Published in final edited form as:

Biochim Biophys Acta Mol Cell Biol Lipids. 2021 July ; 1866(7): 158936. doi:10.1016/j.bbalip.2021.158936.

Polyunsaturated fatty acids, specialized pro-resolving mediators, and targeting inflammation resolution in the age of precision nutrition

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Abstract

Chronic inflammation contributes toward the pathogenesis of numerous diseases including, but not limited to, obesity, autoimmunity, cardiovascular diseases, and cancers. The discovery of specialized pro-resolving mediators (SPMs), which are critical for resolving inflammation, has commenced investigation into targeting pathways of inflammation resolution to improve physiological outcomes. SPMs are predominately synthesized from the n-3 polyunsaturated fatty acids (PUFA) eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids. Therefore, one viable strategy to promote inflammation resolution would be to increase dietary intake of EPA/DHA, which are deficient in select populations. However, there are inconsistencies between the use of EPA/DHA as dietary or pharmacological supplements and improved inflammatory status. Herein, we review the literature on the relationship between the high n-6/n-3 PUFA ratio, downstream SPM biosynthesis, and inflammatory endpoints. We highlight key studies that have investigated how dietary intake of EPA/DHA increase tissue SPMs and their effects on inflammation. We also discuss the biochemical pathways by which EPA/DHA drive SPM biosynthesis and underscore mechanistic gaps in knowledge about these pathways which include a neglect for host genetics/ethnic differences in SPM metabolism, sexual dimorphism in SPM levels, and potential competition from select dietary n-6 PUFAs for enzymes of SPM synthesis. Altogether, establishing how dietary PUFAs control SPM biosynthesis in a genetic-and sex-dependent manner will drive new precision nutrition studies with EPA/DHA to prevent chronic inflammation in select populations.

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1.0 High n-6 and low n-3 PUFA consumption in the western diet may contribute toward chronic inflammation.

The western diet is high in saturated fat and n-6 (ω−6) polyunsaturated fatty acids (PUFAs) and low in long chain n-3 (ω−3) PUFAs. In addition, more than half of the calories consumed in the western diet come from highly processed foods.[1] During the course of human evolution, the ratio of n-6 to n-3 PUFAs has significantly increased from 1:1 to 10:1 today.[2] This observed change in dietary fatty acid consumption in favor of n-6 PUFAs is a result of a change in our dietary patterns including, but not limited to, the use of vegetable oils and processed foods.[3,4] In the United States, the increase in dietary n-6 PUFAs is a consequence of dietary policy changes in which saturated fat was replaced with n-6 PUFAs in an effort to lower serum cholesterol and LDL.[3] However, whether increased intake of n-6 PUFAs has uniform health benefits is currently debated.[3,5–8]

While the optimal ratio of n-6 to n-3 PUFAs for human health and disease remains to be established, the increase in dietary consumption of n-6 PUFAs parallels the increased prevalence of adiposity in western nations.[2,9] Consumption of foods enriched in sugar and high-fat in the western diet and limited physical activity are some of the factors driving the obesity epidemic.[10] Obesity, defined as BMI ≥ 30 kg/m^2, occurs through the deposition of excess lipids into adipose tissue. Excess adiposity leads to a chronic state of meta-inflammation.[11] Individuals with obesity have greater risk for chronic disease and often present with clinical parameters of metabolic syndrome (MetS), such as increased waist circumference, high blood pressure, high fasting triglycerides, decreased high-density lipoprotein (HDL), high low-density lipoprotein (LDL), high total cholesterol and elevated glucose.[12] Since obesity and MetS are associated with increased risk for varying complications, increased dietary intake of n-3 PUFAs may be important for mitigating disease risk.[12–15]

There is some debate about the role of n-6 PUFA consumption for differing aspects of human health including chronic inflammation. The prevailing viewpoint is that increased dietary intake of n-6 PUFAs, in comparison to saturated fatty acids, lowers the risk of differing cardiovascular diseases.[3,16] For instance, decreasing the intake of saturated fat or replacement with mono- or polyunsaturated fatty acids, including n-6 PUFAs, reduces the risk of coronary heart disease.[17] However, a 2018 systematic review on n-6 PUFAs on cardiovascular health reported no benefit for increased consumption of n-6 fatty acids to reduce cardiovascular outcomes except for myocardial infarction.[18]

One n-6 PUFA that is of particular relevance to inflammation is linoleic acid (18:2). Current intake of linoleic acid (the most abundant PUFA in the western diet) is ~7% of total energy in the U.S,, which is 14–18 times the amount required to prevent linoleic acid deficiency.[19,20] The role of linoleic acid on inflammation is debated.[21–26] Some studies suggest that linoleic acid is pro-inflammatory, particularly at the pre-clinical level, while others do not support this notion and even suggest an anti-inflammatory role for linoleic acid.[27,28] There is epidemiological evidence to suggest that linoleic acid intake is inversely associated with total mortality.[29] The debate may stem from the notion that studies on linoleic acid are from a wide range of systems such as obesity to cancer models.[25] Thus,

there is a critical need to investigate if lowering excess n-6 PUFAs including linoleic acid in the diet may potentially improve outcomes related to chronic inflammation. It is also important to establish how gene-diet interactions impact circulating levels of n-6 and n-3 PUFAs.[8] This is discussed below at a molecular level in the context of targeting pathways of inflammation resolution.

2.0 Chronic inflammation is central toward the pathogenesis of obesity and its complications.

Obesity is well established as a state of chronic low-grade inflammation. Adipose tissue depots, liver, muscle and pancreas are primary sites of inflammation in response to diet-induced obesity.[30] There is also evidence for inflammation in the brain, which may drive changes in food intake.[31] In metabolically actives tissues such as the adipose, there is an infiltration of macrophages and other immune cells, as well as a shift away from anti-inflammatory immune cells.[30] Adipocytes and macrophages are a source of pro-inflammatory cytokines such as IL-1, TNFα, and IL-6.[30] Individuals consuming a western diet can have elevated levels of IL-6, IL-1β, and TNFα, characteristic of obesity, in comparison to healthy individuals.[4,9]

Diet-induced obesity is associated with many complications such as cancers, behavioral disorders, non-alcoholic fatty liver disease, cardiovascular complications, and insulin resistance. Notably, MetS is associated with high blood glucose, abnormal cholesterol levels and high triglycerides accompanied by upregulation of pro-inflammatory pathways.[12] High blood glucose and elevated HbA1c is associated with insulin resistance and type 2 diabetes. Adipose tissue in obesity and MetS is characterized by increased lipolysis with the excessive release of free fatty acids, and is also a source of pro-inflammatory cytokines; both of these factors may inhibit insulin action.[32] Systemic inflammatory markers are also risk factors for the development of type 2 diabetes and its macrovascular complications. As an example, the pro-inflammatory interleukin-1β is implicated in the pathogenesis of type 2 diabetes through the activation of the NLRP3 inflammasome.[30]

A prominent feature of MetS is dysregulated lipid metabolism, contributing to increased fasting plasma triglycerides, high LDL cholesterol and low HDL cholesterol.[33] The presence of the small dense LDL phenotype, postprandial hyperlipidemia with accumulation of atherogenic remnants and hepatic overproduction of apoB containing lipoproteins are metabolic risk factors associated with obesity.[33] All these lipid abnormalities are typical features of the MetS and may be associated with a pro-inflammatory gradient.[33]

An often-overlooked complication of obesity is increased risk of infection, potentially due to impairments in pathways of inflammation resolution. For instance, the western diet triggers NLRP3-dependent innate immune reprogramming and mice fed a western diet exhibit impaired cellular functionality that is critical for combatting secondary infections.[34] Several viruses or virus-like agents such as members of adenoviridae, herpesviridae, slow virus (prion), and hepatitides, have been associated with increased risk for infection in response to obesity.[35] Obesity is also a critical factor for vulnerability to influenza A/pdmH1N1 virus infection, and high fat diets rich in saturated fats and cholesterol also negatively

impact the pathogenesis of HIV/SIV infection.[5,36] Mechanistically, obesity increases the risk for infection and drives poor responses to vaccinations in part due to compromised humoral immunity and impaired T cell metabolism including poor memory responses from pulmonary T cells upon influenza infection.[37–40]

Very recently, epidemiological research on the impact of obesity on SARS-CoV-2, which is driving the COVID-19 pandemic, suggests that individuals with obesity are at increased risk for infection and complications of viral infection such as increased mechanical ventillation.[41] The effects of obesity are not just limited to viruses as obese mice display increased susceptibility to bacterial infections such as *Staphylococcus aureus*.[42] Thus, there may be a potential role for diet-driven inflammation that is contributing toward increased risk for infection in individuals with obesity and/or MetS. In fact, a failure to resolve inflammation may be one major factor that is contributing toward increased risk for infection.[43]

3.0 Specialized pro-resolving mediators are critical for resolving inflammation.

A plausible approach to combatting the pro-inflammatory state associated with chronic inflammatory diseases such as obesity and its complications is to increase dietary consumption of the long chain n-3 PUFAs eicosapentaenoic (EPA, 20:5) and docosahexaenoic (DHA, 22:6) acids. Here we briefly cover how EPA and DHA give rise to downstream metabolites that are critical regulators of inflammation resolution and highlight key functional roles for these metabolites in the context of inflammation and infection.

EPA and DHA are enzymatically converted into specialized pro-resolving mediators (SPMs).[44] SPMs act as potent signaling molecules, binding to their receptors on immune cells in various tissues.[45] The role of SPMs is to promote immunoresolution, a process by which inflammation is resolved to its homeostatic state.[45] Each SPM has its own functional role through the binding of specific receptors. EPA derived SPMs are known as the E-series resolvins, while DHA derived SPMs comprise of the D-series resolvins, maresins, and protectins.[46] There is also one class of SPMs produced from arachidonic acid, an n-6 PUFA, known as the lipoxins.[45] An overview of the biosynthesis of EPA- and DHA-derived SPMs is depicted in Figure 1. In addition, Figure 1 shows the major downstream metabolites of arachidonic acid.

To produce the E-series resolvins, EPA undergoes modification by either the cytochrome P450 (CYP450) or cyclooxygenase-2 (COX-2) enzymes to produce the intermediate, 18-HpEPE. Further modification of 18-HpEPE by the enzyme arachidonate 15-lipoxygenase (ALOX15) produces resolvin E3 (RvE3), one of the E-series resolvins. 18-HpEPE can be further metabolized into 18-HEPE by 5-lipoxygenase (ALOX5). 18-HEPE is then converted into the other two E-series resolvins, resolvin E1 (RvE1) and resolvin E2 (RvE2) via leukotriene-A4 hydrolase (LTA4-H) or a reduction reaction, respectively.[47–49] RvE1 specifically binds to the Chemerin 23 (ChemR23) receptor and leukotriene B4 (LTB4) receptor, BLT1.[50]

RvE1 binding to ChemR23 on macrophages induces phagocytosis and clearance of debris, and promotes an immunoresolving phenotypic switch from classically activated (M1-like) to non-activated macrophages (M2-like).[45,50,51] On the other hand, RvE1 binding BLT1 blocks LTB4 binding on lymphocytes, macrophages, and neutrophils to decrease immune cell chemotaxis to the area of injury and clearance of inflammatory neutrophils by non-classically activated macrophages.[50,52–54] It is known that antagonistically inhibiting LTB4 on leukocytes, such as B cells, prevents the development of insulin resistance in C57BL6/J mice.[55] RvE1 also reverses hyperinsulinemia and hyperglycemia in C57BL6/J obese mice through a ChemR23 mediated mechanism independent of a role for adipose tissue inflammation.[47] Similar to RvE1, RvE2 is a partial agonist to ChemR23 and a BLT1-LTB4 antagonist; [56,57] furthermore, RvE2 reduces neutrophil infiltration and chemotaxis.[58] Overexpression of the ChemR23 receptor drives improvements in glucose homeostasis of mice.[59] It is still unknown which receptors RvE3 binds to; however, it is hypothesized that RvE3 reduces neutrophil infiltration but more research is required to identify RvE3's specific functions.[60]

The D-series resolvins, protectins and maresins are produced by DHA. DHA is first metabolized by ALOX15 to produce 17S-HpDHA. 17-HpDHA is then a substrate for ALOX5 and a series of peroxidase and hydrolysis reactions to produce the resolvins RvD1, RvD2, RvD3, RvD4, RvD5, and RvD6. RvD1 binds the human G protein-coupled receptor 32 (GPR32) and N-formyl peptide receptor 2 (ALX/FPR2) whereas RvD2 binds GPR18.[61–63] RvD1 and RvD2 rescue diminished adiponectin levels in obese adipose tissue and decrease monocyte chemoattractant protein-1 (MCP1) and LTB4 stimulated monocyte migration.[64] RvD1 and RvD2 increase macrophage phagocytosis in the context of an infection.[56,65] Furthermore, RvD1 decreases time of epithelial closure and presence of apoptotic cells in diabetic wounds.[66] RvD3 also exerts antimicrobial actions via GPR32, increases neutrophil clearance, and decreases production of inflammatory prostaglandins and leukotrienes.[67] Similarly, RvD4 has shown host protection and bacterial clearance against *Staphylococcus aureus* infections.[68] RvD4 decreases neutrophil infiltration and increases pro-resolving monocytes in deep vein thrombosis.[69] RvD5 binds the GPR32 receptor and increases macrophage phagocytosis during *E. coli* infections.[56] As for RvD6, it has been hypothesized to aid in corneal wound healing and nerve damage.[70]

17S-HpDHA is also converted into Protectin D1 (PD1) and is an isomer of Protectin DX (PDX). PD1 is neuroprotective by increasing nerve regeneration and decreasing perception of pain.[57,71] Furthermore, PD1 along with RvD1 and RvD5 increase survival and decrease antibiotic usage in response to bacterial infections.[57] In addition, DHA is converted by ALOX12 into 14S-HpDHA to produce maresin-1 (MaR1) and maresin-2 (MaR2). MaR1 increases macrophage phagocytosis of apoptotic neutrophils and induces tissue regeneration.[72] Furthermore, the MaR1 precursor 14-HDHA induces a phenotypic switch in macrophages from an M1-like classically activated phenotype to a pro-resolving M2-like phenotype.[45] Lastly, MaR2 increases phagocytosis of apoptotic neutrophils.[57] Taken together, SPMs are critical in orchestrating inflammation resolution and targeting the aforementioned pathways of SPM biosynthesis may be a therapeutic approach, particularly for those diseases associated with SPM deficiency.

4.0 SPM biosynthesis is unbalanced in obesity and its metabolic complications.

There is strong literature support for the notion that obesity drives a deficiency in the concentration of n-3 PUFA-derived SPMs in both human and murine models.[73] In mice, feeding an obesogenic western diet induces systemic inflammation and functional reprogramming, [34] which is accompanied by decreased levels of RvD1, 17-HDHA, and PD1 in white adipose tissue.[73] Strikingly, a high fat diet can drive a reduction in SPM levels within days. For instance, one lab reported that DHA-derived SPMs and their precursors are lowered in white adipose tissue within four days of intervention with a high fat diet compared to mice on a lean diet.[73] This raises the possibility that it is the high fat diet and not the state of obesity itself that may be driving a reduction in the concentration of SPMs.

The effects of obesity are not just on DHA-derived SPMs as a recent study reported that 18-hydroxyeicosapentaenoic acid, the precursor for RvE1 was strongly diminished in white adipose tissue and liver.[47] Administration of dietary EPA or the downstream RvE1 to obese mice strongly improved hyperinsulinemia and hyperglycemia. Another research group reported that SPMs are increased in a model of mouse liver steatosis although the levels of EPA and DHA were decreased in response to the liver steatosis.[66] Thus, this study suggests that obesity may drive an unbalanced concentration of SPMs rather than a universal deficiency. This study underscores the need to study the kinetics of inflammation resolution as mass spectrometry measurements for SPMs at a single time point do not provide a comprehensive picture of the inflammatory profile.

SPM levels appear to be lowered in circulation and secondary lymphoid organs in response to obesity.[37] Notably, the splenic SPM precursors 14-HDHA, 17-HDHA and PDX were decreased in obese male but not female C57BL/6J mice.[74] This lowering of lipid mediators was associated with an increase in the abundance of n-6 PUFAs.[74] Administration of dietary DHA can also restore endogenous biosynthesis of SPMs (14-HDHA, 17-HDHA and PDX) in mice consuming a western diet, and treatment with 17-HDHA reduced inflammatory cytokine expression in adipocytes.[37,73]

Leukocytes from individuals with obesity also exhibit an impaired SPM signature and display a reduction in select SPMs.[74,75] There is unbalanced production of SPMs (i.e., D- and E-series resolvins, PD1, MaR1, and lipoxins) with respect to inflammatory lipid mediators (i.e., LTB4 and prostaglandins) in omental adipose tissue from study subjects with obesity.[76] In a 2019 study by López-Vicario et al., individuals with obesity displayed a notable reduction in leukocyte 17-HDHA. The reduction in 17-HDHA was potentially driven by reduced activity of ALOX15, which is critical for the biosynthesis of SPMs.[75] There is also evidence that MaR1 levels are significantly decreased in type 2 diabetics compared to controls.[77]

A major gap in knowledge is the mechanisms by which components of the western diet may drive an impaired SPM signature. Potential mechanisms include the possibility that n-6 and n-3 PUFAs may compete with each other for esterification into the membrane phospholipid pool.[78] Thus, competition between differing fatty acids from the diet for

membrane phospholipids could impact the bioavailability of fatty acids for downstream SPM biosynthesis. Notably, the n-6 PUFA linoleic acid can bind some of the same enzymes such as 12/15-LOX that generate SPMs from DHA, which could prevent SPM biosynthesis (Figure 1).[79,80] Indeed, a very recent study showed dietary linoleic acid inhibited the synthesis of DHA-derived SPMs in mice.[81] Thus, excess linoleic acid may decrease available substrate for key enzymes used for SPM biosynthesis. Another possibility, which may not be mutually exclusive, is that obesity or the consumption of high fat/high sugar diet may be driving a reduction in the expression of enzymes of SPM biosynthesis and/or a reduction in their activity. The premise for this hypothesis is based on the López-Vicario et al., study described above on enzyme activity. Clearly, more work is needed in this area at a mechanistic level. Finally, there is the possibility that SPM biosynthesis is simply low due to poor intake of dietary n-3 PUFAs in the western diet.[82] Therefore, future studies should compare the role of the western diet on SPM biosynthesis with other dietary patters such as the Mediterranean diet, which contains higher amounts of in n-3 PUFAs.[83]

5.0 The use of dietary n-3 PUFAs to mitigate SPM deficiencies in select populations to improve chronic inflammatory outcomes.

There is suggestion in the literature that administration of long chain n-3 PUFAs has a positive role in the prevention and treatment of the pathologies associated with obesity, MetS, and inflammation.[84] Increased consumption of n-3 PUFAs in the diet can reduce plasma levels of the pro-inflammatory cytokines IL-6 and tumor necrosis factor-alpha (TNFα), as well as plasma C-reactive protein (CRP). [84] These effects are thought to be mediated by SPMs.[84] However, the link between dietary n-3 PUFAs, SPMs, and improvements in inflammation are just starting to emerge. A recent study shows that supplementation with a marine oil known as SPM Active leads to an increase in peripheral blood SPM concentrations and reprograms peripheral blood cells, indicating a role for SPMs in mediating the immune-directed actions of this supplement.[85] This supplement is formulated to provide specific amounts of SPM precursors.

There are studies that demonstrate a positive correlation between n-3 PUFA supplementation and downstream SPM production in humans. As an example, one study reported that human plasma and serum SPM clusters were increased after n-3 PUFA supplementation.[86] Studies administering dietary DHA showed increased 12/15-LOX and decreased 5-LOX expression in lymph nodes and isolated lymph node PMN, which correlated with amplified LXA4 formation.[87] The increase in LXA4 from DHA was unexpected and the underlying mechanism of action remains unclear. Other studies involving n-3 PUFAs have shown increased DHA-derived pro-resolving mediators in women with obesity.[88] Additionally, patients with coronary artery disease with low or absent levels of specific SPMs had complete restoration with Lovaza, which is a prescription EPA/DHA ethyl ester formulation.[89]

One area of study that requires further attention is the role of dietary docosapentaenoic acid (DPA, 22:5) on biosynthesis of downstream SPMs. Dietary supplementation with DPA can increase downstream SPMs. In a double-blind crossover study, DPA supplementation

increased the SPM resolvin RvD5n-3DPA and MaR-1, the vicinal diol 19,20-dihydroxy-DPA and n-6 PUFA derived 15-keto-PGE2.[90] However, the effects of DPA supplementation on inflammation resolution remain to be established and is an area for future investigation.

It is critical to recognize that not all individuals will display SPM deficiencies and thus the need for precision interventions. A major goal of precision nutrition/medicine is to provide targeted interventions for select populations.[91] For instance, only those individuals with obesity that are SPM deficient may be better candidates for dietary intervention with n-3 PUFAs. In fact, it is increasingly recognized that there is tremendous heterogeneity within the population with obesity and it is better to think about 'obesities' rather obesity as a single disease state.[92,93] Therefore, there is likely tremendous heterogeneity in circulating SPM levels across differing inflammatory conditions. Of course, a range of other factors will also impact SPM levels in humans, as discussed in the subsequent sections below.

6.0 Genetic differences in SPM metabolism may be a critical factor in translating n-3 PUFAs for improving inflammation.

There are significant discrepancies in the literature on the potential use of n-3 PUFAs for improving inflammatory outcomes. Of course, there are various causes that may contribute to differences in reported outcomes with n-3 PUFA supplementation studies, particularly through SPM-mediated mechanisms. In Figure 2, we present an overview of these potential causes, which we discuss below in greater detail. Notably, the relative amount of dietary intake of differing n-3 and n-6 PUFAs coupled with differences in each individual's metabolic and microbiome status, sex, and host genetic background will impact the concentration of SPMs, influence disease risk, and ultimately inflammation resolution. Furthermore, age and environmental exposures (not depicted for simplicity in Figure 2) will also impact the individual's metabolic and microbiome status and thereby influence inflammatory outcomes.

One potential source of discrepancy in the literature for n-3 PUFA efficacy for inflammation is that production of EPA- or DHA-derived SPMs can highly depend on the ratio of EPA and DHA in the supplement. Given that both EPA and DHA will compete with arachidonic acid to bind phospholipase A2, the ratio of each n-3 PUFA in the supplement may confound results from study to study.[94] Moreover, each SPM has differing functions that are tissue and cell specific.[46] Therefore, the SPMs that are produced from EPA and/or DHA in the supplement will result in targeted activation of the particular receptors that those SPMs bind.[46] Hence, the formulation of the n-3 PUFA supplement potentially determines the SPM pool that will be produced and actively contribute to the phenotypic outcome of interest measured in the study.

The effects of dietary n-3 PUFAs may be further influenced by the background dietary levels of n-6 PUFAs, notably the n-6 PUFAs linoleic and arachidonic acid (Figure 1). Often, n-6 PUFA levels are not accounted for in clinical trials. Linoleic acid, as discussed above, may have a role in influencing SPM levels, which may a direct effect of linoleic acid or through the biosynthesis of arachidonic acid. Many of the metabolites synthesized from arachidonic acid can be pro-inflammatory. However, SPMs can be synthesized from

arachidonic acid. These SPMs are lipoxins, which consist of LXA4 and LXB4.[44,95] LXA4 binds the ALX/FPR2 receptor and has various effects over a wide variety of conditions ranging from ulcerative colitis remission to periodontal disease and hepatic steatosis.[57,96–98] Thus, the role of n-6 PUFAs on dietary n-3 PUFA mediated SPM synthesis is complicated as not all n-6 PUFA-derived metabolites are pro-inflammatory.

Another potential cause for discrepancy in studies with n-3 PUFAs in humans is the lack of accounting for host-genetics. Clinical studies often include a wide range of individuals with a diverse genetic background. There is strong evidence for the role of host genetics with EPA/DHA metabolism but far less is known about SPM biosynthesis and metabolism. For instance, around 80% of African Americans have two alleles associated with higher arachidonic acid levels whereas only about 45% of European Americans have those same alleles.[99] This suggests that differences between circulating or tissue-specific levels of PUFAs among various genetic or ethnic backgrounds could impact the concentration of downstream SPMs.[99]

Many single nucleotide polymorphisms (SNPs) in the enzymes or receptors of the SPM synthesis pathway have direct clinical translation in metabolic-related diseases in the human population as well. In fact, we have previously shown that when mining the dbSNP and 1000 genomes databases there is a large range of minor allele frequencies present in various enzymes and receptors of SPM production pathways.[47] When examining the first step in the SPM biosynthesis pathways, the CYP450 enzymes with the capacity to metabolize EPA or DHA have numerous polymorphisms related to various metabolic disorders.[100] CYP2C8, CYP2C9, and CYP2C19 contain SNPs that have been associated with increased susceptibility to type 2 diabetes in Indian, Japanese, and Saudi populations.[101–104] Additionally, two SNPs in CYP4F2 are associated with coronary heart disease in the Chinese population.[105] On the other hand, the etiology and risk of developing type 2 diabetes has been associated with the COX-2 enzyme (rs5275 variant) in type 2 diabetic patients.[106] Furthermore, when examining African Americans with the COX-2 G-765C polymorphism, researchers found a higher risk of stroke with that particular COX-2 variant.[107] Three SNPs in the COX-2 enzyme are associated with coronary/carotid calcified plaques in patients from the Diabetes Heart Study.[108]

Further downstream in the E-series biosynthesis pathway, SNPs in FLAP or LTA4-H are correlated with a two-fold risk for myocardial infarction and stroke.[109,110] These particular SNPs in FLAP that were correlated with myocardial infarction and stroke were found to be in greater abundance in the Finnish, English, and Scottish populations.[111] On the other hand, the enzyme bound to FLAP, ALOX5, has SNPs that are associated with modest increases in body mass index and cardiovascular disease risk.[112] Particularly, SNPs in the promoter of ALOX5 are significantly associated with coronary artery disease in white Europeans, with a minor allele frequency of 15%.[113] Polymorphisms in ALOX15, the enzyme that produces RvE3 and 17S-HpDHA, have also been associated with ischemic stroke or coronary artery disease in the Chinese Han population and North Indian population, respectively.[114,115] The ALOX12 polymorphism (rs2073438) is significantly associated with total fat mass and percentage fat mass in obese Chinese men.[116] As for polymorphisms in SPM receptors, one group discovered a polymorphism (rs1878022) in ERV1/ChemR23 that increases its

expression and leads to reduced levels of pro-inflammatory cytokines in adipose tissue and plasma of individuals with morbid obesity.[117] Taken together, these studies highlight the importance of accounting for host-genetics and ethnic differences in future pre-clinical and clinical studies with SPMs and dietary n-3 PUFAs.

7.0 Other factors that could influence SPM availability in humans.

There are likely additional factors that will contribute toward SPM bioavailability in humans. One notable factor is sex. It is established that synthesis of DHA is lower in males compared to females.[118] There are also data demonstrating sex differences in SPM bioavailability in mice and humans. In obese mice, SPM levels were generally higher in female mice than males.[74] In a human study, females were found to have higher levels of SPMs relative to male counterparts. Notably, the sex difference in this study correlated with females having increased protection from inflammation-driven endothelial impairments. The differences in SPM levels between humans may be tissue specific as SPMs were absent in male human tears compared to females.[119]

Another factor that could influence SPM metabolism is the composition and secretion of metabolites from the microbiome. Specific dietary patterns control microbial composition and thereby tissue-specific and circulating inflammatory status. For instance, a recent longitudinal study demonstrated that a shift toward consumption of a Mediterranean diet in male subjects leads to a unique microbial composition that is associated with improved cardiometabolic outcomes. Therefore, each individual’s dietary pattern and thereby their microbiome profile will likely influence SPM metabolism.[120]

A major step forward will be to establish SPM levels in SPM-deficient populations in response to well defined EPA and/or DHA supplements. Clinical studies will also benefit by genotyping individuals, measuring background levels of n-6 PUFAs, accounting for potential sex differences in SPM metabolism, and establishing a role for the microbiome in SPM bioavailability. This will then set the basis for future precision nutrition randomized clinical trials for specific outcomes related to chronic inflammation, infection, insulin resistance, etc. Ultimately, these studies will lead to precision clinical trials and perhaps even improved dietary recommendations for select clinical populations.

8.0 Conclusions.

The western diet is low in the long chain n-3 PUFAs EPA and DHA. This may contribute toward a chronic pro-inflammatory state that is associated with the pathogenesis of differing diseases such as those complications associated with obesity. One approach to targeting SPM deficiencies in select clinical populations to drive inflammation resolution is to increase dietary consumption of long chain n-3 PUFAs. However, key mechanistic gaps in knowledge remain on the causes of SPM deficiencies and approaches to overcoming these deficiencies. Notably, there is a need to understand how to effectively promote SPM biosynthesis with n-3 PUFAs while accounting for background levels of n-6 PUFAs, sex differences in SPM levels, baseline microbiome profiles, and host genetic differences in SPM biosynthesis/metabolism. Ultimately, this line of research from basic molecular studies

to pre-clinical and clinical experimentation will drive precision nutrition trials with EPA and DHA for select populations that are potentially SPM deficient to improve inflammatory outcomes.

Conflicts of interest:

S.R.S. has previously received funding from GSK and Organic Technologies related to n-3 polyunsaturated fatty acids. S.R.S. is using marine oil supplements from Metagenics for a clinical study. S.R.S. is currently supported by Organic Technologies on research related to monounsaturated fatty acids. S.R.S. has organized academic conferences on immunity and diet that have relied on corporate sponsorship.

This work was supported by: R01AT008375 (SRS), R01ES031378 (SRS), and P30DK056350 (SRS). This material is also based upon work supported by the National Science Foundation Graduate Research Fellowship Program under Grant No. 1650116 to AEA. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation.

References

1. Newman TM, Vitolins MZ, Cook KL. From the Table to the Tumor: The Role of Mediterranean and Western Dietary Patterns in Shifting Microbial-Mediated Signaling to Impact Breast Cancer Risk. Nutrients. 2019;11(11). doi:10.3390/nu11112565
2. Simopoulos AP. An increase in the omega-6/omega-3 fatty acid ratio increases the risk for obesity. Nutrients. 2016;8(3):128. doi:10.3390/nu8030128 [PubMed: 26950145]
3. Chilton FH, Murphy RC, Wilson BA, et al. Diet-gene interactions and PUFA metabolism: a potential contributor to health disparities and human diseases. Nutrients. 2014;6(5):1993–2022. doi:10.3390/nu6051993 [PubMed: 24853887]
4. Weaver KL, Ivester P, Seeds M, Case LD, Arm JP, Chilton FH. Effect of dietary fatty acids on inflammatory gene expression in healthy humans. J Biol Chem. 2009;284(23):15400–15407. doi:10.1074/jbc.M109.004861 [PubMed: 19359242]
5. He T, Xu C, Krampe N, et al. High-fat diet exacerbates SIV pathogenesis and accelerates disease progression. J Clin Invest. 2019;129(12):5474–5488. doi:10.1172/JCI121208 [PubMed: 31710311]
6. Brown TJ, Brainard J, Song F, et al. Omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: systematic review and meta-analysis of randomised controlled trials. BMJ. 2019;366:l4697. doi:10.1136/bmj.l4697 [PubMed: 31434641]
7. Patterson E, Wall R, Fitzgerald GF, Ross RP, Stanton C. Health implications of high dietary omega-6 polyunsaturated Fatty acids. J Nutr Metab. 2012;2012:539426. doi:10.1155/2012/539426 [PubMed: 22570770]
8. Chilton FH, Dutta R, Reynolds LM, Sergeant S, Mathias RA, Seeds MC. Precision Nutrition and Omega-3 Polyunsaturated Fatty Acids: A Case for Personalized Supplementation Approaches for the Prevention and Management of Human Diseases. Nutrients. 2017;9(11). doi:10.3390/nu9111165
9. Simopoulos AP. Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases. Biomed Pharmacother. 2006;60(9):502–507. doi:10.1016/j.biopha.2006.07.080 [PubMed: 17045449]
10. Varlamov O Western-style diet, sex steroids and metabolism. Biochim Biophys Acta Mol Basis Dis. 2017;1863(5):1147–1155. doi:10.1016/j.bbadis.2016.05.025 [PubMed: 27264336]
11. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest. 1 2017.
12. Andersen CJ, Murphy KE, Fernandez ML. Impact of obesity and metabolic syndrome on immunity. Adv Nutr. 2016;7(1):66–75. doi:10.3945/an.115.010207 [PubMed: 26773015]
13. Calder PC. Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? Br J Clin Pharmacol. 2013;75(3):645–662. doi:10.1111/j.1365-2125.2012.04374.x [PubMed: 22765297]
14. Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. Biochim Biophys Acta. 2015;1851(4):469–484. doi:10.1016/j.bbalip.2014.08.010 [PubMed: 25149823]

15. Calder PC. The role of marine omega-3 (n-3) fatty acids in inflammatory processes, atherosclerosis and plaque stability. Mol Nutr Food Res. 2012;56(7):1073–1080. doi:10.1002/mnfr.201100710 [PubMed: 22760980]
16. Calder PC. Functional roles of fatty acids and their effects on human health. JPEN J Parenter Enteral Nutr. 2015;39(1 Suppl):18S–32S. doi:10.1177/0148607115595980 [PubMed: 26177664]
17. Willett WC. Dietary fats and coronary heart disease. J Intern Med. 2012;272(1):13–24. doi:10.1111/j.1365-2796.2012.02553.x [PubMed: 22583051]
18. Hooper L, Al-Khudairy L, Abdelhamid AS, et al. Omega-6 fats for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2018;7:CD011094. doi:10.1002/14651858.CD011094.pub3 [PubMed: 30019765]
19. Blasbalg TL, Hibbeln JR, Ramsden CE, Majchrzak SF, Rawlings RR. Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century. Am J Clin Nutr. 2011;93(5):950–962. doi:10.3945/ajcn.110.006643 [PubMed: 21367944]
20. Naughton SS, Mathai ML, Hryciw DH, McAinch AJ. Linoleic acid and the pathogenesis of obesity. Prostaglandins Other Lipid Mediat. 2016;125:90–99. doi:10.1016/j.prostaglandins.2016.06.003 [PubMed: 27350414]
21. Tu TH, Kim H, Yang S, Kim JK, Kim JG. Linoleic acid rescues microglia inflammation triggered by saturated fatty acid. Biochem Biophys Res Commun. 2019;513(1):201–206. doi:10.1016/j.bbrc.2019.03.047 [PubMed: 30952426]
22. Kolar MJ, Konduri S, Chang T, et al. Linoleic acid esters of hydroxy linoleic acids are anti-inflammatory lipids found in plants and mammals. J Biol Chem. 2019;294(27):10698–10707. doi:10.1074/jbc.RA118.006956 [PubMed: 31152059]
23. Vangaveti VN, Jansen H, Kennedy RL, Malabu UH. Hydroxyoctadecadienoic acids: Oxidised derivatives of linoleic acid and their role in inflammation associated with metabolic syndrome and cancer. Eur J Pharmacol. 2016;785:70–76. doi:10.1016/j.ejphar.2015.03.096 [PubMed: 25987423]
24. Ferrucci L, Cherubini A, Bandinelli S, et al. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. J Clin Endocrinol Metab. 2006;91(2):439–446. doi:10.1210/jc.2005-1303 [PubMed: 16234304]
25. Jandacek RJ. Linoleic acid: A nutritional quandary. Healthcare (Basel). 2017;5(2). doi:10.3390/healthcare5020025
26. Whelan J, Fritsche K. Linoleic acid. Adv Nutr. 2013;4(3):311–312. doi:10.3945/an.113.003772 [PubMed: 23674797]
27. Ludwig DS, Willett WC, Volek JS, Neuhouser ML. Dietary fat: From foe to friend? Science. 2018;362(6416):764–770. doi:10.1126/science.aau2096 [PubMed: 30442800]
28. Taha AY. Linoleic acid-good or bad for the brain? npj Sci Food. 2020;4:1. doi:10.1038/s41538-019-0061-9 [PubMed: 31909187]
29. Wang DD, Li Y, Chiuve SE, et al. Association of Specific Dietary Fats With Total and Cause-Specific Mortality. JAMA Intern Med. 2016;176(8):1134–1145. doi:10.1001/jamainternmed.2016.2417 [PubMed: 27379574]
30. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract. 2014;105(2):141–150. doi:10.1016/j.diabres.2014.04.006 [PubMed: 24798950]
31. Cazettes F, Cohen JI, Yau PL, Talbot H, Convit A. Obesity-mediated inflammation may damage the brain circuit that regulates food intake. Brain Res. 2011;1373:101–109. doi:10.1016/j.brainres.2010.12.008 [PubMed: 21146506]
32. Matulewicz N, Karczewska-Kupczewska M. Insulin resistance and chronic inflammation. Postepy Hig Med Dosw (Online). 2016;70(0):1245–1258. [PubMed: 28026827]
33. Klop B, Elte JWF, Cabezas MC. Dyslipidemia in obesity: mechanisms and potential targets. Nutrients. 2013;5(4):1218–1240. doi:10.3390/nu5041218 [PubMed: 23584084]
34. Christ A, Günther P, Lauterbach MAR, et al. Western Diet Triggers NLRP3-Dependent Innate Immune Reprogramming. Cell. 2018;172(1–2):162–175.e14. doi:10.1016/j.cell.2017.12.013 [PubMed: 29328911]
35. Tian Y, Jennings J, Gong Y, Sang Y. Viral infections and interferons in the development of obesity. Biomolecules. 2019;9(11). doi:10.3390/biom9110726

36. Rojas-Osornio SA, Cruz-Hernández TR, Drago-Serrano ME, Campos-Rodríguez R. Immunity to influenza: Impact of obesity. Obes Res Clin Pract. 2019;13(5):419–429. doi:10.1016/j.orcp.2019.05.003 [PubMed: 31542241]
37. Kosaraju R, Guesdon W, Crouch MJ, et al. B Cell Activity Is Impaired in Human and Mouse Obesity and Is Responsive to an Essential Fatty Acid upon Murine Influenza Infection. J Immunol. 2017;198(12):4738–4752. doi:10.4049/jimmunol.1601031 [PubMed: 28500069]
38. Alwarawrah Y, Nichols AG, Green WD, et al. Targeting T-cell oxidative metabolism to improve influenza survival in a mouse model of obesity. Int J Obes. 2020;44(12):2419–2429. doi:10.1038/s41366-020-00692-3
39. Rebeles J, Green WD, Alwarawrah Y, et al. Obesity-Induced Changes in T-Cell Metabolism Are Associated With Impaired Memory T-Cell Response to Influenza and Are Not Reversed With Weight Loss. J Infect Dis. 2019;219(10):1652–1661. doi:10.1093/infdis/jiy700 [PubMed: 30535161]
40. Green WD, Al-Shaer AE, Shi Q, et al. Metabolic and functional impairment of CD8+ T cells from the lungs ofinfluenza-infected obese mice. J Leukoc Biol. 2021, In press.
41. Popkin BM, Du S, Green WD, et al. Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships. Obes Rev. 2020;21(11):e13128. doi:10.1111/obr.13128 [PubMed: 32845580]
42. Farnsworth CW, Schott EM, Benvie A, et al. Exacerbated Staphylococcus aureus Foot Infections in Obese/Diabetic Mice Are Associated with Impaired Germinal Center Reactions, Ig Class Switching, and Humoral Immunity. J Immunol. 2018;201(2):560–572. doi:10.4049/jimmunol.1800253 [PubMed: 29858265]
43. Serhan CN, Chiang N, Dalli J. New pro-resolving n-3 mediators bridge resolution of infectious inflammation to tissue regeneration. Mol Aspects Med. 2018;64:1–17. doi:10.1016/j.mam.2017.08.002 [PubMed: 28802833]
44. Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. Nat Immunol. 2005;6(12):1191–1197. doi:10.1038/ni1276 [PubMed: 16369558]
45. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature. 2014;510(7503):92–101. doi:10.1038/nature13479 [PubMed: 24899309]
46. Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. J Clin Invest. 7 2018.
47. Pal A, Al-Shaer AE, Guesdon W, et al. Resolvin E1 derived from eicosapentaenoic acid prevents hyperinsulinemia and hyperglycemia in a host genetic manner. FASEB J. 6 2020. doi:10.1096/fj.202000830R
48. Oh SF, Pillai PS, Recchiuti A, Yang R, Serhan CN. Pro-resolving actions and stereoselective biosynthesis of 18S E-series resolvins in human leukocytes and murine inflammation. J Clin Invest. 2011;121(2):569–581. doi:10.1172/JCI42545 [PubMed: 21206090]
49. Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, Gronert K. Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. J Exp Med. 2000;192(8):1197–1204. doi:10.1084/jem.192.8.1197 [PubMed: 11034610]
50. Arita M, Ohira T, Sun Y-P, Elangovan S, Chiang N, Serhan CN. Resolvin E1 selectively interacts with leukotriene B4 receptor BLT1 and ChemR23 to regulate inflammation. J Immunol. 2007;178(6):3912–3917. doi:10.4049/jimmunol.178.6.3912 [PubMed: 17339491]
51. Herová M, Schmid M, Gemperle C, Hersberger M. ChemR23, the receptor for chemerin and resolvin E1, is expressed and functional on M1 but not on M2 macrophages. J Immunol. 2015;194(5):2330–2337. doi:10.4049/jimmunol.1402166 [PubMed: 25637017]
52. Scott MJ, Cheadle WG, Hoth JJ, et al. Leukotriene B4 receptor (BLT-1) modulates neutrophil influx into the peritoneum but not the lung and liver during surgically induced bacterial peritonitis in mice. Clin Diagn Lab Immunol. 2004;11(5):936–941. doi:10.1128/CDLI.11.5.936-941.2004 [PubMed: 15358656]
53. Tager AM, Luster AD. BLT1 and BLT2: the leukotriene B(4) receptors. Prostaglandins Leukot Essent Fatty Acids. 2003;69(2–3):123–134. doi:10.1016/S0952-3278(03)00073-5 [PubMed: 12895595]

54. El Kebir D, Gjorstrup P, Filep JG. Resolvin E1 promotes phagocytosis-induced neutrophil apoptosis and accelerates resolution of pulmonary inflammation. Proc Natl Acad Sci USA. 2012;109(37):14983–14988. doi:10.1073/pnas.1206641109 [PubMed: 22927428]
55. Ying W, Wollam J, Ofrecio JM, et al. Adipose tissue B2 cells promote insulin resistance through leukotriene LTB4/LTB4R1 signaling. J Clin Invest. 2017;127(3):1019–1030. doi:10.1172/JCI90350 [PubMed: 28192375]
56. Serhan CN, Chiang N. Resolution phase lipid mediators of inflammation: agonists of resolution. Curr Opin Pharmacol. 2013;13(4):632–640. doi:10.1016/j.coph.2013.05.012 [PubMed: 23747022]
57. Serhan CN, Chiang N, Dalli J, Levy BD. Lipid mediators in the resolution of inflammation. Cold Spring Harb Perspect Biol. 2014;7(2):a016311. doi:10.1101/cshperspect.a016311 [PubMed: 25359497]
58. Tjonahen E, Oh SF, Siegelman J, et al. Resolvin E2: identification and anti-inflammatory actions: pivotal role of human 5-lipoxygenase in resolvin E series biosynthesis. Chem Biol. 2006;13(11):1193–1202. doi:10.1016/j.chembiol.2006.09.011 [PubMed: 17114001]
59. Sima C, Montero E, Nguyen D, et al. ERV1 Overexpression in Myeloid Cells Protects against High Fat Diet Induced Obesity and Glucose Intolerance. Sci Rep. 2017;7(1):12848. doi:10.1038/s41598-017-13185-7 [PubMed: 28993702]
60. Isobe Y, Arita M, Matsueda S, et al. Identification and structure determination of novel anti-inflammatory mediator resolvin E3, 17,18-dihydroxyeicosapentaenoic acid. J Biol Chem. 2012;287(13):10525–10534. doi:10.1074/jbc.M112.340612 [PubMed: 22275352]
61. Krishnamoorthy S, Recchiuti A, Chiang N, et al. Resolvin D1 binds human phagocytes with evidence for proresolving receptors. Proc Natl Acad Sci USA. 2010;107(4):1660–1665. doi:10.1073/pnas.0907342107 [PubMed: 20080636]
62. Bannenberg GL, Chiang N, Ariel A, et al. Molecular circuits of resolution: formation and actions of resolvins and protectins. J Immunol. 2005;174(7):4345–4355. doi:10.4049/jimmunol.174.7.4345 [PubMed: 15778399]
63. Chiang N, Dalli J, Colas RA, Serhan CN. Identification of resolvin D2 receptor mediating resolution of infections and organ protection. J Exp Med. 2015;212(8):1203–1217. doi:10.1084/jem.20150225 [PubMed: 26195725]
64. Clària J, Dalli J, Yacoubian S, Gao F, Serhan CN. Resolvin D1 and resolvin D2 govern local inflammatory tone in obese fat. J Immunol. 2012;189(5):2597–2605. doi:10.4049/jimmunol.1201272 [PubMed: 22844113]
65. Chiang N, Fredman G, Bäckhed F, et al. Infection regulates pro-resolving mediators that lower antibiotic requirements. Nature. 2012;484(7395):524–528. doi:10.1038/nature11042 [PubMed: 22538616]
66. Tang Y, Zhang MJ, Hellmann J, Kosuri M, Bhatnagar A, Spite M. Proresolution therapy for the treatment of delayed healing of diabetic wounds. Diabetes. 2013;62(2):618–627. doi:10.2337/db12-0684 [PubMed: 23043160]
67. Norris P, Arnardottir H, Sanger J, Fichtner D, Keyes G, Serhan C. Resolvin D3 multi-level proresolving actions are host protective during infection. PLEFA. 2018;138:81–89.
68. Winkler JW, Orr SK, Dalli J, et al. Resolvin D4 stereoassignment and its novel actions in host protection and bacterial clearance. Sci Rep. 2016;6:18972. doi:10.1038/srep18972 [PubMed: 26743932]
69. Cherpokova D, Jouvene CC, Libreros S, et al. Resolvin D4 attenuates the severity of pathological thrombosis in mice. Blood. 2019;134(17):1458–1468. doi:10.1182/blood.2018886317 [PubMed: 31300403]
70. Kakazu AH, Thang Luong P, He J, Jun B, Bazan NG, Bazan HEP. A novel resolvin D6 (RvD6) isomer released in tears stimulates corneal innervation and wound healing. Invest Ophthalmol Vis Sci. 7 2019.
71. Balas L, Durand T. Dihydroxylated E,E,Z-docosatrienes. An overview of their synthesis and biological significance. Prog Lipid Res. 2016;61:1–18. doi:10.1016/j.plipres.2015.10.002 [PubMed: 26545300]

72. Serhan CN, Dalli J, Karamnov S, et al. Macrophage proresolving mediator maresin 1 stimulates tissue regeneration and controls pain. FASEB J. 2012;26(4):1755–1765. doi:10.1096/fj.11-201442 [PubMed: 22253477]

73. Neuhofer A, Zeyda M, Mascher D, et al. Impaired local production of proresolving lipid mediators in obesity and 17-HDHA as a potential treatment for obesity-associated inflammation. Diabetes. 2013;62(6):1945–1956. doi:10.2337/db12-0828 [PubMed: 23349501]

74. Crouch MJ, Kosaraju R, Guesdon W, et al. Frontline Science: A reduction in DHA-derived mediators in male obesity contributes toward defects in select B cell subsets and circulating antibody. J Leukoc Biol. 2019;106(2):241–257. doi:10.1002/JLB.3HI1017-405RR [PubMed: 30576001]

75. López-Vicario C, Titos E, Walker ME, et al. Leukocytes from obese individuals exhibit an impaired SPM signature. FASEB J. 2019;33(6):7072–7083. doi:10.1096/fj.201802587R [PubMed: 30840838]

76. Titos E, Rius B, López-Vicario C, et al. Signaling and immunoresolving actions of resolvin D1 in inflamed human visceral adipose tissue. J Immunol. 2016;197(8):3360–3370. doi:10.4049/jimmunol.1502522 [PubMed: 27647830]

77. Miao T, Huang B, He N, et al. Decreased Plasma Maresin 1 Concentration Is Associated with Diabetic Foot Ulcer. Mediators Inflamm. 2020;2020:4539035. doi:10.1155/2020/4539035 [PubMed: 32377160]

78. Pal A, Metherel AH, Fiabane L, Buddenbaum N, Bazinet RP, Shaikh SR. Do Eicosapentaenoic Acid and Docosahexaenoic Acid Have the Potential to Compete against Each Other? Nutrients. 2020;12(12):3718. doi:10.3390/nu12123718

79. Choque B, Catheline D, Rioux V, Legrand P. Linoleic acid: between doubts and certainties. Biochimie. 2014;96:14–21. doi:10.1016/j.biochi.2013.07.012 [PubMed: 23900039]

80. Soler J, Saura P, García-López D, Masgrau L, Lluch JM, González-Lafont À. How Can Linoleic Acid Be the Preferential Substrate of the Enzyme 15-Lipoxygenase-1? A QM/MM Approach. J Phys Chem B. 2016;120(8):1950–1960. doi:10.1021/acs.jpcb.5b09897 [PubMed: 26646740]

81. Marchix J, Catheline D, Duby C, et al. Interactive effects of maternal and weaning high linoleic acid intake on hepatic lipid metabolism, oxylipins profile and hepatic steatosis in offspring. J Nutr Biochem. 2020;75:108241. doi:10.1016/j.jnutbio.2019.108241 [PubMed: 31715523]

82. Stark KD, Van Elswyk ME, Higgins MR, Weatherford CA, Salem N. Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults. Prog Lipid Res. 2016;63:132–152. doi:10.1016/j.plipres.2016.05.001 [PubMed: 27216485]

83. García-Calzón S, Zalba G, Ruiz-Canela M, et al. Dietary inflammatory index and telomere length in subjects with a high cardiovascular disease risk from the PREDIMED-NAVARRA study: cross-sectional and longitudinal analyses over 5 y. Am J Clin Nutr. 2015;102(4):897–904. doi:10.3945/ajcn.115.116863 [PubMed: 26354530]

84. de la Iglesia R, Loria-Kohen V, Zulet MA, Martinez JA, Reglero G, Ramirez de Molina A. Dietary strategies implicated in the prevention and treatment of metabolic syndrome. Int J Mol Sci. 2016;17(11). doi:10.3390/ijms17111877

85. Souza PR, Marques RM, Gomez EA, et al. Enriched Marine Oil Supplements Increase Peripheral Blood Specialized Pro-Resolving Mediators Concentrations and Reprogram Host Immune Responses: A Randomized Double-Blind Placebo-Controlled Study. Circ Res. 2020;126(1):75–90. doi:10.1161/CIRCRESAHA.119.315506 [PubMed: 31829100]

86. Norris PC, Skulas-Ray AC, Riley I, et al. Identification of specialized pro-resolving mediator clusters from healthy adults after intravenous low-dose endotoxin and omega-3 supplementation: a methodological validation. Sci Rep. 2018;8(1):18050. doi:10.1038/s41598-018-36679-4 [PubMed: 30575798]

87. Gao Y, Su J, Zhang Y, et al. Dietary DHA amplifies LXA4 circuits in tissues and lymph node PMN and is protective in immune-driven dry eye disease. Mucosal Immunol. 2018;11(6):1674–1683. doi:10.1038/s41385-018-0070-z [PubMed: 30104626]

88. Polus A, Zapala B, Razny U, et al. Omega-3 fatty acid supplementation influences the whole blood transcriptome in women with obesity, associated with pro-resolving lipid mediator production.

Biochim Biophys Acta. 2016;1861(11):1746–1755. doi:10.1016/j.bbalip.2016.08.005 [PubMed: 27531277]

89. Elajami TK, Colas RA, Dalli J, Chiang N, Serhan CN, Welty FK. Specialized proresolving lipid mediators in patients with coronary artery disease and their potential for clot remodeling. FASEB J. 2016;30(8):2792–2801. doi:10.1096/fj.201500155R [PubMed: 27121596]
90. Markworth JF, Kaur G, Miller EG, et al. Divergent shifts in lipid mediator profile following supplementation with n-3 docosapentaenoic acid and eicosapentaenoic acid. FASEB J. 2016;30(11):3714–3725. doi:10.1096/fj.201600360R [PubMed: 27461565]
91. Zeisel SH. Precision (personalized) nutrition: understanding metabolic heterogeneity. Annu Rev Food Sci Technol. 2020;11:71–92. doi:10.1146/annurev-food-032519-051736 [PubMed: 31928426]
92. Brandão I, Martins MJ, Monteiro R. Metabolically Healthy Obesity-Heterogeneity in Definitions and Unconventional Factors. Metabolites. 2020;10(2). doi:10.3390/metabo10020048
93. Gordon-Larsen P, French JE, Moustaid-Moussa N, et al. Synergizing mouse and human studies to understand the heterogeneity of obesity. Adv Nutr Res. 2021 In press.
94. Sato H, Taketomi Y, Murakami M. Metabolic regulation by secreted phospholipase A2. Inflamm Regen. 2016;36(1):7. doi:10.1186/s41232-016-0012-7 [PubMed: 29259680]
95. Samuelsson B, Dahlén SE, Lindgren JA, Rouzer CA, Serhan CN. Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. Science. 1987;237(4819):1171–1176. doi:10.1126/science.2820055 [PubMed: 2820055]
96. Serhan CN, Chiang N, Dalli J. The resolution code of acute inflammation: Novel pro-resolving lipid mediators in resolution. Semin Immunol. 2015;27(3):200–215. doi:10.1016/j.smim.2015.03.004 [PubMed: 25857211]
97. Börgeson E, Johnson AMF, Lee YS, et al. Lipoxin A4 Attenuates Obesity-Induced Adipose Inflammation and Associated Liver and Kidney Disease. Cell Metab. 2015;22(1):125–137. doi:10.1016/j.cmet.2015.05.003 [PubMed: 26052006]
98. Sansbury BE, Li X, Wong B, et al. Myeloid ALX/FPR2 regulates vascularization following tissue injury. Proc Natl Acad Sci USA. 2020;117(25):14354–14364. doi:10.1073/pnas.1918163117 [PubMed: 32513697]
99. Mathias RA, Pani V, Chilton FH. Genetic variants in the FADS gene: implications for dietary recommendations for fatty acid intake. Curr Nutr Rep. 2014;3(2):139–148. doi:10.1007/s13668-014-0079-1 [PubMed: 24977108]
100. Elfaki I, Mir R, Almutairi FM, Duhier FMA. Cytochrome P450: polymorphisms and roles in cancer, diabetes and atherosclerosis. Asian Pac J Cancer Prev. 2018;19(8):2057–2070. doi:10.22034/APJCP.2018.19.8.2057 [PubMed: 30139042]
101. Distribution of genetic polymorphisms in drug metabolizing gene cytochrome P450 (CYP2C8*3 and CYP2C9*2) in a north indian type 2 diabetes population. ERHM. 2016;1(3). doi:10.14218/ERHM.2016.00004
102. Yamada Y, Matsuo H, Watanabe S, et al. Association of a polymorphism of CYP3A4 with type 2 diabetes mellitus. Int J Mol Med. 2007;20(5):703–707. [PubMed: 17912464]
103. Elfaki I, Almutairi FM, Mir R, Khan R, Abu-duhier F. Cytochrome p450 cyp1b1*2 gene and its association with t2d in tabuk population, northwestern region of saudi arabia. Asian J Pharm Clin Res. 2018;11(1):55. doi:10.22159/ajpcr.2018.v11i1.21657
104. Hoyo-Vadillo C, Garcia-Mena J, Valladares A, et al. Association of CYP2C19 genotype with type 2 diabetes. Health (Irvine, Calif). 2010;02(10):1184–1190. doi:10.4236/health.2010.210174
105. Yu C, Yan Q, Fu C, et al. CYP4F2 genetic polymorphisms are associated with coronary heart disease in a Chinese population. Lipids Health Dis. 2014;13:83. doi:10.1186/1476-511X-13-83 [PubMed: 24886380]
106. Ozbayer C, Kebapci MN, Degirmenci I, Yagci E, Gunes HV, Kurt H. Genetic variant in the 3'-untranslated region of the COX2 gene is associated with type 2 diabetes: A hospital-based case-control study. Prostaglandins Leukot Essent Fatty Acids. 2018;137:39–42. doi:10.1016/j.plefa.2018.07.012 [PubMed: 30293595]
107. Kohsaka S, Volcik KA, Folsom AR, et al. Increased risk of incident stroke associated with the cyclooxygenase 2 (COX-2) G-765C polymorphism in African-Americans: the

Atherosclerosis Risk in Communities Study. Atherosclerosis. 2008;196(2):926–930. doi:10.1016/j.atherosclerosis.2007.02.010 [PubMed: 17350020]

108. Rudock ME, Liu Y, Ziegler JT, et al. Association of polymorphisms in cyclooxygenase (COX)-2 with coronary and carotid calcium in the Diabetes Heart Study. Atherosclerosis. 2009;203(2):459–465. doi:10.1016/j.atherosclerosis.2008.07.018 [PubMed: 18768181]
109. Helgadottir A, Manolescu A, Thorleifsson G, et al. The gene encoding 5-lipoxygenase activating protein confers risk of myocardial infarction and stroke. Nat Genet. 2004;36(3):233–239. doi:10.1038/ng1311 [PubMed: 14770184]
110. Crosslin DR, Shah SH, Nelson SC, et al. Genetic effects in the leukotriene biosynthesis pathway and association with atherosclerosis. Hum Genet. 2009;125(2):217–229. doi:10.1007/s00439-008-0619-0 [PubMed: 19130089]
111. Manev H, Manev R. 5-Lipoxygenase (ALOX5) and FLAP (ALOX5AP) gene polymorphisms as factors in vascular pathology and Alzheimer's disease. Med Hypotheses. 2006;66(3):501–503. doi:10.1016/j.mehy.2005.09.031 [PubMed: 16278051]
112. Šerý O, Hlinecká L, Povová J, et al. Arachidonate 5-lipoxygenase (ALOX5) gene polymorphism is associated with Alzheimer's disease and body mass index. J Neurol Sci. 2016;362:27–32. doi:10.1016/j.jns.2016.01.022 [PubMed: 26944113]
113. Assimes TL, Knowles JW, Priest JR, et al. Common polymorphisms of ALOX5 and ALOX5AP and risk of coronary artery disease. Hum Genet. 2008;123(4):399–408. doi:10.1007/s00439-008-0489-5 [PubMed: 18369664]
114. Zhao J, He Z, Ma S, Li L. Association of ALOX15 gene polymorphism with ischemic stroke in Northern Chinese Han population. J Mol Neurosci. 2012;47(3):458–464. doi:10.1007/s12031-012-9721-9 [PubMed: 22351111]
115. Kaur N, Singh J, Reddy S. Interaction between ALOX15 polymorphisms and coronary artery disease in North Indian population. Clin Exp Hypertens. 2018;40(4):398–405. doi:10.1080/10641963.2017.1384485 [PubMed: 29068244]
116. Xiao WJ, He JW, Zhang H, et al. ALOX12 polymorphisms are associated with fat mass but not peak bone mineral density in Chinese nuclear families. Int J Obes. 2011;35(3):378–386. doi:10.1038/ijo.2010.157
117. López-Vicario C, Rius B, Alcaraz-Quiles J, et al. Association of a variant in the gene encoding for ERV1/ChemR23 with reduced inflammation in visceral adipose tissue from morbidly obese individuals. Sci Rep. 2017;7(1):15724. doi:10.1038/s41598-017-15951-z [PubMed: 29146976]
118. Lohner S, Fekete K, Marosvölgyi T, Decsi T. Gender differences in the long-chain polyunsaturated fatty acid status: systematic review of 51 publications. Ann Nutr Metab. 2013;62(2):98–112. doi:10.1159/000345599 [PubMed: 23327902]
119. English JT, Norris PC, Hodges RR, Dartt DA, Serhan CN. Identification and Profiling of Specialized Pro-Resolving Mediators in Human Tears by Lipid Mediator Metabolomics. Prostaglandins Leukot Essent Fatty Acids. 2017;117:17–27. doi:10.1016/j.plefa.2017.01.004 [PubMed: 28237084]
120. Wang DD, Nguyen LH, Li Y, et al. The gut microbiome modulates the protective association between a Mediterranean diet and cardiometabolic disease risk. Nat Med. 27(2):333–343. doi:10.1038/s41591-020-01223-3

Highlights

- The western diet is generally low in long chain n-3 PUFAs
- Low dietary n-3 PUFAs may contribute to a pro-inflammatory profile
- PUFA-derived SPM levels are unbalanced in chronic inflammatory diseases
- SNPs in enzymes of SPM biosynthesis may have direct clinical translation
- Establishing genetic differences in SPM metabolism will drive precision studies

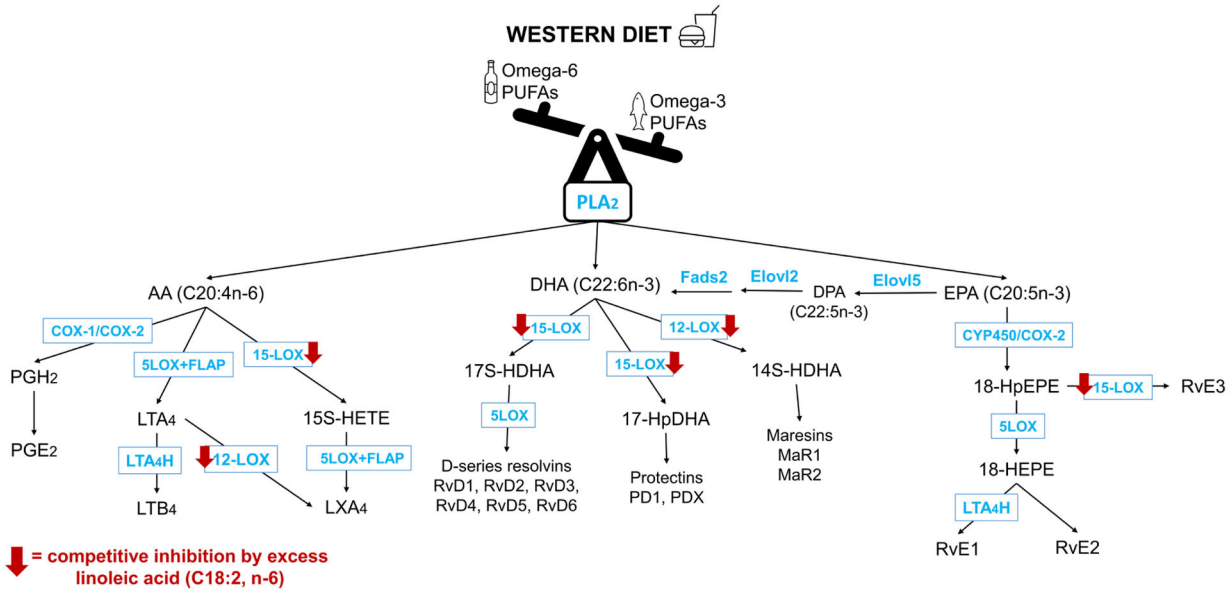

Figure 1: Metabolic pathways by which PUFAs give rise to downstream metabolites of inflammation resolution and their relationship with the obesogenic western diet.

Arachidonic acid (20:4, AA, n-6) gives rise to a range of metabolites such as leukotrienes that drive an inflammatory response (not depicted in detail for simplicity). AA also gives rise to SPMs known as lipoxins. Eicosapentaenoic acid (20:5, EPA, n-3) and docosahexaenoic acid (22:6, DHA, n-3) are precursors for SPMs known as resolvins, protectins, and maresins. Excess consumption of n-6 PUFAs, particularly driven by linoleic acid (18:2, LA, n-6), and low dietary intake of n-3 PUFAs in the western obesogenic diet, may contribute toward a reduction in circulating levels of SPMs. LA may specifically bind key enzymes of SPM biosynthesis. This would limit the ability to resolve inflammation and potentially contribute toward chronic inflammation. In addition, SNPs associated with various enzymes of PUFA metabolism and SPM biosynthesis may be a source of heterogeneity in the concentration of SPMs in the human population.

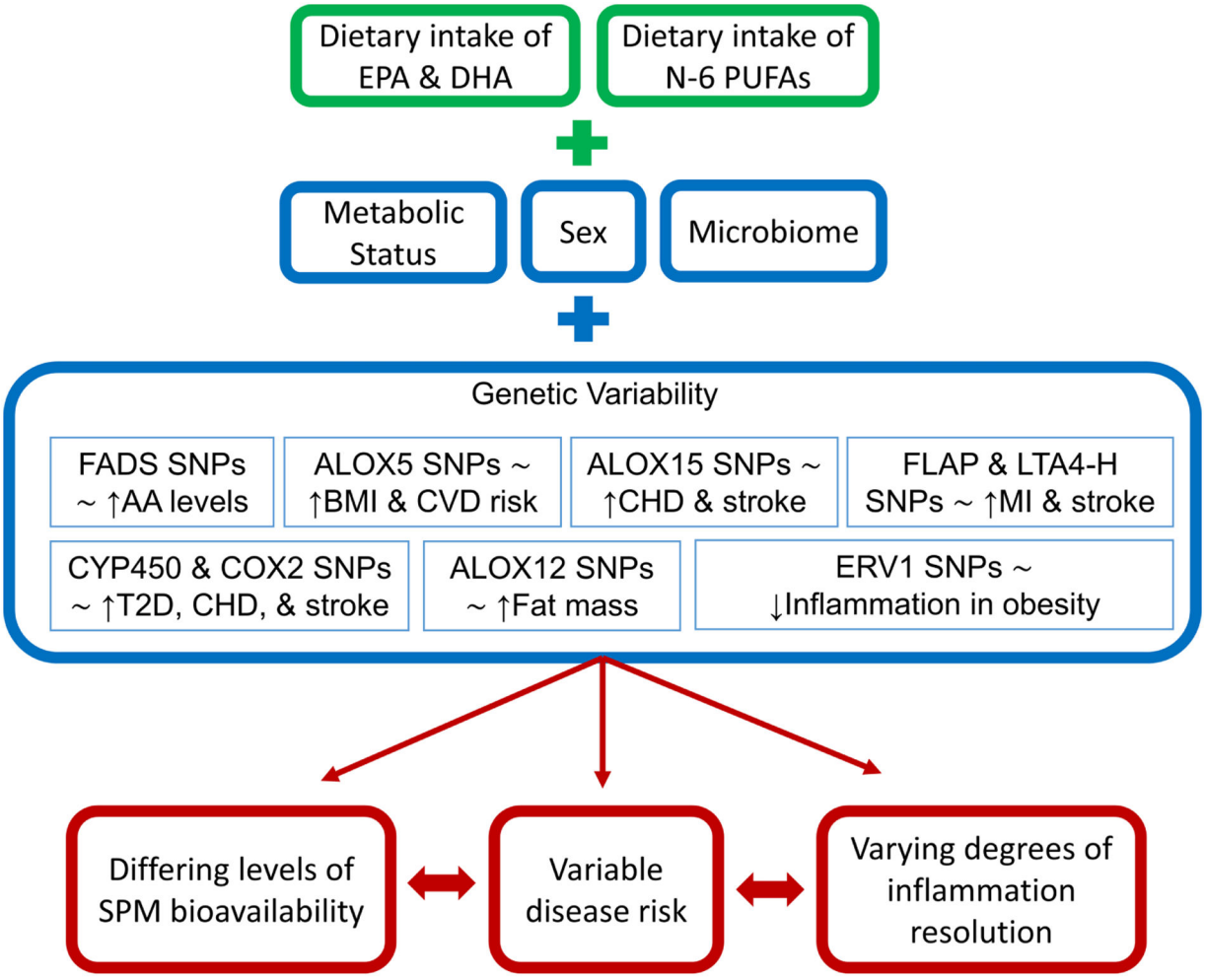

Figure 2: Framework for future precision nutrition studies with dietary EPA and DHA for inflammation resolution.

The depicted framework underscores the need to establish the amount of dietary intake of differing n-3 and n-6 PUFAs and accounting for each individual's metabolic status, microbiome status, and sex. The potential influence of age and environmental exposures on metabolic and microbiome status are not depicted but are also of relevance. In addition, the host genetic background will also impact circulating levels of n-3 and n-6 PUFAs and thereby the synthesis of downstream SPMs. Ultimately, these factors will influence the concentration of SPMs, disease risk and inflammation resolution. For simplicity, we depict a few SNPs associated with PUFA metabolism and their related disease risk phenotypes.