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Review

n-3 Polyunsaturated fatty acids and mast cell activation

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ABSTRACT

Mast cells are known to play a vital role in the development of inflammation in allergic responses. Recent studies have indicated that mast cell activation could be modulated by n-3 PUFAs, which have a wide range of well-documented health benefits. In our review, we summarize the recent findings and potential mechanisms of the effect of n-3 PUFAs on mast cell activation. This knowledge could provide new strategies for the development of therapeutic interventions for diseases mediated by mast cells. *J. Leukoc. Biol.* 97: 859–871; 2015.

Introduction

The connection between n-3 PUFAs and alleviated mast cell activation has gained interest. Here we will first introduce mast cells and n-3 PUFAs. Then we will describe the recent findings on the effect of n-3 PUFAs on FcεRI-mediated and non-FcεRI-mediated mast cell activation, followed with a summary of the potential mechanisms.

MAST CELLS

Mast cells are tissue-resident cells found throughout the body but preferentially in tissues that have direct interaction with the outer environment, such as the skin, airways, and gastrointestinal tract [1]. Mast cells contain many granules that are rich in histamine, heparin, neutral proteases, acid hydrolases, major basic protein, carboxypeptidases, and some preformed cytokines and growth factors [2]. Mast cells are a heterogeneous population of cells, their phenotype largely dependent on the tissue microenvironment in which they mature. Therefore, the granule contents of a connective tissue-derived mast cell differ widely from the granule contents of a mucosal tissue-derived mast cell [3]. Mast cells originate from pluripotent hematopoietic stem cells in the bone marrow [4]. Immature mast cells leave the bone marrow, enter the circulation, and then complete their differentiation in the tissues [5]. Mature mast cells are not present in the circulation under physiologic conditions [6].

Mast cells participate and regulate a great number of pathologic conditions, including allergic reactions. This is because mast cells can respond to and are activated by many different types of stimuli, including allergens, complement, antimicrobial peptides, adenosine, neuropeptides, and physical stimuli, such as a low temperature [7] (Fig. 1). The antigen-initiated activation pathway is mediated by the high-affinity IgE receptor, FcεRI. The crosslinking of IgE-bound FcεRI by bivalent or multivalent antigen results in the initiation of receptor signaling, subsequent signal transduction, and mast cell activation. After activation, 3 categories of mediators are gradually released from the mast cells [8–114] (Table 1). Within seconds, preformed mediators, which are stored in granules, such as histamine and heparin, are released in a process termed "degranulation." Lipid-derived mediators such as PGs and LTs, are released next, within minutes of activation. The last group of mediators to be released consists of those that require gene transcription and protein translation, such as the cytokines, chemokines, and growth factors. Mast cells can also produce other molecules, such as NO, ROS, and antimicrobial peptides [115]. Histamine, PGs, and LTs are responsible for acute-phase reactions in allergic diseases, resulting in vasodilation and increased vascular permeability (Fig. 1) [116]. The late-phase reactions, such as tissue swelling, fibrin deposition, and leukocyte accumulation (Fig. 1), are more often attributed to cytokines and chemokines [116]. By releasing mediators, mast cells play an important role in both the innate and adaptive immune responses and are especially vital in IgE-mediated allergic inflammation (Fig. 1) [117]. Thus, the classic viewpoint is that mast cells are important effector cells in allergic responses, such as allergic asthma.

However, mast cells also play a role in other inflammatory diseases whose pathogenesis does not involve IgE [118], because they express a broad range of receptors that can respond to

Abbreviations: AA = arachidonic acid, ALA = α-linolenic acid, BMMC = bone marrow-derived mast cells, Btk = Bruton's tyrosine kinase, COX = cyclooxygenase, CysLTs = cysteinyl leukotrienes, DAG = diacylglycerol, DGLA = dihomo-γ-linolenic acid, DHA = docosahexaenoic acid, DPA = docosapentaenoic acid, EPA = eicosapentaenoic acid, FcεRI = Fcε receptor I, GPR = G protein-coupled receptor, IFN-γR = IFN-γ receptor, IL-2Rα = IL-2

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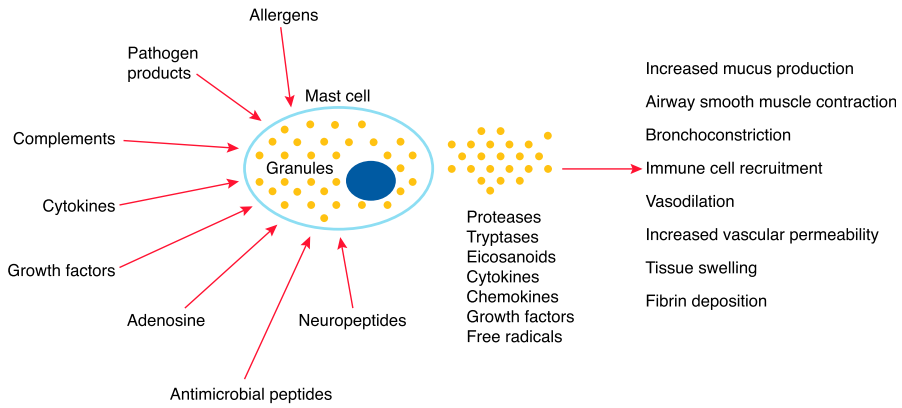

Figure 1. The role of mast cells in inflammation. Mast cells can be activated by a variety of stimuli such as allergens, complement, antimicrobial peptides, adenosine, and neuropeptides. The mediators released from activated mast cells can cause vasodilation, increased vascular permeability, the recruitment of immune cells, tissue remodeling, increased mucus production, and airway smooth muscle contraction.

non-IgE signals. The SCF receptor, c-Kit, is expressed on mast cells and is vital for survival and proliferation [119]. Mast cells express Toll-like receptor 2, which is a pattern recognition receptor that recognizes peptidoglycan, lipoproteins, and lipoteichoic acid on bacterial membranes [120]. Mast cells also express histamine receptors 2 and 4 [121, 122], cysteinyl LT receptor 1 and 2 [123], complement receptors (e.g., C3a receptor, C5a receptor, complement receptor 2, 4, and 5) [124–126], and the platelet-activating factor receptor [127]. P2X7, N-formyl-peptide receptor 1, and neurokinin-1 are expressed on mast cells, which are receptors for ATP, pleurocidin (a antimicrobial peptide) and substance P (a neuropeptide) [128–132]. Activation of these receptors can have profound effects on mast cell function, differentiation, and phenotype [133–135].

N-3 PUFAS

n-3 PUFAs contain more than one carbon double bond, and the first double bond is located at the third carbon from the methyl end (Fig. 2). ALA (C18:3, n-3) is the precursor of other n-3 PUFAs [136]. EPA (C20:5, n-3) and DHA (C22:6, n-3) are the main bioactive forms of n-3 PUFAs in the body, generated from ALA by enzyme-catalyzed desaturation, elongation, and β-oxidation [137] (Fig. 3). n-6 PUFAs are another PUFA family, with the first double bond located at the sixth carbon from the methyl end. AA (C20:4, n-6) is the main n-6 PUFA in the body [138]. The biosynthesis of n-3 and n-6 PUFAs actually shares the same enzymes, including several types of desaturases and elongases (Fig. 3). Twenty carbon chain n-3 and n-6 PUFAs are the precursors for eicosanoids, a group of molecules with multiple functions, which will be discussed in detail later in "AA-derived eicosanoid production inhibition" section. In mammals, n-3 PUFAs cannot be synthesized de novo [139] and must be obtained from the diet or produced from ALA. Fish, shellfish, seed oil, and nuts are good food sources of n-3 PUFAs [140].

The health-promoting role of n-3 PUFAs, especially EPA and DHA, has been well documented for a broad range of health and disease conditions. The consumption of EPA and DHA is associated with a lower risk of cancer, hyperlipidemia, cardiovascular diseases, hypertension, and neurodegenerative diseases [141]. The low incidence of heart disease in the Inuit and Eskimo populations has been attributed to their high seafood intake and diets rich in n-3 PUFAs [142–144]. Our studies using the prostate cancer cell lines, DU145 and PC-3, have shown that PUFA supplementation can alter IFN-γR expression and influence cancer cell responses to IFN-γ treatment [145]. The regulatory functions of n-3 PUFAs on the immune system are also well known. n-3 PUFAs were reported to modulate the activation of many immune cells, including T cells, B cells, mast cells, and basophils [146, 147].

Some in vivo studies have suggested that n-3 PUFAs have a beneficial effect on mast cell-mediated allergic responses. In an ovalbumin-induced mouse model of food allergy, dietary supplementation with fish oil rich in n-3 PUFAs reduced serum anti-ovalbumin IgE and suppressed the inflammatory response in the small intestine [148]. Likewise, *fat-1* transgenic mice, which produce endogenous n-3 PUFAs, have a decreased ovalbumin-induced allergic airway inflammatory response such that challenged *fat-1* mice show decreased leukocyte infiltration, a lower production of proinflammatory cytokines, and higher protectin D1 and resolvin E1 concentrations in the lung compared with wild-type mice that were similarly challenged [149]. In the same model, higher n-3 PUFAs levels in the lung were associated with impaired differentiation of T helper type 2 cells [150].

A number of human studies have demonstrated the potential protective effects of n-3 PUFAs on allergic inflammation, especially in allergic asthma. In a case-control study of 166 asthmatic and 169 normal children, logistic regression analysis showed a positive association between the dietary n-6:n-3 PUFA ratio and the risk of asthma [151]. Some Northern European researchers performed a cohort study on the relationship between fish intake and asthma and found that adults who did not consume any fish during childhood clearly had an elevated risk of developing asthma as an adult [152]. In a double-blind human study, a 5-wk supplementation with n-3 PUFAs significantly decreased exhaled NO from young (22–29-yr-old) asthma patients challenged with low-dose dust mite allergen, reduced the blood eosinophil count and inhibited the antigen-induced cysLT production by isolated leukocytes from these patients [153]. These results indicate that the effect of n-3 PUFAs on allergic responses might be dependent on how n-3 PUFAs are provided to the patients in terms of the PUFA dose, the

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receptor α, PKC = protein kinase C, PPAR = peroxisome proliferator-activated receptor, PUFAs = polyunsaturated fatty acids, ROS = reactive oxygen species, SCF = stem cell factor, Syk = spleen tyrosine kinase

TABLE 1. Mediators produced by activated mast cells

Mediators	Species	Function	n-3 PUFA effect
Preformed mediators			
Histamine	Human, mouse [8, 9]	A neurotransmitter, induces bronchial smooth muscle contraction and vasodilation, increases heart rate [10]	Inhibition [11]
Serotonin	Human, mouse [12, 13]	A neurotransmitter, induces vasoconstriction, reduces appetite, inhibits pain perception [14–16]	Unknown
Heparin	Human, mouse [17, 18]	An anticoagulant, induces the production of bradykinin, increases vascular permeability [19, 20]	Unknown
Tryptase	Human, mouse [21, 22]	Counteracts vasodilator, increases vascular permeability [23–25]	Unknown
Chymase	Human, mouse [26, 27]	Increases vascular and epithelial permeability, promotes vascular smooth muscle cell apoptosis [23, 28, 29]	Unknown
Major basic protein	Human [30]	Induces bronchoconstriction and airway hyper-responsiveness, inhibits epithelial cell function [31, 32]	Unknown
Carboxypeptidase A	Human, mouse [33, 34]	Detoxification of harmful substances such as snake venom toxins [35]	Unknown
Lipid-derived mediators			
PGD_2	Human, mouse, rat [36, 37]	Induces vasodilation and bronchial smooth muscle contraction, inhibits NK cell activity [38–40]	Inhibition [41]
PGE_2	Rat, mouse [42]	Enhances vascular permeability, promotes vascular smooth muscle cell proliferation and contraction [43–45]	Inhibition [46]
LTB_4	Human, mouse [47, 48]	Induces vasodilation and neutrophil chemotaxis, increases vascular permeability [49–51]	Inhibition [52]
LTC_4 and D_4	Human, mouse [53, 54]	Induces vasodilation, smooth muscle contraction, activates eosinophils, promotes eosinophil and neutrophil chemotaxis, increases vascular permeability [55]	Inhibition [52]
PAF	Mouse [56]	Promotes neutrophil chemotaxis, increases vascular permeability, induces smooth muscle contraction [57–59]	Unknown
Cytokines/chemokines/ growth factors			
TNF	Human, mouse [60, 61]	Induces adhesion molecule expression, activates macrophages, induces vasodilation, increases vascular permeability, promotes dendritic cell maturation [62]	Unknown
IL-1β	Human, mouse [63, 64]	Activates COX-2, induces adhesion molecule expression and NO production, promotes vasodilatation, increases vascular permeability [65]	Unknown
IL-4	Human, mouse [66, 67]	Promotes Th2 response, induces IgE production [68]	Inhibition [69]
IL-5	Human, mouse [70, 71]	Stimulates eosinophil differentiation and function [72]	Inhibition [69]
IL-6	Human, mouse [61, 73]	Induces B cell and cytotoxic T cell differentiation, promotes macrophage activation [74]	Unknown
IL-8	Human, mouse [57, 75]	Recruits monocytes/macrophages, promotes angiogenesis [76]	Unknown
IL-10	Human, mouse [71, 77]	Inhibits macrophage activation, promotes regulatory T cell function [78]	Unknown
IL-13	Human, mouse [71, 79]	Promotes eosinophil recruitment and airway smooth muscle cell contractility [80, 81]	Inhibition [69]
IL-17	Human [82]	Promotes tissue remodeling and production of proinflammatory cytokines [83]	Unknown
IL-33	Mouse [84]	Promotes regulatory T cell function and Th2 response [85]	Unknown

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TABLE 1 (*continued*)

Mediators	Species	Function	n-3 PUFA effect
IFN-γ	Rat [86]	Induces macrophages activation, promotes expression of class II MHC, inhibits cancer proliferation [87]	Unknown
TGF-β	Human, mouse [88]	Promotes regulatory T cell function, inhibits cell cycle, down-regulates T cell activation [89]	Unknown
CCL11 (eotaxin)	Mouse [90]	Recruits eosinophils [91]	Unknown
CCL2	Human, mouse [92, 93]	Recruits monocytes, macrophages, and basophils [94, 95]	Unknown
CCL5	Human [92]	Recruits macrophages and eosinophils [96, 97]	Unknown
CXCL1/ CXCL2	Mouse [98]	Recruits neutrophils [98]	Unknown
SCF	Human [99]	Supports the survival and proliferation of mast cells and melanocytes [100]	
VEGF	Human, mouse [101, 102]	Promotes vasculogenesis and angiogenesis [103]	Unknown
NGF	Human, rat, mouse [104–106]	Supports the survival of neurons [107]	Unknown
PDGF	Human [108]	Promotes fibroblast proliferation and tissue remodeling [109]	Unknown
Free radicals			
ROS	Human, rat, mouse [110]	Induces apoptosis, activates COX-2, promotes expression of inflammatory cytokines and chemokines [111]	Inhibition [112]
Other			
Urocortin	Human [113]	Promotes hypotension and increases coronary blood flow [114]	Unknown

COX, cyclooxygenase; PAF, platelet activating factor; SCF, stem cell factor; VEGF, vascular endothelial growth factor; NGF, nerve growth factor; PDGF, platelet-derived growth factor.

specific type of n-3 PUFAs, the age of the subjects, and the severity of their disease.

N-3 PUFAS AND FCεRI-MEDIATED MAST CELL ACTIVATION

FcεRI is expressed on mast cells as a tetrameric $\alpha\beta\gamma2$, which mediates the mast cells' interactions with IgE [154]. The level of FcεRI expression on the cell surface determines the mast cell's response to IgE/antigen [155], and IgE-mediated allergic reactions cannot be established in FcεRIα- or FcεRIβ-deficient mice [156, 157]. The first event after FcεRI cross-linking is the phosphorylation of ITAMs in the β and γ chains. It is generally accepted that the Src family protein tyrosine kinase Lyn, an acylated protein on the cell membrane, is responsible for FcεRI phosphorylation [158]. After initial phosphorylation of FcεRI, the signal cascade proceeds in the cytoplasm and involves interactions among kinases, adaptors, scaffolds, and small G proteins, which eventually lead to activation of MAPK and NF-κb pathways, increased intracellular calcium, and AA metabolism (Fig. 4).

Some in vitro studies have demonstrated that n-3 PUFAs could have a suppressing effect on FcεRI-mediated mast cell mediator release. EPA treatment inhibited the release of PGD_2 from human primary umbilical cord-derived mast cells stimulated with IgE/anti-IgE [41]. EPA and DHA supplementation decreased the content of LTB_4, LTC_4, and histamine in MC/9 mouse mast cells and suppressed the histamine release induced by IgE/antigen [11]. Furthermore, n-3 PUFAs suppressed the production of IL-4, IL-5, and IL-13 by IgE/antigen-activated mouse primary BMMCs and decreased the translocation of transcription factors GATA-1 and -2 into the nucleus [69]. Although these studies did not examine the incorporation of PUFAs into cells or their membranes, they did demonstrate that the capacity of mast cells to signal via FcεRI is disrupted with n-3 PUFA treatment [11, 41, 46, 69, 112, 159–161] (Tables 1 and 2).

Some studies in a rodent basophil-like cell line, RBL-2H3 rat basophil leukemia cells, have suggested that the effect of PUFAs might depend largely on adsorption and membrane fatty acid composition. RBL-2H3 cells treated with EPA solubilized in ethanol for 48 h showed increased degranulation and Syk phosphorylation on IgE/antigen stimulation [162]. RBL-2H3 cells are not a precise model of mast cells and FcεRI signaling, because they have a different membrane molecule profile from primary mast cells and are considered to be closer to basophils [163, 164]. In addition, FcεRI expression in RBL-2H3 cells has not been consistent in different laboratories using the same culture protocol [163]. It is therefore our hypothesis that a cell's response to PUFA supplementation will largely depend on its baseline PUFA membrane content, its adsorption of PUFAs during culture, and the functional parameters analyzed. In all our PUFA studies on cell function, we have been careful to monitor all of these parameters [145].

N-3 PUFAS AND NON-FCεRI-MEDIATED MAST CELL ACTIVATION

Studies in which mast cells were activated via non-FcεRI pathways have indicated that the inhibitory effects of n-3 PUFAs might not be restricted to FcεRI. However, it is important to note that in some studies, mast cells were activated by agents that are not

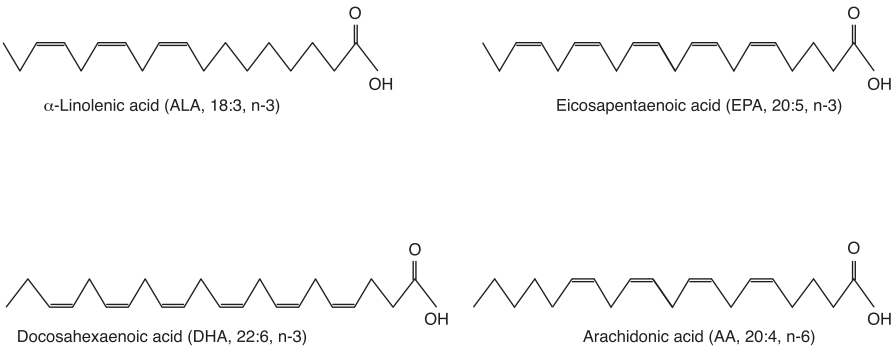

Figure 2. The chemical structure of ALA, EPA, DHA, and AA. ALA, EPA, and DHA are all n-3 PUFA that contain 18, 20, and 22 carbon atoms with 2, 5, and 6 double bonds. AA is an n-6 PUFA containing 20 carbon atoms with 4 double bonds.

physiologic stimuli, such as calcium ionophore. DHA and ALA treatment reduced PGE_2 production and inhibited histamine release by C2 canine mastocytoma cells activated by a G protein activator, the wasp venom peptide mastoparan [46, 160], although some have shown that in these same cells, EPA increased production of PGE_2 and histamine after stimulation with mastoparan [165]. ALA treatment decreased histamine release in RBL-2H3 cells activated by calcium ionophore A23187 [159]. n-3 PUFAs decreased the synthesis of PGD_2 by rat primary peritoneal mast cells activated by calcium ionophore [161]. EPA and DHA treatment decreased the production of ROS, IL-4, and IL-13 by suppressing MAPK activation in a human mast cell line, HMC-1, stimulated with ionomycin/phorbol 12-myristate 13-acetate, which initiates the activation of PKC [112]. These studies suggest that n-3 PUFAs fundamentally change the capacity of mast cells to signal through both calcium-dependent and calcium-independent pathways and open the possibility that PUPA might also incorporate into, and alter, intracellular membrane dynamics.

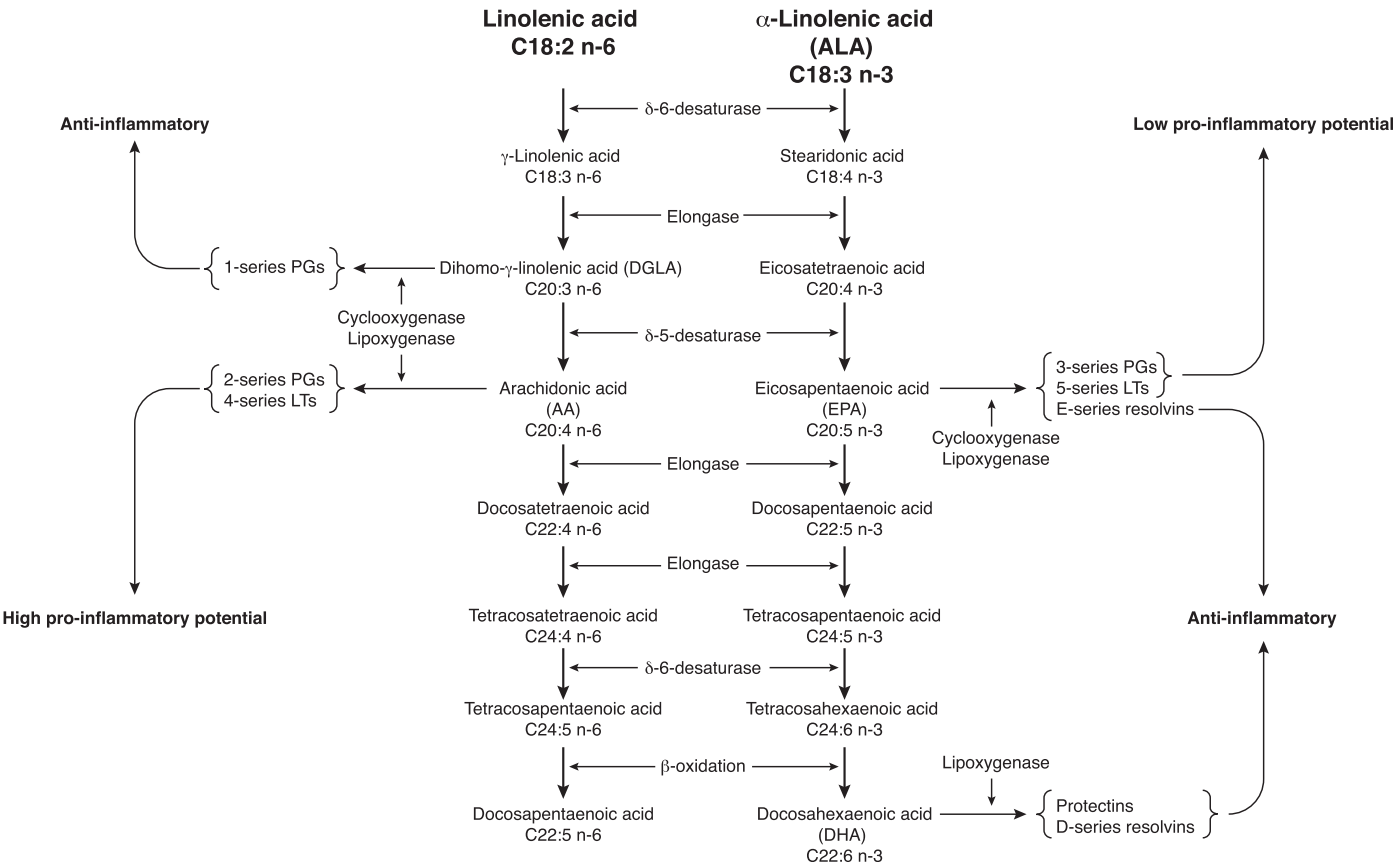

Figure 3. Biosynthesis and eicosanoid production of n-3 and n-6 PUFAs. n-3 and n-6 PUFAs can be synthesized from ALA and linoleic acid, respectively, under the action of the same collection of enzymes. DGLA, AA, and EPA are all precursors of eicosanoids. Two-series PGs and 4-series LTs from AA have high proinflammatory potential. Three-series PGs and 5-series LTs from EPA have low proinflammatory potential. One-series PGs from DGLA, E-series resolvins from EPA, and protectins and D-series resolvins from DHA are anti-inflammatory.

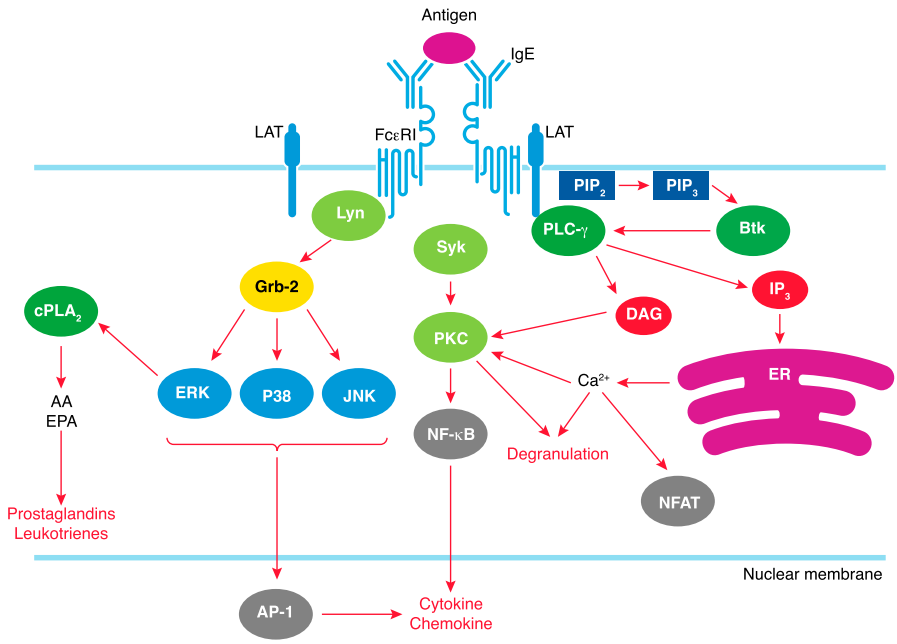

Figure 4. Diagram of FcεRI signaling. The binding of antigen to FcεRI-bound IgE causes receptor crosslinking, which leads to phosphorylation of ITAMs in β- and γ-chains by Lyn. Phosphorylated ITAMs function as docking and activating sites for Syk. Phosphorylated Syk then activates PKC, which is responsible for degranulation and activation of NF-κB. Syk also phosphorylates linker for activation of T cells (LAT), which facilitates the activation of phospholipase C (PLC)-γ to generate DAG and inositol triphosphate (IP_3) from phosphatidylinositol 4,5-bisphosphate (PIP_2). PI_3 kinase transforms PIP_2 to phosphatidylinositol (3,4,5)-triphosphate (PIP_3), which activates Btk. Btk also leads to PLC-γ activation. DAG activates PKC. IP_3 causes calcium release from endoplasmic reticulum (ER). LAT also activates another adaptor protein, growth factor receptor-bound protein 2 (Grb-2), which leads to activation of MAPKs, ERK, JNK, and p38. ERK activates cytosolic phospholipase A_2 ($cPLA_2$), which frees AA and EPA from plasma and the nuclear membrane. Eicosanoids can be generated from AA and EPA. AP-1, activator protein 1; NFAT, nuclear factor of activated T cells.

POTENTIAL MECHANISMS OF N-3 PUFA MODULATION OF MAST CELL MEDIATOR RELEASE

Lipid raft disruption

Lipid rafts are specific membrane microdomains that contain high levels of cholesterol, sphingolipid, transmembrane proteins, and GPI-anchored proteins on the outer leaflet and acylated proteins on the inner leaflet (Fig. 5) [166]. Lipid rafts can be found in plasma membranes and intracellular membranes, such as the Golgi complex, in all cell types [167]. Lipid rafts function as a platform for receptor signaling with concentrated molecules needed for signal transduction. In addition, inhibitory enzymes, such as phosphatases, which reside in nonraft regions, are blocked from influencing signaling [168]. Furthermore, lipid analysis has shown that lipid rafts are rich in sphingolipid and cholesterol, and the phospholipids in lipid rafts contain higher levels of long chain saturated fatty acids compared with nonraft regions [169]. Thus, lipid rafts are in a more ordered state than nonraft regions, and the fluidity is lower, which grants lipid rafts the features of high melting temperature and insolubility in nonionic detergents [166].

Lipid rafts have been shown to exist in mast cells in numerous studies [170]. Some of the lipid raft components appear to be important in maintaining mast cell morphology and mast cell development. After depletion of ganglioside (a raft component), RBL-2H3 cells change from a spindle to a round shape and are smaller [171]. As membrane domains, compelling evidence has shown that lipid rafts are involved in FcεRI endocytosis and FcεRI-mediated signal transduction in mast cells.

TABLE 2. Effect of n-3 PUFAs on mast cell function

Mast cell function	n-3 PUFA effect	Type of n-3 PUFA	Type of mast cell	References
Degranulation	Inhibition	ALA, EPA, DHA	RBL-2H3 MC/9 C2	[11, 159, 160]
Lipid-derived mediator release	Inhibition	ALA, EPA, DPA, DHA	C2 Human primary umbilical cord-derived mast cells Rat primary peritoneal mast cells	[41, 46, 160, 161]
Cytokine/ chemokine production	Inhibition	ALA, EPA, DHA	MC/9 Mouse BMMC HMC-1	[69, 112]
Adhesion	Unknown			
Migration	Unknown			
Phagocytosis	Unknown			
Viability	Unknown			

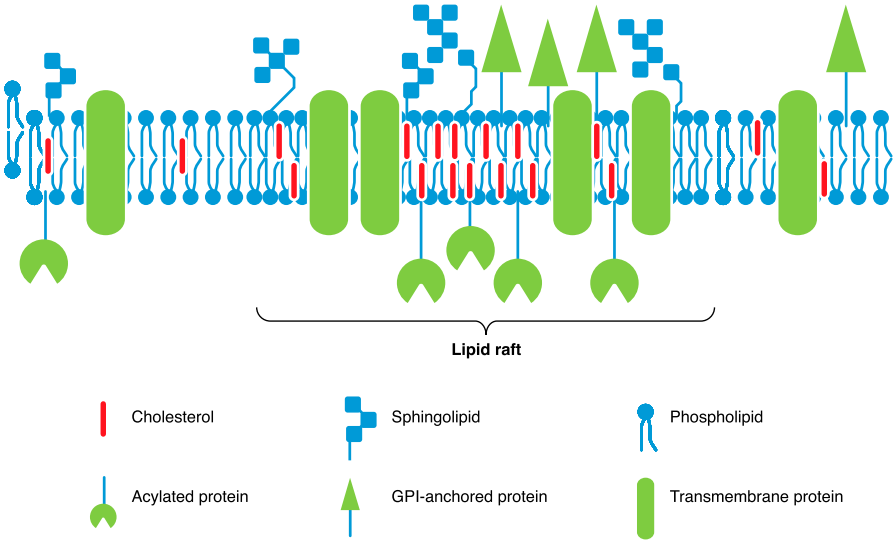

Figure 5. Structure of lipid rafts in cell membranes. Lipid rafts contain high levels of cholesterol, sphingolipid, transmembrane proteins, GPI-anchored proteins, and acylated proteins. Rafts are considered to be packed more tightly than nonraft regions and are in a liquid-ordered state.

Receptors on cell membranes are constantly internalized and replaced by newly formed receptors [172]. It was reported that the ubiquitin ligases Cbl and Nedd4 are recruited into lipid rafts after mast cell activation mediated by FcεRI [173]. Cbl and Nedd4 might function to mediate FcεRI ubiquitination, which provides a sorting signal. Ubiquitin-tagged FcεRI is internalized through clathrin-coated vesicles and transported in the endosomes to the lysosomes for degradation [174]. In stimulated mast cells, GD1b (a ganglioside) in lipid rafts was shown to be internalized together with FcεRI in the same vesicle and to follow the same path to the lysosomes [175]. In addition, GD1b deficiency suppressed FcεRI ubiquitination and endocytosis in mast cells [176]. These results indicate that lipid rafts might not only facilitate the tagging of FcεRI for internalization, but also function as the site of vesicle formation.

Lipid rafts are especially vital for FcεRI-mediated signal transduction, because FcεRI activation requires sequential and extensive protein-protein interactions [177]. Some research has shown that in IgE/antigen-stimulated cells, FcεRI is quickly recruited to lipid rafts, initiating signaling [178]. Many lipid raft components have been shown to regulate FcεRI signaling. Lyn is concentrated in lipid rafts and is more active in raft regions than in nonraft regions, possibly because lipid rafts can protect Lyn from dephosphorylation by phosphatase [179]. Some raft components regulate Lyn activity, such as flotillin-1. Flotillin-1 knockdown RBL-2H3 cells showed impaired Lyn activity with reduced FcεRI phosphorylation, calcium mobilization, and ERK activation after cell activation through FcεRI [180]. In addition to protein components, lipid components in lipid rafts have also been shown to modulate FcεRI signaling. Cholesterol is required for phosphorylation of FcεRI. Treatment with the cholesterol-depleting agent methyl-β-cyclodextrin significantly reduced tyrosine phosphorylation of FcεRI induced by IgE/antigen and suppressed mediator release from mast cells, possibly by disrupting the interaction between FcεRI and Lyn [181]. α-Galactosyl derivatives of ganglioside GD1b were found to down-regulate mast cell activation by promoting phosphatidylinositol hydrolysis and PKC redistribution [182]. These results indicate that lipid rafts have a profound influence on FcεRI signaling and mast cell activation.

As a membrane component, n-3 PUFAs are believed to regulate membrane structure and properties and, therefore, cell function [183]. Fatty acids are the building blocks for some biomolecules, such as lipids, forming the basic structure of membrane phospholipid bilayers and facilitating the acylation of proteins [184]. Thus, fatty acids are important for membrane/lipid raft structure and function. EPA and DHA supplementation decrease AA and increase EPA/DHA levels in membranes, whole cells, and tissues, resulting in alteration in membrane structure and fluidity, protein distribution in membrane, and signal transduction [183, 185]. In recent years, some studies have shown that n-3 PUFAs can reduce the T cell response by altering lipid raft composition. In a study of human T cells, DHA supplementation was shown to increase ALA, DPA (n-3), and DHA levels in lipid rafts, resulting in a decreased n-6:n-3 ratio in the lipid raft fraction [186]. Subsequently, surface IL-2Rα expression was decreased by DHA supplementation and IL-2Rα, IL-2Rβ, and IL-2Rγ were relocated to nonraft regions [186]. Furthermore, STAT5a and STAT5b recruitment to lipid rafts was inhibited [186]. In C2 mast cells, EPA and DHA supplementation have been shown to increase EPA and DHA levels in raft and nonraft regions [187]. Thus, n-3 PUFAs might influence lipid raft function and the response to stimuli in mast cells by modifying their fatty acid profile, just as in T cells.

AA-derived eicosanoid production inhibition

The second group of mast cell mediators produced after IgE/antigen stimulation are eicosanoids (Fig. 3), which are derived from 20 carbon chain n-3 (EPA) and n-6 PUFAs (AA and DGLA [C20:3, n-6]) [188]. Eicosanoids, including PGs, LTs, thromboxanes, and lipoxins, are signaling molecules that modulate a broad range of body functions, including body temperature, immune function, wound healing, pain, and smooth muscle relaxation/contraction [189, 190].

EPA is the precursor of 3-series PGs and 5-series LTs. AA is the precursor of 2-series PGs and 4-series LTs (including CysLTs).

DGLA is the precursor of 1-series PGs (Fig. 3). However, PGs and LTs from EPA have lower proinflammatory potential than those from AA [191]. CysLTs have a strong effect on smooth muscle contraction and increased vascular permeability compared with 5-series LTs [191]. CysLTs can also induce eosinophil migration [192] and activate eosinophils and mast cells to secrete cytokines [193]. One-series PGs are anti-inflammatory; however, the level of DGLA in the body is low compared with that of EPA and AA [194]. In HepG2 human hepatic cells, the level of AA is 7-fold higher than the combination of EPA and DHA, and DGLA is not detectable [195]. In mouse liver tissue, the percentage of AA to total fatty acid is comparable to that with the combination of EPA and DHA and 10-fold higher than DGLA [196]. Competition exists between n-3 PUFAs and n-6 PUFAs as substrates for oxidation by COX and lipoxygenase, the critical enzymes for eicosanoid generation [197], reducing the synthesis of highly proinflammatory eicosanoids from AA (Fig. 3). In addition, newly discovered derivatives from EPA and DHA, protectins and resolvins, were reported to be anti-inflammatory [198] (Fig. 3). Therefore, more n-3 PUFA incorporation would be associated with a decreased production of AA-derived eicosanoids, which are vital proinflammatory mediators produced by mast cells.

Gene expression modification

n-3 PUFAs are the ligands for PPAR [136], which function, together with retinoic X receptors, as nuclear receptors and regulate gene expression in inflammation, lipid metabolism, cell proliferation, and differentiation [199]. PPAR-β and -γ are expressed in human and murine mast cells and have been suggested to be involved in the inhibition of mast cell maturation and the suppression of IgE/antigen-induced production of proinflammatory cytokines [200, 201]. Because NF-κB activation induces the transcription of proinflammatory cytokines and PPAR-γ can interact with NF-κB and limit its translocation to the nucleus [202], PUFA activation of PPAR-γ would inhibit NF-κB and thereby inhibit proinflammatory mediator production in mast cells [203]. In any case, mast cells express PPAR-γ, and it is possible that PUFA activate PPAR-γ to change the mast cell phenotype, including changes in the expression of the antigen response machinery (e.g., FcεRI, Fyn, Lyn, Syk), and degranulation machinery (e.g., calcium channels, vesicle docking molecules), which would render mast cells less susceptible to antigen activation.

Recently, free n-3 PUFAs were reported to bind GPR40 and GPR120 and down-regulate inflammation [204, 205]. Mast cells express a number of GPR, which have a variety of effects on mast cell function, including alterations in gene transcription and FcεRI-mediated activation [206]. However, it is not clear whether mast cells express GPR40 and GPR120, and additional studies are needed to determine whether these receptors play a role in the PUFA effects on mast cell function.

CONCLUDING REMARKS

Considerable evidence has shown that n-3 PUFAs can modify mast cell functions and that this can occur in both an FcεRI-dependent and FcεRI-independent manner. n-3 PUFAs can suppress FcεRI signaling and mast cell activation by altering lipid raft properties, inhibiting AA-derived eicosanoid synthesis by enzyme competition, and reducing cytokine/chemokine production through receptors (Fig. 6). The multiple effects of

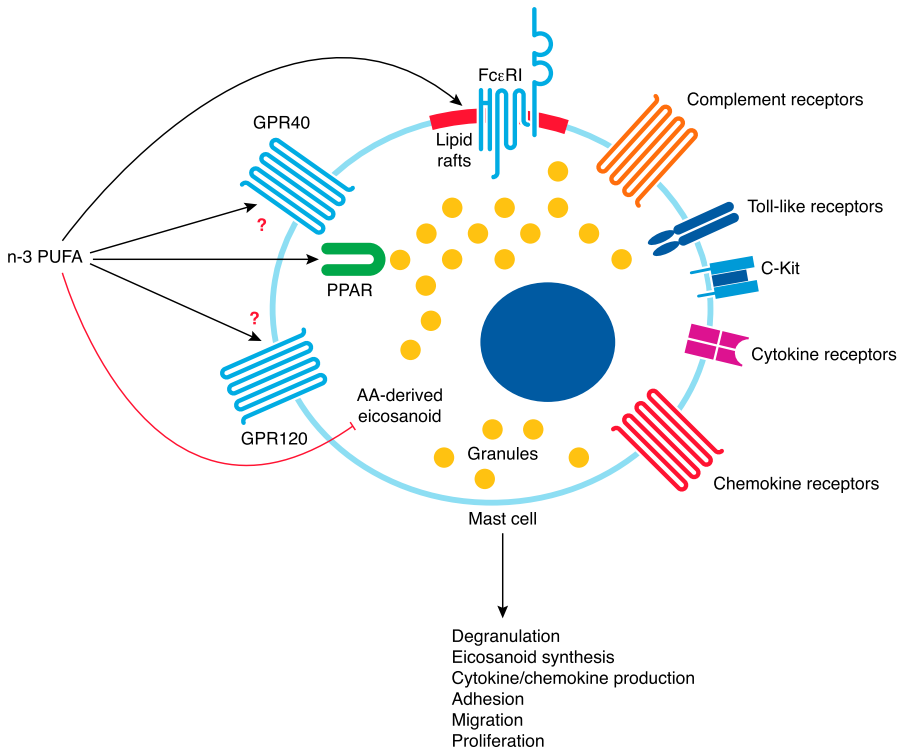

Figure 6. Potential mechanisms of n-3 PUFA modulation of mast cell function. n-3 PUFAs can modulate FcεRI-mediated mast cell mediator release by altering lipid raft function, inhibit the production of AA-derived eicosanoids by competitive inhibition, and suppress the production of cytokines/chemokines by binding to PPAR. GPR40 and GPR120 are also possible receptors that n-3 PUFAs can bind to to modulate mast cell function.

n-3 PUFAs on mast cell biology suggest that they likely interact with multiple processes. Regardless, in vivo studies examining the effects of n-3 PUFAs on mast cell-mediated diseases are necessary to determine whether n-3 PUFA supplementation would be a viable approach to treat mast cell-regulated pathologic entities.

AUTHORSHIP

X.W. wrote the manuscript. M.K. provided critical feedback and edited the manuscript.

DISCLOSURES

The authors report no conflict of interest.

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