FORALLVENT

Position paper on innovative avenues for allergy prevention and treatment

In the comprehensive overview of existing findings which has been established within the FORALLVENT project, it has clearly been shown that a number of protective factors for the development of asthma have been identified in areas with traditional or less developed life styles, where generally the prevalence of asthma and allergic outcomes is much lower than in affluent countries. Across Europe, a north-south and a west-east gradient in the prevalence of asthma and allergies has been demonstrated in large surveys enrolling children (ISAAC) and adults (ECRHS). Strong contrasts also exist on a much lower spatial scale, i.e. among children raised on a farm as compared to the neighbours living in the same rural areas but not on a farm. Since the first observations more than 15 studies have corroborated these findings and shown similar results in Switzerland, Germany, Austria, France, Sweden, Denmark, Finland, Britain, Canada, and New Zealand. Children raised on farms retain protection from allergy at least into young adulthood and according to some studies even to adult life.

The timing and the duration of farm exposures seems to play a critical role. The largest reduction in risk of developing respiratory allergies is seen among those who are exposed prenatally and continue to be exposed throughout their life. The protective factors in these farming environments have not been completely unravelled. There is, however, an indication that the contact to farm animals confers protection. Also the consumption of raw milk produced directly on the farm in childhood years has been shown to be beneficiary with respect to childhood asthma and allergies. Increased levels of microbial exposures may at least in part contribute to the protective effects. Such exposures to infectious agents and their products have been assessed indirectly by measuring antibody levels directed to particular pathogens in European studies or by directly detecting parasitic infections in developing countries and showing a negative association between particular exposures to micro organisms and parasites and allergic disorders.

Moreover, some measures of microbial compounds in farming environment have been performed and the results suggest that the underlying protective nature of these microbial

exposures have not yet been identified. Also the mechanisms by which such environmental exposures confer protection from respiratory allergies are not well understood. A number of gene-by-environment interactions have been observed with polymorphisms in genes of innate immunity receptors and exposure to farming environments. Therefore, it seems likely that increased levels of microbial exposures recognised by innate immune responses affect adaptive immune responses resulting in decreased levels of atopic sensitisation and asthma.

The epidemiological observations have also been transferred into animal models of allergy where it has been shown that exposure to dust from animal sheds either in the form of extracts or in the form of isolated microorganisms can have protective effects on airway hyper-responsiveness and down regulation of Th2 responses. With respect to helminth infections animal models have shown chronic helminth infections and bacterial products to down modulate airway inflammation. The immunological mechanisms are currently under investigation and point towards a role not only for regulatory T cells but also for a particular type of regulatory B cells and IgA antibodies in suppressing airway inflammation. Moreover, in vitro studies with human dendritic cells have shown that dust sample extracts redirect their polarizing capacity away from Th2 immune responses. Extracts from heminth parasites have indicated the presence of molecules capable of inducing regulatory T cell responses via modulating dendritic cells. The protective role of farm milk consumption, intestinal parasitic helminths as well as traditional diet indicates that it is not only inhaled exposures but that also the oral route is important suggesting a possible role of the intestinal mucosa as a target organ educating the immune system.

The gaps in our knowledge

Although we have made significant progress in identifying protective environmental exposures for the development of asthma and allergies, there are still many open questions. We do not know which microorganisms in the farm environment confer the protection from asthma and allergies. These could be bacteria or fungi or their toxins and related immuno-stimulatory molecules. Other sources of exposures might also play a role such as the exposure to non-self from animals and plants. With respect to the consumption of raw farm milk we even know less about the potential asthma and allergy protective substances or factors, be it microbial content, fat content, peptides or others.

Furthermore, the immunological mechanisms whereby the protective effects are exerted are not understood. Although there is some indication that immunological pathways are mediated by the innate immune system, it is not yet clear which receptors in the innate immune system and which signals downstream of them suppress the development of the Th2 response and thereby the production of specific IgE antibodies or skin reactivity to allergens and the new onset of asthma. Also the anatomical location of tolerance induction that controls the development of allergic inflammation in childhood has yet to be identified. These could be either in the airway mucosa by the inhalation route or in the intestinal mucosa after ingestions of farm milk products or early ingestion of dust by young children. The protective regulatory responses not only at the T cell but also at the B cell level have not been investigated in any detail in human allergies. Although our understanding of mucosal immune responses is improving, this knowledge has not yet been applied to the field of allergy prevention.

Finally, it is well known that asthma and allergies have a strong heritable component. Only few candidate genes have been tested for investigating the role of gene-by-environment interactions. Also, limited knowledge has been gained about the role of the environmental exposures and the expression of particular genes which may confer protection from the development of asthma and allergic illnesses. The genetic component may not only be affected by polymorphisms in the human genome or by increased or decreased gene expression in these environments, but also by the environment influencing epigenetic regulation. As to date there are no investigations on epigenetic mechanisms in farming populations.

The future directions proposed

The overall objective of the ‘farm’ studies is to understand the nature and mechanisms of protection from asthma and allergies in natural environments such as those encountered when growing up on a farm or in a rural area of developing country. Understanding both the exposures and the mechanisms can form the base for developing novel preventive strategies in the future. We thus must know more about:

- The precise nature of the protective exposures in farming environments: bacteria, fungi, microbial compounds, non-self immune stimulatory substances, etc.

- The mechanisms of tolerance with respect to immunology, genetic and epigenetic regulation.
- The development of suitable animal models to test candidates for allergy and asthma protection.
- The development of suitable in-vitro studies complementing the animal studies to test candidates for asthma and allergy prevention.
- Finally intervention trials investigating the preventive impact of such exposures in humans.