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

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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 NF-$\kappa$B, and reduce the production of pro-inflammatory enzymes and cytokines, including COX-2, tumor necrosis factor (TNF)-$\alpha$, and interleukin (IL)-1$\beta$. 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: lipopolysaccharide; LT: leukotriene; NF-$\kappa$B: nuclear factor-kappa B, PG: prostaglandin; PPARs: peroxisome proliferator-activated receptors; PUFA: polyunsaturated fatty acids, RvE1: resolvin E1, TNF-$\alpha$: 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, chemo-kine 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