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Implications for eicosapentaenoic acid- and docosahexaenoic acid-derived resolvins as therapeutics for arthritis

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ABSTRACT

Omega-3 polyunsaturated fatty acids are essential for health and are known to possess anti-inflammatory properties, improving cardiovascular health as well as benefiting inflammatory diseases. Indeed, dietary supplementation with omega-3 polyunsaturated fatty acids has proved efficacious in reducing joint pain, morning stiffness and nonsteroidal anti-inflammatory drugs usage in rheumatoid arthritis patients. However, the mechanisms by which omega-3 polyunsaturated fatty acids exert their beneficial effects have not been fully explored. Seminal discoveries by Serhan and colleagues have unveiled a novel class of bioactive lipid mediators that are enzymatically biosynthesized *in vivo* from omega-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), termed resolvins, protectins and maresins. These bioactive pro-resolving lipid mediators provide further rationale for the beneficial effects of fish-oil enriched diets. These endogenous lipid mediators are spatiotemporally biosynthesized to actively regulate resolution by acting on specific G protein-coupled receptors (GPCRs) to initiate anti-inflammatory and pro-resolving signals that terminate inflammation. In this review, we will discuss the mechanism of actions of these molecules, including their analgesic and bone-sparing properties making them ideal therapeutic agonists for the treatment of inflammatory diseases such as rheumatoid arthritis.

1. Introduction

An observation made more than 40 years ago brought great interest to the field of omega-3 polyunsaturated fatty acids as a potential nutraceutical for human diseases. In the late 1970s, epidemiological studies revealed that Greenland Inuits had substantially lower frequency or absence of a vast number of diseases, including acute myocardial infarction, diabetes mellitus, thyrotoxicosis, bronchial asthma, multiple sclerosis and psoriasis, when compared with Western control subjects (Kromann and Green, 1980). These observations stimulated vast research into the mechanism of action of omega-3 fatty acids on human metabolism and health, as evidenced by the sheer number of research articles on this topic (more than 3400, search in the PubMed database). From epidemiology, cell culture and animal studies to randomized controlled trials, the cardioprotective effects of omega-3 polyunsaturated fatty acids are becoming increasingly recognized. Due to this observation, omega-3 polyunsaturated fatty acids are used to supplement the diet, and are also prescribed for hypertriglyceridemia and the prevention of myocardiac infarction (Bradberry and Hilleman, 2013). This encouraged researchers to investigate the anti-inflammatory properties ascribed to omega-3 polyunsaturated fatty acids for various chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and asthma (discussed in recent review Calder (2015)).

Numerous randomized, placebo-controlled, double-blinded studies using omega-3 polyunsaturated fatty acids in rheumatoid arthritis are reported. Almost all of these trials showed some benefit of fish oil, a source of these fatty acids. Such benefits include reduced duration of morning stiffness, reduced number of tender or swollen joints, decreased pain and time to fatigue, increased grip strength, and decreased use of non-steroidal anti-inflammatory drugs (reviewed in Calder (2008), and Miles and Calder (2012)). The dose range of omega-3 polyunsaturated fatty acids reported in these trials varied from 1.6 to 7.1 g/day and averaged 3.5 g/day (Calder, 2008; Miles and Calder, 2012). Thus, evidence-based reports implicate fish oil supplementation as an useful complementary therapy for rheumatoid arthritis. Alongside some of these studies, the authors also investigated inflammatory parameters that are modulated following omega-3 treatment, which include decreased leukotriene B_4 production by neutrophils (Cleland et al., 1988; Kremer et al., 1987, 1990; Sperling et al., 1987), reduced interleukin 1β production by macrophages (Kremer et al., 1990), and lower plasma levels of interleukin 1β (Espersen et al., 1992; Kremer et al., 1995). Thus the mechanisms

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by which omega-3 polyunsaturated fatty acids exert their beneficial effects are of mounting interest. These actions are thought to be mediated, directly or indirectly, by eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the most prevalent omega-3 polyunsaturated fatty acids found in fish oil. One of the traditional theories is that omega-3 polyunsaturated fatty acids compete with the canonical omega-6 substrate arachidonic acid to generate eicosanoids such as prostaglandins of the 3-series and leukotrienes of the 5-series that are thought to be more anti-inflammatory than their arachidonic acid-derived counterparts (reviewed by Calder (2015)). More recently, Serhan discovered that both EPA and DHA could be enzymatically converted *in vivo* to novel bioactive lipid mediators, termed resolvins, protectins and maresins (termed specialized pro-resolving mediators) that stimulate the resolution of inflammation and have proven to be log-orders more potent than their lipid precursors (reviewed in Serhan (2014)). These mediators may represent a potential molecular mechanism to explain the beneficial use of omega-3 fatty acids as nutraceuticals. In the next sections, we will present these newly discovered mediators, their known bioactions and how they can be harnessed therapeutically for the treatment of rheumatoid arthritis.

2. Ideal outcome – resolution of inflammation

In the simplest definition, inflammation is an adaptive response that can be triggered by a variety of noxious stimuli, including infection and injury, that aims to restore homeostasis of the affected tissues, and therefore has a crucial role in the physiology of mammalian organisms (Medzhitov, 2008). Inflammatory responses are highly heterogeneous in terms of the cell types and molecular mediators involved. Inflammation also comes in different modalities that can be classified as acute *versus* chronic and local *versus* systemic. Despite this complexity, all inflammatory responses can be broken down into four common components that align in a universal configuration of the inflammatory pathway: inflammatory inducers, sensors, mediators, and effectors (Medzhitov, 2010). Inflammatory inducers can be exogenous signals (*e.g.* pathogens and toxins) or endogenous signals (*e.g.* ATP or urate crystals) that report on tissue stress, injury, or malfunction. Sensor cells, such as tissue-resident macrophages, dendritic cells and mast cells, detect inducers with specific receptors and respond by producing inflammatory mediators. Depending on the nature of the inducers, sensor cells produce different combinations and amounts of mediators (including cytokines, chemokines, vasoactive amines, lipid mediators and proteolytic cascade products), creating unique mediator signatures. Inflammatory mediators, in turn, act on target tissues triggering changes in the functional state thereof, favouring the migration of leukocytes from the blood and production of effector molecules (such as reactive radicals and proteases), thereby leading to adaptation to deleterious condition in accordance with the inducer (tissue injury or infection) that triggered the inflammatory response (Okin and Medzhitov, 2012).

The development of an appropriate inflammatory response is essential for the host. Indeed, the activation and recruitment of leukocytes are required for the processing and presentation of antigens by leukocytes, and effector function of any immune response (Teixeira et al., 2001). However, inflammatory processes have the potential to cause damage to host tissues. Indeed, the effector molecules produced in this process do not discriminate if their targets are a pathogen or a structure of the host, so the tissue damage is a potential side effect associated with any inflammatory response (Medzhitov, 2008; Nathan, 2006; Wink et al., 2011). Thus, this adaptive response is beneficial only if retained for a short duration. Chronic responses may lead to significant physiological changes. There is a wide range of human diseases associated with an inappropriate or uncontrolled inflammatory response that is triggered by known or unknown stimuli. These include rheumatoid arthritis, asthma, multiple sclerosis, chronic obstructive pulmonary disease and atherosclerosis (Libby, 2002; Vilcek and Feldmann, 2004; Weiner and Selkoe, 2002). Under these conditions, it is clear that tissue inflammation is deleterious. Therefore, an adequate control of inflammation is of fundamental importance for the restoration of the physiological conditions of the organism.

The current paradigm is that inflammation resolves in a highly coordinated, active process dictated by the spatial–temporal generation of pro-resolving mediators that act on specific receptors to modulate cell and tissue reactivity, in a process known as resolution of inflammation (Serhan et al., 2007). Recognizing the proactive nature of resolution of inflammation implicates that chronic, non-resolving inflammation is associated not only with excessive production of pro-inflammatory mediators but also attributed to a defect in endogenous anti-inflammatory mediators and pathways (Bonnans et al., 2002; Claria et al., 2012). A variety of different classes of pro-resolving mediators have now been identified including annexins, lipoxins, E-series resolvins, D-series resolvins, protectins/neuroprotectins, and maresins (reviewed by Perretti and D'Acquisto (2009), Serhan and Chiang (2008), Chiang et al. (2005), Serhan et al. (2009) and Serhan (2014)). These mediators display a multitude of protective actions, such as blocking neutrophil recruitment, promoting the recruitment and activation of monocytes, and mediating the nonphlogistic phagocytosis and lymphatic clearance of apoptotic neutrophils by activated macrophages (Fig. 1). It is therefore evident that pro-resolution mediators are not merely anti-inflammatory, for example, by blocking the binding of a cytokine to a receptor (*e.g.* interleukin 1 receptor (IL-1R), Allen et al. (1993)), but promote tissue restoration and return to homeostasis.

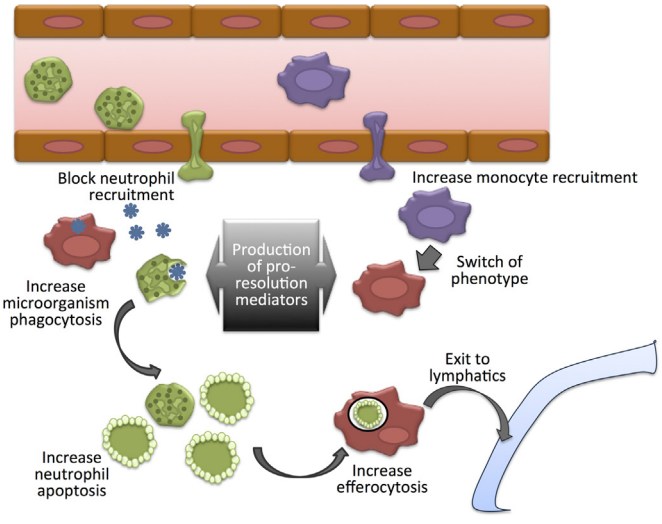

Fig. 1. Key steps in the resolution of inflammation initiated *via* pro-resolving mediators. After eliminating the inciting stimuli, by for example phagocytosis of microorganisms, the recruitment of neutrophils to the site of the inflammation must be discontinued, as neutrophils produce many mediators that could increase tissue damage. Remaining neutrophils must undergo apoptosis, and then be cleared by the monocytes that arrive later in the process and differentiate locally to macrophages. Different resolution mediators such as resolvins and annexin-A1 produced by the cells at the inflammatory site; as well as cell–cell interactions promotes a switch from pro-inflammatory to pro-resolution cell phenotypes and mediators. The inflammatory process will then end with either the incorporation of myeloid cells into the local population or their recirculation *via* lymphatic or blood vessels. Adapted from Norling and Perretti (2013).