

to dermal fibrosis and increased numbers of chimeric cells, suggesting that such an event is a triggering factor (P. Christner, Philadelphia, PA). Other activation factors of such cells, such as infections, can also be postulated. Alternatively, the presence of microchimerism may lead, by an unknown pathway, to a break of tolerance among host cells. Future studies will have to address the identification of infiltrating microchimeric cells, the functions of these cells, and the consequences of treatments of autoimmune disease on microchimerism, before fully determining the role of this phenomenon in human diseases.

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Do common childhood infections 'teach' the immune system not to be allergic?

Gert Folkerts, Gerhard Walzl and Peter J.M. Openshaw

Some environmental change must be responsible for the remarkable increase in prevalence of allergic diseases in affluent societies over the past 20 years. Children are born with a tendency to show allergic-type (type 2 cytokine) immune reactions, a pattern that disappears in the first few years of life. This maturation might be delayed or absent in individuals predisposed to allergy, where reduced exposure to dirt and fewer childhood infections might lead to inefficient maturation and therefore allergy in those who are susceptible¹. This proposal is referred to as the 'hygiene hypothesis'².

Viruses and allergy

What roles do viral infections play in the development of allergic disease? There is no doubt that many respiratory viral infections

Many asthma attacks are precipitated by respiratory viral infections, and severe infections in infancy are strongly linked to asthmatic disorders in childhood. However, as discussed at a recent meeting, an antigenically rich (dirty) environment may be essential for normal immune maturation, preventing atopic disease. Shifts in cytokine production seem to explain these phenomena.*

are bad for patients with respiratory atopic disorders. Even in healthy individuals, viral colds can cause temporary symptoms similar to those seen in hayfever and asthma.

With powerful new detection methods, it has become clear that respiratory viral infections are associated with the great majority of exacerbations in patients with asthma. Moreover, S. Johnston (London, UK) presented data showing that after rhinovirus infections, T cells from asthmatic subjects increase type 2 cytokine production, and that in comparison with responses in normal subjects, production of type 1 cytokines in response to rhinovirus is deficient in asthmatic subjects (Box 1). This might be the reason why eosinophil numbers and/or products are increased in the airways³.

P. Sterk (Leiden) discussed the effects of experimental rhinovirus-16 infection in atopic individuals⁴. Immunochemistry showed an increase in CD3⁺ and CD8⁺ T cells in the lamina propria, whereas CD4⁺ cell numbers remained unchanged. G. Folkerts (Utrecht) argued that the common link

might be that viruses and allergic diseases both cause airway inflammation and therefore airway hyper-responsiveness⁵. When both these diseases are combined, synergy may occur. Indeed, in animal studies, airway eosinophilia and hyper-responsiveness is more than doubled in animals that have an allergic response as well as a viral infection, compared with either alone. The synergistic effect of ovalbumin and virus-induced inflammation can be explained by interleukin 4 (IL-4)-producing CD4⁺ T cells induced by ovalbumin, leading to a switch in virus-specific CD8⁺ T cells from interferon γ (IFN- γ) to IL-5 production.

M. Jordana (Ontario, Canada) showed how it is possible to manipulate the T-cell cytokine balance in ovalbumin-sensitized mice. After ten successive inhalations with ovalbumin, GM-CSF or IL-12 gene transfer into the airways resulted in augmentation or suppression of airway eosinophilia, respectively⁶. Indeed, preliminary evidence by W.W. Busse and colleagues (Madison, WI) suggests that individuals who develop strong Th2 responses clear viruses inefficiently and thus show more severe symptoms. If this is correct, virus-infected asthmatics might suffer from persistent symptoms due to sustained infection, as well as the additive effects of virus- and allergen-induced inflammation.

Respiratory syncytial virus (RSV)

P. Pala (London, UK) summarized recent developments in understanding respiratory syncytial virus (RSV) disease⁷. In 1995, Sigurs reported that RSV bronchiolitis in the first year of life is a strong risk factor (even stronger than heredity) for development of asthma and atopy⁸. Pala presented follow-up data from that study, 7.5 years after RSV bronchiolitis infection (or mild RSV disease in controls). When peripheral blood mononuclear cells were stimulated with a panel of antigens, the frequency of RSV-specific, IL-4-producing cells was found to be higher in ex-bronchiolitics than in controls. These findings suggest that RSV bronchiolitis either expands RSV-specific T helper 2 (Th2) memory cells or that RSV infection is more severe in individuals with a selective (genetic?) bias towards Th2 responses.

Box 1. Key conference outcomes

- Rhinovirus infections can promote the release of Th2 cytokines.
- Increased levels of major basic protein are accompanied by increased levels of the chemokines RANTES and MIP-1 α in nasal aspirates of children with virus-induced asthma exacerbations.
- Rhinovirus infections enhance the number of CD3⁺ and CD8⁺ in the lamina propria of atopic airways.
- The synergistic effect of ovalbumin and virus-induced inflammation might be explained by IL-4-producing CD4⁺ T cells induced by ovalbumin, leading to a switch in virus-specific CD8⁺ T cells from IFN- γ to IL-5 production.
- RSV bronchiolitis either expands RSV-specific Th2 memory cells or RSV infection is more severe in individuals with a genetic bias towards Th2 responses.
- Pertussis vaccination and infections in the first two years of life emerged as strong predictors of atopy.
- Commensal organisms seem crucial for maturation of antigen-specific T cells.
- GM-CSF or IL-12 gene transfer into the airways results in augmentation or suppression of airway eosinophilia, respectively, in an allergic animal model.
- Developing vaccines and other treatments that direct the immune system towards Th1 reactions might be beneficial, both for defences against viruses and for suppression of allergic reactions.

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN- γ , interferon γ ; IL-5, interleukin 5; MIP-1 α , macrophage inflammatory protein 1 α ; Th2, T helper 2.

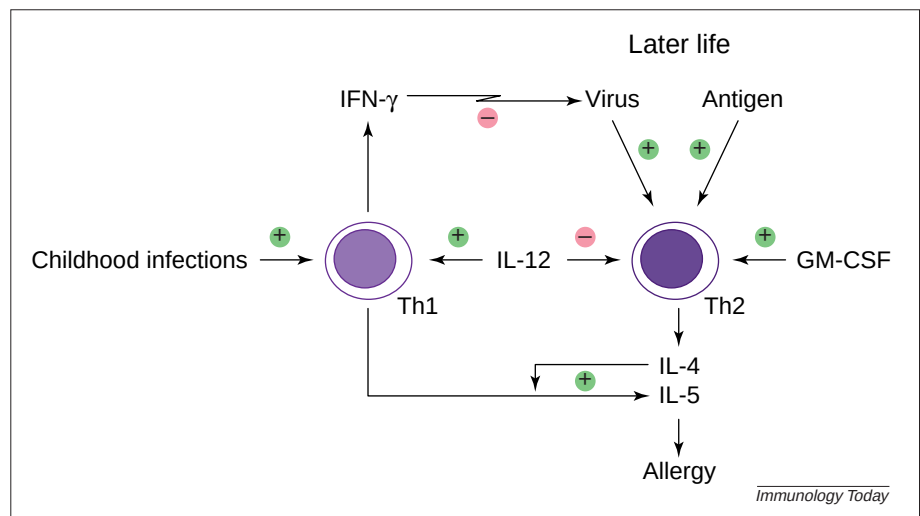


Fig. 1. Childhood infections might be important for the maturation of the immune system. A disturbed Th1 response in later life may lead to a shift in the release of particular cytokines (from IFN- γ to IL-5) and to a decreased capacity to eliminate viruses. Together with the antigen, viruses may exaggerate Th2 responses, leading to an enhanced allergic response. GM-CSF can increase Th2-mediated immune responses, whereas IL-12 is suppressive. Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN- γ , interferon γ ; IL-4, interleukin 4; Th1, T helper 1.

A central unresolved question remains: do severe responses to childhood respiratory viral infections mark out individuals as susceptible to later atopic disease, or do some infections (particularly RSV bronchiolitis)

actually predispose to atopic diseases? Preliminary evidence from preventative trials with antiviral antibody therapy suggest that the latter scenario is correct, but further trials are awaited.

J. Hopkin (Oxford) described a family practitioner study of 2000 children in Oxfordshire, UK, which examined the links between childhood infections, maternal atopy, social factors and childhood allergy. Pertussis vaccination and infections in the first two years of life emerged as strong predictors of atopy. The odds ratio for infections increased dramatically if antibiotics were given; antibiotic use in early life may provide the link between increased allergy and 'infection' in this study. Commensal organisms seem crucial for maturation of antigen-specific T cells, perhaps explaining the adverse effect of some antibiotics (simple penicillins seem not to be associated with atopy). In animal models, gut decontamination can induce Th2-biased responses.

T-cell cytokines and allergy

How can infections provoke asthma attacks and yet protect against allergy? The explanation may lie in the balance of different types of immune reaction responsible for countering different types of infection. Intracellular microorganisms (including viruses) normally trigger Th1 responses. According to the 'hygiene' theory, development of Th1 immunity is defective in an over-clean environment. This gives Th2 immunity the

opportunity to become dominant and favours allergic reactions (Fig. 1).

Concluding remarks

Developing vaccines and other treatments that direct the immune system towards Th1 reactions might therefore be beneficial for both defences against viruses and suppression of allergic reactions. Powerful new tools are becoming available to manipulate immune responses. However, we need to proceed with caution: the effects of such treatments on the development of other diseases are bound to be complex and may not be easy to predict.

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T cells at the turn of the twenty-first century

Lucy R. Wedderburn and Lee Dianda

The Cellular Immunology Unit (CIU) in Oxford, UK, has recently celebrated 36 years of pioneering work in cellular immunology. As part of this celebration, a recent meeting brought together others in the field, to discuss the current understanding of T-cell biology as we begin a new millennium.

Homing directions

Leukocyte recirculation is facilitated by the cells rolling over high endothelial venules

At a recent meeting, several surprising observations on the structure and function of T lymphocytes were revisited, and the most recent cellular, molecular and structural insights into T-cell biology were illustrated.*

(HEVs)¹. Although the shear stress of the cell wall varies greatly between anatomical

sites, as well as in response to exercise or inflammation, the rate of leukocyte rolling remains almost constant (T. Springer, Boston, MA). This is facilitated by an increase in the number of bonds between selectins and their ligands (located on microvilli tips). In addition, the number of microvilli tethers is increased where high shear stress occurs. This 'braking system' permits attachment under conditions of high shear stress; by contrast, under conditions of low stress or high ligand density, leukocytes do not become stalled.