

The nutrition-gut microbiome-physiology axis and allergic diseases

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Summary

Dietary and bacterial metabolites influence immune responses. This raises the question whether the increased incidence of allergies, asthma, some autoimmune diseases, cardiovascular disease, and others might relate to intake of unhealthy foods, and the decreased intake of dietary fiber. In recent years, new knowledge on the molecular mechanisms underpinning a 'diet-gut microbiota-physiology axis' has emerged to substantiate this idea. Fiber is fermented to short chain fatty acids (SCFAs), particularly acetate, butyrate, and propionate. These metabolites bind 'metabolite-sensing' G-protein-coupled receptors such as GPR43, GPR41, and GPR109A. These receptors play fundamental roles in the promotion of gut homeostasis and the regulation of inflammatory responses. For instance, these receptors and their metabolites influence Treg biology, epithelial integrity, gut homeostasis, DC biology, and IgA antibody responses. The SCFAs also influence gene transcription in many cells and tissues, through their inhibition of histone deacetylase expression or function. Contained in this mix is the gut microbiome, as commensal bacteria in the gut have the necessary enzymes to digest dietary fiber to SCFAs, and dysbiosis in the gut may affect the production of SCFAs and their distribution to tissues throughout the body. SCFAs can epigenetically modify DNA, and so may be one mechanism to account for diseases with a 'developmental origin', whereby in utero or post-natal exposure to environmental factors (such as nutrition of the mother) may account for disease later in life. If the nutrition-gut microbiome-physiology axis does underpin at least some of the Western lifestyle influence on asthma and allergies, then there is tremendous scope to correct this with healthy foodstuffs, probiotics, and prebiotics.

KEYWORDS

allergy, asthma, autoimmunity, inflammation, inflammatory bowel disease, lipid mediators

1 | INTRODUCTION

Allergies and asthma associate with Western lifestyle. This simple fact underlies the important role of environment for the pathogenesis of these diseases. Indeed, changes in the environmental factors should provide excellent prospects for disease prevention. The prevailing view on asthma and allergy has been that the environmental factor relates

to excessive hygiene or antibiotic use.^{1,2} However, there have been many arguments against the 'hygiene hypothesis' which prompted searches for other features of Western lifestyle. A 'Western diet' high in energy and low in fiber is one idea proposed by us that may contribute to disease, independently of hygiene or antibiotic use. Differing diets yield a myriad of specific metabolites that can influence the immune response. In recent years, a number of sensing mechanisms have emerged whereby the immune and metabolic systems sense availability of healthy metabolites, which then impacts on physiology.

Contained in this mix is the gut microbiome, as microbes are responsible for the production of some of the most important metabolites that impact on immune or metabolic responses. Understanding the immunological role of dietary or bacterial metabolites, and their sensing mechanisms, is crucial in establishing healthy dietary guidelines to prevent disease. This understanding will also guide new therapeutics that employ approaches such as probiotics, prebiotics, fecal transplantation, or specific small molecules targeting crucial molecular pathways in the nutrition-gut microbiome-physiology axis.

A number of dietary metabolites, particularly fatty acids, influence inflammation via a diverse family of 'metabolite-sensing' G protein-coupled receptors (GPCRs).³ Fatty acid agonists of GPCRs vary in carbon chain length, ranging from short-chain (C2-5), medium-chain (C6-12) and long-chain (C13+) fatty acids. These dietary metabolites are all derived from foodstuffs that are considered healthy, such as dietary fiber (short-chain fatty acids, SCFAs), fish (long-chain fatty acids), or milk and coconut milk (medium-chain fatty acids). The immunologic role of these metabolites and their receptors is now emerging, but as outlined in this review this is a relatively new field and there are many unanswered questions. In addition, while the metabolite-sensing GPCRs provide immediate responses, through cellular signaling, metabolites also promote long-term effects through epigenetic mechanisms, including inhibition of histone deacetylases (HDACs), or by activation of transcription factors such as aryl hydrocarbon receptor (AHR). It is now clear that nutrition and the gut microbiome have a powerful influence on immune responses.

If nutrition and bacterial metabolites do impact on immunology, then allergies, asthma, and certain inflammatory diseases likely relate to Western diet.⁴ In particular, responses occurring at mucosal sites appear to be affected by Western diet.⁵⁻⁷ Asthma, food allergy, and inflammatory bowel disease (IBD) in humans have all been associated with the consumption of a Western diet, which is typically high in fat and sugar and low in fiber.^{5,8,9} Asthma and food allergy involve chronic Th2-cell responses that drive allergic inflammation and can be fatal when responses lead to anaphylaxis. Likewise, atopic dermatitis (eczema) is also increasing in incidence in Western countries,¹⁰ and is characterized by an impaired epidermal barrier leading to an aberrant Th2, Th17, or Th22 response to allergens.¹¹ Although not as obvious as allergic conditions, autoimmune diseases including type 1 diabetes, rheumatoid arthritis, multiple sclerosis, and others are also increasing in Western countries.⁷ Moreover, many metabolic syndrome diseases are now recognized as having an inflammatory component attributable to Western lifestyle, including fatty liver disease, cardiovascular diseases, hyperlipidemia, cancer, and type 1 and 2 diabetes.^{12-15,16}

2 | DIET AS AN ALTERNATIVE OR ADDITIONAL CONTRIBUTOR OVER HYGIENE

The rise in incidence of allergies and inflammatory disease has been explained by the hygiene hypothesis.^{1,2,17} This hypothesis proposes that excess sanitation, antibiotic use, and vaccinations

have led to an under-developed and over-reactive immune system, which then somehow leads to an increase in allergies and inflammatory diseases.¹⁸ Excessive hygiene may skew the immune system so that it over-reacts to normally harmless substances (such as pollen). However, the hypothesis has several flaws, which have been outlined in previous publications.¹⁹⁻²¹ For example, the incidence of asthma in remarkably hygienic Japan is relatively low compared with Australia or the United States. Moreover, socio-economically disadvantaged populations in the United States, with higher levels of infectious diseases such as TB maintain higher incidences of asthma.²² These disadvantaged populations are more prone to metabolic syndrome, and consume diets high in fat and sugar and low in fiber. In general, childhood infections do not protect against allergies and asthma, nor does home hygiene correlate with increased allergies and asthma. Indeed, distinctions in diet among these countries correlate more closely with incidences of allergic and inflammatory diseases than other factors of Western lifestyle such as hygiene, stress, and pollution.²² We and others have argued that the high intake of processed food, high in fat, sugar, food emulsifiers and artificial sweeteners, and low in fiber, has contributed to the increase in prevalence of allergic diseases, as well as other inflammatory and metabolic syndrome associated diseases.^{7,23} Despite our reservations about the hygiene hypothesis, the basic scientific observation that prompted it, that birth order affects allergy and asthma, has been confirmed by numerous studies,²⁴ including a comprehensive study of over 1600 cases of allergies in the United Kingdom.²⁵ However, birth order affects numerous conditions other than allergies and asthma,¹⁹ including type 1 diabetes,²⁶ various cancers,²⁷ and possibly metabolic syndrome diseases.²⁸ Birth order also affects birth weight, and lower birth weight in turn correlates with increased metabolic syndrome related diseases later in life, such as heart disease, stroke, type 2 diabetes, and adiposity.²⁹⁻³¹ Moreover, since the hygiene hypothesis was first proposed, the field of epigenetics has evolved, and many lines of evidence indicate that early life events, including nutrition of the mother, strongly influence later susceptibility of offspring to certain diseases.^{30,32} For instance, maternal diet or metabolism, particularly during the prenatal period, is likely to have pronounced epigenetic influences on individuals later in life.^{30,33} Women with altered metabolic homeostasis during pregnancy give birth to children that are prone to develop obesity, type 1 diabetes, or cardiovascular diseases later in life.³⁴ In mice, maternal high-fat diet feeding during lactation predisposes offspring to obesity and impaired glucose homeostasis.^{35,36} Thus, diet and metabolites of the mother affect metabolic syndrome disorders. In many respects, asthma resembles a metabolic syndrome disorder,³⁷ and is somehow connected to the enigmatic mix of Western lifestyle, the gut microbiome, metabolic syndrome, and inflammatory diseases.

Over the last two decades, global changes in diet have driven obesity to alarming levels, stemming from the consumption of foods high in energy and low in fiber.³⁸ The incidence of obesity-associated metabolic syndrome diseases such as diabetes and fatty liver disease is rising as a result.³⁹ Two broad clusters of inflammatory metabolic diseases have been induced by obesity: those associated with the direct

TABLE 1 Speculation on how environmental elements (particularly relating to nutrition and the microbiome) may impact on allergies and asthma

Phenomenon associating with allergies or asthma	Microbiome/metabolite possibilities	Notes
Growing up on a farm ⁴⁹	Sharing of gut (and lung?) microbiome with that of livestock	Cows, sheep, and goats eat grasses and contain a gut microbiome specialized in breakdown of fiber and production of SCFAs
Growing up with a cat or a dog ⁵⁰	Sharing elements of your dog's gut microbiome is one possibility. Presumably the healthy metabolites would relate to things like tryptophan catabolism	Do health benefits require fecal transfer? Or is this whole phenomenon related to something entirely different like antigen sensitization/skewing of the immune system?
Birth order ^{1,17,24,25}	Metabolic issues, unknown mechanism	Birth order probably relates to other medical conditions, in addition to asthma and allergies
Socio-economic status ²²	Poor diet, lack of dietary fiber	The cheapest food is high in fat and sugar, and obesity is most prevalent in low socio-economic groups (in Western countries)
Junk food ⁵¹ low fiber ⁵²	Energy derived from fat and sugar, general lack of dietary fiber, lower concentrations of SCFAs in gut and blood	It is also possible that metabolites from high fat foods do harm, through unknown mechanisms
Protection through high intake of fruit and vegetables ^{41–45}	Skewing of the gut microbiome for digestion of fiber, production of SCFAs	SCFAs may not be the only beneficial changes—other elements may contribute from a healthy microbiome, involving signaling through MyD88
Mediterranean diet ^{53,54}	High in vegetables, fruit, nuts, and fish. Mediterranean people also consume lots of vinegar (acetate) and olive oil (omega-3)	Relative importance of different metabolites is unknown
Growing up in rural Africa	Low intake of fat and sugar, high intake of dietary fiber	See de Fillipo et al. ⁵⁵
Antibiotic use, particularly in pregnancy or early life ⁵⁶	Skewing of microbiome to one with poor capacity to harvest metabolites from food that is, SCFAs	Antibiotics used extensively in Western countries, including in the food chain. But, respiratory infections could themselves increase asthma risk ⁵⁷

impact of lipids on the immune system, such as diabetes, and those that appear as indirect effects that are poorly understood.⁴⁰ Allergic and inflammatory diseases such as asthma, food allergy, and IBD fall into this second category. Furthermore, diets high in non-digestible fiber protect from allergic and inflammatory diseases in both humans and mice.^{41–45} This suggests that the high consumption of fat and sugar, and low consumption of fiber in Western diet might be contributing to the rising incidence of such diseases. Epidemiology studies back this up (see Table 1). High consumption of fiber associates with protection against mortality from cardiovascular disease, cancer, infectious, and respiratory diseases.^{46,47} Furthermore, fiber can alleviate symptoms of IBD.⁴⁸ Human conditions such as food allergy, asthma, fatty liver, etc., were considered diseases purely of developed countries; however, with globalization, the diet of the developing world begins to mimic that in the West. Table 1 lists certain aspects of the epidemiology of asthma and allergies, and speculates on alternative explanations, such as diet-related mechanisms.

3 | DIET AND MICROBIOTA-RELATED METABOLITES FOR IMMUNE RESPONSES

Energy is harvested from our diet either by the direct metabolism of consumed foods or by the absorption of secondary metabolites

produced from gut bacteria. Lipids, proteins, and various carbohydrates can be metabolized directly. All aforementioned macromolecules are subject to enzymatic digestion and acidic pH to aid absorption. In contrast, dietary fiber is not used as an energy source and is instead fermented by gut bacteria into rapidly absorbed SCFA metabolites. There is now a widespread interest in the biology of dietary fiber, and SCFAs because these are now plausible contributors to allergic disease pathogenesis, as well as many other conditions. A general model on how dietary elements and the microbiome may impact on allergic diseases is shown in Figure 1. The four main mechanisms that will be expanded on include: (i) epithelial integrity and the role of metabolite-sensing mechanisms including GPCRs and HDAC inhibition by metabolites, (ii) metabolite influence on CD103+/Treg biology, (iii) metabolites and the IgA/IgE balance, and (iv), proton (pH) sensing by GPCRs and effects on allergic leukocytes such as eosinophils. This latter topic will be dealt with briefly, as data are still emerging. Discussion on these four main mechanisms will be covered in different sections throughout this review.

3.1 | Fiber and short-chain fatty acids

Dietary fiber consists of non-digestible carbohydrates sourced from plant polysaccharides and oligosaccharides that are resistant to enzymatic and chemical digestion until they reach the large intestine,

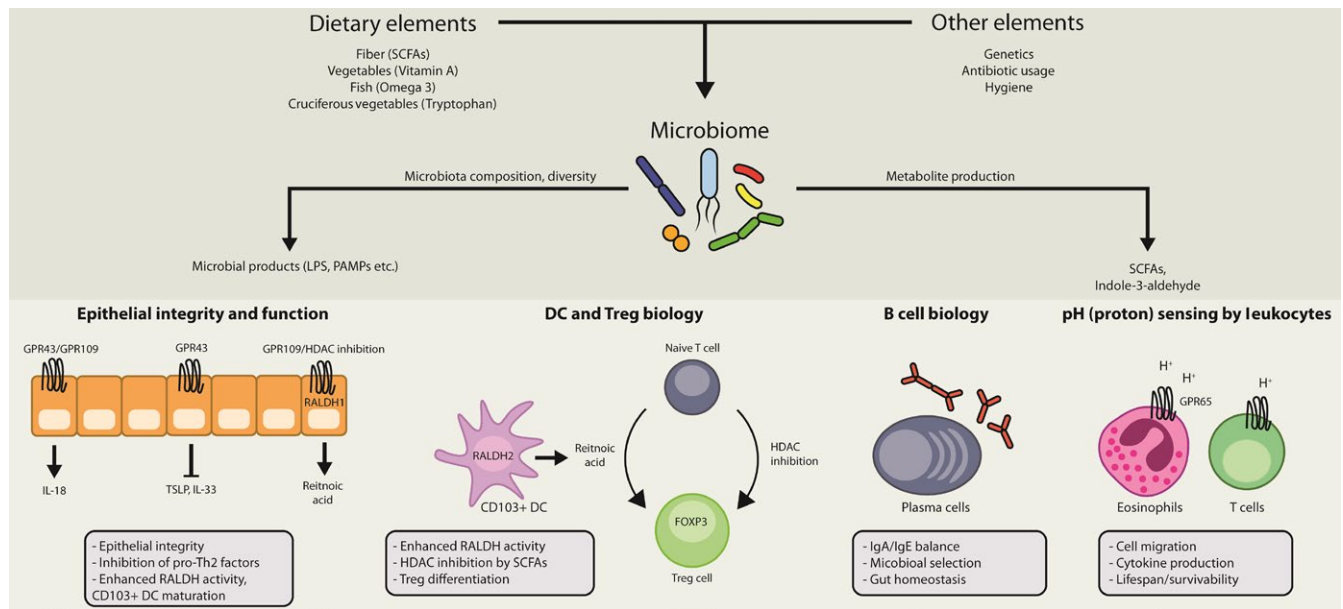


FIGURE 1 The relationship between diet, the gut microbiome, and allergic responses. Diet, genetics, and hygiene combine to influence the microbiota which in turn influences the immune response. Contact between the microbiota and immune system may occur directly through microbial products such as LPS or indirectly through metabolic products such as SCFAs. The microbiota can subsequently enhance intestinal homeostasis and prevent the pathogenesis of allergies by promoting epithelial integrity, Treg differentiation, and IgA release from plasma cells. This is mediated by GPCR activation or epigenetic modification via HDAC inhibition. SCFAs may also lower pH and subsequently activate acid receptors such as GPR65, which may act as surrogate SCFA receptors and further regulate inflammatory responses

where they are fermented to SCFAs by gut bacteria.⁵⁸ Foodstuffs high in fiber include grains, vegetables, fruits, and nuts. Although SCFAs can also be formed from the metabolism of proteins and glycoproteins found in food, carbohydrates are the most significant contributors.⁵⁹ Gut bacteria produce variable amounts and types of SCFAs, depending on gut microbiota composition and their access to carbon.⁵⁹ For instance, consumption of high-fat diet may alter the composition of the gut microbiota away from microbes efficient at digesting fiber, and reduce levels of SCFAs in the colon or blood.⁵⁵ The most abundant SCFAs are acetate (two carbons), propionate (three carbons), and butyrate (four carbons), respectively.^{60,61} They are found at the highest concentrations in the proximal large intestine due to its large microbial population.⁵⁹ For instance, in the colon in humans, acetate concentration is $\sim 60 \text{ mmol l}^{-1}$, and propionate and butyrate $\sim 25 \text{ mmol l}^{-1}$ each,⁶² which are remarkable levels given that concentrations of these two SCFAs in peripheral blood are usually in the low $\mu\text{mol l}^{-1}$ range.⁶³

SCFAs can pass across the gut epithelium and interact directly with cells in the gut-associated lymphoid tissue.⁶⁴ Immunohistochemical staining and mRNA quantification have identified the location of differing monocarboxylate transporter isoforms on the apical side and basolateral side of the colonic epithelium, that transport SCFAs across. While inside colonic epithelial cells, butyrate undergoes beta oxidation to acetyl-CoA and this constitutes their primary energy source.^{61,65,66} From the gut, SCFAs are transported through the hepatic portal vein to the liver⁶³—the primary site of SCFA metabolism.^{60,67} Acetate and propionate are the most common SCFAs to undergo this process and escape the gut into the periphery. Acetate can also be metabolized

by muscle and brain tissue but is a minor energy source compared to blood glucose.^{60,67} If SCFAs are impacting on asthma and allergic responses, as the data suggest, then it is interesting to consider how this might be happening given the relatively small percentage of the total amount of SCFAs produced that actually makes its way to peripheral tissues.

An interesting consideration is what happens to SCFA levels throughout the body upon consumption of high fiber diets, fiber-free diet, Western high-fat diets, etc. In our studies in mice, high-fiber diets increased SCFA levels in the gut and blood. This may have profound consequences for physiology. In a recent study,⁶⁸ microbial colonization was found to regulate global histone acetylation and methylation in multiple host tissues, in a diet-dependent manner. Consumption of a Western-type diet prevented many of the microbiota-dependent chromatin changes that occur in a fiber-rich diet.⁶⁸ This was due to SCFAs since feeding germ-free mice with SCFAs recapitulated chromatin modifications and transcriptional responses associated with bacterial colonization. For more extensive reviews on the biology of SCFAs, see.^{69–71} We believe that there is considerable potential to manipulate gene transcription in tissues, and epigenetic modifications, using diet.

3.2 | Vitamins

Vitamins are organic compounds required for the maintenance of physiological health. Vitamins are usually obtained in trace amounts from our food, requiring a balanced diet that contains foodstuffs such as vegetables, eggs, and fish. The most immunologically relevant

vitamins are vitamins A and D, which enhance or inhibit lymphocyte proliferation and cytotoxicity, respectively.⁷² Vitamin A is typically sourced from vegetables, liver, and eggs. Alternatively, vitamin D is primarily synthesized in the skin upon UVB exposure from sunlight but is also sourced from oily fish.⁷³ Vitamin A is converted to retinoic acid, whereas vitamin D is converted to 1,25(OH)₂VD₃. Retinoic acid activates the retinoic acid receptor which increases cytotoxicity and lymphocyte proliferation.^{74,75} Furthermore, retinoic acid plays a major role in the development of secondary lymphoid organs and stimulates Treg differentiation while preventing Th17 differentiation.⁷⁶ Alongside balancing Treg/Th17 cells, retinoic acid also promotes T-cell immune responses to promote immunity to infection.⁷⁷ In our studies, we established a link between retinoic acid and the prevention of food allergy, and this involved the stimulation of Treg differentiation by intestinal CD103⁺ DCs,⁷⁸ discussed in detail below. Interestingly, CD8α⁺ CD103⁺ DCs cannot induce Treg differentiation via retinoic acid, unlike CD8α⁺ CD103⁺ DCs,⁷⁹ highlighting metabolic differences between two similar immune subsets. 1,25(OH)₂VD₃ activates the vitamin D receptor and members of the retinoic X receptor family which broadly abrogate lymphocyte and leukocyte function.⁷² Furthermore, the gut microbiota, particularly *Bifidobacteria*, is a source of B vitamins.⁸⁰ The role of B vitamins in immunomodulation remains poorly understood although the recent characterization of niacin (B3) and butyrate receptor GPR109a implicates vitamins in the maintenance of intestinal homeostasis alongside SCFAs. Deficiency of vitamins A, D, and E have all been suggested to underpin allergies or asthma.^{81–84}

4 | IMMUNOMODULATION BY DIET AND BACTERIAL METABOLITES

While the role of vitamins in allergic diseases or asthma is unresolved, a stronger case can be made for vegetables in the diet, which are a source of many vitamins, and also dietary fiber. Upon digestion of dietary fiber in the lower colon by bacteria, SCFAs are produced in high amounts. These metabolites can activate metabolite-sensing GPCRs, or affect epigenetic and gene transcription programs, both of which have immunologic outcomes. We believe that these immunomodulatory mechanisms stimulated by SCFAs represent one of the strongest connections linking diet, the microbiome, and allergic diseases. We do not exclude the possibility that numerous other metabolites and mechanisms also contribute to the nutrition-microbiome-physiology axis, and pathogenesis of disease. As outlined below, important information has been obtained through the use of GPCR-deficient mice, or germ-free mice (which produce lower levels of certain metabolites), or HDAC-deficient mice. All of this points to fundamental connections between nutrition and asthma and allergy.

4.1 | Metabolite-sensing GPCRs

A number of metabolite-sensing GPCRs are increasingly being linked to immune regulation. In particular, fatty acids serve as agonists for a

number of GPCRs expressed on immune cells. However, their complex immunological role has only recently become understood. Signaling cascades triggered by different Gα protein subunits can induce intracellular release of Ca²⁺, the production or reduction of cAMP, PIP₃ production, and the activation of β-arrestin. Somehow, these signaling pathways regulate cellular and molecular pathways important for allergic inflammation, as we discuss below.

4.2 | SCFA receptors: GPR41, GPR43, GPR109a

Propionate signals with greater strength via GPR41 than acetate.⁸⁵ Activation of GPR41 induces intracellular release of Ca²⁺ and reduces intracellular cAMP.^{86,87} GPR41 is highly expressed on colonic epithelium, with weaker expression observed in the pancreas and spleen.^{85,88} Expression of GPR41 in adipocytes remains controversial, as multiple studies have either detected^{85,87} or been unable to detect^{89,90} GPR41 expression occurs in numerous adipocyte tissue sites or cell lines. A study of GPR41 KO mice revealed that this receptor was required for SCFA-mediated release of leptin from adipocytes,⁹⁰ consistent with a role for GPR41 in satiety. Moreover, consumption of propionate has been demonstrated to reduce antigen presentation on DCs due to GPR41-dependent modulation of hematopoiesis, and affect allergic airways disease in a mouse model.⁴⁵ Furthermore, GPR41 regulates blood pressure via renin release,⁹¹ suggesting a broader role for SCFA agonists in homeostasis. Like GPR43, mice deficient in GPR41 have been reported to associate with both reduced and enhanced obesity.^{92,93} Such discrepancies may be due to differential downstream activation of G-protein subunits or differences in gut microbiota. Regardless, GPR41 activation likely influences both the immune system and metabolism although the understanding of such mechanisms remains poorly understood.

The two most abundant SCFAs in the gut, acetate and propionate, have an equal affinity for GPR43.^{85,94} GPR43 signals with a dual-coupling mechanism through G_{i/o} and G_q subunits.⁸⁶ Activation of GPR43 induces intracellular Ca²⁺ release and reduces cAMP, but can increase ATP production (the substrate for cAMP) in colonic epithelium in vitro.^{85,95,96} GPR43 is found on neutrophils, macrophages, dendritic cells (DCs), mast cells, and epithelial cells in the intestine and particularly the colon.^{85,94,97,98} However, most of these expression analyses have been done at the transcript level and not protein. Murine studies show that signaling via GPR43 downregulates inflammatory responses.^{22,44} Indeed, GPR43 knockout (KO) mice exhibit exacerbated allergic airway disease⁴⁴ and food allergy (discussed below). Furthermore, observations of impaired proliferation and increased susceptibility to apoptosis in colon cancer cells via GPR43 signaling suggest that SCFAs can regulate inflammatory responses via decreased survivability.⁹⁹ Indeed, direct contact with SCFAs also decreased production of a broad range of pro-inflammatory cytokines from monocytes and macrophages in a receptor-mediated manner.^{100,101} Recently, we showed that high-fiber diet via GPR43, induced oral tolerance to peanut antigens in mice, by enhancing tolerogenic CD103⁺ DC function via retinoic acid metabolism.⁷⁸ This mechanism protected mice from peanut allergy. Furthermore,

GPR43 also plays a role in metabolism. A number of murine studies have demonstrated conflicting effects of GPR43 activation on insulin resistance and obesity.^{102–104} However, these discrepancies may be accounted for by the activation of different G-protein subunits, as we have discussed previously.¹⁰⁵ Downstream of GPR43 activation, $G_{q/11}$ increases glucose-stimulated insulin secretion in murine islets, whereas $G_{i/o}$ decreases it.¹⁰⁶ In addition, fiber and its breakdown products may act via GPR43 to drive an increase in the density of cells that produce the appetite-suppressing hormone peptide YY (PYY), which serves to reduce food intake and prevent diet-induced obesity.¹⁰⁷ At present, there is no clear consensus on the role GPR43 in metabolism.

Although niacin is the most investigated agonist of GPR109a, the SCFA butyrate also demonstrates agonistic activity at millimolar concentrations¹⁰⁸ which do occur in the gut. Activation of GPR109a induces intracellular Ca^{2+} release, reduces cAMP, and activates kinases and β -arrestin 1 and 2 to internalize the receptor.¹⁰⁹ GPR109a is expressed on human adipocytes and immune cells including macrophages and neutrophils but not lymphocytes or eosinophils.^{110,111} Reporter mice reveal that GPR109a is broadly expressed in spleen and bone marrow.¹¹² In addition, GPR109a expression has been observed in the small intestine and colon of mice.¹⁰⁸ GPR109a on adipose tissue is required for the inhibition of lipolysis by niacin which subsequently increases HDL in the blood.¹¹³ Indeed, the increase in HDL from niacin is not observed in mice lacking GPR109a while subsequent increases in GPR109a in the liver can restore these effects.¹¹⁴ This suggests an important role for the expression of GPR109a on adipocytes and hepatocytes for the control of blood cholesterol by niacin. However, immune cells are also altered by GPR109a signaling. Activation of GPR109a on macrophages by niacin inhibited MCP-1-induced chemotaxis of macrophages to the peritoneum in mice and also increased lipid transporter expression associated with the generation of atherosclerotic plaques,¹¹⁰ suggesting a role for GPR109a in protection against atherosclerosis. Consistent with the anti-inflammatory role of this type of receptor, secretion of pro-inflammatory cytokines by human monocytes was reduced in vitro by niacin treatment, and this was abrogated by knockdown of GPR109a by siRNA.¹¹⁵ Furthermore, pro-inflammatory cytokine release from retinal pigment epithelium (cells crucial for maintenance of retinal health) was also abrogated by GPR109a signaling.¹¹⁶ In addition, niacin enhances human neutrophil apoptosis which may be induced by GPR109a due to the abrogation of this effect by pertussis toxin, a potent GPCR antagonist.¹¹¹ Neutrophil apoptosis is important in limiting excessive immune responses by depleting neutrophil numbers, again suggesting GPR109a can abrogate inflammation. However, niacin can induce regulatory responses independent of GPR109a. Migration of DCs to draining lymph nodes in response to contact sensitization was impaired in mice-fed niacin-supplemented diets, an effect unchanged in GPR109a KO mice.¹¹⁷ Niacin may therefore alter DC migration independently of GPR109a to regulate inflammatory responses.

The study that identified butyrate as a novel GPR109a agonist investigated the role of GPR109a in colon cancer. It demonstrated

that GPR109a expression in both human and mouse colon cancer is reduced.¹⁰⁸ Furthermore, in vitro activation of GPR109a by butyrate induced apoptosis of colon cancer cells and also reduced NF- κ B expression in a normal colon cell line.¹⁰⁸ Butyrate has also been demonstrated to induce colonic Treg differentiation via IL-10 release from macrophages and DCs or IL-18 from colonic epithelium, a mechanism dependent on GPR109a.¹¹⁸ As a result, GPR109a KO mice develop severe inflammation in a model of dextran sulfate sodium (DSS) colitis, an effect dependent on hematopoietic cells demonstrated by bone marrow chimeras.^{118,119} This highlights another regulatory effect of GPR109a activation and identifies the role that immune cells play in regulating inflammation in the gut when exposed to dietary metabolites. Therefore, metabolites from both dietary fiber (butyrate) and tryptophan (niacin) may regulate immune responses through GPR109a.

4.3 | GPR65 and allergic disease

GPR65 is a GPCR that is activated by protons, that is, it senses extracellular acidic conditions.¹²⁰ We have suggested that it acts as a surrogate receptor for acidic metabolites such as SCFAs¹²¹ although this is speculative and indeed any condition leading to acidity may activate GPR65. GPR65 is expressed on a variety of immune cells, including T and B lymphocytes, neutrophils, but is particularly high on eosinophils and mast cells.^{122,123} Activation of GPR65 under acidic conditions has been associated with increased viability of eosinophils, as well as lymphomas.^{124,125} Multiple genome-wide association studies have associated single-nucleotide polymorphisms (SNPs) in *Gpr65* with increased susceptibility to IBD. A recent study found that these SNPs were associated with enhanced bacteria-induced colitis due to impaired lysosomal function in epithelial cells due to impaired GPR65 signaling.¹²⁶ We believe that GPR65 plays an important role in allergy because of its role in both epithelial cells, and allergic leukocytes such as eosinophils. One study suggested a role for GPR65 polymorphisms with asthma.¹²⁷ In our unpublished studies, we find a strong association with asthma as well as other allergic diseases.

4.4 | SCFA-mediated HDAC inhibition

SCFAs appear to modulate cellular function by altering the acetylation pattern of gene promoters, an epigenetic mechanism independent of GPCR activation. SCFAs inhibit HDACs,¹²⁸ enzymes that remove acetyl groups from histones.¹²⁹ Inhibition of HDACs enhances the acetylation of the lysine residues in histones. Acetylation of lysine residues induces gene activation by facilitating the access of transcription factors to promoter regions.¹³⁰ As such, inhibition of HDAC activity by SCFAs can increase gene transcription by increasing histone acetylation.

HeLa cells treated with sodium butyrate underwent dramatic increases in global histone acetylation correlating with reduced global HDAC activity.¹³¹ Treatment of HeLa cells with propionate also reduced HDAC activity but to a lesser extent than butyrate, whereas acetate had no effect.¹²⁸ Hepatoma tissue culture cells exposed

to butyrate, propionate, or acetate exhibited increased global histone acetylation (butyrate > propionate, > acetate¹³²). Furthermore, numerous observations of colon cancer cells *in vitro* have demonstrated that propionate and butyrate increased histone acetylation by inhibiting global HDAC activity, whereas acetate had little to no effect.^{128,133,134} Contrastingly, orally administered acetate can specifically inhibit HDAC2 activity and expression in the rodent brain *in vivo*, as determined by Western blot.¹³⁵ Taken together, these studies demonstrate a propensity for SCFAs to inhibit HDAC activity in a wide variety of cell types.

SCFA-mediated HDAC inhibition results in anti-inflammatory effects. Treatment of human macrophages with 1 mmol l⁻¹ acetate *in vitro* significantly reduced global HDAC activity and increased global histone acetylation, correlating with decreased production of inflammatory cytokines including IL-6, IL-8, and TNF α .¹³⁶ Increases in histone acetylation by acetate were mediated by acetyl-CoA synthetases. This may have decreased inflammatory cytokine release by increasing anti-inflammatory chromatin modifications such as ubiquitination of histone H2A in macrophages¹³⁷ although the involvement of SCFA-mediated HDAC inhibition in this response remains unclear. HDAC inhibition, in particular inhibition of HDAC9, increases expression of the forkhead box P3 (Foxp3) transcription factor *in vivo*, which subsequently increased proliferative and functional capabilities of Tregs.^{138,139} Administration of butyrate moderately diminished human Treg proliferation, but increased Treg CTLA-4-mediated suppression of T-cell proliferation *in vitro* despite no change in Foxp3 expression.¹⁴⁰ Butyrate, propionate, and acetate decreased LPS-induced TNF α production *in vitro* from peripheral blood mononuclear cells (PBMCs) in a similar manner to the HDAC inhibitor trichostatin A (TSA).¹⁴¹ Furthermore, NF κ B activity in PBMCs was also reduced *in vitro* by butyrate and propionate (but not acetate) in a similar manner to TSA.¹⁴¹ Similar effects between SCFAs and TSA suggest HDAC inhibition as the mechanism responsible although a direct effect of these SCFAs on histone acetylation in PBMCs is poorly understood. Global HDAC activity in rodent neutrophils was decreased *in vitro* by acetate, propionate, and butyrate with increasing strength, respectively.¹⁴² Correspondingly, butyrate and propionate but not acetate decreased LPS-induced TNF α expression and NOS expression in rodent neutrophils.¹⁴² Similarly, butyrate decreased LPS-induced release of pro-inflammatory mediators nitric oxide, IL-6, and IL-12 from bone marrow-derived macrophages in a manner dependent on HDAC inhibition.¹⁴³ HDAC inhibition from SCFAs, therefore, regulates pro-inflammatory cytokine release from neutrophils and macrophages.

In addition to reducing pro-inflammatory mechanisms, SCFA-mediated HDAC inhibition can promote immune responses. HDAC inhibition by SCFAs enhances the acetylation of genes required for differentiation and IgA class-switching of B cells.¹⁴⁴ IgA production from B cells is required to protect the body from bacterial infection¹⁴⁵ and is generally consistent with proper gut homeostasis. Therefore, the inhibition of HDACs by SCFAs can promote humoral immunity to infection and maintain intestinal homeostasis despite anti-inflammatory effects on neutrophils and macrophages.

4.5 | Mechanism of HDAC inhibition

Butyrate has been found to inhibit HDACs non-competitively,¹⁴⁶ suggesting that it may not interfere with the associated binding between HDAC and substrate. However, it is hypothesized that two butyrate molecules may occupy the hydrophobic cleft of the active site in a similar manner to the well-characterized HDAC inhibitor TSA.¹⁴⁷ The exact mechanism of how butyrate and other SCFAs can directly inhibit HDACs remains unclear.

SCFA transporters may be required for HDAC inhibition. The monocarboxylate transporter Slc5a8 transports SCFAs into DCs, and was required for butyrate- and propionate-induced blockade of murine DC development.¹⁴⁸ Global HDAC activity was reduced and global acetylation was increased in murine bone marrow cells (DC precursors) exposed to butyrate and propionate *in vitro*, accentuating the importance of Slc5a8 in HDAC-mediated effects of SCFAs in DCs.¹⁴⁸ Therefore, SCFAs do not necessarily require GPCRs to induce cellular signaling and may instead enter the cell directly and inhibit HDAC activity.

SCFAs can alter the metabolic profile of cells directly by changing pathways of energy use and production. As discussed above, the SCFA butyrate is a major energy source for colonic epithelial cells.⁶⁶ Butyrate and other SCFAs are transported into epithelial cells from the apical side of the epithelium via monocarboxylate and ATP-binding cassette transporters.¹⁴⁹ This highlights a role for the gut microbiota in providing energy for the host via the fermentation of SCFAs. Furthermore, the balance between butyrate metabolism and the high glycolytic activity of the Warburg effect determines differences in the proliferation of normal and cancerous colonocytes.¹⁵⁰ The switch to Warburg metabolism in cancerous cells changes the outcome of butyrate-induced HDAC inhibition, whereby butyrate stimulates proliferation in healthy colonocytes and prevents proliferation of cancerous colonocytes.¹⁵⁰ As such, the state of metabolism within a cell can impact upon the outcome of SCFA exposure.

4.6 | Aryl hydrocarbon receptor

The aryl hydrocarbon receptor (AhR) is a transcription factor widely expressed throughout the body, including the bone marrow and immune cells.¹⁵¹ Although it is activated by chemical pollutants, its most relevant role is likely in the gut, and maintenance of gut and immune homeostasis through interaction with a number of dietary elements. These include flavonoids commonly sourced from fruit, and metabolites derived from the essential amino acid tryptophan. Tryptophan-rich foods include many of the things we do not eat enough of, like cruciferous vegetables. Breakdown of tryptophan in the stomach by lactobacilli produces indole-3-aldehyde, which activates AhR in innate lymphoid cells and subsequently promotes IL-22 production, a cytokine that enhances epithelial integrity, and resistance to infection.¹⁵² AhR can also influence allergic responses. In a murine model of allergic airways disease, particulate matter characteristic of traffic pollution exacerbated Th2 responses via AhR and the Notch pathway.¹⁵³ Furthermore, lung fibroblasts from asthmatics

express higher levels of AhR and knockdown of AhR subsequently reduces their release of the regulatory cytokine TGF β .¹⁵⁴ AhR activation via dietary precursors also promotes Treg responses and maintains barrier function.¹⁵⁵

The immunomodulatory mechanisms discussed above link diet and the microbiota with immunological responses, particularly asthma and allergies. Below we discuss potential immunological pathways, whereby asthma and allergies may be influenced by diet and/or bacterial metabolites.

5 | ASTHMA AND DIET

Asthma has increased in incidence over the past 40 years.⁶⁴ Approximately, 300 million people have asthma worldwide, with particularly high incidences in Australia and the United States.¹⁵⁶ The most common form of asthma develops when tolerance to inhaled antigens is compromised, and an allergic response develops to normally innocuous inhaled allergens such as pollen.¹⁵⁷ It is worth considering the major cellular and molecular pathways that are thought to lead to asthma, to understand how metabolites may influence these. An important contributor to asthma pathogenesis is the airway epithelium. Reduction in epithelial integrity can arise from genetic predisposition, external insults, or infection, leading to an inflammatory environment that accelerates the development of asthma by further weakening the barrier.¹⁵⁸ A defective epithelial barrier leads to the activation of pattern recognition receptors on epithelial cells which stimulates the release of TSLP, IL-25, IL-33, and GM-CSF, which act on DCs, lymphocytes, eosinophils, basophils, and mast cells to promote inflammatory responses to allergens in the lung.¹⁵⁹ Asthma is typically a Th2 response whereby the release of Th2 cytokines IL-4, IL-5, and IL-13 lead to IgE class-switching, IgE production from plasma cells, and eosinophil recruitment to the lung.¹⁵⁷ However, therapeutic blockade of these cytokines is yet to prove effective in the clinic, suggesting that a myriad of inflammatory or other pathways beyond the Th2 response are important in establishing disease.¹⁶⁰ Another important pathway that may be compromised in asthma are Treg cells. It appears that the maintenance of proper tolerance by Treg cells is important in preventing asthma, suggested by deficiencies in Tregs in asthmatics¹⁶¹ and exacerbation of asthma in mice depleted of Tregs.¹⁶² It is noteworthy that SCFAs control Treg biology, and influence epithelial cell integrity, as these two elements have both been implicated in the pathogenesis of allergic diseases.

5.1 | Asthma incidence and relation to diet and metabolites

Foods that are highly prevalent in a Western countries, with poor nutritional value, have been associated with increased risk of developing asthma. For example, consumption of fast foods, which are high in saturated fat, are associated with increased asthma risk.⁵¹ Indeed, there is an association between obesity (also maternal obesity) and asthma although this may be explained by many factors including

whether excess weight makes breathing more difficult, or may hinder effectiveness of some asthma medications.¹⁶³ Another component common in Western diet is consumption of artificial sweeteners, and when consumed during pregnancy has been associated with increased risk of developing asthma.¹⁶⁴ Interestingly, artificial sweeteners have also been linked with intestinal dysbiosis.¹⁶⁵ Other foods including shellfish and high quantities of meat have also been associated with increased asthma risk.^{166,167}

Unprocessed foods that have high nutritional value, and are commonly consumed in a Mediterranean diet, associate with decreased asthma risk.⁵³ A Mediterranean diet (consisting of high levels of fiber found in fruits, vegetables, legumes and nuts, and unsaturated fatty acids present in olive oil, and fish) is usually high in antioxidants and low in dairy products, red meat, and saturated fats. Indeed, a Mediterranean diet has been suggested to protect children in Crete from symptoms of asthma and rhinitis.⁵⁴ Other reports have found that many individual components of a Mediterranean diet are associated with reduced asthma risk. For instance, consumption of fish, more specifically long-chain omega 3 fatty acids, is inversely related to the incidence of asthma.¹⁶⁸ In addition, many antioxidant rich foods, for example foods high in vitamin C and E, which have anti-inflammatory properties have been associated with reduced asthma risk.¹⁶⁹ Moreover, severe asthmatics consume significantly less fiber (more than 5 g less) than healthy individuals,⁵² suggesting that reduced SCFA production in the gut may associate with asthma incidence. Furthermore, low intake of fruit and vegetables has been associated with asthma.⁸ Unpasteurized milk contains higher amounts of SCFAs and consumption is associated with reduced asthma risk.^{170,171} In addition to the type of diet, the timing of infant feeding may also alter asthma risk. Early feeding of wheat, rye, oats, barley, and fish decreased the risk of asthma.¹⁷² In another study, a low allergen diet where dairy products, egg, soya, fish and shellfish, peanut and tree nuts were avoided, combined with environmental allergy avoidance strategies, was effective in preventing asthma in children considered at high risk of developing asthma and allergic rhinitis.¹⁷³

5.2 | Asthma and the gut microbiota

The role of the microbiota in the development of asthma is suggested by studies showing disruption to the gut microbiota composition. Birth by caesarean section (C-section) has been associated with increased asthma risk in children with a family history of allergy.¹⁷⁴ C-section infants have lower bacterial richness and diversity with an absence of *Bifidobacteria* species, which produce SCFAs.¹⁷⁵ It has been hypothesized that the differential transfer of microbiota in C-section (predominantly environmental) vs normal birth (predominantly vaginal and intestinal) promotes different immune pathways and may explain this association. It is also possible that the association may be due to intra-partum antibiotic prophylaxis, a routine prophylactic antibiotic treatment for C-section which can lead to transfer of antibiotic to neonates (such as through breast feeding) which may impact on the developing microbiota.¹⁷⁶

Clinical studies in humans have shown that even short-term exposure to antibiotics has a drastic impact on microbiota composition and some of these changes are long-lasting or irreversible.¹⁷⁷ For example, amoxicillin is known to deplete *Lactobacillus*, *acidophilus*, and *Bifidobacteria* species, bacteria associated with SCFA production. Furthermore, some studies have reported that dysbiosis due to antibiotic usage can also impact host gene expression of MHC I/II, Reg3γ, IL-25, and Muc2, highlighting the importance of the microbiota in immunity.¹⁷⁸ Indeed, antibiotic use by mothers during pregnancy is associated with increased risk of asthma of offspring in early childhood.¹⁷⁹ There is also a significant correlation if antibiotics were used in the first year of life.¹⁸⁰ This trend was observed consistently regardless of country of origin. Consistent with the effects of early antibiotic use in humans, administration of antibiotics to mice in early life exacerbated features of allergic airways disease (AAD), whereas treatment of adult mice did not alter the development of AAD.¹⁸¹ Nevertheless, discrepancies in the literature arise when considering the role of antibiotics in predisposing to allergic disease. One study of 448 children with atopic parents has demonstrated no relationship between antibiotic intake and asthma.¹⁸² A study of 180 894 children comparing cohort and sibling analyses of antibiotic use and association with asthma revealed that the differing results from studies investigating the impact of antibiotics on the development of asthma are likely caused by respiratory infections or complex familial factors such as genetics and consultation patterns.¹⁸³ This consideration is important because one of the unanswered questions is as follows: what is the precise Western lifestyle factor driving gut microbiota changes and (consequently) asthma and allergies—antibiotic use, or poor diet?

Studies in germ-free mice have further demonstrated the importance of the microbiota for immune responses and asthma. Germ-free mice are more susceptible to AAD, in part due to increased inflammatory natural killer T cells.¹⁸⁴ Germ-free mice also have impaired numbers of Tregs and decreased expression of Foxp3 and CTLA-4.¹⁸⁵ Interestingly, these defects could be reversed by microbial colonization.¹⁸⁶ Another study showed that colonization of germ-free mice with *Clostridium* species (which are high butyrate producers) was important for promoting Treg numbers in the colon.^{187,188} Of note, colonization of germ-free mice can only reverse these effects on the immune system within the first week of birth, but has no effect in later life.¹⁸⁴

In addition to direct disruption of the natural microbiota, the microbiota may be influenced by environmental/external factors. For instance, there is a strong epidemiologic evidence that growing up on a farm associates with reduced incidence of asthma.⁴⁹ Furthermore, despite farming differences, exposure to grains is associated with the protection against atopy.¹⁸⁹ In children who lived on a farm, diversity of microbial exposure was inversely related to risk of asthma.¹⁹⁰ Moreover, studies in mice showed that a common cowshed-derived bacterium, *Acinetobacter lwoffii* F78, was protective against allergic airway inflammation.¹⁹¹ We have speculated previously that gut microbes from livestock may be particularly adept at breakdown of fiber to SCFAs or other protective metabolites.¹⁹² Interestingly, there is also a relationship between animal exposure and development of

allergies. Meta-analysis of the literature shows a favorable association between dog (but not cat) exposure and atopic dermatitis.¹⁹³ Furthermore, mice exposed to dog-associated house mite extract have a skewed microbiota with predominant *Lactobacillus johnsonii* and are protected from OVA or cockroach allergen-induced AAD.¹⁹⁴ Long durations (4–6 months) of breastfeeding have also been suggested to be protective against non-atopic but not atopic asthma.¹⁷² Breast milk contains many immune benefiting components including immune cells, secretory IgA, *Lactobacillus*, SCFAs, mucins, lysozyme, and others.¹⁹⁵

There are clear differences in bacterial composition and their metabolites in allergic individuals compared to non-allergic individuals,¹⁹⁶ implicating the microbiota in susceptibility. This has spurred efforts to treat allergies or asthma with probiotics;¹⁹⁷ however, their effectiveness remains unclear, with conflicting studies.¹⁹⁸

5.3 | Possible mechanisms whereby diet and bacterial metabolites influence asthma

A long-standing view on the cellular basis of asthma has centered on aberrant T-cell responses, particularly Th2 cells (reviewed elsewhere¹⁹⁹). However, an important role for other cell types has emerged, as discussed above, including the lung epithelium¹⁵⁹ and Tregs.²⁰⁰ Importantly, both the epithelium and Tregs have a close association with diet and the gut microbiota.

The mechanisms surrounding the impact of dietary fiber on asthma pathogenesis have been successfully interrogated by mouse models of AAD. High-fiber diet protects mice from house dust mite-induced models of asthma by reducing eosinophilic infiltration of the bronchioles and reducing the production of canonical Th2 cytokines IL-4, IL-5, and IL-13 from T cells.^{45,201} Dietary fiber also reduced serum IgE, goblet cell hyperplasia, and AHR in allergic mice,^{16,184} preventing the onset of clinically similar symptoms of asthmatic anaphylaxis. Furthermore, low- or high-fiber diets altered the microbiota of mice, whereby fiber correlated with increased members of the *Bacteroides* phylum and reduced *Firmicutes*.⁴⁵ This impact of fiber on the gut microbiota closely correlates with what has been found in humans, as the fecal bacteria of children from Burkina Faso that consume diets high in fiber have increased *Bacteroides* and decreased *Firmicutes* compared to European children consuming a Western diet.⁵⁵ Members of the *Bacteroides* phylum have been associated with SCFA production.⁵⁵

To investigate the role of individual SCFAs on asthma pathogenesis, two murine studies administered SCFAs in the drinking water prior to mice undergoing AAD. Both acetate and propionate were demonstrated to reduce eosinophilic infiltration of the bronchioles, Th2 cytokine production, and mucus hypersecretion.^{16,184} The effect of propionate required GPR41 but not GPR43,⁴⁵ suggesting that activation of GPR41 by propionate subsequently reduces AAD. Moreover, propionate reduced the activation of DCs from mediastinal lymph nodes, reducing the expression of activation and co-stimulatory markers CD40, PD-L2, and CD86.⁴⁵ Despite increasing the production of DC precursors in the bone marrow, propionate reduced the capacity for DCs to activate Th2 responses.⁴⁵ As such, propionate appears to

activate GPR41, presumably on DCs or DC precursors and subsequently reduce their capacity to induce Th2 responses required for asthma pathogenesis. Regardless whether this is the main pathway for metabolite influences on asthma, it does support the notion that dietary fiber intake relates to asthma pathogenesis, as originally proposed by us.²²

We demonstrated that acetate administered in the drinking water protects against asthma-like airway inflammation⁴⁴ as well as AHR.²⁰¹ In our latter studies using house dust mite, at a different animal facility, we found that this response did not involve GPR43.¹⁹² However, we uncovered an entirely different pathway. SCFAs inhibit function or expression of HDAC enzymes, and the nutrition state of mothers alters the epigenetic profile of offspring.²⁰² This prompted us to investigate the involvement of nutrition-related epigenetic mechanisms in the prevention of AAD. We assessed the severity of AAD in pups from mothers treated with high fiber or acetate. We took great care to isolate the effect to the in utero period, by restricting the dietary manipulation of the mother to the prenatal period. We also controlled for microbiota transfer from mother to offspring, by performing caesarean section and weaning pups onto new mothers unexposed to SCFAs or diet. Remarkably, high fiber or acetate delivered to the mother during her pregnancy reduced eosinophil infiltration in the BALF and circulation in the blood. Furthermore, high fiber and acetate reduced Th2 cytokine release and total serum IgE in the adult offspring undergoing the house dust mite asthma model. Presence of eosinophils and mucous-secreting cells in the lung were also reduced. In addition, high fiber and acetate improved lung function in mice in the asthma model, such that they showed no hypersensitivity to methacholine challenge. These data demonstrated that the offspring of mothers administered high-fiber diet or acetate are protected from developing asthma and suggested epigenetic mechanisms were involved. Epigenetic effects of high fiber and acetate in the offspring were mediated by exposure to SCFAs either in utero (E13 to birth) or throughout lactation (birth to weaning). High fiber and acetate administered to mothers only when pups were in utero reduced cellular infiltration of the BALF, Th2 cytokine release, serum IgE, and AHR. This demonstrated that only maternal administration of SCFAs was required to maintain protection from asthma in offspring, whereas administration during lactation was too late. The effects of high-fiber diet and acetate on AAD were independent of an altered microbiota in the mother and subsequent transfer of this microbiota to offspring, suggesting a direct epigenetic alteration of the immune compartment is involved in asthma.

Tregs are crucial in maintaining tolerance to innocuous antigens and preventing allergic responses, such as those sometimes observed in asthma.²⁰³ We found that H4 acetylation of the *Foxp3* promoter in T cells was increased by acetate feeding, correlating with increased expression of *Foxp3* transcripts in Tregs. This suggests that SCFAs enhance *Foxp3* expression by epigenetically priming the promoter with increased acetylation of H4 histones. Indeed, we have observed in numerous mouse models, that acetate or butyrate increases Treg number and function,²⁰⁴ suggesting that dietary SCFAs can regulate allergic responses by enhancing the involvement of Tregs. Indeed, asthmatic mice treated with α -CD25 Treg-depleting antibody exhibited

increased cellular infiltration of the BALF, Th2 cytokine release, serum IgE, and worsened lung function. Furthermore, the protective effect of acetate was completely abrogated by α -CD25 treatment. This demonstrated that dietary acetate enhances the involvement of Tregs in the prevention of AAD. Furthermore, Tregs were similarly required for the prevention of AAD in offspring of mothers receiving acetate. These data reveal that exposure to dietary acetate prevents asthma by epigenetically enhancing Treg function. Furthermore, it demonstrates that enhancement of Treg function by acetate is inheritable by epigenetic means as it is transferred to offspring who are not exposed to acetate directly.

Taken together, murine studies using common asthma models now implicate the gut microbiome and intake of dietary fiber in protection from asthma.^{22,44,45,201,205} The details that need resolution include the exact cellular pathways influenced by dietary metabolites (epithelium vs Treg vs DCs), the molecular pathways involved (GPR41 vs GPR43 vs GPR65 vs HDACs), and the contribution of early life exposure to metabolites that may then protect through epigenetic mechanisms.

6 | FOOD ALLERGY AND DIET

The prevalence of food allergies in Western countries is approximately 4% in adults and 5% in children.²⁰⁶ Epidemiologic evidence provides a number of risk factors, including obesity and dietary constituents.²⁰⁷ Food allergy develops because of defects in oral tolerance to dietary antigens, and the induction of Th2-type immune responses. A murine model of food allergy revealed that the release of IL-33 by the gut epithelium induces OX40L expression on DCs in the mesenteric lymph node which subsequently activates Th2 cells, similar to sensitization in AAD.²⁰⁸ IL-4, IL-5, and IL-13 production from Th2 cells stimulate IgE production from B cells which activates eosinophils and mast cells which may subsequently degranulate and release histamine.²⁰⁹

6.1 | Oral tolerance to antigens

The breakdown in oral tolerance that induces food allergy is poorly understood. In a similar mechanism to tolerance in the lung, migration of CD103⁺ DCs from the lamina propria to the mesenteric LN by expression of CCR7 can induce Treg differentiation to maintain tolerance in the gut.^{210,211} CD103⁺ DCs are common within the GIT of mice and are potent stimulators of Treg differentiation via the release of the cytokine TGF- β and retinoic acid.²¹² Moreover, retinoic acid receptor signaling is required for lamina propria DCs to induce IgA class switching,²¹³ whereby IgA is important for maintaining tolerance to commensal bacteria.²¹⁴ Indeed, retinoic acid production appears to be an imprinted phenotype of APCs in the GIT.²¹⁵ These CD103⁺ DCs are crucial in establishing oral tolerance by stimulating Treg responses and suppressing adaptive immune responses to innocuous antigens. The mesenteric LN is the primary site for induction of oral tolerance to both dietary antigens and commensal bacteria.²¹⁶ Indeed, mice lacking mesenteric LNs do not generate oral tolerance to OVA.²¹⁷ Circulating Tregs may be responsible for the induction of systemic

tolerance to antigens consumed orally although this is yet to be investigated experimentally.²¹⁸ In addition, the microbiota appears crucial in maintaining oral tolerance, as germ-free mice are more susceptible to developing allergies.²¹⁹ TLR-4 KO mice also develop severe allergies to dietary antigens, suggesting microbiota-induced stimulation of TLR-4 by bacterial LPS is important for oral tolerance.²²⁰

6.2 | Food allergy associated with diet and metabolites

Alongside avoidance of problematic foods, the consumption of hypo-allergenic foods containing hydrolyzed protein has been recommended for high-risk or allergic infants.^{221,222} However, the role of diet in altering the clinical course of allergy in pediatric or adult cohorts remains poorly understood. Multivitamin supplementation for infants and children at 3 years of age is associated with increased incidence of food allergy.²²³ In contrast, vitamin D insufficiency and deficiency at 1 year of age is associated with an increase in the risk of developing food allergy.⁸⁴ Other metabolites that may associate with food allergy include vitamin A, ω -3 fatty acids, and antioxidants.²²⁴ As with asthma, fiber intake has also been associated with preventing food allergy. A study on infant diet reported by prospective food diaries revealed that dietary intake of high levels of fruits and vegetables is associated with reduced incidences of food allergy by 2 years of age.²²⁵ This suggests that SCFAs from the bacterial fermentation of dietary fiber may play a role in preventing food allergy. A number of rodent studies on diet, the microbiome, and food allergy have been extensively reviewed by Barcik et al.²²⁶ and reveal a complicated network between food and bacteria that alter food allergy pathogenesis. Such dietary constituents such as polyunsaturated fatty acids, vitamin D, selenium, and polyphenols have all been associated with reduced Th2 responses in various murine models of food allergy.²²⁶

6.3 | Food allergy and the gut microbiota

A link between the gut microbiota and food allergy was established using germ-free or antibiotic-treated mice. Germ-free mice and mice treated with broad spectrum antibiotics exhibit increased serum IgE levels, as well as basophil numbers,²²⁷ suggesting that the microbiota is required to regulate IgE and basophil-mediated responses associated with food allergy in humans.²²⁸ Indeed, gnotobiotic mice display poor oral tolerance and exhibit enhanced Th2 responses to OVA challenge.²¹⁹ Selective re-colonization of gnotobiotic mice with a microbiota predominantly composed of clostridia rescued immune regulation by enhancing epithelial integrity, reducing allergen uptake²²⁹ and possibly by enhancing Treg biology. As such, commensal bacteria are clearly important in maintaining oral tolerance to food antigens. Further studies with gnotobiotic mice demonstrated that both microbial and food antigens induced peripheral Treg populations in the gut, which protected against food allergy.²³⁰

A recent human study also identified a strong association between microbial dysbiosis and food allergy incidence. Antibiotic administration during childhood was associated with the onset of various milk

and non-milk food allergies.²³¹ Furthermore, the class of antibiotic also determined the risk of developing food allergy, suggesting that the depletion of particular bacteria may influence allergy susceptibility. Mice treated with antibiotics also exhibit increased severity of allergic airways disease due to skewed fungal overgrowth that stimulated M2 macrophage polarization.²³² Such findings are yet to be corroborated in humans although skewed fungal populations previously associated with atopic dermatitis have been identified in the sputum of asthmatic patients.²³³ Birth by caesarian section is also associated with food allergy,²³⁴ presumably due to the failure to transfer beneficial flora from the mother to the offspring. Although the benefits of microbe colonization from vaginal births remain unclear, there is serious consideration being given to intentional swabbing of C-section babies with mother's vaginal microbiota.²³⁵ As with asthma, breastfeeding for at least 4–6 months and exposure to farm environments during childhood are also associated with protection against food allergy.^{236,237}

Probiotics also highlight the importance of the microbiota (and possibly SCFAs) in determining food allergy. *Bifidobacterium* produces high levels of SCFAs and promotes epithelial integrity.²³⁸ *Bifidobacterium* alleviates food allergy in mice²³⁹ and its administration to pregnant women significantly reduced allergy in offspring, and this correlated with changes in gut microbiota composition.²⁴⁰ Oral immunotherapy with the probiotic *Lactobacillus rhamnosus*, a high SCFA producer, led to peanut unresponsiveness in 82% of allergic children.²⁴¹ As with most probiotic trials, results may vary greatly depending on whether individuals consume dietary fiber as a prebiotic. However, taken together these studies suggest SCFA-producing microbiota may be important for protection against food allergy.

6.4 | Possible mechanisms whereby diet and bacterial metabolites regulate food allergy

The mechanisms by which diet and bacterial metabolites might alter the incidence of food allergy remains poorly understood. To address this problem, we investigated the impact of dietary fiber in a murine model of peanut allergy. Feeding mice with high levels of dietary fiber protects against food allergy.⁷⁸ Similar to our studies on asthma,¹⁹² acetate administered in the drinking water also protected against food allergy. High-fiber diet did not protect against food allergy in mice deficient in Myd88,⁷⁸ an innate signaling molecule important for barrier integrity²⁴² as well as microbiota composition. This suggests that dietary fiber can establish a gut microbiota that enhances the role of Myd88 in protecting against allergy. Dietary fiber reduced anaphylaxis and serum IgE via the induction of tolerance-inducing Tregs by CD103⁺ DCs. These CD103⁺ DCs more readily metabolized vitamin A to retinoic acid via the enzyme RALDH. Retinoic acid promotes Treg cell differentiation and homing to the gut.²⁴³ Moreover, the combination of both vitamin A and fiber in the diet was required to maintain protection against food allergy. These data establish a link between vitamin and fiber intake with the rising incidence of food allergy, whereby Western diets low in fiber and possibly vitamin A may lower the tolerogenic capacity of CD103⁺ DCs, which subsequently lowers the threshold for allergic sensitization.

Furthermore, we established a clear role for vitamin A metabolism in maintaining oral tolerance and protecting against food allergy. Vitamin A is derived from healthy foodstuffs such as vegetables and fish; however, vitamin A deficiency is mostly observed in developing countries. Incidence of food allergies in these countries is higher than first appreciated²⁴⁴ although it is difficult to explain food allergies throughout the world based on vitamin A intake. While vitamin A deficiency appears rare in Western countries, population studies indicate an inadequate intake of vitamin A against recommended levels in up to 5% of children (aged 1–3 years) and up to 35% of adults (age >19) in Canada and the United States.^{245,246} Healthy adults mitigate short-term vitamin A deficiency from stores in their liver; however, infants and children have a much lower capacity for this. Short-term vitamin A deficiency could have a significant impact on a child's oral tolerance, and in support of this, oral tolerance is abrogated in neonatal mice by physiological vitamin A deficiency.²⁴⁷ It is conceivable that there is a critical window when tolerance to many foodstuffs is established, and deficiencies of fiber or vitamin A even for short periods of time, may predispose to food allergy.

An altered gut microbiota may underlie allergies, including food allergies.^{187,227,229,248–250} Our studies in mice demonstrated that a healthy gut microbiota and its manipulation to efficient SCFA production may protect against food allergies. Transfer of a 'high-fiber' microbiota to gnotobiotic mice successfully transferred protection against food allergy.⁷⁸ Interestingly, a high-fiber microbiota did not alter the CD103⁺ DC population of the mesenteric LN, but did promote IgA production and IgA coating of gut bacteria. This suggests that the microbiota established by a high-fiber diet can promote oral tolerance and intestinal homeostasis through SCFA production but is insufficient to maintain all the beneficial effects of a high-fiber diet.

7 | OTHER ALLERGIES: ALLERGIC RHINITIS, ATOPIC DERMATITIS, AND EOSINOPHILIC ESOPHAGITIS

Studies on the immunological impact of diet and dietary metabolites have mostly focused on asthma and food allergy; however, a number of other allergic diseases also associate with diet and the microbiota. In a similar manner to asthma, a Mediterranean diet containing large amounts of fruits and vegetables is associated with protection against allergic rhinitis.⁵⁴ Furthermore, a prospective study of Swedish children revealed that antibiotics during the first week of life increased the risk of developing allergic rhinitis by 8 years of age while living on a farm during childhood was protective.²⁵¹

Consumption of fruits and vegetables has also been associated with protection against eczema, whereby a traditional Columbian diet was negatively associated with the disease.²⁵² Contrastingly, consumption of Western fast food by both children and adolescents was associated with an increased risk of eczema and asthma,⁵¹ further highlighting the detrimental impact of Western diet. Both probiotics and a combination of probiotics and prebiotics reduced the severity of atopic dermatitis, particularly with heterogenous mixtures

of *Lactobacillus* species.^{253,254} This further highlights the potential for both diet and the microbiota to influence not only the pathogenesis of allergic disease, but also the potential to treat such diseases once they are established. Indeed, multi-strain probiotic use to prevent eczema in high-risk infants has been successful in limiting the severity of the allergic response,^{255,256} but more studies are needed to fully characterize whether these probiotics can successfully prevent other allergies.

Eosinophilic esophagitis (EoE) is another allergic disease similar to food allergy, in which an allergic response to certain food antigens occurs in the esophagus. Effective treatment for EoE is avoidance of problematic foods or consumption of elemental diets that lack whole proteins.^{257,258} Although the impact of dietary fiber on EoE is unknown, *Lactococcus lactis* probiotic significantly reduced the symptoms in a murine model of EoE.²⁵⁹ A major product from the fermentation of oat bran oligosaccharide by *L. lactis* is acetate,²⁶⁰ suggesting that SCFA production by probiotics may also reduce allergic inflammation in EoE. Interestingly, protection from *L. lactis* was only observed when administered after EoE induction, whereas preventative administration of *L. lactis* had no effect.²⁶¹

8 | FUTURE DIRECTIONS

The role of diet, the gut microbiota, and metabolites in allergies is a promising avenue for future studies. Can insufficient consumption (or bacterial production) of metabolites explain asthma and allergies in Western countries? Human clinical trials are needed to establish whether individual or combination metabolites prevent or treat disease. If probiotics do prove to be successful, are their metabolites the mechanism of action? And is innate signaling by gut bacteria²⁶² important? Farm animal exposure protects against asthma.^{49,190} Is this exposure somehow related to bacteria efficient at digesting fiber, and producing large amounts of SCFAs? We believe that immunomodulation by SCFAs delivered either directly or derived through bacterial fermentation of dietary fiber remains an under-appreciated therapeutic approach to prevent or treat allergic diseases. Such approaches may also be combined with traditional medicines. Although murine studies described above demonstrated mechanisms of SCFAs on physiology, few studies have investigated SCFA-based treatments in human disease. One problem is the challenge for pharmaceutical or nutraceutical companies to commercialize treatments. Probiotic mixtures is one straightforward approach, or the development of very specialized prebiotics. Probiotics that promote SCFA production have shown potential for alleviating IBD. Such clinical trials highlight the potential for both diet, prebiotics and probiotics to change the way allergic and inflammatory diseases are prevented or treated.

CONFLICT OF INTEREST

The authors declare that they are unaware of any potential conflicts of interest.

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