The immune response critically depends upon interaction with microorganisms in order to develop. Consequently, the role of infections has been investigated in diseases of immunological imbalance such as allergy and asthma. Nevertheless, any effects would be expected to vary upon the type of micro-organism, the time, severity or persistence of exposure, genetic predisposition of the host and possibly other cofactors present.

Therefore, a straightforward hypothesis such as ‘infections protect from allergy’ might grossly underestimate such complexity. In the following text, we describe thoughts and hypotheses that have developed in the last few years in respect to associations between viral infections and allergy and/or asthma.

Viral infections and protection from allergy or asthma

Initially suggested in order to explain the sibling effect through viral infections, the “hygiene hypothesis”’s attractiveness and compatibility with immunological and life-style evidence have established it as the prevailing hypothesis explaining the increase of allergies and asthma. Nevertheless, there are several inconsistencies which remain to be resolved.

When researchers focused on specific pathogens, results have been conflicting, initial studies showing significant protective effects that were not confirmed in subsequent ones: measles and mycobacteria are characteristic examples.
The type of microorganism has been explored: it was suggested that gut-associated pathogens may induce protection, while respiratory ones may not.

However, respiratory infections were also found to either protect or be detrimental for asthma depending on their location (upper vs lower) according to the results of the German MAS study. In the same study, no effect was present in respect to IgE sensitization after the age of 3 and furthermore, there was no protective effect of gastrointestinal infections.

So, when it comes to viruses, there is more contradiction than in respect to bacterial flora or endotoxin/farm exposures.

It would be surprising if the future proved that viruses can be alone in protecting against allergy. More likely, the rate of exposure to a wide range of microorganisms, mostly non-pathogenic, may be more relevant.

**Bronchiolitis in the inception of allergy and/or asthma**

A number of interesting studies, in both men and mice, have supported the idea that severe infection with respiratory syncytial virus (RSV) early in life, may initiate asthma and/or atopic allergy.

However, such an association does not necessarily involve causation. Children who suffer from bronchiolitis have an abnormal cytokine production pattern in comparison to those who get just a cold from the same virus, already from the first day that the infection becomes apparent, suggesting that any defect is pre-existent.

Studies in animal models show that RSV induces the production and infiltration of eosinophils in the lung that are significantly associated with the development of airway hyperresponsiveness, not only after acute RSV infection, but also after allergen exposure. Similar results have been obtained with influenza. Unexpectedly, allergen-specific asthma in this model was due to dual allergen-specific Th1 and Th2 responses and was IFN-gamma dependent. These findings suggest that Th1 cytokine responses may sometimes be a prerequisite for the
induction of allergy, questioning the immunological basis of the hygiene hypothesis which assumes that allergic responses are regulated by Th2 cytokines.

The relation between lower respiratory tract RSV infection in early life and development of wheezing and atopy in later life was investigated by Stein et al. They demonstrated that RSV infection before the age of 3 was associated with an increased risk of infrequent and frequent wheeze at the age of 6. The association declined up to the age of 11 and lost its significance at age 13 onwards. It has to be noted that in the same study children who were affected by infections other than RSV (most of which would have probably been associated with human rhinoviruses (RV) continued to have increased risk of wheeze at puberty, a finding that has not received adequate publicity.

In conclusion, even though mechanistic studies seem to be supportive of the induction story, more natural history and especially intervention studies are needed in order to establish this story to firmer grounds.

Viral infections induce asthma exacerbations
In contrast to the above, there is little doubt that upper respiratory tract infections, common colds, are the major trigger of acute asthma exacerbations, confirmed in several prospective studies with virological confirmation. Unfortunately, such an effect has not been established with other allergic diseases, such as allergic rhinitis, atopic dermatitis, food or drug allergy.

Rhinoviruses are the predominating viruses. The mechanisms of virus-induced exacerbations of asthma involve direct infection of the bronchial epithelium by RV and local induction of inflammation, interaction of virus, allergen or other stimuli-induced inflammation, induction of a systemic immune response and possibly induction of neurogenic inflammation which have been reviewed.
Conclusions

Interactions of infectious agents with the immune system at different times and rates is a major driving force for symptom presentation in individuals with a propensity for allergy and asthma, possibly implicated from the very beginning of disease appearance.

It is increasingly evident, that such interactions are complex and certainly non-linear. This complexity could be better communicated through an ‘incoordination’ hypothesis: the physiological rate of development and response of the human immune system does not match the rate of exposure to various stimuli as they currently appear in modern (especially ‘westernized’) environments. Infectious agents, viruses included, are prominent, but not unique, among those stimuli, as they are major determinants of immune maturation and their ecology considerably affected by environmental changes, including, but not uniquely depending upon hygiene.

This notion is not far away from the ‘turnover’ suggestion by Matricardi and Bonini and in line with evidence on the development of the immune and respiratory systems in normal and atopic asthmatic children.

References

