Chapter 5
Modulation of Inflammatory Cytokines by Omega-3 Fatty Acids

Jing X. Kang and Karsten H. Weylandt

Abstract Many human diseases have been linked to inflammation, which is mediated by a number of chemical molecules including lipid mediators and cytokines. Polyunsaturated fatty acids (omega-6 and omega-3 fatty acids) are the precursors of the lipid mediators and play an important role in regulation of inflammation. Generally, omega-6 fatty acids (e.g. arachidonic acid) promote inflammation whereas omega-3 fatty acids (e.g. eicosapentaenoic acid and docosahexaenoic acid) have anti-inflammatory properties. Omega-3 fatty acids dampen inflammation through multiple pathways. On the one hand, omega-3 fatty acids inhibit the formation of omega-6 fatty acids-derived pro-inflammatory eicosanoids (e.g. PGE_2 and LTB_4), and on the other hand these fatty acids can form several potent anti-inflammatory lipid mediators (e.g. resolvins and protectins). These together directly or indirectly suppress the activity of nuclear transcription factors, such as NFκB, and reduce the production of pro-inflammatory enzymes and cytokines, including COX-2, tumor necrosis factor (TNF)-α, and interleukin (IL)-1β. This chapter focuses on the evidence from recent studies using new experimental models.

Keywords Omega-3 fatty acids · omega-6 fatty acids · lipid mediators · cytokines · inflammation

Abbreviations AA: arachidonic acid; ALA: alpha-linolenic acid; AP-1: activator protein 1; COX: cyclooxygenase; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; IL: interleukin; LA: linoleic acid; LOX: lipoxygenase; LPS: lipopolysaccaride; LT: leukotriene; NF-κB: nuclear factor-kappa B, PG: prostaglandin; PPARs: peroxisome proliferator-activated receptors; PUFA: polyunsaturated fatty acids, RvE1: resolvin E1, TNFα: tumor necrosis factor alpha, TX: thromboxane

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5.1 Introduction

5.1.1 Inflammation and Chronic Diseases

Inflammation is the activation of the immune system in response to infection, irritation, or injury, characterized by an influx of white blood cells, redness, heat, swelling, pain, and dysfunction of the organs. It has important functions in both defense and pathophysiological events maintaining the dynamic homeostasis of a host organism including its tissues, organs and individual cells. However, when inflammation persists, known as chronic inflammation, it can lead to chronic diseases. In fact, abnormalities associated with inflammation comprise a large, unrelated group of disorders which underly a variety of human diseases, including cardiovascular disease, cancer, diabetes and neurodegenerative disease. Thus, information is recently considered as a common mechanism of disease (Libby, 2007).

Inflammation involves various immune-system cells and numerous mediators. Recruitment of blood leukocytes characterizes the initiation of inflammatory response. The migrated or activated immune cells generate and release a variety of mediators that control the progression and resolution of information. Among the numerous inflammatory mediators are cytokines and lipid mediators.

5.1.2 Cytokines and Inflammation

Cytokines are small proteins ranging in molecular weight from 8 to 30 kDa. They are important mediators regulating the development of acute or chronic inflammation. Different cytokines are produced by various cells (particularly activated tissue macrophages) and have a wide range of different biological activities. The key cytokines IL-1, TNF-α and IL-6 exhibit redundant and pleiotropic effects that together contribute to the inflammatory response. Some of the effects mediated by these cytokines include increased vascular permeability, increased adhesion molecules on vascular endothelium, chemokine induction, T-cell and B-cell activation, chemoattraction of leukocytes and induction of cell death (Dinarello, 2000). Nuclear factor-kappa B (NF-κB), a nuclear transcription factor, is involved in regulating expression of these cytokines (Hayden and Ghosh, 2008).

5.1.3 Polyunsaturated Fatty Acids, Lipid Mediators and Inflammation

Some lipid metabolites, derived from polyunsaturated fatty acids (PUFA), act as inflammatory mediators. There are two kinds of PUFA: omega-6 and

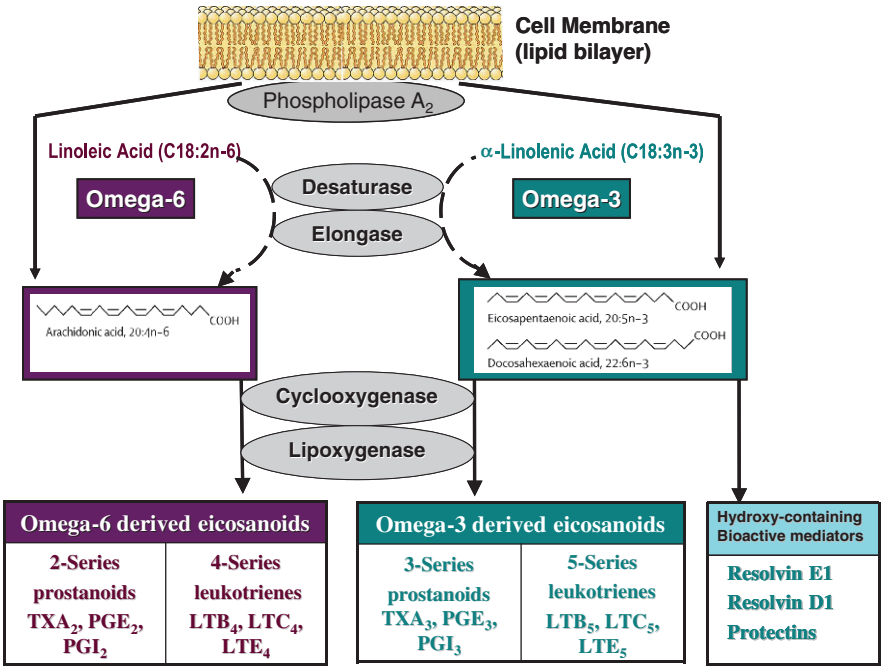

Fig. 5.1 Metabolic pathways for the production of lipid mediators from omega-6 and omega-3 fatty acids

omega-3 (relating to the position of the first double bond in their hydrocarbon chains) (Fig. 5.1). The omega-6 PUFA that can be metabolized to form inflammatory mediators is arachidonic acid (AA). The omega-3 PUFA that can be converted to lipid mediators are primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which mainly found in fish and fish oil.

Following cell activation by inflammatory stimuli, PUFA in membrane phospholipids of various cell types are released by phospholipase A2 and converted to eicosanoids by cyclooxygenases (COX) and the lipoxygenases (LOX) (Fig. 5.1). Metabolism of the omega-6 arachidonic acid by the COX pathway produces prostaglandins (PGs) and thromboxanes (TX). The common PGs generated by immune cells include PGE_2, PGF_2 and PGD_2. These prostaglandins have diverse physiological effects, including increased vascular permeability, increased vascular dilation, induction of neutrophil chemotaxis, and stimulation of smooth muscle cell migration and proliferation (Richard et al., 2000). The thromboxanes (e.g. TXA_2) cause platelet aggregation and constriction of blood vessels (Sellers and Stallone, 2008). Arachidonic acid is also metabolized by the LOX pathway to yield the four leukotrienes (LT): LTC_4, LTB_4, LTD_4, and LTE_4. Three of these (LTC_4, LTD_4, and LTE_4) together make up what was formerly called slow-reacting substance of anaphylaxis

(SRS-A); these mediators induce smooth-muscle contraction. LTB_4 is a potent chemoattractant of neutrophils (Peters-Golden et al. 2005). Thus, many eicosanoids derived from the omega-6 AA are highly pro-inflammatory.

The omega-3 fatty acid EPA is metabolised in mammalian cells through the same COX and LOX pathways to form 3-series prostaglandins and thromboxanes (PGD_3, PGF_3, PGE_3 and TXA_3) and 5-series leukotrienes (LTB_5, LTC_5, LTD_5 and LTE_5), which are much less pro-inflammatory or even have opposing effects as compared to their counterparts derived from AA (Simopoulos, 2002; Calder, 2006). For example, PGE_3 and LTB_5 (unlike PGE_2 and LTB_4 which can induce violent contracture of heart cells) have little effect on myocyte contraction (Li et al., 1997), and they both are potent in inhibiting mitogen-induced lymphocyte proliferation (Shapiro et al., 1993). Thus, inhibition of the formation of AA-derived pro-inflammatory mediators by competing with AA for the COX and LOX enzymes is thought to be a major mechanism underlying the anti-inflammatory effect of omega-3 fatty acids (James et al., 2000).

Recent studies using lipidomics methods (LC-MS/MS) have been able to demonstrate the generation of potent anti-inflammatory mediators from the n-3 fatty acids EPA and DHA (Serhan et al., 2008). The omega-3 derived mediators have been implicated in the resolution of inflammation and therefore termed resolvins and protectins (Schwab et al., 2007). The resolvin formed from EPA is resolvin E1 (RvE1). Those derived from DHA metabolites are named resolvin D (RvD1–RvD6) and the protectins (protectin D1, PD1). RvE1 is the first omega-3 fatty acid derived lipid mediator, for which a distinct receptor, namely ChemR23, has been identified to mediate its antiinflammatory action (Arita et al., 2005a). The protective effect of the DHA-derived lipid mediators has been examined in the model of ischemic brain injury, showing a significant neuroprotective effect by inhibition of NFkB activity, leukocyte migration and COX-2 induction (Hong et al., 2003). Animal study using colitis as an inflammatory disease model showed that pretreatment with resolvin E1 protected mice from TNBS-induced colitis, a hapten based colitis model (Arita et al., 2005b). Thus, these studies demonstrate that derivates (resolvins and protectins) of the n-3 fatty acids EPA and DHA are bioactive mediators with potent anti-inflammatory properties.

The relative abundance or ratio between the long-chain omega-6 (AA) and omega-3 (EPA and DHA) fatty acids in cell membranes depends on their dietary supplies and the conversion (elongation and desaturation) of their precursors linoleic acid (LA) and alpha-linolenic acid (ALA), respectively (Fig. 5.1). In mammals, the conversion of LA to AA is much more efficient than the conversion of ALA to EPA/DHA. LA and ALA are "essential" because the body cannot make them and we must take in via the food we eat. In addition to the competition for the COX and LOX enzymes, omega-6 and omega-3 fatty acids also compete for the enzymes of elongation and desaturation as well as incorporation into phospholipids (Fig. 5.1). When one type of fatty acid predominates in cell membrane phospholipids, it takes up most of these enzymes, leaving behind little for the other. For example, flush of the

omega-3 ALA or EPA into cells would dramatically reduce the omega-6 LA and AA contents in cellular phospholipids. Thus, dietary supplies of these fatty acids can influence their composition in cell membrane phospholipids and modulate the production of pro- or anti-inflammatory mediators and thereby the inflammatory status (Calder, 2006). For this reason, maintaining a balance of omega-6 and omega-3 PUFA is important for optimal biochemical balance in the body.

5.2 Effect of Omega-3 Fatty Acids on NF-κB Activation and Cytokine Production

The anti-inflammatory effects of the long-chain omega-3 polyunsaturated fatty acids EPA and DHA were amongst their earliest identified properties. During the last decades, many studies in both animals and humans have been done to evaluate the beneficial effects of these fatty acids on a variety of inflammatory diseases (Calder, 2006, 2007; Sijben and Calder, 2007; Simopoulos, 2002). The outcomes of theses studies have been reviewed frequently and, therefore, are not the focus of this chapter. Noticeably, the mechanism underlying the anti-inflammatory effects of omega-3 fatty acids remains to be fully elucidated.

The original view that omega-3 fatty acids exert anti-inflammatory effects only by blocking arachidonic acid metabolism (production of pro-inflammatory eicosanoids) was too simplistic. It appears that they also alter expression of inflammatory genes, particularly those encoding cytokines. Although this possible mechanism has been investigated for many years, the study results of the effect on cytokine production were inconsistent for different species and for different clinical conditions (Blok et al., 1996). These differences could be due to the occurrence of confounding factors of diet in the studies using dietary supplementation or a poorly controlled experimental system. In this context, results from well-controlled studies, free of dietary confounding factors, are critical for addressing the effect of omega-3 fatty acids on cytokine production. Here, we review the results on cytokine production from the recent studies using a novel mouse model.

5.2.1 The Fat-1 Transgenic Mouse Model

A well-controlled experimental model that can eliminate or minimize the confounding factors of diet is critical for addressing nutrient-gene interaction. The newly generated fat-1 transgenic mouse was genetically engineered to carry a gene, namely *fat-1,* from the round worm *C. elegans* and is capable of converting n-6 to n-3 fatty acids (which is naturally impossible in mammals), leading to an increase in n-3 fatty acid content with a balanced n-6/n-3 fatty acid ratio in all tissues, without the need of dietary n-3 supply (Kang et al., 2004). Feeding an

identical diet (high in n-6) to the transgenic and wild type littermates can produce different fatty acid profiles in these animals. Thus, this model allows well-controlled studies to be performed, without the interference of the potential confounding factors of diet, ideal for studying the benefits of n-3 fatty acids and the molecular mechanisms of their action (Kang, 2007).

5.2.2 NFκB

Nuclear factor-kappa B (NF-κB) is a widely expressed inducible transcription factor and is involved in the induction of several pro-inflammatory cytokines and enzymes that are critically involved in the pathogenesis of chronic inflammatory diseases. NF-κB is composed of homodimers and heterodimers, the most abundant and best-studied form in mammalian cells consisting of the p65 and p50 subunits. Activation of NF-κB typically involves the phosphorylation of cytoplasmic IκB by the IκB kinase (IKK) complex, resulting in IκB degradation via the proteosomal system. The degradation of IκB releases the NF-κB heterodimers to translocate to the nucleus where they bind to κB motifs in the promoters of pro-inflammatory genes such as TNF-α, IL-1β, IL-6 and COX-2 leading to their induction (Hayden et al., 2006).

Using the fat-1 mouse model, Bhattacharya et al. have shown a significant reduction of NF-κB (p65/p50) activity in LPS-stimulated splenocytes from fat-1 transgenic mice rich in omega-3 fatty acids (EPA and DHA) either on a normal or a calorie restricted diet, accompanied by a lower IL-6 and TNFα secretion from the LPS-treated splenocytes when compared to those in the wild type mice high in omega-6 and low in omega-3 fatty acids (Bhattacharya et al., 2006). These findings are consistent with the observation in a murine macrophage cell culture model showing that omega-3 PUFA could decrease NFκB activity by inhibition of IkB phosphorylation (Novak et al., 2003). Along the line, we also observed a significant decrease in NFκB activity (as measured by a p65 activation assay) in the colons of the omega-3 enriched fat-1 mice with chemically induced colitis (Hudert et al., 2006). In that study the inflammation of colon, in terms of both clinical manifestation and pathology, was significantly less severe in fat-1 transgenic mice than that in wild type littermates. The ratio of long-chain omeg-6 fatty acid to long-chain omega-3 fatty acids was 1.7 in *fat-1* transgenics and 30.1 in wild type mice, accompanied with increased formation of the derivates of n-3 fatty acids (RvE1 and RvD3, and PD1) (Hudert et al., 2006). A similar inhibitory effect on NFκB activity was also found in the fat-1 transgenic mice with colitis-associated colon tumors (Nowak et al., 2007).

As to the potential link of omega-3 PUFA-derived mediators to NFκB activity, Arita et al. showed, by using a NFκB luciferase activation assay, that the EPA-derived resolvin E1 (RvE1) was able to inhibit TNF-α induced NFκB activation (Arita et al., 2005a). This suggests that omega-3 PUFA metabolites may be able to directly regulate the expression of NFκB associated genes.

5.2.3 TNFα

Tumor necrosis factor alpha (TNFα) plays a major pathogenic role in many inflammatory diseases. The expression of TNFα can be induced by the activation of NFκB (Collart et al., 1990). Of interest, TNFα itself is a potent inducer of NFκB activity (Hayden et al., 2006). Increased production of TNFα has been shown to contribute to the development of inflammatory bowel disease (Papadakis and Targan, 2000), acute liver inflammation (Sass et al., 2002; Tilg et al., 2003), retinopathy (Connor et al., 2007) and many other inflammatory conditions. Many previous studies have shown that n-3 PUFA can decrease TNFα production in vitro and in vivo (Babcock et al., 2002; Endres et al., 1989; Novak et al., 2003). Consistent with these observations, our recent studies using the fat-1 mouse model showed that the production of TNFα was significant lower in splenocytes following LPS treatment (Bhattacharya et al., 2006), colons with DSS-induced inflammation (Hudert et al., 2006), livers with D-GalN/LPS-induced hepatitis (Schmocker et al., 2007) and retinas after hypoxia-induced injury (Connor et al., 2007), accompanied with a reduced severity of inflammation in the fat-1 mice rich in omega-3 PUFA when compared to that in wild type mice high in omega-6 PUFA.

5.2.4 IL-1β

Interleukin 1β (IL-1β) (a 17 kD protein) has many functions on many different cells and is secreted by a number of cells including macrophages, monocytes and dendritic cells. IL-1 induces fever and pain and activates various immune cells. It can also induce expression of many inflammatory genes including PLA_2 and COX_2, leading to increased production of pro-inflammatory eicosanoids (White et al., 2008). IL-1β acts via binds to two trans-membrane IL-1 receptors (IL-1R type 1 and 2). Activation of the IL-1R type leads to NFκB activation (Martin and Wesche, 2002). Similar to TNFα , it can be induced by NFκB (Hiscott et al., 1993). Together with TNFα, IL-1β plays an important role in the promotion of inflammatory response. In the fat-1 transgenic mice, we found that increased tissue content of omega-3 PUFA suppressed IL-1β expression in the target tissues of several inflammatory conditions, including DSS-induced colitis (Hudert et al., 2006), D-GalN/LPS-induced hepatitis (Schmocker et al., 2007) and cerulein-induced pancreatitis (unpublished results).

5.2.5 IL-6

Interleukin-6 (IL-6) is another important mediator of fever and inflammation and has been shown to be a prognostic indicator in human pancreatitis (Mayer et al., 2000; Stimac et al., 2006) as well as an indicator of disease severity in

animal models of hepatitis (Sass et al., 2002). Our recent studies with fat-1 transgenic mice showed a significantly decreased expression of IL-6 in *fat-1* mice with hepatitis (Schmocker et al., 2007), lower IL-6 serum levels in the fat-1 mice with pancreatitis (unpublished results) and a reduced secretion of IL-6 from splenocytes from the fat-1 mice following LPS treatment (Bhattacharya et al., 2006).

These studies demonstrate a role played by an increased tissue status of n-3 fatty acids and decreased n-6/n-3 ratio in modulation of cytokine production (mainly NFκB, TNFα, IL-1β and IL-6).

5.3 Discussion and Conclusions

It is evident that omega-3 polyunsaturated fatty acids can modulate both the synthesis of lipid mediators and the production of cytokines. Their effects on lipid mediator formation include a reduction of pro-inflammatory eicosanoids (derived from the omega-6 AA) and an increase in anti-inflammatory mediators (derived from the omega-3 EPA and DHA themselves). The inhibitory effect on cytokine production might be subsequent to the changes in the types and/or amount of lipid mediators formed, or due to a direct effect of the fatty acids themselves on gene expression. Thus, it seems that omega-3 PUFA exert anti-inflammatory effects through a wider variety of metabolic pathways than thought previously. However, the relative contribution of each of them to the anti-inflammatory effect and the relationships among them (action sequence/pathway) remain to be further elucidated. Noticeably, there are looping feedbacks or interplays among cytokines, transcriptional factors and lipid mediators. For example, TNFα activates NFκB, which in turn induces TNFα and COX-2, leading to increased production of PGE_2, and consequently further activation of NFκB by PGE_2, and so on. Since NF-κB seems to be the core factor mediating all the effects/interplays, inhibition of NF-κB may be the key target for the omega-3 PUFA's effects on cytokine production and inflammation. Of interest, omega-3 PUFA appear to act also on some other targets in addition to NFκB. These multiple effects of omega-3 PUFA render them an effective natural anti-inflammatory agent. The possible interactions and working pathways are schemed in Fig. 5.2. However, further investigations are warranted to validate these potential effects and pathways by using qualified experimental models together with state-of-the-art technologies (e.g. lipidomics, genomics and proteomics). The understanding of the anti-inflammatory molecules derived from omega-3 PUFA and their regulatory signaling pathways provides new insights into the molecular pathophysiology of chronic diseases and opportunities for the design of therapeutic strategies.

In summary, omega-3 fatty acids not only modulate the production of lipid mediators but also alter expression of inflammatory genes. This broad spectrum of anti-inflammatory effects explains why omega-3 fatty acid can help in the

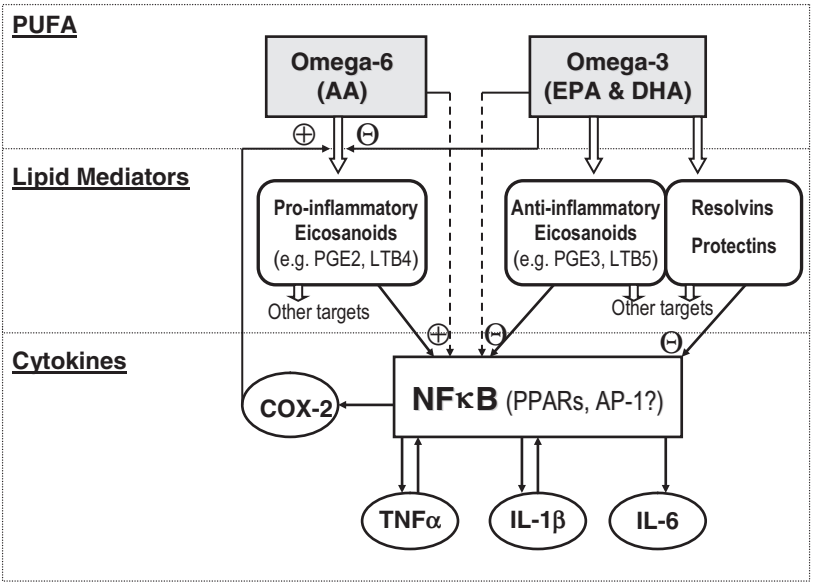

Fig. 5.2 Possible mechanisms by which omega-3 fatty acids modulate the cytokine production and potential interplays of PUFA, lipid mediators and cytokines. ⊕, activation or up-regulation;Θ, inhibition or down-regulation

prevention, and possibly the amelioration of diseases with an inflammatory component, including diabetes, Alzheimer's, cancer, and cardiovascular disease (Calder, 2006; Simopoulos, 2002). Given the safety and multiple health benefits of omega-3 fatty acids, increased intake of the nutrients may be a promising approach to disease prevention, or an alternative therapy for inflammatory diseases.

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