Biochimica et Biophysica Acta 1851 (2015) 469–484

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Review

Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance☆

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ARTICLE INFO

Article history:
Received 16 May 2014
Received in revised form 12 August 2014
Accepted 13 August 2014
Available online 20 August 2014

Keywords:
Inflammation
Eicosanoid
Cytokine
Resolvin
Macrophage
Lymphocyte

ABSTRACT

Inflammation is a condition which contributes to a range of human diseases. It involves a multitude of cell types, chemical mediators, and interactions. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 (n − 3) fatty acids found in oily fish and fish oil supplements. These fatty acids are able to partly inhibit a number of aspects of inflammation including leukocyte chemotaxis, adhesion molecule expression and leukocyte–endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n − 6 fatty acid arachidonic acid, production of inflammatory cytokines, and T-helper 1 lymphocyte reactivity. In addition, EPA gives rise to eicosanoids that often have lower biological potency than those produced from arachidonic acid and EPA and DHA give rise to anti-inflammatory and inflammation resolving mediators called resolvins, protectins and maresins. Mechanisms underlying the anti-inflammatory actions of marine n − 3 fatty acids include altered cell membrane phospholipid fatty acid composition, disruption of lipid rafts, inhibition of activation of the pro-inflammatory transcription factor nuclear factor kappa B so reducing expression of inflammatory genes, activation of the anti-inflammatory transcription factor peroxisome proliferator activated receptor γ and binding to the G protein coupled receptor GPR120. These mechanisms are interlinked, although the full extent of this is not yet elucidated. Animal experiments demonstrate benefit from marine n − 3 fatty acids in models of rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and asthma. Clinical trials of fish oil in RA demonstrate benefit, but clinical trials of fish oil in IBD and asthma are inconsistent with no overall clear evidence of efficacy. This article is part of a Special Issue entitled "Oxygenated metabolism of PUFA: analysis and biological relevance".

1. Introduction

1.1. Inflammation: an overview

Inflammation is a key part of the host's defence mechanism against pathogenic organisms. Inflammation creates an environment that is hostile to pathogens, it initiates pathogen killing, and it induces changes of metabolism in the host. The inflammatory response involves interactions amongst many cell types and the production of, and responses to, a vast number of chemical mediators. Key early steps in the inflammatory response are an increased supply of blood to the site of inflammation and an increase in vascular wall permeability that permits plasma and large molecules to cross the endothelium, so delivering soluble mediators to the site of inflammation. Leukocytes migrate from the blood stream into the surrounding tissue, a process promoted by release of chemoattractants from the site of inflammation and by the up-regulation of adhesion molecules on the endothelium. These newly arrived and activated leukocytes then release chemical mediators at the site of inflammation. These mediators may include lipid-derived mediators (e.g. prostaglandins (PGs), leukotrienes (LTs), endocannabinoids,

Abbreviations: AEA, arachidonoyl ethanolamide; 2-AG, 2-arachidonoylglycerol; ARA, arachidonic acid; CB, endocannabinoid receptor; COX, cyclooxygenase; DHA, docosahexaenoic acid; DP, prostaglandin D receptor; DPA, docosapentaenoic acid; EP, prostaglandin E receptor; EPA, eicosapentaenoic acid; GP130, glycoprotein 130; IBD, inflammatory bowel disease; ICAM, intercellular adhesion molecule; IκB, inhibitory subunit of nuclear factor κB; IL, interleukin; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; MyD88, myeloid differentiation primary response gene 88; NFκB, nuclear factor κB; NSAIDs, non-steroidal anti-inflammatory drugs; PAF, platelet-activating factor; PG, prostaglandin; PPAR, peroxisome proliferator activated receptor; RA, rheumatoid arthritis; RXR, retinoid X receptor; Th1, T-helper 1; Th2, T-helper 2; Th-17, T helper 17; TLR, toll-like receptor; TNF, tumour necrosis factor; TX, thromboxane; VCAM, vascular cell adhesion molecule.

☆ This article is part of a Special Issue entitled "Oxygenated metabolism of PUFA: analysis and biological relevance".

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http://dx.doi.org/10.1016/j.bbalip.2014.08.010
1388-1981/

platelet activating factor (PAF)), peptide mediators (e.g. cytokines, chemokines), reactive oxygen species (e.g. superoxide anion, hydrogen peroxide), amino acid derivatives (e.g. histamine, nitric oxide) and enzymes (e.g. matrix proteases) depending upon the cell type involved, the nature of the inflammatory stimulus, the anatomical site involved, and the stage during the inflammatory response. This influx of cells into the site of inflammatory activity and the presence of the inflammatory mediators produced as a result generate the cardinal signs of inflammation: redness, swelling, heat, pain and loss of function.

The cellular activities involved in the inflammatory response and the chemical mediators produced, although designed to be damaging to pathogens, can cause damage to host tissues. However, inflammation is normally self-limiting and resolves, often rapidly, due to the activation of negative feedback mechanisms like secretion of anti-inflammatory cytokines or pro-resolving lipid mediators, inhibition of pro-inflammatory signalling cascades, shedding of receptors for inflammatory mediators, and activation of regulatory cells. Loss of these regulatory processes can result in excessive, inappropriate or on-going inflammation that can cause irreparable damage to host tissues. As a result, inflammation may become pathological and disease can occur (Table 1). In some cases, such as rheumatoid arthritis (RA), inflammatory bowel diseases (IBD) and asthma, the central role of inflammation to the pathology is well recognized: individuals with these conditions have heavy infiltration of inflammatory cells at the site of disease activity (e.g. the joints, the intestinal mucosa, the lungs), they have elevated concentrations of inflammatory mediators at those sites and in the systemic circulation, and they are treated with anti-inflammatory drugs. In other cases, such as atherosclerosis and obesity, the role of inflammation has emerged more recently and its contribution to the pathology alongside the many other factors involved is less clear. Certainly, individuals with these conditions show infiltration of inflammatory cells at the site of disease activity (e.g. the blood vessel wall, adipose tissue), and have moderately elevated concentrations of inflammatory mediators in the systemic circulation, but they are not treated, primarily, with anti-inflammatory drugs.

This article will describe the actions of marine omega-3 (n−3) fatty acids within the inflammatory system, the mechanisms involved, and the attempts to use these fatty acids to help treat diseases with an inflammatory component. This article is updated and extended from previous reviews on the topic [1,2].

Table 1
Some diseases and conditions with an inflammatory component.

Disease/condition
Rheumatoid arthritis
Crohn's disease
Ulcerative colitis
Lupus
Type-1 diabetes
Cystic fibrosis
Childhood asthma
Adult asthma
Allergic disease
Chronic obstructive pulmonary disease
Psoriasis
Multiple sclerosis
Atherosclerosis
Cancer
Obesity
Non-alcoholic fatty liver disease
Neurodegenerative diseases of ageing
Cachexia
Acute cardiovascular events
Response to surgery, injury, trauma and critical illness

1.2. Marine n−3 fatty acids — an overview

Omega-3 (ω−3 or n−3) fatty acids are a family of polyunsaturated fatty acids characterised by having the last double bond between carbon numbers 3 and 4 in the hydrocarbon (acyl) chain counting the terminal methyl carbon as number one. Longer chain n−3 fatty acids include eicosapentaenoic acid (EPA; 20:5n−3), docosapentaenoic acid (DPA; 22:5n−3) and docosahexaenoic acid (DHA; 22:6n−3). Although EPA, DPA and DHA can be synthesised from simpler plant-derived n−3 fatty acids (Fig. 1), this metabolic pathway does not appear to be very efficient in many humans [3]. It is not possible to fully consider the roles of marine n−3 fatty acids within inflammatory processes without considering also the roles of saturated and n−6 fatty acids. Saturated fatty acids are fatty acids without double bonds in their hydrocarbon chain, while n−6 fatty acids are a family of polyunsaturated fatty acids characterised by having the last double bond between carbon numbers 6 and 7 in the hydrocarbon chain counting the terminal methyl carbon as number one. Within inflammation the major n−6 fatty acid is arachidonic acid (ARA; 20:4n−6), which is synthesised from simpler plant-derived n−6 fatty acids in a pathway that competes with the synthesis of EPA (Fig. 1).

EPA, DPA and DHA are found in significant quantities in fish and other seafood, and so they may be collectively referred to as marine n−3 fatty acids. These fatty acids are found in the flesh of both lean and oily fish, with much greater amounts in the latter, and in the livers of some lean fish (e.g. cod). In people who eat little fish, intakes of marine n−3 fatty acids are low (typically <0.2 g/day [4] and probably much lower than this [5]). A single lean fish meal (e.g. one serving of cod) could provide about 0.2 to 0.3 g of marine n−3 fatty acids, while a single oily fish meal (e.g. one serving of salmon or mackerel) could provide 1.5 to 3.0 g of these fatty acids. Fish oil is prepared from the flesh of oily fish (e.g. tuna) or from the livers of lean fish (e.g. cod liver). In a typical fish oil supplement EPA and DHA together comprise about 30% of the fatty acids present, so that a 1 g fish oil capsule will provide about 0.3 g of EPA + DHA. More concentrated oils are also available. In fish and in traditional fish oil supplements most of the fatty acids are present as components of triacylglycerols. Marine n−3 fatty acids are also available in other forms such as in krill oil, which provides EPA and DHA partly in the form of phospholipids, and as ethyl esters in pharmaceutical grade, highly concentrated preparations.

2. Marine n−3 fatty acids and the fatty acid composition of the phospholipids in the membranes of cells involved in inflammation

It is generally considered that the influence of fatty acids on inflammatory cell responses, and so on inflammatory processes, involves their incorporation into cell membrane phospholipids [6]. Hence there has been much interest in the fatty acid composition of cells involved in inflammation and how that might change when the intake of marine n−3 fatty acids is increased. Cells like lymphocytes, macrophages or neutrophils taken from laboratory rodents fed standard low fat diets in which the bulk of the fat comes from vegetable oil have high amounts (often ~20% of total fatty acids) of ARA in their membrane phospholipids and very low amounts of EPA and DHA [7–9]. Inclusion of EPA or DHA or both in the diets fed to laboratory rats or mice results in increased amounts of those fatty acids in phospholipids of lymphocytes, macrophages and neutrophils [9,10]. Phospholipids of blood cells involved in inflammatory processes taken from humans consuming a typical Western diet typically contain 15 to 20% of fatty acids as ARA, 0.5 to 1% as EPA and 2 to 3% as DHA [11–22]. Increased intake of marine n−3 fatty acids results in increased amounts of EPA and DHA (and also DPA) in these phospholipids [11–22]. In both animal and human experiments incorporation of marine n−3 fatty acids into membrane phospholipids of cells involved in inflammation occurs in a time- [15–22] and dose-dependent fashion [16,20,22] and is largely at the expense of ARA

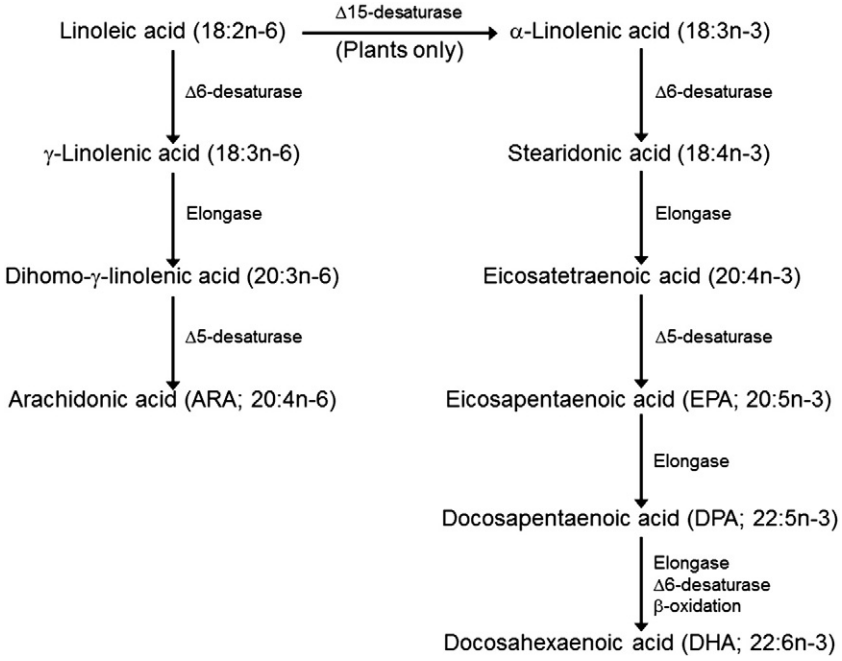

Fig. 1. Pathways of biosynthesis n−6 and n−3 fatty acids. ARA, arachidonic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid.

(Figs. 2 and 3). These changes in fatty acid composition seem to be important in modifying production of lipid mediators, which are generated from membrane phospholipids, and in regulating formation of lipid rafts within membranes in response to an inflammatory stimulus (see later sections).

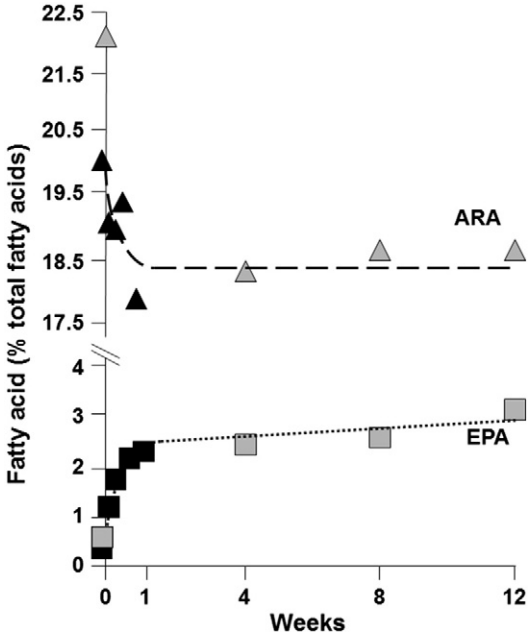

Fig. 2. Time-dependent changes in eicosapentaenoic acid (EPA) and arachidonic acid (ARA) content in human mononuclear cells. Healthy human volunteers consumed fish oil providing 2.1 g EPA and 1.1 g DHA per day for 1 week [21] or for 12 weeks [15]. Blood was sampled at several time points in each study and mononuclear cells prepared. Fatty acid composition of the cells was determined by gas chromatography. Mean values are shown. Squares represent EPA and triangles represent ARA. Black symbols represent data from Faber et al. [21] and grey symbols represent data from Yaqoob et al. [15]. Modified from [2].

3. Marine n−3 fatty acids and lipid mediators involved in inflammatory processes

3.1. Marine n−3 fatty acids and ARA metabolites produced by cyclooxygenase, lipoxygenase and cytochrome P450 pathways

Eicosanoids are generally considered to be oxidized derivatives of 20-carbon fatty acids and include PGs, thromboxanes (TXs), LTs, and lipoxins (LXs). The initial substrate for eicosanoid synthesis is a membrane phospholipid. Because of its prevalence in the phospholipids of membranes of cells involved in inflammatory processes, ARA is usually the major substrate for eicosanoid synthesis (Fig. 4). Prior to synthesis of PGs, TXs, LTs and LXs, ARA is released from the sn-2 position of membrane phospholipids by the action of phospholipase A_2 enzymes which are activated by inflammatory stimuli. ARA may also be released from the sn-2 position of diacylglycerols by the action of diacylglycerol lipase to produce 2-ARA-glycerol followed by the action of monoacylglycerol

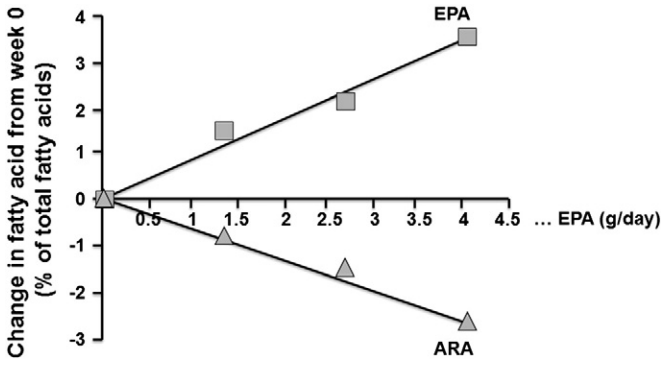

Fig. 3. Dose-dependent changes in eicosapentaenoic acid (EPA) and arachidonic acid (ARA) contents in human mononuclear cells. Healthy human volunteers consumed a supplement providing 0, 1.35, 2.7 or 4.05 g EPA per day for 12 weeks. Blood was sampled at 0 and 12 weeks and mononuclear cells prepared. Fatty acid composition of the cells was determined by gas chromatography. Mean values for change from week 0 are shown; data for ARA have been normalised so that the change from week 0 in the group receiving no supplemental EPA is zero. Squares represent EPA and triangles represent ARA. Data are for the older subjects reported in [20].

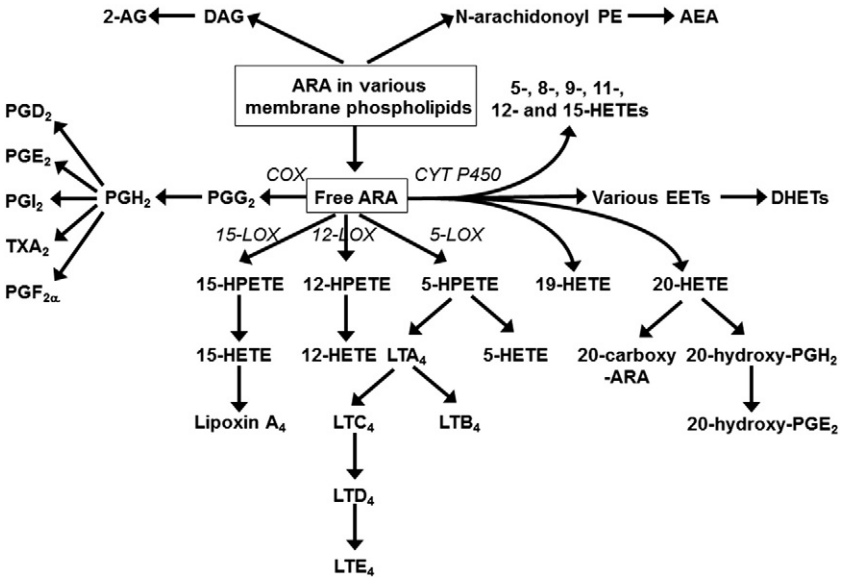

Fig. 4. Overview of the pathways of eicosanoid synthesis from arachidonic acid. AEA, arachidonoyl ethanolamine (anandamide); 2-AG, 2-arachidonoyl glycerol; ARA, arachidonic acid; COX, cyclooxygenase; CYTP450, cytochrome P450 enzymes; DAG, diacylglycerol; DHET, dihydroxyeicosatrienoic acid; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; EET, epoxyeicosatrienoic acid; LOX, lipoxygenase; LT, leukotriene; PE, phosphatidylethanolamine; PG, prostaglandin; TX, thromboxane. Note that not all enzymes are named and that not all metabolites are shown.
Taken from [1].

lipase. The free ARA then acts as a substrate for cyclooxygenase (COX), lipoxygenase (LOX) or cytochrome P450 enzymes (Fig. 4). COX enzymes lead to PGs and TXs, LOX enzymes to LTs and LXs, and cytochrome P450 enzymes to hydroxyeicosatetraenoic and epoxyeicosatrienoic acids (Fig. 4). ARA metabolism results in 2-series PGS and TXs and 4-series LTs and LXs. While COX-1 is said to be involved in cellular housekeeping functions, COX-2 is induced in inflammatory cells by classical inflammatory stimuli such as bacterial endotoxin, resulting in a large increase on PG generation. PGE_2, other 2-series PGs and the 4-series LTs are amongst the best known mediators and regulators of inflammation [23–25]. They act through binding to specific receptors, usually G protein-coupled receptors (Table 2) [26], and their synthesis and action are targets for a range of non-specific and specific anti-inflammatory pharmaceuticals.

Since increased intake of marine n−3 fatty acids decreases the amount of ARA in the membrane phospholipids of cells involved in inflammation, it might be expected that production of ARA-derived mediators would be decreased simply because of a reduced amount of substrate available. Furthermore, EPA has been shown to inhibit ARA metabolism and to decrease expression of the COX-2 gene (see Sections 3.2 and 5). Whatever the exact mechanism involved, animal studies have shown that production of ARA-derived eicosanoids like PGE_2 is decreased by EPA or DHA feeding [9,10,27]. Consistent with this, numerous studies in healthy human volunteers have described decreased production of 2-series PGs and 4 series-LTs by inflammatory cells following use of marine n−3 fatty acid supplements for a period of weeks to months [11–14,20,28–30]. Similar effects of such supplements have been seen in patients with chronic inflammatory diseases such as RA [31–35] and IBD [36–40]. Studies in humans showing that oral marine n−3 fatty acids decrease production of ARA-derived eicosanoids have usually used fairly high intakes of EPA + DHA, most often several grams per day. Data from a dose–response study in healthy volunteers with a preparation of marine n−3 fatty acids rich in EPA are shown in Fig. 5 [20]. An EPA intake of 1.35 g/day for 3 months was not sufficient to influence ex vivo PGE_2 production by endotoxin-stimulated mononuclear cells, whereas an EPA intake of 2.7 g/day significantly decreased PGE_2 production [20], suggesting a threshold for an anti-inflammatory effect of EPA of somewhere between 1.35 and 2.7 g EPA per day.

3.2. Eicosanoid metabolites produced from EPA by cyclooxygenase and lipoxygenase pathways

Since EPA is a 20-carbon highly unsaturated fatty acid it is also a substrate for the COX, LOX and cytochrome P450 enzymes that produce eicosanoids; the metabolism of EPA is analogous to that shown for ARA in Fig. 4. However, the mediators produced from EPA have a different structure from those produced from ARA; EPA gives rise to 3-series PGs and TXs and to 5-series LTs. Increased generation of 5-series LTs has been demonstrated using macrophages from mice fed a diet containing EPA and DHA [10] and neutrophils from humans taking marine n−3 fatty acid supplements for several weeks [11–13]. Transgenic ('fat-1') mice bearing the *Caenorhabditis elegans* 'n−3 desaturase' gene are able to convert n−6 to n−3 fatty acids resulting in elevated n−3 fatty acid content in their tissues. These mice were shown to generate large amounts of PGE_3 within colonic tissue after chemical induction of colonic inflammation [41]. In general, the structural difference between ARA and EPA-derived eicosanoids renders the latter less biologically potent. This has been clearly demonstrated for the action of LTB_5 versus LTB_4 as a leukocyte chemoattractant where the former is 10 to 100-fold less potent [42–44]. One reason for this reduced biological potency is that eicosanoid receptors typically have a lower affinity for the EPA-derived mediator than for the ARA-derived one. This was explored in detail by Wada et al. [45] who identified, for example, 50 to 80% lower potency of PGE_3 compared with PGE_2 towards the EP1, EP2, EP3 and EP4 receptors. Thus, EPA results in decreased production of potent eicosanoids from ARA and increased production of weak eicosanoids. One exception to this is that the DP1 receptor prefers PGD_3 over PGD_2 [45]. This most likely explains observations of Tull et al. [46] studying neutrophil binding to endothelial monolayers under flow conditions. This adhesive interaction was diminished by inhibition of COX, by EPA, by PGD_3 and by a DP1 antagonist. The inhibitory effect of EPA was overcome by co-addition of ARA, or PGD_2 or a DP1 agonist. It was concluded that PGD_2 promotes the adhesive interaction acting via DP1 on neutrophils and that, in the presence of EPA, PGD_3 is formed and binds to DP1 so preventing the action of PGD_2, but not initiating an active response itself.

Table 2
A selection of lipid mediators and their receptors.Modified from [26] with permission from ILSI Europe.

Class	Mediator	Substrate	Receptor(s)
Prostanoids	PGD_2	Arachidonic acid via COX	DP1, DP2
	PGE_2	Arachidonic acid via COX	EP1, EP2, EP3, EP4
	$PGF_{2\alpha}$	Arachidonic acid via COX	FP
	PGI_2	Arachidonic acid via COX	IP
	TXA_2	Arachidonic acid via COX	TP
	PGD_3	Eicosapentaenoic acid via COX	DP1, DP2
	PGE_3	Eicosapentaenoic acid via COX	EP1, EP2, EP3, EP4
Leukotrienes	5-HETE	Arachidonic acid via 5-LOX	BLT2
	5-HPETE	Arachidonic acid via 5-LOX	OXE
	LTB_4	Arachidonic acid via 5-LOX	BLT1, BLT2
	LTC_4, D_4, E_4 (termed cysteinyl-LTs)	Arachidonic acid via 5-LOX	CysLT1, CysLT2
	15-HETE	Arachidonic acid via 15-LOX	BLT2
	15-HPETE	Arachidonic acid via 15-LOX	BLT2
	12-HETE	Arachidonic acid via 12-LOX	BLT2
	LTB_5	Eicosapentaenoic acid via 5-LOX	BLT1, BLT2
Lipoxins	LXA_4	Arachidonic acid via 15-LOX and 5-LOX or 5-LOX and 12-LOX (transcellular)	FPR2/ALX
Endocannabinoids	2-AG	1,2-Diacylglycerol with arachidonic acid at the sn-2 position	CB1, CB2
	AEA (anandamide)	N-arachidonoyl phosphatidylethanolamide via phospholipase D; in turn N-arachidonoyl phosphatidylethanolamide is formed from phosphatidylcholine with arachidonic acid at the sn-1 position and phosphatidylethanolamine	CB1, CB2
Resolvins, protectins and maresins	RvE1	Eicosapentaenoic acid via COX-2 and 5-LOX or 15-LOX and 5-LOX (transcellular)	RvE1 (ChemR23), BLT1
	RvD1	Docosahexaenoic acid via COX-2 and 5-LOX or via 15-LOX and 5-LOX (transcellular)	RvD1 (GPR32), ALX/FPR2
	PD1 (NPD1)	Docosahexaenoic acid via 15-LOX (transcellular)	Not yet known
	MaR1	Docosahexaenoic acid via 12-LOX (transcellular)	Not yet known
Choline phospholipid	PAF	1-alkyl,2-arachidonoyl-glycerophosphocholine via phospholipase A_2 and acetylation	PAF-R

Abbreviations: AEA, arachidonoyl ethanolamide; AG, arachidonoylglycerol; COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; MaR, maresin; NP, neuroprotectin; P, protectin; PAF, platelet-activating factor; Rv, resolvin; TX, thromboxane.

3.3. Marine n−3 fatty acids and endocannabinoids

Endocannabinoids are bioactive mediators produced by metabolism of phospholipids [47]. The two major ARA containing endocannabinoids are arachidonoyl ethanolamide (AEA), also known as anandamide, and 2-arachidonoylglycerol (2-AG). AEA is formed by a pair of reactions involving conversion of phosphatidylethanolamine to N-acylphosphatidylethanolamine followed by the action of phospholipase D. 2-AG is formed as a result of the sequential actions of phospholipase C and a diacylglycerol lipase. AEA and 2-AG act via the CB1 and CB2 receptors [47], and anti-inflammatory properties have been reported for both [48,49]. Increased availability of marine n−3 fatty acids in the diets of laboratory animals results in lower concentrations of AEA and 2-AG [50–52], probably because of the reduction in ARA in membrane phospholipids. Conversely, and mirroring what is seen in the classical eicosanoid system, dietary marine n−3 fatty acids increase the concentrations of endocannabinoids with either EPA or DHA in their structure. These include docosahexaenoyl ethanolamide and eicosapentaenoyl ethanolamide [50,52,53]. Ethanolamides that contain marine n−3 fatty acids still bind to the CB1 and CB2 receptors [54,55] and have marked anti-inflammatory properties in cell culture systems [56,57]. For example, both docosahexaenoyl ethanolamide and eicosapentaenoyl ethanolamide decreased endotoxin-induced interleukin (IL)-6 and monocyte chemotactic protein (MCP)-1 production by adipocytes [56]. Furthermore, docosahexaenoyl ethanolamide was a potent inhibitor of nitric oxide and MCP-1 production by endotoxin-stimulated macrophages [57], effects that were seen at the level of gene expression [57].

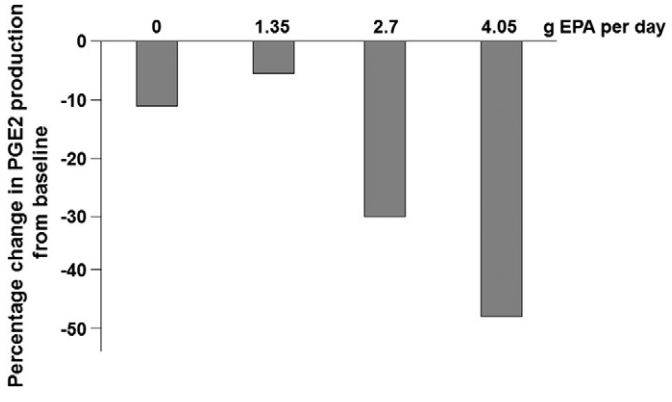

Fig. 5. Impact of increased intake of eicosapentaenoic acid (EPA) on prostaglandin (PG) E_2 production by endotoxin-stimulated mononuclear cells. Healthy human volunteers consumed a supplement providing 0, 1.35, 2.7 or 4.05 g EPA per day for 12 weeks. Blood was sampled at 0 and 12 weeks and mononuclear cells prepared. They were cultured with endotoxin for 24 h and PGE_2 concentrations in the culture medium were measured by immunoassay. Mean values for percentage change from week 0 are shown. Data are for the younger subjects reported in [20].

3.4. Inflammation resolving metabolites produced from EPA and DHA by cyclooxygenase and lipoxygenase pathways

One of the important steps forward in the field of n−3 fatty acid biology has been the elucidation of the structures, actions and mechanisms of pro-resolving lipid mediators produced from marine n−3 fatty acids. These include the resolvins produced from EPA (E-series) and DHA (D-series) and protectins and maresins produced from DHA; protectins are also referred to as neuroprotectins when generated within neural tissue. The synthesis of resolvins, protectins and maresins involves the COX and LOX pathways, with different epimers being produced in the presence and absence of aspirin [58–62] (Figs. 6 and 7). These pathways operate in a transcellular manner with the early steps occurring in one cell type and the latter in another [58–61]. More recently, analogous compounds have been shown to be produced from the third marine n−3 fatty acid DPA [63].

As might be expected, resolvin synthesis is increased by feeding laboratory rodent diets rich in marine n−3 fatty acids [64] and was shown to occur in fat-1 mice in which colitis had been induced [41]. Mas et al. [65] reported increased levels of resolvins in the blood of humans consuming increased intakes of marine n−3 fatty acids. Healthy volunteers consumed a supplement providing 1.4 g EPA plus 1 g DHA per day for 3 weeks. Serum and plasma contained

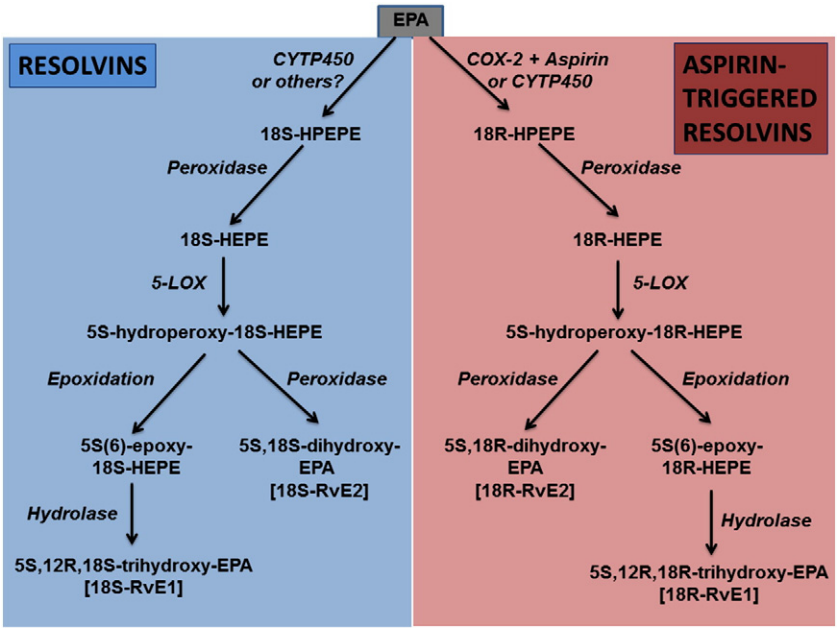

Fig. 6. Outline of the pathways of resolvin and aspirin-triggered resolvin biosynthesis from eicosapentaenoic acid (EPA). COX, cyclooxygenase; CYTP450, cytochrome P450 enzymes; HEPE, hydroxyeicosapentaenoic acid; HPETE, hydroperoxyeicosapentaenoic acid; LOX, lipoxygenase; Rv, resolvin. Note: not all intermediates and enzymes are shown.

the precursors 18R/S-hydroxyeicosapentaenoic acid and 17R/S-hydroxydocosahexaenoic acid and lower concentrations of resolvin D1, resolvin D2 and 17R-resolvin D1. In addition, protectin D1 was present but could not be quantified [65]. Recently human milk was reported to contain resolvins E1 and D1 [66].

The biological effects of resolvins, protectins and maresins have been examined extensively in cell culture and animal models of inflammation [58–62]. These models have shown them to be anti-inflammatory and inflammation resolving. For example, resolvin E1, resolvin D1 and protectin D1 all inhibited transendothelial migration of neutrophils, so preventing the infiltration of neutrophils into sites of inflammation; resolvin D1 inhibited IL-1β production; and protectin D1 inhibited TNF-α and IL-1β production [58–61]. The protectin D1 isomer protectin DX also possesses biological activity, as reviewed elsewhere recently [62]. Resolvins reduce inflammation and protect experimental animals in models of inflammatory disease including arthritis [67], colitis [68] and asthma [69–72]. The biological activities of resolvins are mediated via specific G-protein coupled receptors (Table 2).

3.5. Marine n−3 fatty acids and platelet-activating factor

PAF, also known as PAF-acether is a phospholipid mediator of leukocyte function and inflammation. It is produced by a variety of cells, especially platelets, endothelial cells, neutrophils, monocytes, macrophages and basophils. Its production is upregulated by inflammatory stimuli.

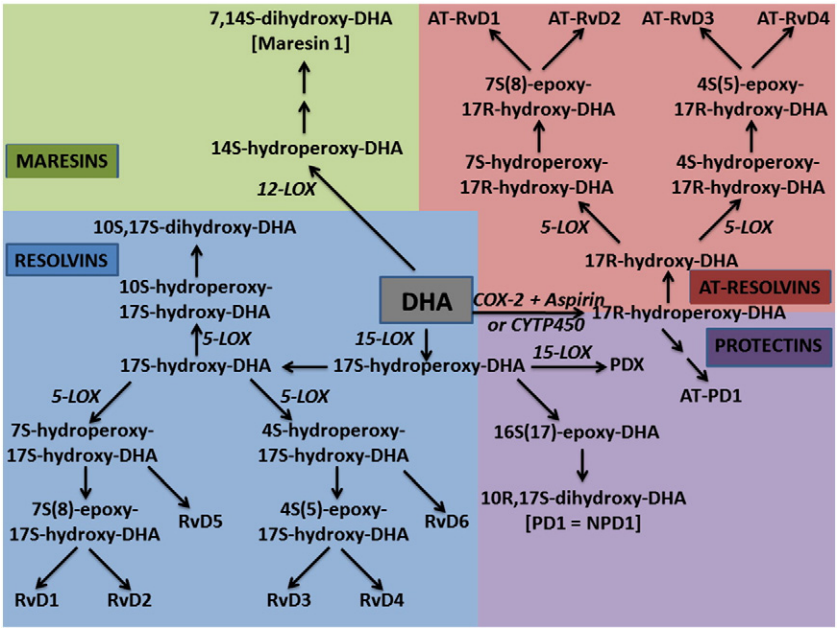

Fig. 7. Outline of the pathways of resolvin, protectin, aspirin-triggered resolvin and protectin, and maresin biosynthesis from docosahexaenoic acid (DHA). AT-P, aspirin-triggered protectin; AT-Rv, aspirin-triggered resolvin; COX, cyclooxygenase; CYTP450, cytochrome P450 enzymes; LOX, lipoxygenase; NP, neuroprotectin; P, protectin; PDX, protectin DX (10S,17S-dihydroxy-DHA); Rv, resolvin.

The primary source of PAF in inflammatory situations is the membrane phospholipid 1-alkyl,2-arachidonoyl-glycerophosphocholine which is cleaved into 1-alkyl,2-lyso-glycerophosphocholine by phospholipase A_2 before acetylation of the sn-2 position to produce PAF.

Studies examining the effect on marine n−3 fatty acids on PAF generation report inconsistent findings. A study with the monocytic THP-1 cell line reported that EPA decreased PAF production upon stimulation with a calcium ionophore [73], while a study with an eosinophilic cell line found that DHA but not EPA decreased PAF production in response to a calcium ionophore [74]. Those authors proposed that DHA was inhibitory because having DHA at the sn-2 position of the substrate phospholipid impairs its ability to act as a substrate for phospholipase A_2. However, Sperling et al. [75] reported that EPA but not DHA inhibited PAF production by human monocytes. Rat feeding studies also produce inconsistencies: feeding marine n−3 fatty acids was reported to lower the concentration of the PAF in plasma [76] and to decrease PAF production by peritoneal cells [77] but to have no effect on PAF production by blood neutrophils [78,79]. These latter studies reported effects of dietary marine n−3 fatty acids on production of PGE_2, TXB_2 and LTB_4 (decreased) and LTB_5 (increased) [78,79]. Supplementation trials with marine n−3 fatty acids in healthy subjects reported no effect on PAF production by neutrophils [80–82]. In contrast, there are reports that supplementation with high dose marine n−3 fatty acids reduces PAF production by monocytes from healthy volunteers [75] and from patients with RA [83].

4. Marine n−3 fatty acids and protein mediators involved in inflammatory processes

4.1. Marine n−3 fatty acids and cytokines

Cytokines are small proteins that are released by cells, especially, but not exclusively, those that act within the inflammatory and immune systems. Cytokines act through specific receptors to affect the activity of the same (i.e. the releasing) or other cells. Cytokines include TNF, various ILs, interferons, chemokines, and lymphokines. They are produced by a broad range of cells including monocytes and macrophages, T lymphocytes, B lymphocytes and mast cells, as well as other cell types like endothelial cells, fibroblasts and adipocytes; a given cytokine may be produced by more than one type of cell. Cytokines are associated with inflammatory diseases, with higher levels of TNF, IL-1β, IL-6 and IL-8 being a common feature of many inflammatory conditions [26,84,85].

Much of the focus of early research on marine n−3 fatty acids and inflammation was on their effects on the production of classic pro-inflammatory cytokines TNF, IL-1β and IL-6, usually examined in response to stimulation of monocytic cells with bacterial endotoxin. Early studies demonstrated that EPA and DHA inhibited endotoxin-stimulated production of IL-6 and IL-8 by cultured human endothelial cells [86,87], while EPA or fish oil inhibited endotoxin-induced TNF production by cultured monocytes [88–91]. Feeding fish oil to mice decreased production of TNF, IL-1β and IL-6 by endotoxin-stimulated macrophages [27,92,93] and decreased circulating TNF, IL-1β and IL-6 concentrations in mice injected with endotoxin [94]. Some animal studies also report that marine n−3 fatty acids increase the concentration of the anti-inflammatory cytokine IL-10 [95]. Several studies providing marine n−3 fatty acid supplements to healthy human volunteers have reported decreased production of TNF, IL-1β and IL-6 by endotoxin-stimulated monocytes or mononuclear cells [12,14,28,30], although not all studies report this effect. Some of the studies that fail to show an effect of marine n−3 PUFAs on cytokine production have provided <2 g EPA + DHA per day, which may be an insufficient dose. In patients with RA, fish oil supplements resulted in decreased IL-1 production by monocytes [96], decreased plasma IL-1β concentrations [97] and decreased serum TNF concentrations [98].

4.2. Marine n−3 fatty acids and adhesion molecules

Adhesion molecules are proteins expressed on the surface of many cell types including endothelial cells and leukocytes. These molecules form ligand pairs that promote interaction between the different cell types and it is through these interactions that leukocytes in the bloodstream interact with the blood vessel wall and then leave the bloodstream to move to a site of inflammatory activity. Many adhesion molecules are upregulated by inflammatory stimuli such as endotoxin [86]. Furthermore, higher levels of adhesion molecule expression have been associated with some inflammatory conditions [99–104] and in animal models blocking certain adhesion molecules with antibodies or thorough gene knockout reduces or prevents the pathology [105,106].

Effects of fatty acids on adhesion molecules have most frequently been examined in cell culture models, especially using endothelial cells and monocytic cells. Cell culture models demonstrated decreased expression of adhesion molecules on endothelial cells [86,107,108] and monocytes [109] exposed to marine n−3 fatty acids, especially DHA. Rat feeding studies have found that including marine n−3 fatty acids in the diet can result in lower adhesion molecule expression on macrophages [110] and lymphocytes [111]. In some of these studies the lower adhesion molecule expression was shown to have a functional effect such as decreasing adhesion between inflammatory cells and endothelial cells [86,108,111]. More recent studies have demonstrated that both EPA and DHA can reduce the adhesive interaction between monocytes and endothelial cell monolayers studied under flow conditions [46,112]. Supplementing the diet of healthy humans with fish oil providing about 1.5 g EPA + DHA per day resulted in a lower level of expression of intercellular adhesion molecule (ICAM)-1 on the surface of blood monocytes stimulated ex vivo with interferon-γ [113]. Consumption of 1.8 g EPA + DHA per day by patients with peripheral vascular disease decreased the adhesive interaction of their monocytes to endothelial monolayers in culture [114]. Dietary fish oil providing 1.1 g EPA + DHA per day was found to decrease circulating levels of soluble (i.e. circulating in plasma) vascular cell adhesion molecule (VCAM)-1 in elderly subjects [115], but it is not clear if this represents decreased surface expression of VCAM-1. EPA (1.8 g per day) decreased the concentrations of soluble ICAM-1 and soluble VCAM-1 in the bloodstream of patients with metabolic syndrome [109].

4.3. Marine n−3 fatty acids and matrix metalloproteinases

Matrix metalloproteinases (MMPs) are proteases that are able to degrade extracellular matrix proteins and many MMPs are linked to the tissue damage seen in inflammatory conditions. Their synthesis is regulated by many factors including inflammatory cytokines and eicosanoids. Numerous in vitro studies showed that marine n−3 fatty acids reduced mRNA or protein levels of various MMPs in cancer cells [116–119], myocytes [120], fibroblasts [121], keratinocytes [122], macrophages [123] and chondrocytes [124]. MMPs to be affected in vitro include MMP-1, -2, -3, -9, -10 and -13, with several studies reporting effects on MMP-1 and -9 in multiple cell types. There are relatively few studies investigating the impact of dietary marine n−3 fatty acids and MMPs. Dogs fed fish oil showed reduced MMP-2 and -9 in the knee synovium [125]. Human studies found no effects of supplemental marine n−3 fatty acids on serum MMP-9 in healthy subjects [126], in patients at risk of coronary heart disease [127] or in post-myocardial infarction patients [128]. Although Yusof et al. [129] saw no effect of 1.8 g EPA + DHA per day on serum MMP-2 in patients awaiting carotid endarterectomy, there were lower mRNA levels for MMP-7, -9, and -12 within the atherosclerotic plaques of those patients [130]. There do not appear to be studies of marine n−3 fatty acids and MMPs in patients with chronic inflammatory diseases.

5. Alternate mechanisms of action of marine n−3 fatty acids involving altered pro- and anti-inflammatory transcription factor activation

Nuclear factor kappa B (NFκB) is one of the main transcription factors involved in up-regulation of the genes encoding proteins involved in inflammation including many cytokines, adhesion molecules and COX-2 [131,132]. In its inactive state NFκB exists as a trimer in the cytosol; one of the subunits of this trimer as an inhibitory subunit called inhibitory subunit of NFκB (IκB). NFκB is activated through a signalling cascade triggered by various extracellular inflammatory stimuli, including endotoxin binding to toll-like receptor (TLR) 4. This cascade involves phosphorylation of IκB, which then dissociates from the remaining dimer and is degraded. This allows translocation of the remaining NFκB dimer to the nucleus where it binds to response elements and upregulates gene expression [133]. As described above, marine n−3 fatty acids decrease cell surface expression of adhesion molecules and production of inflammatory cytokines and COX-2 metabolites. One common mechanism to explain these effects would be an impact on the NFκB system. In line with this, EPA or fish oil decreased endotoxin-induced activation of NFκB in human monocytes [88–90] and this was associated with decreased IκB phosphorylation [90,91]. Likewise, DHA reduced NFκB activation in response to endotoxin in cultured macrophages [134] and dendritic cells [135,136], an effect that involved decreased IκB phosphorylation [134]. In contrast, saturated fatty acids, especially lauric acid (12:0), directly enhanced NFκB activation in macrophages [134] and dendritic cells [135]. Lauric acid did not activate NFκB or induce COX-2 expression in macrophages not expressing TLR4 [134], suggesting that lauric acid somehow interacts directly with TLR4. Both EPA and DHA were able to prevent lauric acid-induced activation of NFκB and COX-2 expression in macrophages [134]. Myeloid differentiation primary response gene 88 (MyD88) is a cell membrane-associated adapter protein used by TLR4 in the early stages of the signalling cascade that eventually activates NFκB. Although DHA inhibited COX-2 expression in macrophages bearing constitutively active TLR4, this effect did not occur in macrophages not bearing constitutively active MyD88 [134] suggesting that DHA acts upstream of MyD88. It is known that TLR4, MyD88 and other signalling proteins associate into lipid rafts in inflammatory cells exposed to endotoxin. Wong et al. [137] demonstrated that exposure of macrophages to lauric acid induced this same association and that DHA inhibited the ability of both endotoxin and lauric acid to promote recruitment of signalling proteins into rafts. Thus, the differential effects of fatty acids on inflammatory signalling initiated through TLR4 and impacting on NFκB appear to relate to their ability to promote or disrupt raft formation within the membrane of inflammatory cells.

A second mechanism by which marine n−3 fatty acids might influence NFκB activation involves peroxisome proliferator activated receptor (PPAR)-γ. This is a transcription factor which acts in an anti-inflammatory manner [138]. For example PPAR-γ knock-down mice show enhanced susceptibility to chemically-induced colitis [139] and PPAR-γ agonists reduce murine colitis [139–141]. One of the actions of PPAR-γ is to physically interfere with the translocation of NFκB to the nucleus [142]. PPAR-γ can be activated by marine n−3 fatty acids [143–146] and DHA induced PPAR-γ in dendritic cells, an effect associated with inhibition of NFκB activation and reduced production of the pro-inflammatory cytokines TNF and IL-6 following endotoxin stimulation [136]. Furthermore, DHA induced a number of known PPAR-γ target genes in dendritic cells, suggesting that this is an important anti-inflammatory mechanism of action of DHA and perhaps also of EPA [147]. Eicosanoids and lipid mediators produced from arachidonic acid, EPA and DHA can also bind and regulate PPAR-γ [143,144,146], this being an important mechanism by which these fatty acids affect inflammatory processes. A recent paper reported that the EPA derivatives PGD_3 and 15-deoxy-PGD_3 activate PPAR-γ in adipocytes, a process linked to the induction of the anti-inflammatory adipokine adiponectin [148]. Thus, activation of PPAR-γ may itself be one of the anti-inflammatory mechanisms of action of marine n−3 fatty acids and this may also link to the inhibition of NFκB activation described above. PPAR-γ can also form heterodimers with the retinoid-X-receptor (RXR); thus modulation of PPAR-γ expression of activity by marine n−3 fatty acids could also impact on genes regulated by RXR. Furthermore, marine n−3 PUFAs may affect activation of RXR itself [149,150]. Indeed, the PPAR-γ:RXR heterodimer was identified to be the target activated by DHA to induce its effects on dendritic cells [147]. Marine n−3 fatty acids may also act on inflammation through regulating the activation state of other transcription factors including activator protein 1 [151–154].

Recently a further mechanism by which marine n−3 fatty acids might affect NFκB activation has been identified. GPR120 is a G-protein coupled cell membrane receptor expressed on macrophages [155] which can bind long chain fatty acids. A synthetic agonist of GPR120 inhibited the macrophage response to endotoxin, an effect which involved maintenance of cytosolic IκB and a decrease in production of TNF and IL-6 [155], suggesting that GPR120 is involved in anti-inflammatory signalling. Furthermore the effects of the GPR120 agonist were similar to those of EPA and DHA. Oh et al. [155] found that both EPA and DHA, but not ARA, or palmitic or myristic acids, enhanced GPR120-mediated gene activation and they went on to study the effects of DHA in further detail. The ability of DHA to inhibit responsiveness of macrophages to endotoxin, such as inhibition of IκB kinase phosphorylation, IκB phosphorylation and degradation, and TNF, IL-6 and MCP-1 production already well demonstrated, was abolished in GPR120 knockdown cells. These findings suggest that the inhibitory effect of DHA (and probably also of EPA) on NFκB might occur via GPR120 which induces signalling that interferes with the pathway that activates NFκB.

Thus, recent studies suggest three alternative mechanisms by which EPA and DHA might act to suppress inflammatory signalling via NFκB: activation of PPAR-γ which physically interacts with NFκB preventing its nuclear translocation, interfering with early membrane events involved in activation of NFκB via TLR4 and MyD88, and action via GPR120 which initiates an anti-inflammatory signalling cascade that inhibits signalling leading to NF-kB activation (Fig. 8). The extent to which these three mechanisms are interlinked is not clear at this stage.

6. Marine n−3 fatty acids and T cell reactivity

T lymphocytes (aka T cells) play central roles in the immune system acting as both effector cells and regulatory cells. The major families of T cells express either CD4 or CD8 on their surface. Different immunologic stimuli trigger differentiation of naive $CD4^+$ T cells along different developmental pathways resulting in different T cell phenotypes emerging. Initially these were described as T-helper 1 (Th1) and T-helper 2 (Th2) cells and were associated with different types of host defence and with different pathological or disease states. For example Th1 cells are involved in defence against bacteria and viruses and are associated with some chronic inflammatory conditions including RA [156]. On the other hand Th2 cells are involved in defence against parasites and are associated with allergic inflammation [156]. In more recent years other subclasses of T cells have been described including T-helper 17 (Th17) cells and regulatory T cells; again both of these cell types have a role in host defence and in inflammatory disease [157,158].

In vitro experiments demonstrate that both EPA and DHA can inhibit T-cell proliferation [8,159–162] and decrease the production of the key Th1 cytokine IL-2 [8,161,162]. Animal feeding studies with fairly high amounts of fish oil, or of EPA or DHA, also report reduced T-cell proliferative responses [163–167], alterations in Th1 cytokine gene expression [164] and modified production of Th1 and Th2 cytokines [166,168,169]. However the exact effect of marine n−3 fatty acids on Th1 and Th2 cytokines depends upon the model being used. Some studies in healthy human subjects have shown that increased intake of EPA + DHA decreases human T-cell proliferation [17,28] and IL-2 production [28]. Recent studies have explored the effects of marine n−3 fatty acids on Th17 cells [170–172]. Following

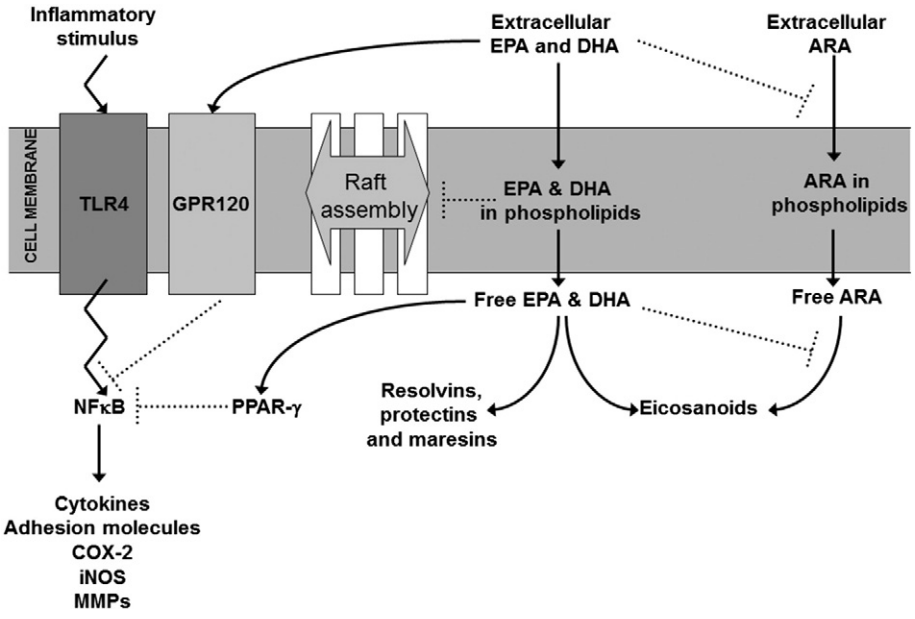

Fig. 8. Depiction of the interrelationship amongst the key anti-inflammatory actions of marine n−3 fatty acids. ARA, arachidonic acid; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GPR, G-protein coupled receptor; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase; NFκB, nuclear factor κ B, PPAR, peroxisome proliferator activated receptor. Dotted lines indicate inhibition.
Taken from [1].

induction of colitis in fat-1 mice, Th17 cell number in lymphoid tissues and the expression of Th17 cell type cytokine and chemokine receptor genes in the colonic mucosa were lower than seen in wild type mice [170]. Furthermore expression of the gene encoding IL-27, which suppresses Th17 cells, was higher in the fat-1 mice [170]. Another study demonstrated that including fish oil in a high fat diet fed to wild type mice resulted in lower expression of Th17 cell type cytokine genes in the colonic mucosa following induction of colitis [171]. IL-6 induces polarisation of Th17 cells acting via membrane-bound glycoprotein 130 (GP130). Allen et al. [172] found reduced responsiveness of $CD4^+$ T cells from fat-1 mice to IL-6 which was associated with lower GP130 homodimerisation.

The functional effects of marine n−3 fatty acids on T-cells have been linked with changes in membrane order [8], altered patterns of eicosanoid production [160] and modification of early signal transduction events, including reduced generation of diacylglycerol [166,167] and inhibition of the activation of specific isoforms of protein kinase C [173,174] and of mitogen-activated protein kinases [175,176]. One early event reported to be affected by marine n−3 fatty acids following T-cell activation is the phosphorylation of the signalling enzyme phospholipase C-γ1 which was decreased by fish oil feeding in rats [177] and by in vitro exposure of the JURKAT T cell line to EPA [178]. Effects of EPA on more upstream signalling proteins in T-cells have been demonstrated [178–180] including inhibition of the anchoring of the protein called linker of activated T-cells into the plasma membrane [180]. These in vitro studies identified that the effects of EPA and DHA on early signalling events in T-cells seem to involve the disruption of the formation of signalling platforms in the plasma membrane i.e. of lipid rafts [133]. Recent research suggests that raft disruption underlies the mechanism of the inhibitory action of marine n−3 fatty acids on Th1-type cells [153,181–189] and likely on other T cell subsets [172].

7. Clinical relevance of the anti-inflammatory effects of marine n−3 fatty acids

7.1. Preamble

The ability of marine n−3 fatty acids to down-regulate several aspects of inflammation (summarized in Table 3) suggests that these fatty acids might be important in determining the development and severity of inflammatory diseases and that they may be useful as a component of therapy. The evolving identification of candidate mechanisms of action to explain the functional effects observed (see Table 3) adds significant biological plausibility to this approach. Consequently fish oil supplements have been evaluated to differing extents and with varying success in a range of inflammatory conditions.

7.2. Joint inflammation: rheumatoid arthritis

RA is a chronic inflammatory autoimmune disease that affects the joints, with infiltration of activated T lymphocytes, macrophages and antibody-secreting B lymphocytes into the synovium (the tissue lining the joints) and proliferation of fibroblast-like synovial cells called synoviocytes [190]. These cells and new blood vessels form a tissue termed pannus which leads to progressive destruction of cartilage and bone. This is most likely due to cytokine- and eicosanoid-mediated induction of destructive enzymes such as MMPs. Expression of both COX-1 and COX-2 is increased in the synovium of patients with RA [191] and synovial fluid from patients with RA contains high levels of pro-inflammatory eicosanoid products of both the COX and LOX pathways [191] and high levels of pro-inflammatory cytokines including TNF, IL-1β, IL-6, and IL-8 and granulocyte/macrophage colony stimulating factor [192]. Patients with RA are treated with non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit COX metabolism of ARA, indicating the importance of these mediators to the disease.

Researchers became interested in the therapeutic potential of marine n−3 fatty acids in RA quite early on, because of the recognition that these fatty acids target ARA metabolism which was known to be involved in the disease. An early dietary study in mice compared fish oil with vegetable oil in a model of arthritis induced by type II collagen injection: mice fed on a diet containing fish oil had delayed onset (mean 34 days vs. 25 days) and reduced incidence (69% vs. 93%) and severity (mean peak severity score 6 · 7 vs. 9 · 8) of the disease [193]. In another study, both EPA and DHA suppressed streptococcal cell wall-induced arthritis in rats, with EPA being the more effective of the two fatty acids [194]. More recently a comparison of fish oil, which provides marine n−3 fatty acids in triacylglycerol form, and krill oil, which provides marine n−3 fatty acids partly in the form of phospholipids, was made in

Table 3
A summary of the anti-inflammatory actions of marine n−3 fatty acids and the likely mechanisms involved.Modified from [1].

Anti-inflammatory effect	Likely mechanism involved
Decreased leukocyte chemotaxis	Decreased production of some chemoattractants (e.g. LTB_4); Down-regulated expression of receptors for chemoattractants
Decreased adhesion molecule expression and decreased leukocyte–endothelium interaction	Down-regulated expression of adhesion molecule genes (via NFκB, PPAR-γ, GPR120 etc.)
Decreased production of eicosanoids from arachidonic acid	Lowered membrane content of arachidonic acid; Inhibition of cyclooxygenase; Down-regulated expression of cyclooxygenase-2 gene (via NFκB, PPAR-γ, GPR120 etc.)
Decreased production of arachidonic acid containing endocannabinoids	Lowered membrane content of arachidonic acid
Increased production of "weak" eicosanoids from EPA	Increased membrane content of EPA
Increased production of anti-inflammatory EPA and DHA containing endocannabinoids	Increased membrane content of EPA and DHA
Increased production of pro-resolution resolvins, protectins and maresins	Increased membrane content of EPA and DHA; presence of aspirin
Decreased production of inflammatory cytokines	Down-regulated expression of inflammatory cytokine genes (via NFκB, PPAR-γ, GPR120 etc.)
Modified T cell reactivity	Disruption of membrane rafts and intracellular signalling (via increased content of EPA and DHA in specific membrane regions)

mice subjected to collagen-induced arthritis [195]. Both chemical formulations of marine n−3 fatty acids slowed the onset of arthritis, decreased its severity, reduced paw swelling, and decreased knee joint pathology compared with the control group, and for some outcomes krill oil appeared superior to fish oil. The latter observation may be explained by reports of more effective delivery of marine n−3 fatty acids from phospholipids, as found in krill oil, than from triacylglycerols, as found in fish oil [196].

Supplemental marine n−3 fatty acids decreased inflammatory cytokines [96,97,197] and eicosanoids [33,83,198] in patients with RA. These effects should reduce pain and cartilage destruction; if pain is reduced then patients may decrease their use of pain-controlling drugs like NSAIDs. In accordance with this idea, Cleland et al. [34] found that patients with RA who use fish oil supplements were more likely to reduce use of NSAIDs and to be in remission than those patients who did not use fish oil. Randomized controlled trials of fish oil in RA report improvements in several clinical outcomes including reduced duration of morning stiffness, reduced number of tender or swollen joints, reduced joint pain, reduced time to fatigue, increased grip strength and decreased use of NSAIDs (see [199,200] for references). The dose of marine n−3 fatty acids used in these trials has typically been high, between about 1 and 7 g per day and averaging about 3.5 g per day [199,200]. Meta-analyses of trials of fish oil in RA have been conducted [201,202]. One meta-analysis included data from nine trials published between 1985 and 1992 inclusive and from one unpublished trial and concluded that dietary fish oil supplementation for 3 months significantly reduced tender joint count and morning stiffness [201]. A more recent meta-analysis of n−3 fatty acids and pain included data from 17 trials [202]; this analysis indicated that fish oil reduces patient assessed joint pain, duration of morning stiffness, number of painful and/or tender joints, and use of NSAIDs. Thus there is fairly robust evidence of the efficacy of marine n−3 fatty acids in RA.

7.3. Airway inflammation: asthma

Asthma is a chronic inflammatory disease that affects the airways. It is characterised by reversible airflow obstruction and bronchospasm, due to increased contractility of the surrounding smooth muscles, and common symptoms which include wheezing, coughing, chest tightness, and shortness of breath. Asthma is characterised by leukocytic infiltration into the lungs; there is a predominance of eosinophils but other cell types including mast cells, neutrophils, macrophages and T lymphocytes are present. There is increased production of a range of cytokines and chemokines, including TNF, IL-4, IL-5, IL-6, IL-8, IL-12, and IL-13, and of ARA-derived eicosanoids, including PGD_2, LTC_4, LTD_4 and LTE_4. The 4-series LTs have been detected in the blood, bronchoalveolar lavage fluid and urine of asthmatics [203]. In addition to the role of ARA-derived eicosanoids as mediators of the symptoms of asthma, like bronchoconstriction, PGE_2 is also involved in regulating the development of the Th2 phenotype of T lymphocytes that predispose to allergic inflammation [204] and promotes the formation of immunoglobulin E by B lymphocytes [205]. Thus, ARA-derived eicosanoids are involved in determining the immunologic allergic predisposition to asthma and as mediators of the airway inflammatory response.

DHA reduced eosinophil infiltration into the lung and improved lung function to challenge with methacholine in a model of asthma induced by exposure to ovalbumin in ovalbumin-sensitised mice [206]. This model has also been used to compare what happens in fat-1 mice in comparison to wild type [71]. Fat-1 transgenic mice had higher levels of n−3 fatty acids in their lungs and when sensitised to and then challenged with ovalbumin, they showed decreased airway inflammation with decreased leukocyte accumulation and improved lung function upon challenge with methacholine. Fat-1 mice had lower lung concentrations of several pro-inflammatory cytokines including IL-1α, IL-5, and IL-13 and they had increased lung tissue amounts of protectin D1 and resolvin E1 [71]. Using the same model, administration of resolvin E1 throughout the ovalbumin sensitisation and challenge phases reduced eosinophil and lymphocyte infiltration into the lung and improved lung function to challenge with methacholine [69]. Haworth et al. [70] demonstrated that the effects of resolvin E1 in this model are at least partly due to suppression of the production of IL-6 and IL-23 and to increased production of interferon-γ in the lung. More recently, resolvin D1 and aspirin-triggered resolvin D1 were tested in this model [72]. Resolvin D1 reduced eosinophil infiltration into the lung, decreased IL-5 concentration and promoted inactivity of NFκB by inhibiting IκB degradation. The effect of aspirin-triggered resolvin D1 was more potent: it decreased lung eosinophilia, decreased production of a range of inflammatory peptide and lipid mediators, and improved the lung response to methacholine [72].

Studies have reported anti-inflammatory effects of fish oil in patients with asthma, such as decreased production of 4-series LTs [79,207,208] and improved leukocyte chemotaxis [207,208]. Randomized controlled trials of fish oil in adult asthma have reported little benefit [9], although one trial showed a divergent response identifying sub-groups of responders and non-responders [209]. One small trial in school children with asthma found a trend towards improved lung function after low dose marine n−3 fatty acids [210]. A second trial in school children reported significant improvement in lung function and a significant decline in disease score after 10 months [211]. Thien et al. [212] included eight studies published between 1988 and 2000 in a systematic review. They identified that there was no consistent effect of fish oil on lung function, asthma symptoms or asthma medication use,

although they stated one study in children showed improved lung function and reduced asthma medication use. Clearly, more needs to be done in this area.

7.4. Intestinal inflammation: inflammatory bowel disease

IBD is a chronic inflammatory disease that affects the gastrointestinal mucosa. The two main forms of IBD are Crohn's disease, which can affect any part of the gastrointestinal tract, and ulcerative colitis, which primarily affects the colon. In both forms of IBD, there are large infiltrates of neutrophils into the inflamed tissue, although other inflammatory cell types are also present. There are different T-cell response profiles associated with ulcerative colitis and Crohn's disease. A Th1 pattern of cytokine formation occurs in Crohn's disease with increased expression of TNF, interferon-γ, IL-1β, IL-6 and IL-12, whereas ulcerative colitis has a modified Th2 profile, where cytokines including IL-5 and IL-10 are upregulated, although IL-4 appears not to be. Eicosanoids are also involved in IBD and induction of colitis in laboratory animals results in the production of inflammatory eicosanoids such as PGE_2 and LTB_4 in the colonic mucosa [213,214]. In human IBD, the intestinal mucosa contains elevated levels of inflammatory eicosanoids derived from ARA such as LTB_4 [215], PGE_2, PGD_2, TXB_2, and 5-, 11-, 12- and 15-hydroxyeicosatetraenoic acid [216].

There have been several studies of dietary fish oil in animal models of colitis; these studies report than marine n−3 fatty acids decrease chemically induced colonic damage and inflammation compared with an n−6 fatty acid-rich diet [214,217–219]. These effects on disease severity were, in all cases, associated with a reduction in the amount of ARA-derived eicosanoids including PGE_2, TXB_2, LTB_4 and LTC_4 in the colonic mucosa. A more recent study investigated chemically-induced colitis in fat-1 mice [41]. These mice showed much less colonic damage and inflammation than wild-type mice, and this was associated with a marked change in the pattern of inflammatory mediators present in colonic tissue. Colonic tissue TNF, IL-1β and inducible nitric oxide synthase mRNA levels and NFκB activation were lower in fat-1 mice while colonic tissue from fat-1 mice (but not from wild type) contained LTB_5, PGE_3, resolvin E1, resolvin D3, and protectin D1. A study in IL-10 knockout mice, which spontaneously develop colitis, demonstrated significantly reduced colonic inflammation of the mice when fed fish oil compared to n−6 fatty acid-rich corn oil [220]. That resolvins may significantly contribute to the reduced inflammation seen with fish oil feeding in these models is supported by the study of Arita et al. [68] in which administration of resolvin E1 to mice protected against chemically-induced colitis which was associated with decreased infiltration of granulocytes into colonic tissue and decreased expression of several inflammatory genes (TNF, IL-12, COX-2, and inducible nitric oxide synthase) within that tissue.

EPA and DHA are incorporated into gut mucosal tissue of patients with IBD who supplement their diet with fish oil [37,221,222] and this is associated with reduced inflammation [36–40]. Some randomized controlled trials of fish oil in IBD have reported clinical benefits including improved clinical score, improved gut mucosal histology, improved sigmoidoscopic score, lower rate of relapse and decreased use of corticosteroids (see [223] for references). The dose of marine n−3 fatty acids used in these trials has typically been high, between 2.5 and 6 g per day and averaging about 4 g day per day. However, a number of trials do not report benefits (see [223]). One study with an enterically coated fish oil preparation showed a significantly lower rate of relapse over 12 months in patients with Crohn's disease [224] but two more recent trials with a similar design and fish oil preparation and using a similar dose of EPA + DHA could not replicate this finding [225]. A meta-analysis identified 13 studies of fish oil supplementation in IBD reporting outcomes related to clinical score, sigmoidoscope score, gut mucosal histology score, induced remission and relapse, but concluded that that there were sufficient data to perform meta-analysis only for relapse in ulcerative colitis. There was no benefit seen [226]. More recent meta-analyses considering maintenance of remission in patients with Crohn's disease or with ulcerative colitis have identified marginal effects, if any [227–229]. Thus, despite some favourable studies, there is at best only weak evidence that marine n−3 fatty acids have clinical benefits in human IBD.

8. Summary and conclusions

Inflammation is a condition which contributes to a range of human diseases. It involves a multitude of cell types, chemical mediators, and interactions. EPA and DHA are the major n−3 PUFAs found in oily fish and fish oil supplements. There is substantial evidence that these fatty acids are able to partly inhibit a number of aspects of inflammation including leukocyte chemotaxis, adhesion molecule expression and leukocyte–endothelial adhesive interactions, production of eicosanoids like PGs and LTs from the n−6 fatty acid ARA, production of inflammatory cytokines, and T cell reactivity. EPA and DHA act through a variety of mechanisms, including acting via cell surface (GPR120) and intracellular (PPAR-γ) receptors that control inflammatory cell signalling and gene expression patterns. Some effects of marine n−3 fatty acids on inflammatory cells appear to be mediated by, or at least are associated with, changes in fatty acid composition of cell membranes. Changes in fatty acid composition can modify lipid raft formation, cell signalling leading to altered gene expression, and the pattern of lipid mediator production. Cells involved in the inflammatory response are typically rich in the n−6 fatty acid ARA, but the contents of ARA and of EPA and DHA can be altered through oral administration of EPA and DHA. Eicosanoids produced from ARA, like PGE_2 and 4-series LTs, have roles in inflammation. EPA also gives rise to eicosanoids but these are usually less potent than those produced from ARA. EPA and DHA give rise to resolvins, and DHA to protectins and maresins which are anti-inflammatory and inflammation resolving. Increased membrane content of EPA and DHA (and decreased ARA content) results in a changed pattern of production of eicosanoids, including endocannabinoids, and resolvins and protectins. Thus, fatty acid exposure and the fatty acid composition of human inflammatory cells influence the function of those cells and the contents of ARA, EPA and DHA appear to be especially important. Dose-dependent actions of marine n−3 PUFAs on inflammatory responses have not been well described, but it appears that a dose of at least 2 g per day is necessary to achieve an anti-inflammatory effect. As a result of their anti-inflammatory actions marine n−3 fatty acids may have therapeutic efficacy in inflammatory diseases. Work with animal models of RA, IBD and asthma has demonstrated efficacy of fish oil and of mediators derived from EPA and DHA, like some of the resolvins. There have been a number of clinical trials of fish oil in patients with RA, IBD or asthma. These trials have typically used high doses of EPA + DHA, often above the anti-inflammatory threshold of 2 g per day. Most trials in RA report clinical improvements (e.g. improved patient assessed pain, decreased morning stiffness, fewer painful or tender joints, decreased use of NSAIDs), and when the trials have been pooled in meta-analyses statistically significant clinical benefit has emerged [201,202]. Thus, evidence for clinical efficacy of marine n−3 fatty acids in RA is fairly robust. Some trials of fish oil in IBD indicate benefits (e.g. improved clinical score, improved gut mucosal histology, improved sigmoidoscopic score, lower rate of relapse and decreased use of corticosteroids) but the findings are inconsistent and meta-analyses conclude that there is currently no clear evidence of efficacy of marine n−3 fatty acids in human IBD [226–229]. Trials of fish oil in adult asthma do not show benefit. In childhood asthma one trial showed a reduction of disease severity and an improvement in lung function [221], but another did not [220]. Meta-analyses combining findings from studies in adults and in children conclude that there is currently no clear evidence of efficacy of marine n−3 fatty acids in asthma [212]. It is not clear why anti-inflammatory effects observed with marine n−3 fatty acids in IBD and asthma do not translate into more consistent clinical improvements. Thus, there is a need to

know more about the actions of marine n−3 fatty acids in patients with inflammatory disorders in order optimize the strategy for their therapeutic use. In particular, a better understanding of dose–response relationships in different patient groups, of the relative importance of EPA and DHA, and of those factors that limit the effectiveness of EPA and DHA is needed.

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