Review Article

THE INTERACTION BETWEEN RESPIRATORY ALLERGIES AND INFECTION

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ABSTRACT

The link between allergy and infection, or the microbial world, is receiving world-wide attention. Infectious organisms may play a role in allergy prevention, but some organisms have been linked to the causation of atopic disease. Many (sometimes the same) organisms may exacerbate atopic disease, including diseases of the respiratory tract.

INTRODUCTION

By way of introduction, defining the concepts under discussion may be useful. Allergic rhinitis implies an inflammatory disease of the nose, where inflammation has an allergic basis.[1] This form of allergy is usually mediated by immunoglobulin E (IgE).[1] Asthma is defined as an inflammatory disease of the lower airways, and is characterised by airway hyper-responsiveness to multiple triggers which produce intermittent and reversible symptoms.[2]

The term 'allergy' is very loosely and inconsistently defined, but for the purposes of this article, is a non-specific reaction of the human body, mediated by immunological mechanisms.[3] The term 'atopy' is equally confusing and is hereby defined as an inherited tendency to produce IgE-mediated allergy and resultant symptoms from the inflammatory disease state.[3]

The human body is exposed to a multitude of microbes and infectious organisms throughout life. Many of these organisms 'colonise' the skin, gastrointestinal tract (GIT) and airway. Today we recognise that this colonisation includes the lower airway, previously thought to be sterile.[4] These colonising organisms play an important role in disease prevention, including allergic disease. However, new evidence of immune dysregulation suggests that early colonisation, especially of the GIT and airway, by pathogenic micro-organisms, has deleterious effects that may contribute to the allergic and atopic potential of young children.

By the same token, atopic individuals who have an underlying allergic condition have frequent disease exacerbations, mostly produced by infectious organisms, viruses and bacteria, depending on the specific condition.

We should consider the relationship between 'infection' and respiratory atopy in either disease causation (or prevention) (Figure 1) and disease exacerbation.

MICROBES, DISEASE CAUSATION AND PREVENTION

Significant work has revealed that the infant GIT microbiota, depending on its make-up, may have allergy protective benefits or contribute to disease causation. This is the principle of 'oral tolerance', frequently attributed to early allergen exposure in the infant diet,[5] but significantly benefited by the presence of healthy or probiotic bacteria.[6] The term 'Hygiene Hypothesis' was first coined in 1989 by Professor David Strachan in London.[7] Derived from his study showing that a child's risk of developing allergic rhinitis or "hay fever" was inversely related to the number of older siblings in the family, it was suggested that microbial exposure in early life protects against allergic rhinitis, eczema, and asthma. It is now recognised that the concept is better explained by declining microbial diversity[8] and hence better terms may be used, such as:

- "microbial hypothesis" (avoiding an overemphasis on cleanliness);
- "old friends hypothesis" (implying that microbes that were beneficial for immune system development have

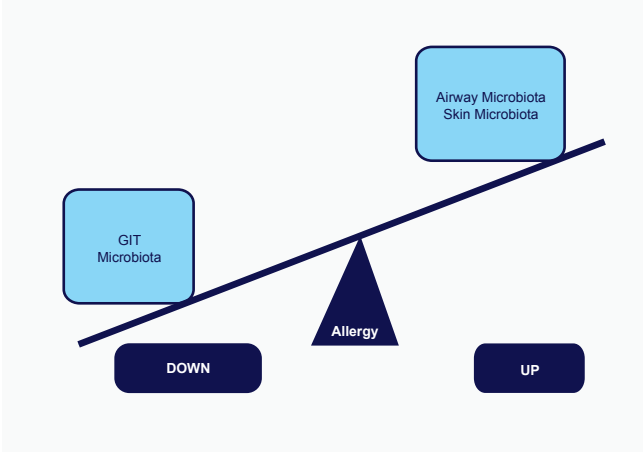

Figure 1: Microbial interaction in allergic disease causation

been eliminated or replaced);
- "biodiversity hypothesis" or "biome depletion".

Lower GIT microbial diversity in infancy has been linked to a greater risk of asthma in later life.[6] There are many ways in which the microbial diversity can be improved in young children, including natural vaginal birth, birth out of hospital, birth and infancy on a farm, and avoiding unnecessary antibiotics. What is missing from the body of evidence is that artificial probiotic supplementation is able to reverse these effects. There is emerging evidence of probiotic supplementation in pregnancy being able to reduce the incidence of atopic dermatitis (AD)[9] and mitigate the severity of AD in children,[10] but as yet there is little convincing evidence that probiotic supplementation reduces airway allergy.

New data on the 'atopic march', however, suggests that early AD in children has a direct effect on later airway allergy through the production of cutaneous and systemic thymic stromal lymphopoietin (Figure 2).[11] This substance is released from inflamed skin and may explain why diseased skin sets up a child for the allergic march and airway allergy later in life. It has the ability to influence generation of TH2 lymphocytes and IgE production in susceptible airways.

A further aetiological factor has been identified in AD that relates to airway allergy. This operates through the gene and resultant structural protein known as filaggrin. Filaggrin defects increase the risk of developing allergic sensitisation, atopic eczema, and allergic rhinitis.[12] Filaggrin gene mutations also increased the risk of asthma in people with atopic eczema.[13] Restoring skin barrier function in filaggrin deficient people in early life may help prevent the development of sensitisation, and halt the development and progression of allergic disease.

At the opposite end of the spectrum of 'declining microbial diversity' and disease causation is a paradoxical concept that the presence of so-called 'commensal' organisms in the infant hypopharynx in early life may in fact relate to asthma onset in later life. This work, made famous by Hans Bisgaard, has revealed that infants who have early 'colonisation' of the nasopharynx are significantly more likely to develop wheeze, more severe wheeze and later asthma. The most consistent effect is shown for *Haemophilus influenzae* but *Streptococcus pneumoniae* also plays a role.[14] The odds ratio (OR) for association of early *Haemophilus influenzae* colonisation, and asthma at 5 years of age is 4.57 (CI 2.18 – 9.57).[14] It seems likely, however, that this association is not direct causation (organism – asthma) but rather representative of an underlying immune defect placing children at risk of both early colonisation and subsequently asthma.

There is now increasing evidence that the asthma phenotype expression is strongly influenced by respiratory viral infection. Whilst allergy may contribute to asthma initiation, viruses and recurrent viral infections are now understood to be equally important. The effect on asthma, however, is strongest when both factors (allergy and infection) operate in synergy.[15] New evidence suggests that susceptibility to recurrent viral infections, failure to generate protective immune tolerance to aero-allergens, and the interaction of these factors with airway inflammation may result from innate immune defects of respiratory epithelial (including mucosal dendritic) cells.[15-18] The resultant viral interaction with airway cells produces up-regulation of high-affinity IgE receptors on myeloid precursor cells, amplifying local airway inflammation (Figure 3). The genetic profile and polymorphisms of these associations are now being discovered.[19] Toll-like receptor 1 single nucleotide polymorphisms (TLR1 SNPs) has been associated with both atopy and multiple viral presence in host airways.[19]

MICROBES AND RESPIRATORY ATOPIC DISEASE EXACERBATION

Whilst wheeze in children is a common problem, most children

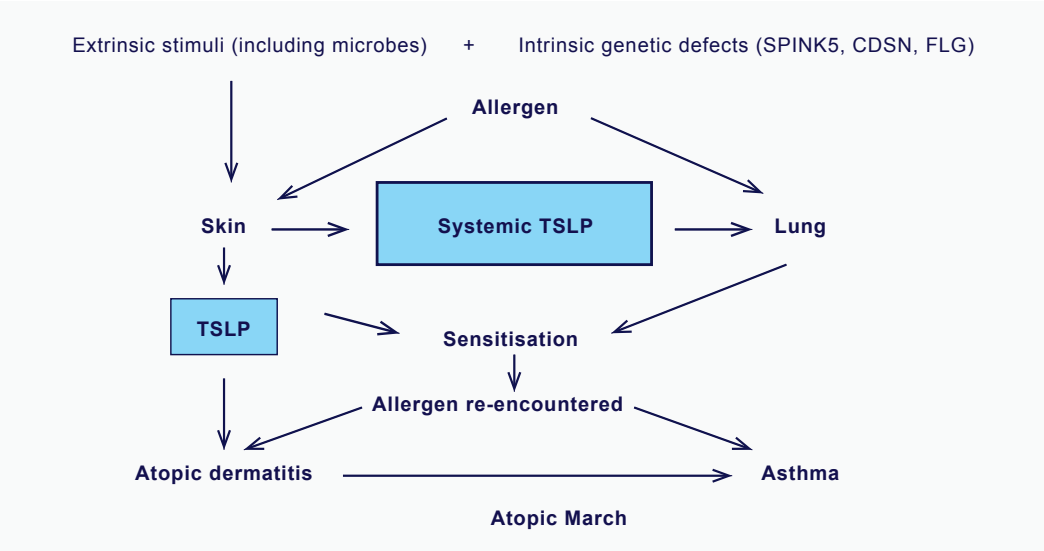

Figure 2: Thymic stromal lymphopoietin (TSLP) in the allergic march[11]

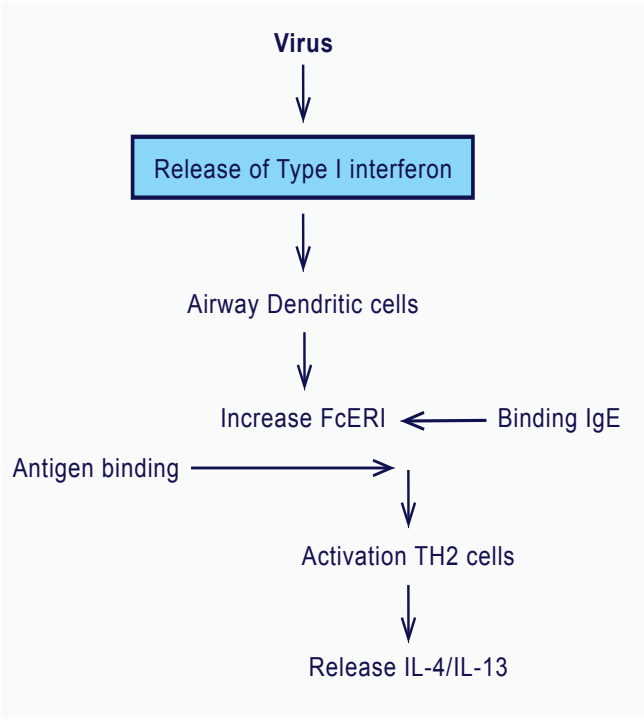

Figure 3: Viral-airway inflammatory interactions in atopic asthma

who wheeze, even children who wheeze recurrently, do not go on to develop asthma. Some years ago it was demonstrated that of the respiratory viruses producing wheeze, the greatest risk for recurrent wheeze comes with Rhinovirus (RV). Presence of RV increases the risk for recurrent wheeze 3.3 fold ($p < 0.05$).[20]

In addition to recurrent wheeze, it is now widely accepted that acute exacerbations of asthma are largely driven by RV infections.[21] The mechanisms therefore, for asthma causation operate at the point of exposure to viruses, to manifest an asthma exacerbation.[22] Early work has also suggested that atopic individuals, through increased intracellular adhesion molecule 1 (ICAM-1), are more likely to attract and retain RV in the lower airway (Figure 4).[23]

Whilst the mere presence of RV produces asthma exacerbations, persistence of RV determines more severe asthma exacerbations.[24] In a study by Kling et al., fifty children who were

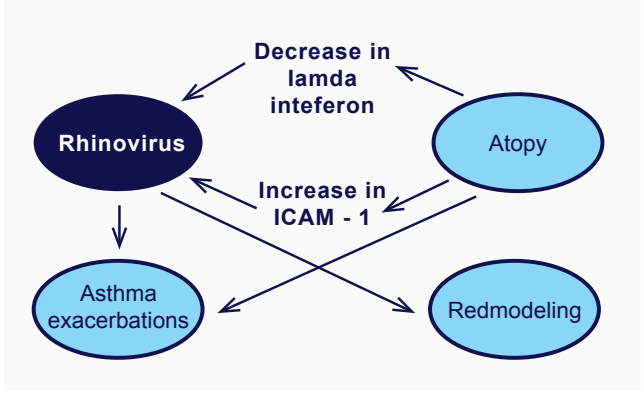

Figure 4: Rhinovirus and asthma exacerbations

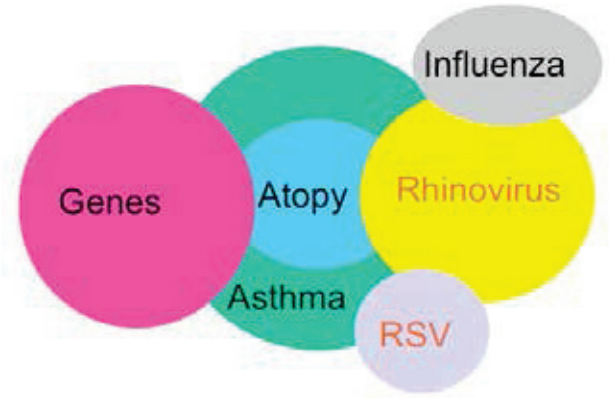

Figure 5: Viruses and asthma

admitted with an asthma exacerbation were characterised: 74% were atopic, RV nucleic material (RNA) was isolated from the airway in 82%, whilst respiratory syncytial virus (RSV) RNA was found in only 12%. Peak expiratory flow rate (PEFR) was lower at 6 weeks in children with RV RNA that persisted until 6 weeks ($p = 0.009$). In addition, exacerbations were more severe in children with RV RNA at 6 weeks.[24]

The RV story builds; today 4 serotypes of RV (A-D) have been identified. In one study RV was detected in 87.5% of acute asthmatic children. The novel RV type C (RVC), was present in the majority of children with acute asthma (59.4%) and associated with more severe asthma. Children with RVC ($n = 76$) had higher asthma severity scores than children whose HRV infection was RVA or RVB only ($n = 34$; $p = 0.018$).[25] This evidence suggests that RVC is the causal agent of more severe disease.

The host genetic profile creating this association is becoming evident. There is clear and new evidence that expression of human cadherin-related family member 3 (CDHR3) enables the cells normally unsusceptible to RV-C infection to support both virus binding and replication, and the asthma susceptibility gene product CDHR3 mediates RV-C entry into host cells, and suggests that rs6967330 mutation could be a risk factor for RV-C wheezing illnesses.[26] In addition, variants at the 17q21 locus were associated with asthma in children who had had HRV wheezing illnesses and with expression of two genes at this locus.[27] The 17q21 variants were associated with HRV wheezing illnesses in early life, but not with RSV wheezing illnesses.[27]

A final word on influenza virus and asthma exacerbations. The 'swine flu' pandemic of 2009 highlighted the importance of influenza in exacerbations of asthma.[28] In that pandemic, next to pregnant women, asthmatics had the highest mortality, suggesting the important role of influenza in asthma. As a result, it is now widely recommended that asthmatic adults and children receive annual influenza vaccine. The interaction of atopy, asthma and viruses is reflected in Figure 5.

CONCLUSION

The interaction between respiratory allergies, infection and

microbial colonisation is clearly a complex issue. Microbes have the potential to influence allergy development through the concept of tolerance promotion. This is especially true of probiotic organisms in the infant GIT. It is, however, also evident that both bacteria and viruses may induce airway atopic asthma. This reflects a defect in innate immunity in genetically susceptible individuals.

Finally, exacerbations of asthma are almost exclusively driven by RV and influenza infections of the airway. HR type C seems to be an important culprit.

There is significant progress in disease understanding from a pathophysiological perspective. Still missing from the equation, however, is evidence of therapeutic interventions to put these mechanisms right. It might have seemed that a universal unifying hypothesis of disease causation and therapy lay in the arena of vitamin D deficiency or some other similar panacea. Despite good evidence that recurrent infections, allergy and asthma are more common in vitamin D insufficient individuals,[29-31] the benefit of vitamin D supplementation is controversial.[32]

Certainly it must be said that infectious diseases and allergy are intimately linked. This may provoke renewed interest in anti-infective agents as therapy. As a word of caution, there is no evidence that routine use of antibiotics influences either asthma onset or exacerbations of asthma. We live in a world of excess antimicrobial resistance of micro-organisms, and antibiotics in airway atopic conditions have a very limited role.

There are a number of additional unanswered questions, including what impact pollution has on airway atopy, what the role of climate change will be on this model and finally what the relationship is between allergy in the nose and viral upper respiratory tract infections.

This field is unravelling daily. It is very likely that new discoveries will ensue to reduce the burden of allergic disease through manipulation of the microbial world we live in and live with. It is hoped that both prevalence of atopic diseases and incidence of disease exacerbations will be mitigated.

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