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Review

n−3 Fatty acids uniquely affect anti-microbial resistance and immune cell plasma membrane organization☆

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ABSTRACT

It is now well established that dietary lipids are incorporated into macrophage and T-cell membrane microdomains, altering their structure and function. Within cell membranes, there are specific detergent-resistant domains in which key signal transduction proteins are localized. These regions are classified as "lipid rafts". Rafts are composed mostly of cholesterol and sphingolipids and therefore do not integrate well into the fluid phospholipid bilayers causing them to form microdomains. Upon cell activation, rafts compartmentalize signal-transducing molecules, thus providing an environment conducive to signal transduction. In this review, we discuss recent novel data describing the effects of *n*−3 PUFA on alterations in the activation and functions of macrophages and T-cells. We believe that the modifications in these two disparate immune cell types are linked by fundamentally similar changes in membrane lipid composition and transmembrane signaling functions. We conclude that the outcomes of *n*−3 PUFA-mediated immune cell alterations may be beneficial (e.g., anti-inflammatory) or detrimental (e.g., loss of microbial immunity) depending upon the cell type interrogated.

Contents

Abbreviations: AA, arachidonic acid; ALA, alpha-linolenic acid; APC, antigen presenting cell; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FO, fish oil; LA, linoleic acid; LPS, lipopolysaccharide; Mtb, *Mycobacterium tuberculosis*; PA, palmitic acid; PUFA, polyunsaturated fatty acids.

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1. Introduction

A growing number of dietary supplementation studies using healthy human subjects as well as animal disease models have clearly shown that long chain $n-3$ polyunsaturated fatty acids (PUFA) found in fish oil (FO), specifically, eicosapentaenoic acid (EPA; $20:5^{\Delta 5,8,11,14,17}$) and docosahexaenoic acid (DHA, $22:6^{\Delta 4,7,10,13,16,19}$), are capable of modulating critical determinants which link infectious disease and inflammation (Belluzzi et al., 2000; Davidson et al., 2004; Prescott and Stenson, 2005; Hudert et al., 2006; Jia et al., 2008; Bouwens et al., 2009; Weaver et al., 2009). Since EPA and DHA have pleiotropic properties, with respect to molecular mechanisms of action, we will confine our discussion to recent novel findings pertaining to the impact of $n-3$ PUFA on macrophage and T cell membrane structure and function. Review articles on $n-3$ PUFA and immunosuppression can be consulted for additional details (Chapkin et al., 2007; Calder, 2009; Kim et al., 2010).

2. Effect of $n-3$ PUFA on membrane-mediated macrophage functions in tuberculosis (TB) pathogenesis and immune control of TB

Mycobacterium tuberculosis (*Mtb*) is a slow-growing acid-fast bacillus transmitted by inhalation of bacterium-containing droplet nuclei, generated when people with active TB cough or sneeze (Glickman and Jacobs, 2001). Once *Mtb* gains access to alveoli, it is phagocytosed by alveolar macrophages (Rook, 1994). Phagocytosis occurs through specific cellular receptors, including complement receptors, Fc receptor, scavenger receptor and mannose receptor (Ernst, 1998). Toll-like receptors (TLR) also seem to play a role in mycobacterial immune recognition (Reiling et al., 2002). Mycobacterial components (e.g., lipoarabinomannan and lipoproteins) (Means et al., 1999) interact with TLR2 and TLR4 and trigger intracellular signaling pathways, resulting in secretion of pro-inflammatory cytokines (e.g., interleukin-12 (IL-12) and tumor necrosis factor-α (TNFα)), and chemokines (e.g., IL-8, RANTES, MCP-1) (Algood et al., 2003), which subsequently induce activation and migration of additional inflammatory cells, such as T cells, monocytes, dendritic cells, natural killer cells, B cells and neutrophils from the bloodstream to the site of infection (Jo, 2008; Russell, 2007). Over time, the infiltrating cells organize in a multicellular structure called a tuberculous granuloma, the pathophysiological hallmark of *Mtb* infection (Russell, 2007; Saunders and Cooper, 2000).

The development of a protective immune response to TB depends on both innate and adaptive cellular immune mechanisms, mediated mainly by the coordinated recruitment, activation and interaction of T cells and macrophages (Bhatt and Salgame, 2007; Flynn and Chan, 2001). Dendritic cells also play an important role as cytokine producers and antigen presenting cells. They internalize and process *Mtb* and then migrate to lymphoid nodes to present mycobacterial antigens to T cells (McShane et al., 2002). The interaction of T cells with antigen presenting cells leads to activation and clonal expansion of T cells that recognize *Mtb* specifically (Kaufmann and Flesch, 1988). Resistance to TB is characterized by a $CD4^+$ T cell response (Saunders et al., 2002). Between 2 and 4 weeks post infection, specialized $CD4^+$ T cells are activated, recruited to the lung and programmed to secrete protective Type 1 helper cytokines (e.g., IFNγ, TNFα and IL-2) which, in turn, enhance the antimycobacterial functions of macrophages (Flynn and Chan, 2001). IFNγ induces macrophage activation of antibacterial responses leading to up-regulation of over 200 responsive genes (e.g., inducible nitric oxidase and MHC) (Boehm et al., 1997). In addition to $CD4^+$ T cells, other discrete T-cell subsets, such as $CD8^+$, γδ and CD1-restricted T cells, play a role in the immune response to *Mtb* (Peters and Ernst, 2003).

Macrophages exert their antimycobacterial activity by different mechanisms (Liu and Modlin, 2008). From a membrane perspective, initially after uptake, bacteria are enclosed in specialized endocytic compartments called phagosomes. Lysosomes are vacuolar organelles of the late endocytic pathway which contain hydrolytic enzymes capable of degrading mycobacteria. Phagosomes can sequentially fuse with early and late endocytic organelles (e.g., lysosomes) in a process known as phagosome maturation (Vergne et al., 2004). During the fusion process, phagosomes acquire proteins essential for membrane-organelle docking, membrane traffic and fusion events (Desjardins, 1995), including Rab GTPases and GTP-binding glycoproteins, resulting in bacterial killing. Mycobacterial phagosomes retain Rab5, a GTPase that mediates the interaction with early endocytic compartments (Desjardins et al., 1994), but exclude Rab7 (Press et al., 1998) and other lysosomal markers, which regulates late endosomal membrane trafficking. As a result, mycobacterial phagosomes cannot mature to phagolysosomes (Press et al., 1998; Via et al., 1997). Second, activated macrophages generate reactive oxygen and nitrogen species which have antimycobacterial activity (Nathan and Shiloh, 2000; Shiloh and Nathan, 2000). As mentioned earlier, immune stimulation of macrophages, via T cells, TLR agonists, or cytokines such as IFNγ, TNFα and GM-CSF, enhances their activation and antimycobacterial capacity; improving their ability to control the infection (Crowle et al., 1987; Rook et al., 1986). However, *Mtb* has the ability to avoid destruction within macrophages (Houben et al., 2006), in fact, bacteria can survive and grow within these cells. This pathogen prevents maturation of macrophages and dendritic cells (Hanekom et al., 2003), impairing the activation of a wide range of antimycobacterial responses.

Cytokines induce effective macrophage killing and can influence the polarization of the adaptive immune response and the subsequent development of resistance or susceptibility to mycobacterial infection (Sharma and Bose, 2001). *Mtb* induces secretion of IL-12 (Ladel et al., 1997), IL-6 (Zhang et al., 1995) and TNFα (Flynn et al., 1995) by murine macrophages and mouse dendritic cells. These pro-inflammatory cytokines are required for a protective response to TB (Flynn et al., 1995). For example, IL-12 is critical for activation and migration of murine dendritic cells (Cooper et al., 1995) and TNFα is required for granuloma formation in mice (Flynn et al., 1995). On the other hand, TNFα is also associated with the histopathological damage during TB, mediating necrosis and tissue dysfunction (Rook and al Attiyah, 1991).

3. Impact of dietary lipids on the immune response to TB and other infections

Lipids serve as structural membrane components, a source of energy and regulators of the host immune response. For example, the incorporation of cholesterol into host cell membranes has a detrimental impact on the response against TB. This lipid seems to be required for *Mtb* internalization, phagosomal maturation prevention and mycobacterial survival (Gatfield and Pieters, 2000; de Chastellier and Thilo, 2006). Conversely, other lipids have been shown to promote phagosomal maturation. For example, arachidonic acid (AA, 20:4 $n-6$), ceramide and sphingomyelin induce actin assembly, acidification and lysosome fusion in *Mtb*-containing phagosomes, favoring more effective mycobacterial control in mouse macrophages (Anes et al., 2003).

Docosahexaenoic acid (DHA; 22:6 $n-3$) and eicosapentaenoic acid (EPA; 20:5 $n-3$) are long chain $n-3$ PUFA synthesized by sequential desaturation–elongation reactions from α-linolenic acid (ALA, 18:3 $n-3$), a dietarily essential fatty acid. Diets rich in these