

The Maturation of the Fetal and Neonatal Immune System^{1,2}

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Abstract

The prevalence of allergic diseases has risen markedly since the 1960s, particularly in the developed countries of the Western world. These diseases manifest initially during infancy and childhood and are apparently becoming more persistent in successive birth cohorts. The importance of genetic susceptibility in the disease process is widely recognized, and it is further recognized that the ultimate expression of the disease is the result of complex interactions between genetic and environmental factors, with nutrition representing 1 main variable, neither of which have yet been comprehensively characterized. There is increasing evidence that the level of complexity inherent in the pathogenesis of allergic diseases may be even greater than is currently contemplated, as an additional set of crucial factors appear to be involved. Notably, it appears likely that the ultimate effects of the "gene-environment" interaction within individuals may also be related to the developmental status of the relevant target tissues at the time the interactions occur. Examples of the latter, discussed below, are elements of innate and adaptive immune function and aspects of food allergy and of airway function relevant to atopic asthma. J. Nutr. 138: 1773S–1781S, 2008.

Immune function during fetal life

The initial stage of hematopoiesis in the human fetus occurs in extraembryonic mesenchymal tissue and in the mesoderm of the yolk sac, and pluripotent erythroid and granulomacrophage progenitors are detectable in the latter at around wk 4 of gestation. These cells appear subsequently in the fetal circulation and by wk 5 to 6 in the liver, which at that stage of development is the major site of hematopoiesis. The spleen and thymus are seeded from the liver, and by wk 8 of development, CD7⁺ precursor cells are found in the thymus (1–3); hematopoietic stem cells do not appear in bone marrow until around wk 12 of gestation (4). T cells recognizable by expression of characteristic T-cell receptor (TcR)³/CD3 are found in peripheral lymphoid organs from wk 13 to 15 of gestation onward (5–7), despite the lack of well-defined thymic cortical and medullary regions and mature epithelial components (1). These early T cells also express CD2 (adhesion function) and CD5 (also expressed in

young B cells) (2). The maturation of nonlymphoid components within peripheral lymphoid tissues progresses even more slowly and takes up to 20 wk (7–10).

It is feasible that the fetal gastrointestinal tract may be an additional site for extrathymic T-cell differentiation in the human fetus, as has been reported in the mouse (11). T cells are detectable in the intestinal mucosa by 12 wk of gestation (12), and many of these express the CD8 $\alpha\alpha$ phenotype, in particular within Peyer's patches (13). In the mouse, CD8 $\alpha\alpha$ cells appear to be thymus independent and are believed to develop in the gut. Although there is no direct evidence for this in humans, it is noteworthy initially that fetal gut lamina propria lymphocytes are an actively proliferating population as indicated by constitutive expression of Ki67, and there is little or no overlap between gut-derived and blood-derived TcR β transcripts (14).

The gut mucosa may also be a major site for differentiation of TcR γ/δ cells during fetal life. Rearranged TcR γ genes are first detectable in the gut at 6 to 9 wk of gestation (15), which is earlier than they are observed in the thymus. The liver is another important extrathymic site for TcR γ/δ differentiation in humans, including a unique subset expressing CD4 (16).

The capacity to respond to polyclonal stimuli such as phytohemagglutinin is first seen at 15 to 16 wk of gestation (17). The degree to which the fetal immune system can respond to foreign antigens has not been clearly established. The offspring of mothers infected during pregnancy with a range of pathogens including measles (18), ascaris (19), malaria (20), schistosomes (21), and helminths (22) display evidence of pathogen-specific T-cell reactivity at birth, whereas infection with other organisms such as toxoplasma (23) may induce tolerance. Additionally, vaccination of pregnant women with tetanus toxoid results in the

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³ Abbreviations used: AFH, atopic family history; IFN- γ , interferon- γ ; IL, interleukin; RTE, recent thymic emigrants; TcR, T-cell receptor; Th, T-helper cells.

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appearance of IgM in the fetal circulation that is indicative of fetal T-cell sensitization because IgM antibodies do not cross the placenta and thus must derive from the fetus (24). Also, there is a variety of evidence based on *in vitro* lymphoproliferation of cord blood mononuclear cells, which suggests that environmental antigens (including dietary and inhalant allergens) to which pregnant women are exposed may in some circumstances prime T-cell responses transplacentally.

It is also noteworthy that, despite the low absolute numbers of CD4⁺ and CD8⁺ CD45RO⁺ T cells in cord blood of term newborns, fetal spleen and cord blood samples from premature infants contain these cells in relatively high frequency (25). These "postactivated" or "memory" T cells were unresponsive to recombinant interleukin (IL)-2, suggesting they may have been anergized by earlier contact with self- or environmental antigens (25).

These findings collectively suggest that the fetal immune system develops at least partial functional competence before birth but lacks full capacity to generate sustained immune responses (Table 1).

Although IgM responses develop in the fetus following maternal tetanus vaccination, there is no evidence of class-switching to IgG in the offspring until they are actively vaccinated (24). Because the fetal immune system can generate at least primary immune responses against external stimuli, the question arises as to how immune responses within or in close contact with the fetal compartment are regulated. The necessity for tight control of these responses becomes obvious in light of findings that a variety of T-cell cytokines are exquisitely toxic to the placenta (26), as discussed furthering detail below. It is also pertinent to question how potential immunostimulatory interactions between cells derived from fetal and maternal bone marrow are regulated at the maternofetal interface. In particular, it has been clearly demonstrated that fetal cells readily traffic into the maternal circulation (27–30), potentially sensitizing the maternal immune system against paternal human leukocyte antigens present on the fetal cells. However, it is clear from recent studies (31) that, in the vast majority of circumstances, the maternal immune system successfully eradicates fetal cells from the peripheral circulation while remaining functionally tolerant of the fetus. This suggests that tolerance of the fetal

TABLE 2 Features of immune developmental factors on allergic responses

Neonatal dendritic cells mount weak Th1-inducing signals to T cells, leading to preferential generation of Th2-immune responses
Fetus is protected by an overweight of Th2 cytokine during pregnancy
A slow postnatal maturation of IFN- γ production capacity is linked to a genetic risk for atopy
Postnatal maturation of adaptive immunity is driven by microbial signals
Tolerizing capacity of fetal immune system occurs prenatally
Prenatal maternofetal allergen transfer triggers transient fetal immune responses

allograft is a regionally controlled process that is localized to the maternofetal interface.

The mechanisms that regulate the induction and expression of immune responses in this milieu are complex and multilayered. The first line of defense appears to be local immunosuppressively acting production within the placenta by trophoblast cells and macrophages of metabolites of tryptophan generated via indoleamine 2,3-dioxygenase, which are markedly inhibitory against T-cell activation and proliferation (32). Constitutive production of high levels of IL-10 by placental trophoblast cells provides a second broad-spectrum immunosuppressive signal to dampen local T-cell responses (33).

A second line of defense operates to protect against T-cell activation events that evade suppression via these pathways. One such mechanism involves expression of FasL on cells within the placenta, providing a potential avenue for apoptosis-mediated elimination of locally activated T cells (34,35). The latter is complemented by a series of mechanisms that operate to selectively dampen production at the fetomaternal interface of T-helper (Th)1 cytokines, in particular of interferon- γ (IFN- γ). This cytokine plays an important role in implantation (36), but, if produced in suprathreshold levels at later stages of pregnancy, triggered, for example, by local immune responses against microbial or alloantigens, IFN- γ (and other Th1 cytokines) can potentially cause placenta detachment and fetal resorption (37). These Th2-trophic mechanisms involve local production of a range of immunomodulators including IL-10 (33), which programs antigen-presenting cells for Th2 switching (38); progesterone, which directly inhibits IFN- γ gene transcription (39–41); and prostaglandin E₂, which promotes Th2 switching via effects on antigen-presenting cells, dendritic cells in particular (38).

Surface phenotype characteristics of T cells in early life

Total lymphocyte counts in peripheral blood are higher in infancy than in adulthood (42), and at birth, T-cell levels are twice those of adults. Longitudinal studies on individual infants indicate a further, rapid doubling in T-cell numbers in the circulation during the first 6 wk of life, which is maintained throughout infancy (43). Surface marker expression on infant T cells differs markedly from that observed in adults. The most noteworthy characteristics are frequent expression of CD1 (44) and PNA (45) antigens and CD38 (43,46,47). These 3 antigens are considered to mark mature thymocytes as opposed to circulating "mature" naive T cells.

Recent analyses performed on CD38⁺ cord blood cells have reinforced this view. In particular, animal model studies on thymic output have led to the development of an accurate technique for phenotypic identification of recent thymic emigrants (RTE), which are newly produced peripheral naive T cells that retain a distinct phenotypic signature of recent thymic maturation that distinguishes them from long-lived naive T cells

TABLE 1 Maturation steps of the developing immune system

Maturation step	Fetus, neonate, infant	Adulthood
Pluripotent erythroid and granulomacrophage progenitors in the liver	Wk 5–6 of gestation	
CD7 ⁺ precursor cells in the thymus	Wk 8 of gestation	
Stem cells in bone marrow	Wk 12 of gestation	
T cells in peripheral lymphoid organs	Wk 13–16 of gestation	
Fetal T cells respond to mitogen	Wk 15–16 of gestation	
Maternal vaccination	Fetal IgM response, no class switch	
Mature thymocytes	CD1, PNA, CD38	
CD45RO ⁺ /CD4 ⁺ T cells	At birth: <10%	>65%
Peripheral T cells	Cord blood: CXCR-4	CCR-1, -2, -5, -6, CXCR-3, -4
Cytotoxic effector function	At birth: reduced	
B cell Ig production	At birth: attenuated	
Mitogenic response	At birth: elevated	Reduced
Antigenic response	At birth: reduced, short-lived	Sustained

produced at remote sites. This approach involves the measurement of TcR excision circles, which are stable extrachromosomal products generated during the process of variable/diverse/joining TcR gene rearrangement. These excision DNA circles are not replicated during mitosis and as a consequence become diluted with each round of cell division. Employing this procedure, Hassan and Reen (47) have demonstrated that the majority of circulating CD4⁺ CD45R⁺ human T cells at birth are RTE as reflected by their high level of expression of TcR excision circles. These researchers also demonstrated that, analogous to thymocytes, the RTE were highly susceptible to apoptosis (47), and unlike mature adult-derived CD4⁺ CD45RA⁺ naive T cells, they were uniquely responsive to cytokines with the common γ -chain, particularly IL-7 (47,48). Although IL-7 promotes their proliferation and survival, IL-7-exposed RTE could not reexpress recombination-activating gene-2 gene expression *in vitro*. These findings suggest that postthymic naive peripheral T cells in early infancy are at a unique stage in ontogeny as RTE, during which they can undergo homeostatic regulation including survival and antigen-independent expansion while maintaining their preselected TcR repertoire (47).

The patterns of postnatal change in T-cell surface marker expression have been analyzed in several recent studies. Of relevance to the preceding conclusions are observations noting the presence of relatively high numbers of T cells coexpressing both CD4 and CD8 during infancy, which is also a hallmark of immaturity (43,49,50). In contrast, expression of CD57 on T cells, which marks non-MHC-restricted cytotoxic cells, is infrequent, as are T cells coexpressing IL-2 and human leukocyte antigen DR, which is indicative of recent activation (49). The expression of other activation markers such as CD25, CD69, and CD154 is also low (43). Of particular interest in relation to the understanding of overall immune competence during postnatal life are changing patterns of surface CD45RA and CD45RO on T cells. T cells exported from the thymus express the CD45RA isoform of the leukocyte common antigen CD45 and, after activation, switch to CD45RO expression. Most postactivated neonatal CD4⁺ CD45RO⁺ T cells are short-lived and die within a matter of days, but a subset of these is believed to be programmed to enter the long-lived recirculating T-cell compartment as T memory cells (51).

The proportion of CD45RO⁺ cells within the CD4⁺ T-cell compartment progressively increases from a baseline of <10% at birth up to 65% in adulthood, reflecting age-dependent accumulation of antigenic exposure (43,49,51–56). The rate of increase within the TcR α/β and TcR γ/δ populations is approximately equivalent and is slightly more rapid for CD4⁺ T cells relative to CD8⁺ T cells (56). The relative proportion of CD45RO⁺ putative memory T cells attain adult-equivalent levels within the teen years (49,56), but it is noteworthy that the population spread during the years of childhood is very wide (56).

This suggests substantial heterogeneity within the pediatric population in the efficiency of mechanisms regulating the generation of T helper memory.

Functional phenotype characteristics of T cells during infancy and early childhood

T-cell function during infancy exhibits a variety of qualitative and quantitative differences relative to that observed in adults. Of particular note, when a limiting dilution analytic system is used, it has been demonstrated that at least 90% of peripheral blood CD4⁺ T cells from adults can give rise to stable T-cell clones, whereas the corresponding (mean) figure for immunocompetent T-cell precursors in infants was <35% (57). It was

also observed that cloning frequencies within the infant population were bimodally distributed, with a significant subset of normal healthy subjects displaying particularly low cloning frequencies of $\leq 20\%$ (57).

In apparent contrast to these findings, the kinetics of initial T-cell proliferation induced by polyclonal T-cell mitogens such as phytohemagglutinin in short-term cultures is higher at birth than subsequently during infancy and adulthood (58,59). However, proliferation is not sustained, which may reflect the greater susceptibility of neonatal T cells to apoptosis postactivation (47) and/or decreased production of IL-2 (60). In contrast, activation induced by TcR stimulation and cross-linking CD27 (61) or CD28 (62) is reduced.

In addition to these deficiencies, neonatal T cells are hyperresponsive to IL-4 (63) and hyporesponsive to IL-12 (64) relative to adults, the latter being associated with reduced receptor expression (65). They also exhibit heightened susceptibility to anergy induction poststimulation with bacterial superantigen, employing protocols that do not tolerize adult T cells (66,67). The latter has been ascribed to deficient IL-2 production (66) but may alternatively be related to developmentally linked deficiencies in the Ras-signaling pathway, which have been associated with secondary unresponsiveness to alloantigen stimulation by T cells from neonates (68). Additional aberrations in intracellular signaling pathways reported in neonatal T cells include phospholipase C and associated Lck expression (69), protein kinase C (70), and CD28, which is associated with dysfunction in FasL-mediated cytotoxicity and reduced NF- κ B production (62).

A recent study also reported distinct profiles of chemokine receptor expression and responsiveness in neonatal T cells. In particular, adult peripheral blood T cells expressed CCR-1, -2, -5, and -6 and CXCR-3 and CXCR-4, whereas those from cord blood expressed only CXCR-4, reflecting markedly attenuated capacity to respond to signals from inflammatory foci (71). Evidence from a range of studies indicates that both cytotoxic effector functions (72,73) and capacity to provide help for B-cell immunoglobulin production (72–76) are attenuated during infancy. These functional deficiencies are likely to be the result of a combination of factors that include decreased expression of CD40L (72,74,75), reduced expression of cytokine receptors (65,77), and decreased production of a wide range of cytokines following stimulation (57,60,78–84).

The mechanisms underlying these reduced cytokine responses are unclear, but factors intrinsic to the T cells themselves (57,85), as well as those involving accessory cell functions (85–87), appear to be involved.

Vaccine immunity in early life

Investigations on vaccine immunity during infancy and early childhood are of intrinsic importance. In addition, they provide a unique experimental window through which to study the postnatal development of human adaptive immune function and are thus of particular relevance to this article; some recent key findings are summarized below.

As discussed previously, important aspects of immune function are immature at birth and do not reach adult capacity for several years. For example, the *in utero* generation of tetanus-specific IgM following maternal immunization with tetanus toxoid demonstrates the ability of the fetus to generate an active, albeit immature, immune response because no switch from IgM to IgG is evident until later during infancy, following boosting (88).

After birth, there is a progressive maturation of the capacity to generate adult-like responses, both quantitatively and qualitatively. After measles-mumps-rubella vaccination, the seroconversion rate against measles is age-dependent, with those vaccinated between 9 and 11 mo having significantly lower antibody titers than those vaccinated between 15 and 17 mo (89). In another study, Gans et al. (90) observed that although antibody responses were lower in infants receiving the measles vaccine at 6 mo than those vaccinated at 9 or 12 mo, there was no significant difference in *in vitro* antigen-specific IFN- γ or IL-12 production. However, when these responses were compared with those of adults, the infants produced significantly lower levels of IL-12 after *in vitro* stimulation with measles antigen (90). In mice, substantial B- and T-cell vaccine responses were obtained as early as y 1 of life. However, neonatal responses differed qualitatively from those in adults, with neonates having a decreased ratio of IgG2a/IgG1 and higher *in vitro* vaccine-specific IL-5 and decreased IFN- γ (91).

In a prospective cohort of 132 infants, Rowe et al. have examined the response to the tetanus component of the diphtheria/tetanus/acellular pertussis (DPT) vaccine and compared these responses to age-related changes in systemic Th1 and Th2 cytokine function (92,93). The results indicate early Th1 and Th2 cytokine responses to the vaccine antigen. Although Th2 vaccine-specific responses persisted throughout the study period, Th1 responses were transient. These results are similar to those observed in mice, with balanced Th1/Th2 vaccine responses generated in neonatal animals. Both Th2 and Th1 secondary responses have been observed in mice first vaccinated as neonates, suggesting that Th1 and Th2 cells can contribute to a sustained immune response in mice (94,95).

In this context, it is important to note that it has been demonstrated that given a mature source of accessory cells, peripheral blood T-cell IFN- γ production in response to polyclonal mitogen stimulation can be boosted to approximate those of adults (85,86). Similarly, vaccination with the use of powerful stimuli such as Bacillus Calmette-Guérin (53,96) or selective Th1-driving agents such as IL-12 (97), 16s plasmid DNA (98), and CpG-containing oligonucleotides (99) can all induce adult-like Th1 responses in early life, presumably through activation of accessory cell function.

As discussed in more detail later, slow postnatal maturation of IFN- γ production capacity is linked to genetic risk for atopy. There is some evidence to suggest that delayed Th1 maturation may reduce the capacity of children at high risk of atopy to respond to vaccination efficiently in infancy. In response to Bacillus Calmette-Guérin vaccination in infancy, for example, failure to develop long-lasting delayed-type hypersensitivity responses to tuberculin was associated with increased risk of atopy at 12 y (100). In addition, children who develop atopic dermatitis had a reduced ability to respond to pneumococcal vaccination (101). With regard to the DTP vaccine, it has been observed that infants at high risk of atopy had specific responses to tetanus toxoid that were consistently more Th2 skewed, displaying higher Th2/Th1 ratios (93). This difference was no longer evident in these subjects at age 18 mo (93). Furthermore, in another study Prescott et al. (102) have shown that *in vitro* proliferative responses to tetanus toxoid during infancy were inversely related to the atopic phenotype. Apparently, as outlined by the authors, these differences appear transient, and after the completion of the standard priming/boosting vaccine schedule at age 6 y, there was no significant difference in vaccine response between atopic patients and their nonatopic counterparts (103).

Variations in kinetics of postnatal maturation of immune functions

Recent studies from a number of groups have highlighted the importance of the early postnatal period in relation to the development of long-lasting response patterns to environmental allergens. In particular, it is becoming clear that initial priming of the naive immune system typically occurs before weaning and may consolidate into stable immunologic memory before the end of the preschool years. Allergen exposure is believed to occur mainly through the intestinal mucosa, but the skin and respiratory tract may be equally involved. The predominant role of the intestinal mucosa may be reflected by the almost exclusive sensitization pattern to nutritive allergens in the first years of life. Because the underlying immunologic processes involve the coordinate operations of the full gamut of innate and adaptive immune mechanisms, issues relating to developmentally determined functional competence during this life phase may be predicted to be of major importance (Table 2).

In relation to initial priming of the T-cell system against allergens, reports from numerous groups indicate the presence of T cells responsive to food and inhalant allergens in cord blood (104–112). Cloning of these cells and subsequent DNA genotyping indicated fetal as opposed to maternal origin (109), and the array of cytokines produced *in vitro* in their responses are dominated by Th2 cytokines, although IFN- γ is also observed, suggestive of a Th0-like pattern (109). The issue of how initial priming of these cells occurs remains to be resolved. It is possible that transplacental transport of allergen, perhaps conjugated with maternal IgG, may be responsible, and some indirect supporting evidence based on *in vitro* perfusion studies has been published recently to support this notion (113–116). Alternatively, initial T-cell priming may be against cross-reacting antigens as opposed to native allergen, and the uncertain relation between maternal allergen exposure and newborn T-cell reactivity is consistent with this view (117,118). The mucosal T-cell epitope map of the typical cord blood T-cell response to ovalbumin, involving multiple regions of the ovalbumin molecule (119), suggests major qualitative differences relative to conventional adult T-cell responses.

Regardless of how initial T-cell responses are primed, it is clear that direct exposure to environmental allergens during infancy drives the early responses down 1 of 2 alternate pathways.

In the majority of (nonatopic) subjects, the Th2 cytokine component of these early responses progressively diminishes, and by age 5 y, *in vitro* T-cell responses to allergens comprise a combination of low-level IFN- γ and IL-10 production (119–121). In contrast, a subset of children develop positive skin prick test reactivity to 1 or more allergens, and *in vitro* stimulation of peripheral blood mononuclear cells with the latter elicits a mixed or Th0-like response pattern comprising IL-4, IL-5, IL-9, IL-10, IL-13, and IFN- γ (122). This latter pattern closely resembles that seen in the majority of adult atopic patients and much more commonly develops in atopic family history-positive (AFH⁺) children than in their AFH[−] counterparts.

It is increasingly debated whether it remains useful to describe these differing responses in human atopic and non-atopic patients within the framework of the murine Th1/Th2 paradigm, which was based on the concept of reciprocal and/or antagonistic patterns of Th-memory expression. In humans a more balanced Th1/Th2/Th0 response is predominant in non-atopics with distinct deviations in certain phases of atopy, reflecting the difficulty of predicting disease likelihood on cytokine profiling in newborns and infants. In this context, recent studies from Macaubas and Holt (121) and Macaubas

et al. (123) indicate that reciprocal patterns of expression of the transcription factor GATA-3, analogous to those that distinguish Th1 from Th2 polarized cell lines (with regard to down-regulation vs. up-regulation, respectively, poststimulation), are reiterated during the allergen-specific recall responses of CD4⁺ T cells from nonatopic vs. atopic subjects. This suggests that the Th1/Th2 model still provides a potentially useful framework for the study of allergic responses despite the strong likelihood of large interspecies differences.

The central issue in relation to understanding the initial phase of allergic sensitization in childhood concerns the molecular basis for genetic susceptibility to development of Th2-polarized memory against inhalant allergens, and the key to the resolution of this puzzle may lie in a more comprehensive understanding of the mechanisms that drive postnatal maturation of adaptive immune function. In this regard, it has been reported earlier that genetic risk for atopy was associated with delayed postnatal maturation of Th-cell function, in particular Th1 function, and that this may increase risk for consolidating Th2-polarized memory against allergens during childhood. The evidence originally presented was based on decreased peripheral blood T-cell cloning frequency and diminished IFN- γ production by T-cell clones in AFH⁺ infants relative to their counterparts (124), and these findings have been substantiated in several independent laboratories employing bulk culture studies with neonatal peripheral blood mononuclear cells (125–129). It has been proposed that this phenomenon may derive from inappropriate postnatal persistence of 1 or more of the mechanisms responsible for selective damping of Th1 immunity during fetal life (130). Alternatively, because the postnatal maturation of adaptive immunity is essentially driven by microbial signals from the outside environment (130–132), 1 or more deficiencies in relevant receptors or downstream signaling pathways may retard this process. The recently described genetic variations in CD14 may be an archetypal example (133), and similar variants in 1 or more of the Toll receptor genes constitute additional likely candidates. These possibilities are of particular interest in light of recent reports that environmental exposure to airborne bacterial lipopolysaccharide in childhood may be protective against Th2-mediated sensitization to inhalant allergens (134, 135).

Further research is required to elucidate the complex regulatory mechanisms that govern generation of different patterns of allergen-specific Th memory during childhood. However, it is also becoming clear that an additional, and related, set of complexities needs to be considered. It is now evident that only a subset of atopic patients progress to development of severe persistent allergic diseases, in particular atopic asthma (136), and it is likely that these subjects suffer additional and/or particularly intense inflammatory insults to target tissues. In this context, epidemiologic evidence suggests that risk for development of persistent asthma is most marked in children who display early allergic sensitization to inhalants (137,138) and who develop severe wheezing and lower respiratory tract infections during infancy (138–140). This has given rise to the suggestion that susceptibility to development of the airways remodeling characteristic of chronic asthma (141) may in many circumstances be the long-term result of inflammation-induced changes in lung and airway differentiation during critical stages of early growth during childhood. It is additionally noteworthy that resistance to respiratory infections is also mediated by the same Th1 mechanisms just identified as attenuated in children at risk of atopy (142), suggesting that the same set of genetic mechanisms may be responsible for airways inflammation

induced via the viral infection and atopic pathways in children at high risk of asthma.

An additional variable that merits more detailed research is the role of airway dendritic cell populations in this complex equation. In the adult, these cells regulate the Th1/Th2 balance in immune responses to airborne antigens (143) and also mediate primary and secondary immunity to viral pathogens. However, airway dendritic cell networks develop very slowly postnatally, apparently “driven” by exposure to inhaled airborne irritants (144), in particular bacterial lipopolysaccharides (145–148). Hence, the rate at which this key cell population gains competence to respond to maturation-inducing stimuli and then to orchestrate appropriately balanced T-cell responses against viral pathogens and allergens may be a key determinant of overall susceptibility to allergic disease. Very recent epidemiological studies suggest that this propensity to respond and to mount immune responses in a protective and tolerizing manner may occur very early in life, presumably in fetal life (149). Understanding these mechanisms may govern new strategies in the prevention of allergic diseases.

Because the fetal and neonatal immune systems harbor relevant features of a tolerizing milieu, this very early time frame after birth, yet to be defined in more precise detail, should reveal substantive answers to the questions of how and when to foster primary prevention of allergic diseases.

Other articles in this supplement include references (150–159).

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