Occasional reviews

Immune mechanisms of childhood asthma

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Asthma is the most common chronic disease of childhood in developed countries. Recent studies suggest that most asthmatics are diagnosed by the age of five, with symptoms first occurring during infancy and early childhood. Allergy is known to play a significant role in childhood asthma. The prevalence of allergic diseases including asthma has increased significantly over the past 40 years. The reasons for this increase are not known but are under active investigation. Understanding the pathogenesis of childhood asthma may lead to the development of novel therapies or even preventive strategies. Little is known about the cellular and molecular mechanisms underlying this disorder. T cells are critical for the initiation and maintenance of the mature asthmatic inflammatory response. Complex interactions between T and B lymphocytes and antigen presenting cells (APC) lead to inflammation, cytokine production, IgE production, and bronchial hyperresponsiveness (BHR). T cell differentiation which will lead to expression of the asthmatic phenotype probably occurs in early childhood under the influence of complex genetic and environmental factors. This review will focus on current knowledge about immune mechanisms of childhood asthma in developed countries. Topics to be discussed include the role of T cells in asthma, maternal-fetal immunological interactions which may promote atopy, the importance of allergens, the antibody response to allergens in early life, T cell function and allergen specific T cell immunity in neonates, cytokine profiles of neonatal lymphocytes, and potential strategies for prevention of childhood asthma.

Role of T cells in asthma

T cells are critical to the pathogenesis of allergic asthma in adults. Chronically activated T memory cells sensitised against a variety of allergens are believed to be responsible for the maintenance of airway inflammation. Soluble interleukin (IL)-2 receptor levels are raised in children with asthma, suggesting that activated T cells are important in childhood asthma as well. Current data support the predominance of a T helper 2 phenotype in allergic asthma.

Allergens induce CD4+ T helper cells to produce type 2 (Th2) cytokines such as IL-4, IL-5, IL-6, IL-10, and IL-13. IL-5 attracts and activates eosinophils, while IL-4 is essential for B cell isotype switching to IgE. CD8+ T cells may lead to IgE class switching via IL-13 rather than IL-4. These events lead to eosinophilic bronchitis, mucus hypersecretion, and bronchial smooth muscle contraction. However, some studies suggest that T helper type 1 (Th1) cytokines such as IL-2, interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), and IL-15 may promote allergic airway inflammation as well. Thus, asthma as a paradigm of an exclusively Th2 mediated disease may not take into account all the complexities involved in its pathobiology.

Complete activation of T cells requires an antigen specific signal transduced by the T cell receptor and an antigen non-specific co-stimulatory signal (fig 1). T cell receptor signals without co-stimulation result in a state of prolonged inactivation or anergy. The best characterised co-stimulatory pathway is the CD28/B7 pathway. CD28 is constitutively expressed on T cells and binds to B7-1 (CD80) and B7-2 (CD86) on APC. Engagement of the T cell receptor plus co-stimulation through CD28 leads to full T cell activation. CTLA4, a B7 counter-receptor which is upregulated after activation, is presumed to be a negative regulator of T cell activation.

Additional co-stimulatory molecules include ICOS and CD40/CD40 ligand (CD40L). ICOS is structurally homologous to CD28 but is upregulated after T cell activation. Activated T cells express CD40L which engages CD40 on APC and induces them to produce cytokines such as IL-12. IL-12 induces dendritic cells, monocytes, and natural killer cells to produce IFN-γ, thus promoting a Th1 effector response. Less well characterised co-stimulatory molecules such as intercellular adhesion molecule 1, 4-1BB, and heat stable antigen are currently being studied.

Murine models have provided strong evidence for the role of T cell activation in asthma. In these models systemic sensitisation to an allergen followed by aerosolised allergen challenge lead to features characteristic of human asthma. Inhibition of CD28/B7 co-stimulation diminishes allergic pulmonary inflammation. CTLA4-Ig is a fusion protein composed of a soluble form of CTLA4 linked to the Fc portion of human IgG1. It inhibits CD28/B7 co-stimulation by binding B7 molecules on the cell surface. In a murine model of allergen induced airway inflammation, treatment with CTLA4-Ig during aerosolised allergen challenge significantly lowered BHR, serum IgE, airway inflammatory cells, and thoracic T cell activation, originally shown by Krinzman et al and subsequently confirmed.
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Figure 1 Co-stimulatory pathways of T cell activation. Complete activation of T cells requires at least two signals: (1) the interaction of the T cell receptor (TCR) with antigen (Ag)/major histocompatibility complex class II (MHC II) on the antigen presenting cell (APC) and (2) an antigen non-specific co-stimulatory signal. The best characterised co-stimulatory pathway is the CD28/B7 pathway. CD28 is constitutively expressed on T cells and binds to B7-1 or B7-2 on APC. CTLA4, another B7 counter-receptor, is upregulated after T cell activation and is presumed to be a negative regulator of T cell activation. Activated T cells express other co-stimulatory molecules including CD40 ligand (CD40L) which engages CD40 on APC and may upregulate B7 molecule expression.

Maternal-fetal immunological interactions and childhood asthma

Epidemiological data showing associations between various maternal factors and childhood asthma have spurred interest in understanding how the intraterine environment might influence the fetal and neonatal immune response to allergens. Maternal factors associated with an increased risk of childhood asthma include younger age, smoking, lack of prenatal care, and weight gain of less than 20 lbs (9.1 kg) during pregnancy. A maternal history of allergy or asthma is more strongly associated with atopy in children than paternal history, suggesting that maternal factors are important in the development of asthma. Maternal-fetal immunological interactions and childhood asthma should be considered as potentially influencing the immune response to allergens in early life.

Role of allergens in childhood asthma

Asthma associated allergens in developed countries are primarily perennial indoor allergens such as house dust mite (HDM), animal dander, and cockroaches. Increased exposure to indoor allergens may be relevant to the recent increased incidence and severity of asthma in children. Most clinical studies support the hypothesis that allergy plays a major role in the pathogenesis of childhood asthma. By the age of six, children who wheezed had significantly more positive skin tests to aeroallergens than children who never wheezed. Risk factors for childhood asthma consistently include allergen exposure and allergy. Higher cockroach allergen levels in the home have been associated with a significantly increased risk of developing asthma in children.
younger than five years old in Boston (G Litonjua, 1999, personal communication). The age of onset of asthma in children of atopic parents and the risk of sensitised children developing BHR is related to the level of HDM exposure. 

Zimmerman et al found a linear relation between the number of positive skin tests and the severity of asthma in children older than six. Other investigators have confirmed a relationship between atopy and the severity of asthma symptoms and BHR. The age at which allergic sensitisation occurs is important: children who become sensitised in infancy or early childhood are at higher risk of developing asthma than those who become sensitised later. Studies performed in developing countries have shown less of an association between sensitisation to indoor allergens and asthma. Thus, while allergen exposure and allergic sensitisation increase a child’s risk of developing asthma, the molecular mechanisms leading to airway inflammation and BHR in some but not all sensitised children have yet to be elucidated. The type and kinetics of allergen exposure, for example, might account for some of the geographical differences seen in the prevalence of allergy and asthma.

Fetal immunoglobulin production and the antibody response to environmental allergens in the perinatal period

Immune responses to allergens early in life, perhaps even in utero, may be critical to the pathogenesis of childhood asthma. There is therefore great interest in understanding the fetal, neonatal, and early childhood immune response to antigens, particularly to inhaled allergens. Production of IgM, IgG subclasses and IgE in response to T cell derived activation signals—for example, CD40 and cytokines, is similar in neonatal B cells and antigenically naive adult B cells. Fetal B cells are capable of isotype switching. T cell dependent isotype switching and immunoglobulin production for certain pathogens such as toxoplasmosis can occur in a fetus; however, other congenital infections such as varicella zoster virus do not induce specific immunoglobulin by birth or early childhood. Impaired fetal and neonatal B cell responses may be due to reduced production of T cell cytokines such as CD40L or to reduced function of neonatal dendritic cells. Immune responses to airborne environmental antigens in the perinatal period may be a universal phenomenon and a necessary determinant of the asthmatic phenotype later in life. In one study children produced IgG antibodies but not IgG2 antibodies against an inhaled allergen between three and 12 months of age; data suggest that IgG antibodies increase with age although the majority of the studies were not performed prospectively.

Antibodies to inhaled allergens start to rise significantly at the age of two and reach levels comparable to those of adulthood by the age of five. In contrast, the antibody response to dietary allergens such as ovalbumin (OVA) occurs during the first two years and generally disappears by the age of five.

T cell function in neonates

Lymphocytes are first observed in the fetal thymus at 8–9 weeks of gestation and migrate to the circulation at about 14–16 weeks. After 22 weeks gestation most circulating T cells are of the naive (CD45RA high CD45RO low) phenotype. In most studies third trimester fetuses and neonates do not have circulating memory (CD45RO high) T cells; gradual increases in the proportion of memory T cells and their production of cytokines such as IFN-γ are likely due to increasing antigenic exposure and T cell activation. Both neonatal T cells and adult naive T cells have a reduced capacity to proliferate and produce cytokines compared with memory or effector T cells, suggesting that deficiencies of neonatal T cell function may be due in part to lack of antigenic experience.

Antigen-specific proliferation and cytokine production following congenital or postnatal infections are usually reduced in neonates compared with older children and adults, perhaps due to defects in T cell activation, co-stimulation, or antigen processing. Naive cord blood T cells are more difficult to activate in vitro than naive adult peripheral blood T cells and have an impaired ability to translate IL-2 mRNA, a cytokine which stimulates T cell proliferation. Some studies have found that neonatal T cells have a reduced capacity to express CD40L, while other data suggest that CD40L expression is comparable in neonatal and adult T cells. CD40L expression during antigen specific T cell activation in neonates has not yet been characterised. Cayabyab et al found that CD28-mediated co-stimulation is similar in neonatal and adult T cells; in contrast, another study suggests that neonatal T cells may require co-stimulatory signals in addition to CD28.

The requirement for additional co-stimulatory signals in the neonate may be related to low levels of inducible NF-κB, a transcription factor which upregulates IL-2 gene transcription. Differences in T helper and antigen presenting functions.
Accessory cell function necessary for T cell activation. Neonatal dendritic cell immaturity may be a factor in the development of allergic disease as dendritic cells are important APCs in airway epithelium. 

It will be interesting to determine whether co-stimulatory molecule expression on neonatal dendritic cells promote hypersensitivity to inhaled allergens or tolerance, a state of antigen specific unresponsiveness.

In summary, T cell functions in the fetus and neonate which are impaired compared with adults include cell mediated cytotoxicity, antigen specific cytokine production, help for B cell antibody responses, upregulation of some co-stimulatory molecules (such as CD40L), and antigen presentation. Fetal and neonatal B cells have the capacity to be activated and undergo isotype switching but may be more susceptible to tolerance induction. The deficiencies of the neonatal immune system may reflect lack of previous antigenic exposure since neonatal and adult naive lymphocytes share many characteristics. Further elucidation of how the immune response develops in early life will lay the groundwork for understanding how pathological responses to environmental allergens occur.

Development of allergen specific T cell immunity in neonates

Prospective studies on peripheral blood T cell reactivity to different allergens in fetuses, infants, and young children have been initiated in order to understand the mechanisms of their T cell responses. At 10 weeks gestation thymic T cells proliferate in response to the mitogen phytohaemagglutinin (PHA) and histocompatibility antigens. Peripheral blood mononuclear cell (PBMC) proliferative responses to PHA can be detected by 17 weeks and increase with gestational age.

Fetal PBMC proliferative responses to inhaled and dietary allergens are detectable at 22 weeks gestation and also increase with gestational age. How these proliferative responses are generated when it is known that most circulating fetal and neonatal T cells are of the naive phenotype is not known. In one study PBMC from fetuses whose mothers had been exposed to birch tree pollen beyond the 22nd week of pregnancy had a significantly higher proliferative response to birch tree pollen than fetuses whose mothers were not exposed, suggesting that maternal allergen exposure “primes” fetal T cells. The critical period for exposure of the fetus to allergens may be from five to seven months of gestation.

The existence of fertilally derived allergen reactive T cells in cord blood has been demonstrated, but transplacental transfer of allergens or peptides as a mechanism for sensitising fetal T cells in utero has not been proved.

Proliferative responses of cord blood mononuclear cells (CBMC) to inhaled and food allergens have been reported in some infants. In one study lymphoproliferative responses to HDM and OVA were present in close to half of the newborn infants tested. In another recent study most of the newborn infants had positive lymphoproliferative responses to inhalant or food allergens. The frequencies of the responses were comparable in neonates with and without a family history of atopy. Proliferative responses to food allergens decreased during the first year of life, while responses to inhaled allergens persisted. Cord blood lymphoproliferative responses to food or inhaled allergens may predict the subsequent development of allergic disorders in early childhood.

In children who developed allergic disease by one year of age proliferative responses to perennial inhalant and food allergens were significantly lower at six months than at birth. Analysis of allergen specific T cells from such children would test the hypothesis that induction of tolerance or the movement of sensitised cells to sites of allergen exposure had occurred.

Cross sectional studies suggest that lymphoproliferative responses to inhaled allergens increase between infancy and adulthood. In one study specific T cell reactivity to HDM was seen in the majority of two and three year old children; the lymphoproliferation results were similar in atopic and non-atopic children.

Many adults have aeroallergen specific T cell reactivity demonstrable in vitro. Allergen specific CD4+ T cells can be isolated from peripheral blood lymphocytes of both atopic adults and non-atopic controls; however, the cytokine pattern of the clones is Th2-like (IL-4, IL-5) in atopic adults and Th1-like (IL-2, IFN-γ) in non-atopic controls. The cytokine profiles of allergen specific lymphocytes in neonates and young children are beginning to be elucidated.

In summary, cord blood lymphocyte proliferation studies show that neonates have T cells capable of recognising specific allergens. How allergen specific T cells in neonates are related to the subsequent development of asthma in childhood is the focus of current investigation.

Th1/Th2 effector cells and cytokines in neonates

Pregnancy is considered a Th2 state and there is some evidence that the neonatal immune response is biased toward the Th2 type. If a neonatal Th2 bias exists, it is not clear whether it represents persistence of the Th2 state of pregnancy or an immune system which has not yet encountered sufficient antigenic stimulation. Neonatal CD4+ T cells are similar to naive adult T cells in their ability to release sufficient IL-4 at priming to support clonal expansion into Th2 cells. However, naive cord blood T cells are much more responsive than adult naive T cells to IL-4 stimulation, a characteristic which might help to promote a Th2 immune response in neonates. A Th2 bias may be more pronounced in infants with family histories of atopy or in infants who subsequently develop allergic manifestations. Neonatal specific T cell clones generated from CBMC of newborn infants with atopic parents produced more IL-4 and IL-5 than T cells
from those with non-atopic parents; enhanced Th2 cytokine production correlated with atopic manifestations at the age of three. Allergen stimulation of CBMC led to increases in IL-5 and IFN-γ mRNA production in a proportion of neonates, regardless of family history of atopy; by 18 months, however, a mixed Th1/Th2 (IL-5 and IFN-γ) response to OVA and HDM allergens was observed only in children with a family history of atopy. OVA or mitogen stimulated CBMC produced IL-10, an IFN-γ inhibitory cytokine. In a recent study cord blood T cell responses to HDM or OVA allergens generated the Th2 cytokines IL-4, IL-5, and IL-9 mRNA as well as IL-10 and IL-13 protein, regardless of the infant’s family history of allergy. In a prospective study of children from birth until the age of two inhaled allergen stimulated CBMC produced IL-4, IL-5 and IL-9 (mRNA), IL-6, IL-10, and IL-13 (protein) but very little IFN-γ (mRNA or protein). Interestingly, the Th2 allergen specific responses were lower in neonates who later developed atopic disease than in those who did not become atopic. Allergen specific cytokine production changed with age: between birth and two years IL-4 mRNA production decreased in non-atopic children but persisted in atopic children; IFN-γ mRNA production increased between birth and six months in non-atopic children but not in atopic children. Whether absolute levels of Th1 and Th2 cytokines are significantly different in atopic and non-atopic children at the age of two is less clear. A slightly different pattern of allergen specific T cell cytokine expression was found by the same group in a different study, with increasing Th1 and Th2 cytokine production between birth and the age of two in atopic children. A mixed Th1/Th2 cytokine response to allergen stimulation in young children has been associated with atopy: by the age of five years PBMC from children with a positive skin prick test to HDM displayed an allergen specific mixed Th1/Th2 response (IL-4, IL-5, IFN-γ mRNA) while PBMC from skin prick test negative controls produced only the Th1 cytokine IFN-γ mRNA.

Further evidence that the immune system of the neonate might be biased toward Th2 responses comes from data indicating that the capacity to produce IFN-γ is low during infancy. Activated CBMC produce less IL-12 and IFN-γ than adult PBMC. Neonatal T cells produce less IFN-γ and IL-4 after polyclonal stimulation than adult T cells. IFN-γ producing T cell populations increase with age, correlating with memory surface antigen expression and increased antigen exposure. Thus, the reduced capacity to produce IFN-γ in infancy is probably due in part to lack of antigenic experience. Additional studies suggest that reduced IFN-γ production is associated with a genetic predisposition to atopy or to the development of atopy in early childhood. IFN-γ production by PHA stimulated young children was lower in neonates with a family history of atopy. The development of atopic eczema at one year of age was associated with decreased PBMC IFN-γ production in response to a dietary allergen in a study of neonates with an atopic parent. Reduced IFN-γ production by food allergen stimulated CBMC was associated with an increased risk of allergic disorders, primarily atopic dermatitis, at age six in a prospective study of 21 infants. The cytokine response to inhaled allergens was not tested. Low IL-2 and IFN-γ production by mitogen stimulated lymphocytes at the age of nine months has been associated with development of skin test reactivity to aeroallergens at the age of six years. Children who developed atopic symptoms or a positive skin prick test at one year had significantly lower cord blood IFN-γ secretion at birth than children who did not develop atopy. CD4+ T cell clones from children up to the age of four years produced less IFN-γ than those from adults; production was lowest in children from allergic families. There is decreased production of IFN-γ and increased production of IL-6 by mitogen stimulated CBMC of neonates with a family history of allergy.

In summary, studies to date suggest that stimulation of CBMC with allergens in vitro leads predominantly to Th2 cytokine production. During the first years of life there appear to be no significant allergen specific PBMC cytokine production between atopic and non-atopic children. Non-atopic children show a decrease in Th2 responses and an increase in Th1 responses, while atopic children develop increasing Th2 or mixed Th1/Th2 responses. Allergen specific cytokine production may be different at birth in infants who will later develop atopy than in those who will not develop atopy. The capacity to produce IFN-γ is lower in infants than adults and may be lowest in infants with atopy or a genetic predisposition to atopy. The potential to greatly expand our knowledge of the developing immune system, there are limitations to these studies. These limitations include differences in detecting mRNA versus protein cytokine levels, whether in vitro stimulation reflects the in vivo encounter of antigen in the airway, and the applicability of analyses of PBMC to pulmonary processes. There are obvious limitations in our ability to study pulmonary inflammatory cells from infants and young children more directly. Despite the data which suggest a primarily Th2 type immune response in the neonate, studies of congenital infections demonstrate that some fetuses are capable of generating a Th1 type immune response against certain pathogens. HIV specific cytotoxic T cells have been detected in a congenitally infected neonate. Fetal T cells can be primed to HIV in utero, and HIV specific Th immunity may be protective in neonates. It has been hypothesised that the reduced incidence of certain respiratory infections during infancy and young childhood may delay the switch from the Th2 state of prenatal and neonatal life to the Th1 state of adulthood. The interaction between childhood viral respiratory illnesses and asthma, however,
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is quite complex. Respiratory viral infections can stimulate either Th1 or Th2 immune responses.6–14 Respiratory syncytial virus (RSV) bronchiolitis in childhood, for example, is associated with IgE production, airway inflammation, BHR, and chronic wheezing later in life.15 The balance between Th1 and Th2 cytokines, rather than polarised Th1 or Th2 responses, is probably critical in determining the immune response to environmental allergens and pathogens in early life. The host and antigen factors responsible for an imbalance of Th1 and Th2 cytokines, leading to autoimmunity or allergic disorders, remain undefined.

Prevention of childhood asthma

Most cases of childhood asthma begin during infancy. Six year old children who wheeze already have altered lung function.61 Interventions designed to prevent asthma should therefore begin soon after birth.62 Maternal smoking during pregnancy is associated with reduced pulmonary function in infants and children. There is a clear association between postnatal exposure to tobacco smoke and increased wheezing and asthma in children.62–63 Maternal smoking cessation is therefore a prenatal intervention likely to reduce asthma in children.176 Several studies have shown that allergen avoidance can be effective in preventing asthma exacerbations or ameliorating asthma symptoms.6, 88, 178 Reducing exposure to indoor allergens during infancy and early childhood may decrease allergic sensitisation and asthma. Reducing maternal prenatal allergen exposure can reduce or delay atopy but does not decrease asthma in children.177–179 Ongoing studies are evaluating the effect on childhood asthma of aeroallergen avoidance from 18 weeks gestation through the first year of life.95 As we have seen, immune responses to inhaled and dietary allergens have been observed in neonates and young children, regardless of their atopic status. Early environmental exposures may in fact be critical for the proper development of the immune system, including the development of tolerance to ubiquitous non-pathogenic antigens. Determining which environmental exposures early in life lead to protective immunity and which are potentially detrimental is an area of active research.

The use of vaccines, Th1 selective adjuvants, or immunotherapy has been proposed in order to induce allergen specific Th1 memory development in early childhood.116 In a murine model intranasal BCG vaccine prevented allergen induced pulmonary inflammation, concomitant with increased local IFN-γ production.181 Such strategies, while very interesting, have the potential to cause autoimmune disease or permanently alter the immune response in unforeseen ways. Use of a Th1 driving adjuvant to alter Th2 predominant vaccine specific responses in neonatal mice did not completely restore the normal Th1/Th2 balance and caused significant local toxicity.184, 185 Tumor necrosis factor α (TNF-α) is a Th1 cytokine which plays a significant role in the pathogenesis of inflammatory diseases such as sepsis and rheumatoid arthritis. Administration of inhibitors of TNF-α has ameliorated rheumatoid arthritis but increased mortality from sepsis.186 These findings show that manipulation of the immune response through inhibition of cytokines does not always lead to the desired or expected result. Undertaking similar investigations in babies and young children who are at risk of developing asthma but still healthy would require special precautions.

Conclusions/future directions

Asthma causes significant morbidity in children. Its prevalence and severity have increased in the developed world over the past 40 years. Allergic sensitisation appears to play an important role in childhood asthma. Recent studies have found evidence for peripheral T cell responses to inhaled allergens and allergen specific Th2-like cytokine expression in neonates.190, 196 The questions of why hypersensitivity to airborne allergens develops and why only some allergic children become asthmatic have not yet been answered. There are probably multiple genetic and environmental factors which determine whether the clinical atopic or asthmatic phenotype is expressed in an individual child. Future studies should focus on prospectively correlating a child's genetic predisposition to atopy or asthma with his or her exposure to allergens, allergen specific lymphocyte proliferation, and cytokine profiles and subsequent development of atopy or asthma. Investigating the cellular and molecular mechanisms of T cell responses which lead to asthma is critical. There is increasing evidence that co-stimulatory molecules, including CD28/B7/CTLA4 and CD40/CD40L, and transcription factors play key roles in the pathogenesis of chronic inflammatory diseases such as asthma. Understanding the immune response to allergens in early life may allow us to develop strategies for preventing childhood asthma.

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