Dietary influences on intestinal immunity

Marc Veldhoen and Verena Brucklacher-Waldert

Abstract | The function of the gastrointestinal tract relies on a monolayer of epithelial cells, which are essential for the uptake of nutrients. The fragile lining requires protection against insults by a diverse array of antigens. This is accomplished by the mucosa-associated lymphoid tissues of the gastrointestinal tract, which constitute a highly organized immune organ. In this Review, we discuss several recent findings that provide a compelling link between dietary compounds and the organization and maintenance of immune tissues and lymphocytes in the intestine. We highlight some of the molecular players involved, in particular ligand-activated nuclear receptors in lymphoid cells.

Nuclear receptors
A class of proteins found within cells that are responsible for sensing external cues (such as hormones) and that work with other proteins to regulate the expression of specific genes, thereby controlling the development, homeostasis and metabolism of the organism.

Laboratory for Lymphocyte Signalling and Development, The Babraham Institute, Cambridge, CB22 3AT, UK. Correspondence to M.V.
e-mail: marc.veldhoen@babraham.ac.uk
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"Dis-moi ce que tu manges, je te dirai ce que tu es" (tell me what you eat and I will tell you what you are), concluded gastronome Jean Anthelme Brillat-Savarin in the nineteenth century. Our diet is known to be a risk factor for disorders ranging from cardiovascular and metabolic disease to cancer. Evidence for the influence of dietary choices on the development of immune disorders is continually emerging. Such disorders include diabetes and inflammatory bowel disorders, but also multiple sclerosis, degenerative disorders such as dementia, and asthma. A marked increase in the incidence of chronic inflammatory disorders (such as asthma) seems to follow a geographical pattern of industrialization and improved living conditions and to be inconsistent with an underlying genetic cause[1]. Despite the identification of multiple susceptibility genes for chronic inflammatory disorders, each individual gene of interest contributes only a modest proportion of disease heritability. By contrast, dietary habits are consistently found in epidemiological studies to be a risk factor for these same diseases. These findings may represent an underlying evolutionary genetic cause whereby our genes have not been able to adapt to quickly changing dietary habits (BOX 1). Alterations in our exposure to, and colonization by, a large variety of microorganisms, especially during early life, are an additional confounding risk factor. The contributions that microorganisms make to the health of their hosts (which often involve diet-sourced metabolites) are beyond the scope of this Review, but are discussed elsewhere[2].

Epidemiological studies particularly associate inflammatory disorders with a so-called 'Western diet', which is characterized by high levels of processed red meat, sugars, fat and refined grains, and a lower content of vegetables, fruits and fish. This diet is chosen by many individuals in developed countries, and increasingly so elsewhere, and correlates with the dramatic increase in the incidence of chronic inflammatory disorders (such as diabetes, multiple sclerosis and asthma) over the past six decades[3,4]. Shared molecular pathways between nutrient- and pathogen-sensing systems could stand at the intersection of metabolic and inflammatory responses, thereby providing a possible mechanistic link between diet and disease[5]. The interface between dietary components and the gastrointestinal tract is multifaceted and involves at least intestinal epithelial cells (IECs), the microbiota and heterogeneous populations of immune cells. Research on the impact of dietary compounds on IEC function and the permeability of the intestinal epithelial barrier is currently focused on mucins, short-chain fatty acids and related metabolites, as well as some of their G protein-coupled receptors[6,7]. Furthermore, the interplay between diet and the microbiota is highly complex, with numerous connections, and is under intense investigation.

Nuclear receptors are targets of numerous naturally occurring and man-made compounds, such as hormones, lipids and vitamins. Many of these ligand-activated transcription factors are involved in immune cell development and function[8]. The activity of nuclear receptors is highly cell-type and context specific, despite their ability to regulate a large number of genes and their widespread expression pattern. This suggests that nuclear receptors connect the cellular transcriptional machinery with (external) environmental cues, such as the diet. Indeed, they have been found to interact with dietary substances, thereby directly bridging diet

ILCs
Lymphoid cells derived from the common lymphoid progenitor that lack expression of an antigen receptor. ILCs have important roles in innate immune responses to infectious microorganisms and in lymphoid tissue formation.

Box 1 | **An evolutionary perspective of dietary change**

Our genome changes at a molecular level by approximately 0.5% every million years[107]. We, *Hominini*, developed more than 5–6 million years ago, during which time dietary requirements have gradually changed and led to an increase in the intake of animal products that are high in energy and fat. Adaptation to dietary patterns as a result of the ecological niche occupied, genetic specialization and cultural conventions contributed to a diet that was high in vitamins, phytochemicals, fruit and vegetables, and lean meat and fish (which contain high levels of protein and unsaturated fat). This diet supported the expansion and development of the species, and increased brain size. Indeed, our ability to absorb, store and process dietary components has been an important evolutionary selection criterion, providing certain individuals with increased survival chances in times of need.

The agricultural revolution, approximately 10,000 years ago, and the industrial revolution, 200 years ago, led to dramatic changes in our environment, lifestyle and diet[108]. The post-agricultural diet is particularly rich in carbohydrates, especially grains. Although these changes have been hugely beneficial for the expansion of our species, the adaptation of our genome does not seem to be synchronized with these changes, as suggested by the high prevalence of gluten intolerance in modern humans. The post-industrial diet of the developed world is even higher in carbohydrates (in particular in processed, refined grains) and saturated fats, and is dominated by food that has been processed, modified, stored and transported great distances with subsequent losses in vitamins, minerals and phytochemicals. These changes have resulted in a disconnection between our environment and our genome, which has not evolved at a sufficient rate or had the opportunity to adapt, as most 'symptoms' of the Western diet occur after the reproductive age. They manifest as a reduction in the quality of life, with an increased incidence of chronic disorders, such as cancer, type 2 diabetes and cardiovascular disease. All of these conditions share elements of low-grade inflammation, and they could be largely prevented by changes in lifestyle and diet[109].

with immunity. This Review focuses on recently identified molecular pathways that provide new insights into direct interactions between dietary compounds and the physiology of lymphoid cells in the immune system.

Lymphoid cells at the intestinal mucosa

An increasing amount of data has emerged showing direct effects of dietary components — such as vitamins, phytochemicals and fatty acids — on the maintenance of long-term health. Key to understanding the contribution of these compounds to health are two important insights. The first is the increased knowledge of the role of ligand-activated nuclear receptors and G protein-coupled receptors in immune cells. The second is the discovery of new populations of immune cells, such as innate lymphoid cells (ILCs), and the improved understanding of T helper (T_H) cell subsets, including regulatory T (T_{Reg}) cells, T follicular helper (T_{FH}) cells and T_H17 cells.

The immunological challenge of how to discriminate self from non-self is particularly complex at epithelial barrier sites, such as the intestine. At these sites, large amounts of antigens — which include harmless food antigens, antigens derived from resident microorganisms and pathogens, and toxins produced by such pathogens — are encountered over a lifetime. Immune cells in the intestine are positioned to contribute both to protecting the fragile monolayer that lines the gut and to regulating the access of luminal antigens to the intestinal tissues, thereby balancing levels of tolerance and inflammation (BOX 2). Failure to correctly discriminate harmless antigens from potentially harmful ones can result in chronic inflammation.

Box 2 | **The landscape of the intestinal immune system**

The intestine can be viewed as an integrated network of mutualistic interactions between diverse cell populations, the microbiota and microbial products. A monolayer of polarized intestinal epithelial cells (IECs) lines the intestine and is composed of enterocytes, glycoprotein-secreting goblet cells, hormone-producing enteroendocrine cells, and Paneth cells, which produce antimicrobial factors. The combined actions of these cells establish an epithelial monolayer that is covered in glycoproteins, IgA and microbicidal peptides that protect the integrity of the tissue. Symbiotic microorganisms of the gut microbiota offer additional protection, by preventing the multiplication of other microorganisms and their attachment to IECs, as well as by modulating the responses of IECs and immune cells[110]. The epithelial cell barrier not only separates the luminal contents of the intestine from host tissues, but also facilitates controlled exchange of nutrients and antigens. Specialized routes of transport — for example, through enterocytes, microfold (M) cells, goblet cells and *trans*-epithelial dendritic cells — allow for the uptake and processing of luminal products in the underlying tissue[111,112].

The intestinal immune cells are organized in distinct lymphoid structures (such as Peyers's patches, colonic patches, cryptopatches, isolated lymphoid follicles and mesenteric lymph nodes), are present as scattered cells underneath the IECs or are located in the outer layer of connective tissues (known as the lamina propria). The development of organized lymphoid structures is supported by innate lymphoid cells (ILCs) — specifically, by lymphoid tissue inducer (LTi) cells in the fetus and by LTi-like cells in adults[113]. In addition, an ILC population of natural killer (NK)-like cells ($NKp46^+$ ILC22 cells in mice; $CD56^+NKp44^+$ cells in humans) can be found, which, like LTi cells, can secrete interleukin-22 (IL-22) and possibly IL-17 (REF. 62). Two populations of $CD4^+$ T cells are enriched in the lamina propria: T helper 17 (T_H17) cells and regulatory T cells[114,115], reflecting the delicate balance between immunity and tolerance. Their activity and numbers are controlled by various subpopulations of dendritic cells and macrophages.

T cells. T_H cells have a prominent role in orchestrating protective responses, while promoting tolerance against innocuous antigens. To fulfil their specific requirements, T_H cells differentiate into functional lineages, with each having a specialized role in immune responses (BOX 3). The differentiation of T_H cell lineages is thought to predominantly, but not exclusively, be defined by cytokines present in the microenvironment[9]. However, the rigid distinction between the T_H cell lineages has been blurred in recent years.

T_{Reg} cell populations mainly originate in the thymus, and these cells are termed naturally occurring T_{Reg} cells. However, T_{Reg} cell populations can also arise from precursor cells in the periphery, and in this case they are termed induced T_{Reg} cells. These induced T_{Reg} cells accumulate throughout life and are found at mucosal surfaces of the intestine[10]. T_H17 cells are a subset of T_H cells that are also enriched at mucosal sites. The generation and

maintenance of T_H17 and induced T_{Reg} cells in the intestine has an important role in the equilibrium between immunity and tolerance. The differentiation of both subsets critically depends on the activity of transforming growth factor-β (TGFβ)[11–13]. Stimulation of naive T cells increases the expression of the T_{Reg} cell transcriptional regulator forkhead box P3 (FOXP3), which suppresses retinoic acid receptor-related orphan receptor-γt (RORγt) and RORα[14,15], important regulators of T_H17 cells[16]. The presence of additional inflammatory signals suppresses FOXP3 expression, resulting in the development of T_H17 cells[13]. T_{Reg} cells can inhibit pro-inflammatory events in many cell types, whereas T_H17 cells recruit additional immune cell types, including highly pro-inflammatory granulocytes, thereby enhancing the inflammatory response. However, the view that T_{Reg} cells solely maintain immune tolerance and that the only role of T_H17 cells is in inflammation is a considerable oversimplification[17,18]. Indeed, it has been reported that T_{Reg} cells can be converted into pathogenic T cells[19], whereas T_H17 cells can acquire tolerogenic characteristics[17] and neutralizing interleukin-17 (IL-17) aggravates chemically induced colitis[20].

Innate lymphoid cells. ILCs are a recently identified group of lymphocytes that have an important role at the mucosae[21] (BOX 4). Although they are present in low numbers, they are essential for generating lymphoid structures and orchestrating immune responses[22] owing to their capacity to produce large amounts of immune mediators. In adult mice, two subsets of ILCs are predominantly found in the gastrointestinal tract: lymphoid tissue inducer-like (LTi-like) cells and IL-22-producing ILC22 cells[118,119]. IL-22 is an important immune mediator in the gastrointestinal tract, as it regulates the expression of microbicidal factors, such as regenerating islet-derived protein 3 (REG3) family members, and has a role in wound healing and tissue regeneration[23]. ILCs express particularly high levels of the nuclear receptors RORγt, RORα and aryl hydrocarbon receptor (AHR)[16,24,25].

Fruits, vegetables and nuclear receptors

Vitamins and nuclear receptors. Many chemicals present in plants, especially those that are responsible for their organoleptic properties, are beneficial for our health. Such chemicals include β-carotene in carrots, resveratrol in the skins of red grapes and in other fruits, and the antioxidant catechin in green tea. Many of these compounds cannot be generated by humans, and their main source is our diet. Some, such as vitamins, have long been known to make a vital biological contribution to health. In particular, metabolites of vitamins A and D have taken centre stage in influencing immunological health[26,27]. Others, however, are likely to be beneficial but have not as yet been shown to be essential to health and are referred to as phytochemicals.

Vitamin A is an essential fat-soluble compound that is required for many biological processes. It is obtained from plants in the form of carotenoids (such as β-carotene) and as retinol from animal material, and it can be converted into several bioactive metabolites, including retinal and retinoic acid (FIG. 1a). The conversion of carotenes into retinal requires enzymatic oxidation, and the retinal subsequently can be reversibly reduced to retinol and taken up by cells. This retinol can then be converted into retinoic acid through a two-step process. Oxidation to retinal by members of the alcohol dehydrogenase (ADH) family or retinol dehydrogenase (RDH) family is the first step in this process. The second step is controlled by members of the retinal dehydrogenase (RALDH) family, also known as the aldehyde dehydrogenase (ALDH) family, and results in all-*trans*-retinoic acid and 9-*cis*-retinoic acid. Retinoic acids are small, lipophilic, rapidly diffusing molecules that can be generated by epithelial cells and intestinal dendritic cells (DCs). They have a crucial role in immune tolerance against food antigens through the recruitment or induction of T_{Reg} cells[28–30]. Although there are many forms of ADH and RALDH, intestinal DCs express some isoforms (namely ADH1

Box 3 | **The biology of T helper cell subsets**

T helper (T_H) cell subsets are defined by a selective expression pattern of effector molecules (cytokines and chemokines), cell-surface molecules and transcriptional regulators.

T_H1 cells are associated with expression of the transcription factor T-bet and are mainly involved in responses against intracellular pathogens, as well as in autoimmunity and immunopathology. They produce interferon-γ (IFNγ), which, together with interleukin-12 (IL-12), is instrumental for their differentiation.

T_H2 cells participate in responses against large pathogens such as helminths and are implicated in allergic responses. They depend on the transcription factor GATA3 and are identified by the expression of IL-4, IL-5, IL-6 and IL-13. IL-4 is the main factor responsible for the development of T_H2 cells.

Regulatory T (T_{Reg}) cells — which require expression of forkhead box P3 (FOXP3) for their maintenance and function — are crucial for restraining other immune cell responses, but may reduce antitumour responses and weaken the efficacy of vaccinations. Most T_{Reg} cells develop as a distinct lineage in the thymus, but under particular conditions involving the presence of transforming growth factor-β (TGFβ) — such as those existing at mucosal sites, near tumours or during infections — T_{Reg} cells can arise from T_H cell precursors in the periphery.

T_H17 cells are responsible for responses against extracellular pathogens, but they are also implicated in the initiation of autoimmune disorders and contribute to immunopathology[116]. Their differentiation generally requires both TGFβ and IL-6 (REF. 13), and is further supported by other factors. T_H17 cells are identified by the expression of retinoic acid receptor-related orphan receptor-γt (RORγt) and, to a lesser extent, the closely related nuclear receptor RORα[16,25]; they also express high levels of the aryl hydrocarbon receptor (AHR)[24].

T follicular helper (T_{FH}) cells provide support for the generation of high-affinity antibodies. They are located in germinal centres, directly providing support to B cells, and use the transcription factor B cell lymphoma 6 (BCL-6) for their function[117].

Box 4 | **Innate lymphoid cells and tissue organization**

Innate lymphoid cells (ILCs) are a recently identified group of lymphoid cells derived from the common lymphoid progenitor that have a more innate character than classical lymphocytes. They lack expression of an antigen receptor, but make an important contribution to immune homeostasis[21]. ILCs develop in the absence of recombined antigen receptors and clonal selection, but depend on the lymphoid cell growth factors interleukin-7 (IL-7) and thymic stromal lymphopoietin (TSLP)[118]. At least three main groups are recognized, and these originate from distinct fetal liver-derived precursors. The first group depends on the nuclear receptor retinoic acid receptor-related orphan receptor-γt (RORγt) for its development. This group includes lymphoid tissue inducer (LTi) cells (also known as ILC17 cells) and cells expressing natural killer (NK) cell markers (such as NKp46) that are referred to as ILC22 cells[119]. The second group (commonly referred to as type 2 ILCs or ILC2 cells) comprises cells that do not express RORγt but depend on RORα for their development[120]. A third group, termed ILC1 cells, produces the T helper 1 (T_H1)-type cytokine interferon-γ (IFNγ) and includes NK cells.

The specific roles of the various ILC subsets are currently under investigation. However, ILCs with LTi cell functions are essential for the prenatal development of secondary lymphoid organs, such as the lymph nodes and Peyer's patches[121], but not the spleen or nasopharynx-associated lymphoid tissue. In adult mice, RORγt$^+$ ILCs localize mainly to the intestinal lamina propria[119,122], where they are required for the development of lymphoid structures such as cryptopatches and isolated lymphoid follicles. Isolated lymphoid follicles are required for T cell-independent immunoglobulin class switching to IgA in the intestine. ILC22 cells are important for intestinal immune homeostasis and the production of antimicrobial peptides, whereas ILC2 cells have characteristics in common with T_H2 cells.

and ADH4) constitutively and others according to their location in the intestine (that is, Peyer's patch DCs express RALDH1 and mesenteric lymph node DCs express RALDH2)[31].

Metabolites of vitamin A direct transcriptional responses by binding to retinoic acid receptors (RARs) and retinoid X receptors (RXRs). The RARs are a nuclear receptor family comprising three isotypes, and more isoforms are generated through alternative gene expression and splicing at each receptor gene. All-*trans*-retinoic acid binds to RARs that are heterodimerized with RXRs, and these complexes subsequently bind to specific DNA sequences[32]. All-*trans*-retinoic acid can isomerize to 9-*cis*-retinoic acid, which is the physiological ligand for RXR homodimers[27]. RARs rarely form homodimers, whereas RXRs can either homodimerize or pair with other lipid-sensing nuclear receptors, such as the vitamin D receptor (VDR), peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs), pregnane X receptor (PXR) and farnesoid X receptor (FXR).

Like vitamin A, vitamin D can be obtained from our diet. Alternatively, vitamin D3 can be derived from the isomerization of pre-vitamin D3, which is generated through photochemical synthesis from pro-vitamin D3 (also known as 7-dehydrocholesterol) when the skin is exposed to ultraviolet B radiation. The physiologically active vitamin D3 metabolite 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D3$; also known as calcitriol) can be subsequently produced in the liver or kidneys, or by cells of the immune system[33] (FIG. 2a). The metabolism of vitamin D3 into biologically active $1,25(OH)_2D3$ primarily takes place in the liver and kidneys. Although the required enzymes to generate $1,25(OH)_2D3$ are found in macrophages and DCs[33], it is unclear whether they are sufficient to generate physiological quantities. $1,25(OH)_2D3$ binds to the VDR, which, like RARs, forms a heterodimer with an RXR following activation. Importantly, the primary site of uptake of both vitamin A and vitamin D is mucosal sites, in particular the gastrointestinal tract, and many of the nuclear receptors (such as RORs, RARs, RXRs, LXRs and PPARs) that bind to these vitamins are expressed by immune cells present in the mucosa, in particular T_{Reg} cells, T_H17 cells and ILCs.

Vitamin A at the intestinal mucosa. Metabolites of vitamin A function as small signalling molecules and make important contributions to immune homeostasis. The metabolites have a role in the differentiation and function of B and T cell subsets and influence their homing properties (FIG. 1b).

Early reports linked vitamin A to the inhibition of T_H1 cell responses and therefore — under the then prevailing dichotomous model of T_H cell differentiation — to enhanced T_H2 cell activity. More recently, this oversimplification of the roles of vitamin A in T_H cell-mediated immunity has been readdressed in the context of induced T_{Reg} and T_H17 cells[28,30,34]. TGFβ, which is crucial for the differentiation of both subsets, increases RAR expression[35]. The potency of TGFβ for the generation of induced T_{Reg} cells is enhanced by the presence of retinoic acid[32,36,37]. In line with a potential role of vitamin A in balancing T_H17 and induced T_{Reg} cells in the gastrointestinal tract, exogenous and CD103$^+$ DC-derived retinoic acid has been shown to inhibit the induction of T_H17 cells *in vivo,* and administration of an RAR antagonist decreases the number of T_{Reg} cells in the lamina propria[28,30,34]. In addition, retinoic acid enhances the expression of the microRNA miR-10a[38]. In induced T_{Reg} cells, miR-10a inhibits the expression of B cell lymphoma 6 (BCL-6), which is an important factor in T_{FH} cell differentiation. Retinoic acid thereby constrains the conversion of induced T_{Reg} cells into T_{FH} cells[35] (FIG. 1b).

However, this does not imply that dietary vitamin A supplementation alone would be sufficient to prevent or cure intestinal inflammatory disorders[39]. Mediators such as growth factors normally function in a concentration-dependent manner and within an environmental context. This possibly reflects the interplay between different nuclear receptors and their binding partners, resulting in a variety of outcomes[35]. In an inflammatory microenvironment, or in the presence of particular microbial components, low vitamin A concentrations contribute to T_H1-type and T_H17-type immune responses[35]. Indeed, vitamin A deficiency decreases the T_H17 cell response during infections[40]. Retinoic acid induces miR-10a expression in T_H17 cells, which, as in induced T_{Reg} cells, suppresses BCL-6 expression. Although BCL-6 is known to inhibit T_H17 cell development[41], miR-10a also induces the expression of T-bet (which is associated with T_H1-type immune responses) in the presence of retinoic acid[35]. This suggests that the function of the T_H17 cells, and possibly their conversion to T_H1-like cells[42], is also directly influenced by retinoic acid concentrations. The effects of retinoic acid on transcriptional events (both direct effects through RAR and RXR, and indirect

PPARs
A group of nuclear receptor proteins involved in altering lipid and glucose metabolism. Their ligands include free fatty acids and eicosanoids.

LXRs
A group of nuclear receptor proteins important in regulating cholesterol, fatty acid and glucose homeostasis. A ligand is oxysterol.

FXR
A member of the nuclear receptor family of transcription factors, with a role in maintaining bile acid, cholesterol and glucose homeostasis. Bile acids are natural ligands.

Lamina propria
Connective tissue beneath the intestinal epithelium containing various myeloid and lymphoid cells.

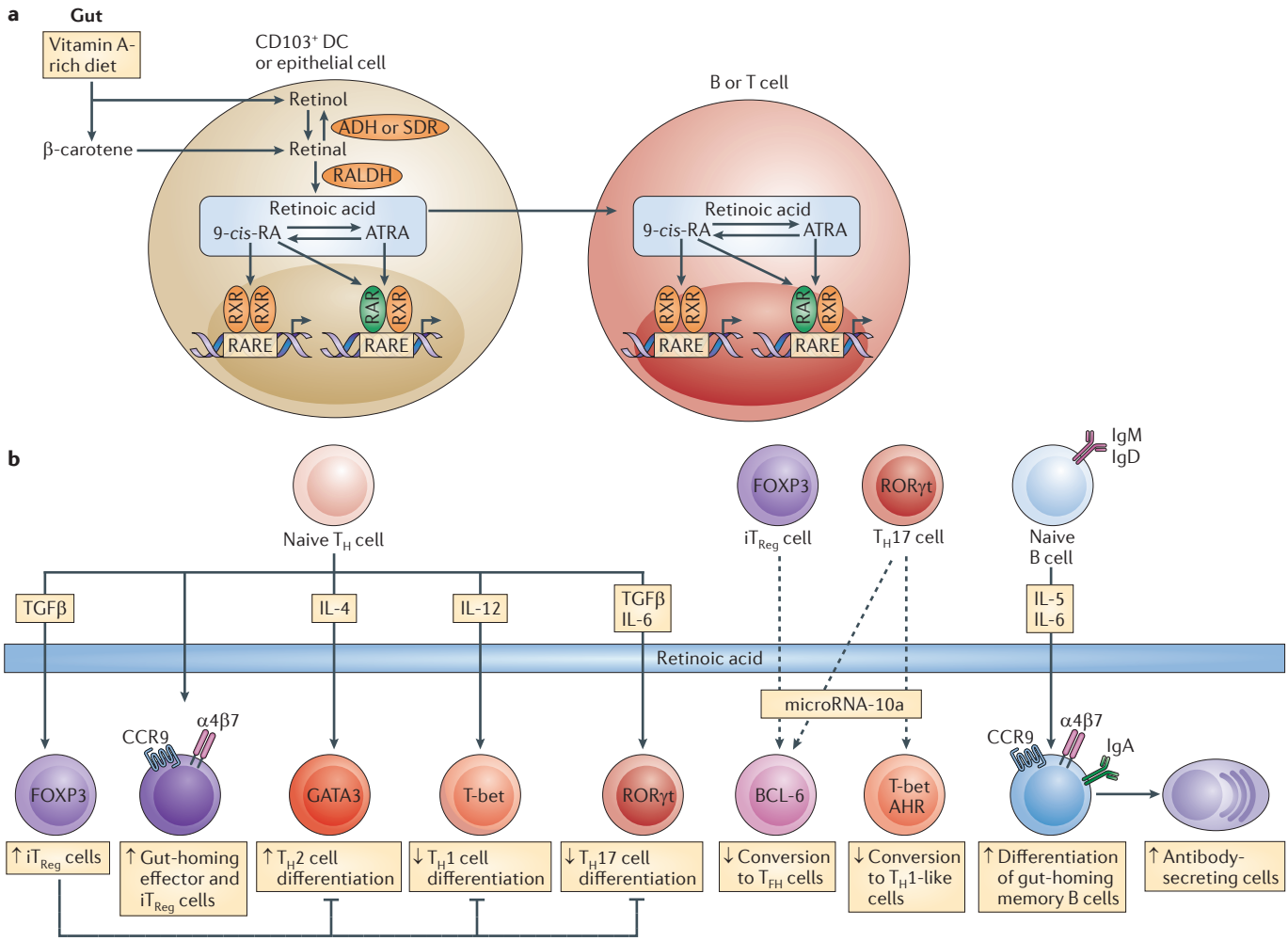


Figure 1 | **The molecular and cellular mechanisms of action of vitamin A.** **a** | The enzymes of the retinoid dehydrogenase family (namely, alcohol dehydrogenase (ADH), the short-chain dehydrogenases/reductases (SDRs) and the retinal dehydrogenases (RALDHs)) metabolize dietary vitamin A and β-carotene in CD103$^+$ dendritic cells (DCs) and epithelial cells into the active compound, retinoic acid, which is present as two isomers: all-*trans*-retinoic acid (ATRA) and 9-*cis*-retinoic acid (9-*cis*-RA). Retinoic acid functions by binding to retinoid X receptor (RXR)–retinoic acid receptor (RAR) heterodimers (which are receptors for both ATRA and 9-*cis*-RA) or to RXR–RXR homodimers (which are receptors for 9-*cis*-RA), which then bind to retinoic acid response elements (RAREs) in the cell nucleus. **b** | Data obtained from *in vitro* experimentation indicates that retinoic acid induces the expression of gut-homing receptors and exerts direct and indirect immunomodulatory effects on T cell differentiation as indicated. The precise role of retinoic acid *in vivo* remains to be determined. In induced regulatory T (iT_{Reg}) cells and T helper 17 (T_H17) cells, retinoic acid induces the expression of microRNA-10a, thereby inhibiting the conversion of these cells to T follicular helper (T_{FH}) cells and T_H1-like cells. In B cells, retinoic acid contributes to the differentiation of gut-homing IgA-secreting plasma cells. α4β7, α4β7 integrin; AHR, aryl hydrocarbon receptor; BCL-6, B cell lymphoma 6; CCR9, CC-chemokine receptor 9; FOXP3, forkhead box P3; IL, interleukin; RORγt, retinoic acid receptor-related orphan receptor-γt; TGFβ, transforming growth factor-β.

effects through FOXP3, T-bet and BCL-6) indicate that retinoic acid can modulate T cell sensitivity to the microenvironment through the regulation of cell-surface receptors and signalling components. Indeed, retinoic acid might inhibit the sensitivity of induced T_{Reg} and T_H17 cells to IL-6 and IL-23, respectively, by limiting the re-expression of IL-6 receptor subunit-α (IL-6Rα) by induced T_{Reg} cells and the RORγt-induced expression of IL-23R by T_H17 cells[43]. This would prevent possible T_H17 cell development at the very early stages of induced T_{Reg} cell generation and directly affect the biology of T_H17 cells.

Importantly, retinoic acid affects the trafficking of lymphocytes to the intestinal mucosae, which may largely explain its role in immune homeostasis (FIG. 1b). It achieves this — possibly together with TGFβ — by inducing the expression of the gut-homing receptors α4β7 integrin and CC-chemokine receptor 9 (CCR9) on CD4$^+$ T cells[31,36,44,45], CD8$^+$ T cells[46] and B cells[47]. Vitamin A deficiency decreases the number of α4β7 integrin-expressing T cells in the secondary lymphoid organs, and the cells lacking expression of α4β7 integrin fail to home to the intestine[31]. The effects of retinoic acid may explain the tissue tropism observed

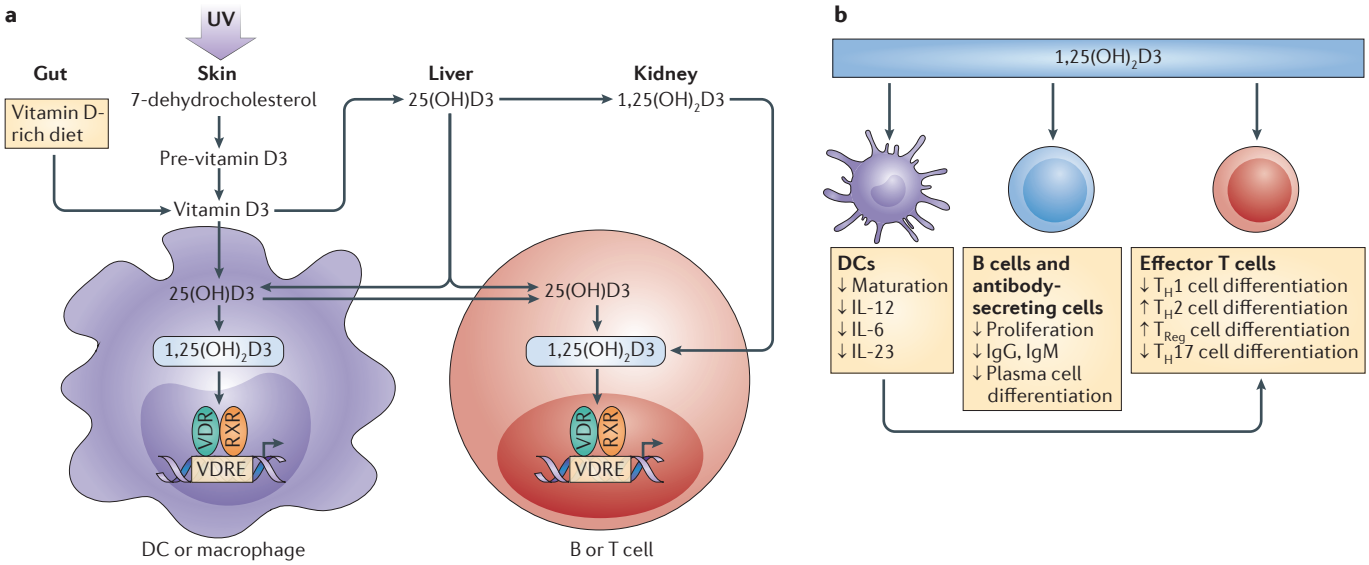


Figure 2 | **The molecular and cellular mechanisms of action of vitamin D.** **a** | Vitamin D can be obtained from the diet. In addition, vitamin D3 can be photochemically synthesized from pro-vitamin D3 (7-dehydrocholesterol) in the skin. Vitamin D3 is hydroxylated to 25-hydroxyvitamin D3 (25(OH)D3) and subsequently in the kidney to 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D3$), which physiologically is the most active metabolite. Cells of the immune system can also enzymatically process 25(OH)D3 to $1,25(OH)_2D3$, which binds to vitamin D receptor (VDR)–retinoid X receptor (RXR) heterodimers. The receptor heterodimer then binds to the vitamin D response element (VDRE) in the nucleus. **b** | $1,25(OH)_2D3$ exerts its effects on several immune cell types, including dendritic cells (DCs), B cells and T cells. $1,25(OH)_2D3$ decreases the maturation of DCs and their production of pro-inflammatory cytokines, and directly and indirectly influences T helper (T_H) cell differentiation as indicated. In B cells and antibody-secreting cells, $1,25(OH)_2D3$ inhibits proliferation, plasma cell differentiation and immunoglobulin production. IL, interleukin; T_{Reg}, regulatory T; UV, ultraviolet.

when induced T_{Reg} cells are generated *in vitro* with TGFβ and retinoic acid, which induces the expression of both CCR9 and α4β7 integrin[36]. Whether vitamin A influences the balance of T_H cells in the intestine should be viewed in the context of its ability to increase the homing of T cells with specificity for antigens in the gut, T_{Reg} cells and T_H17 cells[40], without affecting the steady-state levels of T_H cells. Future work will need to carefully dissect the effects of retinoic acid on T cell migration versus its direct effects on T_H cell differentiation.

Antigen-experienced B cells that express α4β7 integrin are equally abundant in the lymph nodes of vitamin A-deficient mice and control mice. However, the normally broad repertoire of IgA antibodies that these B cells produce is reduced in the Peyer's patches of vitamin A-deficient mice[47], which is in line with the requirement for RARα in IgA-secreting memory B cells[48]. Retinoic acid produced by intestinal DCs synergizes with DC-derived IL-6 and IL-5 to promote the secretion of IgA (FIG. 1b). Consequently, vitamin A-deficient mice lack IgA-secreting cells in the small intestine[47]. In addition, vitamin A suppresses immunoglobulin class switching to isotypes that are able to induce strong immune activation associated with immune pathology and allergy (such as IgG1 and IgE)[49], possibly by inhibiting T_{FH} cell differentiation[35]. Vitamin A thus enables the discriminate homing and development of less aggressive immune cells, thereby limiting the potential for immunopathology at the delicate epithelial sites. These findings suggest that appropriate vitamin A levels are crucial for a balanced T cell response to infection and after vaccinations, and for the maintenance of tolerance to innocuous antigens[29,40].

Vitamin D. Like vitamin A, vitamin D has been shown to alter B and T_H cell responses (FIG. 2b), similarly inhibiting T_H1 cell activity and enhancing T_H2 cell activity. An increase in T_{Reg} cell numbers has also been reported after exposure to $1,25(OH)_2D3$ (REF. 50), which was recently directly linked with the binding of VDR–RXR to an enhancer in the *FOXP3* gene[44]. It has been suggested that vitamin D directly imposes a delay in T cell receptor (TCR)-mediated signalling to diminish the risk of immunopathology[51], a potentially important fail-safe mechanism in an antigen-rich environment such as the intestine. $1,25(OH)_2D3$ can also indirectly influence T_H cell differentiation by suppressing DC maturation and secretion of IL-12 (REF. 52), IL-6 and IL-23 (REF. 53) (FIG. 2b), and this may favour the differentiation or clonal expansion of induced T_{Reg} cells[53,54]. In addition, a more direct effect on T_H17 cell differentiation and migration has been proposed[55], whereby $1,25(OH)_2D3$ suppresses the generation of T_H17 cells and negatively regulates their expression of the homing receptor CCR6. CCR6 and its ligand CC-chemokine ligand 20 (CCL20) have a role in controlling the migration of T_H17 cells into the tissues[56,57].

Both RARs and VDR can form heterodimers with RXRs. If RXRs are a limiting factor, then retinoic acid and 1,25(OH)$_2$D3 will antagonize each other's functions by competing for the same nuclear receptor partner[27]. Vitamin D deficiency results in decreased numbers of the T cells that line the epithelial monolayer, which are known as CD8αα$^+$ intraepithelial lymphocytes (IELs). This is due to a cell-intrinsic defect that causes a reduction in the proliferative capacity of CD8αα$^+$ IELs in the absence of vitamin D[58]. Interestingly, the development of CD8αα$^+$ IELs also crucially depends on TGFβ[59]. This may indicate a potential synergistic effect between TGFβ and vitamin D, as seen with vitamin A. This is likely to involve interplay between various nuclear receptors, such as RXRs, RORγt, RORα and AHR, which are expressed differentially by CD8αα$^+$ IELs, TCRγδ$^+$ IELs, T_H17 cells and T_{Reg} cells. Vitamins A and D thus have the ability to alter lymphocyte activation and homing, thereby contributing to intestinal immune homeostasis, which is characterized by a state of tolerance towards most antigens.

AHR and the phytochemical I3C. The AHR has been recently shown to be highly expressed by T_H17 cells and to be present at increased levels in T_{Reg} cells[24,60]. Furthermore, AHR expression was found in ILC subsets[61–63] and in IELs[64] (FIG. 3a). This highly conserved basic helix–loop–helix (bHLH) transcription factor belongs to the PER–ARNT–SIM (PAS) domain-containing superfamily of sensory proteins and is primarily known to mediate responsiveness to environmental pollutants. Targets of transcriptional gene regulation by AHR include metabolizing enzymes, notably cytochrome P450 enzymes of the CYP1 family. Similarly to RARs and RORs, AHR is responsive to lipophilic ligands, which are rapidly metabolized by CYP1 enzymes. The physiological role of AHR is currently poorly understood. Oxidation and chemical condensation of diet-obtained tryptophan or some of its metabolic derivatives can generate high-affinity AHR ligands, such as 6-formylindolo[3,2-b]carbazole (FICZ), which initiate the AHR transcriptional programme and are ideal substrates for the CYP1 enzymes[65].

Most of the ligands responsible for AHR activity in the intestine are obtained from plants of the *Brassica* genus, which includes the cruciferous vegetables, such as green cabbages and broccoli. These vegetables are rich in glucobrassicin, a chemical that is synthesized from glucose and tryptophan. The phytochemical indole-3-carbinol (I3C), which is derived from the indolic glucosinolate glucobrassicin, is formed as part of the plant defence response. In rodents and humans, oral intake of I3C, but not intraperitoneal administration of I3C, increases the activity of AHR-regulated enzymes such as CYP1A1 in the gastrointestinal tract. In an analogous manner to the conversion of tryptophan into FICZ, the formation of AHR ligands from I3C requires oxidation and acid-catalysed chemical condensation. This occurs in the stomach, owing to its highly active metabolizing environment and low pH (the level of acidity is determined by gastrin that has been activated by peptidyl α-amidating monooxygenase, which requires dietary vitamin C as a cofactor). These reactions generate the AHR ligands 3,3′-diindolylmethane (DIM) and indolo[3,2-b]carbazole (ICZ)[66] (FIG. 3a). In addition to I3C, other naturally occurring compounds derived from fruit and vegetables might be AHR ligands, such as the flavonoid quercetin, which is found in apples, and possibly resveratrol, which is found in red wine. This makes AHR an important sensor of environmental cues, as it is able to initiate transcriptional regulation in response to environmental (dietary) factors. Indeed, mice fed a synthetic purified diet that is free of vegetable material, but supplemented with all essential nutrients, have substantially altered intestinal immunity and architecture[61,64]. Specifically, the absence of vegetable material results in decreased numbers of IELs and RORγt$^+$ ILCs in the intestine compared with the numbers in mice fed a standard diet or the synthetic diet supplemented with I3C[61,64]. In line with a crucial role for AHR in the postnatal development of LTi-like cells, the organogenesis of cryptopatches and isolated lymphoid follicles, which depends on LTi-like cells, is absent in AHR-deficient mice and those fed a diet that is devoid of vegetables[61]. The reduction or absence of cryptopatches and isolated lymphoid follicles also suggests that fewer IgA-producing B cells can be recruited to keep harmful microorganisms at bay, which could contribute to disease[67].

Analyses of AHR-deficient mice have revealed a pronounced phenotype with fewer cells that normally express high levels of AHR, such as IELs (both TCRγδ$^+$ and TCRαβ$^+$CD8αα$^+$ subsets) and RORγt$^+$ ILCs (FIG. 3a). Accordingly, AHR activity is required for the maintenance of IELs and the proliferative capacity of postnatally developed RORγt$^+$ ILCs[61–64]. AHR is also expressed by other γδ T cells, T_H17 cells and prenatally developed RORγt$^+$ ILCs, but these cell types do not seem to rely on its activity for their maintenance. Although AHR is ubiquitously expressed, including in epithelial cells, tissue-specific deletion of *Ahr* in lymphocytes is sufficient to impair the maintenance of IELs and the formation of lymphoid clusters in the intestine[61,64].

Dietary lipids

The digestion of dietary lipids gives rise to fatty acids (and some fatty acids can also be biosynthesized from molecules generated during the metabolism of dietary carbohydrates). Polyunsaturated fatty acids are derived from plant-based products and fish and serve as substrates for the synthesis of biologically active compounds such as steroid hormones. Saturated fatty acids — which owing to the absence of double bonds have a higher energy yield per carbon atom than unsaturated fatty acids — are preferentially incorporated into adipose tissue stores. Fatty acids are involved in immunological processes (FIG. 3b). Saturated fatty acids are generally thought to have a role in promoting inflammation, whereas unsaturated fatty acids have both pro-inflammatory and anti-inflammatory properties[68–70]. Omega-3 and omega-6 polyunsaturated fatty acids are precursors of prostaglandins, which are potent regulators of inflammation. Omega-3 fatty acids exert their

IELs
A T cell population found within the epithelial layer of mammalian mucosal linings. This population consists of specialized subsets of cells, such as particular γδ T cell subsets and αβ CD8αα$^+$ T cells.

Cytochrome P450 enzymes
A superfamily of diverse enzymes involved in drug metabolism and bioactivation, accounting for a very large number of different metabolic reactions, including those for lipids, hormones and xenobiotics (such as drugs and chemicals).

γδ T cells
A small subset of T cells that express a distinct T cell receptor on their surface consisting of a particular γ-chain, which correlates with their presence in particular tissues, coupled to a δ-chain.

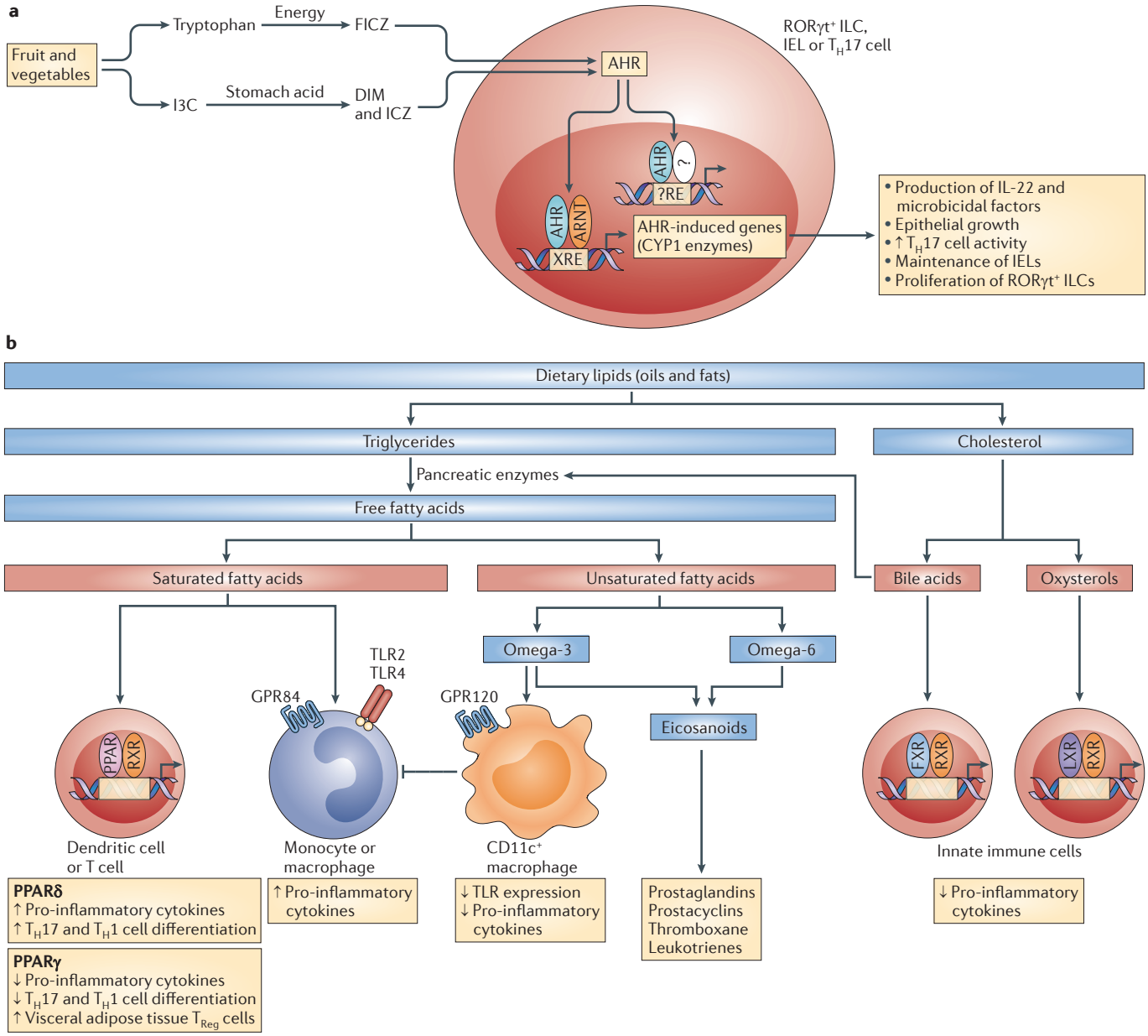


Figure 3 | **The molecular and cellular mechanisms of action of AHR ligands and dietary lipids.** **a** | Ligands for the aryl hydrocarbon receptor (AHR) can be obtained from the diet. Irradiation of the amino acid tryptophan, followed by oxidation and condensation, generates the AHR ligand 6-formylindolo[3,2-b]carbazole (FICZ). Similarly, vegetable-derived indole-3-carbinol (I3C), under the acidic conditions of the stomach, can form the high-affinity AHR ligands indolo[3,2-b] carbazole (ICZ) and 3,3′-diindolylmethane (DIM). Following ligand binding, AHR translocates to the nucleus, where it forms a heterodimer with AHR nuclear translocator (ARNT) and possibly with alternative partners. AHR–ARNT binds to xenobiotic response elements (XREs), thereby inducing AHR-dependent gene expression, which contributes to the maintenance of intraepithelial lymphocytes (IELs), the proliferation of RORγt+ innate lymphoid cells (ILCs), the production of interleukin-22 (IL-22) and microbicidal mediators, epithelial growth and increased T helper 17 (T_H17) cell activity. **b** | Triglycerides, which are contained in oils and fats, give rise to free fatty acids after their breakdown by pancreatic lipases. Saturated fatty acids activate peroxisome proliferator-activated receptors (PPARs) in dendritic cells and T cells, either promoting or inhibiting inflammation. G protein-coupled receptor 84 (GPR84), Toll like receptor 2 (TLR2) and TLR4 — which bind to medium- and long-chain fatty acids — are expressed by monocytes and macrophages and induce the secretion of pro-inflammatory cytokines. The expression of TLR2 and TLR4 and the production of pro-inflammatory cytokines can be counteracted by omega-3 polyunsaturated fatty acids, which are sensed by GPR120-expressing CD11c+ macrophages. Omega-3 and omega-6 polyunsaturated fatty acids serve as substrates for the synthesis of biologically active eicosanoid compounds. In innate immune cells, oxysterols and bile acids (which are metabolites of cholesterol) bind to liver X receptors (LXRs) and the farnesoid X receptor (FXR), respectively, to inhibit pro-inflammatory cytokine production. Bile acids also contribute to the breakdown of triglycerides by emulsifying the fats. The PPARs, LXRs and FXR form active transcription factors via heterodimerization with retinoid X receptors (RXRs). RORγt, retinoic acid receptor-related orphan receptor-γt; T_{Reg}, regulatory T.

anti-inflammatory effects by replacing omega-6 fatty acids in metabolic pathways, and this results in the production of lower levels of pro-inflammatory mediators and higher levels of mediators with anti-inflammatory properties. Increasing the omega-3/omega-6 balance can be achieved through the increased consumption of fish products and reduced intake of vegetable oil.

Dietary fats are dissolved in micelles by bile salts in the upper part of the gastrointestinal tract and subsequently taken up by enterocytes. Omega-3 fatty acids can then interact directly with immune cells. They bind to GPR120 (G protein-coupled receptor 120; also known as omega-3 fatty acid receptor 1)[71], which is expressed by inflammatory $CD11c^+$ macrophages[72]. By activating GPR120, omega-3 fatty acids mediate potent anti-inflammatory effects, through the inhibition of both Toll-like receptor (TLR)- and cytokine-mediated signalling pathways, and thereby indirectly influence the lymphocyte compartments. Omega-6 fatty acids, like long-chain fatty acids, activate GPR40 (also known as free fatty acid receptor 1)[73], which is expressed by I cells (cells secreting peptide hormones that stimulate the release of enzymes that aid the digestion of fat and protein) in the mucosal epithelium of the small intestine[74]. The expression of GPR40 by immune cells has not yet been reported, but oxidized omega-6 fatty acids give rise to immune modulators such as prostaglandins.

Medium-chain fatty acids (6–12 carbons in length) bind to GPR84, which is present on leukocytes[70]. The activation of GPR84 on monocytes and macrophages by unsaturated medium-chain fatty acids amplifies the production of some pro-inflammatory mediators[70]. Fats can also directly trigger TLRs, thereby linking nutrient- and pathogen-sensing pathways. Indeed, medium-chain fatty acids and saturated long-chain fatty acids have been shown to activate TLR2 and TLR4 signalling in macrophages, resulting in the secretion of pro-inflammatory cytokines[68]. This can be prevented by pre-treatment of the cells with omega-3 polyunsaturated fatty acids. Both T_{Reg} cells and IL-17-producing cells have been reported to express TLR2 and to be influenced by its ligands[75–79]. This suggests that the balance between immune reactivity and tolerance can be directly affected by dietary lipids.

Lipids and peroxisome proliferator-activated receptors. Unsaturated long-chain fatty acid derivatives that are generated by the lipoxygenase pathway (such as oxidized fatty acids) are detected by PPARs, which are important regulators of cell differentiation, development and metabolism (FIG. 3b). PPARs are another group of ligand-activated nuclear receptors that function as transcription factors and regulate the expression of various genes. PPARs exert their effects on gene transcription by dimerizing with RXRs[80,81]. PPARs are widely expressed by various haematopoietic cells, including DCs and lymphocytes[82]. It is therefore likely that these cells are influenced by oxidized fatty acids. Indeed, the activation of PPARδ (also known as PPARβ) can enhance both T_H1 and T_H17 cell responses through increased production of myeloid cell-derived cytokines and T cell-intrinsic effects[83].

By contrast, PPARγ activators are reported to inhibit the differentiation of T_H1 and T_H17 cells indirectly through cytokine-mediated modulation of DCs[84]. In addition, at mucosal sites, epidermal fatty acid-binding protein (E-FABP), a lipid chaperone, is required for optimal T_H17 cell differentiation and may counteract the generation of induced T_{Reg} cells[85]. An absence of E-FABP increases the expression of PPARγ in T cells, which subsequently fail to express RORγ and RORα, resulting in reduced T_H17 cell polarization. A PPARγ antagonist counteracts this, which suggests that PPARγ activation can directly inhibit T_H17 cell development, possibly through negative modulation of IL-6 responsiveness[86]. In agreement, PPARγ ligation has been shown to actively inhibit T_H17 cell differentiation by stabilizing the binding of the co-repressor silencing mediator for retinoid and thyroid hormone receptors (SMRT; also known as NCOR2) at the RORγt gene promoter[87]. This suggests that the types and quantities of dietary lipids, and of the lipid metabolites generated via the lipoxygenase pathway, affect intestinal immune homeostasis.

The inhibition of IL-6 responsiveness and prevention of RORγt gene transcription by PPARγ may also be involved in the generation of a distinct population of T_{Reg} cells that has recently been described in the visceral adipose tissues that surround the intestine. Visceral adipose tissue T_{Reg} cells influence the inflammatory state of adipose tissue[88], and PPARγ is a crucial molecular orchestrator of their accumulation, phenotype and function[89]. Currently, there are no reports that this population of T_{Reg} cells is found in the intestine, but it seems likely that visceral adipose tissue T_{Reg} cells are influenced by dietary lipids.

Lipids and the liver X receptor. Animal-derived foods contain cholesterol in addition to fatty acid-containing lipids. Cholesterol is an important component of the cell membrane and has long been known to be necessary for cell growth and proliferation. Metabolites of cholesterol, such as oxysterols and bile acids (which are secreted into the upper gastrointestinal tract), activate the nuclear receptors LXR and FXR, respectively[90,91] (FIG. 3b). They have an essential role in integrating nutrient absorption and lipid metabolism with liver and intestinal homeostasis, but our knowledge of their role in lymphocyte biology is limited. LXR and FXR, which are expressed by multiple immune cell types, form functional transcription factors through heterodimerization with RXRs. FXR is highly expressed in the liver and intestine and contributes to the modulation of intestinal immunity, by negatively regulating the expression of many pro-inflammatory mediators in innate immune cells[92]. LXR is required for the function of macrophages in response to bacterial infections, but its ligands can inhibit the production of pro-inflammatory mediators such as IL-6 (REF. 93). In addition, the activity of LXR is required for apoptotic cell clearance and the maintenance of immune tolerance by macrophages[94].

LXRs can inhibit lymphocyte proliferation[95] and decrease T cell clonal expansion by altering the cellular sterol content through a pathway requiring the LXR target gene ATP-binding cassette subfamily G member 1 (*Abcg1*). Accordingly, the loss of LXR expression confers

a proliferative advantage to lymphocytes, resulting in enhanced homeostatic and antigen-driven responses. Furthermore, LXR negatively regulates T_H17 cell differentiation by preventing AHR-induced IL-17 production[96]. Thus, overexpression of LXR in naive $CD4^+$ T cells inhibits differentiation to the T_H17 cell lineage, whereas a deficiency of LXR promotes T_H17 cell differentiation. The mechanism for this inhibition is thought to involve sterol regulatory element-binding protein 1 (SREBP1), which is encoded by a downstream target gene of LXR and directly competes with AHR for binding to the E-box element in the *Il17* promoter, which overlaps with the AHR-binding site. The inhibition of T_H17 cell differentiation through LXR- and PPAR-mediated signalling provides a direct link between cellular cholesterol levels and cell differentiation. This suggests that some cholesterol metabolites, which are possibly generated from dietary fats, can restrain the differentiation of T cells into T_H17 cells; this is in contrast to the positive signals derived from other, as yet unidentified cholesterol metabolites that activate RORα and RORγt[97].

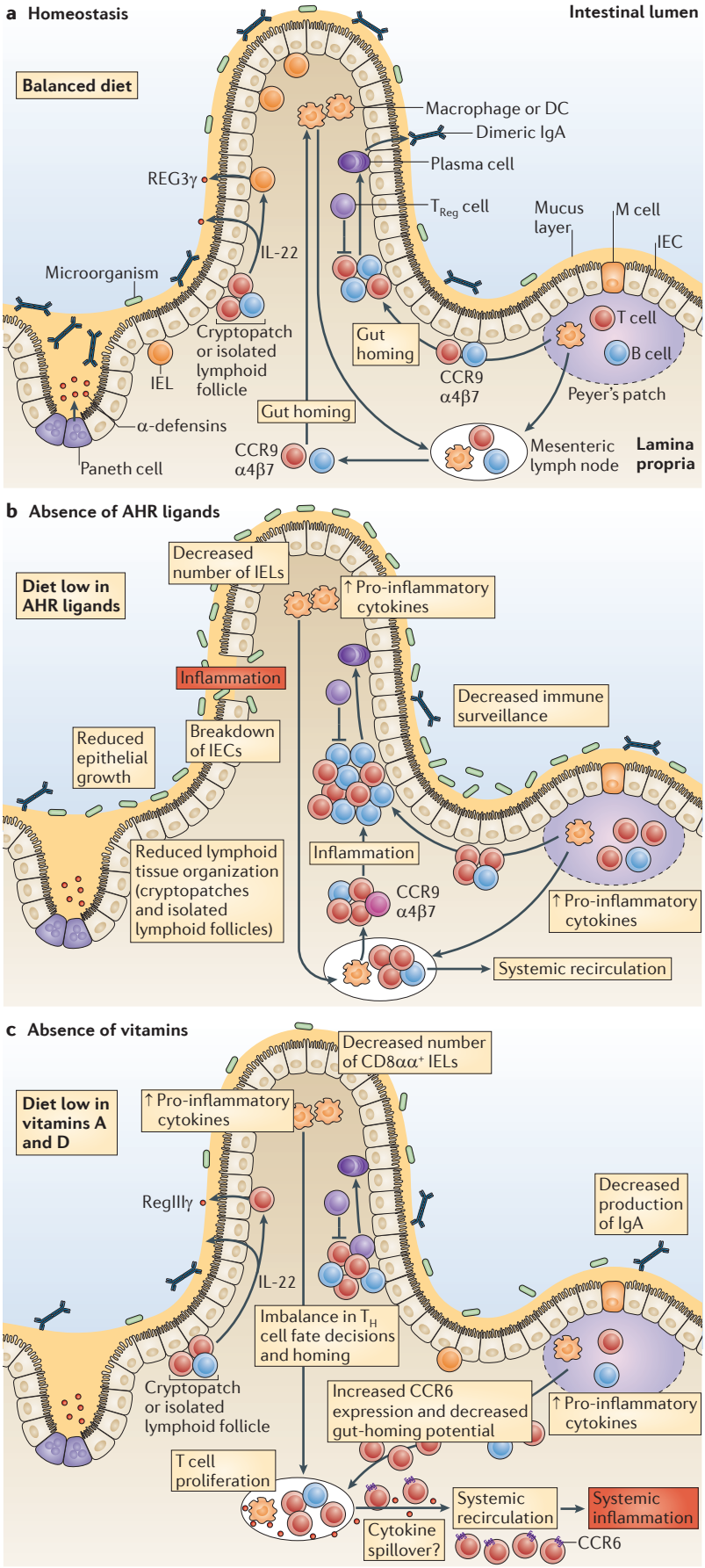
Dietary products and disease

A balanced diet maintains intestinal mucosal homeostasis (FIG. 4a). A lack of vitamins, phytochemicals and unsaturated fatty acids can result in an imbalance in immune homeostasis, leading to inflammation and pathology. A prime example is the failure of AHR-deficient animals or those on a diet devoid of vegetables to maintain IELs, which has consequences for both immunity and barrier maintenance[64] (FIG. 4b). Firstly, IELs are involved in stimulating epithelial cell turnover in the small intestine, thereby maintaining the intestinal villi and providing protection against mechanical or microorganism-induced damage[64,98]. Secondly, IELs are essential mediators of host–microorganism homeostasis. They can directly lyse target cells through the expression of granzymes and perforin[64], and can secrete antimicrobial factors, such as REG3γ, in response to microorganisms that penetrate the intestinal epithelium[99]. In addition, AHR is directly involved in the production of IL-22 by $ROR\gamma t^+$ ILCs and T_H17 cells[24,62]. Indeed, AHR ligands such as FICZ and DIM enhance the secretion of IL-22, which favours intestinal homeostasis, for example by increasing the expression of REG3γ in response to bacterial infections[62,63]. Lastly, these same dietary AHR ligands could influence the balance between T_H17 cells and T_{Reg} cells, and the activation status of and IL-22 production by T_H17 cells[14,24,60]. The role of AHR might also extend to other T_H cell subsets. T_H17 cells can convert to a T_H1-like status, resembling bona fide T_H1 cells but maintaining some characteristics of their T_H17 cell ancestry, including the expression of AHR[42]. Together, these data provide molecular insight into how a diet that is low in fruit and vegetables can contribute to inflammatory disorders[100], and how a high vegetable intake could have a protective effect[101].

The involvement of dietary compounds in inflammatory disease pathogenesis is not limited to inflammation in the intestine (FIG. 4c). RORs, PPARs and AHR have also been implicated in the regulation of various metabolic pathways and energy homeostasis, with potential roles in several disorders, including autoimmune diseases, asthma, cancer and obesity. Vitamins A and D, AHR ligands and lipids that activate PPARγ and LXRs have all been shown to be involved in models of autoimmunity. For example, low levels of $1,25(OH)_2D3$ are found in patients with autoimmune disorders[102], but it remains unknown how this affects the activity and specificity of other nuclear receptors that interact with VDR, such as RXRs and their binding partners. Direct or indirect effects of dietary metabolites on T_{Reg} cells and T_H17 cells may form a molecular basis for the protective effects observed in models of autoimmunity[43,55,87,96]. In addition, recent results highlight that several nuclear receptors — at least RORα, RORγt and AHR — are involved in the development and function of ILCs. Nuclear receptor activation contributes to lymphoid organization in the intestine, such as the formation of cryptopatches and isolated lymphoid follicles. Failure to generate these tertiary lymphoid tissues can aggravate and prolong disease as a result of the failure to bring together different cellular components of the immune response, such as DCs, B cells and T_{Reg} cells, which dysregulates their activity[103].

Many of the dietary metabolites absorbed in the gastrointestinal tract are subsequently catabolized and exert their effects in tissues other than the intestine. As such, the dietary composition can have effects far beyond the gastrointestinal tract. For example, lipolysis in adipose tissues results in the production of fatty acids that activate macrophages, and this can contribute to the chronic low-grade inflammation that is seen in disorders such as type 2 diabetes, coronary artery disease and some cancers and degenerative diseases. The intestine digests and absorbs dietary products to supply the body with essential nutrients. Changes in the microbiota will result in alterations in intestinal microbial metabolism and in the composition of the microorganism populations that occupy the epithelial lining, which can both affect barrier function and contribute to the dissemination of bacteria and their products to sterile tissues, thereby enhancing systemic inflammation.

In addition to being induced by microorganisms and their products, inflammatory diseases in sites distal from the intestine are promoted by the dissemination of pro-inflammatory cytokines, such as tumour necrosis factor or IL-23, and of migratory cells, such as T_H17 cells. In agreement, disorders such as inflammatory bowel disease are frequently associated with various extra-intestinal immune-mediated symptoms. The decreased expression of lymphocyte gut-homing receptors in the absence of vitamins and the increase in CCR6 expression[55] could further enhance the spread of chronic inflammation to remote body parts[56]. Furthermore, components of our microbiota will themselves be influenced by immunological events and will alter their behaviour in response to ongoing inflammatory cues, such as IL-17 and metabolic products, or when immunity is compromised, such as in the case of HIV-infected individuals. In addition, immune cells function not only to protect the tissues against pathogens and their products, but also to maintain tissue architecture and homeostasis. These cells crucially depend on stress signals for their function, and the presence of high levels of systemic cytokines can lead to their aberrant activation, resulting in a pathological inflammatory response[104].



Finally, for immune resolution and wound healing to progress, the inflammatory response must be controlled to allow for the re-establishment of the extracellular matrix, cellular influx and tissue remodelling. In addition to the role of cytokines (such as IL-22, which is partly regulated by AHR), arachidonic acid metabolites (such as eicosanoids), which are generated by the lipoxygenase or cyclooxygenase pathways, are crucial for tissue repair processes[105]. Importantly, eicosanoids are derived from dietary unsaturated essential fatty acids, some of which function through the activation of PPARγ[106]. This implies that, through the activation of lipid-binding nuclear receptors, the types and quantities of dietary fats directly affect immune cell activation and the ability to resolve ongoing inflammation, and that these fats are crucial mediators in immune homeostasis and wound repair.

Figure 4 | **The cellular network in intestinal homeostasis and inflammation. a** | Intestinal immune homeostasis is maintained by many mechanisms. These include: the production of dimeric IgA by plasma cells, which limits the epithelial translocation of antigens; and the presence of the mucus layer and the constitutive production of α-defensins by Paneth cells, which shield the epithelial surface from direct microbial exposure. Interleukin-22 (IL-22) secretion by lymphocytes, NKp46$^+$RORγt$^+$ innate lymphoid cells (ILCs) and lymphoid tissue inducer-like (LTi-like) cells (which are located in cryptopatches and isolated lymphoid follicles) induces the expression of antimicrobial peptides, such as regenerating islet-derived protein 3γ (REG3γ). Intraepithelial lymphocytes (IELs) support epithelial cell growth and have a role in immune surveillance. Dendritic cells (DCs) in the villi and in Peyer's patches sample antigens, produce cytokines and have a role in recruiting B and T cells to the intestine through the induced expression of homing factors, such as CC-chemokine receptor 9 (CCR9) and α4β7 integrin. T helper (T_H) cells are instrumental in orchestrating the inflammatory response. Regulatory T (T_{Reg}) cells limit inflammation; T_H17 cells have both pro- and anti-inflammatory properties; and T_H1 cells are directly involved in fighting pathogens. **b** | In the absence of dietary aryl hydrocarbon receptor (AHR) ligands, RORγt$^+$ ILCs — and hence cryptopatches and isolated lymphoid follicles — and IELs are decreased in number. The epithelial barrier is compromised and immunity is reduced, increasing the risk of bacterial dissemination into the lamina propria. Furthermore, the absence of IELs reduces the ability of the intestine to repair tissue damage and the lack of AHR-induced IL-22 decreases the production of microbicidal factors. Microbial infection and/or tissue damage induces the production of pro-inflammatory cytokines by CD103$^+$ DCs and macrophages, thereby promoting the differentiation and proliferation of T_H1 and T_H17 cells and resulting in an overt inflammatory response. **c** | A diet low in vitamins A and D decreases the number of CD8αα$^+$ IELs and decreases the production of IgA, but increases the secretion of pro-inflammatory cytokines by DCs and macrophages. In addition, both vitamins have direct and indirect roles in constraining T_H cell differentiation. Consequently, T_H17 and T_H1 cell differentiation is promoted in their absence, creating an inflammatory environment. This local inflammation may spread to remote body parts through cytokine 'spillover' and/or the active migration of gut-resident cells as a result of decreased expression of gut-homing receptors and simultaneous upregulation of CCR6 expression.

Conclusion and perspective

An increasing number of studies are unravelling the molecular mechanisms that underlie the direct effects of dietary products on immune cells. Recent results highlight a major role for ligand-activated nuclear receptors — such as RARs, RORs, RXRs and AHR — in mediating the effects of dietary products on immune cells. Allosteric interactions between the heterodimeric nuclear receptors are likely to create complexes with unique properties that affect the balance between immune activation and tolerance. The mechanisms affecting the heterodimeric interactions of RXRs with RORs, RARs, PPARs and VDR remain to be elucidated, together with the kinetics of these interactions and their integration with other metabolic signalling nodes (such as those involving AHR) that affect tolerance and inflammation at mucosal sites. For example, the activation of LXRs inhibits the expression of RORγt[96], providing another example of negative regulation of T_H17 cell differentiation through a protein–protein interaction, in addition to the previously established inhibitory interaction between FOXP3 and RORγt[15]. This is indicative of the complex network of nuclear receptors that exists in intestinal immune cells; the composition and activation of this network can be directly altered by dietary compounds, thereby influencing immune homeostasis.

The challenge that lies ahead is to identify the molecular and cellular mechanisms through which particular dietary products have direct effects on our health. An in-depth understanding of the principles and mechanisms underlying the influence of food on the immune system will be pivotal not only for the development of therapeutic approaches but also for disease prevention.

1. Eder, W., Ege, M. J. & von Mutius, E. The asthma epidemic. *N. Engl. J. Med.* **355**, 2226–2235 (2006).
2. Maslowski, K. M. & Mackay, C. R. Diet, gut microbiota and immune responses. *Nature Immunol.* **12**, 5–9 (2011).
This article gives an insight into the diet–microbiota model as the basis for the greater incidence of asthma and autoimmunity in developed countries.
3. Bach, J. F. The effect of infections on susceptibility to autoimmune and allergic diseases. *N. Engl. J. Med.* **347**, 911–920 (2002).
4. Devereux, G. The increase in the prevalence of asthma and allergy: food for thought. *Nature Rev. Immunol.* **6**, 869–874 (2006).
5. Hotamisligil, G. S. Inflammation and metabolic disorders. *Nature* **444**, 860–867 (2006).
6. Fukuda, S. *et al.* Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature* **469**, 543–547 (2011).
7. Macia, L. *et al.* Microbial influences on epithelial integrity and immune function as a basis for inflammatory diseases. *Immunol. Rev.* **245**, 164–176 (2012).
8. Glass, C. K. & Ogawa, S. Combinatorial roles of nuclear receptors in inflammation and immunity. *Nature Rev. Immunol.* **6**, 44–55 (2006).
9. Zygmunt, B. & Veldhoen, M. T helper cell differentiation: more than just cytokines. *Adv. Immunol.* **109**, 159–196 (2011).
10. Josefowicz, S. Z. *et al.* Extrathymically generated regulatory T cells control mucosal T_H2 inflammation. *Nature* **482**, 395–399 (2012).
11. Bettelli, E. *et al.* Reciprocal developmental pathways for the generation of pathogenic effector T_H17 and regulatory T cells. *Nature* **441**, 235–238 (2006).
12. Chen, W. *et al.* Conversion of peripheral $CD4^+CD25^-$ naive T cells to $CD4^+CD25^+$ regulatory T cells by TGF-β induction of transcription factor Foxp3. *J. Exp. Med.* **198**, 1875–1886 (2003).
13. Veldhoen, M., Hocking, R. J., Atkins, C. J., Locksley, R. M. & Stockinger, B. TGFβ in the context of an inflammatory cytokine milieu supports *de novo* differentiation of IL-17-producing T cells. *Immunity* **24**, 179–189 (2006).
14. Lochner, M. *et al. In vivo* equilibrium of proinflammatory $IL\text{-}17^+$ and regulatory $IL\text{-}10^+$ $Foxp3^+$ $ROR\gamma t^+$ T cells. *J. Exp. Med.* **205**, 1381–1393 (2008).
15. Zhou, L. *et al.* TGF-β-induced Foxp3 inhibits T_H17 cell differentiation by antagonizing RORγt function. *Nature* **453**, 236–240 (2008).
16. Ivanov, I. I. *et al.* The orphan nuclear receptor RORγt directs the differentiation program of proinflammatory $IL\text{-}17^+$ T helper cells. *Cell* **126**, 1121–1133 (2006).
17. Esplugues, E. *et al.* Control of T_H17 cells occurs in the small intestine. *Nature* **475**, 514–518 (2011).
18. O'Connor, W. Jr., Zenewicz, L. A. & Flavell, R. A. The dual nature of T_H17 cells: shifting the focus to function. *Nature Immunol.* **11**, 471–476 (2010).
19. Zhou, X. *et al.* Instability of the transcription factor Foxp3 leads to the generation of pathogenic memory T cells *in vivo*. *Nature Immunol.* **10**, 1000–1007 (2009).
20. Ogawa, A., Andoh, A., Araki, Y., Bamba, T. & Fujiyama, Y. Neutralization of interleukin-17 aggravates dextran sulfate sodium-induced colitis in mice. *Clin. Immunol.* **110**, 55–62 (2004).
21. Monticelli, L. A., Sonnenberg, G. F. & Artis, D. Innate lymphoid cells: critical regulators of allergic inflammation and tissue repair in the lung. *Curr. Opin. Immunol.* **24**, 284–289 (2012).
22. Eberl, G. & Littman, D. R. The role of the nuclear hormone receptor RORγt in the development of lymph nodes and Peyer's patches. *Immunol. Rev.* **195**, 81–90 (2003).
23. Zenewicz, L. A. *et al.* Innate and adaptive interleukin-22 protects mice from inflammatory bowel disease. *Immunity* **29**, 947–957 (2008).
24. Veldhoen, M. *et al.* The aryl hydrocarbon receptor links T_H17-cell-mediated autoimmunity to environmental toxins. *Nature* **453**, 106–109 (2008).
25. Yang, X. O. *et al.* T helper 17 lineage differentiation is programmed by orphan nuclear receptors RORα and RORγ. *Immunity* **28**, 29–39 (2008).
26. Deeb, K. K., Trump, D. L. & Johnson, C. S. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. *Nature Rev. Cancer* **7**, 684–700 (2007).
27. Mora, J. R., Iwata, M. & von Andrian, U. H. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nature Rev. Immunol.* **8**, 685–698 (2008).
28. Coombes, J. L. *et al.* A functionally specialized population of mucosal $CD103^+$ DCs induces $Foxp3^+$ regulatory T cells via a TGF-β and retinoic acid-dependent mechanism. *J. Exp. Med.* **204**, 1757–1764 (2007).
29. Hadis, U. *et al.* Intestinal tolerance requires gut homing and expansion of $FoxP3^+$ regulatory T cells in the lamina propria. *Immunity* **34**, 237–246 (2011).
30. Sun, C. M. *et al.* Small intestine lamina propria dendritic cells promote *de novo* generation of Foxp3 T reg cells via retinoic acid. *J. Exp. Med.* **204**, 1775–1785 (2007).
31. Iwata, M. *et al.* Retinoic acid imprints gut-homing specificity on T cells. *Immunity* **21**, 527–538 (2004).
32. Elias, K. M. *et al.* Retinoic acid inhibits Th17 polarization and enhances FoxP3 expression through a Stat-3/Stat-5 independent signaling pathway. *Blood* **111**, 1013–1020 (2008).
33. Sigmundsdottir, H. *et al.* DCs metabolize sunlight-induced vitamin D3 to 'program' T cell attraction to the epidermal chemokine CCL27. *Nature Immunol.* **8**, 285–293 (2007).
34. Mucida, D. *et al.* Reciprocal T_H17 and regulatory T cell differentiation mediated by retinoic acid. *Science* **317**, 256–260 (2007).
This is the first description of retinoic acid as a modulator of T_H17 cell and T_{Reg} cell development.
35. Takahashi, H. *et al.* TGF-β and retinoic acid induce the microRNA miR-10a, which targets Bcl-6 and constrains the plasticity of helper T cells. *Nature Immunol.* **13**, 587–595 (2012).
36. Benson, M. J., Pino-Lagos, K., Rosemblatt, M. & Noelle, R. J. All-*trans* retinoic acid mediates enhanced T reg cell growth, differentiation, and gut homing in the face of high levels of co-stimulation. *J. Exp. Med.* **204**, 1765–1774 (2007).
37. Hill, J. A. *et al.* Retinoic acid enhances Foxp3 induction indirectly by relieving inhibition from $CD4^+CD44^{hi}$ cells. *Immunity* **29**, 758–770 (2008).
38. Meseguer, S., Mudduluru, G., Escamilla, J. M., Allgayer, H. & Barettino, D. Micro-RNAs-10a and -10b contribute to retinoic acid-induced differentiation of neuroblastoma cells and target the alternative splicing regulatory factor SFRS1 (SF2/ASF). *J. Biol. Chem.* **286**, 4150–4164 (2010).
39. DePaolo, R. W. *et al.* Co-adjuvant effects of retinoic acid and IL-15 induce inflammatory immunity to dietary antigens. *Nature* **471**, 220–224 (2011).
40. Hall, J. A. *et al.* Essential role for retinoic acid in the promotion of $CD4^+$ T cell effector responses via retinoic acid receptor α. *Immunity* **34**, 435–447 (2011).
41. Nurieva, R. I. *et al.* Bcl6 mediates the development of T follicular helper cells. *Science* **325**, 1001–1005 (2009).
42. Hirota, K. *et al.* Fate mapping of IL-17-producing T cells in inflammatory responses. *Nature Immunol.* **12**, 255–263 (2011).
43. Xiao, S. *et al.* Retinoic acid increases $Foxp3^+$ regulatory T cells and inhibits development of Th17 cells by enhancing TGF-β-driven Smad3 signaling and inhibiting IL-6 and IL-23 receptor expression. *J. Immunol.* **181**, 2277–2284 (2008).
This study showed the molecular mechanisms by which retinoic acid affects both T_{Reg} cell and T_H17 cell differentiation.
44. Kang, S. W. *et al.* 1,25-dihyroxyvitamin D3 promotes FOXP3 expression via binding to vitamin D response elements in its conserved noncoding sequence region. *J. Immunol.* **188**, 5276–5282 (2012).
45. Mora, J. R. *et al.* Selective imprinting of gut-homing T cells by Peyer's patch dendritic cells. *Nature* **424**, 88–93 (2003).
References 31 and 45 first identified a role for retinoic acid-producing DCs in promoting T cell homing to the intestine.
46. Johansson-Lindbom, B. *et al.* Functional specialization of gut $CD103^+$ dendritic cells in the regulation of tissue-selective T cell homing. *J. Exp. Med.* **202**, 1063–1073 (2005).
47. Mora, J. R. *et al.* Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells. *Science* **314**, 1157–1160 (2006).
48. Wang, N. S. *et al.* Divergent transcriptional programming of class-specific B cell memory by T-bet and RORα. *Nature Immunol.* **13**, 604–611 (2012).
49. Worm, M., Krah, J. M., Manz, R. A. & Henz, B. M. Retinoic acid inhibits $CD40^+$ interleukin-4-mediated IgE production *in vitro*. *Blood* **92**, 1713–1720 (1998).
50. Jeffery, L. E. *et al.* 1,25-dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. *J. Immunol.* **183**, 5458–5467 (2009).
51. von Essen, M. R. *et al.* Vitamin D controls T cell antigen receptor signaling and activation of human T cells. *Nature Immunol.* **11**, 344–349 (2010).
52. D'Ambrosio, D. *et al.* Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3. Involvement of NF-κB downregulation in transcriptional repression of the p40 gene. *J. Clin. Invest.* **101**, 252–262 (1998).
53. Penna, G. & Adorini, L. 1 α,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *J. Immunol.* **164**, 2405–2411 (2000).

54. Gorman, S. *et al.* Topically applied 1,25-dihydroxyvitamin D3 enhances the suppressive activity of $CD4^+CD25^+$ cells in the draining lymph nodes. *J. Immunol.* **179**, 6273–6283 (2007).
55. Chang, J. H., Cha, H. R., Lee, D. S., Seo, K. Y. & Kweon, M. N. 1,25-dihydroxyvitamin D3 inhibits the differentiation and migration of T_H17 cells to protect against experimental autoimmune encephalomyelitis. *PLoS ONE* **5**, e12925 (2010).
56. Hirota, K. *et al.* Preferential recruitment of CCR6-expressing Th17 cells to inflamed joints via CCL20 in rheumatoid arthritis and its animal model. *J. Exp. Med.* **204**, 2803–2812 (2007).
57. Reboldi, A. *et al.* C-C chemokine receptor 6-regulated entry of T_H17 cells into the CNS through the choroid plexus is required for the initiation of EAE. *Nature Immunol.* **10**, 514–523 (2009).
58. Bruce, D. & Cantorna, M. T. Intrinsic requirement for the vitamin D receptor in the development of $CD8\alpha\alpha$-expressing T cells. *J. Immunol.* **186**, 2819–2825 (2011).
59. Konkel, J. E. *et al.* Control of the development of $CD8\alpha\alpha^+$ intestinal intraepithelial lymphocytes by TGF-β. *Nature Immunol.* **12**, 312–319 (2011).
60. Quintana, F. J. *et al.* Control of T_{reg} and T_H17 cell differentiation by the aryl hydrocarbon receptor. *Nature* **453**, 65–71 (2008).
References 24 and 60 provide the first demonstration that AHR, through the sensing of external cues, has a role in T_H17 cell and T_{Reg} cell biology.
61. Kiss, E. A. *et al.* Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. *Science* **334**, 1561–1565 (2011).
62. Lee, J. S. *et al.* AHR drives the development of gut ILC22 cells and postnatal lymphoid tissues via pathways dependent on and independent of Notch. *Nature Immunol.* **13**, 144–151 (2011).
63. Qiu, J. *et al.* The aryl hydrocarbon receptor regulates gut immunity through modulation of innate lymphoid cells. *Immunity* **36**, 92–104 (2011).
64. Li, Y. *et al.* Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. *Cell* **147**, 629–640 (2011).
References 61 and 64 identified diet-derived AHR ligands as crucial factors in the development and maintenance of gut-associated lymphoid cells and tissues.
65. Wincent, E. *et al.* The suggested physiologic aryl hydrocarbon receptor activator and cytochrome P4501 substrate 6-formylindolo[3,2-b]carbazole is present in humans. *J. Biol. Chem.* **284**, 2690–2696 (2009).
66. Bjeldanes, L. F., Kim, J. Y., Grose, K. R., Bartholomew, J. C. & Bradfield, C. A. Aromatic hydrocarbon responsiveness-receptor agonists generated from indole-3-carbinol *in vitro* and *in vivo*: comparisons with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Proc. Natl Acad. Sci. USA* **88**, 9543–9547 (1991).
67. Knoop, K. A. & Newberry, R. D. Isolated lymphoid follicles are dynamic reservoirs for the induction of intestinal IgA. *Front. Immunol.* **3**, 84 (2012).
68. Shi, H. *et al.* TLR4 links innate immunity and fatty acid-induced insulin resistance. *J. Clin. Invest.* **116**, 3015–3025 (2006).
69. Solinas, G., Naugler, W., Galimi, F., Lee, M. S. & Karin, M. Saturated fatty acids inhibit induction of insulin gene transcription by JNK-mediated phosphorylation of insulin-receptor substrates. *Proc. Natl Acad. Sci. USA* **103**, 16454–16459 (2006).
70. Wang, J., Wu, X., Simonavicius, N., Tian, H. & Ling, L. Medium-chain fatty acids as ligands for orphan G protein-coupled receptor GPR84. *J. Biol. Chem.* **281**, 34457–34464 (2006).
71. Hirasawa, A. *et al.* Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nature Med.* **11**, 90–94 (2005).
This was the first study to demonstrate that the G protein-coupled receptor GPR120 functions as a receptor for unsaturated long-chain free fatty acids.
72. Oh, D. Y. *et al.* GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* **142**, 687–698 (2010).
73. Itoh, Y. *et al.* Free fatty acids regulate insulin secretion from pancreatic β cells through GPR40. *Nature* **422**, 173–176 (2003).
74. Liou, A. P. *et al.* The G-protein-coupled receptor GPR40 directly mediates long-chain fatty acid-induced secretion of cholecystokinin. *Gastroenterology* **140**, 903–912 (2011).
75. Martin, B., Hirota, K., Cua, D. J., Stockinger, B. & Veldhoen, M. Interleukin-17-producing γδ T cells selectively expand in response to pathogen products and environmental signals. *Immunity* **31**, 321–330 (2009).
76. Nyirenda, M. H. *et al.* TLR2 stimulation drives human naive and effector regulatory T cells into a Th17-like phenotype with reduced suppressive function. *J. Immunol.* **187**, 2278–2290 (2011).
77. Oberg, H. H. *et al.* Differential but direct abolishment of human regulatory T cell suppressive capacity by various TLR2 ligands. *J. Immunol.* **184**, 4733–4740 (2010).
78. Reynolds, J. M. *et al.* Toll-like receptor 2 signaling in $CD4^+$ T lymphocytes promotes T helper 17 responses and regulates the pathogenesis of autoimmune disease. *Immunity* **32**, 692–702 (2010).
79. Sutmuller, R. P. *et al.* Toll-like receptor 2 controls expansion and function of regulatory T cells. *J. Clin. Invest.* **116**, 485–494 (2006).
80. Forman, B. M., Umesono, K., Chen, J. & Evans, R. M. Unique response pathways are established by allosteric interactions among nuclear hormone receptors. *Cell* **81**, 541–550 (1995).
81. Kliewer, S. A. *et al.* A prostaglandin J2 metabolite binds peroxisome proliferator-activated receptor γ and promotes adipocyte differentiation. *Cell* **83**, 813–819 (1995).
References 80 and 81 first showed that fatty acid metabolites interact with PPARγ.
82. Clark, R. B. *et al.* The nuclear receptor PPARγ and immunoregulation: PPARγ mediates inhibition of helper T cell responses. *J. Immunol.* **164**, 1364–1371 (2000).
83. Dunn, S. E. *et al.* Peroxisome proliferator-activated receptor δ limits the expansion of pathogenic Th cells during central nervous system autoimmunity. *J. Exp. Med.* **207**, 1599–1608 (2010).
84. Faveeuw, C. *et al.* Peroxisome proliferator-activated receptor γ activators inhibit interleukin-12 production in murine dendritic cells. *FEBS Lett.* **486**, 261–266 (2000).
85. Li, B., Reynolds, J. M., Stout, R. D., Bernlohr, D. A. & Suttles, J. Regulation of Th17 differentiation by epidermal fatty acid-binding protein. *J. Immunol.* **182**, 7625–7633 (2009).
86. Wang, L. H. *et al.* Transcriptional inactivation of STAT3 by PPARγ suppresses IL-6-responsive multiple myeloma cells. *Immunity* **20**, 205–218 (2004).
87. Klotz, L. *et al.* The nuclear receptor PPARγ selectively inhibits Th17 differentiation in a T cell-intrinsic fashion and suppresses CNS autoimmunity. *J. Exp. Med.* **206**, 2079–2089 (2009).
88. Feuerer, M. *et al.* Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nature Med.* **15**, 930–939 (2009).
89. Cipolletta, D. *et al.* PPAR-γ is a major driver of the accumulation and phenotype of adipose tissue T_{reg} cells. *Nature* **486**, 549–553 (2012).
90. Janowski, B. A. *et al.* Structural requirements of ligands for the oxysterol liver X receptors LXRα and LXRβ. *Proc. Natl Acad. Sci. USA* **96**, 266–271 (1999).
91. Makishima, M. *et al.* Identification of a nuclear receptor for bile acids. *Science* **284**, 1362–1365 (1999).
92. Vavassori, P., Mencarelli, A., Renga, B., Distrutti, E. & Fiorucci, S. The bile acid receptor FXR is a modulator of intestinal innate immunity. *J. Immunol.* **183**, 6251–6261 (2009).
93. Joseph, S. B., Castrillo, A., Laffitte, B. A., Mangelsdorf, D. J. & Tontonoz, P. Reciprocal regulation of inflammation and lipid metabolism by liver X receptors. *Nature Med.* **9**, 213–219 (2003).
94. A-Gonzalez, N. *et al.* Apoptotic cells promote their own clearance and immune tolerance through activation of the nuclear receptor LXR. *Immunity* **31**, 245–258 (2009).
95. Bensinger, S. J. *et al.* LXR signaling couples sterol metabolism to proliferation in the acquired immune response. *Cell* **134**, 97–111 (2008).
96. Cui, G. *et al.* Liver X receptor (LXR) mediates negative regulation of mouse and human Th17 differentiation. *J. Clin. Invest.* **121**, 658–670 (2011).
97. Kallen, J. A. *et al.* X-ray structure of the hRORα LBD at 1.63 A: structural and functional data that cholesterol or a cholesterol derivative is the natural ligand of RORα. *Structure* **10**, 1697–1707 (2002).
98. Boismenu, R. & Havran, W. L. Modulation of epithelial cell growth by intraepithelial γδ T cells. *Science* **266**, 1253–1255 (1994).
99. Ismail, A. S. *et al.* γδ intraepithelial lymphocytes are essential mediators of host–microbial homeostasis at the intestinal mucosal surface. *Proc. Natl Acad. Sci. USA* **108**, 8743–8748 (2011).
100. Amre, D. K. *et al.* Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. *Am. J. Gastroenterol.* **102**, 2016–2025 (2007).
101. Hou, J. K., Abraham, B. & El-Serag, H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. *Am. J. Gastroenterol.* **106**, 563–573 (2011).
102. Arnson, Y., Amital, H. & Shoenfeld, Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. *Ann. Rheum. Dis.* **66**, 1137–1142 (2007).
103. Lochner, M. *et al.* Microbiota-induced tertiary lymphoid tissues aggravate inflammatory disease in the absence of RORγt and LTi cells. *J. Exp. Med.* **208**, 125–134 (2011).
104. Sherlock, J. P. *et al.* IL-23 induces spondyloarthropathy by acting on ROR-γt+ $CD3^+CD4^-CD8^-$ entheseal resident T cells. *Nature Med.* **18**, 1069–1076 (2012).
105. Lawrence, T., Willoughby, D. A. & Gilroy, D. W. Anti-inflammatory lipid mediators and insights into the resolution of inflammation. *Nature Rev. Immunol.* **2**, 787–795 (2002).
106. Kliewer, S. A. *et al.* Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors α and γ. *Proc. Natl Acad. Sci. USA* **94**, 4318–4323 (1997).
107. Kumar, S. Molecular clocks: four decades of evolution. *Nature Rev. Genet.* **6**, 654–662 (2005).
108. Cordain, L. *et al.* Origins and evolution of the Western diet: health implications for the 21st century. *Am. J. Clin. Nutr.* **81**, 341–354 (2005).
This review explains how our nutritional characteristics have changed through time.
109. Willett, W. C. Balancing life-style and genomics research for disease prevention. *Science* **296**, 695–698 (2002).
110. Cerf-Bensussan, N. & Gaboriau-Routhiau, V. The immune system and the gut microbiota: friends or foes? *Nature Rev. Immunol.* **10**, 735–744 (2010).
111. Hooper, L. V. & Macpherson, A. J. Immune adaptations that maintain homeostasis with the intestinal microbiota. *Nature Rev. Immunol.* **10**, 159–169 (2010).
112. McDole, J. R. *et al.* Goblet cells deliver luminal antigen to $CD103^+$ dendritic cells in the small intestine. *Nature* **483**, 345–349 (2012).
113. Cherrier, M. & Eberl, G. The development of LTi cells. *Curr. Opin. Immunol.* **24**, 178–183 (2012).
114. Atarashi, K. *et al.* Induction of colonic regulatory T cells by indigenous *Clostridium* species. *Science* **331**, 337–341 (2011).
115. Gaboriau-Routhiau, V. *et al.* The key role of segmented filamentous bacteria in the coordinated maturation of gut helper T cell responses. *Immunity* **31**, 677–689 (2009).
116. Veldhoen, M., Hocking, R. J., Flavell, R. A. & Stockinger, B. Signals mediated by transforming growth factor-β initiate autoimmune encephalomyelitis, but chronic inflammation is needed to sustain disease. *Nature Immunol.* **7**, 1151–1156 (2006).
117. Yu, D. *et al.* The transcriptional repressor Bcl-6 directs T follicular helper cell lineage commitment. *Immunity* **31**, 457–468 (2009).
118. Vonarbourg, C. *et al.* Regulated expression of nuclear receptor RORγt confers distinct functional fates to NK cell receptor-expressing RORγt+ innate lymphocytes. *Immunity* **33**, 736–751 (2010).
119. Sawa, S. *et al.* Lineage relationship analysis of RORγt+ innate lymphoid cells. *Science* **330**, 665–669 (2010).
120. Wong, S. H. *et al.* Transcription factor RORα is critical for nuocyte development. *Nature Immunol.* **13**, 229–236 (2012).
121. Eberl, G. *et al.* An essential function for the nuclear receptor RORγt in the generation of fetal lymphoid tissue inducer cells. *Nature Immunol.* **5**, 64–73 (2004).
122. Sonnenberg, G. F., Fouser, L. A. & Artis, D. Border patrol: regulation of immunity, inflammation and tissue homeostasis at barrier surfaces by IL-22. *Nature Immunol.* **12**, 383–390 (2011).

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Competing interests statement
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FURTHER INFORMATION
Marc Veldhoen's homepage:
http://www.babraham.ac.uk/lymphocyte/veldhoen.html

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