Published in final edited form as:
Nat Med. ; 18(4): 492–494. doi:10.1038/nm.2723.

Breathe easy: microbes protect from allergies

Arya Khosravi and **Sarkis K. Mazmanian***
Division of Biology, California Institute of Technology, Pasadena, California, 91125, USA

Abstract

Changes in gut microbial composition have been linked to inflammatory bowel disease, obesity and allergies in humans. A new study shows that pattern recognition of commensal bacteria by B cells reduces allergic inflammation in mice, adding to the mounting evidence for the 'hygiene hypothesis'.

Twenty-three years ago, a study consisting of a single figure and insightful speculation redefined our relationship with microbial organisms[1]. Over a century earlier, Koch and Pasteur validated the germ theory of disease, effectively branding microbes as agents of infection. This realization promoted a campaign committed to eradicating infectious diseases by targeting their root cause. Vaccine development, antibiotic treatments, improved sanitation practices and the adoption of a hygienic lifestyle were part of the armory in the war against microorganisms. However, these very advances may be a Pyrrhic victory over infectious disease as, in turn, reduced exposure to microbes seems to contribute to the development of atopic and inflammatory disorders. In this issue of Nature Medicine, Hill *et al*.[2] provide experimental support for the notion that microbes may protect from allergic disease.

In 1989, David Strachan evaluated the associated risk between allergic rhinitis and sixteen perinatal, social and environmental factors[1]. He found that family size had a significant inverse correlation with the development of allergy. Extrapolating that smaller family size may reduce individual exposure to respiratory infections; Strachan suggested that such infections might be protective against the development of atopic disease. From this proposal arose the hygiene hypothesis, which redefined our relationship with the microbial world, prompting us to better understand how microorganisms benefit host health and development. In the decades that followed, multiple studies have supported Strachan's suggestion that microbial exposure may benefit host immune function. Notably, these studies have identified the commensal microbiota (consisting of over a 100 trillion microbes that colonize all environmentally exposed surfaces of a mammalian host) as an important modulator of host immune responses. In particular, specific microbes in the gut have been shown to influence intestinal immune development and protection from disease[3, 4].

These effects extend beyond the gut, as microbes and their products have been shown to affect systemic infectious and inflammatory diseases[5, 6, 7]. The microbiota has a crucial role even outside the immune compartment, modulating weight gain, various endocrine disorders

*To whom correspondence should be addressed: sarkis@caltech.edu.

and nociceptive recognition[8, 9, 10]. However, with the exception of epidemiological studies that further support Strachan's initial observations, very little convincing evidence has emerged that determines whether and how the microbiota contributes to the development of allergic disease. Hill *et al*.[2] now provide a major leap forward by characterizing a mechanism by which commensal bacteria may be preventing the development of atopic disease.

Hill *et al*.[2] show that antibiotic-mediated depletion of the microbiota is sufficient to predispose mice to allergic disease (Fig. 1). Mice treated with wide-spectrum antibiotics had an altered immune profile, with increases in serum concentrations of IgE and circulating basophils, two important mediators in atopic disease. Furthermore, after respiratory exposure to house dust mite allergen, antibiotic-treated mice showed a heightened allergic response characterized by increased alveolar inflammation and exaggerated immune responses consistent with allergic reaction. The phenotype in antibiotic-treated mice was similar to that in germ-free mice, suggesting the microbiota's influence on host immune function is plastic since it is reversed after pharmacologic disruption of host-microbial symbiosis.

In an elegant set of experiments, the authors decipher aspects of the molecular interplay between specific microbial-host factors that promote proper immune development, preventing allergic disease[2]. Increases in serum IgE in mice after antibiotic treatment promoted basophil expansion and subsequent susceptibility to allergic disease. Compared to conventionally raised mice—with an intact microbiota—both antibiotic-treated and germ-free mice showed a higher proportion of bone marrow basophilic precursor cells and higher expression of their proexpansion receptor CD123, as well as increased expansion of these cells after stimulation *ex vivo*. The authors then sought to determine whether there was a mechanistic link between the increased serum IgE concentration and the basophil expansion. No increases in circulating basophils were observed after antibiotic treatment of Rag1-knockout mice, which lack B cells, or in mice in which IgE was neutralized, suggesting that communication between the microbiota and B cells is crucial in preventing proallergy immune development. Intriguingly, humans with high serum IgE concentrations also have increased basophil proportions, suggesting that IgE may regulate basophil-mediated allergic disease.

Speculating that direct microbial sensing by immune cells affects allergy, the authors showed that the commensal microbiota modulates B cell production of IgE antibody in a myeloid differentiation factor 88 (MyD88)-dependent manner[2]. MyD88-deficient mice with an intact microbiota showed high circulating levels of basophils and high serum IgE concentration, similar to antibiotic-treated and germ-free mice. This phenotype was reproduced in mice in which MyD88 expression was selectively deficient in B cells. Furthermore, exposure of antibiotic-treated mice with the microbial molecule CpG, a Toll-like receptor (TLR)-dependent microbial ligand, was sufficient to reduce serum IgE as well as the frequency and total number of circulating basophils. What remains to be determined is whether these B cells reside in systemic compartments or are located in intimate association with the microbiota at mucosal surfaces. In other words, where (and how) do microbial products contact B cells?

Previous work has shown that germ-free mice show T helper type 2 skewing, an immune profile consistent with increased allergic reactions[11]. Hill *et al*.[2] uncover a link between the microbiota and B cells, mediated through MyD88-dependent ligand reception that promotes appropriate host immune development. The indication that MyD88-deficient mice seem phenotypically similar to germ-free and antibiotic-treated mice suggests two things. First, if the microbiota promotes systemic immune development and function through MyD88 signaling, some of the immunological defects reported by studies in MyD88-knockout mice may reflect the absence of this beneficial influence. Second, certain TLRs might have, in part, evolved to aid in communication with the commensal microbiota rather than to recognize and respond to infectious agents[12].

Hill *et al*.[2] provide compelling evidence that perturbations to the microbiota are sufficient to promote the development of allergic disease. However, future studies should address whether the susceptibility to allergic disease persists after cessation of antibiotic treatment. Are there lasting effects to host immune function after disruption of the microbiota? If not, it would suggest multiple factors are at play in the development of hygiene-meditated atopic disease, as it does not seem likely that allergies simply arise after an unfortunate coincidence of allergen exposure during antibiotic treatment. Rather, allergy susceptibility may reflect a combination of multiple environmental ‘hits’ to the microbiota, including antibiotics, infection and diet changes, paired with possible genetic defects in the host that prevent appropriate recovery of the microbiota after disruption. This study, supported by dozens of epidemiological reports, strongly urges the consideration of host genetic factors associated with allergic disease in the context of their possible role in mediating host-microbe symbiosis[13]. On the basis of these emerging findings, consideration should be given to the microbiota hypothesis as a basis for observations linking microbes to immune-mediated diseases rather than a view of infectious agents affecting allergy.

Although infectious diseases remain a substantial threat to human health, especially in this age of antibiotic-resistant ‘superbugs’, we are becoming ever more aware of the dramatic contribution of microbes to host physiology. Appropriately, we are now starting to realize a role for various immune factors, such as TLRs, previously considered only in the context of pathogen eradication, in maintaining and promoting host-microbe symbiosis. With these new insights compelling us to consider the microbiota as part of the organismal unit, we have the potential of redefining and discovering many aspects of our biology.

References

1. Strachan DP. Br Med J. 1989; 299:1259–1260. [PubMed: 2513902]
2. Hill DA, et al. Nat Med. 2012; 18:538–546. [PubMed: 22447074]
3. Ivanov II, et al. Cell. 2009; 139:485–498. [PubMed: 19836068]
4. Mazmanian SK, Round JL, Kasper DL. Nature. 2008; 453:620–625. [PubMed: 18509436]
5. Clarke TB, et al. Nat Med. 2010; 16:228–231. [PubMed: 20081863]
6. Lee YK, Menezes JS, Umesaki Y, Mazmanian SK. Proc Natl Acad Sci USA. 2011; 108(suppl 1): 4615–4622. [PubMed: 20660719]
7. Ichinohe T, et al. Proc Natl Acad Sci USA. 2011; 108:5354–5359. [PubMed: 21402903]
8. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Proc Natl Acad Sci USA. 2007; 104:979–984. [PubMed: 17210919]

9. Petruzzelli M, Moschetta A. Cell Metab. 2010; 11:345–346. [PubMed: 20444415]
10. Amaral FA, et al. Proc Natl Acad Sci USA. 2008; 105:2193–2197. [PubMed: 18268332]
11. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. Cell. 2005; 122:107–118. [PubMed: 16009137]
12. Round JL, et al. Science. 2011; 332:974–977. [PubMed: 21512004]
13. Garn H, Renz H. Immunobiology. 2007; 212:441–452. [PubMed: 17544829]

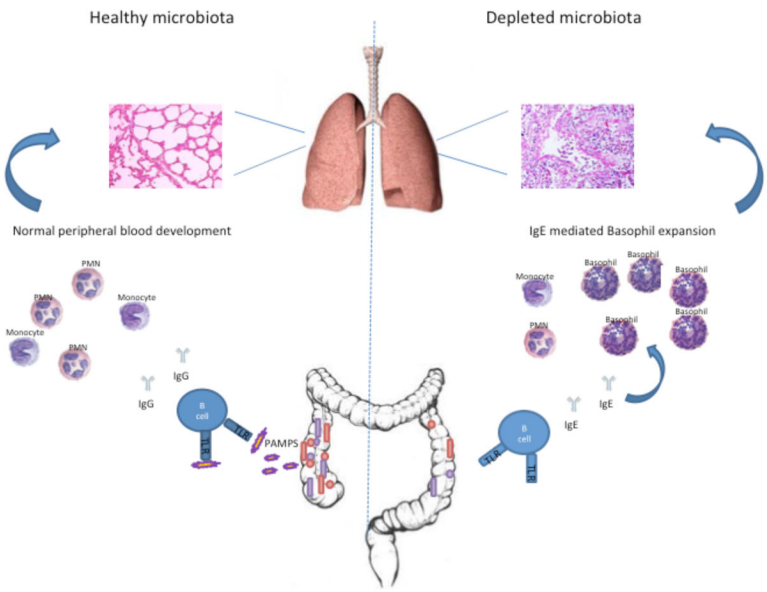

Fig. 1.

Hill *et al*.[2] show that the absence of MyD88-dependent microbial stimulation promotes IgE production by B cells, resulting in basophil expansion in the bone marrow and subsequent susceptibility to allergic disease. In this model, intestinal bacteria are depicted as the source of microbial products that induce antiallergic immune responses; however, microbes at other anatomical locations may affect T helper type 2 (T_H2) immunity. PAMP, pathogen-associated molecular pattern; PMN, polymorphonuclear cell.