

# How fats we eat modulate our immunity? ☆

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Received 20 August 2019 – Accepted 10 January 2020

**Abstract** – The development and optimal functioning of our immune system is directly influenced by our diet. Any deficiency or excess of certain nutrients can affect the number and activity of immune cells. Among the nutrients identified, dietary fatty acids are described as having major effects on immunity. Indeed, the fatty acid composition of the membranes of immune cells seems to be easily modulated under the effect of dietary fats and the resulting rapid changes in composition are likely to generate functional effects on the reactivity and functioning of these cells within a very short period of time. Among the different mechanisms identified to explain the impact of dietary fatty acids on the immune function, the synthesis of lipid mediators from polyunsaturated fatty acids is a key one notably in the context of inflammation.

**Keywords:** n-3 PUFA / n-6 PUFA / immunity / diet / lipid mediators

**Résumé – Comment les graisses que nous consommons modulent-elles notre immunité?** Le développement et le fonctionnement optimal de notre système immunitaire sont directement influencés par notre alimentation. Toute carence ou excès de certains nutriments peut affecter le nombre et l'activité des cellules immunitaires. Parmi les nutriments identifiés, les acides gras alimentaires sont décrits comme ayant des effets majeurs sur l'immunité. En effet, la composition en acides gras des membranes des cellules immunitaires semble être facilement modulée sous l'effet des graisses alimentaires et les changements rapides de composition qui en résultent sont susceptibles de générer des effets fonctionnels sur la réactivité et le fonctionnement de ces cellules dans un délai très court. Parmi les différents mécanismes identifiés pour expliquer l'impact des acides gras alimentaires sur la fonction immunitaire, la synthèse de médiateurs lipidiques à partir d'acides gras polyinsaturés est un mécanisme clé, notamment dans le contexte de l'inflammation.

**Mots clés :** AGPI n-3 / AGPI n-6 / immunité / régime alimentaire / médiateurs lipidiques

## 1 Introduction

The immune system brings together all the resources that enable to protect the body against threatening agents or situations, both internal and external to the organism.

The immune function is influenced by many factors, including genetics, sex, early life events, age, hormonal status, stress... The nutritional status of the host is one of these modulating factors.

Adequate supply and balance of dietary nutrients are required for proper efficiency of the immune system, its development, maintenance, and functioning. Adequate intakes of micro- and macronutrients are therefore important in our Western societies, which are more characterized by a non-adequate modern dietary pattern: too much saturated fatty

acids, salt, and sugar; low levels of n-3 fatty acids (Myles, 2014; Maggini *et al.*, 2018). Among the macronutrients of interest, dietary lipids are described as having major effects on our immune system.

If the link between our diet and the development and optimal functioning of our immune system has been the subject of research for many years, the impact of dietary fat on immunity, on the other hand, has been investigated since the end of the 1970s as reminded by Boissonneault (2008). From the first review in 1978, discussing fatty acids and immunity, many others followed dealing with the *in vitro* and *in vivo* evidence suggesting that dietary lipids play a role in modulating immune function.

It was then suggested that the observed effects involved modifications of the physical properties of the immune cell membrane, any modification of membrane order, also called fluidity, may have consequences of disrupting membrane processes, which are essential for the immune cells' response to any activation of the immune system.

\* Contribution to the Topical Issue "Lipids and health / Lipides et santé".

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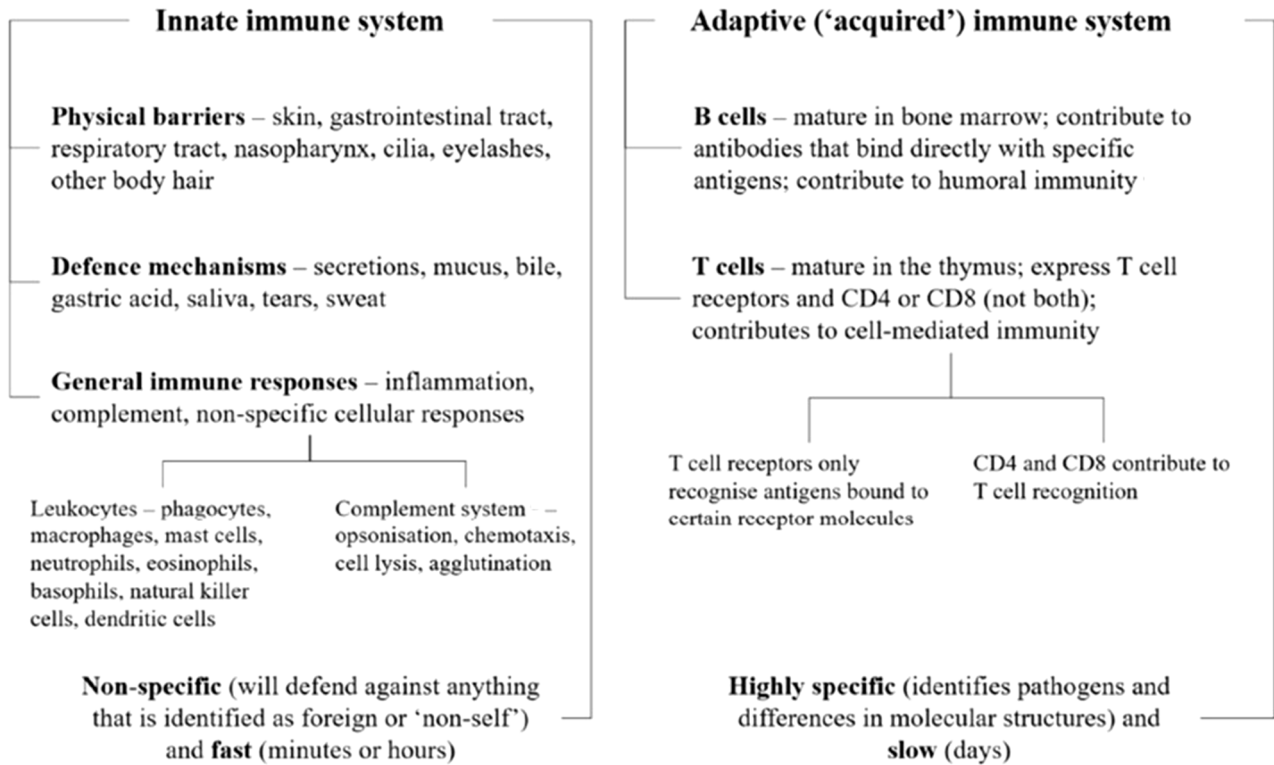


Fig. 1. Overview of the innate and adaptive immune systems. Modified from Maggini et al. (2018) with permission from MDPI.

The subsequent discovery that eicosanoids, biologically active lipid mediators produced from 20 carbon polyunsaturated fatty acids (PUFA), notably from arachidonic acid (ARA, 20:4n-6), can play a role in inflammation (a component of the immune response) and in regulating immune cell functions, has led to research on the effects of ARA. The observations made highlighted the possibility that the effects of dietary fatty acids on immunity could be explained by a change in the production of these lipid mediators (Kinsella et al., 1990; Calder et al., 1992; Calder, 2013).

The more recent discovery of other bioactive lipid mediators from n-3 PUFA and known as specialized pro-resolution lipid mediators derived because of their role as key signaling molecules in the resolution of inflammation suggest that these lipid mediators appear to have beneficial effects on multiple modalities of immune function (Calder, 2017; Gilroy and Bishop-Bailey, 2019).

The purpose of this article is to provide a non-exhaustive overview of the mechanisms known to date to explain how fats we eat, in particular dietary n-6 and n-3 PUFA, can influence how our immune system works.

## 2 General data on the immune system

The immune response acts to protect the host from infectious agents that exist in the environment, such as microbes (viruses, bacteria, fungi...), and from other insults such as abnormalities of host tissues (cancer), and tissue trauma. Under certain conditions, the immune system can itself cause disease by involuntarily responding against host tissues

as in cases of autoimmunity or contribute to the etiology of other diseases (atherosclerosis, psoriasis).

As summarized by Maggini et al. (2018), the immune system utilizes three distinct layers according to the nature of the threat. The first one includes physical and biochemical barriers, such as skin, epithelial lining of the gastrointestinal and respiratory tracts, and such as secretions, mucus and gastric acids, respectively. The second layer includes numerous different immune cells spread throughout the body such as monocytes, granulocytes, lymphocytes, T and B cells. The third layer corresponds to the antibodies or immunoglobulins.

There are two types of immunity (Fig. 1). Innate immunity acts as the first line of defense and involves the physical and biochemical barriers associated with an unspecific cellular response mediated mainly by monocytes, neutrophils, natural killer (NK) cells and dendritic cells. All work together to fight off pathogens before they can start an active infection. Acquired (adaptive) immunity acts as a second line of defense by providing long-term protection against particular pathogens through the production of antibodies specific to them. The acquired immune response involves T lymphocytes that will release chemical mediators (cytokines) (cell-mediated immunity), as well as B lymphocytes that will produce antibodies that contribute to the recognition and elimination of pathogens (humoral immunity). When the immune response is brought into play, both types of immunity are likely to occur (Hubler and Kennedy, 2016).

To quote Maggini et al. (2018), “optimal immune function is dependent on a healthy immune system”, an adequate nutrition is essential to ensure all the needs required for the

development, maintenance and expression of the immune system. To guarantee the latter, dietary fats are among the macronutrients having crucial roles on the immune system.

### 3 Dietary fats: what are we talking about?

Dietary fats we consume are mainly triglycerides, which are the main form of lipids in commonly occurring oils and fats.

Triglycerides are composed of three fatty acids esterified to a glycerol backbone. Dietary fatty acids are important sources of energy, major constituents of all cell membranes, key components involved in the metabolic, structural and functional pathways within the body, and precursors to signalling molecules. Dietary fatty acids can be saturated (SFA), monounsaturated (MUFA), or polyunsaturated (PUFA).

Concerning the latter, n-3 and n-6 PUFA are important components of the human's diet. The respective precursors of each family are the alpha-linolenic acid (ALA, 18:3n-3) and the linoleic acid (LA, 18:2n-6). Both are of plant origin. LA and ALA are described as essential fatty acids as they cannot be synthesized in higher animals including humans; they must be provided by the diet. Rich dietary sources of LA include many vegetable oils, such as sunflower, safflower, corn, and soybean oils. ALA is found in green plant tissues, in some common vegetable oils, including soybean and rapeseed oils, in some nuts (*e.g.* walnuts), and in flaxseeds and flaxseed oil.

In the body, LA and ALA are the substrates for the synthesis of very-long chain PUFA. By an analogous set of reactions catalyzed by the same enzymes, ALA can be converted to eicosapentaenoic (EPA, 20:5n-3) and docosahexaenoic acids (DHA, 22:6n-3), while LA can be converted to ARA. In humans, evidence suggests that the conversion of ALA into EPA and DHA may be limited (Burdge and Calder, 2006), partly due to the body's use of ALA and pathway intermediates as energy sources, and partly due to the inefficiency of the enzymes themselves. Estimates vary, but only a small proportion of ALA is converted to EPA (8 to 21%) and especially to DHA (0.05 to 9%) (Burdge and Wootton, 2002; Arterburn *et al.*, 2006; Harnack *et al.*, 2009; Blanchard *et al.*, 2013). For this reason, the direct consumption of EPA and DHA is more effective for increasing their concentration in the body than is the consumption of ALA. The primary source of EPA and DHA is seafood, especially oily fish (tuna, salmon, mackerel, herring, and sardine). Dietary sources of ARA are meat, poultry, eggs, and organ meats.

N-6 and n-3 PUFA play vital roles in human health from conception onwards through every stage of human development, maturation and aging. However, most Western diets are described as generally containing an excess of n-6 PUFA, notably LA in the USA, over n-3 PUFA, particularly lacking in ALA, EPA and DHA (Baker *et al.*, 2016; Sioen *et al.*, 2017).

Diets rich in n-6 PUFAs are described as increasing the risk of development of inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, and asthma (Wall *et al.*, 2010). On the other hand, epidemiological studies and several randomised control trials demonstrate positive effects of the consumption of EPA and DHA on hypertension, diabetes, reduction in cardiovascular disease morbidity and mortality,

better visual and neurological development, and improvements in inflammatory disorders (Simopoulos, 2011; Baker *et al.*, 2016).

### 4 Dietary fatty acids as main components of the immune cell membranes

It is admitted that dietary fatty acids can influence cellular responses and cell function of the immune cells by modulating the fatty acid composition of their membrane phospholipids.

As explained by Innes and Calder (2018), the fatty acid makeup of membrane phospholipids influences membrane order and lipid raft assembly, many second messengers being derived from membrane phospholipids, and the fatty acid composition of these messengers affecting their biological activity and potency. Another major point is that some lipid mediators are formed from fatty acids released from membrane phospholipids upon cellular activation.

#### 4.1 Fatty acid composition of the immune cell membranes

To date, the fatty acid composition of immune cell membranes is relatively well described. Data obtained in human and rodents have shown that membrane phospholipids from different immune cells (T and B lymphocytes, monocytes, neutrophils) contain mainly ARA, which alone represents about 15 to 25% of the total fatty acids contained in the membranes. The exact proportion of ARA depends of the cell type and the lipid fraction examined. The proportion of LA is between 6 and 10%. In contrast, EPA and DHA, n-3 long chain PUFA derived from ALA, are minor constituents (Calder *et al.*, 1990, 1994): ALA is rare ( $\leq 0.1\%$  of total fatty acids), and EPA and DHA account for about 0.1 to 0.8% and 2 to 4% of total fatty acids, respectively (Kew *et al.*, 2003a; Miles *et al.*, 2004; Calder, 2015).

#### 4.2 Dietary fats as modulators of this composition

Overall, it appears that dietary fats influence the fatty acid composition of membrane phospholipids in numerous studies, principally by increasing the amounts of the provided fatty acids. The consumption of certain fatty acids not only modifies their proportion in the lipids of the membranes of immune cells but may also have an impact on those of other fatty acids. This is the case, for example, of the ARA in the case of an EPA + DHA contribution.

Thus, it has been shown that the enrichment of the diet with a given fatty acid increases the content of this fatty acid in the membranes of immune cells. Thus, in rodents, a diet rich in ARA, as well as a diet rich in EPA and DHA, leads to the respective enrichment in ARA and EPA and DHA of membranes of different cellular types (lymphocytes, macrophages and neutrophils) (Calder, 2015). Marshall and Johnston (1983) reported the fatty acid changes induced by feeding fats containing high ALA to LA ratio after a 2-month feeding period on the fatty acid composition of peripheral blood lymphocyte, thymocyte or splenocyte of rats. They observed that the n-3 PUFA reciprocally replaced the n-6 PUFA when

higher ratios of ALA to LA were fed, the magnitude of fatty acid change increasing as the ALA/LA ratio increased. [Tiwari et al. \(1986\)](#) assessed the LA proportion in the membrane of splenocytes from mice fed with diets high or low in LA for 1, 4 or 6 weeks. They observed that the higher the LA level in the diet, the higher the level in the splenocyte membranes. The same authors observed that these changes in the fatty acid composition of splenocyte membranes were reflected in the fatty acid composition of B and T cell membranes ([Tiwari et al., 1987](#)).

In healthy elderly subjects, an enrichment of the ARA diet induces an increase in the proportion of ARA in blood mononuclear cells ([Thies et al., 2001a](#)), while an intake of ALA, in the form of flax oil, induces an increase in the EPA content of mononuclear cells and neutrophils ([Kelley et al., 1993](#); [Mantzioris et al., 1994](#); [Kew et al., 2003b](#)).

More studies have tested the effects of a diet enriched with fish oil or purified sources of EPA and DHA in healthy subjects. Consumption of such diets is accompanied by an increase in the EPA and DHA content of blood immune cells, which is dose-dependent (significant after 1 day of fish oil nutritional supplementation and maximum after 7 days), and at the expense of n-6 PUFA, such as ARA ([Yaqoob et al., 2000](#); [Thies et al., 2001a](#); [Miles et al., 2004](#); [Faber et al., 2011](#)).

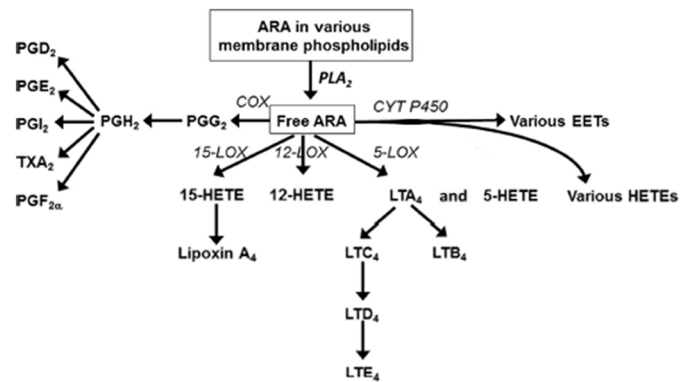
In his article on the relationship between n-3 PUFA, inflammation and immunity, [Calder \(2001\)](#) reviewed human studies having assessed the impact of n-3 PUFA supplementation on the ARA, EPA and DHA contents in the main membrane lipid fractions (total lipids, phospholipid, or individual phospholipids) of different immune cell types such as neutrophils, monocytes, T and B lymphocytes.

A dietary supply in EPA + DHA, which ranges from 0.3 to 14.4 g EPA + DHA/day for 2 to 12 weeks, induces an enrichment in n-3 PUFA in the membranes of the different cell types, at the expense of the ARA, whose proportion is reduced. The observed modifications are of different amplitudes, depending on the dose of EPA + DHA provided, the duration of administration, the cell type and the lipid fraction under observation. Slight variations are observed in neutrophils from the smallest amounts of EPA + DHA administered (−8% for ARA, +12% for DHA with EPA unchanged after 12 weeks of supplementation). On the other hand, the increased EPA and DHA proportions observed in neutrophil phospholipids in a dose-dependent manner after 4 weeks of supplementation with 2.25 g EPA + DHA/day remain unchanged beyond this time of 4 weeks.

Overall, it is generally accepted that the fatty acids in our diet contribute to the physical and functional properties of membranes and their representativeness is a major determinant of membrane fluidity. In addition to their role as membrane components, dietary fatty acids also act as substrates for the formation of bioactive oxygen derivatives.

## 5 Polyunsaturated fatty acids, as precursors of major lipid mediators

[Maskrey et al. \(2013\)](#), [Duffney et al. \(2018\)](#), and [Gilroy and Bishop-Bailey \(2019\)](#) recently published very comprehensive reviews about the different lipid mediators involved in immune regulation and inflammation resolution.



**Fig. 2.** Simplified overview of the pathways of eicosanoid synthesis from ARA. ARA: arachidonic acid; COX: cyclooxygenase; CYT P450: cytochrome P450 enzymes; EET: epoxyeicosatrienoic acid; HETE: hydroxyeicosatetraenoic acid; LOX: lipoxygenase; LT: leukotriene; PLA2: phospholipase A2; PG: prostaglandin; TX: thromboxane. Reprinted with modifications from [Innes and Calder \(2018\)](#) with permission from Elsevier.

As they wrote, lipids are important signalling molecules that regulate an array of immune responses, such as vascular hyper reactivity, pain, leukocyte trafficking and clearance, so-called resolution. Thus, they present in their respective reviews the major pathways involved in the biosynthesis of these mediators as well as their roles in inflammation and resolution. For more details, readers are invited to refer directly to their respective reviews.

In a very simplified way, lipid mediators are mainly synthesized from ARA for the n-6 series, and from EPA and DHA for the n-3 series. Their biosynthetic pathways involve common enzymes, and are at the origin of a set of different molecules.

While DHA and EPA are upstream molecules for pro-resolving lipid mediator synthesis (described below), ARA is primarily further metabolized into eicosanoids, which are recognized as inflammatory lipid mediators.

Indeed, it is generally accepted that lipid mediators from n-6 PUFA are considered to be rather pro-inflammatory, while those from n-3 PUFA are rather anti-inflammatory, the overall effect of these n-3 metabolites being to dampen inflammation and immune responses. There are, however, some exceptions to this statement.

### 5.1 ARA as precursor of eicosanoids

ARA is by far the most widely studied PUFA in the context of lipid mediator synthesis. ARA, once released from cell membrane phospholipids, is a substrate for cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 enzymes (CYT P450) to yield the eicosanoid family of mediators, which are important pro-inflammatory mediators in inflammatory response and inhibit immune function ([Lewis et al., 1990](#); [Tilley et al., 2001](#); [Kalinski, 2012](#)) ([Fig. 2](#)).

The first well-described lipid mediators are 2-series prostaglandins (PG) and thromboxans (TX), synthesized from ARA through the action of COX.

Data concerning the most common PG, which are PGE2 and PGI2, indicate roles in enhancing vasodilatation, oedema formation and vascular permeability.

More precisely, as mentioned by Kalinski (2012), PGE2 is described as regulating multiple aspects of inflammation and multiple functions of different immune cells as presented PGE2 is a mediator of active inflammation, promoting local vasodilatation and local attraction and activation of neutrophils, macrophages, and mast cells at early stages of inflammation. In addition, PGE2 exhibits immunosuppressive and anti-inflammatory properties, by suppressing lymphocyte proliferation and natural killer cell activity and by inhibiting production of tumour necrosis factor (TNF)-alpha, interleukin (IL)-1, IL-6, IL-2 and interferon (IFN)-gamma.

Even the majority of these eicosanoids are considered as being pro-inflammatory, some of them may be trigger immunosuppressive effects in specific situations as explained by Gilroy and Bishop-Bailey (2019) (such as inhibition of the production of pro-inflammatory mediators, reduction of the ability of inflammatory leukocytes to phagocytose and kill microorganisms).

ARA can also be converted by LOX in 4-series leukotrienes (LT) and lipoxins (LX). In specific situations, some LT are involved in signalling pathways driving inflammatory responses as well as vascular permeability, or present chemo-attractant and pro-inflammatory properties. LX are anti-inflammatory mediators at nanomolar concentrations. These bioactive eicosanoids are described as being able to stimulate monocyte-derived macrophages to ingest and clear apoptotic neutrophils once mobilized on the site of inflammation and resolution.

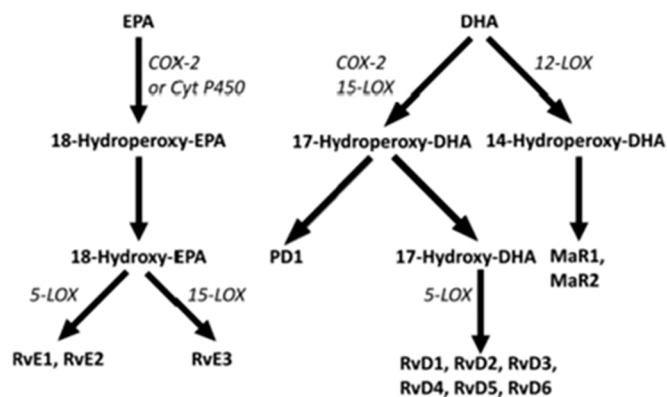
LTB4, among its many roles, inhibits lymphocyte proliferation and promotes natural killer cell activity. 4-series LT also regulate production of pro-inflammatory cytokines; for example, LTB4 enhances production of TNF-alpha, IL-1, IL-6, IL-2 and IFN-gamma.

ARA can also be metabolized in epoxyeicosatrienoic (EET) and hydroxyeicosatetraenoic (HETE) acids by CYT P450. These metabolites possess anti-inflammatory properties, by regulating for example for some of them, diverse signalling pathways pertinent to platelet aggregation, inflammation and cellular injury.

Thus, ARA acid gives rise to a range of mediators which have opposing effects to one another, so the overall physiological effect will be governed by the concentration of those mediators, the timing of their production and the sensitivities of target cells to their effects.

## 5.2 EPA and DHA as precursors of pro-resolving lipid mediators

The same type of molecules is described for EPA and DHA metabolized to 3-series of PG and TX, and to 5-series LT, which can competitively inhibit the release and metabolism of ARA, thereby reducing the body's inflammatory response and protecting from immune-mediated damage. 3-series PG are described as anti-inflammatory or less inflammatory than 2-series PG issued from ARA. In the same way, 5-series LT are described as anti-inflammatory or less inflammatory than 4-series LT.



**Fig. 3.** Overview of the pathways of specialized pro-resolving mediators' synthesis from EPA and DHA. COX: cyclooxygenase; CYT P450: cytochrome P450 enzymes; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; LOX: lipoxygenase; MaR: maresin; PD: protectin D; Rv: resolvins. Modified from Calder (2017) with permission from Portland Press.

CYT P450 also metabolize EPA into series of related biologically active mediators.

In addition to these metabolites, new endogenous bioactive derivatives from EPA and DHA have been recently described. These metabolites include resolvins produced from EPA (RvE) and DHA (RvD), and protectins (PD) and maresins (MaR) produced from DHA (Gilroy and Bishop-Bailey, 2019) via the COX and LOX pathways (Fig. 3). The powerful biological effects of Rv, MaR and PD would be at the basis of the anti-inflammatory effects described for n-3 PUFAs.

These lipid mediators have indeed been described as playing a central role in the resolution of the inflammation. Duffney *et al.* (2018) define the resolution phase of a normal inflammatory response as being characterized by lipid mediator "class switching," in which cells downregulate enzymes responsible for the production of pro-inflammatory lipids, such as PG and LT, while upregulating enzymes responsible for the production of specialised pro-resolving lipid mediators. These mediators are unique in that they exert pro-resolving and anti-inflammatory effects without suppressing the immune response.

The biological effects of Rv, PD and MaR have been extensively studied *in vitro* as well as *in vivo* models of inflammation, and have been described as anti-inflammatory and inflammation resolving (Calder, 2017). RvE1, RvD1 and PD1 are described as inhibiting neutrophil migration and preventing neutrophil infiltration into inflammation sites. RvD1 inhibits the production of IL-1beta (a pro-inflammatory cytokine) and PD1 inhibits the production of TNF-alpha (involved in the inflammatory reaction) and IL-1beta (Caughey *et al.*, 1996; Wada *et al.*, 2007).

Regarding the roles of Rv, MaR and PD on the immune T and B cells, Duffney *et al.* (2018) reported that the production of IFN-gamma and TNF-alpha by specific subtypes of T cells is reduced by PD1. Recently, it has been shown that RvD1, RvD2, and MaR1 could similarly block the production of IFN-gamma and TNF-alpha by T cells.

RvD1, RvD2, and MaR1 are also described as suppressing the differentiation of naive T cells into specific subtypes while

increasing the production of regulatory T cells known for their ability to produce pro-resolution factors to control inflammation such as transforming growth factor (TGF)-beta.

Concerning the B cell function, this one can be augmented, by a supplementation with the specialised pro-resolving lipid mediators or their precursor PUFA, in response to an increased antibody production, altered B cell cytokine production, skewed B cell differentiation/lineage, and limited spontaneous IgE class switching implicated in allergic asthma.

The discovery of these specialized pro-resolving lipid mediators, that actively promote the resolution of inflammation, has opened new avenues for the treatment of chronic inflammatory diseases, and has made them very promising therapeutic candidates, as reviewed by [Duffney et al. \(2018\)](#).

In their review, [Gilroy and Bishop-Bailey \(2019\)](#) also explain that one of the broader immunomodulatory properties of RvE1 is its ability to inhibit the accumulation of neutrophil and dendritic cells at sites of inflammation. Other actions of RvE1 include the inhibition of the biosynthesis of pro-inflammatory chemokine and cytokines, and the suppression of pro-inflammatory mechanisms while enhancing pro-resolution pathways.

RvD1 and D2 are described as also having both anti-inflammatory and pro-resolution properties by blocking neutrophil infiltration, while also enhancing macrophage efferocytosis of apoptotic bodies.

PD1 is described as inhibiting the Toll-like receptors (TLR)-mediated activation (TLR are among the receptors involved in the first line of the actors deployed by the immune system against infection) while suppressing inflammatory cytokines and pro-inflammatory lipid mediator synthesis.

Concerning maresins, such as MaR1 and MaR2, a number of data are still missing.

In addition to the n-3 PUFA strongly implicated in the resolution of inflammation, [Innes and Calder \(2018\)](#) have recently proposed a complete review of the involvement of n-6 PUFA in the inflammatory response.

The authors recall that n-6 PUFA are described as being able to inhibit the anti-inflammatory and inflammation resolving effects of EPA and DHA because it is commonly believed that increasing dietary intake of ARA or its precursor LA will increase inflammation.

However, Innes and Calder report on studies in healthy human adults that have found that increased intake of ARA or LA does not increase the concentrations of many inflammatory markers, epidemiological studies even suggesting that ARA and LA may be linked to reduced inflammation.

## 6 Dietary fatty acids as modulators of the immune cell function

Modulation of the fatty acid composition of immune cell membranes under the influence of diet may have an impact on the activity of the immune cells, disrupting the immune functions ([Calder, 2011](#); [Kim et al., 2013](#)).

Indeed, cell membrane fatty acids influence fundamental properties of the plasma membrane, notably membrane fluidity. Any modification of this fluidity or membrane order will have repercussions on the physical properties of these

membranes, particularly within specific regions such as lipid rafts.

Since cell membranes serve as reservoirs for the formation of products with profound immune effects, these changes are not without consequences.

Thus, data obtained in humans have shown that the lipid content of our diet can modulate the immune response. For example, it has been observed that the proliferation of peripheral blood mononuclear cells cultured in the presence of specific mitogens was increased or even doubled in healthy women fed a diet for 40 days with a reduced fat content of 41 to 26 or 31% of total energy intake ([Kelley et al., 1992a](#)). In another study, conducted in healthy humans, it was shown that a decrease in diet lipid content of 30 to 25% of total energy intake induced a significant increase in the number of circulating B and T lymphocytes after 11 weeks, as well as an increase in their proliferation measured *in vitro* ([Kelley, 2001](#)). Similar data were obtained for lymphocyte proliferation (increased) and secretion (decreased) measured *in vitro* of IL-1 and TNF in elderly subjects whose lipid intakes were reduced by 36–27% of total energy intake for 6 months ([Meydani et al., 1993](#)). The results of two other studies conducted in elderly confirm the beneficial impact of a reduction in the lipid content of about 10% of the total energy intake with the demonstration of an increase in the proliferation capacity ([Rasmussen et al., 1994](#)) as well as an increased activity ([Barone et al., 1989](#)) of NK lymphocytes.

In his review about the impacts of the Western diet on immunity, [Myles \(2014\)](#) summarized the immunologic impacts of the different classes of dietary fatty acids. In addition to being characterized by an over consumption of refined sugars and salt, the Western diet is also characterized by its richness in SFA, n-6 PUFA and poverty in n-3 PUFA.

### 6.1 SFA

SFA are considered to be the most inflammatory compared to other fatty acid families.

They are described as capable of activating TLR-mediated pro-inflammatory signalling pathways in some immune cells such as macrophages and monocytes ([Huang et al., 2012](#)). TLR are involved in the detection of invading pathogens to evaluate if it is bacterial, viral and fungal. Then they activate the innate immune responses for host defence. Numerous studies with cells in culture and in animal models of mutated or deleted TLR4 or TLR2 subsequently demonstrated that SFA indeed can activate TLR4- and TLR2-mediated pro-inflammatory signalling pathway leading to expression of pro-inflammatory marker gene products ([Lee et al., 2001](#); [Lee et al., 2004](#); [Wong et al., 2009](#)).

As explained by [Myles \(2014\)](#), TLR4 senses bacteria, by binding the lipopolysaccharide (LPS) of the bacteria, which contains SFA, mostly stearic and palmitic acids. This suggests that TLR4 can generate inappropriate signalling when exposed to certain SFA if in too great of frequency, amount, or homogeneity rather than in a more biological balance and dosage. As a result, this signalling anomaly may induce an inappropriate immune response in the case where SFA may be perceived as a bacterial invader.

## 6.2 N-6 PUFA

Concerning the n-6 PUFA, the growth and development of lymphoid tissues and the structural and functional integrity of T and B lymphocytes are described as sensitive to their level, notably ARA and LA intakes, any deficiency in these PUFA may induce a loss of functional integrity of different cell types (monocytes, macrophages, neutrophils) (Guadarrama-Lopez *et al.*, 2014).

With regard to LA, Blair *et al.* (1993) showed that a variation in its content between 3 and 8.3% of the total energy intake was accompanied by a variation in urinary PGE2 content, which is increased in women who consumed a diet richer in LA.

For ARA, it has been shown that supplementation at a rate of 1.5 g/day for 50 days in young healthy male subjects did not affect different parameters of the immune response; at the same time, the number of circulating neutrophils was increased by a factor of 4 (Kelley *et al.*, 1997; Kelley *et al.*, 1998a). Finally, *in vitro* data have shown the regulatory effect of ARA metabolites on the development and function of immunity cells including thymocyte growth and differentiation, T cell proliferation and migration, macrophage regulation, and pro-inflammatory cytokine production. Experimental data have also shown a direct relationship between the ARA content of phospholipids in immune cells and the ability of these cells to produce PGE2, such that this synthesis is increased when animals receive a diet enriched in ARA (Peterson *et al.*, 1998), and decreased when animals are fed a diet enriched in EPA and DHA (Chapkin *et al.*, 1991).

## 6.3 N-3 PUFA

As mentioned by Teague *et al.* (2016), EPA and DHA are bioactive molecules with great potential for manipulating the immune system, being able to influence both innate and adaptive immunity. N-3 PUFA have pleiotropic effects based on molecular mechanisms including lowering of ARA levels, and thereby downstream of pro-inflammatory mediators, and generation of specialized pro-resolving lipid mediators (Whelan *et al.*, 2016).

Among the different dietary fatty acid classes, n-3 PUFA are described as having major anti-inflammatory effects, notably in the case of different physiopathological conditions with inflammatory components such as atherosclerosis and cardiovascular disease, inflammatory bowel, and allergic diseases. (Calder, 2001, 2017; Myles, 2014).

The existing data to date on the impact of n-3 PUFA on immune function mainly concern n-3 long-chain PUFA, EPA and DHA, and few their metabolic precursor ALA.

Kelley *et al.* (1991) studied for 8 weeks the effects of adding linseed oil to the diet of 10 healthy men (aged 21–37 years) in order to increase their level of ALA intake from 1 to 18 g/day. This diet has resulted in increased levels of ALA, EPA and DHA in the lipids contained in peripheral mononuclear blood cells (Kelley *et al.*, 1993), and decreased proliferation of these same cells in response to different recall antigens (Kelley *et al.*, 1991). Overall, ALA tended to suppress some of indices of cell-mediated immunity (T-cell functions) without affecting any of the indices of humoral immunity (B-cell functions) tested.

In another study, healthy subjects (aged 24–44 years) were fed a diet containing flaxseed oil *versus* sunflower oil for 4 weeks, with lipids accounting for 30% of the total energy intake in both diets and the ALA intake level being 13.7 and 1.1 g respectively (Caughey *et al.*, 1996). The diet enriched with ALA (linseed oil) reduced the production of pro-inflammatory cytokines (TNF-alpha, IL-1) measured *in vitro*.

Baker *et al.* (2016) recently reviewed the few controlled intervention studies investigating the effects of increased ALA consumption – from 2 to 20 g per day, for 8 to 24 weeks – on immune function other than inflammation have been conducted in adult human subjects.

Baker and co-authors quote, for example, Wallace *et al.* (2003) who reported, in a randomised, placebo-controlled, double-blind, parallel study in 40 healthy males (aged 18–39 years) randomised to receive placebo or 3.5 g ALA per day or 0.44, 0.94 or 1.9 g/day (EPA + DHA) for 12 weeks, no effect of ALA on the functional activity of monocytes and lymphocytes. On the contrary, the two higher doses of EPA + DHA resulted in a significant decrease in IL-6 production by stimulated mononuclear cells.

In a placebo-controlled, double-blind, parallel study in 150 healthy men and women (aged 25–72 years) randomly assigned to placebo, 4.5 or 9.5 g ALA/d, 0.77 or 1.7 g EPA + DHA/d for 6 months, Kew *et al.* (2003b) observed no effect of ALA (and EPA + DHA) on the functional activity of neutrophils, monocytes, or lymphocytes.

Thies *et al.* (2001a) assessed in a randomized, placebo-controlled, double-blind and parallel assay in healthy subjects (aged 55–75 years), the effects of a 12-week dietary supplementation with moderate levels of ALA (2 g/d) *versus* other PUFA (gamma-linolenic acid (GLA), ARA, DHA or EPA + DHA) on the proliferation of mitogen-stimulated human peripheral blood mononuclear cells (PBMC) and on the production of cytokines by those cells. Although some of the other PUFA (GLA and EPA + DHA) caused a significant decrease (up to 65%) in lymphocyte proliferation, the treatment with ALA not affected the production of IL-2 or IFN-gamma by PBMC, or the number or proportion of T or B lymphocytes, helper or cytotoxic T lymphocytes or memory helper T lymphocytes in the circulation. The same type of study was conducted to assess the effects of the same dietary supplementations on the NK cell activity of human PBMC. A treatment with ALA had no effect on the NK cell activity in healthy subjects (Thies *et al.*, 2001b).

As a conclusion, Baker *et al.* (2016) acted that except very high intakes of ALA suppressing some aspects of immune function, it seems that moderate-high intakes of ALA (2 to 9.5 g/d) for at least 20 weeks may have no impact on the immune function.

Similarly, different authors have investigated the effects of EPA and DHA supplementation. Thus, *in vitro* data showed that supplementation of the culture medium with EPA and DHA inhibited the production of different pro-inflammatory cytokines (TNF-alpha, IL-1, IL-6) for different cell types (Babcock *et al.*, 2002; Zhao *et al.*, 2004).

In humans, the impact of fish consumption as a source of EPA and DHA has also been studied. A study testing the effects of consuming 120 to 188 g of fish per day (or 1.23 g/day of EPA + DHA) for 6 months in elderly subjects showed a reduction in lymphocyte proliferation, as well as in the

production of different pro-inflammatory cytokines measured *in vitro* (IL-1, IL-6 and TNF-alpha (Meydani *et al.*, 1993). On the other hand, a study conducted in healthy subjects consuming 500 g salmon per day (2.3 g EPA and 3.6 g DHA/day) for 40 days, *versus* a control diet, did not show any effects on different parameters of the immune response (Kelley *et al.*, 1992b).

A number of studies have also evaluated the effects of fish oil-based supplementation, with tested amounts ranging from 2 to 30 g per day (or 0.55 to 8 g/day of EPA + DHA), over periods ranging from 4 to 52 weeks (Kelley, 2001). Most studies have shown a 25 to 75% decrease in the secretion of these cytokines measured *in vitro* in response to EPA and DHA supplementation of 2.4 g/day or more for at least 4 weeks in healthy subjects (Kelley *et al.*, 1998b; Kelley *et al.*, 1999; Babcock *et al.*, 2002). Conversely, there does not appear to be any effects on these cytokines for lower EPA + DHA supplementation (Mølviq *et al.*, 1991; Cooper *et al.*, 1993; Schmidt *et al.*, 1996).

Finally, other data have shown the effect of DHA alone (6 g/day for 12 weeks) with a decrease in the number of circulating neutrophils, a decrease in the production of cytokines (IL-1 beta and TNF-alpha) and pro-inflammatory eicosanoids from ARA (PGE2 and LTB4) of around 25 to 70%. In contrast, DHA supplementation has not reduced the proliferation of B and T lymphocytes suggesting that DHA can be used specifically to inhibit inflammatory responses without inhibiting immune responses involving B and T lymphocytes (Kelley *et al.*, 1999).

Recently, Whelan *et al.* (2016) reviewed from pre-clinical models the emerging evidence that n-3 PUFA (from fish oil) could target the function of B cells which are involved in inflammatory and humoral immune responses. Existing data suggest that n-3 PUFA may modify B cell antigen presentation, cytokine production and antibody generation. Several mechanisms of action are mentioned, including involvement of Th2 cytokines, enhanced production of specialized pro-resolving lipid mediators, and targeting protein lateral organization in lipid microdomains.

The impact of an intake of EPA + DHA in the form of fish oil has also been investigated on the synthesis of resolvins (Calder, 2017). Thus, in rodents, an increased synthesis of resolvins was observed in animals fed a fish oil supplemented diet. In humans, significant concentrations of RvE1 and RvD1 were observed in the plasma of healthy volunteers subjected to 3 weeks of nutritional supplementation with fish oil.

Regarding the effects of EPA and DHA on the immune cell functional responses, it is difficult to construct a dose-response relationship from the existing literature. According to Calder (2017), some of the studies that fail to show an effect of n-3 PUFA on cytokine production have provided less than 2 g of EPA + DHA per day, which may be an insufficient dose. Others have indicated reduction in the production of inflammatory mediators with a minimum of 1.2 g per day of supplementation with EPA + DHA for 6 weeks (Kelley, 2001). Therefore, further studies are needed to establish adequate intake levels of n-3 PUFA.

## 7 Conclusion

Taken together, these data show an effect of dietary fatty acids on immune and inflammatory responses. However, the contradictory effects observed between studies may be explained by differences in lipid contents and fatty acid composition of the different diets tested, supplementation times, as well as the populations tested (age and health status).

There are many data on the effects of EPA and DHA diet supplementation on the functionality of immune cells. Among these, mention is made of the ability of these PUFA to decrease the production of pro-inflammatory eicosanoids from ARA, or pro-inflammatory cytokines, which can reduce the inflammatory component of the immune response.

Progress in understanding the mechanisms of action of n-3 PUFA has been made over the past 10 years, including the identification of novel bioactive lipid mediators with major inflammatory properties.

These specialized pro-resolving lipid mediators, associated with eicosanoids, are key signalling molecules in the immune functions, notably the resolution of inflammation, by playing a pivotal role in regulating the inflammatory profile and promoting return to homeostasis. But it seems that the interaction of n-3 and n-6 PUFA and their lipid mediator derivatives in the context of immunity and inflammation is complex and still not properly understood.

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**Cite this article as:** Buaud B. 2020. How fats we eat modulate our immunity?. *OCL* 27: 22.