Published in final edited form as:
Prostaglandins Leukot Essent Fatty Acids. 2009 ; 81(2-3): 187–191. doi:10.1016/j.plefa.2009.05.010.

Dietary docosahexaenoic and eicosapentaenoic acid: Emerging mediators of inflammation☆

Robert S. Chapkin[a,b,*], **Wooki Kim**[a,b], **Joanne R. Lupton**[a,b], and **David N. McMurray**[a,b]

[a] Program in Integrative Nutrition and Complex Diseases (RSC, WK, JRL, DNM), Center for Environmental and Rural Health (RSC, JRL, DNM), Vegetable and Fruit Improvement Center (RSC), Texas A&M University, College Station, TX 77843-2253, USA

[b] Department of Microbial and Molecular Pathogenesis, Texas A&M University,Health Science Center (DNM), College Station, TX, USA

Abstract

The inflammatory response is designed to help fight and clear infection, remove harmful chemicals, and repair damaged tissue and organ systems. Although this process, in general, is protective, the failure to resolve the inflammation and return the target tissue to homeostasis can result in disease, including the promotion of cancer. A plethora of published literature supports the contention that dietary n-3 polyunsaturated fatty acids (PUFA), and eicosapentaenoic (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) in particular, are important modulators of a host's inflammatory/immune responses. The following review describes a mechanistic model that may explain, in part, the pleiotropic anti-inflammatory and immunosuppressive properties of EPA and DHA. In this review, we focus on salient studies that address three overarching mechanisms of n-3 PUFA action: (i) modulation of nuclear receptor activation, i.e., nuclear factor-κB (NF-κB) suppression; (ii) suppression of arachidonic acid–cyclooxygenase-derived eicosanoids, primarily prostaglandin E_2-dependent signaling; and (iii) alteration of the plasma membrane micro-organization (lipid rafts), particularly as it relates to the function of Toll-like receptors (TLRs), and T-lymphocyte signaling molecule recruitment to the immunological synapse (IS). We propose that lipid rafts may be targets for the development of n-3 PUFA-containing dietary bioactive agents to down-modulate inflammatory and immune responses and for the treatment of autoimmune and chronic inflammatory diseases.

1. Introduction

Complementary and alternative medicine is commonly practiced by Americans (40-60%) to ameliorate an array of diseases and to promote optimal health [1]. With respect to dietary lipids, the anti-inflammatory properties of fish oil, containing long-chain n-3 polyunsaturated fatty acids (PUFA), has been extensively evaluated in experimental rodent and cell culture model systems over the past three decades. A plethora of dietary studies using rodent species have demonstrated that dietary fish oil reduces pro-inflammatory responses, in part, by diminishing T-cell proliferative capacity in response to mitogenic stimuli and antigenic stimulation [2-6]. Similar suppressive effects were observed with respect to the dendritic cell, endothelial cell, macrophage, and neutrophil components of the inflammatory response [7-12]. By using

☆*Sources of support*: National Institutes of Health Grants CA59034, CA129444, DK071707, and P30ES09106; US Department of Agriculture Grant 2006-34402-17121, “Designing Foods for Health”.

* Correspondence to: Department of Nutrition and Food Science, Faculty of Nutrition, Kleberg Biotechnology Center, MS 2253, Texas A&M University, College Station, TX 77843-2253, USA. Tel.: +1979 845 0419; fax: +1979862 2378., E-mail address: r-chapkin@tamu.edu (R.S. Chapkin).

purified diets enriched with fish oil or eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) ethyl esters, a number of studies have demonstrated that both EPA and DHA are bioactive and suppress antigen-specific delayed hypersensitivity reactions and mitogen-induced proliferation of T-cells, as well as modulate murine T-helper cell (Th1/Th2) balance [13-15]. The loss of lymphoproliferative activity was accompanied by reduction in interleukin (IL)-2 secretion and IL-2 receptor α chain mRNA transcription, suggesting that dietary n-3 PUFA act, in part, by interrupting the autocrine IL-2 activation pathway [16]. In addition, dietary DHA blunted the production of intracellular second messengers, including diacylglycerol and ceramide, following mitogen stimulation *ex vivo* [16-18]. These data conclusively demonstrate that dietary n-3 PUFA modulate components of the intracellular signaling pathways regulating T-cell activation. In theory, these alterations in T-cell function could reflect both the *direct* effects of dietary n-3 PUFA in impairing the ability of the target T-cell population to respond to activating stimuli, and the *indirect* effects of n-3 PUFA on the activity of other cells (accessory cells or other T-cell populations) to suppress the response of the target cells; or a combination of these two distinct mechanisms. Most previous studies addressing these issues have been carried out in unseparated populations of T-cells and accessory cells stimulated with mitogenic agents, which act indiscriminantly on generic T-cell surface ligands. Our laboratory demonstrated that n-3 PUFA affect T-cell receptor-mediated activation by both direct and indirect (accessory cell) mechanisms [19]. Other studies have affirmed these observations [11,20].

2. Immunosuppressive effects of n-3 PUFA in humans

Epidemiological data collected in the 1970s indicate that Greenland Eskimos, who typically consume large amounts of n-3 PUFA, have a decreased incidence of inflammatory disease relative to Americans. Similar observations were made in the Japanese population, which led to the correlation between a decreased incidence of inflammatory disease and increased cold water fish consumption [21,22]. Although scientists have tested the effects of dietary fish oil supplementation in humans, in general, the data are inconclusive regarding the ability of n-3 PUFA to suppress chronic inflammatory diseases. For example, there have been at least 14 randomized placebo-controlled double-blind studies of n-3 PUFA-rich fish oil in patients with rheumatoid arthritis (see review, [22]). Several investigators have reported that patients consuming n-3 PUFA supplements were able to lower or discontinue their anti-inflammatory drugs [23,24]. However, confirmatory, definitive studies are needed in order to make recommendations for clinical practice. Although a growing body of published reports support the contention that n-3 PUFA are safe and may be effective for maintenance of remission of inflammatory bowel diseases (IBD) [25-29], there are not sufficient data to recommend the routine use of EPA/DHA for maintenance of remission in IBD. Similarly, with regard to airway inflammation, which is a major component of asthma, preliminary research indicates that certain subjects with bronchial asthma may respond favorably to fish oil supplementation [30-33]. Therefore, while these clinical studies are promising, additional research clearly is required.

3. Human cytokines

Inflammation is a component of several acute and chronic human diseases, and is characterized by activation/production of at least four classes of active compounds: (i) inflammatory cytokines, (ii) arachidonic acid (AA) (20:4n-6)-derived eicosanoids, (iii) inflammatory mediators (e.g., platelet activating factor), and (iv) adhesion molecules. In order to evaluate the therapeutic value of long-chain n-3 PUFA, a number of investigators have examined the effect of diet on blood inflammatory cell populations and plasma biomarkers of inflammation in healthy adults. In general, the consumption of EPA and DHA are associated with lower levels of inflammatory mediators and soluble adhesion molecules [7,30,34–38]. In contrast,

alpha linolenic acid (18:3n-3), a precursor to EPA and DHA, may not elicit anti-inflammatory effects [39,40].

It is now apparent that chronic inflammatory diseases are characterized by interactions among multiple genes and environmental factors such as diet [41]. Hence, it is important to understand the role of genetic variation in inflammation and chronic disease. More specifically, it is likely that the complex effects of n-3 PUFA on cytokine biology and plasma biomarkers of inflammation can be explained, in part, by polymorphisms and genotypes of the responsive subjects [42,43]. With regard to dietary lipid source, both the relative and absolute dietary intake of n-3 and n-6 PUFA, which compete for the same transport and acylation pathways, influence the tissue levels of EPA and DHA [44]. This is further complicated by the fact that common genetic variants of the FADS1/FADS2 gene cluster differently convert n-3 and n-6 PUFA catalyzed by the Δ5 and Δ6 desaturase, respectively [45]. Other factors that may influence the effects of long-chain n-3 PUFA on immune function in healthy humans include dose-related effects [46] and age [46,47]. Indeed, there is some evidence that dietary EPA and DHA may differentially influence immune cell function in healthy human subjects [48]. For example, DHA, but not EPA, suppressed T-cell activation as assessed by CD69 expression [49]. Clearly, additional work is needed in order to elucidate the distinct anti-inflammatory properties of EPA and DHA. The following sections describe three mechanistic models that accommodate diverse views on the immunosuppressive properties of n-3 PUFA.

4. Putative mechanisms of action

Lipid rafts and long-chain n-3 PUFA

There are a number of mechanisms which functionally link the pleiotropic effects of EPA and DHA to inflammation. Examples include (i) alteration of membrane self-organizing lipid raft domains, (ii) modulation of nuclear receptor activation, and (iii) metabolic interconversion into bioactive eicosanoids/docosanoids (Fig. 1).

Defining the molecular and cellular mechanisms that regulate immunological homeostasis is the focus of intense research. Recent studies on the various functional capacities of T-cells and antigen-presenting cells, e.g., dendritic cells, have demonstrated the presence of specific detergent-resistant domains (rafts) in which key signal-transduction proteins are localized. Typically, upon cell activation, rafts compartmentalize the activated receptor complexes and associated signal-transducing molecules, thus providing an environment conducive to signal transduction [50]. While evidence for the existence of lipid rafts in the plasma membrane has provoked debate, new sophisticated imaging approaches have started to define cell surface nanoscale organization [51-53]. Recently, a number of investigators have documented the unique membrane altering properties of long-chain n-3 PUFA (see [54,55] for details). Data from these and other studies demonstrate that DHA is a unique fatty acid, because it significantly alters basic properties of cell membranes, including fatty acid chain order and fluidity, phase behavior, elastic compressibility, ion permeability, fusion, rapid flip-flop, and resident protein function [55,56]. Because of its polyunsaturation, DHA is sterically incompatible with sphingolipid and cholesterol and, therefore, is capable of altering lipid raft behavior and protein function in living cells [14,57,58]. Although the complexity of this issue precludes drawing any conclusions, based on our observations [14,57-60], we have hypothesized that dietary DHA alters plasma membrane microdomain lipid composition, thereby directly influencing protein signaling complexes that regulate immune responses and inflammation. Alternatively, DHA may inhibit signaling protein post-translational lipidation, which subsequently may alter lipid raft targeting and protein function. This may explain how DHA elicits immunological hyporesponsiveness, thereby suppressing inflammatory mediators in humans. Unfortunately, no studies to date have compared the membrane altering domain

properties of DHA with EPA in innate immune cells with antigen-presenting function or conventional T-cell populations.

The mechanisms by which the body senses the diverse molecular factors that trigger inflammation have recently been elucidated. The recognition of conserved pathogen-associated molecular patterns (PAMPs) enables the innate immune system to generate an appropriate immune response [61]. Germline encoded pattern recognition receptors (PRRs) include Toll-like receptors (TLRs), Nod-like receptors (NLRs), and C-type lectin receptors, all of which regulate immune activation in response to diverse stimuli, including infection and tissue injury. It is now recognized that the lipid components of the diet can modulate transmembrane TLRs and the consequent inflammatory and immune responses. In a series of seminal findings, Hwang and colleagues demonstrated that DHA acts as a pan-inhibitor of various TLRs and NLRs, suppressing nuclear factor-κB (NF-κB)-related signal transduction [20,62,63]. These data provide a putative link between n-3 PUFA, NF-κB, innate immunity (epithelial cells, macrophages, dendritic cells), and adaptive immune (T-cells) responses. Interestingly, lipid rafts have been implicated in the regulation and activation of TLR signaling complexes [64, 65]. It is currently unclear whether alteration of lipid rafts by n-3 PUFA is a major mechanism by which DHA alters TLR signaling in a variety of cell types.

Effects of n-3 PUFA on eicosanoid/docosanoid metabolism

The long-chain n-3 PUFA present in dietary fish oil, EPA and DHA, affect diverse physiological processes by dampening arachidonic acid-derived eicosanoid (prostaglandin and leukotriene) signaling [10,66]. This is significant because AA-derived mediators can act to both promote and inhibit inflammation [67-69]. Interestingly, the AA pool(s) for eicosanoids in humans is not quickly influenced by dietary n-6 PUFA because of a large pool(s) size of AA and a low conversion of metabolic precursors to AA. In contrast, the n-3 PUFA pool(s), which is considerably smaller, is immediately influenced by n-3 PUFA supplementation [70]. Recently described resolvins, docosatrienes, and neuroprotectins derived from EPA and DHA represent endogenous biochemical mediators that can counter-regulate inflammation [71]. Given their potent bioactivity, it is now clear that these n-3 PUFA metabolites contribute to the termination of inflammation [72]. With respect to disease states, lipid mediator informatics-lipidomics approaches suggest that the biosynthesis of these proresolving molecules may be defective in patients with chronic inflammation [69,71].

Although EPA is normally found in much lower abundance than DHA in tissues [66], the recent discovery of EPA-derived novel autoxidation has generated much interest in the inflammation field [73]. Non-enzymatic highly reactive cyclopentenone isoprostane compounds (A_3/J_3-isoprostanes) appear capable of activating NF-E2-related factor 2 which, in turn, can enhance antioxidant gene expression that regulates detoxification of reactive oxygen species [74]. At present, further work is needed to understand precisely how n-6/n-3 PUFA consumption modulates non-enzymatic and enzymatically oxidized proresolving forms of EPA and DHA.

Nuclear receptor activation/gene transcription

Additional insight into the mechanisms by which dietary n-3 PUFA inhibit inflammatory responses was provided by the identification of several nuclear receptors, e.g., peroxisome proliferator-activated receptors (PPARs) and retinoid X receptors, which are activated at micromolar concentrations by EPA and DHA [75-78]. Interestingly, PPARs can transrepress inflammatory responses mediated by the transcription factor NF-κB [79]. This is significant because activation of NF-κB appears to link inflammation and immunity to cancer development and progression [80,81]. Other molecular pathways that do not require PPARs and may be involved in the PUFA-mediated regulation of inflammation include hepatocyte nuclear factor

4α (HNF4α) [82]. Interestingly, EPA and DHA-CoA thioesters may act as suppressor ligands of HNF4α [83].

In summary, a growing number of dietary supplementation studies using healthy human subjects, as well as animal disease models, have clearly shown dietary fish oil to possess anti-inflammatory properties. The primary effector molecules are n-3 fatty acids, EPA, and DHA, which are present in relatively low quantities in the western diet. Although the mechanisms of EPA and DHA action are still not fully defined in molecular terms, it is becoming increasingly clear that these long-chain fatty acids alter immune cell membrane lipid microdomain properties, modulate nuclear receptor activation, and alter the spectrum of cyclooxygenase and lipoxygenase metabolites, which collectively may explain their pleiotropic properties (Fig. 1). Unfortunately, at present there are limited data to support the notion that n-3 PUFA ameliorate clinical symptoms in patients affected by diseases characterized by active inflammation. It is highly likely that genetic differences contribute to variable response to n-3 PUFA supplementation, making it difficult to determine how best to use EPA and/or DHA in the prevention and/or treatment of inflammatory and autoimmune diseases.

In conclusion, this workshop on DHA as a required nutrient raised some important issues. If DHA has significant health benefits for humans, which can be documented, then a DRI value should be considered. For the nutrient to be “required” means that it is unlikely to be obtained in sufficient amounts from a precursor substance and thus a specified amount would have to be obtained as DHA *per se*. Data summarized by Burdge and Calder [84] suggest that the conversion of alpha linolenic acid to DHA is less than 0.5% and that the beneficial effects of DHA occur at the level of 500 mg/day. This gap between intake and efficacy suggests that DHA is conditionally essential and that a DRI value for DHA should be considered. The next consideration is the selection of an endpoint for the determination of a DRI value. From the reports presented, it is unlikely that anti-inflammation would be the most important endpoint, since this is an emerging field rather than having coronary heart disease (CHD) as the endpoint for which there are extensive data. However, the anti-inflammatory data presented in this paper are important because they provide a clear biological mechanism(s) by which DHA may exert its beneficial effect. Since inflammation is considered to have a major impact on CHD, if CHD risk reduction is used as the endpoint for a DRI value for DHA, then these data on inflammation could be used to help establish a mechanistic basis.

Acknowledgments

Designing Foods for Health is gratefully acknowledged. RSC, WK, JL, and DNM have no conflicts of financial or personal interest in any company or organization sponsoring the research, including advisory board affiliations. RSC, WK, JL, and DNM compiled data from collaborative experiments and evaluated the literature.

References

1. Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 fatty acid supplementation for inflammatory joint pain. Pain 2007;129:210–223. [PubMed: 17335973]
2. Arrington JJ, McMurray DN, Switzer KC, Fan YY, Chapkin RS. Docosahexaenoic acid suppresses function of the CD28 costimulatory membrane receptor in primary murine and Jurkat T cells. J Nutr 2001;131:1147–1153. [PubMed: 11285317]
3. Arrington JL, Chapkin RS, Switzer KC, Morris JS, McMurray DN. Dietary n-3 polyunsaturated fatty acids modulate purified murine T-cell subset activation. Clin Exp Immunol 2001;123:1–10. [PubMed: 11167990]
4. Anderson MJ, Fritsche KL. Dietary polyunsaturated fatty acids modulate in vivo, antigen-driven CD4 $^{+}$ T-cell proliferation in mice. J Nutr 2004;134:1978–1983. [PubMed: 15284386]

5. Zhang P, Smith R, Chapkin RS, McMurray DN. Dietary (n-3) polyunsaturated fatty acids modulate murine Th1/Th2 balance toward the Th2 pole by suppression of Th1 development. J Nutr 2005;135:1745–1751. [PubMed: 15987859]
6. Zhang P, Kim W, Zhou L, et al. Dietary fish oil inhibits murine antigen-specific Th1 cell development by suppression of clonal expansion. J Nutr 2006;136:2391–2398. [PubMed: 16920860]
7. Prescott SM. The effect of eicosapentaenoic acid on leukotriene B production by human neutrophils. J Biol Chem 1984;259:7615–7621. [PubMed: 6330066]
8. Hughes DA, Pinder AC. n-3 polyunsaturated fatty acids inhibit the antigen-presenting function of human moncytes. Am J Clin Nutr 2000;71(Suppl):357S–360S. [PubMed: 10617997]
9. Novak TE, Babcock TA, Jho DH, Helton WS, Espat NJ. NF-κB inhibition by ω-3 fatty acids modulates LPS-stimulated macrophage TNFalpha transcription. Am J Physiol Lung Cell Mol Physiol 2003;284:L84–L89. [PubMed: 12388359]
10. Bagga D, Wang L, Farias-Eisner R, Glaspy JA, Reddy ST. Differential effects of prostaglandin derived from ω-6 and ω-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion. Proc Natl Acad Sci 2003;100:1751–1756. [PubMed: 12578976]
11. Zeyda M, Saemann MD, Stuhlmeir KM, et al. Polyunsaturated fatty acids block dendritic cell activation and function independently of NF-κB activation. J Biol Chem 2005;280:14293–14301. [PubMed: 15684433]
12. Massaro M, Scoditti E, Carluccio MA, Montinari MR, De Caterina R. Omega-3 fatty acids, inflammation and antiogenesis: nutrigenomic effects as an explanation for anti-atherogenic and anti-inflammatory effects of fish and fish oils. J Nutrigenet Nutrigenomics 2008;1:4–23.
13. Fowler KH, Chapkin RS, McMurray DN. Effects of purified n-3 ethyl esters on murine T lymphocyte function. J Immunol 1993;151:5186–5197. [PubMed: 8228217]
14. Fan YY, Ly LH, Barhoumi R, McMurray DN, Chapkin RS. Dietary docosahexaenoic acid suppresses T-cell protein kinase C-theta lipid raft recruitment and interleukin-2 production. J Immunol 2004;173:6151–6160. [PubMed: 15528352]
15. Ly LH, Smith R, Switzer KC, Chapkin RS, McMurray DN. Dietary eicosapentaenoic acid modulates CTLA-4 expression in murine $CD4^+$ T-cells. Prost Leuk Essent Fatty Acids 2006;74:29–37.
16. Jolly CA, Jiang YH, Chapkin RS, McMurray DN. Dietary n-3 polyunsaturated fatty acid modulation of murine lymphoproliferation and interleukin-2 secretion: correlation with alterations in diacylglycerol and ceramide mass. J Nutr 1997;127:37–43. [PubMed: 9040541]
17. Fowler KH, McMurray DN, Fan YY, Aukema HM, Chapkin RS. Purified dietary n-3 polyunsaturated fatty acids alter diacylglycerol mass and molecular species composition in concavalin A-stimulated murine splenocytes. Biochim Biophys Acta 1993;1210:89–96. [PubMed: 8257724]
18. Jolly CA, Laurenz JC, McMurray DN, Chapkin RS. Diacylgycerol and ceramide kinetics in primary cultures of activated T-lymphocytes. Immunol Lett 1996;49:43–48. [PubMed: 8964608]
19. Chapkin RS, Arrington JL, Apanasovich TV, Carroll RJ, McMurray DN. Dietary n-3 PUFA affect TCR-mediated activation of purified murine T cells and accessory cell function in co-cultures. Clin Exp Immunol 2002;130:12–18. [PubMed: 12296847]
20. Weatherill AR, Lee JY, Zhao L, Lemay DG, Youn HS, Hwang DH. Saturated and polyunsaturated fatty acids reciprocally modulate dendritic cell functions mediated by TLR4. J Immunol 2005;174:5390–5397. [PubMed: 15843537]
21. Calder PC. n-3 polyunsaturated fatty acids, inflammation and immunity: pouring oil on troubled water or another fishy tale? Nutr Res 2001;21:309–341.
22. Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr 2006;83(Suppl):1505S–1519S. [PubMed: 16841861]
23. Kremer JM, Jubiz W, Michalek A, et al. Fish-oil fatty acid supplementation in active rheumatoid arthritis. Ann Intern Med 1987;106:497–502. [PubMed: 3030173]
24. Kremer JM. n-3 fatty acid supplements in rheumatoid arthritis. Am J Clin Nutr 2000;71(Suppl):349S–351S. [PubMed: 10617995]
25. Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, Miglioli M. Effect of enteric-coated fish-oil preparation on relapses in Crohn's disease. N Engl J Med 1996;334:1557–1560. [PubMed: 8628335]
26. Belluzzi A, Boschi S, Brignola C, Munarini A, Cariani G, Miglio M. Polyunsaturated fatty acids and inflammatory bowel disease. Am J Clin Nutr 2000;71(Suppl):339S–342S. [PubMed: 10617993]

27. Turner D, Zlotkin SH, Shah PS, Griffiths AM. Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2007;2
28. Turner D, Steinhart AH, Griffiths AM. Omega 3 fatty acids (fish oil) for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2007;3
29. De Ley M, de Vos R, Hommes DW, Stokkers P. Fish oil induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2007;4
30. Von Schacky C, Kiefl R, Jendraschak E, Kaminski WE. n-3 fatty acids and cysteinyl-leukotrience formation in humans in vitro, ex vivo and in vivo. J Lab Clin Med 1993;121:302–309. [PubMed: 8381847]
31. Nagakura T, Matsuda S, Shichijyo K, Sugimoto H, Hata K. Dietary supplementation with fish oil rich in ω-3 polyunsaturated fatty acids in children with bronchial asthma. Eur Respir J 2000;16:861–865. [PubMed: 11153584]
32. Stephensen CB. Fish oil inflammatory disease: is asthma the next target for n-3 fatty acid supplements? Nutr Rev 2004;62:486–489. [PubMed: 15648824]
33. Schachter, HM.; Reisman, J.; Tran, K., et al. Health effects of omega-3 fatty acids on asthma. Summary, Evidence Report/Technology Assessment No. 91, AHRQ Publication No. 04-E013–1. Agency for Healthcare Research and Quality; Rockville, MD: 2004 Mar.
34. Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med 1989;320:265–271. [PubMed: 2783477]
35. Kelly DS, Taylor PC, Nelson GJ, et al. Docosahexaenoic acid ingestion inhibits natural killer cell activity and production of inflammatory mediators in young healthy men. Lipids 1999;34:317–324. [PubMed: 10443964]
36. Thies F, Miles EA, Nebe-von-Caron G, et al. Influence of dietary supplementation with long-chain n-3 and n-6 polyunsaturated fatty acids on blood inflammatory cell populations and functions and on plasma soluble adhesion molecules in healthy adults. Lipids 2001;36:1183–1193. [PubMed: 11795850]
37. Lopez-Garcia E, Schulze MB, Manson JE, et al. Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial in women. J Nutr 2004:1806–1811. [PubMed: 15226473]
38. Luu NT, Madden J, Calder PC, et al. Dietary supplementation with fish oil modifies the ability of human monocytes to induce an inflammatory response. J Nutr 2007;137:2769–2774. [PubMed: 18029497]
39. Kew S, Banerjee T, Minihane AM, et al. Lack of effect of foods enriched with plant- or marine-derived n-3 fatty acids on human immune function. Am J Clin Nutr 2003;77:1287–1295. [PubMed: 12716684]
40. Zhao G, Etherton TD, Martin KR, Gillies PJ, West SG, Kris-Etherton PM. Dietary α-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. Am J Clin Nutr 2007;85:385–391. [PubMed: 17284733]
41. Kornman KS. Interleukin 1 genetics, inflammatory mechanisms, and nutrigenetic opportunities to modulate diseases of aging. Am J Clin Nutr 2006;83(Suppl):475S–483S. [PubMed: 16470016]
42. Grimble RF, Howell WM, O'Reilly G, et al. The ability of fish oil to suppress tumor necrosis factor α production by peripheral blood mononuclear cells in healthy men is associated with polymorphisms in genes that influence tumor necrosis factor α production. Am J Clin Nutr 2002;76:454–459. [PubMed: 12145022]
43. Shen J, Arnett DK, Peacock JM, et al. Interleukin1β genetic polymorphisms interact with polyunsaturated fatty acids to modulate risk of the metabolic syndrome. J Nutr 2007;137:1846–1851. [PubMed: 17634253]
44. Chapkin RS, McMurray DN, Lupton JR. Colon cancer, fatty acids and anti-inflammatory compounds. Curr Opin Gastroenterol 2007;23:48–54. [PubMed: 17133085]
45. Schaeffer L, Gohike H, Muller M, et al. Common genetic variants of the FADS1 FADS2 gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids. Hum Mol Genet 2006;15:1745–1756. [PubMed: 16670158]

46. Rees D, Miles EA, Banerjee T, et al. Dose-related effects of eicosapentaenoic acid on innate immune function in healthy humans: a comparison of young and older men. Am J Clin Nutr 2006;83:331–342. [PubMed: 16469992]
47. Meydani SN, Endres S, Woods MM, et al. Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between young and older women. J Nutr 1991;121:547–555. [PubMed: 2007907]
48. Sierra S, Lara-Villoslalda F, Comalada M, Olivares M, Xaus J. Dietary eicosapentaenoic acid and docosahexaenoic acid equally incorporate as docosahexaenoic acid but differ in inflammatory effects. Nutrition 2008;24:245–254. [PubMed: 18312787]
49. Kew S, Mesa MD, Tricon S, Buckley R, Minihane AM, Yaqoob P. Effects of oils rich in eicosapentaenoic and docosahexaenoic acids on immune cell composition and function in healthy humans. Am J Clin Nutr 2004;79:674–681. [PubMed: 15051614]
50. Jury EC, Flores-Borja F, Kabouridis PS. Lipid rafts in T cell signalling and disease. Semin Cell Dev Biol 2007;18:608–615. [PubMed: 17890113]
51. Gaus K, Chklovskaia E, Fazekas de St Groth B, Jessup W, Harder T. Condensation of the plasma membrane at the site of T lymphocyte activation. J Cell Biol 2005;171:121–131. [PubMed: 16203859]
52. Hancock JF. Lipid rafts: contentious only from simplistic standpoints. Nat Rev Mol Cell Biol 2006;7:456–462. [PubMed: 16625153]
53. Jacobson K, Mouritsen OG, Anderson RGW. Lipid rafts: at a crossroad between cell biology and physics. Nat Cell Biol 2007;9:7–14. [PubMed: 17199125]
54. Zimmerberg J, Gawrisch K. The physical chemistry of biological membranes. Nat Chem Biol 2006;2:564–567. [PubMed: 17051226]
55. Wassall SR, Stillwell W. Docosahexaenoic acid domains: the ultimate non-raft membrane domain. Chem Phys Lipids 2008;153:57–63. [PubMed: 18343224]
56. Stillwell W, Wassall SR. Docosahexaenoic acid: membrane properties of a unique fatty acid. Chem Phys Lipids 2003;126:1–27. [PubMed: 14580707]
57. Fan YY, McMurray DN, Ly LH, Chapkin RS. Dietary (n-3) polyunsaturated fatty acids remodel mouse T-cell lipid rafts. J Nutr 2003;133:1913–1920. [PubMed: 12771339]
58. Chapkin RS, Wang N, Fan YY, Lupton JR, Prior IA. Docosahexaenoic acid alters the size and distribution of cell surface microdomains. Biochim Biophys Acta 2008;1778:466–471. [PubMed: 18068112]
59. Ma DWL, Seo J, Davidson LA, et al. n-3 PUFA alter caveolae lipid composition and resident protein localization in mouse colon. Faseb J 2004;18:1040–1042. [PubMed: 15084525]
60. Ma DWL, Seo J, Switzer KC, et al. n-3 PUFA and membrane microdomains: a new frontier in bioactive lipid research. J Nutr Biochem 2004;15:700–706. [PubMed: 15590275]
61. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell 2006;124:783–801. [PubMed: 16497588]
62. Lee JY, Plakidas A, Lee WH, et al. Differential modulation of Toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. J Lipid Res 2003;44:479–486. [PubMed: 12562875]
63. Zhao L, Kwon MJ, Huang S, et al. Differential modulation of nods signaling pathways by fatty acids in human colonic epithelial HCT116 cells. J Biol Chem 2007;282:11618–11628. [PubMed: 17303577]
64. Lee HK, Dunzendorfer S, Soldau K, Tobias PS. Double-stranded RNA-mediated TLR3 activation is enhanced by CD14. Immunity 2006;23:301–304.
65. Nakahira K, Kim HP, Geng XH, et al. Carbon monoxide differentially inhibits TLR signaling pathways by regulating ROS-induced trafficking of TLRs to lipid rafts. J Exp Med 2006;203:2377–2389. [PubMed: 17000866]
66. Smith WL. Cyclooxygenases, peroxide tone and the allure of fish oil. Curr Opin Cell Biol 2005;17:174–182. [PubMed: 15780594]
67. Tilley SL, Coffman TM, Koller BH. Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. J Clin Invest 2001;108:15–23. [PubMed: 11435451]

68. Mandal AK, Zhang Z, Kim SJ, Tsai PC, Mukherjee AB. Cutting edge: yin-yang: balancing act of prostaglandins with opposing functions to regulate inflammation. J Immunol 2005;175:6271–6273. [PubMed: 16272277]
69. Mangino MJ, Brounts L, Harms B, Heise C. Lipoxin biosynthesis in inflammatory bowel disease. Prost Lipid Mediators 2006;79:84–92.
70. Hamazaki T, Fischer S, Urakaze M, Sawazaki S, Yano S, Kuwamori T. Urinary excretion of $PGI_{2/3}$-M and recent n-6/3 fatty acid intake. Prostaglandins 1989;37:417–424. [PubMed: 2503856]
71. Serhan CN, Yacoubian S, Yang R. Anti-inflammatory and proresolving lipid mediators. Annu Rev Pathol Mech Dis 2008;3:279–312.
72. Flower RJ, Perretti M. Controlling inflammation: a fat chance? J Exp Med 2005;201:671–674. [PubMed: 15753201]
73. Yin H, Brooks JD, Gao L, Porter NA, Morrow JD. Identification of novel autoxidation products of the ω-3 fatty acid eicosapentaenoic acid in vitro and in vivo. J Biol Chem 2007;282:29890–29901. [PubMed: 17711863]
74. Brooks JD, Milne GL, Yin H, Sanchez SC, Porter NA, Morrow JD. Formation of highly reactive cyclopentenone isoprostane compounds (A_3/J_3-isoprostanes) in vivo from eicosapentaenoic acid. J Biol Chem 2008;283:12043–12055. [PubMed: 18263929]
75. Kliewer SA, Sundseth SS, Jones SA, et al. Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors α and γ. Proc Natl Acad Sci USA 1997;94:4318–4323. [PubMed: 9113987]
76. Xu HE, Lambert MH, Montana VG, et al. Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. Mol Cell 1999;3:397–403. [PubMed: 10198642]
77. De Urquiza AM, Liu S, Sjoberg M, et al. Docosahexaenoic acid, a ligand for the retinoid X receptor in mouse brain. Science 2000;290:2140–2144. [PubMed: 11118147]
78. Fan YY, Spencer TE, Wang N, Moyer MP, Chapkin RS. Chemoprotective n-3 fatty acids activate RXRα in colonocytes. Carcinogenesis 2003;24:1541–1548. [PubMed: 12844485]
79. Pascual G, Fong AL, Ogawa S, et al. A SUMOylation-dependent pathway mediates transrepression of inflammatory response by PPARγ. Nature 2005;437:759–763. [PubMed: 16127449]
80. Karin M, Greten FR. NF-κB: linking inflammation and immunity to cancer development and progression. Nat Rev Immunol 2005;10:749–759. [PubMed: 16175180]
81. Karrasch T, Jobin C. NF-κB and the intestine: friend or foe? Inflamm Bowel Dis 2008;14:114–124. [PubMed: 17763472]
82. Ahn SH, Shah YM, Inoue J, et al. Hepatocyte nuclear factor 4α in intestinal epithelial cells protects against inflammatory bowel disease. Inflamm Bowel Dis. 2008 March 13;
83. Hertz R, Magenheim J, Berman I, Bar-Tana J. Fatty acyl-CoA thioesters are ligands of hepatic nuclear factor-4alpha. Nature 1998;392:512–516. [PubMed: 9548258]
84. Burdge GC, Calder PC. Dietary alpha-linolenic acid and health-related outcomes: a metabolic perspective. Nutr Res Rev 2006:26–52. [PubMed: 19079874]

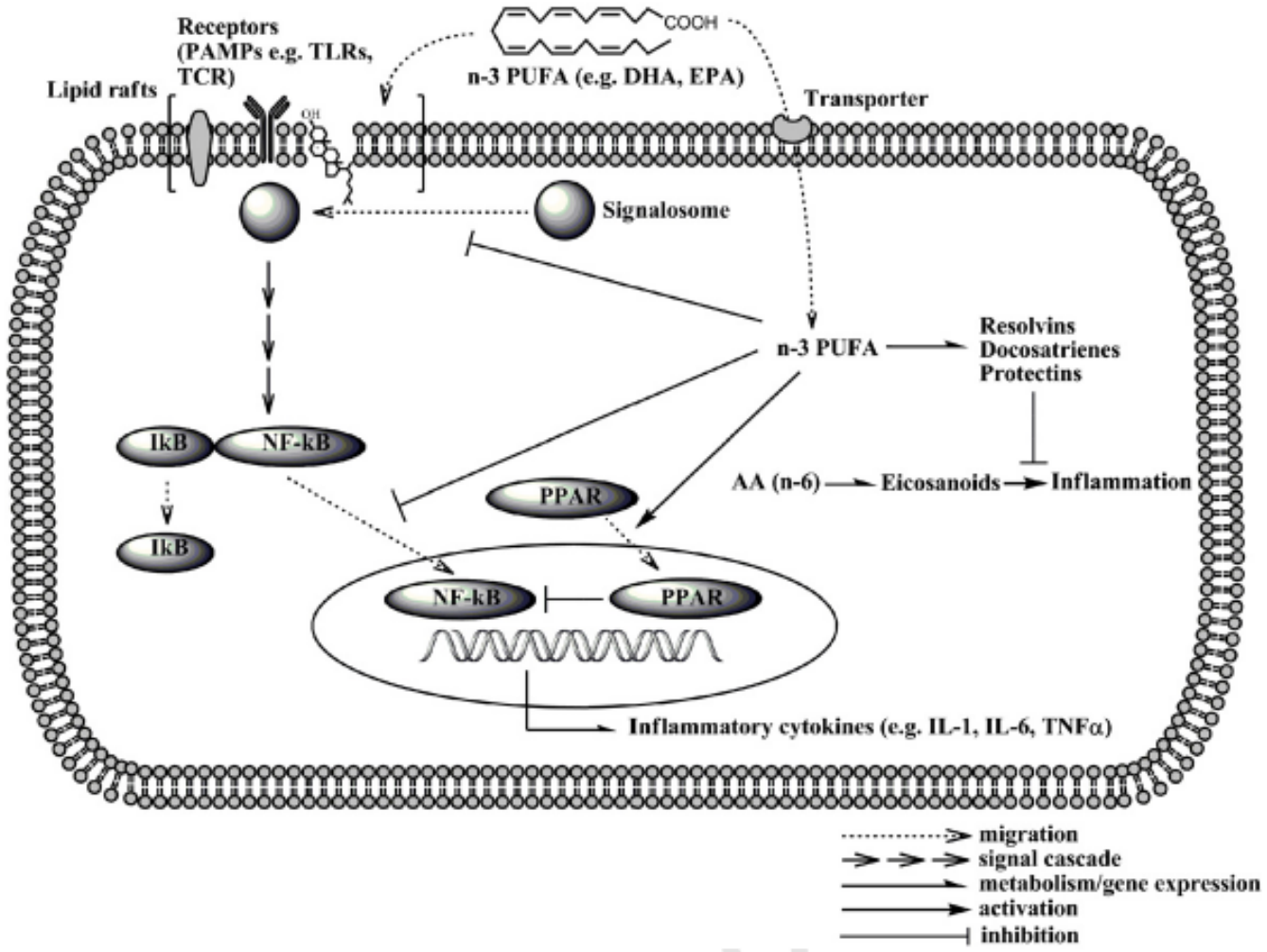

Fig. 1.

Proposed molecular model by which EPA and DHA modulate immune cell function and inflammation. n-3 PUFA suppress nuclear receptor activation, e.g., NF-κB, arachidonic acid-cyclooxygenase-derived eicosanoids, and alter plasma membrane micro-organization (lipid rafts), particularly as it relates to the function of Toll-like receptors, and T-lymphocyte signaling molecule recruitment to the immunological synapse. We propose that lipid rafts may be targets for the development of n-3 PUFA-containing dietary bioactive agents to down-modulate chronic inflammatory responses: AA, arachidonic acid ($20:4^{\Delta 5,8,11,14}$, an n-6 PUFA); DHA, docosahexaenoic acid ($22:6^{\Delta 4,7,10,13,16,19}$); (EPA, eicosapentaenoic acid ($20:5^{\Delta 5,8,11,14,17}$); NF-κB, nuclear factor κB; IκB, inhibitor of NF-κB; IL, interleukin; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acids; TLR, Toll-like receptors are a member of the pattern recognition receptor family. These receptors recognize highly conserved pathogen-associated molecular patterns (PAMPs) to generate an immune response; TNFα, tumor necrosis factor alpha.