

The impact of diet on asthma and allergic diseases

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Abstract | The incidence of allergic diseases is increasing, both in developed and developing countries, concomitantly with the rise in living standards and the adoption of a ‘western lifestyle’. For two decades, the hygiene hypothesis — which proposes that the lack of early childhood exposure to infectious agents increases susceptibility to allergic diseases in later life — provided the conceptual framework for unravelling the mechanisms that could account for the increased incidence of allergic diseases. In this Review, we discuss recent evidence that highlights the role of diet as a key factor influencing immune homeostasis and the development of allergic diseases through a complex interplay between nutrients, their metabolites and immune cell populations. Although further investigations are still required to understand these complex relationships, recent data have established a possible connection between metabolic homeostasis and allergic diseases.

Allergic diseases

Diseases caused by an inappropriate initiation of type 2 immune responses to innocuous environmental antigens that result in several conditions, including asthma, allergic rhinitis, food allergy and atopic dermatitis.

The incidence of allergic diseases — such as atopic dermatitis, allergic rhinitis and allergic asthma — has increased greatly over the past three decades (especially in developed countries). These conditions are among the most common chronic diseases in the world, affecting approximately 235 million people worldwide according to estimates from the World Health Organization ([WHO asthma fact sheet](#)). The increasing incidence of allergic diseases as populations become urbanized suggests that factors related to a ‘western lifestyle’ are driving this increase. Several hypotheses have been suggested, such as the hygiene hypothesis, which is based on epidemiological data showing a direct link between the decrease of infectious burden and the rising incidence of allergic diseases¹. Although the lack of exposure to microbial products in early life is one possible cause of this increase, other changes that are associated with a western lifestyle — such as pollution, exposure to tobacco smoke, sedentary lifestyle and reduced duration or absence of breastfeeding during the first months of life — might also contribute to the increased incidence of allergic diseases.

Diet might also influence susceptibility to allergic diseases, as it contributes to the education and regulation of the immune system. Indeed, through maternal metabolism, diet could have an impact on our health even before birth, and some interventional studies have reported immunomodulatory effects of specific nutrients on the neonate and a reduction of early sensitization to allergens^{2,3}. In addition to *in utero*

immunomodulatory effects, maternal diet could influence the immune response of the breastfed child to dietary and environmental antigens, as breast milk contains both food allergens and aeroallergens. In contrast to the widespread idea that food allergens in milk may contribute to allergen sensitization and food allergy in the neonate, recent evidence indicates that maternal exposure to allergens during lactation, or exposure of the neonate to allergens in early life, may in fact favour the induction of oral tolerance to these innocuous antigens and therefore prevent the development of allergies in the offspring.

Later in life, dietary compounds from solid food are processed by the commensal flora into a range of secondary metabolites, which regulate immune homeostasis through various receptors, including G protein-coupled receptors (GPCRs) and nuclear receptors. Imbalances in diet that lead to obesity or micronutrient deficiency can promote inflammation, and have been suggested as factors that influence susceptibility to allergic diseases and asthma⁴.

This Review provides an integrative view of the current knowledge on the role of diet in the development of allergic diseases, discussing both epidemiological data and functional studies in experimental models. In addition, a mechanistic rationale for diet supplementation to prevent, treat or at least mitigate allergic diseases is discussed. As excellent reviews have recently been published that summarize the effect of dietary compounds on the development and function of the

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Asthma

A respiratory disorder that is characterized by reversible expiratory airflow limitation or bronchial hyperresponsiveness, and has various clinical, biological and therapeutic characteristics.

Breastfeeding

Recognized as the main source of active and passive immunity in early life. Breast milk contains antibodies that react with infectious agents present in the mother's environment, and confers passive immunity to the breastfed child against infectious agents that the child is likely to encounter shortly after birth.

Oral tolerance

An immune state induced by the oral administration of innocuous antigens (such as food proteins) that leads to local and systemic unresponsiveness.

G protein-coupled receptors

(GPCRs). A large family of receptors that have seven transmembrane domains and are implicated in various signal transduction pathways and cellular responses.

Obesity

Defined by a body mass index of the 95th percentile or above for age and sex standards.

Polyunsaturated fatty acid

(PUFA). An unsaturated fatty acid with a carbon chain that has more than one double bond per molecule.

Mediterranean diet

A diet based on a high consumption of olive oil, fish and vegetables.

Vitamin A

A vitamin that is oxidized into retinal, which in turn is converted into retinoic acid (RA). Oxidation to retinal is mediated by alcohol dehydrogenases (ADHs) or retinol dehydrogenases (RDHs) and then by retinal dehydrogenases (RALDHs; also known as aldehyde dehydrogenases (ALDHs)), producing all-*trans*-RA and 9-*cis*-RA.

immune system^{5,6}, as well as on the role of diet, microbiota and their metabolites in shaping immune response and inflammation^{7,8}, we do not discuss these topics in detail. Similarly, the role of polyunsaturated fatty acid (PUFA) metabolites, eicosanoids and pro-resolving mediators in allergic diseases is not reviewed here, as these molecules are whole research areas that have been reviewed recently^{9–11}.

Maternal and early-life diets and allergic diseases

Epidemiology. Allergic diseases usually start early in life. The diet of the pregnant (and eventually breastfeeding) mother is the earliest possible nutritional influence. Many epidemiological cohort studies (which were mostly observational) have investigated associations between maternal diet during pregnancy and/or lactation and allergic outcomes in the offspring. However, most of these studies failed to report consistent associations¹². Discrepancies are unsurprising, as dietary patterns are often loosely defined with regards to their content of nutrients, vitamins and antioxidant molecules. Furthermore, other parameters that might also influence the development of allergic diseases are not always recorded: for example, the atopic status of the parents, caesarean or vaginal delivery, number of siblings, exposure to common allergens, maternal and early-life viral infections, and exposure to tobacco smoke. Despite these confounding factors, some maternal dietary patterns deserve further investigation. For example, diets that are rich in fruit and vegetables, such as the Mediterranean diet, have consistently been associated with a lower risk of allergic sensitization (which is defined as a positive skin prick test to allergens) and allergic rhinitis in children, whereas a high maternal consumption of vegetable oils, margarine and processed foods is associated with a higher risk of allergic sensitization¹².

Studies that focus on individual foods or nutrients, including interventional studies, have led to more consistent conclusions. Maternal fish oil supplementation during pregnancy has been associated with a reduced risk of allergen sensitization and atopic dermatitis in children², and regular fish consumption by the infant before the age of 1 year was associated with a reduced risk of allergic disease and sensitization to food and airborne allergens during the first 4 years of life¹³. Furthermore, fish oil supplementation in early infancy, leading to an increase in the levels of omega-3 PUFAs, was associated with decreased allergen-specific T helper 2 (T_H2) cell responses and increased polyclonal T_H1 cell responses, although no difference was observed in regulatory T (T_{Reg}) cell populations at 6 months of age¹⁴. Whether such a change in the balance of T_H1 and T_H2 cells could indicate a reduced risk of subsequent allergies remains unclear. Analyses of antioxidant molecules and other nutrients do not support an association between childhood allergies and their status during pregnancy or early childhood, although a longitudinal study using a large Danish cohort showed that maternal vitamin A and vitamin E intake may protect children against allergic rhinitis¹⁵.

In addition to the nutritional intake of the mother, a recent prospective cohort study has reported that a higher maternal intake of food allergens during early pregnancy was associated with a lower risk of allergy and asthma in the offspring at 8 years of age. Indeed, maternal peanut intake was associated with a lower risk of childhood peanut allergy, maternal milk intake was associated with a lower risk of childhood asthma and allergic rhinitis, and maternal wheat intake during the second trimester was associated with a lower risk of atopic dermatitis in children³. This study highlights the first and second trimesters of pregnancy as critical periods for the development of allergy susceptibility in offspring.

Other epidemiological studies have addressed the effects of breastfeeding on the development of allergic diseases during childhood. Although there is evidence that breastfeeding protects against atopic dermatitis, wheeze in early childhood and allergy to cow's milk¹⁶, data are inconsistent about the role of breastfeeding in protection against asthma. Some studies have concluded that exclusive breastfeeding for at least 3 months protects against asthma between 2 and 4 years of age (albeit with a stronger protection in children from families with a history of atopic diseases)^{17,18}. By contrast, other studies have reported no benefit of exclusive breastfeeding in children from non-atopic families¹⁹ or in decreasing the risk of asthma in children at 5 years of age²⁰. However, a recent systematic review that includes a meta-analysis of studies on breastfeeding and asthma in children reported that breastfeeding protects against asthma until the age of 6 years, with a more pronounced effect in children under 2 years of age²¹. Thus, despite the careful analysis of published studies based on the strict criteria proposed by Kramer²² (that is, strict diagnostic criteria for atopic outcomes, separate assessments of high-risk children, records of confounding variables and adequate statistical power), it is still difficult to draw definitive conclusions.

The discrepancies between these studies could be attributed to the poor definition of asthma, which has many phenotypes²¹. Interestingly, analysis of a birth cohort in which children were stratified into wheezers, those with allergic asthma and those with non-allergic asthma showed that breastfeeding for 4 months reduced the risk of allergen sensitization and also reduced the risk of both allergic and non-allergic asthma in the offspring up to 8 years of age²³. Other variables might contribute to the different results: human breast milk contains food and airborne allergens, such as ovalbumin (from eggs), bovine β -lactoglobulin (from cow's milk), gliadin (from wheat), Arah1 and Arah2 (from peanuts)^{24,25}, and Derp1 (from house dust mites)²⁶, as well as IgA that is specific for food and environmental allergens²⁷. In addition, immunosuppressive cytokines — such as interleukin-10 (IL-10) and transforming growth factor- β (TGF β) — have been detected in breast milk, and epidemiological studies have shown a correlation between the levels of TGF β in breast milk and protection against wheeze and atopic dermatitis in breastfed children²⁸. Thus, it is possible that allergens, allergen-specific immunoglobulins or immune complexes, and immunosuppressive cytokines

that are transferred from the lactating mother through breast milk might modify the immune response to allergens in the infant and decrease their susceptibility to the subsequent development of allergy.

Although no epidemiological studies have directly addressed the effect of allergen levels and/or allergen-specific immunoglobulins in breast milk on the development of allergy in the breastfed child, clinical studies based on allergen avoidance during lactation in allergic mothers (which often also includes avoidance during pregnancy) have been informative. Most of these studies indicate that — in contrast to the widespread (and accurate) view that allergen avoidance in adults is necessary to prevent allergy symptoms — allergen avoidance in the maternal diet is ineffective and unnecessary to prevent the development of allergy in the child²⁹. This might be owing to the idea that early exposure to dietary and environmental allergens is required for the generation of allergen-specific T_{Reg} cells, which could prevent against the development of allergic diseases. This hypothesis has been tested in mice, and studies have shown that breast milk-mediated transfer of antigens or immunoglobulins prevents antigen-specific immune responses³⁰ and the development of allergic airway disease^{31,32}.

The introduction of solid foods into the infant's diet occurs between 4 and 6 months of age, according to the recommendations of both the American Academy of Pediatrics and the European Academy of Allergy and Clinical Immunology^{33,34}. Although delaying the introduction of solid foods was first thought to prevent allergies, more recent studies have not supported this hypothesis¹⁶. The prospective birth cohort study (known as PASTURE/EFRAIM) further shows that an increased diversity of food antigen exposure in the first year of life is inversely correlated with the development of asthma, food allergy, allergic rhinitis and atopic sensitization up to 6 years of age³⁵. In addition, consumption of unprocessed cow's milk during the first year of life was inversely associated with asthma, allergic rhinitis and atopy³⁶. Further data identified whey proteins (including bovine serum albumin, α -lactalbumin and β -lactoglobulin) as the components in the unprocessed milk that were associated with a reduced risk of asthma but not atopy³⁷. Therefore, although consumption of unprocessed milk cannot be recommended owing to its possible contamination with pathogens, further investigation about ways in which to preserve the protective effect of unprocessed milk while guaranteeing our safety upon consumption would be of interest.

In summary, epidemiological studies indicate a crucial role for both maternal and early childhood food exposure in protection against the development of allergic diseases. Current data do not support maternal dietary restrictions during pregnancy and lactation or delayed introduction of allergenic foods into the infant's diet. By contrast, the inclusion of food allergens in maternal and early childhood diet might be beneficial for the prevention of allergy and asthma. Confirming these results in case-control studies will be important to identify therapeutic strategies or guidelines that might help to control the increasing burden of allergic diseases.

Mechanisms of mother-to-child transfer. Experimental studies have demonstrated that maternal diet influences immune responses in the offspring even before birth, due to the fetus being supplied with nutrients through the placenta. In a mouse model of allergic airway inflammation³⁸, *in utero* exposure to a diet that was rich in methyl donors (including folic acid, vitamin B12 and choline) increased the severity of allergic airway disease in the offspring and was associated with increased gene methylation, which is an epigenetic process that in most cases inhibits gene expression. Among the methylated genes described in this study, runt-related transcription factor 3 (*Runx3*) negatively regulates allergic asthma³⁸, and its diet-induced methylation might contribute to the observed increase in allergic airway disease. Such a mechanism could occur in humans, as it is known that dietary folic acid intake induces CpG methylation, which can be transmitted across generations³⁹. This result requires further investigation, as folic acid is currently prescribed as an essential nutrient during pregnancy owing to its important role in neural tube development. Furthermore, protection was also transferred during pregnancy in a model of allergic airway inflammation and relied on the maternal-fetal transfer of antigen-specific IgG⁴⁰. Such a mechanism could occur in humans, as it is known that maternal IgG is selectively transferred through the placenta by the neonatal Fc receptor (FcRn)⁴¹.

The study of animal models is increasing our understanding of the effects of breastfeeding on the development of allergic diseases after birth and the underlying mechanisms of action. The oral administration of antigen to lactating mice tolerizes the offspring to the administered antigen and prevents antigen sensitization and allergic airway symptoms⁴⁰ or food allergy⁴² in young offspring. The exposure of lactating mice to an allergen through aerosols or intragastric administration also protected the offspring from developing allergic airway inflammation in adulthood³¹. This protection was dependent on the presence of the allergen together with TGF β in breast milk, which led to T_{Reg} cell induction in the offspring (FIG. 1); this mechanism is reminiscent of the human data that have associated levels of TGF β in breast milk with protection against allergen sensitization²⁸. In a mouse model, breastfeeding by allergic mothers also induced antigen-specific protection against the development of allergic airway disease in the offspring³². However, in this study, protection did not rely on the presence of TGF β and free antigen in the milk but required the transfer of IgG immune complexes through FcRn, which resulted in the induction of antigen-specific T_{Reg} cells (FIG. 1). However, a similar mechanism is unlikely to occur in humans, as extremely low concentrations of IgG are detected in human milk, but IgG is actively transferred through the placenta during the third trimester of pregnancy⁴¹.

Longitudinal epidemiological studies that assess the levels of maternal allergen exposure, allergen and allergen-specific IgG in cord blood, the levels of allergen-specific IgA in milk and the subsequent development of

Immune complexes

Complexes of antigen bound to antibody and, sometimes, to components of the complement system. The levels of immune complexes are increased in many autoimmune disorders, in which they become deposited in tissues and cause tissue damage.

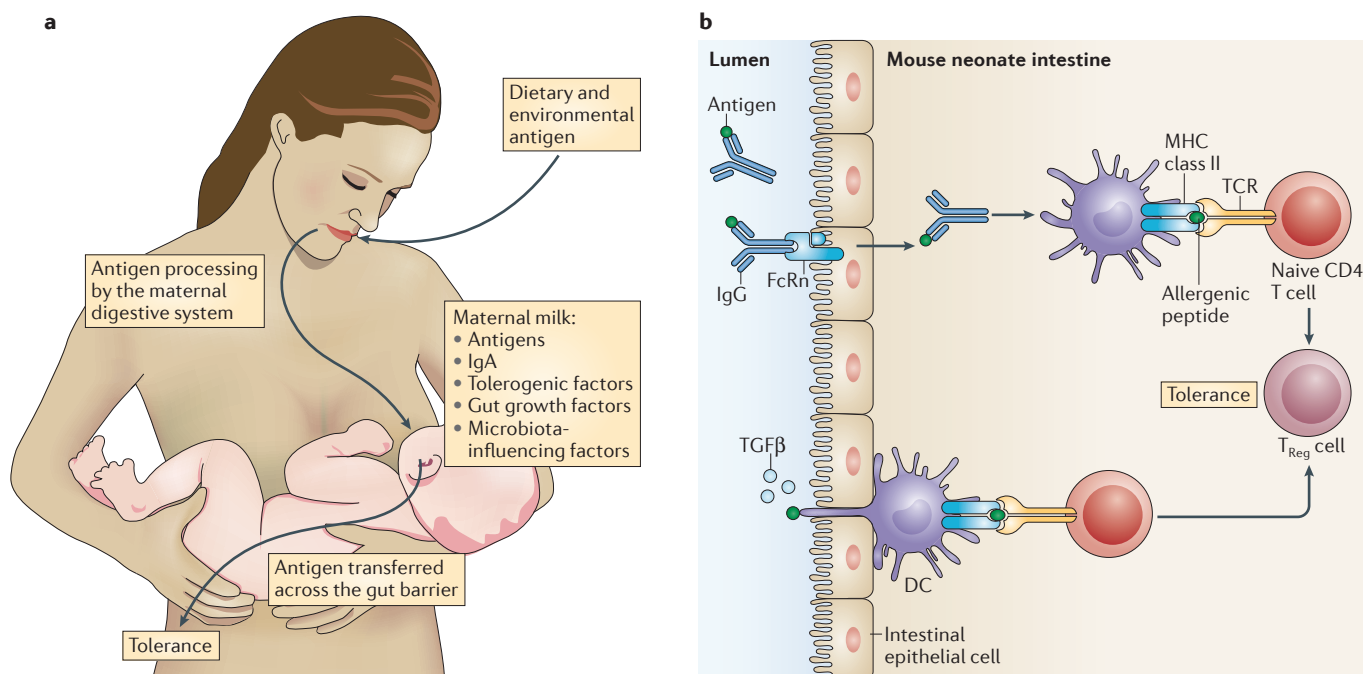


Figure 1 | Possible mechanisms of mother-to-child transfer of protection against allergic airway inflammation.

a | Human breast milk contains free dietary and environmental antigens, IgA, tolerogenic factors (such as interleukin-10, transforming growth factor- β (TGF β), lactoferrin and antioxidants), gut growth factors (such as cortisol, thyroxine, epidermal growth factor and TGF β) and microbiota-influencing factors (such as prebiotics (oligosaccharides and glycoconjugates) and casein). These factors can be transferred to the infant during breastfeeding. **b** | Mouse models show that allergens can be transmitted to the neonate either in their free form from a non-allergic mother or in antigen–IgG immune complexes from an allergic mother. Transfer of antigen–IgG immune complexes through the intestinal barrier of the neonate requires the presence of the neonatal Fc receptor (FcRn). Once in the intestinal mucosa, immune complexes can be captured by dendritic cells (DCs), which can subsequently prime naive CD4⁺ T cells to differentiate into antigen-specific regulatory T (T_{Reg}) cells. Free antigens can also be captured by intestinal DCs, and the presence of TGF β from milk has been shown in mice to promote the priming of naive T cells into antigen-specific T_{Reg} cells, thereby promoting immune tolerance. Figure adapted with permission from REF. 169, Elsevier. TCR, T cell receptor.

childhood allergy are required to better understand the effects of such parameters on the development of asthma in the offspring and might lead to new recommendations or strategies for the prevention of allergy.

Obesity

Epidemiology. Although obesity is a proven risk factor for cardiometabolic diseases, epidemiological studies have shown that obese individuals with a body mass index (BMI) of ≥ 30 kg per m² have a 92% increased risk of asthma⁴³. Meta-analysis studies in both adults and children have confirmed the causative effect of obesity on the development of asthma. In contrast to a single study⁴⁴, a meta-analysis shows no differential effects between females and males⁴³. Indeed, bariatric surgery and dietary restriction in obese patients with asthma were shown to improve bronchial hyperresponsiveness, airway inflammation and clinical outcomes⁴⁵. By contrast, a high-fat meal was shown to increase airway neutrophilia and impair bronchodilator recovery in obese patients with asthma⁴⁶.

Although only some studies have reported a relationship between obesity and allergic rhinitis or food allergy, being overweight has been positively associated with the risk of developing atopic dermatitis in early childhood⁴⁷. In addition, the severity of atopic dermatitis symptoms

increases with body weight⁴⁸. Interestingly, higher maternal BMI is also associated with an increased risk of asthma, but not rhinitis, atopic dermatitis or allergen-specific IgE production in the offspring⁴⁹; this suggests that diet has crucial *in utero* effects on the development of asthma.

Mechanisms. Obesity results from dysregulated energy homeostasis, when energy expenditure is lower than intake. Excessive energy is mainly stored in the form of triglycerides in white adipose tissue (WAT). WAT is not solely composed of lipid-laden adipocytes, but is an immunologically active tissue containing innate and adaptive immune cells that reciprocally interact with adipocytes. The characteristics of immune cells (including cell type, phenotype, abundance and function) dynamically change with the metabolic status of the tissue: there is a broadly anti-inflammatory phenotype (that is associated with T_H2 cells and T_{Reg} cells) in WAT from lean individuals and a pro-inflammatory phenotype (that is associated with T_H1 cells and T_H17 cells) in WAT from obese individuals⁵⁰.

Interestingly, in addition to the exacerbation of early-onset (allergic) asthma^{4,51}, obesity can induce asthma in adults. Various mechanisms could account for obesity-induced or obesity-exacerbated asthma. Mechanical

Triglycerides

Contained in oils and fats, triglycerides give rise to free fatty acids after their breakdown by pancreatic lipases. Dietary fats are dissolved in micelles by bile salts in the upper part of the gastrointestinal tract and are subsequently taken up by enterocytes.

White adipose tissue

A type of adipose tissue that specializes in energy storage and is most commonly found in subcutaneous and visceral adipose tissues.

Table 1 | Main asthma endotypes

Endotype	Natural history	Clinical and physiological features	Pathobiology and biomarkers	Genetics	Response to therapy
Early-onset allergic asthma	• Early onset • Mild to severe	Allergic symptoms and other diseases	• Thick SBM • Specific IgE and T_H2-type cytokines	Chromosome 17q12 and T _H 2 cell-related genes	Responsive to corticosteroids and T _H 2 cell-targeted response
Late-onset eosinophilic asthma	• Adult onset • Often severe	• Sinusitis • Less allergic	• Corticosteroid-refractory eosinophilia • IL-5	Not known	Responsive to antibody against IL-5 and cysteinyl leukotriene modifiers, but is corticosteroid refractory
Obesity-related asthma	Adult onset	• Very symptomatic • Airway hyper-responsiveness is less clear	• Oxidative stress • Lack of T_H2 cell biomarkers	Not known	Responsive to weight loss and antioxidants
Neutrophilic asthma	Adult onset	• Low FEV1 • More air trapping	• Sputum neutrophilia • T_H17 pathway components and CXCL8	Not known	Possibly responsive to macrolide antibiotics

Table adapted with permission from REF. 55, Nature Publishing Group. CXCL8, CXC-chemokine ligand 8; FEV1, forced expiratory volume in 1 second; IL-5, interleukin-5; SBM, subepithelial basement membrane; T_H, T helper.

obstruction has an obvious role as it alters lung function⁵². Obesity-induced asthma is considered to be a distinct endotype from allergic asthma, with a later onset, a more severe outcome, and the presence of neutrophils^{53,54} and an IL-17 signature⁵⁵ (TABLE 1). Neutrophils and an IL-17 signature are only present in a few experimental models⁵⁶, and most studies using these models confirm that obesity exacerbates allergic asthma and that the observed effects are not solely dependent on T_H2 cell responses⁵⁷. Furthermore, IL-17A-producing innate lymphoid cells (known as ILC3s) are required for the increased basal antigen-independent airway hyperreactivity that is induced by a high-fat diet or by genetic obesity in mice⁵⁸. This increase was dependent on IL-1 β -producing inflammatory classically activated macrophages (also known as M1 macrophages) in the lungs, as well as on the activation of the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome, which can be mediated by cholesterol crystals. These results indicate that obesity induces changes in ILC3 and myeloid cell populations in the lungs that contribute to antigen-independent lung inflammation and airway hyperreactivity.

Increased concentrations of the adipokines resistin and leptin — which are released by visceral and subcutaneous fat in obesity — have pro-inflammatory activity (including in the lungs), whereas adiponectin, which is found at lower levels in obese mice than in lean mice, exerts anti-inflammatory effects (including in the airways)^{59,60}. However, the direct cellular and molecular targets of adipokines were not determined in these studies. Of note, high levels of leptin, defective apoptotic cell clearance by alveolar macrophages (which have been shown to have a pro-inflammatory phenotype⁶¹) and increased systemic oxidative stress are observed in obese individuals⁶². Leptin also potentiates⁶³, whereas adiponectin inhibits⁶⁴, human eosinophil chemotaxis. Compared with lean mice, diet-induced obesity was shown to enhance eosinophil trafficking from the bone marrow to the lungs and delay their transit through

the airway epithelium into the lumen, which contributed to increased allergic inflammation⁶⁵. However, an earlier study reported a reduction in the levels of lung eosinophilia and IL-5, as well as a reduction in pro-inflammatory cytokine production by cells in lung-draining lymph nodes after antigen re-stimulation, in antigen-sensitized high-fat diet-fed mice⁶⁶. However, increased sputum IL-5 concentrations and submucosal eosinophil numbers have been correlated with BMI in individuals with severe obesity⁶⁷. This result indicates that obesity promotes airway eosinophilia, whereas it decreases adipose tissue eosinophilia (BOX 1). Although a causal link between these opposing effects of obesity on two distinct tissues has not been demonstrated, specific obesity-induced immune cell ‘redistribution’ (for example, of eosinophils) represents an attractive option for further investigation into the cellular mechanisms of asthma exacerbation by obesity⁶⁸.

In addition, further evidence for a link between metabolism and allergic diseases has been shown in a mouse model of obesity-exacerbated asthma in which the AMP-activated protein kinase activator metformin — which reverses obesity-associated insulin resistance — decreased eosinophil infiltration into lung tissue⁶⁹. Adaptive immune cells that contribute to an allergic response might also be sensitive to the altered nutritional status that is found in obesity. The serine/threonine protein kinase mammalian target of rapamycin complex 1 (mTORC1) functions as an integrator of various nutritional and metabolic cues, including glucose, amino acids, ATP and insulin, and its signalling is increased by obesity and a high-fat diet in mammals⁷⁰. The regulatory-associated protein of mTOR (RAPTOR)–mTORC1 pathway is essential for the metabolic reprogramming in T cells that leads to antigen-triggered quiescence exit and the differentiation of T_H2 cells⁷¹. Thus, integration of nutritional and metabolic cues through mTORC1 might influence the development of diseases associated with a dysregulated type 2 response, such as asthma.

Adipokines
Cytokines that are secreted by adipocytes.

Box 1 | ILC2–eosinophil–macrophage axis in allergy and obesity

In the lungs and skin, allergen sensitization induces the synthesis of epithelial cell-derived or keratinocyte-derived interleukin-25 (IL-25), IL-33 and thymic stromal lymphopoietin, which stimulate type 2 innate lymphoid cells (ILC2s) to produce IL-5 and IL-13. These cytokines in turn promote eosinophilia and T helper 2 (T_H2) cell responses, resulting in the development or exacerbation of allergic asthma¹⁰⁹ and atopic dermatitis¹¹⁰.

In a strikingly similar manner, lean visceral adipose tissue (and gut tissue) contains high numbers of ILC2s, eosinophils and alternatively activated macrophages (also known as M2 macrophages). In lean adipose tissue, adipocyte-derived IL-25 and/or IL-33 stimulate the production of IL-5 and IL-13 by ILC2s, leading to the recruitment and accumulation of eosinophils, which, in turn, through IL-4 synthesis, promotes the differentiation of alternatively activated macrophages and contributes to glucose homeostasis, insulin sensitivity¹⁶⁷ and thermogenic beige adipocyte differentiation¹⁶⁸. Importantly, adipose tissue eosinophilia and glycaemia are inversely correlated, and a high-fat diet strongly reduces both eosinophilia and the number of alternatively activated macrophages in adipose tissue.

The impact of dietary components on allergy

Several classes of dietary components affect the development and homeostasis of the immune system and thus may prevent or potentiate the development of allergy. In several studies, adherence to a Mediterranean diet was inversely correlated with the incidence of asthma and allergic rhinitis, especially in children⁷². Dietary components that are predominant either in a western diet (such as saturated fatty acids and cholesterol) or in a Mediterranean diet (such as unsaturated fatty acids, vitamins and fibre) have been shown to differentially modulate immune function and to exacerbate or protect against allergic diseases, respectively. Their complex mechanisms of action involve specific receptors.

Saturated fatty acids. Meat, cheese, ice cream and other dairy products are among the biggest sources of saturated fat in the western diet. Saturated fatty acids or their metabolites activate the nuclear receptors peroxisome proliferator-activated receptors (PPARs). These receptors exist in three isoforms — known as PPAR α , PPAR β/δ and PPAR γ — and are widely expressed by cells of the immune system⁷³.

In mice, PPAR β/δ and PPAR γ agonists, but not PPAR α agonists, inhibit IgE-dependent degranulation of mast cells *in vitro*⁷⁴. Activation of PPAR α or PPAR γ by synthetic agonists inhibits type 2 responses and allergic asthma through the direct regulation of eosinophils⁷⁵, dendritic cells (DCs)⁷⁶ and epithelial cells⁷⁷. Activation of PPAR γ by synthetic agonists also inhibits T_H17 cell responses in allergic inflammation⁷⁸, and exerts its anti-inflammatory effects in part through an IL-10-dependent mechanism⁷⁹ and the upregulation of the negative regulator phosphatase and tensin homologue (PTEN)⁸⁰. The nitrated fatty acid 10-nitro-oleate attenuates allergic airway disease through PPAR γ -dependent and PPAR γ -independent mechanisms⁸¹. *Cis-9,trans-11*-conjugated linoleic acid (c9,t11-CLA), which naturally occurs in milk fat, reduces allergic airway inflammation in mice, most probably through a PPAR γ -related mechanism and by reducing the production of eicosanoid precursors⁸². By contrast, a PPAR β/δ agonist failed to inhibit airway inflammation in a mouse model of asthma⁸³. Furthermore,

the activation of PPAR α by a synthetic ligand inhibits (and PPAR α deficiency exacerbates) atopic dermatitis and alters the balance of T_H1 and T_H2 cells in mice⁸⁴; PPAR α mRNA expression was shown to be decreased in patients with atopic dermatitis⁸⁴. In humans, systemic activation of PPAR γ also decreases allergic skin inflammation⁸⁵, and data from mice show that this effect is possibly mediated in part by suppressing the function of DCs⁸⁶. However, in an atopic dermatitis mouse model using a non-protein antigen, topical application of either PPAR γ or liver X receptor (LXR) agonists (see below) failed to inhibit skin inflammation⁸⁷.

Thus, on the basis of the findings obtained with synthetic ligands and PPAR-deficient animals, it is possible that saturated fatty acids from the diet might modulate allergic responses in part through PPAR-dependent mechanisms.

Medium-chain fatty acids. Medium-chain fatty acids (MCFAs) are saturated fatty acids that are found in oils, such as coconut oil and palm kernel oil. In a mouse model of food allergy, administration of MCFAs decreased the delivery of allergens into the bloodstream while increasing the delivery of allergens into Peyer's patches⁸⁸. In addition, consumption of MCFAs induces the production of thymic stromal lymphopoietin, IL-25 and IL-33 by gut epithelial cells, and these cytokines were shown to promote T_H2 cell responses in the spleen, thereby increasing allergic sensitization and anaphylactic responses to peanut protein⁸⁸ (FIG. 2). MCFAs, which bind to the GPCR GPR84, might also directly affect adaptive immune cells, as *in vitro*-differentiated GPR84-deficient T_H2 cells secrete higher levels of IL-4, IL-5 and IL-13 than control T_H2 cells in response to CD3 crosslinking⁸⁹. MCFAs also bind to PPAR γ ⁹⁰ and might thus act on the wide range of immune cells that express this nuclear receptor. However, the PPAR γ -dependent effect of MCFAs on immune cells has not yet been investigated. Together, these studies show that MCFAs might aggravate the development of food allergy by delivering more allergens into the system and also by directly acting on immune cells.

Polyunsaturated (very) long-chain fatty acids. The omega-3 PUFAs linolenic acid, eicosapentaenoic acid (EPA) and docohexaenoic acid (DHA), and the omega-6 PUFAs linoleic acid and arachidonic acid, are key fatty acids; omega-3 fatty acids are generally considered to be anti-inflammatory and omega-6 fatty acids pro-inflammatory. It is thought that these molecules might influence susceptibility to allergic diseases. Indeed, in children who are allergic to cow's milk, higher levels of linoleic acid and total omega-6 PUFA levels in the blood are associated with an increased risk of atopic asthma, whereas higher levels of EPA were associated with a decreased risk of non-atopic asthma⁹¹. By contrast, lower circulating levels of omega-6 PUFAs were measured in children with atopic dermatitis and correlated with decreased activity of fatty acid desaturase 2 (FADS2) and elongation of very-long-chain fatty acids protein 5 (ELOVL5), which are enzymes involved in the synthesis of PUFAs⁹².

Peroxisome proliferator-activated receptors (PPARs). Nuclear receptors that are activated by many ligands, including food-derived saturated fatty acids, and that function as transcription factors to regulate the expression of genes that are involved in both metabolism and immune functions.

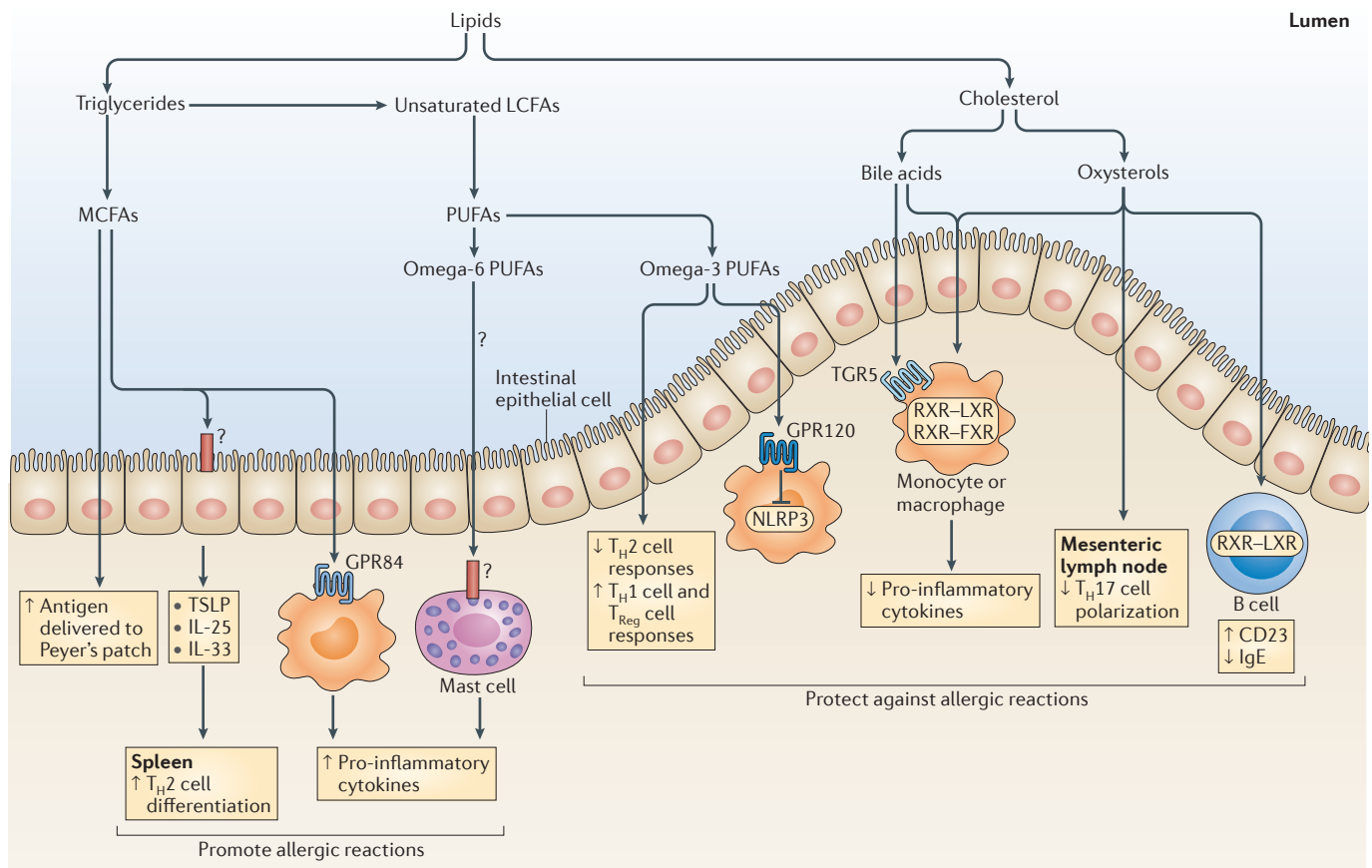


Figure 2 | Immune modulation by lipids. Triglycerides give rise to short-chain fatty acids (SCFAs; not shown), medium-chain fatty acids (MCFAs) and polyunsaturated fatty acids (PUFAs). MCFAs decrease allergen delivery into the bloodstream (not shown) but increase the delivery of allergens into Peyer's patches, thereby possibly increasing allergen presentation by dendritic cells in the gut (not shown). MCFAs also induce the production of the type 2 cytokines thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25) and IL-33 by intestinal epithelial cells through an unknown receptor; these cytokines have been shown to promote T helper 2 (T_H2) cell differentiation, thus increasing the probability of allergen sensitization. MCFAs also act directly on monocytes and macrophages through G protein-coupled receptor 84 (GPR84), which leads to the increased production of pro-inflammatory cytokines. Omega-6 PUFAs increase the production of the pro-inflammatory mediators tumour necrosis factor and prostaglandin D2 through an unknown receptor on mast cells. By contrast, omega-3 PUFAs have anti-inflammatory effects through the activation of GPR120 on macrophages, which inhibits NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome activation. Omega-3 PUFAs also directly inhibit T_H2 cell responses and promote T_H1 cell and regulatory T (T_{Reg}) cell responses. The cholesterol metabolites bile acids and oxysterols bind to nuclear retinoid X receptor (RXR)–liver X receptor (LXR) and RXR–farnesoid X receptor (FXR) heterodimers. Bile acids also bind to the G protein-coupled receptor-family membrane receptor TGR5, which is expressed by monocytes and macrophages. The activation of LXR is known to reduce the production of pro-inflammatory cytokines by monocytes and macrophages, reduce IgE production by B cells — by increasing expression of the low-affinity IgE receptor (CD23) — and inhibit polarization of T_H17 cells. Therefore, LXR activation might protect against the development of allergic reactions by functioning at various key steps of the process, although a direct link between cholesterol metabolites and the regulation of allergic reactions has not been formally demonstrated.

Human studies indicate that diet supplementation with omega-3 PUFAs might have beneficial effects in patients with allergic asthma and atopic dermatitis, and experimental mouse models demonstrate that omega-3 PUFA supplementation protects mice from the development of food allergy⁹³ and atopic dermatitis⁹⁴. Furthermore, *Fat1*-transgenic mice, which have increased levels of omega-3 PUFAs, show decreased allergic airway inflammation⁹⁵. Omega-3 PUFAs act on key immune cells that are involved in the allergic response. DHA directly inhibits IgE isotype switching in B cells by

interfering with CD40 and IL-4 receptor signalling⁹⁶. It also directly inhibits T_H2 cell responses and promotes T_H1 cell responses¹⁴, potentially by targeting IL-13. Indeed, DHA was shown to reduce *IL13* transcription in human T cells, and splenocytes from allergic mice on a DHA-supplemented diet secreted lower levels of IL-4 and IL-13 than from allergic mice on a control diet⁹⁷. DHA could indirectly dampen the type 2 response by promoting the development of T_{Reg} cells, as shown in fish oil-fed mice in a model of atopic dermatitis⁹⁸. In mast cells, EPA and DHA suppressed the generation

of reactive oxygen species and the release of IL-4 and IL-13, whereas omega-6 PUFAs increased the production of pro-inflammatory mediators (such as tumour necrosis factor (TNF) and prostaglandin D2) *in vitro*⁹⁹.

Long-chain and medium-chain fatty acids bind to GPR40 (also known as FFAR1) and GPR120 (also known as FFAR4), but the studies mentioned above did not investigate which of these receptors was responsible for the observed effects. However, activation of GPR120 by omega-3 PUFAs has anti-inflammatory effects in macrophages¹⁰⁰ and inhibits NLRP3 inflammasome activation¹⁰¹ (FIG. 2). Inflammasome activation has been shown to interfere with insulin resistance and to be involved in obesity-induced airway hyperreactivity⁵⁸. These results suggest that GPR120 could potentially be used as a unique target to treat metabolic disorders and associated allergic diseases. In addition to fatty acids, bacterial metabolites of diet-derived lignans and isoflavones have been inversely associated with asthma and wheezing¹⁰².

Although a maternal diet enriched in omega-3 PUFAs during pregnancy might represent a possible strategy for reducing the risk of developing allergy during childhood², the overall results of such studies have been disappointing⁹. Thus, although the anti-inflammatory effects of omega-3 PUFAs are well established, their possible role in protection against allergy requires further investigation to potentially develop a prophylactic diet.

Cholesterol and its derivatives. In innate immune cells, oxysterols and bile acids (which are metabolites of cholesterol) bind to LXR α and LXR β ⁶, retinoic acid receptor-related orphan receptor- α (ROR α) and ROR γ ¹⁰³, and farnesoid X receptor (FXR; also known as NR1H4). These receptors form heterodimers with retinoid X receptor- α (RXR α), RXR β and RXR γ , which are transcriptional regulators that inhibit the production of pro-inflammatory cytokines. To some extent, bile acids also bind to nuclear pregnane X receptor (PXR; also known as NR1I2), constitutive androstane receptor (CAR; also known as NR1I3) and vitamin D3 receptor (VDR). Bile acids also bind to the GPCR family membrane receptor TGR5 (also known as GPBAR1)¹⁰⁴.

Activation of LXR by a synthetic agonist reduces IgE production by decreasing JUN amino-terminal kinase (JNK) phosphorylation and increasing the expression of the low-affinity IgE receptor (Fc ϵ R2; also known as CD23) on B cells¹⁰⁵. Likewise, a synthetic LXR agonist also attenuates IgE production and airway remodelling, but not type 2 cytokine production, in a model of chronic airway inflammation¹⁰⁶. Activation of LXR also regulates neutrophil homeostasis by controlling their clearance by macrophages and by repressing granulopoiesis through a direct effect on IL-17, IL-23 and granulocyte colony-stimulating factor signalling¹⁰⁷. Activation of LXR by synthetic ligand inhibits (and LXR deficiency favours) T_H17 cell polarization through regulation of sterol regulatory element-binding protein 1 (SREBP1), which interacts with aryl hydrocarbon receptor (AHR) — a key regulator of *IL17* transcription¹⁰⁸ — and might thus affect

IL-17-associated allergic inflammation (FIG. 2). ROR α is essential for the development of type 2 ILCs (ILC2s), which are involved in protease-induced lung allergic inflammation¹⁰⁹ and atopic dermatitis¹¹⁰.

Fibres and short-chain fatty acids. Although fibre-enriched diets protect individuals from inflammatory diseases, such as inflammatory bowel disease, their protective role in allergic diseases has only recently been demonstrated. Dietary fibres are non-digestible saccharides that are fermented by anaerobic colonic bacteria into short-chain fatty acids (SCFAs) — mostly acetate, propionate and butyrate — which bind to the receptors GPR41 (also known as FFAR3) and GPR43 (also known as FFAR2), with different affinities and specificities, although butyrate also binds to GPR109A (also known as HCAR2)¹¹¹. High-fibre feeding increased the release of SCFAs and protected mice from experimentally induced airway allergic inflammation, whereas low-fibre feeding had opposite effects¹¹². The beneficial effects of a high-fibre diet are due to the activation of GPR41 by propionate. Propionate promoted the development of inflammatory monocytes that, upon migration into the lungs, become DCs with an impaired ability to promote the differentiation of naive T cells into T_H2 cells¹¹². The effects of SCFAs are not mediated solely through GPR41, as GPR43-deficient mice fed with acetate show exacerbated allergic inflammation¹¹³. SCFAs, particularly butyrate, also modulate cell activity through inhibition of histone deacetylase (HDAC) activity¹¹¹. Indeed, treatment with the HDAC inhibitor trichostatin A decreased allergic inflammation in mice¹¹⁴, suggesting that SCFAs might also have beneficial effects on allergy by modulating HDAC activity.

Of note, it was reported that SCFAs induced the development of colonic T_{Reg} cells through different mechanisms, with butyrate acting either indirectly by activating gut DCs and macrophages through GPR109A¹¹⁵ or directly by inhibiting HDAC3 activity¹¹⁶. Finally, acetate promotes the expansion and function of gut T_{Reg} cells in a GPR43-dependent manner¹¹⁷. Although these studies mostly focused on colonic T_{Reg} cell homeostasis, a similar mechanism might occur in other organs (FIG. 3).

Together, these findings suggest that fibre-enriched diet prevents allergic airway inflammation in mice. In humans, supplementation of infant formula with a mixture of fermentable oligosaccharides was associated with a reduction in the incidence of asthma and atopic dermatitis in high-risk infants¹¹⁸.

Vitamin A. Vitamin A is found in plants (such as carrots, lettuce, sweet potatoes and red peppers) as carotenoids (β -carotene) and in fish and animal products (such as tuna, liver, whole milk and eggs) as retinol, both of which are processed into active retinoic acid (RA) through a multistep enzymatic process. RA is generated by epithelial cells and intestinal DCs. All-*trans*-RAs activate the nuclear receptors RA receptor- α (RAR α), RAR β and RAR γ , which form heterodimers with RXR. All-*trans*-RAs can isomerize to 9-*cis*-RA, which is the physiological ligand for RXR homodimers.

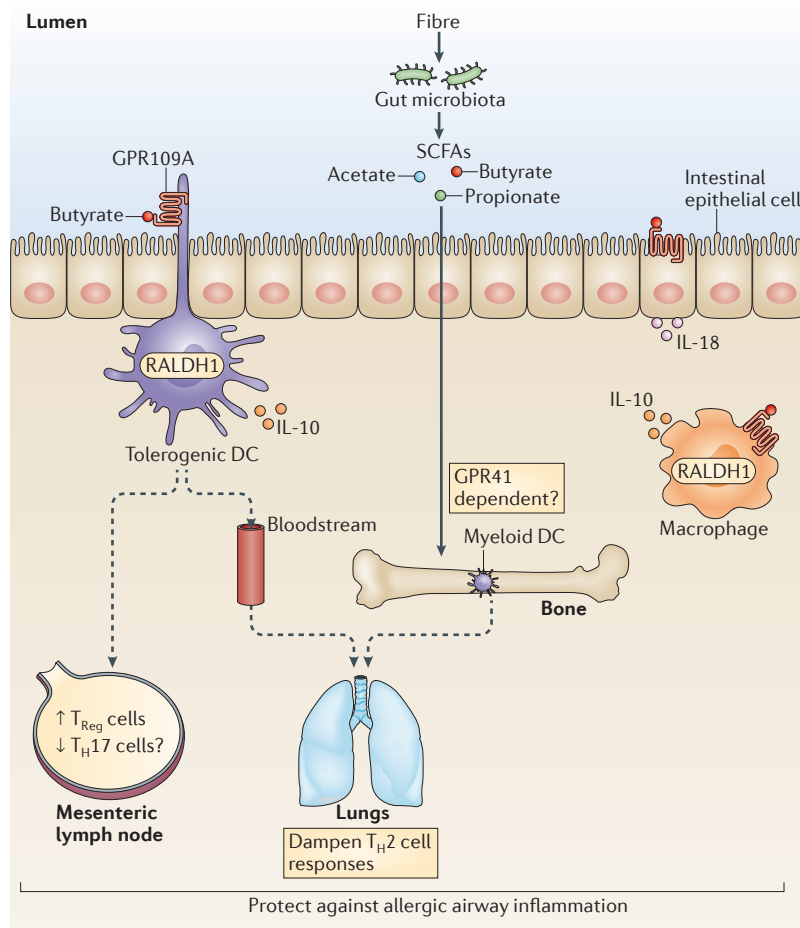


Figure 3 | Immune modulation by fibres and short-chain fatty acids. Commensal gut bacteria release the short-chain fatty acids (SCFAs) acetate, butyrate and propionate through the fermentation of fibres; these metabolites bind to G protein-coupled receptor 41 (GPR41) and GPR109A. Butyrate-mediated activation of GPR109A on colonic macrophages and dendritic cells (DCs) contributes to interleukin-10 (IL-10) secretion and to increased expression of the tolerogenic enzyme retinal dehydrogenase 1 (RALDH1; also known as ALDH1A1). IL-18 has a role in gut homeostasis. Migration of these activated tolerogenic DCs to the draining mesenteric lymph nodes promotes the development of regulatory T (T_{Reg}) cells; they may also inhibit the development of T helper 17 ($T_{\text{H}}17$) cells, although this has not been formally demonstrated. These DCs might also circulate through the bloodstream to distant organs such as the lungs, where they might dampen $T_{\text{H}}2$ cell responses, thereby protecting against allergic airway inflammation. Propionate might promote the development of myeloid DCs from bone marrow progenitors in a GPR41-dependent manner; these myeloid DCs might then circulate towards the lungs to inhibit $T_{\text{H}}2$ cell responses. Dashed arrows indicate cell migration.

Defective dietary vitamin A, or deficient RA intake or signalling, leads to increased airway hyperreactivity in adults¹¹⁹. Mesenteric lymph node (MLN) DCs from vitamin A-deficient mice induce inflammatory $T_{\text{H}}2$ cells that express lung-homing and/or skin-homing receptors, and upon administration of oral antigen and skin challenge, vitamin A-deficient mice develop skin allergy¹²⁰. Thus, in a balanced diet containing sufficient levels of vitamin A, RA might prevent allergic responses not only by favouring the generation of T_{Reg} cells (see below) but also by preventing MLN DCs from inducing inflammatory $T_{\text{H}}2$ cells (FIG. 4a,b).

The administration of all-*trans*-RA inhibits pathological $T_{\text{H}}17$ cell responses and promotes T_{Reg} cell function in a mouse model of neutrophilic asthma¹²¹. All-*trans*-RA inhibits the differentiation of human eosinophils and basophils *in vitro*¹²². It also inhibits IgE synthesis from human B cells that have been stimulated with CD40 and IL-4, by decreasing IL-6 secretion and by increasing the expression of CD23 and CD54 (also known as ICAM1)¹²³. Furthermore, it was reported that RAR signalling inhibited $T_{\text{H}}1$ cell responses and increased the development of $T_{\text{H}}2$ cells in mice¹²⁴. However, these findings contrast with other studies, mainly those that are based on pharmacological activation or inhibition of RAR and RXR, which show no effect of RA on IgE production in a mouse model of allergic asthma¹²⁵ and show an increase of human $T_{\text{H}}2$ cell differentiation *in vitro*¹²⁶. In addition, RXR antagonist treatment inhibited the differentiation of $T_{\text{H}}2$ cells *in vitro* and prevented experimentally induced allergic lung inflammation¹²⁷, and vitamin A supplementation was shown to promote allergic responses¹²⁸. These contrasting results on the role of RA in $T_{\text{H}}2$ cell differentiation might be explained by the different doses of biologically available RA that were used in the studies. Indeed, it was shown that RA promotes the differentiation of $T_{\text{H}}17$ cells at physiological concentrations but inhibited their development at higher doses¹²⁹. Thus, although the effects of vitamin A on allergic diseases remain controversial, the most recent experimental^{119,120} and clinical¹⁵ data suggest that sufficient levels of vitamin A might be required to control allergic diseases.

Vitamin D3. Vitamin D3 is synthesized in the skin but is also provided by the diet. Vitamin D3 is converted in the liver into 25-hydroxyvitamin D3 (25(OH)VD3) by mitochondrial sterol 26-hydroxylase (CYP27A1). 25(OH)VD3 is the main circulating form of vitamin D3 and is metabolized in the kidneys into 1,25-dihydroxyvitamin D3 (1,25(OH)₂VD3) by mitochondrial 25(OH)VD3 1 α -hydroxylase (CYP27B1) and is the most physiologically active vitamin D3 metabolite. This later step can also take place in various immune cell types; macrophages and monocyte-derived DCs, as well as intestinal and dermal DCs, express the two sets of enzymes that are needed to convert vitamin D3 into 1,25(OH)₂VD3. Vitamin D3 functions through its interaction with the nuclear VDR, which forms heterodimers with RXR.

Experimental dietary vitamin D3 deficiency affects lung volume in the absence of airway inflammation¹³⁰, and neonatal vitamin D3 deficiency increased $T_{\text{H}}2$ cell responses while decreasing the number of IL-10-secreting T cells, which resulted in more severe allergic airway inflammation and remodelling than in mice on a vitamin D3-containing diet¹³¹ (FIG. 4c). Vitamin D3 or VDR agonists also reduce antigen-induced airway inflammation¹³², in part by downregulating IgE production by B cells¹³³ and by reducing granulocyte numbers¹³⁴, whereas vitamin D3 deficiency leads to airway hyperresponsiveness¹³⁵. Vitamin D3 agonists also decreased atopic dermatitis in mice¹³⁶. Vitamin D3 exerts a CYP27B1-dependent and VDR-dependent negative regulatory effect on IgE-mediated

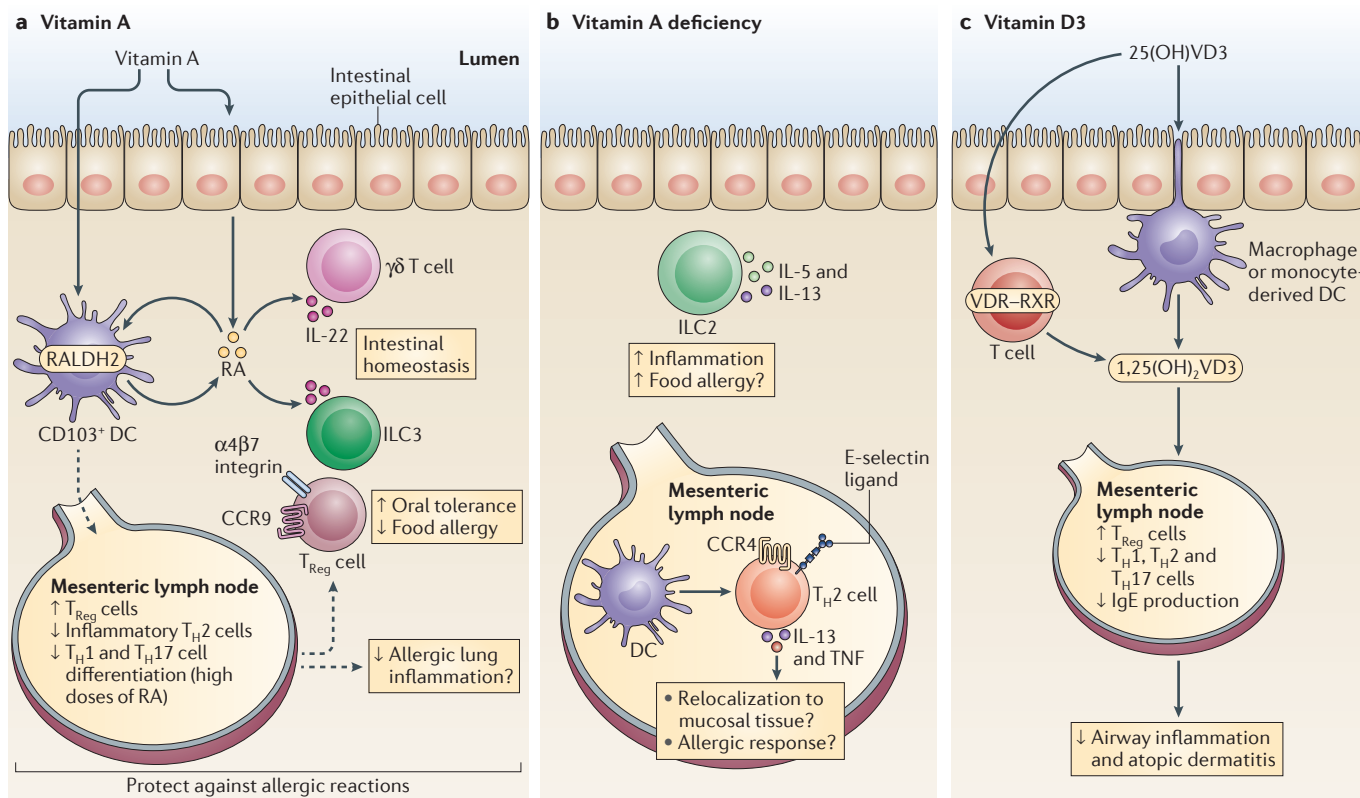


Figure 4 | Impact of vitamin A and vitamin D3 on allergic reactions. **a** | CD103⁺ dendritic cells (DCs) metabolize dietary vitamin A into retinoic acid (RA) in a process mediated by retinal dehydrogenase 2 (RALDH2). RA binds to retinoid X receptor–RA receptor (RXR–RAR) heterodimers or to RXR–RXR homodimers, which then bind to RA response elements in the nucleus (not shown). In a vitamin A-enriched diet, RA produced by intestinal CD103⁺ DCs or intestinal epithelial cells has been shown to activate interleukin-22 (IL-22) production by $\gamma\delta$ T cells and by type 3 innate lymphoid cells (ILC3s)¹⁷⁰, thus contributing to intestinal homeostasis. RA-producing DCs migrate into the mesenteric lymph nodes and prime naive T cells to differentiate into regulatory T (T_{Reg}) cells that express gut-homing receptors (such as CC-chemokine receptor 9 (CCR9) and $\alpha 4\beta 7$ integrin); these cells could migrate back into the lamina propria and contribute to the control of food allergy. Data from *in vitro* studies indicate that RA exerts direct effects on T cells by inhibiting the differentiation of T helper 1 (T_H1) and T_H17 cells. These mechanisms could contribute to protection against the development of allergic responses. **b** | Vitamin A deficiency strongly decreases ILC3 numbers (not shown) and results in greatly increased numbers of ILC2s, which produce IL-5 and IL-13 (REF. 171). Mesenteric lymph node DCs from vitamin A-deficient mice induce inflammatory T_H2 cells that produce high levels of IL-13 and tumour necrosis factor (TNF), and express CCR4 and E-selectin ligands that could enable them to relocate into the lungs and/or skin, thereby favouring the development of allergic responses. **c** | Vitamin D3 is synthesized in the skin but is also provided by diet. Vitamin D3 is converted to 25-hydroxyvitamin D3 (25(OH)VD3) in the liver. 25(OH)VD3 can then be converted into 1,25-dihydroxyvitamin D3 (1,25(OH)₂VD3) — the most physiologically active vitamin D3 metabolite — by intestinal DCs. Vitamin D3 functions through the nuclear vitamin D3 receptor (VDR), which forms dimers with RXR. In addition, 25(OH)VD3 can be converted into 1,25(OH)₂VD3 by T cells. 1,25(OH)₂VD3 can have both direct and indirect effects on T cell differentiation; it decreases the development of T_H1, T_H2 and T_H17 cells, and increases T_{Reg} cell development, thus repressing the development of allergic responses. Vitamin D3 also decreases IgE production by B cells. Solid arrows indicate experimental evidence; dashed arrows indicate hypothetical mechanisms.

activation of mast cells in a model of passive cutaneous anaphylaxis¹³⁷. In humans, vitamin D deficiency was correlated with exacerbations of asthma¹³⁸ and increased the likelihood of developing atopic dermatitis in obese individuals¹³⁹.

However, a recent study did not provide support for a protective effect of a high (endogenous) maternal 25-hydroxyvitamin D (25(OH)D) concentration on the outcomes of allergic airway disease and lung function at 20–25 years of age, and a high maternal 25(OH)D concentration was indeed associated with an increased risk

of allergic diseases in offspring¹⁴⁰. This finding might be in line with an earlier study in mice, which reported that vitamin D3 increased the differentiation of T_H2 cells and inhibited that of T_H1 cells¹⁴¹. It was also reported that 1,25(OH)₂D3 inhibits IL-17A production in patients with asthma irrespective of their clinical responsiveness to steroids¹⁴². Regarding vitamin D supplementation, an ongoing clinical trial (ClinicalTrials.gov identifier: NCT00920621) is attempting to determine whether vitamin D3 supplementation during pregnancy and lactation affects the development of allergy in offspring¹⁴³.

Overall, vitamin D3 seems to be a pleiotropic regulator of immune function that might exert different effects depending on the timing of exposure (prenatal versus postnatal) and the dose, and possibly also on genetic variability, which can influence individual susceptibility.

Tryptophan and its metabolites. In humans, tryptophan is an essential amino acid that is found in most dietary proteins from both animals and plants. It might influence allergic diseases through its metabolites and metabolizing enzyme. Indoleamine 2,3-dioxygenase (IDO) is the rate-limiting enzyme that catabolizes dietary tryptophan into kynurenine, 3-hydroxykynurenine and xanthurenic acid, which are key regulators of T cell function. In humans, low IDO activity has been associated with atopy¹⁴⁴ and with exacerbations of asthma induced by viral infections¹⁴⁵. In allergic mice, administration of a Toll-like receptor 9 (TLR9) agonist increased IDO activity in resident lung cells and, in turn, decreased the severity of the asthmatic phenotype by promoting T_H2 cell death in the inflamed lungs¹⁴⁶. Furthermore, oral tolerance mediated by CD103⁺ DCs requires their expression of IDO to induce T_{Reg} cell differentiation¹⁴⁷. The mechanisms underlying the regulation of IDO expression in allergy remain elusive, but allergen itself might be a key contributor: the house dust mite allergen Derp1 — which has protease activity — suppresses IDO activity in DCs that are isolated from house dust mite-sensitive patients with asthma, but enhances IDO activity in healthy individuals¹⁴⁸. Therefore, activation of IDO might represent a potential therapeutic approach, as allergen immunotherapy was shown to be partially dependent on IDO in an experimental model of allergic airway inflammation¹⁴⁹.

In addition to some plant-derived or microbiota-derived tryptophan metabolites^{150,151}, kynurenine functions through AHR, which is a nuclear receptor that metabolizes toxic compounds and is a key regulator of T_{Reg} cell and T_H17 cell function¹⁵². AHR also has a key role in mast cell differentiation, growth and function¹⁵³. The activation of AHR suppresses experimental sensitization to peanut, thus affecting DC phenotype and function, and leading to decreased cytokine production by T cells¹⁵⁴. In addition, the plant-derived tryptophan metabolite 6-formylindolo(3,2-b)carbazole (FICZ), which functions as an AHR ligand, inhibits lung eosinophilia and T_H2 cell responses in an asthma model¹⁵⁵.

Therefore, tryptophan metabolites are potent regulators of pathways that could be therapeutically targeted or modulated by specific dietary compounds to inhibit lung inflammation.

Vitamin E. Vitamin E has eight natural forms (α - δ -tocopherol and α - δ -tocotrienol), of which α -tocopherols and γ -tocopherols are the most abundant in food. Tocopherols have a dual action: they function mainly as scavengers of reactive oxygen species (γ -tocopherol is also a scavenger of reactive nitrogen species), but α -tocopherol and γ -tocopherol also exert anti-inflammatory and pro-inflammatory activities, respectively, in mouse models of allergic airway inflammation, including in models of airway hyperreactivity and eosinophilia¹⁵⁶. This differential

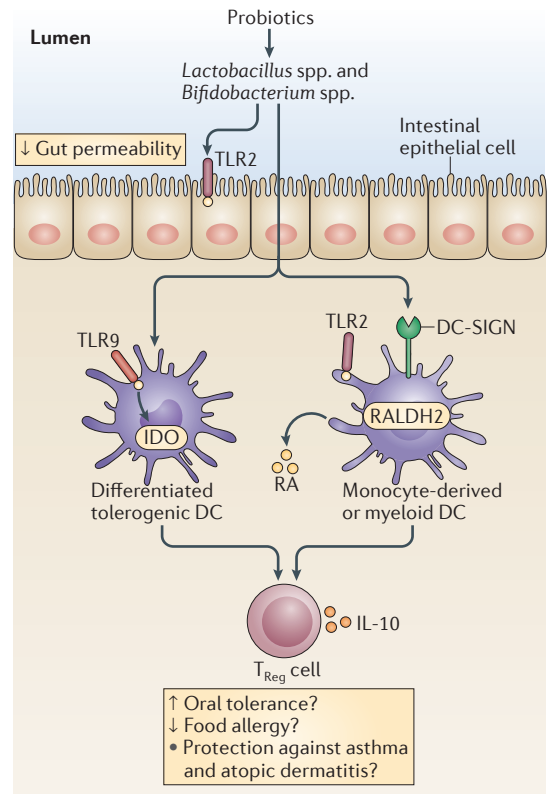


Figure 5 | Possible mechanisms of the beneficial effects of probiotics in allergy. Probiotics might modulate immune functions through direct activation of Toll-like receptors (TLRs) on immune or non-immune cells or through the release of short-chain fatty acids (SCFAs; not shown), which are products of fibre fermentation by the microbiota. The activation of TLR2 on intestinal epithelial cells decreases gut permeability, which in turn maintains oral tolerance and thus protects against the development of food allergy. In mesenteric lymph nodes, the activation of TLR2 on myeloid dendritic cells (DCs) induces their differentiation into tolerogenic DCs that express retinal dehydrogenase 2 (RALDH2). This enzyme converts vitamin A into retinoic acid (RA), which, together with activation of the C-type lectin receptor DC-specific ICAM3-grabbing non-integrin (DC-SIGN), promotes the development of regulatory T (T_{Reg}) cells. The activation of TLR9 on differentiated tolerogenic DCs leads to increased expression of indoleamine 2,3-dioxygenase (IDO), which contributes to T_{Reg} cell development. These T_{Reg} cells might recirculate systemically towards the gut, skin or lungs, where they could inhibit T helper 2 cell responses and IgE production by B cells, thus protecting against food allergy, eczema and asthma, although this has not yet been formally demonstrated.

effect is attributed to an opposing action of α -tocopherol and γ -tocopherol on adhesion molecule signalling through effects on protein kinase C α in endothelial cells¹⁵⁶. In humans, differences in outcomes from clinical reports on the associations of vitamin E and asthma may, in part, reflect the opposing regulatory effects of α -tocopherol and γ -tocopherol, the tocopherol isoforms in vehicles for the supplements and individual variations

Dysbiosis

Modification of the commensal (gut) bacterial flora.

in γ -tocopherol levels in the blood¹⁵⁷. Finally, the dietary component lycopene, which is found in tomatoes, also exerts a beneficial effect in human asthma owing to its antioxidant properties¹⁵⁸.

Taken together, it seems that several families of dietary compounds can positively or negatively modulate allergic diseases by acting on both the innate and the adaptive immune responses.

Probiotics. Dysbiosis in patients with allergic disease is characterized by a lower number of *Bifidobacterium* spp. and *Lactobacillus* spp.¹⁵⁹, which are bacteria that colonize the gut of breastfed infants¹⁶⁰. By contrast, daily administration of *Lactobacillus* spp., *Bifidobacterium* spp. and *Propionibacterium* spp. — which were selected for their ability to induce anti-inflammatory immune responses — to mothers with high-risk children for 1 month before birth and to their child during their first 6 months of life significantly decreased IgE-associated allergic diseases, but this only occurred in babies that were delivered by caesarean¹⁶¹. A systematic review of studies that assessed the effects of probiotic supplementation on atopic dermatitis showed that it was effective in preventing or decreasing atopic dermatitis symptoms in 16 out of 21 studies¹⁶². Interestingly, studies that failed to correlate probiotic supplementation with atopic dermatitis prevention did not administer probiotics during the last 4 weeks of pregnancy or to the babies during their first 3 months of life¹⁶³, thus suggesting a key role of probiotics during the perinatal period.

The mechanisms of action of probiotics remain only partially understood (FIG. 5). Some strains are only effective in particular types of allergies. *Lactobacillus rhamnosus* str. GG improves eczema but not pollen allergies in humans¹⁵⁹. Probiotics were shown to promote tolerance by acting on DCs, by promoting T_{Reg} cell development and/or by inhibiting T_H1, T_H2 and T_H17 cell responses

in a mouse model of atopic dermatitis¹⁶⁴. TLR activation seems to be crucial for the effect of probiotics on immune cells. In humans, *Bacillus infantis* induces T_{Reg} cell development and IL-10 production through TLR9-dependent activation of IDO in plasmacytoid DCs and through the activation of retinal dehydrogenase 2 (RALDH2; also known as ALDH1A2) — in a process that is dependent on TLR2 and DC-specific ICAM3-grabbing non-integrin (DC-SIGN; also known as CD209) — in monocyte-derived DCs and myeloid DCs¹⁶⁵. Probiotics might also alleviate allergies by functioning upstream of the immune response through the modulation of gut permeability, by preventing bacterial and antigen translocation (and probably ensuing antigen sensitization) as shown in human atopic dermatitis¹⁶⁶.

Conclusions and perspectives

Diet has a key role in the homeostasis of the immune system by inducing oral tolerance, thereby preventing overt reactions to innocuous antigens, which lead to allergic diseases. Excessive calorie intake or deficiency in fibres, micronutrients or compounds from vegetables leads to alterations in secondary metabolite production, obesity and inflammation. Although some of the cellular and molecular mechanisms involved in obesity-induced asthma have been described, the functional connection between the balance of ILC2s and ILC3s, T_H1 and T_H2 cells, and T_H17 and T_{Reg} cells in adipose and lung tissues remains to be established. Dietary intervention represents a possible approach that could safely contribute to the prevention or alleviation of allergic diseases. However, understanding the fundamental mechanisms by which individual dietary compounds promote or inhibit the development of allergies is essential to propose specific and personalized guidelines for food avoidance or intake. In particular, a better understanding of the mechanisms linking metabolic and allergic diseases is essential.

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Competing interests statement

The authors declare no competing interests.

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