

Childhood infections, the developing immune system, and the origins of asthma

Peter J. M. Openshaw, PhD, Yuko Yamaguchi, BSc, and John S. Tregoning, PhD

London, United Kingdom

Asthma is an immune-mediated inflammatory condition characterized by increased responsiveness to bronchoconstrictive stimuli. Viruses have been shown to play an important role in asthma, with viral infection being present during about 85% of exacerbations. However, the role they play in the onset of asthma is more controversial. Some respiratory viral infections might be protective, but there is a strong association between respiratory syncytial virus-induced bronchiolitis in infancy and recurrent wheeze up to 12 years of age. Both the respiratory tract and the immune system undergo rapid maturation during the first year of life, and it seems that postnatal development is affected by and affects responses to viral infections. Understanding postnatal developmental changes in the immune system might help to explain the origins and pathogenesis of asthma and thus the effectiveness or ineffectiveness of specific asthma therapies. (*J Allergy Clin Immunol* 2004;114:1275-7.)

Key words: Common cold, bronchiolitis, developmental immunity, childhood asthma, respiratory syncytial virus

ASTHMA AND RESPIRATORY SYNCYTIAL VIRUS

Asthma is an immune-mediated inflammatory condition characterized by increased responsiveness to bronchoconstrictive stimuli. Viruses have been shown to play an important role in asthma, with viral infection being present during about 85% of exacerbations. However, the role they play in the onset of asthma is more controversial.

Abbreviations used

DC: Dendritic cell

RSV: Respiratory syncytial virus

Some respiratory viral infections might be protective, but there is a strong association between respiratory syncytial virus (RSV)-induced bronchiolitis in infancy and recurrent wheeze up to 12 years of age. Both the respiratory tract and immune system undergo rapid maturation during the first year of life, and it seems that postnatal development is affected by and affects responses to viral infections. Understanding postnatal developmental changes in the immune system might help to explain the origins and pathogenesis of asthma and thus the effectiveness or ineffectiveness of specific asthma therapies.

The association of RSV infection with the later onset of asthma has been reported by different groups from different regions,^{1,2} including Tucson, Arizona,³ and Borlas, Sweden.⁴ In the Swedish study 47 children hospitalized with RSV-induced bronchiolitis were followed, to determine the risk of asthmatic symptoms, to the age of 7.5 years. Multivariate analysis of these observations indicated that RSV was an independent risk factor for the development of asthma and possibly also for allergic sensitization. Studies of the peripheral blood lymphocytes from these children suggested that patients with bronchiolitis had a higher frequency of IL-4-producing T cells in response to RSV or cat allergen than control children.

It is necessary to show that prevention or delay of RSV infection affects the prevalence of childhood wheeze to prove a causal relationship between RSV disease and childhood asthma. In a study of immunoprophylactic treatment of children with a polyclonal RSV antibody (which delays the age of first RSV infection), improved lung function and reduced atopy at the age of 7 to 10 years were demonstrated compared with that seen in the control group.⁵

Specific studies are eagerly awaited, but it seems likely that virus infection during the period of postnatal maturation of the lung and immune system undoubtedly affects

From the Department of Respiratory Medicine, National Heart and Lung Institute, Paddington Campus, Imperial College London, London.

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Reprint requests: Peter J. M. Openshaw, PhD, Department of Respiratory Medicine, Imperial College London (St Mary's Campus), Paddington, London, W2 1PG, United Kingdom. E-mail: p.openshaw@imperial.ac.uk. 0091-6749/\$30.00

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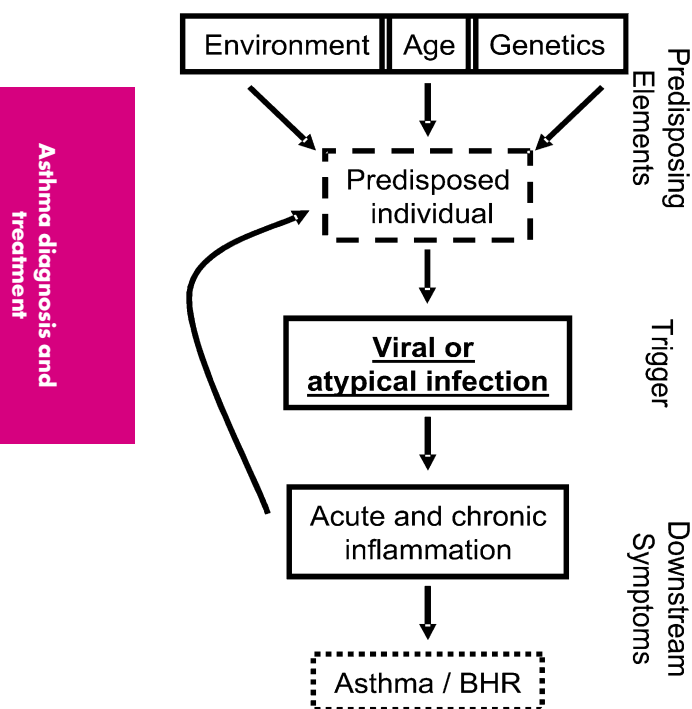


FIG 1. Multifactorial influences on the development of asthma, showing influences in the development of asthma or bronchial hyperreactivity (BHR). Genetics, age (more specifically infancy), and environmental factors can all predispose an individual to asthma. A trigger, often a viral infection, then leads to chronic inflammation and ultimately to asthma. Pulmonary inflammation itself is also a factor that can predispose individuals to asthma.

the local environment both physiologically and immunologically.

THE HYGIENE HYPOTHESIS AND THE T_H1 - T_H2 MODEL OF IMMUNE BALANCE

In developed countries the incidence of asthma has increased dramatically in the last 2 decades. An explanation for this phenomenon is known as the hygiene hypothesis.⁶ This states that improved hygiene decreases early exposure to bacterial and parasitic infections that assist in the development of T_H1 responses. A proper balance between T_H1 and T_H2 responses is thought to be important in the proper regulation of immune responses. Newborns generally have T_H2 -skewed patterns of immunity, and in the absence of immune-maturing infections, young children remain prone to the development of T_H2 responses and thus atopic disease. According to the hypothesis, T_H1 -driven infections should educate and improve the immune response in neonates and infants.

In animal models it has been shown that certain viruses (eg, RSV and pneumonia virus of mice) enhance allergic T_H2 cytokine response and perivascular inflammation, whereas other (eg, influenza) infections do not.⁷ Recently, the simple and early version of the hygiene hypothesis has

been revised, and the association between an enhanced T_H2 immune state and allergic disease has been questioned. For example, influenza infection can, under some circumstances, enhance allergic disease caused by T_H1 -polarized dendritic cells (DCs) producing IFN- γ .⁸ This study is timely with regard to the reappraisal of the T_H1 - T_H2 imbalance model of the hygiene hypothesis.⁹ In this revised model T_H2 bias is not the sole contributor to immune disease. The increase of T_H1 -mediated autoimmune diseases, such as diabetes,¹⁰ and deficiency of $CD4^+/CD25^+$ regulatory T cells also appear linked to excessive hygiene.¹¹ The presence or absence and correct development of these cells in neonates might be important, with their development in the thymus being affected by common infantile viral infections. It is possible that some neonatal viral infections specifically affect immune regulation and development and that this leads to inappropriate levels of both T_H1 and T_H2 cells in later life, causing allergic and autoimmune disease.

NEONATAL IMMUNITY

Most experimental data showing the relationship between the T_H1 - T_H2 response and allergic disease are based on observations made in adult animals with mature immune systems. Immune function in neonates differs from that of adults. At birth, the immune system is not fully mature. Prenatal life is characterized by successive waves of colonization of the periphery with cells originally from the liver, followed by cells from bone marrow.

Selection of T lymphocytes occurs in the thymus, so that emerging cells are tolerant to self-antigens but are significantly reactive to escape deletion. This process is not complete at birth, and the thymus continues to be active during the first years of life. In mice the thymus is quite immature neonatally, and it is possible to induce lifelong tolerance to antigens by exposure in the first few days of life. This can happen in human fetuses exposed to some infective agents that cross the placenta, inducing tolerance in the developing immune system.¹²

Neonatal antigen-presenting cells tend to be deficient in the production of IL-12, and T cells are relatively scarce in the newborn period. Furthermore, T cells making IFN- γ (T_H1 cells) are more prone to apoptosis after antigen exposure. This might partially explain the T_H2 -skewed immunity in newborns. However, it is becoming clear that mature functions can be demonstrated on all arms of the adaptive immune system when given the right conditions.¹³ For example, lymphocytes themselves are not necessarily deficient, as shown by the effects of transferring neonatal T cells into an adult mouse and observing clearance of a *Pneumocystis carinii* infection.¹⁴ Neonatal immune cells rather appear to be deficient in providing strong stimuli to responding cells because neonatal antigen-presenting cells fail to upregulate MHC class II and costimulatory molecules.¹⁵ Antigen presentation by DCs has been shown to be important during adult RSV infection, with an increase in the numbers of pulmonary

DCs and a change of phenotype.¹⁶ They might therefore be important in neonatal immune development. Antibody levels and classes are also different in early life to adulthood. Neonatal antibody is characterized by increasing levels of maternal immunoglobulin during the last trimester, replaced during the first year of life by neonatal IgM, then IgG, and finally IgA production *de novo*. These special features of the neonatal immune system mean that young children are much more susceptible to infectious diseases, such as diphtheria, pertussis, measles, and mumps, and with aging, mortality decreases abruptly, so that by the age of 10 years it is reduced 10- to 100-fold.

AGE AND THE AFTERMATH OF RSV INFECTION

In studies of the effects of age on responses to RSV infection in a neonatal mouse model, we found that the time course of viral infection was similar in adults and neonates.¹⁷ Neonates did differ in their response to primary RSV infection, showing reduced viral replication and poor IFN- γ responses. Importantly, these neonates did not have overt disease during primary infection, but when rechallenged with RSV in adult life, they showed enhanced disease. This was characterized by increased weight loss and inflammatory cell recruitment, including T_H2 cells, neutrophils, and IFN- γ -producing CD8 T cells. This model suggests that RSV infection at a very young age has the potential to cause long-term alterations to the immune system.

The above observations suggest that the susceptibility of children to RSV and to virus-associated wheeze is strongly dependent on postnatal age of infection and the developmental stage of the immune system. Host genetics undoubtedly also play an important part, but studies of the interactions between genetic variation and the postnatal environment need to be performed. For now, it seems that children are particularly prone to chronic inflammation triggered by viral or atypical bacterial infections. It is possible that chronicity or persistence of pathogens in the lung might perpetuate the inflammation, which is exacerbated by new infections. This persistent inflammation drives the airway reactivity characteristic of asthma (Fig 1). Importantly, RSV has been shown to be persistent in a mouse model.¹⁸ If this model is correct, infection is placed centrally in the pathogenesis of asthma; this clearly

opens the possibility of new preventative and therapeutic stratagems for those with recurrent wheezing disorders.

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