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Anti-inflammatory and Immunomodulatory Effects of Marine n-3 Polyunsaturated Fatty Acids on Human Health and Diseases

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Abstract The pharmaceutical effects of n-3 polyunsaturated fatty acids (n-3 PUFAs) as dietary nutrients on human health and diseases have gained much attention and are investigated for decades. Docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA) are the three major n-3 PUFAs enriched in marine organisms, such as fish, shrimp, algae, and so on. It has been well known that n-3 PUFAs, especially DHA and EPA, are beneficial in reducing the risk of cardiovascular and cerebrovascular diseases. Accumulating evidence suggests that n-3 PUFAs might cure inflammatory diseases through several mechanisms, such as plasma membrane remodeling of lymphocytes, down-regulating pro-inflammatory cytokines, and alternating adhesion molecule expressions. Several molecular targets of n-3 PUFAs on immune-regulation have also been identified, such as GPR120 (FFA4), protein kinase C (PKC), and PPAR-γ. However, it remains inconclusive if dietary n-3 PUFAs function the same both *in vitro* and *in vivo* based on cohort studies. This review will focus on the molecular targets and mechanisms of anti-inflammatory and immunomodulatory effects of n-3 PUFAs on human health and diseases, such as obesity, tumor, diabetes, and autoimmune diseases.

Key words n-3 polyunsaturated fatty acids; immune-regulation; anti-inflammation; mechanism

1 Introduction

In 1978, Dyerberg and Bang first reported that the incidence and mortality of cardiovascular and cerebrovascular diseases in Eskimos are significantly lower than that of people living in other parts of the world based on the epidemiological study. The reasonable explanation is the high content of n-3 PUFAs (DHA and EPA) in arctic fish consumed in their diets (Dyerberg *et al*., 1978; Dyerberg and Bang, 1978). Since then, scholars have paid much attention to n-3 PUFAs for their potential therapeutic role in treating various human diseases, such as cardiovascular diseases, thrombosis, atherosclerosis, stroke, and diabetes (Dawczynski *et al*., 2013; Jacobo-Cejudo *et al*., 2017; Nosaka *et al*., 2017; Phang *et al*., 2011).

Marine fish, shellfish and microalgae are enriched in n-3 PUFAs. For example, the contents of EPA plus DHA are 717–1533 mg (100 g)$^{-1}$ in salmon, 236 mg (100 g)$^{-1}$ in Alaskan pollock, 44 mg (100 g)$^{-1}$ in channel catfish, and 253 mg (100 g)$^{-1}$ in Atlantic cod (Cladis *et al*., 2014). It is estimated that demand for n-3 PUFAs world widely would be 241 thousand metric tons with a value of US $4.96 billion. However, debates over the actual effects of n-3 PUFAs on improving human health have never stopped and contradictory findings are reported periodically (Djousse *et al*., 2010; Poreba *et al*., 2017; Wu *et al*., 2012; Zhang *et al*., 2013). It seems that the source and dosage of n-3 PUFAs, trial duration, sex, and age could influence the effects and conclusions (Abbott, 2016; Chen *et al*., 2017). In addition, the ratio of different PUFAs (n-3: n-6) and fat-soluble small molecules, such as vitamins and other unknown molecules, may contribute to the discrepancies.

Many reviews and meta-analysis about n-3 PUFAs have been reported. However, most of them are related to the effects of n-3 PUFAs on human health and diseases such as cardiovascular diseases, non-alcoholic fatty liver, and atherothrombosis (Alexander *et al*., 2017; Auger *et al*., 2016; Chen *et al*., 2016; Chiesa *et al*., 2016; de Castro and Calder, 2017; Fialkow, 2016a; Kelley, 2016; Rizos and Elisaf, 2017; Siscovick *et al*., 2017). The benefits of dietary n-3 PUFAs in neuron development are also discussed (Luchtman and Song, 2013; Marszalek and Lodish, 2005; Wurtman, 2008). This review article will be focused on the effects of n-3 PUFAs on inflammation and immune regulation including their potential targets and molecular mechanisms in the following human diseases:

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obesity, cancer, type I diabetes mellitus, and autoimmune diseases. The intrinsic immune association of these human diseases is a promising starting point to understand the effects of n-3 PUFAs on regulating inflammation and immunity and to evaluate both *in vitro* and *in vivo* findings about n-3 PUFAs.

1.1 N-3 Polyunsaturated Fatty Acids (n-3 PUFAs)

Fatty acids are the fundamental components of the cell membrane and the starting materials for the biosynthesis of a variety of important biological molecules. However, the term 'essential fatty acids' are applied only to those polyunsaturated fatty acids (PUFAs) that are necessary for maintaining human health and cannot be synthesized by the cells in the human body (Spector, 1999).

PUFAs can be divided into two classes: n-3 and n-6. The nomenclature is based on the location of the farthest ethylenic linkage from the carboxyl group. Strictly speaking, except for alpha-linolenic acid (ALA), other n-3 PUFAs are not 'essential fatty acids', because they can be transformed and synthesized from ALA in the human body (Fig.1) (Arnoldussen and Kiliaan, 2014; Edwards and O'Flaherty, 2008). Nevertheless, since the rate of conversion of ALA to other n-3 PUFAs, like EPA and DHA, is far from meeting daily needs, dietary intake of PUFAs are necessary (Williams and Burdge, 2006).

So far, there is no uniform dosage for the daily intake of dietary n-3 PUFAs. Based on current studies, different research institutions have given their own recommendations based on age, gender and health status (Tables 1–2).

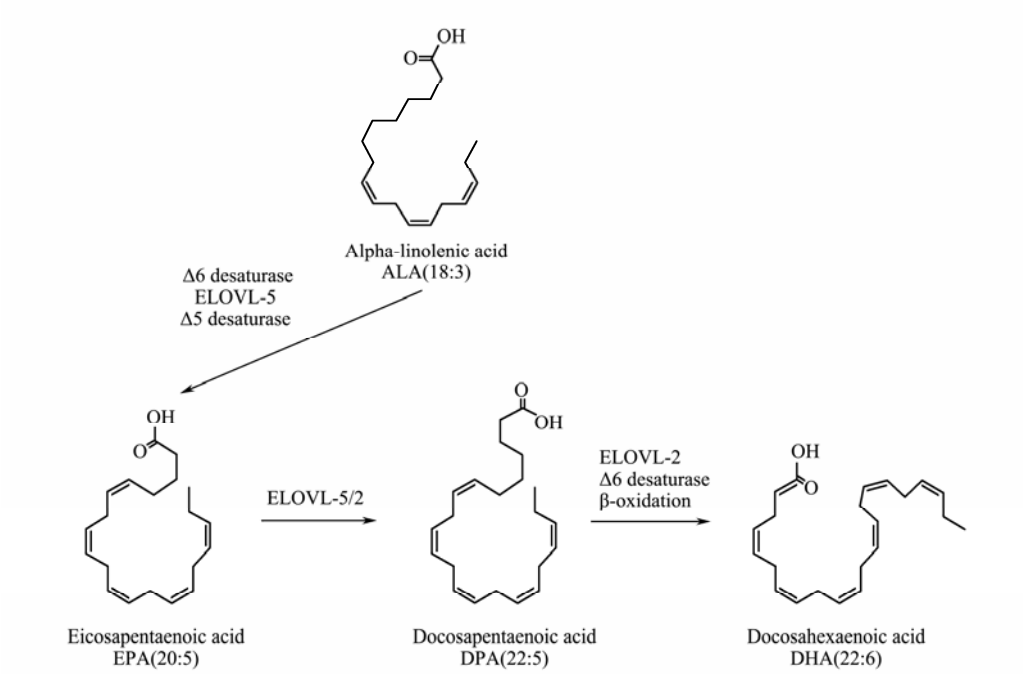

Fig.1 The biosynthetic pathway of n-3 PUFAs from ALA.

Table 1 Daily recommended dietary intake of n-3 PUFA in adults

Organization	n-3 PUFA (EPA and DHA) daily recommendation	Subjects
Department of Health (DOH, UK)	200 mg	Healthy individuals
International society for the study of fatty acids and lipids (ISSFAL)	500 mg	Healthy individuals
Dietary Guidelines Advisory Committee	496 mg	Healthy individuals
World Health Organization (WHO)	200 – 500 mg	Healthy individuals
Chinese Nutrition Society (CNS)	Fish dish (280 – 525 g week^{-1})	Healthy individuals
National Institutes of Health (NIH)	300 mg	pregnant and lactating women
British Nutrition Foundation (BNF)	500 – 1000 mg	Cardiovascular patients
American Heart Association (AHA)	1000 mg	Cardiovascular patients
	Fish dish (twice/week)	Healthy individuals
European Society of Cardiology (ESC)	1000 mg	Cardiovascular patients
Belgian Superior Health Council	1000 mg	Cardiovascular patients
Food and Agriculture Organization of the United Nations (FAO)	250 mg	Healthy individuals
	2000 mg	Cardiovascular patients
	500 mg	Healthy individuals
The Heart Foundation	1000 mg	Cardiovascular patients
	1200 mg	Hyperlipemia patients

Notes: Dietary guidelines for Americans: Washington 2005, position statement on fish, fish oils, n-3 polyunsaturated fatty acids and cardiovascular health, AIFST conference 2008, fats and fatty acids in human nutrition 2010; Kris-Etherton *et al*., 2002a; Van de Werf *et al*., 2003.

Table 2 Daily recommended dietary intake of n-3 PUFA in childhoods

Organization	Recommendation (mg d^{-1})		Age
	Male	Female	
Institute of Medicine (IOM, USA)	900	900	4 – 8
	1200	1000	9 – 13
	1600	1100	14 – 18
Dietary Guidelines Advisory Committee (USA)	900	900	4 – 8
	1200	1000	9 – 13
	1600	1100	14 – 18
Ministry of Health, Labor and Welfare (MHLW, Japan)	1300	1100	3 – 5
	1400	1300	6 – 7
	1700	1400	8 – 9
	1700	1500	10 – 11
	2100	1800	12 – 14
	2300	1700	15 – 17

Notes: 'Population nutrient intake goals for preventing diet-related chronic diseases', 2014, http://www.who.int/nutrition/topics/5_population_nutrient/en/index25.html. 'Overview of dietary reference intakes for Japanese', 2015, http://www.mhlw.go.jp/bunya/kenkou/sessyu-kijun.html. Trumbo *et al*., 2002.

1.2 Inflammation and Immune Regulation

Inflammation is a complex biological response of the host to infections and injuries from pathogens, damaged cells, or irritants (Ferrero-Miliani *et al*., 2007). Immunocyte recruitment and inflammatory cytokines secretion at lesions are always involved in the response. The function of inflammation is to eliminate the cause of cell damage and to initiate tissue repair. Cellular signaling pathways play pivotal roles in inflammation. Three classical signal transduction pathways, JAK-STAT, MAPK, and Nf-κB, are associated with inflammation. They can regulate the inflammation individually or form a regulatory network (Fig.2) (Arbabi and Maier, 2002; Davis, 2000; Dell'Albani *et al*., 2001; Jiang *et al*., 1997; Seger and Krebs, 1995).

Immune regulation is the interaction between immune cells and immune molecules within the immune system, as well as with other systems, to make the immune response at a proper level (Boothby and Rickert, 2017; Jin *et al*., 2017; Thaiss *et al*., 2016; Verbist *et al*., 2012). To

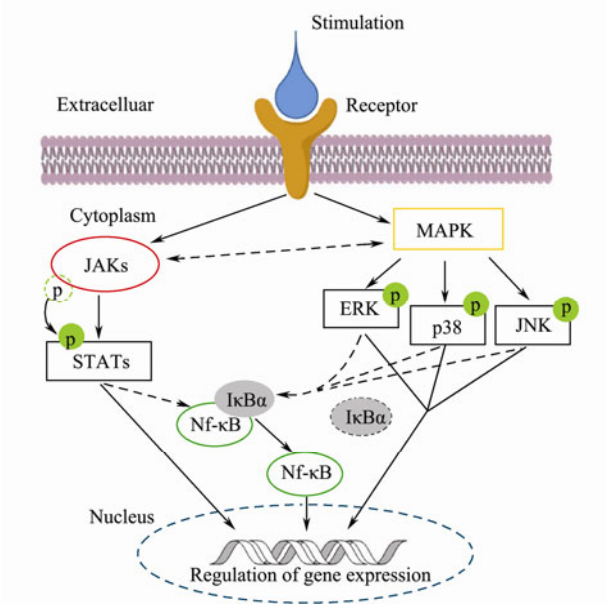

Fig.2 The cross-talk of JAK, MAPK and Nf-κB signaling pathways.

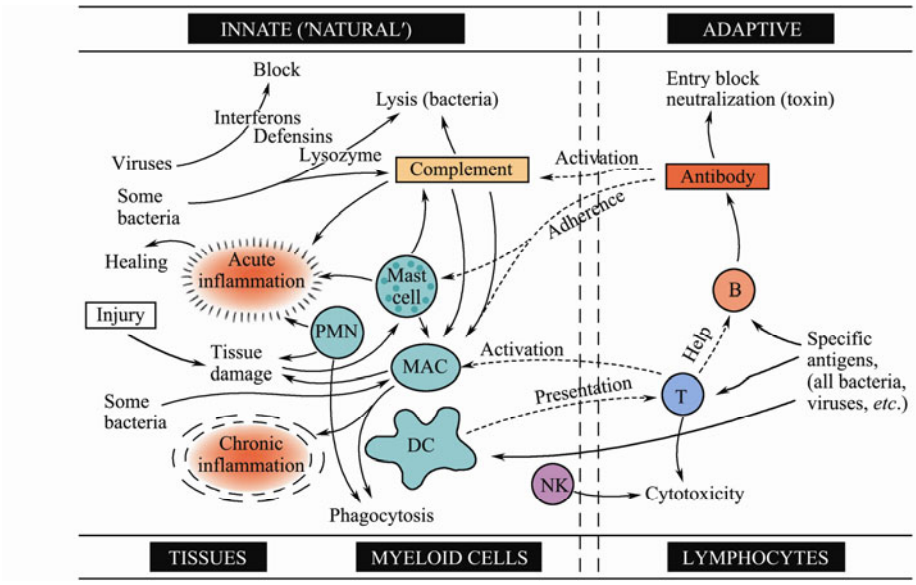

Fig.3 Relationship between inflammation and immune regulation (cited from Immunology at a glance. 10th ed, 2013, with permission from Wiley-Blackwell).

function properly, immune system should have the ability to detect various pathogens from viruses to bacteria, or some other microorganisms like dust mite, and to distinguish them from the body's own tissues. Disorders of the immune system are catastrophic, which would result in autoimmune diseases, inflammatory diseases and cancers (O'Byrne and Dalgleish, 2001). The human immune system can be classified into innate immune system and adaptive immune system. Though, inflammation and immune regulation are different concepts, there is a close relationship between them in the process of host resisting pathogens (Fig.3) (Playfair and Chain, 2013).

2 Function of n-3 PUFAs in Regulating Obesity- and Cancer-Induced Inflammation

Mounting evidence shows that there is a strong association between obesity and cancer (Bandini *et al*., 2017; Carreras-Torres *et al*., 2017; Dobbins *et al*., 2013; Hidayat *et al*., 2016; Sun *et al*., 2015; Zhang *et al*., 2014). Actually, obesity is not only a risk factor for cancer, both obese and cancer patients have some similar physiologic index because they all suffer a long-term disease-associated inflammation (Divella *et al*., 2016). For example, an elevated levels of pro-inflammatory factors, such as C-reactive protein, TNF-α, and IL-6, can be observed in their blood circulation.

Recently, the benefits of n-3 PUFAs to the obese and cancer patients have gained much attention. Studies show that n-3 PUFAs can suppress adipogenesis, and dietary n-3 PUFAs supplementation is helpful to lose weight for the obese, but show little effect in healthy human subjects (Hooper, 2007; Li *et al*., 2008). N-3 PUFAs can influence glucose and lipid metabolism through lowering triacylglycerol concentration, boosting high density lipoprotein (HDL) cholesterol levels in plasma, and improving insulin sensitivity (Delarue *et al*., 2004; Kris-Etherton *et al*., 2002b). Furthermore, experiments on animal model indicate that the weight loss is not on account of less caloric intake, but the regulation of lipid metabolism-related gene expression, more energy expenditure and modulation of adipocyte differentiation (Buettner *et al*., 2006; Huang *et al*., 2016; Ralston *et al*., 2015).

For cancer patients, n-3 PUFAs have showed anti-tumor effect both *in vitro* and *in vivo* (Xue *et al*., 2014; Zou *et al*., 2013). Besides that, n-3 PUFAs can reduce the side effects of chemotherapy and radiotherapy during cancer treatment and also have chemoprevention effects. (Calviello *et al*., 2009; Fasano *et al*., 2010). The mechanisms underlying the anti-tumor effects of n-3 PUFAs are multiple including cell cycle arrest and apoptosis induction (So *et al*., 2015).

Except for the above mentioned function of n-3 PUFAs on obesity and cancer, they also exhibit the ability of alleviating obesity- and cancer-induced inflammation. In patients, cyclooxygenase and 5-lipoxygenase convert membrane-derived arachidonic acid (AA, an n-6 PUFA) into pro-inflammatory eicosanoids, which is an important reason for long-lasting inflammation (Flachs *et al*., 2009). Different from n-6 PUFAs, the metabolites of n-3 PUFAs are beneficial in anti-inflammation (James *et al*., 2000a). Additional consumption of n-3 PUFAs can significantly suppress AA conversion to pro-inflammatory eicosanoids (Lee *et al*., 1985; Lokesh and Kinsella, 1987). Inflammatory cytokine production will be inhibited too. For example, after intervention of n-3 PUFAs, the levels of TNF-α and IL-6 at nidus are decreased (Muurling *et al*., 2003; Perez-Echarri *et al*., 2008). In addition, when n-3 PUFAs combine with cancer chemopreventive agents, such as curcumin, the synergistic effects are observed by reducing inflammatory ROS level through downregulating of iNOS, COX-2, and cLPA2 (Saw *et al*., 2010).

3 Benefits of n-3 PUFAs on Auto-Immune Disease and Type I Diabetes

Auto-immune disease is caused by over response to the self-antigen of the body's immune system. In recent years, many diseases have been classified as autoimmune diseases, such as systematic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS), autoimmune hemolytic anemia (AIHA) and others (Emmungil *et al*., 2014; Giacomelli *et al*., 2017; Kamesaki, 2017).

Type I diabetes is characterized as absolutely insufficient in insulin production, and it usually occurs in children and adolescent. The assumption that type I diabetes is an auto-immune disease was firstly proposed in 1965 (Eisenbarth *et al*., 1988). To date, some evidence supports the hypothesis: 1) when treating leukemia patients through bone marrow transplantation from type I diabetes donor, the acceptor develops diabetes mellitus; 2) insulitis is mainly caused by lymphocyte, macrophage or monocyte infiltration; 3) immunosuppressive agents can slow the pathogenesis of pancreatic islet beta cell injury in newly diagnosed type I diabetes patients (Bottazzo *et al*., 1985; Domenick and Ildstad, 2001; Hyslop *et al*., 2016; Orban *et al*., 2011).

Mounting work suggests that long-term consumption of n-3 PUFAs can provide symptom relief of auto-immune diseases and type I diabetes. In autoimmune-mediated glomerulonephritis, intake of n-3 PUFAs can decrease proteinuria and improve glomerular filtration rate (GFR) (Holman *et al*., 1994; Pestka, 2010). The study of DAISY (Diabetes Autoimmunity Study in the Young) found that dietary supplementation of n-3 PUFAs from 1 year old could reduce the risk of islet autoimmunity in children with type I diabetes (Norris *et al*., 2007). Another case-control study in Norway showed that by supplying cod liver oil for 1 year old, significantly reduced incidence of childhood-onset type 1 diabetes is observed (Stene and Joner, 2003). Besides that, n-3 PUFAs can improve glucose metabolism through enhanced insulin secretion and more resistance to cytokine-induced β cell death (Wei *et al*., 2010), as well as reshaped Th1 and Th2 balance through modulation of T cell differentiation. Studies showed that the oxidation of n-3 PUFAs is

partially responsible for the adverse effect observed in human and animal models (Albert *et al*., 2016; Grimm *et al*., 2016; Mason and Sherratt, 2017). And antioxidants, such as vitamin E, have been used along with n-3 PUFAs to overcome the oxidation-related side effects (Meydani, 1996).

4 Potential Targets and Mechanism of n-3 PUFAs in Anti-Inflammation and Immune Regulation

Potential targets and molecular mechanisms of n-3 PUFAs in anti-inflammation and immune regulation are described in the following sections.

4.1 Influencing the Metabolism of Arachidonic Acid

PUFAs are important components of the phospholipids in cell membranes. The most common PUFA in phospholipid membrane of immunocytes is arachidonic acid (AA, n-6 PUFA) (Calder, 2013). When inflammation occurs, AA will be converted into eicosanoids, including prostaglandins (PGs) and leukotrienes (LTs), through the respective cyclooxygenase (COX), isomerase and 5-lipooxygenase pathway. The eicosanoid PGE2 is a COX metabolite of AA, which can be pro-inflammatory and modulates cytokine production. The 4-series LTs, lipoxygenase metabolites of AA, with chemotactic ability to promote leucocytes move towards a site of inflammation and upregulate pro-inflammatory cytokine production (Sperling *et al*., 1993a). The n-3 PUFAs (DHA and EPA) can competitively inhibit oxygenation of AA due to EPA is also a substrate for both COX-2 and 5-lipoxygenase. However, the metabolites of EPA have a very different structure from those made from AA (James *et al*., 2000b). Recent studies have discovered a novel series of lipid mediators from n-3 PUFAs: resolvins and protectins (Bannenberg *et al*., 2005; Serhan *et al*., 2004). The biological function of resolvins and protectins have been examined in a number of models and have shown anti-inflammatory effects. For example, resolvin E1 and protectin D1 both inhibit transendothelial migration of neutrophils, therefore interrupting the infiltration of neutrophils into sites of inflammation (Schwab *et al*., 2007; Serhan *et al*., 2008).

4.2 Remodeling of Lipid Membrane

As indicated above, AA is a key structural and functional component of lipid membrane in cells, especially in immunocytes, such as macrophages, neutrophils, and lymphocytes (Calder, 2013). It is reported that fatty acid composition of inflammatory cells and immunocytes is sensitive to dietary fatty acids (Pollock *et al*., 2016; Yaqoob *et al*., 2000a). Further studies show that more consumption of n-3 PUFAs will change fatty acid profiles of lipid membrane in cells (Chapkin *et al*., 1991; Sperling *et al*., 1993b). AA will be displaced by n-3 PUFA at plasma membranes and lead to a suppressed generation of inflammatory precursors (Wang and Huang, 2015; Yaqoob *et al*., 2000b).

On the other hand, n-3 PUFAs can alter lipid rafts, which are nanoscale regions of the plasma membrane, enriched in cholesterol, sphingomyelin, and phospholipids (Turk and Chapkin, 2013). Studies show that n-3 PUFAs are inserted into both raft and non-raft regions of the plasma membrane, and result in enhanced clusters of lipid raft region (Fig.4). Then, the cell signaling transduction will be influenced, for example, DHA can suppress ERK1/2 and STAT3 in regulating inflammation both *in vitro* and *in vivo* (Turk *et al*., 2012). And the lipid raft dependent phosphorylation of PLCγ-1 in T cell can be regulated by n-3 PUFAs as well (Fan *et al*., 2004).

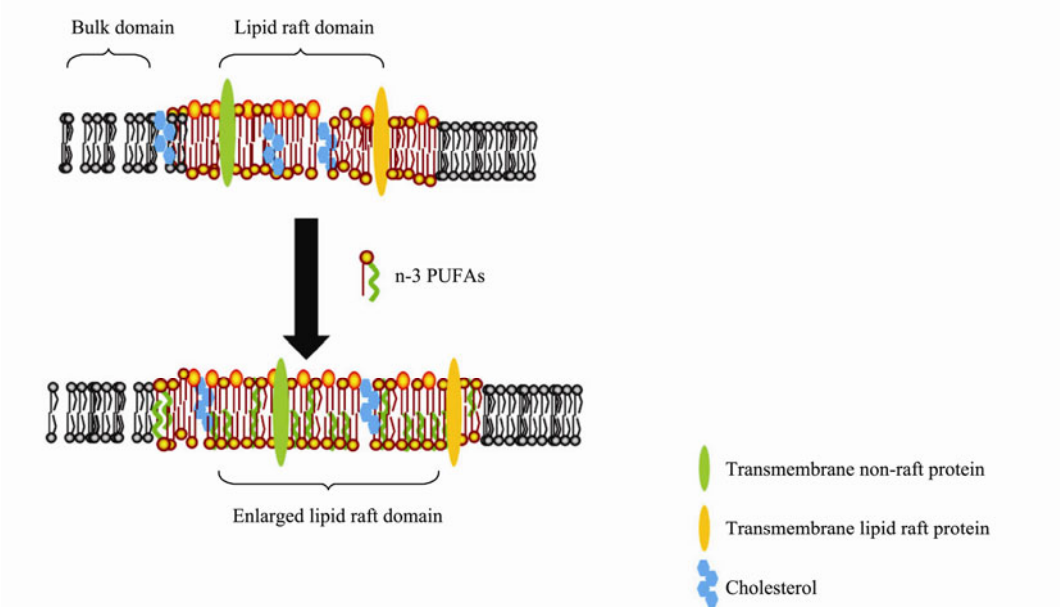

Fig.4 Putative model for the effect of n-3 PUFA on lipid rafts. Lipid rafts are cholesterol and phospholipid-enriched nanoscale region. Upon treatment with n-3 PUFAs, they are incorporated into phospholipids and induce enlarged clustering of lipid raft domains.

4.3 Eicosanoid-Independent Mechanisms

There is increasing insight that eicosanoid-independent mechanisms play an important role of n-3 PUFAs in regulating inflammation and immune response. In other words, n-3 PUFAs can directly regulate signaling pathways, modulate transcription factor activity, and act on gene expression (Calder, 2003; Simopoulos, 2002). For instance, n-3 PUFAs can inhibit MAPK activation in PKC-dependent and independent ways, therefore interfere in MAPK signaling transduction (Denys *et al*., 2001a). Additionally, alteration of transcription factor activity and gene expression level regulated by n-3 PUFAs has been described for PPAR, LXR, Nf-κB, AP-1, CREB and SREBP (Jia *et al*., 2006; Jump, 2004; Ntambi and Bene, 2001; Shi and Pestka, 2006). Chen *et al* found that DHA could induce S-phase cell cycle arrest and inhibit cell proliferation. After treating cells with DHA, the DNA replication site appears far away from upstream of ori-β, which indicates that n-3 PUFAs could influence DNA synthesis (Chen and Istfan, 2001).

4.4 Targeting at Mediators of Inflammation and Immune Response

Last but not the least, n-3 PUFAs have impact on mediators of inflammation and immune response, such as lymphocytes, NK cells, macrophages, T cells, platelet activating factor (PAF), and so on (Lu *et al*., 2008; Monk *et al*., 2013; Rombaldova *et al*., 2017).

GPR120 is a G protein-coupled receptor for n-3 PUFAs in macrophages, and is also known as free fatty acid receptor 4 (FF4) (Moniri, 2016). The ligand specificity of GPR4 is much higher for PUFAs, such as DHA and EPA, than saturated long-chain fatty acids. However, it is hard to distinguish different PUFAs, for example, linoleic acid (n-6 PUFA) and palmitoleic acid (n-7 PUFA) almost have similar binding affinity with GPR120 (Galindo *et al*., 2012). Two isoforms of GPR120 have been identified as a long isoform and a short isoform. The long isoform only responds to β-arrestin-induced signaling, but the short isoform can trigger both G protein-mediated Ca^{2+} signaling and β-arrestin-mediated phosphorylation and internalization (Watson *et al*., 2012). High GPR120 expression is found in bone marrow-derived macrophages and in primary intraperitoneal macrophages (Oh *et al*., 2010). The mechanism of n-3 PUFAs in regulating GPR120 signaling has been elucidated that β-arrestin-2 is recruited after GPR120 activation, and the subsequent internalization of the GPR120/β-arrestin-2 complex leads to its binding with TAB1, which suppresses TAK1 activation and causes Nf-κB pathway blockade (Oh *et al*., 2010). X. Li *et al*. studied the effect of n-3 PUFAs on LPS-induced inflammation in macrophage and found that n-3 PUFAs could reduce COX-2 expression and decrease PGE2 synthesis in a concentration- and time-dependent manner, besides that TLR4 signaling through phosphorylation of Akt/JNK and Nf-κB p65 is repressed by n-3 PUFAs activated GPR120 too (Li *et al*., 2013). Liu *et al*. raised another potential mechanism that n-3 PUFAs activate cytosolic phospholipase A2 (cPLA2), which inhibits the NF-κB signaling pathway *via* EP4 receptor and leads to the inhibition of LPS-induced IL-6 secretion in macrophages (Liu *et al*., 2014).

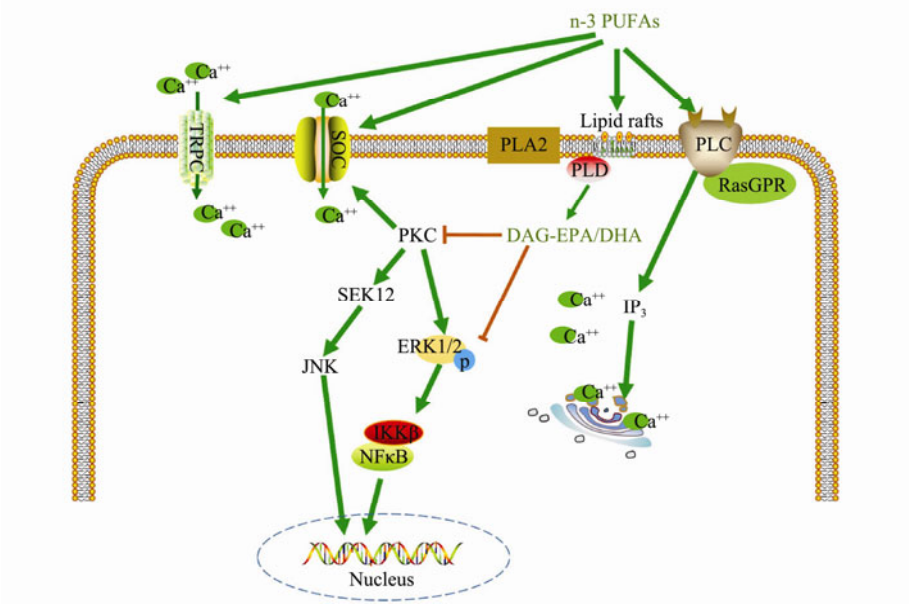

Fig.5 Schematic representation of the regulation of n-3 PUFA in T-cell signaling. N-3 PUFAs activated by PLD will increase the DAG containing n-3 PUFA (DAG-DHA/EPA) which, in turn, will upregulate $[Ca^{2+}]_i$ by TRPC channels, modulate RasGRP, and act on different isoforms of PKC. All of these effects of n-3 PUFAs will inhibit inflammatory gene transcription and lead to immunosuppression.

T cell is another immunocyte highly related to inflammation, especially Th1, Th2, Th17 and Treg subgroups. T cells play a central role in the immune system because they are involved in both innate immunity and adaptive immunity (Bedoui *et al*., 2016; Eisenbarth and Flavell, 2009). In the process of host defends against pathogens, T

cells mediate the occurrence and development of inflammation. For example, in rheumatoid arthritis (RA) patients HIF-1 transcription is induced by Th1 cytokines TNFα and IL-1β, which can lead to angiogenesis and inflammation in hypoxia (Larsen *et al*., 2012). Recently, Th17 and Treg identified as two new subsets of T cells are tightly associated with autoimmune and inflammatory diseases. It is reported that Th17 cells represent a pro-inflammatory subgroup; however, Treg cells have a suppressive effect (Noack and Miossec, 2014).

Some studies have showed that n-3 PUFAs can inhibit T cell proliferation *in vitro* (Calder *et al*., 1991; Calder *et al*., 1992; Camps *et al*., 1992). The animals treated with n-3 PUFAs also show a down-regulated T cell proliferation (Fowler *et al*., 1993; Peterson *et al*., 1998), suppressive cytokine production (Jolly *et al*., 1997), and modified Th1 and Th2 subsets (Wallace *et al*., 2001). The underlying mechanisms of n-3 PUFAs-regulated T cell activity have been interpreted as reduced generation of diacylglycerol (Fowler *et al*., 1993), inhibition of PKC activation (Denys *et al*., 2005), and repressed ERK/MAPK signaling transduction (Denys *et al*., 2001b). Calcium signaling as the second messenger also is the target of n-3 PUFAs in regulating T cell function (Yog *et al*., 2010). Chow and Jondal found that n-3 PUFAs could increase $[Ca^{2+}]_i$ in Jurkat T-cells (Chow and Jondal, 1990), and a similar effect of n-3 PUFAs on monocytes is observed too (Aires *et al*., 2007). The upregulation of $[Ca^{2+}]_i$ is due to the activation of calcium release-activated calcium (CRAC) channels after treated with n-3 PUFAs, and a stimulated production of diacylglycerol (DAG)-n- 3PUFAs by activating phospholipase D (PLD) can be observed. Moreover, n-3 PUFAs seem to inhibit PKC activation *via* diminished ERK1/2 phosphorylation (Denys *et al*., 2004). Furthermore, immunologic synapse involved in APC presenting antigens to T cells is dependent on Ca^{2+} mediated mitochondrial redistribution (Quintana *et al*., 2007). Studies have shown that when T cells are treated with n-3 PUFAs the formation of immunologic synapse will be inhibited, which is associated with the change of $[Ca^{2+}]_i$ and is consistent with immune suppression caused by n-3 PUFAs in autoimmune disease (Yog *et al*., 2010). Based on current studies, multiple signaling pathways are interlinked to each other as the targets of n-3 PUFAs in regulating T cell function (Fig.5).

To briefly summarize the discovered mechanisms of n-3 PUFAs in immune regulation, firstly, n-3 PUFAs can influence the composition of lipid membrane and change lipid raft regions, then the phosphorylation of PKC which is an integral part of lipid microdomains will be down-regulated (Akhtar, 2010); secondly, metabolites of inflammatory precursor are transformed into anti-inflammatory agents; thirdly, n-3 PUFAs will interfere in downstream cell signaling cascade, including PKC, MAPK, Nf-κB, $[Ca^{2+}]_i$ and so on.

5 Perspectives

Since the first publication by Dyerberg, many studies have been carried out to understand physiological function and health care effect of n-3 PUFAs. The epidemiology, clinical and experimental researches in recent years have shown that n-3 PUFAs are essential fatty acids for human health (Brantsaeter *et al*., 2017; Marushka *et al*., 2017). It has been well accepted that n-3 PUFAs as dietary supplementation and animal feed should be used with care because they are easily oxidized (Ballou and DePeters, 2008). However, whether n-3 PUFAs can be used as drug in clinics is still a controversial issue (Calder, 2013; Fialkow, 2016b). Although the negative results are reported occasionally, the overall impact of n-3 PUFAs on human health is still positive. In the future, more detailed research, including sex, age, ethnicity, trial duration and health conditions, may be able to answer the different roles of n-3 PUFAs being played in human. There is no doubt that more in-depth studies of n-3 PUFAs are called for to meet the goal of improving human health and preventing inflammatory diseases.

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