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N-3 Polyunsaturated fatty acids modulate B cell activity in pre-clinical models: Implications for the immune response to infections

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Abstract

B cell antigen presentation, cytokine production, and antibody production are targets of pharmacological intervention in inflammatory and infectious diseases. Here we review recent pre-clinical evidence demonstrating that pharmacologically relevant levels of n-3 polyunsaturated fatty acids (PUFA) derived from marine fish oils influence key aspects of B cell function through multiple mechanisms. N-3 PUFAs modestly diminish B cell mediated stimulation of classically defined naïve $CD4^+$ Th1 cells through the major histocompatibility complex (MHC) class II pathway. This is consistent with existing data showing that n-3 PUFAs suppress the activation of Th1/Th17 cells through direct effects on helper T cells and indirect effects on antigen presenting cells. Mechanistically, n-3 PUFAs lower antigen presentation and T cell signaling by disrupting the formation of lipid microdomains within the immunological synapse. We then review data to show that n-3 PUFAs boost B cell activation and antibody production in the absence and presence of antigen stimulation. This has potential benefits for several clinical populations such as the aged and obese that have poor humoral immunity. The mode of action by which n-3 PUFA boost B cell activation and antibody production remains unclear, but may involve Th2 cytokines, enhanced production of specialized proresolving lipid mediators, and targeting of protein lateral organization in lipid microdomains. Finally, we highlight evidence to show that different n-3 PUFAs are not biologically equivalent, which has implications for the development of future interventions to target B cell activity.

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Keywords

B cells; n-3 polyunsaturated fatty acids; humoral immunity, lipid microdomains

1. Overview of n-3 polyunsaturated fatty acids (PUFAs) and immunity in pre-clinical models

Long chain n-3 polyunsaturated fatty acids (PUFAs) are bioactive molecules abundant in select oily fish and fish oil supplements. The two major long chain n-3 PUFAs of interest for modulating immune responses are eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids. Studies over several decades, particularly in pre-clinical models, have demonstrated that n-3 PUFAs have the potential to mitigate inflammation by targeting select cell types through multiple molecular mechanisms (Calder et al., 2012). The objective of this review it to focus on emerging evidence that n-3 PUFAs can target the function of B cells. We review the role of B cells in inflammatory and humoral immune responses and then highlight the role of n-3 PUFAs in modifying B cell antigen presentation, cytokine production, and antibody generation. Throughout the review, we compare findings on B cells with other key immune cells and point to relevant mechanisms by which n-3 PUFAs may be targeting B cell function.

2. B cells respond to innate stimuli, present antigen to T cells, and generate antibodies

B cells are widely known to be the primary lymphocyte in the humoral arm of the adaptive immune response. B cells have been mostly studied in conjunction with diverse antibody production; however recent reports have shed light on novel aspects of B cell immunology including response to innate immune stimuli, antigen presentation, and regulatory cytokine production.

Naïve B cells are currently classified into two general subsets, B1 and B2 (Baumgarth, 2011; Choi et al., 2012). Both subsets are important in antibody production, but differ not only in cell surface markers, but also location and function. B1 B cells are defined as $CD19^{high}CD23^{-}CD43^{+}IgM^{high}IgD^{variable}$ whereas B2 cells are characterized as $CD19^{high}CD23^{-}CD43^{+}IgM^{low}IgD^{high}$ (Choi et al., 2012). B1 B cells are innate-like B cells that express antigen receptors of limited diversity and are sustained through self-renewal and not bone marrow precursors (Baumgarth, 2011; Choi et al., 2012; Wardemann et al., 2002). B1 cells are found predominantly in the peritoneal and pleural cavities with small numbers in the spleen and lymph nodes, and are enriched for clones bearing self-reactive antigen receptors (Baumgarth, 2011; Ha et al., 2006). B1 B cells are further subdivided into B1a ($CD5^{+}$) and B1b ($CD5^{-}$) subtypes (Baumgarth, 2011; Choi et al., 2012). Both B1a and B1b B cells arise from precursors in the fetal liver but are not generated efficiently from adult bone marrow (Montecino-Rodriguez et al., 2006). B1a cells are thought to be the source of natural IgM, the circulating immunoglobulin produced in the absence of microbes (Wardemann et al., 2002). B1b cells, in contrast, are the predominant source of IgM against T-independent antigens (Alugupalli et al., 2004; Haas et al., 2005).

In contrast to B1 cells, B2 cells are a heterogeneous population that originates in the bone marrow as immature, naïve B cells with surface bound IgM (Northrup and Allman, 2008). Dependent on the cytokine milieu, such as the presence of IL-7 and Flt-3 ligand, immature B cells leave the bone marrow and migrate to the spleen, where they gain surface IgD and become transitional 1 (T1) B cells (Carvalho et al., 2001; Tussiwand et al., 2009). Transitional 2 (T2) B cells reduce surface IgM and upregulate surface bound IgD, and then enter the mature B cell pool, recirculating through the primary follicles of secondary lymphoid organs (Pieper et al., 2013). Mature B2 cells have a diverse repertoire of antigen receptors as a result of various genetic recombination within the genes encoding immunoglobulin heavy and light chains. B2 B cells are grouped into two subtypes, follicular and marginal zone B cells, based on homing location in the spleen and B cell receptor signaling strength (Allman and Pillai, 2008; Pillai and Cariappa, 2009).

Follicular B cells ($CD19^{high}CD23^{high}CD21^{mid}CD1d^{mid}IgM^{low}IgD^{high}$) organize in the primary follicles of the splenic white pulp and the cortical areas of peripheral lymph nodes and comprise the majority of recirculating mature B cells (Pillai and Cariappa, 2009). Upon antigen encounter, follicular B cells can endocytose and process antigen and then present antigenic peptides in the context of major histocompatibility complex (MHC) class II to cognate $CD4^+$ T cells (Pillai and Cariappa, 2009). The interaction of antigen-specific B2 B cells with cognate $CD4^+$ helper T cells initiates the germinal center response, wherein antigen-specific B cells proliferate, undergo class-switch recombination, and somatic hypermutation of genes encoding the B cell receptor (Liu and Arpin, 1997; MacLennan, 1994). Within the germinal center, B cells interact with T follicular helper cells and follicular dendritic cells, and are selected on the basis of receptor affinity for antigen, resulting in the clonal expansion of B cells bearing high affinity for antigen, a process called affinity maturation (Takemori et al., 2014). The ultimate products of the germinal center response are long-lived plasma cells, which secrete high affinity class-switched antibody, and memory B cells, which respond to subsequent antigen encounter with rapid differentiation into plasma cells. Long-lived plasma cells and memory B cells represent the cellular basis for humoral immunity (Shlomchik and Weisel, 2012).

Marginal zone B cells are located outside the marginal sinuses of the spleen, bordering the red pulp where they assess the periphery for pathogens before being trapped by the spleen. Marginal zone B cells are not only classified by their expression of cell surface receptors ($CD19^{high}CD23^{-}CD21^{high}IgM^{high}CD1d^{high}IgD^{low}$) but also are noncirculating mature B cells (Wen et al., 2005). Marginal zone B cells have high expression of Toll-like receptors compared to follicular B cells and are rapidly recruited into early adaptive immune responses in a T cell-independent manner (Treml et al., 2007). In contrast to the humoral response generated through the germinal center reaction, marginal zone B cells differentiate into short-lived extrafollicular plasmablasts that secrete low affinity antibodies, and do not become memory B cells (Allman and Pillai, 2008; Otero et al., 2003).

Recently, two new B cell subpopulations have been described, B10 cells and innate response activator (IRA) B cells. B10 cells are defined by their ability to produce IL-10 and are phenotypically similar to B1 and marginal zone B cells (Candando et al., 2014). B10 cells function in a T cell-dependent manner to regulate immune responses (Matsushita and

Tedder, 2011). IRA B cells are a specialized subset of B1a cells that are characterized by GM-CSF secretion upon antigen encounter (Rauch et al., 2012). Both B10 and IRA B cells have been demonstrated to be potent regulators of inflammatory diseases (Djoumerska-Alexieva et al., 2013; Kalampokis et al., 2013; Rauch et al., 2012; Weber et al., 2014). Further investigation into these novel subpopulations is still needed.

3. Dietary supplementation with n-3 PUFAs targets the function of antigen presenting cells including B cells to dampen T cell cytokines

Cytokines generated from Th1/Th17 cells have a pro-inflammatory role in several diseases such as diet-induced obesity (Chen et al., 2014; Winer et al., 2009). Therefore, suppressing the activation of these cells with n-3 PUFAs has clinical utility. Several lines of evidence suggest that n-3 PUFAs can diminish the activation of naïve $CD4^+$ T cells to dampen the production of classically defined Th1 cytokines (Shaikh et al., 2012). It is hypothesized that the effects of n-3 PUFAs on Th1 cytokine levels are driven by indirect effects of n-3 PUFAs on antigen presenting cells (Rockett et al., 2012) and by direct effects on T cells (Kim et al., 2008).

Overall, there is very little information on how n-3 PUFAs target B cell antigen presentation through the MHC class II pathway. To date, there is only one study on how n-3 PUFAs target B cells to influence cognate T cell activation. Administration of fish oil to healthy C57BL/6 mice suppressed the ability of $B220^+$ B cells to stimulate Th1 cytokine secretion (Rockett et al., 2012). This finding was consistent with a few *in vitro* or *ex vivo* studies that have shown that in human cells such as monocytes or macrophages, n-3 PUFAs lower MHC class II surface expression, which suppressed antigen presentation (Hughes and Pinder, 1996, 2000; Hughes et al., 1996a; Hughes et al., 1996b).

More compelling evidence for n-3 PUFAs suppressing antigen presentation has come from studies with dendritic cells (Sanderson et al., 1997). These studies demonstrate that dendritic cell activation in response to lipopolysaccharide (LPS) is suppressed by n-3 PUFAs *in vitro* and *ex vivo* (Draper et al., 2011; Ganea et al., 2011; Wang et al., 2007; Zeyda et al., 2005). Generally, surface levels of MHC class II and/or co-stimulatory molecules are suppressed, associated with a decrease in pro-inflammatory cytokine secretion (i.e. IL-6, TNF-α and IL-12p70) after LPS activation. The consequence of suppressing dendritic cell activation with n-3 PUFAs is presumably diminished naïve $CD4^+$ T cell activation; however, *in vivo* evidence of n-3 PUFAs suppressing T cell activation by targeting DCs remains to be fully established (Teague et al., 2013b).

There are a few experiments that have addressed how dietary supplementation with n-3 PUFAs can influence antigen presentation by MHC class I molecules to cytotoxic $CD8^+$ T cells. This pathway of antigen presentation is relevant for clearance of select pathogens, removal of tumor antigens, and presentation of autoantigens in autoimmune diseases (Bowness et al., 2009). Initially, it was discovered that fusion of tumor cells with lipid vesicles containing DHA esterified into phosphatidylcholine modified the conformation of MHC class I, which increased lysis of T27A cancer cells by $CD8^+$ T cells (Jenski et al., 1993; Pascale et al., 1993). In contrast, another study showed that treatment of JY B

lymphoblasts with DHA at a high dose suppressed MHC class I antigen presentation to $CD8^+$ T cells by suppressing B-T cell adhesion (Shaikh and Edidin, 2007). Follow up studies revealed that the differences between the two studies were attributed to the methods of lipid treatment (Shaikh and Edidin, 2008).

There is good evidence to show that n-3 PUFAs can directly suppress *ex vivo* activation of $CD4^+$ Th1 cells. N-3 PUFAs, upon stimulation of naïve $CD4^+$ T cells with anti-CD3/CD28 antibodies or with select hybridomas, suppress Th1 cytokine secretion and proliferation (Kim et al., 2013; Zhang et al., 2006; Zhang et al., 2005). Recent studies with a model of diet-induced obesity and/or colitis have also demonstrated that the activation of pro-inflammatory Th17 cells was also inhibited by dietary supplementation with n-3 PUFAs (Monk et al., 2012a; Monk et al., 2012b).

Far less is known about the ability of n-3 PUFAs to target other subsets of T cells. In particular, it is unclear if n-3 PUFAs enhance the formation of classically defined $CD4^+$ Th2 cytokines, which have a beneficial role in metabolic disorders. Petursdottir and Hardardottir showed that n-3 PUFAs increase the secretion of murine Th2 cell IL-4 indirectly by targeting antigen presenting cells (Petursdottir and Hardardottir, 2009). Recently, a study showed that select Th2 cytokines were elevated with n-3 PUFA intervention with mice on a 129 background (Gurzell et al., 2012). The potential for n-3 PUFAs to increase Th2 cytokines is essential to address given that Th2 cytokines can also exacerbate some types of inflammation (Masuoka et al., 2012). Indeed, a recent study demonstrated that DHA, but not EPA, was pro-inflammatory in a mouse model of asthma (Schuster et al., 2014). In contrast, some experiments suggest that n-3 PUFAs dampen Th2 cytokines (Jang et al., 2014; Park et al., 2013). Jang et al. demonstrated that fat-1 mice, in response to a challenge with ovalbumin, had suppressed Th2 cytokines and infiltration of inflammatory cells into the lungs (Jang et al., 2014). Given the disparity in the literature, more research is needed in this area.

Even less is known about how n-3 PUFAs target other T cell types such as regulatory T cells. Regulatory T cells maintain tolerance to self-antigens and thereby have a critical role in autoimmunity. Van den Elsen et al. recently demonstrated that regulatory T cells were positively impacted by n-3 PUFAs in a mouse model of food allergy (van den Elsen et al., 2013). A previous study had shown DHA suppressed the action of regulatory T cells (Yessoufou et al., 2009).

3.1. Lipid microdomains and the immunological synapse are mechanistic targets of n-3 PUFAs

The molecular mechanisms of long chain marine n-3 PUFAs are highly pleiotropic and therefore the underlying mode of action of n-3 PUFAs on each cell type is likely unique based on the subcellular distribution of EPA and DHA in the lipidome (Calder, 2012; Mozaffarian and Wu, 2012). We do not cover all of the potential mechanisms by which n-3 PUFAs can exert their effects, which potentially include lowering of arachidonic acid levels and thereby downstream lipid mediators, generation of specialized proresolving lipid mediators, and targeting of G protein coupled receptors (Calder, 2014; Shaikh and Teague, 2012). Here we focus on how n-3 PUFAs may target the spatial distribution of lipids and

proteins within cholesterol-enriched lipid microdomains of the immunological synapse (Shaikh et al., 2012).

The immunological synapse is a highly organized membrane junction between antigen presenting cells and T cells (Fooksman et al., 2010). The formation of the synapse is highly dependent on the underlying lipid composition, which may be driven by the formation of lipid rafts (Anderson and Roche 2014; Zech et al., 2009). Lipid rafts are operationally defined as sphingolipid-cholesterol enriched regions of the membrane that concentrate specific signaling proteins (Lingwood and Simons, 2010). The accumulation of rafts within the synapse has been debated, which is beyond the scope of this review.

Numerous studies have demonstrated that n-3 PUFAs can remodel the biochemical composition of detergent resistant membranes, a very crude approximation of lipid rafts (Fan et al., 2003; Schley et al., 2007; Stulnig et al., 2001). More sophisticated imaging and spectroscopic studies reveal that n-3 PUFAs diminish the clustering of lipid rafts and serve to increase their molecular order, which suggests that n-3 PUFA acyl chains enhance the formation of lipid rafts (Kim et al., 2014; Kim et al., 2008; Rockett et al., 2012; Teague et al., 2013c; Yog et al., 2010). Albeit unclear, it appears that n-3 PUFAs, due to their highly disordered structure, can promote the translocation of cholesterol between non-raft and raft regions to promote an increase in the size and order of rafts (Grimm et al., 2011; Shaikh, 2012). It is important to note that EPA and DHA are not identical and can exert different effects on lipid rafts, as demonstrated in several model systems including artificial bilayers and cells from *in vitro* or *in vivo* treatment with n-3 PUFAs (Rockett et al., 2011; Rockett et al., 2012; Shaikh et al., 2009; Williams et al., 2012).

N-3 PUFAs directly target the activation of naïve $CD4^+$ T cells by promoting the formation of lipid rafts within the immunological synapse and thereby preventing the recruitment of select T cell signaling proteins, which was mediated by the underlying actin cytoskeleton (Hou et al., 2012). More recently, it was demonstrated that n-3 PUFAs could prevent the accumulation of MHC class II molecules within the B-T cell synapse, which influences the recruitment of T cell receptor kinase theta into the synapse and downstream IL-2 secretion (Rockett et al., 2013). The effects were mediated by cholesterol as demonstrated with cholesterol depletion experiments. Downstream of the plasma membrane, n-3 PUFAs exert their effects by targeting transcription factors to modify gene expression (Calder, 2012). For instance, n-3 PUFAs have been shown to bind peroxisome proliferator-activated receptors (PPARs) and liver x receptors. Numerous studies illustrate that n-3 PUFAs activate PPARs, which leads to suppression of the production of pro-inflammatory cytokines in addition to stimulating fatty acid oxidation genes (Jump, 2011; Oliver et al., 2010).

4. N-3 PUFA supplementation enhances B cell activation and antibody production in healthy mice and pre-clinical models of disease

Overall, very little research has focused on how n-3 PUFAs influence B cell development in the bone marrow and the production of differing B cell subsets and ultimately B cell activation and antibody production in response to antigen. A few studies in the past focused on antibody production, revealing highly mixed results (Jang et al., 2014; Lauritzen et al.,

2011; Selvaraj and Cherian, 2004; Weise et al., 2011). Differences between these studies were vast, ranging from experiments using birds to rats with different doses and intervention times with n-3 PUFAs.

Recent measurements with mice show that n-3 PUFAs or specialized proresolving lipid mediators synthesized from n-3 PUFAs enhance several aspects of B cell activation and antibody production (Table 1). Rockett et al. first reported that n-3 PUFAs administered to C57BL/6 mice enhanced innate B cell cytokine secretion in response to LPS stimulation *ex vivo* (Rockett et al., 2010; Rockett et al., 2012). Activation was assessed in terms of upregulation of B cell surface molecules and release of TNFα, IFNγ, and IL-6. Gurzell et al. confirmed these findings in a colitis-prone Smad3$^{-/-}$ mouse model (Gurzell et al., 2012). Administration of a DHA-enriched fish oil enhanced B cell activation and increased the percentage of B220^{+}MHC II^{+} B cells in the mesenteric lymph nodes and Peyer's patches accompanied by an increase in fecal IgA. A common observation amongst these studies was a correlation between the enhancement in B cell activation with n-3 PUFAs accompanied by a significant disruption in the ability of sphingolipid-cholesterol enriched lipid rafts to form (Gurzell et al., 2012; Rockett et al., 2012; Teague et al., 2014).

Subsequent *in vivo* studies show that n-3 PUFAs, modeling clinically relevant levels, increased the activity of B1 and B2 subsets. Teague et al., reported that short term consumption of n-3 PUFAs as fish oil decreased the percentage of naïve B cells in the bone marrow but increased the frequency of all major B cell subsets in the spleen upon stimulation with trinitrophenylated-LPS (TNP-LPS), which was accompanied by an increase in splenic B cell surface IgM expression and a decrease in CD19 expression (Teague et al., 2013a). In the same study, long-term consumption of n-3 PUFAs increased the frequency of transitional 1 and marginal zone B cells, enhanced circulating TNP-LPS specific IgM levels and rescued the decrement in IgM levels in diet-induced obesity (Teague et al., 2013a). The improvement in antibody production in obese mice opens a new avenue of research given that obesity is associated with decreased humoral immunity (Milner et al., 2013; Sheridan et al., 2012). More recent work has revealed that EPA and DHA ethyl esters differentially enhanced *ex vivo* splenic B cell activation and modestly elevated natural IgM and IgA in murine diet-induced obesity (Teague et al., 2014). Similarly, fish oils enriched in EPA compared to DHA had different effects on *ex vivo* B cell activation and upregulation of activation markers (Gurzell et al., 2015). Mechanistically, the differential effects of EPA and DHA ethyl esters or EPA or DHA enriched fish oils correlated with changes in lipid microdomain organization (Gurzell et al., 2015; Teague et al., 2014). These studies particularly highlight the differences in the bioactivity of EPA and DHA, which is essential to understand.

Tomasadottir et al. demonstrated for the first time that fish oil, in a murine model of peritonitis, increased the frequency of B1 cells accompanied by an increase in the levels of antigen-specific IgM antibodies (Tomasdottir et al., 2014). In contrast to the study by Teague et al., this study showed no change in the frequency of B2 cells. The differences between these two studies suggest that the effects of n-3 PUFAs are highly antigen specific. More studies are needed in this area, particularly with T-dependent antigens, which are highly relevant toward the development of vaccines.

4.1. Potential mechanisms by which dietary n-3 PUFAs boost humoral immunity

It is unclear how n-3 PUFAs may enhance humoral immunity. One possibility is that n-3 PUFAs boost humoral immunity by a direct effect of n-3 PUFAs on B cell lipid rafts. A recent study showed that B cell activation with EPA and DHA enhanced the packing of lipid microdomains but had no influence on long range diffusion of Toll-like receptor 4, which is involved in responding to LPS stimulation (Teague et al., 2014). Therefore, studies at the level of the membrane need to address more short-range effects of n-3 PUFAs, such as conformational changes and clustering within nanoscale domains (Shaikh and Edidin, 2008).

The effects of n-3 PUFAs on B cells may lie at the level of B cell development in the bone marrow or upon exit into the circulation. For instance, n-3 PUFAs may target IL-7 signaling, which is central in B cell development (Clark et al., 2014). At the molecular level, n-3 PUFAs may also target antibody production at the molecular level through the production of specialized pro-resolving lipid mediators. Two recent studies highlight the potential role of specialized pro-resolving lipid mediators on B cell activity (Table 1). In an initial report, Phipps and co-workers demonstrated that resolvin D1 (RvD1) and 17-hydroxydocosahexaenoic acid (17-HDHA) increased antigen specific IgM from human $CD19^+$ B cells stimulated with CpG ODN 2395 and anti-IgM (Ramon et al., 2012). 17-HDHA increased both IgM and IgG levels in the supernatants after 7 days of incubation in a dose-dependent manner (Ramon et al., 2012). B-cell proliferation assays revealed 17-HDHA did not influence the number of B cells but increased the number of B cells secreting IgM and IgG in a dose-dependent manner. RvD1 and 17-HDHA are both found in the spleen and synthesized from DHA and could potentially be elevated in response to murine dietary consumption of DHA. A follow up study revealed that 17-HDHA enhanced murine antibody production in response to stimulation with influenza infection, ovalbumin and in response to immunization with influenza hemagglutinin in the absence of adjuvant, suggesting a potential role for 17-HDHA as an adjuvant (Ramon et al., 2014).

It is also possible that n-3 PUFA boost B cell mediated immunity via indirect effects through Th2 cytokines. We propose that the enhancement in antibody production observed in recent studies with n-3 PUFA may be an indirect consequence of the suppression in inflammation. Indeed, cytokines secreted from Th2 cells have a role in regulating humoral immunity and inflammation. Th2 cells are characterized by secretion of IL-4, IL-5, IL-10 and IL-13 (Mosmann et al., 1986). The main Th2 cytokine, IL-4, acts as an anti-inflammatory cytokine and is secreted by activated Th2 and natural killer T cells. Signaling through the IL-4 receptor promotes proliferation and differentiation of Th2 cells via a positive feedback manner and, as a result, promotes the production and secretion of the other major Th2 cytokines (IL-5, -10, and -13) (Zeng, 2013).

IL-4 also upregulates the expression of MHC class II molecules, as well as the Fc receptor, CD23, and promotes class switching from IgM to IgG1 and IgE. Importantly, IL-4 production by Th2 T cells inhibits production of the pro-inflammatory cytokines TNF-α, IL-1 and IL-6 (Zhu and Paul, 2008). IL-5 stimulates proliferation and differentiation of B cells and eosinophils. IL-5 is important for the induction of IgA class switching in mucosal B cells, protection against parasitic infection, and pathology of asthma due to stimulation of eosinophils (Takatsu, 1998). In addition, B-1 cells constitutively express the IL-5 receptor

and respond to IL-5 for survival, proliferation and differentiation to natural antibody-secreting plasma cells (Takatsu et al., 2009). Cells of both the innate and adaptive immune responses express IL-10, including dendritic cells, macrophages, mast cells, NK cells, eosinophils, neutrophils, T cells, and B cells (Ouyang et al., 2011). IL-10 is a potent inhibitor of inflammation and targets white blood cells to elicit anti-inflammatory responses directly through inhibition of the production of the pro-inflammatory cytokines IFN-γ, IL-2, IL-3, TNFα and GM-CSF (Ouyang et al., 2011). T cells and NK cells produce IL-13, which has pleiotropic effects as a suppressor of inflammatory responses (Wynn, 2003). Similar to IL-4, IL-13 induces B cell proliferation, CD23 expression, and class switching to the IgE and IgG4 antibody subclasses (Wynn, 2003). Similar to IL-5, IL-13 also plays a central role in allergic asthma through regulation of eosinophil mediated inflammation (Martinez and Vercelli).

Given that recent studies show that n-3 PUFAs are increasing IL-5 and that B1 cell function is enhanced, it is intriguing to hypothesize that IL-5 may be responsible for boosting B1 cell function in mouse models (Gurzell et al., 2012; Teague et al., 2013a; Tomasdottir et al., 2014). Furthermore, one study showed that IL-13 was also increased with n-3 PUFAs, which may be an additional mechanism by which B cell proliferation could be enhanced (Gurzell et al., 2012). Future studies are needed in this area to resolve if Th2 cytokines are boosting B cell activity upon n-3 PUFA supplementation.

5. Clinical implications for boosting B cell antibody production

B cells are critical for both innate and adaptive immune responses through natural and antigen-driven antibody responses as well antigen presentation and cytokine production. These B cell functions are critical for the host defense response against pathogens, protection against reinfection, as well as tissue homeostasis. Therefore, boosting B cell antibody production or activities, perhaps through n-3 PUFA supplementation, may have clinical relevance in certain patient populations such as the obese (Shaikh et al., 2015; Sheridan et al., 2012).

Defective B cell antibody production, as a result of genetic deficiencies or hypogammaglobulinemia, increases susceptibility to infection (Notarangelo, 2010). These infections are mainly bacterial, however chronic viral infections are also common with impaired antibody production (Conley et al., 2009; Notarangelo, 2010). Treatment of B cell dysfunction in patients mostly relies on immunoglobulin replacement therapy to aid in reducing the incidence of infections (Notarangelo et al., 2009). However, these treatments are costly and frequent indicating that alternative methods of boosting antibody production need to be explored. In addition to human studies, multiple murine models of B cell deficiencies have reported increased susceptibility to both T-dependent and T-independent pathogens (Wang et al., 2011).

Antibody production is not only important in the primary immune response to pathogens, but is also essential for establishing memory through the production of antibodies and antibody-secreting plasma cells. This is the immunological basis behind effective vaccination strategies. However, the antibody response of healthy individuals to routine

prophylactic vaccinations varies substantially and the mechanisms for the wide variation are poorly understood (Dietert et al., 2000). It has been hypothesized that this could be a result of nutritional status and/or environmental exposures as well as genetics (Chance, 2001; Dietert et al., 2000; Heilmann et al., 2006; Rytter et al., 2014). Given the preclinical results with n-3 PUFAs, supplementation after vaccination may benefit patients that are lower antibody responders.

Increasing B cell function and antibody production through n-3 PUFA supplementation may also benefit multiple patient populations that have been reported to have an altered humoral immune response. For example, the aging population has been reported to have compromised immune responses to infection (Gross et al., 1995; Vu et al., 2002), and decreased antibody production after influenza vaccination (Frasca and Blomberg, 2014). Recently, studies have shown age-related intrinsic B cell and plasmablasts defects before and after vaccination when compared with younger individuals (Sasaki et al., 2011). In addition to age decreasing B cell function, chronic infection has also been associated with aberrant B cell activation, including phenotypic and functional alterations (Moir and Fauci, 2008). Boosting these aspects of immunity with n-3 PUFAs in these patient populations could decrease hospitalizations from infection and improve vaccine efficacy.

Decreased antibody production has recently been associated with chronic diseases. For example, several human studies have reported that cardiovascular disease is associated with decreased plasma IgM (Tsimikas et al., 2007). Supporting a causal relationship, IgM secretion by B1a cells has been shown to be protective in atherosclerosis (Kyaw et al., 2012). Moreover, IgM antibodies facilitate the removal of apoptotic cells and oxidized LDL as well as other cellular debris that have a proven role in the pathogenesis of atherosclerosis (Tsimikas et al., 2007). Therefore, boosting IgM production and/or B1 B cell activity may be protective in cardiovascular diseases and possibly other chronic inflammatory conditions.

Antibody production, more specifically IgA, has been reported to be important in maintenance of commensal bacteria in the gut (Kato et al., 2014). Conversely, decreased IgA production leads to overgrowth of commensal intestinal bacteria, specifically filamentous bacteria (Suzuki et al., 2004). Upset of the intestinal “microbiome” has been associated with multiple chronic inflammatory diseases including inflammatory bowel disease (Schippa and Conte, 2014), asthma (Russell et al.), obesity (Festi et al., 2014), and colorectal cancer (Irrazábal et al., 2014). Furthermore, IgA-deficient patients have a higher incidence of immune diseases (Aytekin et al., 2012). Taken together, these data suggest that increasing IgA levels may have a beneficial effect on intestinal homeostasis and thereby lower the incidence of chronic inflammatory diseases.

6. Conclusions

In summary, our understanding of how n-3 PUFAs impact B cell function and of the underlying mechanisms is in its early stages. There is increasing pre-clinical evidence to show that n-3 PUFAs can modify B cell antigen presentation, cytokine levels, and antibody production through multiple mechanisms. These results have broad implications for treating

a variety of infectious disease in humans, which will require extensive new studies in rodent and human models.

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Table 1

Summary of studies demonstrating that n-3 PUFAs or specialized proresolving lipid mediators synthesized from n-3 PUFAs boost B cell activation and antibody production.

Study Design	Model system	Major Findings	Reference
C57BL/6 mice consuming high fat diet + menhaden fish oil.	Ex vivo	Enhanced cytokine secretion from splenic $B220^+$ B cells.	(Rockett et al., 2010)
C57BL/6 mice consuming menhaden fish oil.	Ex vivo	Enhanced cytokine secretion from splenic $B220^+$ B cells.	(Rockett et al., 2012)
$SMAD3^{-/-}$ mice consuming DHA-enriched fish oil.	Ex vivo and in vivo	Enhanced cytokine secretion from B cells; surface markers upregulated on B cells; increased fecal IgA.	(Gurzell et al., 2012)
C57BL/6 lean and obese mice consuming menhaden fish oil	In vivo	Enhanced frequency of B cells and elevated antigen-specific IgM.	(Teague et al., 2013a)
C57BL/6 mice consuming obesogenic diet with either EPA or DHA ethyl esters	Ex vivo and in vivo	EPA and DHA differentially enhance B cell cytokine secretion, natural IgM levels and fecal IgA.	(Teague et al., 2014)
$SMAD3^{-/-}$ mice consuming EPA- or DHA-enriched fish oils	Ex vivo	DHA, more effectively than EPA, enhances B cell cytokine secretion and activation markers.	(Gurzell et al., 2015)
Treatment of human B cells with RvD1 and 17-HDHA	In vitro	Enhanced antibody production from B cells.	(Ramon et al., 2012)
Administration of 17-HDHA	Ex vivo and in vivo	Mice immunized with 17-HDHA + antigen or upon live flu infection enhanced antibody production and antibody secreting cells.	(Ramon et al., 2014)