

Role of innate immunity in the development of allergy and asthma

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Purpose of review

Asthma is essentially a developmental disease, in which the normal growth and development of the respiratory and immune systems are affected by environmental exposures acting on underlying genetic predispositions. The purpose of this review is to examine the role of innate immunity in the lungs in the development of allergy and asthma.

Recent findings

Both the innate and adaptive arms of the immune system are immature at birth and undergo prolonged periods of postnatal maturation. As such, they are vulnerable to adverse environmental exposures, both before and after birth. Both genetic predispositions and environmentally induced epigenetic changes in gene expression are likely to contribute to the risk of asthma; however, the relative contributions are unclear. Increasing interest is focused on deficient innate responses of the respiratory epithelium to viral infections and how these may increase the risk of asthma. However, definitive proof that these are primary and not secondary effects is lacking. Although most research has concentrated on the role of respiratory viral infections in increasing the asthma risk, the recent suggestion that the lung has a resident bacteriome and potentially important viral–bacterial interactions in the lungs broadens research scope in this area.

Summary

Classic risk factors for asthma include a family history of asthma and allergies, early and persistent allergic sensitization and viral lower-respiratory infections in early life. However, these factors do not fully explain the risk. Perhaps, the resident pulmonary microbiome and the immune response that this generates during respiratory viral infections will provide the 'missing link' in the epidemiology.

Keywords

bacteria, environmental exposures, epigenetics, genetic predisposition, viral infections

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Introduction

Although there is some evidence that asthma can develop at any age and that the phenotypic expression of asthma can differ in different life stages, most asthma has its origin in early life. Asthma is essentially a developmental disease, in which the normal growth and development of the respiratory and immune systems are affected by environmental exposures acting on underlying genetic predispositions. Both of these body systems are functionally immature at birth and undergo prolonged periods of postnatal development and, as such, are vulnerable to a variety of environmental exposures. The purpose of this review is to examine the role of innate immunity in the lungs in the development of allergy and asthma. Early life influences on respiratory development and on the risk of asthma have been reviewed recently by

us and by others [1–5,6*] and will not be considered here.

Innate immunity in lung defence

The epithelial surface of the lungs is essentially open to the external environment and is subjected to a constant barrage of noxious and potentially damaging environmental exposures including oxidant and irritant gases, particulate matter and microorganisms. A series of defence mechanisms have evolved to protect the airway epithelium from injury, including: the antioxidant capacity of the epithelial lining fluid; mucociliary clearance; the barrier function of the epithelium itself; and, of relevance to this review, the innate and adaptive immune systems.

Innate immunity describes the automatic, nonspecific immune responses to potentially pathogenic invasion

by microorganisms (e.g. bacteria, viruses, and fungi) (reviewed in [7^{••}]). Phylogenetically, these are 'ancient' responses that are encoded in genomic DNA. The innate immune system consists of a series of sensing elements, known as pattern recognition receptors that respond to microbial components and trigger inflammatory responses. Pattern recognition receptors include toll-like receptors (TLRs) located either on the cell surface (TLR1, TLR2, TLR4, TLR5, TLR6) or in the cytosol (TLR3, TLR7, TLR8, TLR9); nucleotide-binding oligomerization domain (NOD)-like receptors (NLR), which exist in 'inflammasomes' consisting of one or two NLRs, an adapter molecule (e.g. apoptosis-associated Speck-like protein, ASP) and caspase-1; retinoic acid inducible gene-I (RIG-I)-like receptors and melanoma differentiation-associated gene 5 (MDA5), which are RNA helicases important for viral recognition and initiation of type-1 interferon responses; and cytosolic DNA sensors that sense bacterial DNA and also initiate type-1 interferon responses. Cells primarily involved in innate immune responses in the lungs include epithelial cells; macrophages and dendritic cells; and inflammatory cells, such as neutrophils. Dendritic cells, located within and below the airway epithelium, form an extensive network that provides surveillance of the airway lumen via dendrites that protrude between epithelial cells. This network forms an important part of innate immune defences as well as a link to the adaptive immune system [8[•]]. The complexity of the ligands, signalling pathways, and inflammatory responses involved in innate immune responses in the lungs is beyond the scope of this brief review and interested readers are referred to recent publications [7^{••},9]. In addition, the central role of dendritic cells has also been comprehensively reviewed [10].

The adaptive immune system lends specificity to the host response via antigen recognition through antigen-specific receptors that enable triggering of targeted cellular and humoral responses. These two limbs of the immune system do not work in isolation but interact [9,10]. Dendritic cells and T helper cells including the relatively recently described Th-17 subset that secrete interleukin (IL)-6, IL-17, and IL-21 and are capable of mediating neutrophilic inflammation are intimately involved in these interactions.

Although some aspects of innate responses are functional at birth, full maturity is not reached until much later in childhood. Neonatal dendritic cells have a decreased ability to process and present antigen that can, in part, be explained by a decreased ability to secrete IL-12 [11]. Naive T-cells in cord blood are more akin to 'recent thymic emigrants'. These cells have 'promiscuous' receptors that respond to a range of peptides, as opposed to the highly specific antigen

receptors characteristic of mature T-cells circulating in adult blood. Although neonatal T-cells will respond to antigen by proliferating and secreting cytokines, the majority appear to undergo apoptosis and do not appear to form long-lived memory cells. Those neonatal T-cells that do not undergo apoptosis following activation develop a regulatory T-cell phenotype. The neonatal adaptive immune system has a Th-2 bias due to active suppression of fetal Th-1-like function [12,13]. This bias persists after birth, with maturation of Th-1 functions lagging behind maturation of Th-2 functions over the first year or two of life (reviewed in [11]) and appears to be more exaggerated in children at high risk of developing asthma and allergies. Delayed postnatal maturation of adaptive immune function is a risk factor for both respiratory infections in early life and the subsequent development of asthma [11,14].

Postnatal maturation of the immune system is driven by environmental exposures. Exposure to microbial products and upper respiratory viral infections accelerate maturation of innate immunity, although some exposures appear to delay immune maturation (see below). Data from animal studies also suggest that microbial stimulation may also increase the risk of allergic sensitization depending on the exposure 'dose' and the developmental timing (reviewed in [15]). However, one must always be careful in extrapolating findings from animal studies into humans.

Genetic and epigenetic influences on immune function development and the risk of asthma

Increasing evidence suggests that several pathways underlie the development of asthma and that these may have separate genetic susceptibilities [2,5,16,17]. These include delayed lung growth; heightened bronchial responsiveness; delayed immune maturation; sensitization to aeroallergens; and propensity to lower respiratory viral infections in early life. Although some overlap between these susceptibilities undoubtedly exists, the extent of this overlap is unclear and will require further study using modern techniques [2,18^{••}]. Delayed immune maturation at birth, as indicated by cord blood cytokine levels or responses to stimulation *in vitro*, is seen in infants born to parents with allergy/asthma [13,19]. However, the extent to which this represents a genetic predisposition or epigenetic phenomena [13,20] is not clear. The gene for interferon (IFN)- γ is heavily developmentally regulated, primarily by methylation of CPG moieties in the promoter region. Postnatal demethylation is associated with an increased capacity to secrete IFN- γ ; however, the extent to which this demethylation is under genetic or environmental control is not clear.

Impact of antenatal environmental exposures on immune function development and the risk of asthma

An increasing array of antenatal exposures is thought to impact on immune function and increase the risk of allergies and asthma. Cigarette smoke exposure, especially maternal smoking during pregnancy but also exposure to 'second hand' smoke, is perhaps the most well recognized risk factor, associated with decreased cord blood cytokine levels, impaired cytokine responses, and attenuation of TLR-mediated responses to microbial stimuli [21]. Other antenatal exposures associated with decreased neonatal immune responses include maternal diseases, for example asthma [13] and type 2 diabetes [19]; maternal diet, especially diets rich in methyl donors such as folate and vitamin B12 (reviewed in [22]), however most evidence comes from animal studies and the situation in humans is less clear; and season of birth [19]. Maternal diet may also have a positive effect on fetal immune development, lowering the risk of asthma in the offspring (reviewed in [23]). Again, how these exposures alter immune development is not known but epigenetic mechanisms are likely to be involved, as evidenced by the third generational effects of (grand)-maternal smoking increasing the risk of asthma in children born to females exposed to tobacco smoke products *in utero*.

Respiratory infections and the risk of asthma

Much current interest is being generated by the studies showing the wheezing with lower respiratory viral infections in the first years of life are major risk factors for subsequent asthma (e.g. reviewed in [10]). Earlier literature using surrogate markers of respiratory infections, for example number of siblings and day care attendance in early life, were interpreted as showing a protective effect on the development of asthma with increasing 'respiratory infections'. These 'data' were incorporated into the so-called 'hygiene hypothesis' and incorrectly interpreted as suggesting that fewer respiratory infections led to delayed immune maturation and an increased risk of asthma and allergies. However, these studies rarely differentiated between upper and lower respiratory infections, did not account for exposures to noninfectious microbial products and rarely measured immune maturation. Unequivocal evidence demonstrates the increase in asthma risk for infants and young children who wheeze with respiratory viral infections (reviewed in [10]). Evidence is also mounting that a genetic predisposition increases both the frequency and severity of lower respiratory viral infections [14,24,25]. Although direct evidence from infants and young children is lacking, there is an increasing acceptance that patients with asthma respond differently to respiratory viral infections and that defects

in innate immune responses in the respiratory epithelium may underlie these differences (e.g. reviewed in [26,27]). These differences include decreased antiviral responses with less secretion of type 1 and 3 interferons which, in turn result in less epithelial cell apoptosis and increased viral shedding. Impaired neutrophil responses have also been reported in adult asthmatics [28], although the relevance of this to the initiation of asthma in early life is not immediately apparent.

Viral-allergen interactions in asthma

Epidemiological data from longitudinal birth cohort studies has suggested a synergistic interaction between wheezing with respiratory viral infections and sensitization to aeroallergens in early life (reviewed in [29]). The more severe the atopy, as judged by allergen-specific IgE antibody levels, the higher the risk of subsequent asthma for a given number of lower respiratory infections [30]. Interestingly, this risk extended well below the levels of IgE antibodies conventionally taken to indicate allergic sensitization. The precise mechanism for this interaction is not clear; however, recent evidence from both animal studies and from studies in children with acute severe asthma exacerbations [31] may give a clue. A 'lung-bone marrow axis' has been postulated [6•], in which secretion of type 1 interferon by epithelial cells in response to viral infections leads to upregulation of the high affinity IgE receptor on airway mucosal dendritic cells (AMDC). In the presence of preexisting IgE antibodies, for example against aeroallergens, cross-linking of these receptors results in upregulation of the ability of AMDC to present allergen triggering Th-2 memory cell responses and a marked release of TH-2 cytokines, in particular IL-4 and IL-13. The increase of IL-4/IL-13 stimulates the release of pro-inflammatory alternatively activated macrophages from the bone marrow, and these home to the airway mucosa where, in the presence of a high IL-13 environment, precipitate further inflammation [10]. At this stage, this proposed mechanism for viral-allergen interactions is speculative and needs to be confirmed by systematic study in young children. In addition, whether mechanisms such as these operate in infants and young children and whether they can explain the epidemiological data linking wheezing with respiratory viral infections and early allergic sensitization with the risk of subsequent asthma remain to be proven.

Conclusion

Traditionally, the lung has been considered to be sterile, lacking a resident microbial population such as exists in the gastrointestinal tract, the pharynx and on the skin. However, the recent application of metagenomic techniques has challenged this assumption. Hilty *et al.* [32••] studied the pulmonary microbiome in adults with asthma

and chronic obstructive pulmonary disease and adult control and demonstrated a rich microbial flora. There were differences in adults with disease when compared with adult controls or with children with severe asthma. The relevance of this pulmonary bacteriome to immune development and risk of asthma and allergies is not known; however, by analogy with the gastrointestinal system, it is likely to be important.

Immune responses to bacteria, especially in asthmatics, have been recognized for some time. The boosting of specific IgE antibodies against bacteria has been demonstrated in children during acute asthma exacerbations [33]. More recently, we have reported the presence of specific IgE antibodies against *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Staphylococcus aureus* in a birth cohort of children followed to 14 years of age. Consistent with previous reports, we found that anti-Staph IgE were more frequently found and were at higher levels in atopics and increased the risk of asthma in these children [34]. More interestingly, IgE antibodies directed against *H. influenzae* and *S. pneumoniae* were at higher levels than those against *S. aureus*, were equally common in atopic and nonatopic teenagers and were protective against asthma in this community-based cohort. Taken together, these observations raise the possibility that bacteria resident in the respiratory tract gain entry through the epithelial barrier at times when this is weakened, as is postulated during respiratory viral infections, and are 'recognized' by the immune system.

These data raise the possibility that the resident respiratory bacteriome present during a respiratory viral infection may influence the immune response to that viral infection and may help to determine the risk of subsequent asthma. Certainly, epidemiological studies have difficulty in defining how respiratory viral infections in early life increase the risk of, or protect against, the development of asthma. Although early allergic sensitization against aeroallergens is clearly an important risk factor, data from longitudinal cohort studies suggest that this is also not a straight-forward relationship. Perhaps, the resident pulmonary microbiome and the immune response that this generates during respiratory viral infections will provide the 'missing link' in the epidemiology.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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