

Increase in dietary fiber dampens allergic responses in the lung

Gary B Huffnagle

A new study in mice provides a link between dietary fiber intake, amounts of intestinal and systemic short-chain fatty acids, changes in the microbiome and allergic responses in the airways. The findings support the growing appreciation of a potential therapeutic role of diet in treating allergic diseases (pages 159–166).

Increased intake of dietary fiber, especially soluble fiber and resistant starch, is linked to lowering the risk of inflammatory diseases. Most research on fiber has focused on gastrointestinal inflammatory diseases; however, there have also been intriguing associations reported in humans between a westernized diet and increased asthma incidence, as well as between a Mediterranean diet and lower asthma incidence^{1,2}. Although these are both complex diets, the former is typically lower in fiber, whereas Mediterranean diets are typically higher in fiber.

Dietary fiber has been well documented to be metabolized by indigenous gut microbiota into short-chain fatty acids (SCFAs), which can dampen inflammatory pathways in macrophages and dendritic cells (DCs), promote the development of regulatory T (T_{reg}) cells and maintain intestinal epithelial integrity and health^{3–5}. In this issue of *Nature Medicine*, Trompette *et al.*⁶ provide a proof-of-principle demonstration of how the intake of high amounts of dietary fiber regulates the immune system in the lungs, which includes a surprising increase in the hematopoiesis of DCs that cannot reactivate T helper type 2 (T_{H2}) effector cells, resulting in lower allergic airway inflammation. These findings suggest that changes in diet influence inflammatory diseases not only in the gut but also in other organs, such as the lung.

The authors fed mice a standard laboratory chow diet, which contains a modest amount of fiber, or a diet specifically formulated to be low

in crude fiber and then repetitively exposed the mice intranasally to an extract of house dust mite (HDM) as an airway allergen challenge⁶. The mice fed the chow diet developed all the manifestations of allergic (T_{H2}) airway disease that have been reported previously for this model: elevated levels of airway eosinophils and lymphocytes, interleukin-4 (IL-4), IL-5, total IgE, mucus production and airway hyper-reactivity. The authors also observed that mice fed a fiber-deficient diet developed exacerbated disease. To address whether increasing the fiber content of the diet could mitigate the development of allergic airway disease, one group of mice was fed a diet supplemented with a soluble fiber mixture (30% pectin), and the control group was fed an equivalent amount of a bulking fiber (30% cellulose); although in mice (and humans), pectin is fermented by the microbiome into readily absorbed metabolites, the major class being SCFAs, cellulose is left almost completely undegraded by the mammalian bacterial microbiome. A diet high in soluble fiber significantly lowered the indices of allergic inflammation and improved airway resistance compared to the diet supplemented with nondigestible fiber. Thus, using two complementary approaches, the authors were able to demonstrate that dietary fiber could modulate experimental allergic airway inflammation *in vivo*.

Trompette *et al.*⁶ then addressed whether SCFAs were downstream mediators of the anti-inflammatory effect of dietary fiber. The authors noted that the overall bacterial diversity in the gastrointestinal tract was increased by the high-fiber diet and was decreased by the low-fiber diet, a result that supports the concept that other metabolic pathways beside SCFA production may have been upregulated. However, clostridial species (especially groups

IV and XIVa), which are major producers of SCFAs³, disappeared from the mice fed the low-fiber diet but were found in all the other groups fed varying amounts of dietary fiber. Analysis of both serum and cecum contents showed that the levels of SCFAs correlated with the level of fiber in the diet. To demonstrate that systemic SCFAs could be a mediator of the anti-inflammatory effect of dietary fiber, mice were given propionate, one of the SCFAs whose levels are markedly increased after inclusion of fiber in the diet, by intraperitoneal injection before intranasal HDM exposure. Propionate significantly reduced allergic inflammation and improved airway resistance compared to control mice. Two of the receptors for SCFAs, including propionate, are G protein-coupled receptor 41 (GPR41) and GPR43 (ref. 7); however, the protective effect of propionate was abrogated in GPR41-deficient mice but not those lacking GPR43. These experiments identify a pathway linking dietary fiber, the composition of the gut microbiome and the modulation of pulmonary inflammation and lay the groundwork for future in-depth investigation of the metagenomic and metabolomic changes in the gut microbiome that occur after ingestion of high amounts of dietary fiber.

One of the intriguing features of the study was that airway DCs, which express GPR41, had a less activated phenotype in mice fed a high-fiber diet, and conversely, mice fed a low-fiber diet had airway DCs that were more activated compared to those from mice fed the control diet. Despite the connection between SCFAs, group IV and XIVa clostridia and T_{reg} cell activation⁵, there was no evidence of increased numbers of T_{reg} cells in the lungs of the mice fed a high-fiber diet. Thus, attention was turned to the potential early regulation of DC precursor production in the bone marrow because the

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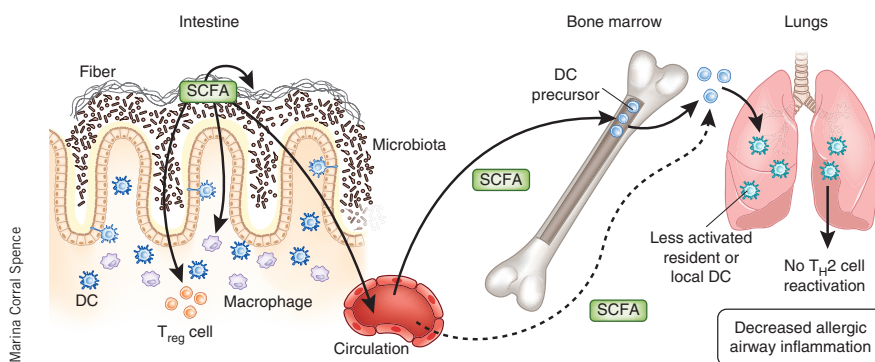


Figure 1 Different amounts of dietary fiber intake can change allergic airway responses and modify susceptibility to inflammatory disease. Dietary fiber is metabolized by the indigenous gut microbiota into SCFAs that can increase microbial diversity, dampen inflammatory pathways in macrophages and DCs, promote the development of T_{reg} cells and serve as a growth factor for intestinal epithelium integrity and cellular health^{3–5}. Trompette *et al.*⁶ now show that intestinal SCFAs enter the circulation and reach the bone marrow, where they enhance formation of precursors of DCs (hematopoiesis) and decrease activation of DCs from the circulation.

protective effect of propionate treatment was not evident 1 day after the final allergen challenge but was evident at day 4, suggesting that newly recruited DCs might be responsible for this effect. The authors found that propionate treatment led to enhanced hematopoiesis of DC precursors, which then migrated to the lungs and became less capable of reactivating T_H2 cells in the airways. This finding is consistent with reports from many investigators linking various aspects of myeloid hematopoiesis and allergic airway inflammation in humans and experimental rodent models^{8–10}. Overall, what emerges from these studies is a model (Fig. 1) of diet-microbiome-mediated immune regulation through circulating metabolites acting on the source of inflammatory cells (hematopoiesis) that influences the sensitivity of the lung to the development of allergic inflammation.

Changes in microbiota have been implicated in the etiology of many complex chronic inflammatory diseases. One of the current best examples of a well-delineated pathway connecting diet, microbial metabolites, leukocyte biology and health or disease is a previous study in mice that showed that dietary phosphatidylcholine could augment atherosclerotic plaque macrophage formation through production of the microbiome metabolite trimethylamine *N*-oxide¹¹. Through the years, numerous human studies have drawn associations between alterations in gut microbiota and an increased risk for allergic diseases or asthma². This association has been supported by animal studies in which disruption of the intestinal microbiota by oral administration of poorly absorbable broad-spectrum antibiotics was able to promote the development of allergic

airway disease^{12–14}. Future metabolomic profiling will most likely identify other systemically circulating bacterial metabolites, aside from SCFAs, that are influenced by the diet.

In addition to the bone marrow, another target organ that is subject to changes in microbial metabolite production and can influence systemic leukocyte activation is the liver. Little is known about the role of the liver in dietary regulation of allergic disease. Overall there continues to be a growing appreciation and understanding of the association between the metabolic activity of intestinal microbiota, diet and immune regulation in the airways, which will ultimately involve SCFAs as well as other small-molecule metabolites derived from the microbiome.

COMPETING FINANCIAL INTERESTS

The author declares no competing financial interests.

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Drug-resistant tuberculosis: a new shot on goal

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Modification of a natural product with antibiotic properties to block its efflux from *Mycobacterium tuberculosis* results in a new drug candidate for tuberculosis with a promising therapeutic profile in mice (pages 152–158).

Inadequate research and development of antibiotics and the spread of resistance to them have reduced society's access to one of the most important classes of life-saving drugs^{1,2}. Thus,

it is noteworthy when academic and government laboratories mount the kind of effort that was once the province of drug companies, develop a drug candidate against resistant forms of a major bacterial pathogen and do so using an uncommon approach. In this issue of *Nature Medicine*, Lee *et al.*³ have accomplished this by pulling together the efforts of investigators from five universities in the United States, Switzerland and Spain and from the US National Institutes of Health to develop a drug

candidate for tuberculosis (TB). The authors developed a semisynthetic antibiotic by modifying a natural product called spectinomycin to increase its potency, narrow its antimicrobial spectrum and thwart its efflux from the causative agent, *Mycobacterium tuberculosis* (Mtb) (Fig. 1). The effectiveness of the new agent in mice raises hope that compounds in this series may have clinical utility.

The world's leading threats among drug-resistant bacteria are the ESKAPE pathogens

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