al.: Expression and activity of Toll-like receptors 1-9 in the human term placenta and changes associated with labor at term. Biol Reprod 2009, 80:243–248.
41. Fallon PG, Jolin HE, Smith P, et al.: IL-4 induces characteristic Th2 responses even in the combined absence of IL-5, IL-9, and IL-13. Immunity 2002, 17:7–17.
42. Jones CA, Finlay-Jones JJ, Hart PH: Type-1 and type-2 cytokines in human late-gestation decidual tissue. Biol Reprod 1997, 57:303–311.
43. Gustafsson C, Mjosberg J, Matussek A, et al.: Gene expression profiling of human decidual macrophages: evidence for immunosuppressive phenotype. PLoS One 2008, 3: e2078.
44. Rindsjo E, Joerink M, Johansson C, et al.: Maternal allergic disease does not affect the phenotype of T and B cells or the immune response to allergens in neonates. Allergy 2010, 65:822–830.
45. Breckler LA, Hale J, Jung W, et al.: Modulation of in vivo and in vitro cytokine production over the course of pregnancy in allergic and non-allergic mothers. Pediatr Allergy Immunol 2010, 21:14–21.
46. Osei-Kumah A, Wark PA, Smith R, et al.: Asthma during pregnancy alters immune cell profile and airway epithelial chemokine release. Inflamm Res 2010, 59:349–358.
47. Breckler LA, Hale J, Taylor A, et al.: Pregnancy IFN-gamma responses to foetal alloantigens are altered by maternal allergy and gravidity status. Allergy 2008, 63:1473–1480.
48. Prescott SL, Breckler LA, Witt CS, et al.: Allergic women show reduced T helper type 1 alloresponses to fetal human leucocyte antigen mismatch during pregnancy. Clin Exp Immunol 2010, 159:65–72.
49. Brown M, Gustafson M, Saldana S, et al.: Correlation of human decidual and cord blood mononuclear cell cytokine production. Hum Immunol 2004, 65:1336–1343.
50. Clifton VL, Murphy VE: Maternal asthma as a model for examining fetal sex-specific effects on maternal physiology and placental mechanisms that regulate human fetal growth. Placenta 2004, 25(Suppl A):S45–S52.
51. Scott NM, Hodyl NA, Murphy VE, et al.: Placental cytokine expression covaries with maternal asthma severity and fetal sex. J Immunol 2009, 182:1411–1420.
52. Williams PJ, Searle RF, Robson SC, et al.: Decidual leucocyte populations in early to late gestation normal human pregnancy. J Reprod Immunol 2009, 82:24–31.
53. Gordon S: Alternative activation of macrophages. Nat Rev Immunol 2003, 3:23–35.
54. McIntire RH, Ganacias KG, Hunt JS: Programming of human monocytes by the uteroplacental environment. Reprod Sci 2008, 15:437–447.
55. Ban YL, Kong BH, Qu X, et al.: BDCA-1+, BDCA-2+ and BDCA-3+ dendritic cells in early human pregnancy decidua. Clin Exp Immunol 2008, 151:399–406.
56. Kammerer U, Schoppet M, McLellan AD, et al.: Human decidua contains potent immunostimulatory CD83(+) dendritic cells. Am J Pathol 2000, 157:159–169.
57. Miyazaki S, Tsuda H, Sakai M, et al.: Predominance of Th2-promoting dendritic cells in early human pregnancy decidua. J Leukoc Biol 2003, 74:514–522.
58. Collins MK, Tay CS, Erlebacher A: Dendritic cell entrapment within the pregnant uterus inhibits immune surveillance of the maternal/fetal interface in mice. J Clin Invest 2009, 119:2062–2073.
59. Holt PG, Clough JB, Holt BJ, et al.: Genetic 'risk' for atopy is associated with delayed postnatal maturation of T-cell competence. Clin Exp Allergy 1992, 22:1093–1099.
60. Adlerberth I, Wold AE: Establishment of the gut microbiota in Western infants. Acta Paediatr 2009, 98:229–238.
61. Björkstén B: Effects of intestinal microflora and the environment on the development of asthma and allergy. Springer Semin Immunopathol 2004, 25:257–270.
62. Rook GA, Stanford JL: Give us this day our daily germs. Immunol Today 1998, 19:113–116.

63. Holt PG, Upham JW, Sly PD: Contemporaneous maturation of immunologic and respiratory functions during early childhood: implications for development of asthma prevention strategies. J Allergy Clin Immunol 2005, 116:16–24.
64. Sly PD, Boner AL, Bjorksten B, et al.: Early identification of atopy in the prediction of persistent asthma in children. Lancet 2008, 372:1100–1116.
65. Bach JF: The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002, 347:911–920.
66. Basten A, Fazekas de St Groth B: Special regulatory T-cell review: T-cell dependent suppression revisited. Immunology 2008, 123:33–39.
67. von Mutius E, Radon K: Living on a farm: impact on asthma induction and clinical course. Immunol Allergy Clin North Am 2008, 28:631–47.
68. Macaubas C, de Klerk NH, Holt BJ, et al.: Association between antenatal cytokine production and the development of atopy and asthma at age 6 years. Lancet 2003, 362:1192–1197.