ASK AN EXPERT

Canadian experts in the field of allergies, autoimmunity and microbiome were asked to give their opinion about breakthroughs with considerable importance in healthcare management and medicine. This section presents the thoughts and opinions of those specialists who spend their lives studying these issues from different perspectives.

Immune system over-reactivity – are allergens the real aggressors? Who is to blame?

Christine McCusker, MSc, MD, FRCP[1] & Adam Byrne, MSc, MD, FRCPC

1. Clinical Director, Clinical Immunology Laboratory (MCH), Head of Immunology, Special Interest Section-CSACI and Research Director, Meakins-Christie Laboratories MUHC-Research Institute

The immune system is a dynamic and versatile defence system capable of differentiating pathological molecules (or antigens) from harmless ones and forming appropriate responses. This system evolves in response to environmental changes and adapts to counter perceived threats. However the recent and rapidly changing profiles of these environmental exposures in the Western world may have led to the maladaptive responses seen in allergic (atopic) diseases. These increasing diseases include asthma, allergic rhinitis, food allergies and eczema which result from inappropriate responses to otherwise benign proteins or allergens. All allergens stimulate immune activation; non-allergic individuals form active immune tolerance, the appropriate adaptive response. In those with allergies, however, allergens induce proliferation and differentiation of CD4 T-cells into the TH2 phenotype which produces cytokines IL-4, IL-5, IL-9 and IL-13(1). These cytokines, in turn, can induce reactive airways and stimulate a B-cell switch to produce allergen-specific antibodies of the IgE class. IgE then binds to receptors on effector cells, including mast cells. (2). Allergen contact subsequently leads to IgE cross-linking, activation of the effector cells and the release of mediators such as histamine and tryptase (2). The rapid release of these mediators results in symptoms including hives, eczema, rhinitis, asthma, and anaphylaxis (2).

Activation of TH2 immunity appropriately occurs in response to threats such as parasitic infections. In the absence of these and other immune stimulators, genetically susceptible individuals may respond to allergen exposure with skewed activation of TH2 cells (3). Environmental influences such as increased hygiene and a reduction in exposure to complex antigenic environments and infection which collectively reduce overall immune stimulation may be causatively linked to the disproportionately increased frequency of allergic disease in the western world. This hygiene hypothesis, first proposed as an explanation for this burgeoning frequency of atopy, was based on observations that farm children experienced less atopy than their urban raised peers (4) and children of lower birth order also developed fewer allergies compared with elder siblings.

The microbiome hypothesis, a refinement of this concept, suggests that exposure to complex microbial flora, both pathogenic and commensal, results in the development of appropriate immune-regulation to allergens (3). The microbiome is the sum of symbiotic microbial species present in an individual, estimated to be over 100 billion in the GI tract alone (5). Evidence suggests that balanced immune regulation depends upon a healthy microbiome. In germ-free mice with no microbiome, T-cell dysregulation toward TH2 (6) and higher susceptibility atopic disease (7) is shown. Colonization of the germ-free mice with Bacteroides fragilis restored appropriate T cell balance (8).

In humans, alterations in the microbiome have been associated with increased atopy. One study showed lower numbers of total commensal microorganisms, including notable decreases in Bacteroides species, in food sensitive children compared with a control group (9). In asthmatic adults alterations in the pulmonary microbiome, including increased Proteobacteria and decreased Bacteroides

species, has been demonstrated (10). Events linked to altered gut microbiota including Caesarean section delivery, perinatal antibiotic use, and bottle feeding are also associated increased atopy (9). As such reducing infectious disease spread and external modulation of the microbiome through increased hygiene, antibacterial wipe use, and antibiotic use may be promoting the development of atopy in at risk individuals.

The practice of recommending food avoidance for pregnant and breastfeeding mothers, coupled with delayed introduction of "allergenic" food in infants, may also be contributing to the increase in food allergies. One study examining peanut allergy prevalence in genetically similar populations in Israel and England found a marked increase in peanut allergy in English children. They identified the key major lifestyle difference in peanut allergic versus non allergic children as delayed age at first introduction to peanuts (11). In the subsequent, randomized control trial there was a significant decrease in peanut allergies in children encouraged to consume peanuts early (between the ages of 4-11 months) as compared to those avoiding until 2 years of age (12). These results suggest that the development of tolerance to foods may be achieved with early introduction in the diet although the optimal timing and form of these introductions remain to be confirmed.

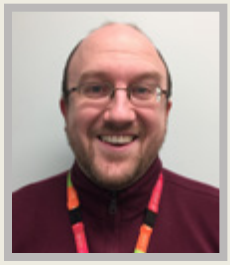
In summary current evidence suggests that promoting the formation of appropriate immune responses to allergens depends on the development of complex microbiota and introduction of complex antigens early in infant development. Allergens are otherwise harmless proteins. Promoting the formation of immunotolerance and targeting TH2 pathways will be the keys to reduction and prevention of atopic diseases. ■

References

1. Ngoc P Ly, Gold DR, Tzianabos AD, Weiss ST, Caladon JR. Cytokines, allergy and asthma. Curr Opin Allergy Clin Immunol. 2005;5:161-166
2. Kumar S, Verma A, Das M, Dwivedi P. Molecular mechanisms of IgE mediated food allergy. Int Immunopharmacol. 2012;13:432-439
3. Riiser A. The human Microbiome, asthma and allergy. Allergy Asthma Clin Immunol 2015;10:35-41
4. Von Mutius E, Vercelli D. Farm living: Effects on childhood asthma and allergy. Nat Rev Immunol. 2010 ;10:861-868.
5. Rey R, Peterson D, Gordon J. Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell 2006;124:837-848
6. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell. 2005;122:107-118.
7. Rodriguez B, Prioult G, Bibiloni R, Nicolis I, Mercenier A, Butel MJ, et al. Germ-free status and altered caecal subdominant microbiota are associated with a high susceptibility to cow's milk allergy in mice. FEMS Microbiol Ecol. 2011;76:133-144
8. Troy E, Kasper D. Colonization of the germ-free mice with Bacteroides fragilis restored appropriate T-cell balance. Front Bioscience (Landmark Ed) 2010;1:25-34.
9. Chen CC, Chen KJ, Kong MS, Chang HJ, Huang JL. Alterations in the gut microbiotas of children with food sensitization in early life. Pediatr Allergy Immunol 2015; epub
10. Hilty M, Burke C, Pedro H, Cardenas P, Bush A, Bossley C, et al. Disordered microbial communities in asthmatic airways. PLoS One. 2010;5:e8578.
11. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl Jj Med. 2015;372:803-813
12. Greenhawt, M. The learning early about peanut allergy study: The benefits of early peanut introduction, and a new horizon in fighting the food allergy epidemic. Pedatric Clin North Am. 2015;62:1509-1521.

Christine McCusker

Christine McCusker is an allergist/immunologist and Director of the Pediatric Allergy, Immunology, and Dermatology division at the McGill University Health Center. She is a Research Director at the Meakins-Christie Laboratories, MUHCRI. Her research, including one of the recently named top 10 discoveries of the year in Quebec, focuses on the role of early life environments in the education of the immune system, the prevention of asthma



Adam Byrne

Adam Byrne is a pediatric clinical immunology and allergy fellow at the McGill University Health Centre. He completed his pediatrics training at the University of Ottawa. He completed his medical school training and M.Sc. in Biochemistry at Memorial University in Newfoundland.