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REVIEW



## Role of dietary lipids in food allergy

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### ABSTRACT

The prevalence of food allergy is raising in industrialized countries, but the mechanisms behind this increased incidence are not fully understood. Environmental factors are believed to play a role in allergic diseases, including lifestyle influences, such as diet. There is a close relationship between allergens and lipids, with many allergenic proteins having the ability to bind lipids. Dietary lipids exert pro-inflammatory or anti-inflammatory functions on cells of the innate immunity and influence antigen presentation to cells of the adaptive immunity. In addition to modifying the immunostimulating properties of proteins, lipids also alter their digestibility and intestinal absorption, changing allergen bioavailability. This study provides an overview of the role of dietary lipids in food allergy, taking into account epidemiological information, as well as results of mechanistic investigations using *in vivo*, *ex vivo* and *in vitro* models. The emerging link among high-fat diets, obesity, and allergy is also discussed.

### KEYWORDS

Polyunsaturated fatty acids; phospholipids; glycerolipids; immune response; inflammation; obesity

### Introduction

Even if the true prevalence of food allergies is very difficult to estimate, a growing body of evidence indicates that they are rapidly increasing, particularly in industrialized countries (Sicherer and Sampson 2018). Undoubtedly, genetic predisposition is a crucial factor in food allergy development, although, by itself, it cannot explain this exponential rise. In fact, in addition to the lack of early exposure to infectious agents, that is the basis for the hygiene hypothesis, other environmental factors are believed to play a role in allergic diseases (Julia, Macia, and Dombrowicz 2015; Benedé et al. 2017). Among them, stand lifestyle influences, such as diet, physical inactivity and obesity, which may be behind the cases of allergy appearing in adulthood (Kamdar et al. 2015).

Lipids are extrinsic factors that modulate the allergenic properties of proteins (Bublin, Eiwegger, and Breiteneder 2014; Gómez del Moral and Martínez-Naves 2017). They change the susceptibility of allergens to gastroduodenal digestion and facilitate their intestinal transport, either by providing lipid-mediated uptake or by disrupting the intestinal epithelial barrier (Mine and Zhang 2003; Wang et al. 2009; Angelina et al. 2016). Furthermore, lipids behave as adjuvants activating innate and adaptive immune responses (Traidl-Hoffmann et al. 2005). As a result, lipids might promote tolerogenic responses, but also favor Th2 polarization, and thus, influence the sensitization process (van Wijk et al. 2005; Shindo et al. 2012; Abós-Gracia et al. 2013; Angelina et al. 2016). Additionally, in allergic subjects, fat can boost anaphylactic reactions following allergen exposure (Grimshaw et al. 2003).

This study provides an overview of the role of dietary lipids in food allergy, taking into account epidemiological information, as well as results of mechanistic investigations in *in vivo*, *ex vivo* and *in vitro* models aimed to discern their involvement in cellular and molecular events that take part in sensitization and anaphylaxis to food proteins.

### Polyunsaturated fatty acids, inflammation and allergy prevention

Among the dietary components that may play a role in the alarming increase in the prevalence of food allergies stands the over-intake of *n*-6 polyunsaturated fatty acids (PUFAs) with respect to *n*-3 PUFAs by the population of Western countries along the second half of the twentieth century, mainly due to the incorporation in the diet of vegetable oils and margarines instead of animal-based fats (Simopoulos 2016). The main sources of linoleic acid (LA, 18:2*n*-6), the simplest *n*-6 PUFA, are corn, sunflower and soybean oils, while the *n*-3 PUFA  $\alpha$ -linolenic acid (ALA, 18:3*n*-3) is found in green plants, soybean, rapeseed and flaxseed oils and walnuts (Russo 2009). Downstream metabolites of *n*-6 PUFAs are generally described as pro-inflammatory, while those derived from *n*-3 PUFAs have the potential to resolve inflammation and to improve allergic symptoms (Calder 2006; Wendell, Baffi, and Holguin 2014). Accumulation of a high proportion of arachidonic acid (AA, 20:4*n*-6), synthesized from its main dietary precursor LA or ingested as part of eggs and meat products, in cell membrane phospholipids (PLs) results in an increased synthesis of eicosanoids, essentially leukotrienes and prostanoids (prostaglandins and

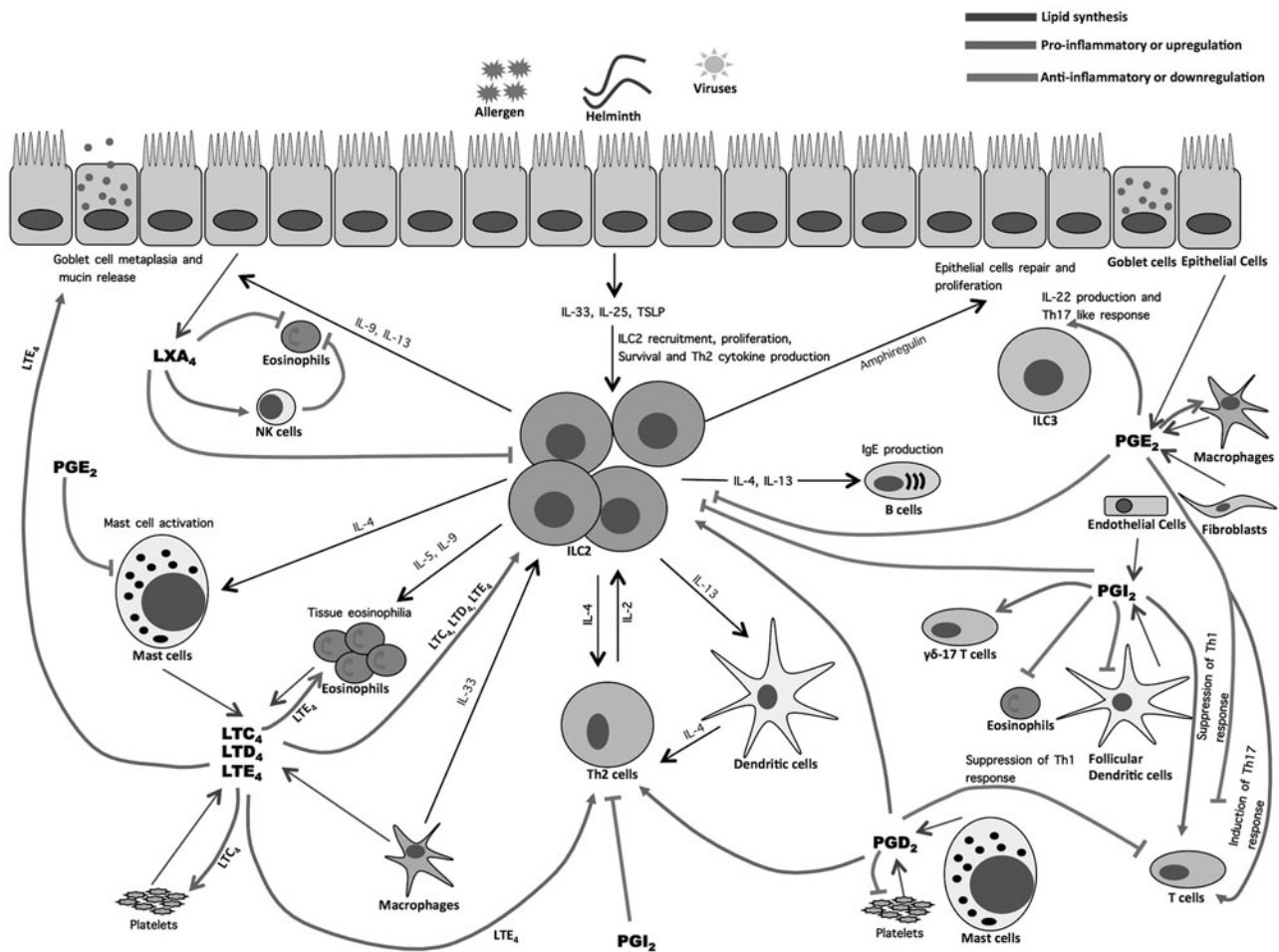


**Figure 1.** Production and effects of lipid mediators on type 2 inflammation. Leukotrienes (LT), generated by mast cells, eosinophils, macrophages, and platelets activate group 2 innate lymphoid cells (ILC2s) and Th2 cells. Mast cells and platelets are prime producers of prostaglandin (PG) D<sub>2</sub>, which also activates ILC2s and Th2 cells and suppresses the Th1 response. PGE<sub>2</sub>, a product from epithelial cells, macrophages, and fibroblasts suppresses activation of ILC2s, but also enhances IL-33 synthesis by macrophages and potentiates group 3 innate lymphoid cells (ILC3) and Th17 cells. PGE<sub>2</sub> also blocks mast cell activation. PGI<sub>2</sub> has mostly anti-inflammatory roles on ILC2s, Th2 cells, eosinophils, and follicular DCs. Lipoxin (LX) A<sub>4</sub> suppresses PGD<sub>2</sub>-derived activation of ILC2s and promotes eosinophil apoptosis by natural killer (NK) cells. Reprinted from Samuchiwal and Boyce (2018), with permission from Elsevier.

thromboxanes). As shown in Figure 1, these, among other lipids, such as platelet activating factor and sphingolipids, act as clinically relevant mediators of allergic diseases because of their role in inflammatory conditions, communication between cells of the innate and adaptive immune system, and control of type 2 responses through their cell signaling effects (Schauberger et al. 2016; Miles and Calder 2017; Samuchiwal and Boyce 2018). Conversely, *n*-3 PUFAs (mainly eicosapentaenoic acid, EPA, 20:5*n*-3, and docosapentaenoic acid, DPA, 22:5*n*-3) compete as substrates with AA, leading to less potent inflammatory mediators (Calder 2015), or even to alternative mediators with anti-inflammatory effects, named resolvins, protectins and maresins (Levy et al. 2007; Haworth et al. 2008). *n*-3 PUFAs can also modulate the expression of genes pertinent to inflammation and lipid metabolism, suppressing pro-inflammatory genes and increasing genes critical for lipid peroxidation, energy utilization, and lipid homeostasis through activation of transcription factors, but also through changes in epigenetic markers, such as DNA methylation in sites within pathways linked to inflammation (Deckelbaum, Worgall, and Seo 2006; Hussey, Lindley, and Mastana 2017).

Populations with diets rich in long chain *n*-3 PUFAs, found in oily fishes, such as tuna, salmon or sardines, benefit from a low incidence of inflammatory processes, such as rheumatoid arthritis (Tedeschi et al. 2018). Furthermore, a considerable number of observational studies have shown beneficial associations between maternal fish intake during pregnancy, percentage of EPA in breast milk and lower risk of allergic disease in children, although the evidence from epidemiological studies investigating the effects of fish intake during infancy and childhood on atopic outcomes in those infants and children is not sufficiently consistent (Kremmyda et al. 2011). Similarly, meta-studies on the effects of fish oil supplementation during pregnancy and lactation, infancy or childhood highlight conflicting results regarding the therapeutic or preventive clinical effects of *n*-3 PUFA in childhood atopy, even if early fish or fish oil provision is associated with immunologic changes in cord blood or peripheral blood, namely decreased Th2 cytokine production, with less clear effects on the Th1 response (Krauss-Etschmann et al. 2008; Furuhejelm et al. 2011; Klemens, Berman, and Mozurkewich 2011; Kremmyda et al. 2011; Noakes et al. 2012; D'Vaz et al. 2012; Lee et al.

2013; D'Auria et al. 2014). The latest meta-analyses to date on the potential of PUFAs, administered to infants, either as supplements in infant formula or given to the pregnant or breastfeeding mother, to prevent the development of allergy revealed no evidence on infant or childhood asthma, dermatitis or food allergy (Gunaratne, Makrides, and Collins 2015; Best et al. 2016a; Schindler, Sinn, and Osborn 2016; Zhang et al. 2017). Overall, the quality of evidence is low, partly because of the use of variable sources of PUFAs, different intakes and *n*-3 to *n*-6 ratios, and inconsistent durations of supplementation, stressing the need for further high quality studies particularly aimed to examine clinical outcomes in the offspring in later life (Barman 2016; Schindler et al. 2016). In any case, studies available so far on the long term prevention potential of prenatal fish oil supplementation on allergic respiratory diseases do not provide conclusive results (Best et al. 2016b; Hansen et al. 2017).

Interestingly, the potential health benefits of *n*-3 PUFAs are not exclusively associated with fish or fish oil consumption. Children growing up in farms are at a much lower risk of suffering allergy than those from non-farming environments. While the protective effect against allergy exerted by living in a farm seems not to be linked *per se* to serum fatty acid (FA) composition at 4 months of age (Jonsson et al. 2016), continuous consumption of unprocessed farm milk was found to protect from childhood onset asthma, by virtue of its higher *n*-3 PUFA content, lower *n*-6 to *n*-3 ratio, and absence of heat treatment (Brick et al. 2016). In this respect, it should be noted that diagnosed cow's milk allergy results in the elimination of milk from the diet, further changing serum FA profiles (Lumia et al. 2014). In fact, serum FA composition is not only the result of diet but also of metabolic processes, in turn tuned by genetic factors, the allergenic status itself and even the type of allergic manifestation (Lattka et al. 2012; Barman et al. 2014, 2015). In general terms, whereas evidence for the effect of *n*-3 PUFAs arising from human studies is weak due to the concurrence of complex environmental factors, the use of *in vitro* or *ex vivo* cell cultures and animal models has helped to clarify their mode of action.

### Effects of polyunsaturated fatty acids on cells of the innate and adaptive immune system

It has been demonstrated that *n*-3 PUFAs exert immunomodulatory actions on cells of the innate immune system (macrophages and dendritic cells, DCs). On the murine macrophage RAW 264.7 cell line, considered one of the most suitable *in vitro* models for inflammation-related investigations, *n*-3 PUFAs significantly reduce TNF- $\alpha$  and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) production in response to lipopolysaccharide (LPS) stimulation (Babcock et al. 2002; Novak et al. 2003). EPA and DHA also inhibit LPS-induced DC maturation *in vitro*, leading to reduced expression levels of MHC class II molecules and of the co-stimulatory factors CD40, CD80 and CD86, and hindering the production of IL-12, IL-23, IL-27, TNF- $\alpha$  and IL-6, cytokines that promote pro-inflammatory Th1 and Th17 responses, with somehow

contradictory results regarding the secretion of IL-10 (Weatherill et al. 2005; Zeyda et al. 2005; Wang et al. 2007; Zapata-González et al. 2008; Kong et al. 2010; Draper et al. 2011). Modulation of the DC maturation status influences subsequent T cell activation, reducing T cell proliferation and production of IL-2 and IFN- $\gamma$  (Weatherill et al. 2005; Zeyda et al. 2005; Wang et al. 2007; Zapata-González et al. 2008). *Ex vivo* studies with splenic DCs from *n*-3 PUFA-fed mice also revealed suppressed DC functions and, although no subsequent change in IL-2 or IFN- $\gamma$  production from CD4<sup>+</sup> T lymphocytes was detected, there was a measurably decrease in CD69 (a marker of T cell activation) surface expression (Teague et al. 2013). One study, however, reported that DCs stimulated with DHA (but also with AA) display an activated phenotype, but yet seemed to result in low T cell responses (Carlsson et al. 2015).

These actions of *n*-3 PUFAs are mediated, at least in part, by the inactivation of the nuclear factor  $\kappa$ B (NF- $\kappa$ B) pathway, which controls the expression of pro-inflammatory genes involved in the production of cytokines, chemokines, and adhesion molecules (Calder 2015). A variety of integral membrane receptors, such as Toll-like receptors (TLR) switched by microbial products like LPS, or receptors which respond to pro-inflammatory cytokines derived from tissue injury, trigger the NF- $\kappa$ B pathway. These receptors use similar signal transduction mechanisms, which include phosphorylation of mitogen-activated protein kinases (MAPKs) or activation of IRAK1, to upregulate NF- $\kappa$ B (Lawrence 2009). DHA appears more effective than EPA in counteracting LPS-induced NF- $\kappa$ B activation and production of pro-inflammatory agents (Weldon et al. 2007).

In addition to infectious agents, and unlike unsaturated FA, saturated FA, such as lauric acid, activate TLR4, the LPS receptor, and this induces NF- $\kappa$ B activation, leading to the expression of inducible cyclooxygenase (COX-2, which catalyzes the conversion of AA to prostaglandins) and other inflammatory markers in macrophages and DCs (Lee et al. 2003; Weatherill et al. 2005). Conversely, DHA inhibits COX-2 expression induced by saturated FA or LPS, although it fails to inhibit COX-2 expression induced by activation of signaling components downstream of TLR4 (Lee et al. 2001). Furthermore, DHA also suppresses NF- $\kappa$ B activation and COX-2 expression induced by agonists for TLR2, 3, 5 and 9 in the RAW 264.7 cell line, which suggests that modulation of TLRs by different types of FA, in turn controlled by the type of dietary fat consumed, constitutes the means by which they regulate genes implicated in inflammatory processes (Lee et al. 2004). The molecular mechanism through which dietary saturated FA and *n*-3 PUFAs reciprocally modulate TLR4 involves dimerization and recruitment of the receptor into lipid rafts in a reactive oxygen species (ROS)-dependent manner (Wong et al. 2009). Lipid rafts are sphingolipid/cholesterol-rich specialized microdomains in the plasma membrane, which exist in a liquid-ordered phase and favor the propagation of cell signal transduction events (Balamuth et al. 2001). It is hypothesized that *n*-3 PUFAs alter the saturated FA-rich PL composition of lipid rafts, exchanging the highly ordered

structure for a more flexible one and inhibiting downstream signaling pathways (Wong et al. 2009). Upon feeding mice with a diet enriched in *n*-3 PUFAs, the cholesterol content of lipid rafts in colonocytes is reduced by 46% compared to mice fed a diet enriched in *n*-6 PUFAs (Ma et al. 2004).

PUFAs are also activators of the peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), which antagonizes the inflammatory actions of NF- $\kappa$ B in macrophages and DCs. PPAR $\gamma$  binds both *n*-3 and *n*-6 PUFAs with equal affinity and lacks FA class specificity (Switzer et al. 2004). Whether the anti-inflammatory action of EPA and DHA on DCs and macrophages is dependent on PPAR $\gamma$  is controversial, with studies reporting either blocking (Zapata-González et al. 2008) or no effect of specific PPAR $\gamma$  inhibitors on their function (Draper et al. 2011; Zhang and Fritsche 2004).

The ability of PUFAs to restrain innate immune responses in antigen presenting cells (APCs), such as DCs, links to adaptive immune responses. Moreover, reduced signal transduction through the T cell receptor (TCR) and the CD28 co-stimulatory receptor (which is engaged by ligands CD80 and CD86 on APCs and sustains productive antigen-specific responses and T cell survival) is known to be a key contributor to the diminished CD4<sup>+</sup> T cell proliferation and cytokine production in *n*-3 PUFA fed mice (Arrington et al. 2001a, Brix et al. 2010). It was hypothesized that this effect could be mediated by the regulatory cytokine IL-10, since IL-10 inhibits the initial step of CD28 signaling, but the use of IL-10 gene knock-out mice revealed that IL-10 is not involved in the suppressive effect of PUFAs on T cell functions (Ly et al. 2005). Ly et al. (2006) found that dietary *n*-3 PUFAs do not change CD28 expression in resting CD4<sup>+</sup> T cells, but EPA upregulates cytotoxic T lymphocyte-associated protein 4 (CTLA-4) co-receptor expression, shifting the balance between these two signals in favor of CTLA-4 and resulting in reduced T cell activation and proliferation. CTLA-4 is similar to CD28 in sequence and binds the same ligands, but delivers an inhibitory signal to the activated T cell. Nevertheless, later work by Brix et al. (2010) did not support an active involvement of CTLA-4, but rather proposed that the incorporation of *n*-3 PUFAs into lipid rafts causes reduced signal transduction through TCR/CD28 in response to DC signals, that further affects the modulation of other co-stimulatory molecules such as inducible T cell co-stimulator (ICOS) and CTLA-4. These authors demonstrated that, while T cell responsiveness is reduced in *n*-3 PUFA-rich T cells, these still can be activated depending on the strength of the DC signal, although they require a higher threshold of stimulation. Interestingly, the membrane *n*-6 to *n*-3 PUFA ratio affects the activation of T cells, as cells with lower ratios are slower to respond to CD80/CD86 signaling (Brix et al. 2010). Furthermore, studies by Ly et al. (2005, 2006) evidenced that EPA and DHA modify T cell responses through different mechanisms, probably linked to a differential remodeling of membrane raft lipid composition and stability that eventually modulates signal-transducing proteins that associate to the rafts upon T cell activation (Fan et al. 2003). Although controversial, it is thought that DHA, in particular, due to its high degree of unsaturation,

is sterically incompatible with cholesterol and this enhances lipid raft disruption (Wassall and Stillwell 2008).

An alternative to supplementation with exogenous PUFAs is provided by fat-1 transgenic mice, which express FA *n*-3 desaturase and produce endogenous *n*-3 PUFAs from *n*-6 PUFAs (Kang et al. 2004). The advantage of this model lies in that mice have constitutively higher tissue levels of *n*-3 PUFAs and decreased *n*-6 to *n*-3 ratios without a corresponding change in the total level of FAs. Using the fat-1 mouse model, it was demonstrated that *n*-3 PUFAs influence the formation of lipid rafts in CD4<sup>+</sup> T cells, in turn changing membrane translocation and activation status of key signaling molecules, and also affecting APC-T cell interactions and CD4<sup>+</sup> T cell activation, proliferation, and differentiation (Kim et al. 2008; Yog et al. 2010; Jang et al. 2014).

The dietary effect of *n*-3 PUFAs on T cell proliferation *ex vivo* depends upon the propensity of the stimulus to bias T cells toward a putative Th1-like or Th2-like subset, specifically decreasing the viability of CD4<sup>+</sup> T cells treated with Th1-biasing stimuli (Arrington et al. 2001b). Thus, it has been shown that *n*-3 PUFAs inhibit the proliferation of purified antigen-specific CD4<sup>+</sup> T cells fully polarized to a Th1 phenotype, which points at the suppression of the IL-2 activation pathway (Denys, Hichami, and Khan 2005; Zhang et al. 2006). Activated Th2 cells differ from activated Th1 cells in raft organization, so that Th2 stimulation, unlike Th1 stimulation, fails to form a stable association of TCR components with raft domains (Balamuth et al. 2001). This may explain why *n*-3 PUFAs hinder proliferation and cytokine secretion by Th1 cells, which may account for their anti-inflammatory effects, but not by Th2 cells (Wallace et al. 2001; Switzer et al. 2004). However, there is no evidence for an enhanced susceptibility of CD4<sup>+</sup> T cells of fish oil-fed mice to be polarized toward a Th2 phenotype, at least in *ex vivo* cultures (Zhang et al. 2005; Petursdottir and Hardardottir 2009). *In vitro* culture with DHA of CD4<sup>+</sup> T cells subjected to TCR and CD28 stimulation has been reported to diminish IFN- $\gamma$  and to stimulate IL-4 secretions, in parallel with the downregulation of T-bet and upregulation of GATA-3 (the transcription factors which control, respectively, the differentiation of Th1 and Th2 cells) (Attakpa et al. 2009). Increased Th2 polarization and IL-4 secretion were also found to occur in the presence of APCs of mice fed fish oil (Petursdottir and Hardardottir 2009). Nevertheless, in most animal models of allergic asthma, using either dietary supplementation or Fat-1 mice, it was shown that increased levels of *n*-3 PUFAs do not enhance, but suppress, Th2 responses, leading to reduced eosinophil infiltration, mucus secretion, serum antibody levels and airway inflammation (Johansson et al. 2010; Bilal et al. 2011; Bargut et al. 2013; Jang et al. 2014); and similar effects were noted in mouse models of systemic sensitization (MacLean et al. 2013), atopic dermatitis (Sierra et al. 2006), and food allergy (van den Elsen et al. 2013a). In any case, the impact of PUFAs on the Th1 to Th2 balance may depend on whether PUFAs are endogenously converted or dietary provided and, in the latter case, on the ratio of *n*-6 to *n*-3

PUFAs in the diet, the weight relative intake of these FAs, the source of *n*-3 PUFAs (whether ALA, DHA or EPA), the immunological functionality of the subjects of the intervention, and the efficiency of their *n*-3 PUFA metabolism (Mizota et al. 2009).

There is less information on the influence of *n*-3 PUFAs on the polarization of CD4<sup>+</sup> T cells into other effector T cell subsets. Feeding mice fish oil, EPA, or DHA reduced spleen T cell activation and differentiation into pro-inflammatory Th17 cells in comparison with corn oil, as shown by reduced expression of IL-17 and ROR $\gamma$ t, the Th17 transcription factor, without affecting regulatory T (Treg) cell polarization (Monk et al. 2013). The suppressive effect of *n*-3 PUFAs was attributed to a reduced lipid raft-dependent responsiveness to IL-6, a cytokine that drives the generation of Th17 cells (Allen et al. 2014). On the other hand, in mice, dietary *n*-3 PUFAs were claimed to enhance hepatic Treg generation and to up-regulate TGF- $\beta$  and IL-10 expression (Lian et al. 2015). However, *in vitro* culture with DHA and dietary DHA decrease the *in vitro* inhibitory function of Treg cells (CD4<sup>+</sup> CD25<sup>+</sup>) on effector T cell (CD4<sup>+</sup> CD25<sup>-</sup>) proliferation, despite DHA treatment upregulates Foxp3, the Treg transcription factor, both at mRNA and protein levels, probably by interfering with critical downstream components of the Foxp3-driven suppressor pathway (Yessoufou et al. 2009). Still, low dietary *n*-6 to *n*-3 PUFA ratios decrease the Th1 to Treg balance and attenuate inflammation in mice with dextran sulphate-induced colitis (Huang et al. 2017a).

On human B cells, DHA specifically inhibits IgE class-switching and subsequent IgE production, without altering the numbers of IgA or IgG secreting cells, by down-regulating CD40- and IL-4-dependent downstream events, which include NF- $\kappa$ B and STAT6 signaling pathways, likely as a result of an altered lipid raft organization (Weise et al. 2011). Thus, in addition to the already mentioned ability of *n*-3 PUFAs to counteract NF- $\kappa$ B activation, DHA and EPA, unlike AA, also interfere with IL-4-mediated STAT6 phosphorylation, indispensable for IgE synthesis (Ahmed, Barrow, and Suphioglu 2016).

Similar to other membrane events, Fc $\epsilon$ RI signaling following IgE crosslinking requires precise interactions with secondary messengers that occur on lipid rafts, and thus, it is susceptible to be altered by *n*-3 PUFAs (Basiouni et al. 2012). According to Wang et al. (2015), *n*-3 PUFAs inhibit degranulation, lipid-derived mediator release and cytokine and chemokine production from mast cells activated through Fc $\epsilon$ RI. These effects were associated with a reduced Fc $\epsilon$ RI expression on lipid rafts, albeit not with changes in total or cell surface Fc $\epsilon$ RI expression, that subsequently inhibited Fc $\epsilon$ RI-mediated signal transduction. Conversely, other authors did not found any effects of *n*-3 PUFAs on Fc $\epsilon$ RI-mediated mast cell degranulation or even reported an increase (Nakano et al. 2005; Teshima et al. 2007; van den Elsen et al. 2013b). Nonetheless, the ability of dietary *n*-3 PUFAs to suppress IL-4 and IL-13 secretion by mast cells, associated with the inhibition of the generation of ROS or the interference with the transcriptional factor GATA-3, was

deemed responsible for their lowering effect on the severity of the allergic symptoms (Park et al. 2013; van den Elsen et al. 2013b).

Accordingly, decreased incidence of allergic signs in mice fed *n*-3 PUFA-rich diets, as compared to those fed control diets or *n*-6 PUFA-rich diets, was attributed to the hindrance of mast cell activation, as protection was not accompanied by differences in the levels of specific antibodies (Thang et al. 2013; Kunisawa et al. 2015). The offspring from mice fed diets high in *n*-3 PUFAs was reported to be protected from peanut anaphylaxis through enhanced anti-inflammatory IL-10 responses in colon and spleen associated with changes in gut microbiome (Myles et al. 2014). However, other mouse studies reported beneficial effects of fish oil both on the sensitization and effector phases of food allergy (de Matos et al. 2012), linked to the expansion of tolerogenic CD11b<sup>+</sup> CD103<sup>+</sup> DCs in the mesenteric lymph nodes and Foxp3<sup>+</sup> Treg cells in the intestine (van den Elsen et al. 2013a, 2013c). DHA prevented more effectively than EPA the production of specific IgE and IgG1 and the development of allergic responses (van den Elsen et al. 2014). Administration of DHA to rats during lactation and/or to the offspring in the weaning diet enhances its ability to acquire oral tolerance, yielding lower levels of specific IgE antibodies after systemic sensitization (Richard et al. 2016).

The positive association between *n*-6 PUFA derived eicosanoids and allergic sensitization and elicitation of adverse responses was deemed responsible for the lower allergenicity of high oleic peanuts, which have a 10 times higher ratio of oleic acid (OA; 18:1) to LA than normal peanuts (Huong Nguyen et al. 2003; Derbyshire 2014). *In vitro* studies showed that interaction with OA causes protein aggregation and reduces IgE binding to peanut and cashew allergens (Chung et al. 2015).

### Phospholipids and susceptibility to proteolytic degradation of allergens

PLs are an essential part of plant and animal cell membranes and thus, they are present in all living species from which foods are derived (Küllenberg et al. 2012). Dietary PLs are mainly glycerophospholipids, which usually contain a saturated FA in the stereospecific numbering (*sn*)-1 position and an unsaturated FA in the *sn*-2 position, such as LA in soybeans, OA in egg yolk, or EPA and DHA in fish products. The head group attached to the *sn*-3 phosphate can be choline or ethanolamine, the most abundant ones in foods, but also serine or inositol. Phosphatidylcholine (PC) is common in eggs, pig or chicken liver, soybeans and beef. The main function of PLs is to deliver their FAs for incorporation into cell membranes, with crucial effects on membrane composition, fluidity, and function, depending on the FAs and their *sn*-positions, and implications on allergic diseases as indicated above. In addition to being present in foods, PLs (mainly PC) are synthesized by the liver and transported in the bile to the proximal small intestine, where they contribute to the absorption of cholesterol and other lipids. PC is also secreted by the stomach mucosa and it

takes part in gastric digestion (Mackie and Macierzanka 2010; Lichtenberger 2013). Interaction of lipid binding proteins with dietary or endogenously secreted PLs exerts an important influence on their gastrointestinal stability and subsequent immunoreactivity (Mackie and Macierzanka 2010).

PC, as well as other PLs, have been shown to protect certain food allergens, such as  $\alpha$ -lactalbumin (Bos d 4) and lysozyme (Gal d 4), from gastric digestion *in vitro*. This effect is attributed to the establishment of polar, but mainly hydrophobic interactions, which allow insertion of proteins into PC vesicles, facilitated by the adoption of a partially unfolded molten globule structure at acidic pH that favors the exposure of amino acid side chains (Moreno, Mackie, and Mills 2005a; Jiménez-Sáiz et al. 2011). Recombinant allergens from celery (Api g 1), apple (Mal d 1), peach ( Pru p 1) and hazelnut (Cor a 1), homologous to Bet v 1 from birch pollen and rapidly digested by pepsin, change their conformation upon interaction with PC, although only Mal d 1 penetrates the vesicles, resisting digestion and retaining basophil degranulation capacity (Schimek et al. 2005; Sancho et al. 2011). PC vesicles also protect sunflower 2S albumins and nonspecific lipid transfer protein (nsLPT1) against gastric enzymes, albeit to different extents (Berez et al. 2013). Conversely, the digestibility of allergens, such as  $\beta$ -lactoglobulin (Bos d 5), the 2S albumin from Brazil nut (Ber e 1), grape nsLPT1, thaumatin-like protein from kiwi (Act d 2) or ovalbumin (Gal d 2), that maintain a high degree of structural stability at low pH, and are, consequently, very resistant to pepsin, does not change in the presence of PC (Moreno et al. 2005b; Vassilopoulou et al. 2006; Bublin et al. 2008; Mandalari et al. 2009; Martos et al. 2010). Binding of proteins to PC is pH-dependent, so that proteins that, by virtue of their negative charge, cannot penetrate the vesicles, but associate loosely to their outer surface through electrostatic interactions may become more sensitive to proteolytic degradation (Mogensen et al. 2007). The nature of the PL head group determines the association, because unlike switcherionic PLs, such as PC or phosphatidylethanolamine (PE), interaction with negatively charged PLs, such as phosphatidylserine or phosphatidylglycerol, is likely to be dominated by electrostatic effects. Thus, the 11S and 7S globulins from yellow mustard seeds and peanut (Sin a 2 and Ara h 1 respectively) bind phosphatidylglycerol vesicles, which protects them from gastric digestion, even though they do not interact with the physiological surfactant PC (Angelina et al. 2016). The structure and length of the FA chains also play a role. LysoPLs, which result from the duodenal hydrolysis of PLs at the *sn*-2 position by pancreatic phospholipase A<sub>2</sub>, exert different effects than the PLs they derive from by virtue of their higher solubility (Mandalari et al. 2009).

Noteworthy, the rate of gastric digestion of proteins adsorbed to oil droplets, such as those that stabilize emulsions, increases in parallel with the extent of protein unfolding at the interface (Mackie and Macierzanka 2010). Therefore, as part of an emulsion, the allergen  $\beta$ -lactoglobulin becomes more susceptible to pepsin digestion although, in the presence of PC in vesicular form, the protein is

displaced from the oil droplets to the solution, where it regains its native structure and resistance to the enzyme (Macierzanka et al. 2009).

In the duodenum, bile salts disrupt the vesicle structure and integrate PC, mainly lysoPC, into micelles with cholesterol and lipolysis products, to facilitate lipid digestion and fat absorption (Birru et al. 2014). *In vitro* digestion experiments have shown that mixed micelles, as well as soluble free bile salts, may induce protein denaturation and proteolysis depending on protein structure. For instance, it was found that they accelerate the hydrolysis of proteins such as myoglobin or ovalbumin, but protect  $\beta$ -lactoglobulin or grape LTP, which possess lipid binding pockets and/or secondary lipid binding sites where ligands might load, reducing polypeptide mobility and avoiding increased flexibility and susceptibility to proteolysis (Vassilopoulou et al. 2006; Gass et al. 2007; Mandalari et al. 2009; Martos et al. 2010; Maldonado-Valderrama et al. 2011).

When the PL backbone is the long chain amino alcohol sphingosin instead of glycerol, the PLs are termed sphingophospholipids (SPs), the most representative being sphingomyelin (sphingosine esterified to one FA and phosphocholine). Milk and eggs, which are the major foods responsible for food allergies in children, are the richest dietary sources of sphingomyelin. SPs from milk, among other lipids, but not those from eggs, are able to activate invariant natural killer T cells (iNKTs), as it will be explained below (Jyonouchi et al. 2011). Sphingosine 1-phosphate, a metabolite of sphingomyelin from the diet as well as from plasma membranes, determines trafficking of T cells from the blood or lymph to secondary lymphoid organs (Lamichhane, Kiyono, and Kunisawa 2013). In a murine model of food allergy-induced diarrhea, sphingosine 1-phosphate was shown to mediate infiltration of effector Th2 cells and mast cells in the colon, enhancing the allergic response (Kurashima et al. 2007).

## Glycerolipids and intestinal absorption

The absorptive intestinal epithelial cells of the small intestine assemble glycerolipids (GL), mainly triglycerides (TGs), PLs, cholesterol and proteins into lipoprotein particles termed chylomicrons, which transport absorbed lipids via the lymphatic vessels and systemic circulation to different tissues. Unlike dietary long-chain TGs (>12C-atoms; LCTs), abundant in allergenic foods such as peanuts or milk, short and medium-chain TGs (MCTs) do not require chylomicrons for absorption and, therefore, do not induce chylomicron formation. Wang et al. (2009) found that absorption and systemic dissemination of allergens is enhanced when they are administered to mice together with LCTs, whereas MCTs lead to less antigen absorption. Interestingly, while the LCT-induced formation of chylomicron particles promotes oral tolerance and protects mice against anaphylaxis, co-administration of MCTs induces a marked allergic sensitization (Li et al. 2013). A plausible explanation is that, unlike LCT-assisted absorption, that takes place through epithelial cells, MCTs promote delivery of antigens to

Peyer's patches, which favors subsequent transport to the draining mesenteric lymph nodes and increases their immunogenicity (Roth-Walter et al. 2008). Prolonged feeding of MCT-based diets stimulates the expression of epithelial Th2-biasing cytokines such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) and causes spontaneous sensitization (Li et al. 2013). In fact, co-administration of food proteins and MCTs can be used to induce food allergy in mice, characterized by high specific serum IgE and IgG1 levels, increased numbers of lamina propria Th2 cells, mast cells, and eosinophils, and hypothermia and mast cell degranulation following challenge (Khodoun et al. 2018).

### Activation of immune responses by the lipid fraction of foods

Many inhalant and food allergens have the ability to bind lipids (Bublin, Eiwegger, and Breiteneder 2014; Thomas 2014). Allergens homologous to Bet v 1, present in apples, hazelnuts and celery, cause pollen-related oral allergy syndrome, which represents the most frequent food allergy in European adults (Schimek et al. 2005). These proteins have hydrophobic regions which may function as ligand-binding sites and establish associations, not only with PLs, but also with multiple lipophilic molecules, particularly in foods with a high lipid content (Radauer, Lackner, and Breiteneder 2008). Oleosins, proteins which stabilize oil bodies in peanut, sesame seeds, and hazelnut, are associated with severe systemic reactions (Leduc et al. 2006; Zuidmeer-Jonghejan et al. 2014; Schwager et al. 2016) and nsLTPs, capable of binding a variety of lipophilic ligands, are considered major food allergens with clinical relevance in the Mediterranean area (Egger et al. 2010). Whereas, as mentioned, lipid binding is largely regarded as a means to provide proteolytic stability to allergens through the reduction of polypeptide mobility (Petersen et al. 2014), it has also been proposed that ligand occupancy can promote digestion of certain proteins through the opposite phenomenon. Thus, according to Abdullah et al. (2016), LA increases the digestibility of wheat nsLTP by inducing solvent exposure of buried Tyr79, a main site for proteolytic cleavage by chymotrypsin, but it does not affect the digestibility of peach nsLTP, whose residue Tyr79 is normally accessible.

In addition to modifying the extent to which the intact protein structure is preserved, lipids may change the immunomodulating properties of proteins. For instance, bioactive lipids present in the aqueous extract of pollen grains favor activation of DCs to elicit Th2 responses (Traidl-Hoffmann et al. 2005; Gutermuth et al. 2007). Similarly, several reports attribute to the whole lipid content, or to complex lipid fractions of foods, the ability to enhance the sensitizing properties of proteins (van Wijk et al. 2005; Shindo et al. 2012). Lipid-free Ber e 1 was not found to elicit IgE or IgG1 antibody responses in BALB/c mice following intraperitoneal administration without adjuvant, whereas co-administration of Brazil nut lipids and, in particular, of a specific complex fraction able to bind Ber e 1 (composed of TG, sterylglucosides, PE, PC, phosphatic acid etc.), exerts a strong adjuvant

effect on antibody generation (Dearman, Alcocer, and Kimber 2007; Mirotti et al. 2013). Egg yolk, which amounts to one third in weight of a fresh whole egg and contains 65% lipids in dry matter, may play a role during the sensitizing phase of egg allergy by exerting local Th2-biasing effects through the upregulation of intestinal IL-33 expression (Pablos-Tanarro et al. 2018). Besides, egg yolk also directly stimulates proliferation of Th2 cells during *in vitro* DC presentation of allergens to T cells from egg white sensitized mice (Pablos-Tanarro et al. 2018). In this respect, food lipids, such as those from mustard and peanut, reduce the capacity of human DCs to capture the allergens Sin a 2 and Ara h 1, increase their resistance to lysosomal degradation and promote a pro-inflammatory phenotype in DCs, factors that contribute to skip tolerogenic responses (Angelina et al. 2016). While lipid-induced resistance to proteolytic processing may underlay the mechanism behind the initial Th2 polarization in response to these proteins, interference with TLR-signaling pathways has also been put forward as a plausible explanation (Angelina et al. 2016). Additionally, peanut lipids have been reported to induce a pro-inflammatory response in skin keratinocytes that may play a role in their capacity to sensitize via the skin, regarded as a major site of sensitization in the development of peanut allergy (Palladino et al. 2018).

Another innate pathway involved in the recognition of lipid-binding proteins by T cells has to do with CD1, a non-polymorphic MHC class I-like molecule expressed by APCs and epithelial cells that presents lipid antigens making them immunogenic. Invariant natural killer T cells (iNKTs) represent a specialized T cell subset that simultaneously possesses markers characteristic of natural killer cells (NKs) and conventional T cells (De Libero and Mori 2005). TCRs of iNKTs recognize lipids presented by DCs through CD1d, and this triggers the upregulation of costimulatory molecules and the secretion of cytokines, such as IFN- $\gamma$  and IL-4. This process involves the uptake of lipids by DCs, processing by lysosomal enzymes, incorporation to cytoplasmic CD1d and traffic to the plasma membrane, albeit lipid antigens can also be loaded on the cell surface (Girardi and Zajonc 2012; Gilleron et al. 2016). A variety of endogenous and exogenous lipids can bind CD1d molecules and stimulate iNKTs, mainly PLs, SPs, and GLs, and even hydrophobic peptides, with the semi-invariant TCRs of iNKTs being able to recognize a range of chemically diverse ligands (Brutkiewicz 2006).

iNKTs are considered to play a crucial role in allergic asthma, both as effector cells and as amplifiers of specific Th2 responses (Iwamura and Nakayama 2010). These cells have also been implicated in food allergy. According to Jyonouchi et al. (2011), peripheral blood from milk allergic children contains fewer iNKTs than blood from healthy donors, but these cells are more responsive to milk sphingomyelin, which suggests a role for milk lipids and iNKTs, through production of Th2 cytokines, in sensitization to milk. Interestingly, an increase in peripheral blood iNKTs was observed upon acquisition of food tolerance following oral immunotherapy, thus reinforcing the involvement of these cells in milk allergy (Cianferoni et al. 2017).

The lipid-binding food allergens Ber e 1 and Pru p 3, with the assistance of a Brazil nut lipid fraction and a specific lipid ligand, respectively, stimulate mouse iNKTs through CD1d to produce IL-4 and Th2-associated antibodies (Mirotti et al. 2013; Tordesillas et al. 2017). Indeed, exogenous factors present in the intestinal lumen can induce CD1d expression on intestinal epithelial cells (Colgan et al. 2003). It was found that monocyte-derived DCs upregulate CD1d expression following exposure to polar lipids (including PLs and glycolipids), GLs and free FA, resulting in *in vitro* iNKT activation. Direct interaction of PUFA with PPAR $\gamma$  was deemed responsible for enhanced CD1d expression in DCs (Abós-Gracia et al. 2013). Furthermore, the loading of lipid antigens, such as PLs, on CD1 molecules allows DCs to behave as receptors to specifically stimulate TCR $\alpha\beta^+$  T cells and TCR $\gamma\delta^+$  T cells from pollen allergic subjects, without an influence on T cells from non-allergic donors, thus showing that the immunogenic effect of CD1-mediated lipid presentation is not restricted to the activation of iNKTs (Agea et al. 2005; Russano et al. 2006).

### High-fat diets, intestinal homeostasis and food allergy

Diet is known to influence the protective function of the intestinal barrier depending on individual factors, such as genetic predisposition and composition of the intestinal microbiota (Duca et al. 2014). Fat is among the dietetic components that augment intestinal permeability, causing bacterial translocation, metabolic endotoxemia and low grade inflammation, which precede several metabolic disturbances, including type II diabetes, nonalcoholic fatty liver disease and cardiovascular pathologies, as well as food allergy (Bischoff et al. 2014). Metabolic endotoxemia designates an increase over a defined threshold of the serum concentration of LPS, a component of the outer membrane in Gram-negative bacteria which is a major trigger of the inflammatory responses that underlie these diseases. It has been shown that high energy and, particularly, high fat intakes lead to high concentrations of circulating LPS (Erridge et al. 2007; Amar et al. 2008; Ghanim et al. 2009; Pendyala, Walker, and Holt 2012). In this respect, the use of mouse models has allowed to establish a link between dietary fat and enhanced intestinal permeability via different mechanisms (Frazier, DiBaise, and McClain 2011; Teixeira et al. 2012; Nie, Luo, and Lin 2018).

As shown by Cani et al. (2007a, 2008), a high-fat diet increases intestinal permeability by reducing the expression of epithelial tight junction proteins, such as ZO-1 and occludin, boosts plasma LPS concentration, and induces obesity, diabetes, and liver insulin resistance in the C57BL/6J mouse, but not in its LPS receptor CD14 knockout counterpart, which highlights the role of LPS as a link between dietary fat and the onset of metabolic diseases. Furthermore, expanded LPS levels are closely correlated with changes in the intestinal microbiota, namely, reductions in Gram-negative *Bacteroides*, but also in Gram-positive members of the *Eubacterium rectale*-*Clostridium coccoides* group and

*Bifidobacterium* (Cani et al. 2007a). In fact, the modification of the microbiota profile of high-fat fed mice by means of antibiotic treatment restores intestinal permeability and reduces metabolic endotoxemia and associated inflammation, providing evidence that changes in intestinal microbial composition in response to a high-fat diet are responsible for the impairment of metabolic parameters (Cani et al. 2008). The observation that prebiotics that selectively increase the level of bifidobacteria normalize plasma endotoxemia reinforces the involvement of the intestinal microbiota (Cani et al. 2007b, 2009).

A number of subsequent studies highlighted the interaction of high-fat diets and bacteria to promote pro-inflammatory changes in the intestine. Simulation of the human gut ecosystem via transplantation of human fecal samples into germ-free C57BL/6J mice showed that the initial structure of the microbial community can be rapidly altered by a high-fat, high-sugar 'Western' diet, which modifies gene expression and metabolic pathways in the microbiome (Turnbaugh et al. 2009). High-fat diets induce ileal TNF- $\alpha$  expression and increase plasma TNF- $\alpha$  concentration in conventional, but not in germ-free mice, and fecal slurries from conventional mice fed a high-fat diet are sufficient to activate the NF- $\kappa$ B pathway when transferred to germ-free mice (Ding et al. 2010; Rabot et al. 2010).

It is a common observation that rodents from the same genetic background do not always exhibit the same metabolic phenotype in response to a high-fat diet, being able to become, for instance obesity-prone or obesity-resistant, or diabetic-prone or diabetic-resistant (de La Serre et al. 2010; Serino et al. 2012). In this respect, and according to Serino et al. (2012), it is the gut microbial profile which shapes a specific phenotype, independently from the genetic background or the diet. Conversely, while the study by de La Serre et al. (2010) showed that a high-fat diet induces microbial dysbiosis, this was not always associated with enhanced intestinal permeability, plasma LPS and inflammation, pointing at independent yet unknown factors.

Studies on intestinal dysbiosis associated to high-fat diets fed to mice have reported a decrease in Bacteroidetes and an increase in both Firmicutes and Proteobacteria (Hildebrandt et al. 2009; Myles et al. 2013). Increases in the relative proportion of Bacteroidales and Clostridiales (orders belonging to the phyla Bacteroidetes and Firmicutes respectively) have also been indicated (de La Serre et al. 2010). Another study described, after 1 week, a reduction in the abundance of genera from the Clostridia class in the ileum, which concurred with a decreased IL-10 expression and an enhanced paracellular permeability, and an increase in *Bacteroides* in the large intestine (Hamilton et al. 2015). Ingestion of different FAs in a high-fat diet differently influences the composition of the intestinal microbiota: dietary saturated FAs (palm oil), with a negative impact on metabolic parameters, result in significantly lower populations of Bacteroidetes, while monounsaturated FAs (olive oil) beneficially alter the bacterial population by increasing Bacteroidaceae, and n-3 PUFAs (flaxseed/fish oil) have a bifidogenic effect (Patterson et al. 2014). Overall, even if it is

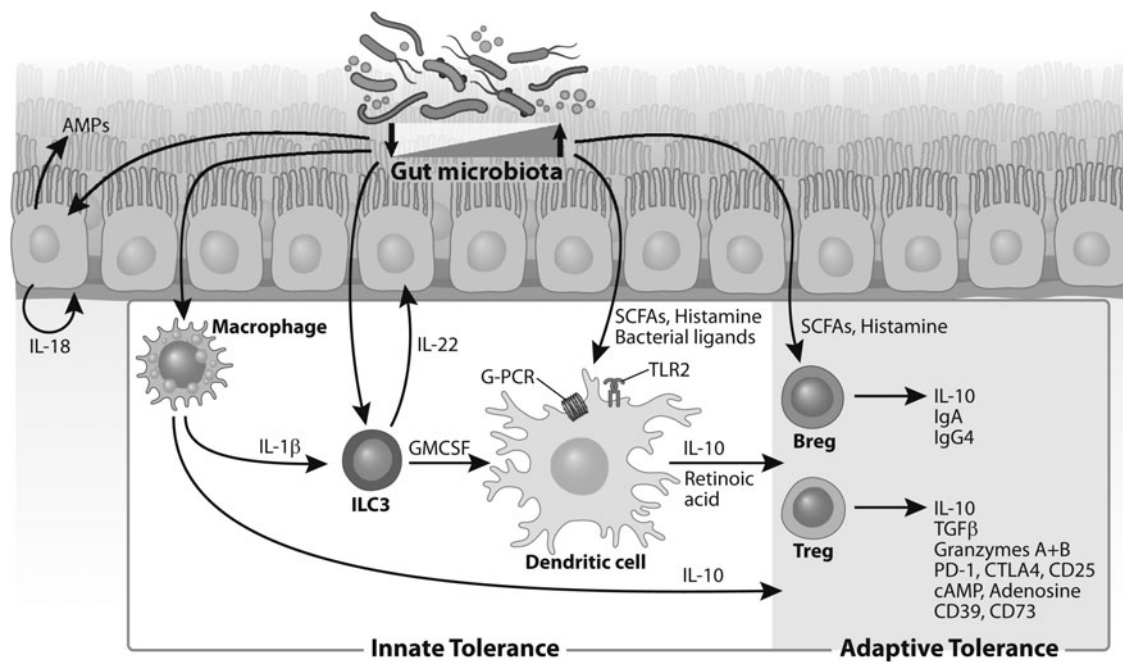


**Figure 2.** Interactions between the microbiota and innate and adaptive immune systems within the mucosa in tolerance induction. Microbial metabolites strengthen the epithelial barrier by inducing the release of IL-18 and antimicrobial peptides (AMPs) from epithelial cells and that of IL-22 from group 3 innate lymphoid cells (ILC3). Mucosal macrophages secrete IL-10 and IL-1 $\beta$ , that stimulates GM-CSF release from ILC3s, further promoting IL-10 and retinoic acid secretion by DCs, which are essential for induction of Breg and Treg cells. Mucosal DCs, Breg and Treg cells can be influenced directly by microbial metabolites, such as short-chain fatty acids (SCFAs) or bacterial ligands that activate Toll-like receptors (TLR). cAMP, Cyclic AMP; CTLA4, cytotoxic T lymphocyte-associated protein 4; PD-1, programmed cell death 1. Reprinted from Sampson et al. (2018), with permission from Elsevier.

widely recognized that the amount and type of fat in the diet has a dominating role in shaping gut microbiota, and that changes in some key populations may be relevant to the development of inflammatory diseases (Zhang et al. 2010), the bacterial markers that could predict an altered metabolic phenotype are not yet clear.

A high-fat parental diet causes dysregulation of immune functions in the offspring, with consequences in its susceptibility to allergic sensitization, due to diet-induced changes in maternal microbiota that are passed on to the progeny, which also inherits increased colonic inflammation and decreased Treg cell frequency (Myles et al. 2013). Interestingly, either pre or perinatal exposure exerts a higher effect on pups than direct exposure to fat (Odaka et al. 2010; Myles et al. 2013). In humans, a maternal high-fat diet has also been associated with a distinct neonatal gut microbiome at birth that persists until 4 to 6 weeks of age (Chu et al. 2016).

Another possible mechanism of fat-induced LPS absorption implicates its transport in chylomicrons, whose formation is induced by long-chain TGs (Ghoshal et al. 2009). Subsequent production of pro-inflammatory cytokines, such as TNF- $\alpha$ , that propagate the extension of local and systemic inflammation, would trigger the alteration of junctional proteins, promoting tight junction disruption and affecting barrier function (Mazzon and Cuzzocrea 2008). It is also likely that the increased free FAs associated to high-fat diets directly use TLRs to activate inflammatory signaling (Myles 2014).

According to Johnson and Ownby (2016), poor homeostatic processes and consequent failure to appropriately and

timely down-regulate inflammation, rather than a tendency to mount Th2 responses to antigens, are the cause of deviations from the tolerogenic status. The barrier function of the intestine prevents the entrance of antigens from the intestinal lumen to the underlying mucosal tissue, where they come across the cells of the gut-associated immune system. Therefore, dietary factors that favor allergen passage through the weakening of the intestinal barrier could facilitate the development of food allergy. Indeed, an augmented intestinal permeability is considered a factor promoting sensitization to food antigens in predisposed individuals while, in already sensitized patients, it may contribute to amplify the immune response arising as a consequence of occasional allergenic food contacts (Heyman 2005). As mentioned, perturbations in intestinal homeostasis can lead to inflammation and to increased concentrations of cytokines, free radicals and lipid mediators, and the altered rate, route and mode of antigen presentation may lead to abrogation of oral tolerance (MacDonald and Monteleone 2005; Roth-Walter et al. 2008; Price et al. 2014; Gavrovic-Jankulovic and Willemsen 2015). It has also been speculated that diets high in saturated fat alter TLR4 signaling, resulting in a systemic hyporesponsiveness to LPS that might mimic the low LPS exposure status that underlies sensitization according to the hygiene hypothesis (Myles et al. 2013).

The intestinal microbiota is a major contributor to the capacity to resolve inflammation and return to a homeostatic state, also recognized as a key factor in the development of innate and acquired immune responses and in the induction of tolerance (Figure 2) (Sampson et al. 2018). Although allergic patients are not characterized by

a consistent microbial pattern, perturbations of a healthy gut microbiome correlate with or predispose to food allergy (Chinthrajah et al. 2016; Blázquez and Berin 2017; Huang et al. 2017b). In mice, intestinal dysbiosis can drive allergic diseases (Morin et al. 2012). On the other hand, mice genetically susceptible to develop food allergy have a characteristic microbiota that transmits this susceptibility when transferred to germ-free mice (Noval Rivas et al. 2013). Certain microorganisms stimulate and instruct Treg cells to suppress Th2 responses and avoid the production of IL-4 and IgE (Ohnmacht et al. 2015). A specific but wide diversity of bacterial species, including *Clostridium* (clusters IV, XIVa and XVIII) are inductors of the accumulation of Treg cells (Atarashi et al. 2011, 2013; Geva-Zatorsky et al. 2017). The mechanism implicates antigens and metabolites from the gut microbiota, such as short chain fatty acids which stimulate vitamin A metabolism and generation of retinoic acid (Ohnmacht et al. 2015; Schilderink et al. 2016). *Clostridium* also favors epithelial integrity, regulating the passage of food antigens, and promotes the expression of antimicrobial peptides and mucus (Stefka et al. 2014).

### The association between obesity and allergy

In the long term, high-fat diets lead to fat storage and obesity. The parallel rise in the prevalence of allergic diseases and obesity in the past 3 decades suggests a causal connection between them. Indeed, increasing epidemiological evidence links obesity with asthma, although an association with other atopic disorders, such as allergic rhinitis, dermatitis and food allergy is less clear (Baumann and Lorentz 2013). In this respect, it should be noted that, in the longitudinal studies that establish a causal relationship between obesity and asthma, dietary factors or a sedentary lifestyle, common risk factors to both conditions, are difficult to discern from adiposity itself and the results vary with age and gender, although these aspects remain controversial (Peters, Dixon, and Forno 2018). Furthermore, a high body mass index and other adiposity parameters negatively impact lung function, which worsens asthmatic symptoms, raising the question as to whether allergic mechanisms mediate the association (Leiria, Martins, and Saad 2015). The picture is further complicated by the existence of different phenotypes of the asthmatic disease (Gómez-Llrente et al. 2017). An association of obesity with food allergy (particularly to milk and shrimp) was established in children and adolescents, based on questionnaires and measurements of total and allergen-specific IgE. In obese allergic children, C-reactive protein was positively correlated to total IgE, suggesting that inflammation was the link between obesity and atopy (Visness et al. 2009). Other studies, however, failed to find a significant relationship, although they only included adolescents or adults and just took into account questions concerning symptoms of food allergy or skin prick tests to non-food allergens (Irei et al. 2005; Silverberg, Silverberg, and Lee-Wong 2012).

In fact, obesity is regarded as a low grade chronic inflammatory state characterized by high circulating levels of pro-

inflammatory cytokines (IL-6, IL-8, TNF- $\alpha$ , IL-1 $\beta$ ), which are also common to allergic diseases (Hersoug and Linneberg 2007). These are secreted by cells of the adipose tissue, mainly adipocytes and macrophages, which also produce adipokines, such as leptin and adiponectin associated to reduced immunological responses and inflammatory processes (Kelishadi et al. 2017). The concentration of leptin, a member of the IL-6 family of cytokines, is considerably enhanced and that of adiponectin decreases with increasing obesity. Leptin levels correlate positively with IgE levels in allergic subjects (Matsuda et al. 2006). This could be explained by the observation that leptin constrains the expansion of Treg cells (De Rosa et al. 2007). In obesity, increased leptin secretion by adipocytes promotes macrophage function and Th1 cell expansion, release of pro-inflammatory mediators, and reduced Treg cell responsiveness and function (Matarese et al. 2010). Leptin can also contribute to the pathogenesis of allergic diseases by inducing basophil activation, degranulation and release of Th2 cytokines (Suzukawa et al. 2011). For its part, adiponectin exhibits anti-inflammatory actions, as it induces the production of the anti-inflammatory mediators IL-10 and IL-1 receptor antagonist, whereas it significantly impairs IFN- $\gamma$  production (Wolf et al. 2004). Overall, and given the inhibitory effect of cytokines such as IL-6 on Treg cells (Kimura and Kishimoto 2010), the crosstalk between these elements in the obese condition leads to a depletion of Treg cells in the adipose tissue that may reduce the defenses against allergic diseases (Feuerer et al. 2009).

### Conclusions

Certain lipids mediate cell communication events by transmitting signals as primary or secondary messengers, acting as cofactors of protein phosphorylation or concentrating signal transduction complexes into lipid rafts. For instance, *n*-6 and *n*-3 PUFAs exert pro-inflammatory or anti-inflammatory functions on cells of the innate immunity, influence antigen presentation to cells of the adaptive immunity and impact activation of effector cells, such as mast cells, and thus, contribute to allergic diseases through different modes of action. Allergenic foods often have a high lipid content and many allergenic proteins have the ability to bind lipids. In addition to modifying the immunostimulating properties of proteins, dietary lipids also alter their digestibility and intestinal absorption, changing allergen bioavailability. On the other hand, dietary exposure to high-fat diets influences the composition of the microbiota with a direct impact on the development of allergy. Moreover, changes in the gut microbial communities alter energy uptake from nutrients, which, thought adiposity, confers additional impact on inflammatory mediators and immune cells. Future clinical and basic studies are required to unravel the complex mechanisms by which lipids contribute to allergy. Increased understanding of the associations of quality and quantity of dietary lipids, obesity, and allergic predisposition will allow future directions in prevention and treatment of food allergy.

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