Circulating Polyunsaturated Fatty Acids (PUFAs) as Biological Indicators in Trauma

16

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Contents

Introduction 347
PUFA Biosynthesis and Metabolism 347
The Role of PUFAs in Trauma-Induced Inflammation and Coagulation 350
Specialized Pro-Resolving Lipid Mediators (SPMs) 353
Effects of Dietary Supplementation with PUFAs in Trauma Populations 353
Traumatic Brain Injury (TBI) and Concussions 355
Acute Respiratory Distress Syndrome (ARDS) 356
Orthopedic Trauma and Arthritis 357
Genetic and Epigenetic Determinants of PUFA Biosynthesis and Metabolism 357
Future Directions 361
Applications to Prognosis, Other Diseases, and Conditions 362
Glossary: Mini-Dictionary 362
Key Facts of PUFAs 363
Summary Points 364
References 364

Abstract

Dietary polyunsaturated fatty acids (PUFAs) play a vital role in cell growth, development, and function, especially in maternal and early child development. In particular, long-chain omega-3 (ω-3 or n-3) and omega-6 (ω-6 or n-6) PUFAs (≥20 carbons) like eicosapentaenoic acid (EPA, 20:5n-3), docosahexaenoic acid (DHA, 22:6n-3), and arachidonic acid (ARA, 20:4n-3) orchestrate critical cell membrane functions and trigger several inflammatory responses. With the

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increase in multi-omic-based studies and network-based analyses, the traditional silos for studying inflammation, coagulation, and physiologic responses to trauma as independent factors have been destroyed. In this chapter, we discuss the role PUFAs, specifically ARA, EPA, and DHA, play in modulating levels of inflammation and coagulation following trauma. We discuss what we have learned from past studies that aim to exploit the anti-inflammatory, antithrombotic, and pro-resolving properties of dietary n-3 PUFAs and highlight areas where further studies are needed to optimize the delivery of n-3 PUFAs for trauma care.

Keywords

PUFAs · Arachidonic acid · Omega-3 · EPA · DHA · Eicosanoids · Prostaglandins · Leukotrienes · Thromboxanes · Resolvins · Specialized lipid mediators · Traumatic brain injury · Trauma-induced coagulation · Inflammation

Abbreviations

ALA	Alpha-Linolenic Acid
ALI	Acute Lung Injury
ARA	Arachidonic Acid
ARDS	Acute Respiratory Distress Syndrome
ASCL6	Acyl-CoA Synthetase 6
COX	Cyclooxygenase
CYP450	Cytochrome P450
DGLA	Dihomo-Gamma-Linolenic Acid
DHA	Docosahexaenoic Acid
ELOVL	Elongase of Very Long Chain
EPA	Eicosapentaenoic Acid
FADS	Fatty Acid Desaturase
FC	Free Cholesterol
GLA	Gamma-Linolenic Acid
iPSC	Inducible Pluripotent Stem Cell
LA	Linoleic Acid
LC PUFA	Long-Chain Polyunsaturated Fatty Acid
LOX	Lipoxygenase
LPS	Lipopolysaccharide
LT	Leukotriene
LX	Lipoxin
mTBI	Mild Traumatic Brain Injury
NFLC	Neurofilament Light Chain
NSAID	Nonsteroidal Anti-Inflammatory Drug
PCS	Post Concussion Symptom
PEEP	Positive End-Expiratory Pressure
PG	Prostaglandin
PUFA	Polyunsaturated Fatty Acid
SNP	Single Nucleotide Polymorphism
SPMs	Specialized Pro-resolving Lipid Meditators

TBI	Traumatic Brain Injury
TH	Thromboxane

Introduction

Omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) are essential components of cell membranes and are precursors to several bioactive molecules in the body, regulating blood pressure, inflammation, and coagulopathic responses. There is increasing evidence that suggests omega-3 PUFAs can protect against heart disease, (Aung et al. 2018; Kromhout et al. 2012) traumatic brain injury, concussions (Barrett et al. 2014), prevent diabetes (Lee et al. 2014), and protect against certain kinds of cancer (Marventano et al. 2015; Gleissman et al. 2010; Simopoulos 2006). Understanding how endogenous and dietary PUFAs regulate key cellular events to promote repair and resolution from inflammation can be transformative to a wide array of diseases and health problems, including the treatment and management of acute traumatic injuries. In this chapter, we discuss the fundamental mechanisms regulating PUFA biosynthesis and metabolism and how endogenous and dietary PUFAs affect the inflammatory, coagulopathic, and metabolic responses following a traumatic injury. We also summarize key findings from clinical trials that highlight the importance of monitoring PUFAs as biological indicators for improved recovery after trauma.

PUFA Biosynthesis and Metabolism

Dietary polyunsaturated fatty acids (PUFAs) play a vital role in cell growth, development, and function, especially in maternal and early child development. In particular, long-chain omega-3 (ω-3 or n-3) and omega-6 (ω-6 or n-6) PUFAs ($\geq$20 carbons) like eicosapentaenoic acid (EPA, 20:5n-3), docosahexaenoic acid (DHA, 22:6n-3), and arachidonic acid (ARA, 20:4n-3) orchestrate critical cell membrane functions and trigger several inflammatory responses (Hester et al. 2014; Liu et al. 2012; Weaver et al. 2009). While these long-chain PUFAs (LC-PUFAs) cannot be synthesized de novo in mammals, they can be metabolized from essential dietary PUFAs linoleic acid (LA, 18:2n-6) and alpha-linolenic acid (ALA, 18:3n-3). Endogenous synthesis of these long-chain PUFAs largely occurs in the liver and is regulated by two types of enzymes: (1) fatty acid desaturase (i.e., FADS1 and FADS2) and (2) elongation of very long-chain fatty acids (i.e., ELOVL2 and ELOVL5), as illustrated in Fig. 1 (Zhang et al. 2016). Historically, the two desaturase steps (i.e., FADS1 and FADS2) have been considered the rate-limiting steps in this biosynthetic pathway, but over the past two decades, there is growing awareness that genetic variants influencing any *FADS* and *ELOVL* expression can significantly impact the production of long-chain PUFAs.

The long-chain n-6 PUFA: ARA is arguably the most important of all cellular PUFAs (Surette 2008). When cells are activated by external stimuli, ARA is released

Fig. 1 The PUFA biosynthetic pathway. Essential dietary n-6 PUFA linoleic acid (LA) and n-3 PUFA alpha-linolenic acid (ALA) are converted into respective n-6 (illustrated in orange rectangles) and n-3 (illustrated in blue rectangles) long-chain PUFAs (≥20C) through a series of elongation and desaturation steps. Conversion of the n-6 PUFA arachidonic acid (ARA) into pro-inflammatory eicosanoids (illustrated in red) occurs through the COX, 5-LOX, and 15-LOX enzymes. Conversely, these same pathways are utilized to convert ARA into anti-inflammatory lipoxins and act on n-3 PUFAs to produce the specialized pro-resolving lipid mediators (SPMs) illustrated in purple. Specifically, eicosapentaenoic acid (EPA) is the precursor for E-series resolvins, and docosahexaenoic acid (DHA) is converted by 5-LOX, 15-LOX, and COX-2 into D-series resolvins. The 12- and 15-LOX enzymes act on DHA to produce protectins and maresins, also SPMs. The SPMs formed from DHA are collectively known as docosanoids

from cell membranes and transformed into powerful ARA-derived metabolites through CYP450, cyclooxygenase (COX), and lipoxygenase (LOX) pathways, which provoke a cascade of pro-inflammatory and pro-thrombotic events, including activation of leukocytes and platelets (Hester et al. 2014; Garcia de Acilu et al. 2015; Chilton et al. 2014; Funk 2001; Sergeant et al. 2016; Jamieson et al. 2017). The importance of these pathways is evident by the number of anti-inflammatory drugs that target ARA metabolism (e.g., ibuprofen) and cyclooxygenase-2 (COX-2) inhibitors (e.g., rofecoxib, celecoxib) (Houston and Teach 2004; Loewen 2002). Recent evidence, however, demonstrates that dietary n-3 PUFAs can directly compete with ARA metabolism and ARA-derived metabolites by producing anti-inflammatory, antithrombotic, "pro-resolution" mediators (Weaver et al. 2009; Sergeant et al. 2016; Mathias et al. 2014; Arm et al. 2013). These n-3-derived anti-inflammatory metabolites are often referred to as specialized pro-resolving lipid mediators (SPMs) (Fig. 1) (Serhan and Levy 2018; Serhan et al. 2015a; Serhan et al. 2015b; Colas et al. 2014).

Dietary n-3 PUFAs including ALA, EPA, and DHA have been consistently associated with less inflammation and improved health outcomes. Dietary foods rich in n-3 PUFAs including fish, olive oil, and nuts continue to be recommended to counteract the "inflammatory" effects of n-6 PUFAs and ARA in particular. In fact, there are several studies that show the benefit of a lower n-6/n-3 ratio of PUFAs, such as in the Mediterranean diet which is approximately 3:1, unlike the modern Western diet where the ratio can be up to 15 or 20:1. This is largely due to the fact that n-3 and n-6 PUFAs are metabolized by the same enzymes, so by increasing the consumption of n-3 PUFAs, one can stack the pathway toward the n-3 arm, which subsequently generates more resolvins and docosanoids and less n-6-derived eicosanoids. Yet, the optimal tuning of n-3 PUFAs in one's diet to achieve the best pro-resolving properties remains unknown.

Despite consistent scientific literature supporting the concept that n-6 and n-3 PUFAs and their derived metabolites have different and often opposing effects, supplementation with dietary n-3 PUFAs and fish oil (which is rich in EPA and DHA) has produced mixed results. Some studies reveal benefits in patient outcomes after fish oil consumption, whereas others have failed to show any benefit. As a result, their use in clinical medicine remains controversial. Specific to trauma applications, dietary PUFAs have been administered as an adjuvant therapy to critically injured patients suffering from traumatic brain injury (TBI), concussions, and acute respiratory distress syndrome (ARDS), but there remains no consensus on their use (Garcia de Acilu et al. 2015; Parish et al. 2014; Sabater et al. 2011; Sabater et al. 2008; Li et al. 2015; Kagan et al. 2015; Zhu et al. 2014; Schott and Huang 2012; Rice et al. 2011). Given the heterogeneity of the patient populations and the injury types, as well as the genetic variability influencing PUFA metabolism, there is a need for improved clinical and translational studies that can help unlock the mechanisms by which PUFAs can be used for trauma care. We postulate that there will continue to be confusion in this important area until there is a much better understanding of the immunomodulatory effects of dietary PUFAs both during normal and injured states in humans.

The Role of PUFAs in Trauma-Induced Inflammation and Coagulation

Initiation of the acute inflammatory response after a traumatic injury is a complex process that involves various cell types including macrophages, leukocytes, platelets, endothelial cells, and tissues that experience the damage. Under hemorrhage, the vasculature responds to the change in blood pressure and flow by constricting through the release of vasopressin, epinephrine, and/or norepinephrine. Neutrophils migrate to the site of injury, and there is a storm of inflammatory cytokines that modulate T and B cells to respond to the injury. With the disruption of the vascular endothelium, there is also activation of platelets and formation of thrombus to stop bleeding. Trauma-induced coagulopathy is a common phenomenon, where changes in platelet reactivity, thrombin and fibrinogen production, and endothelial dysfunction affect the patient's response to injury (Cardenas et al. 2014; Chang et al. 2016).

At the cellular level, PUFAs orchestrate critical events in regulating both inflammation and coagulation responses (Fig. 2) (Hester et al. 2014; Liu et al. 2012; Weaver et al. 2009). This is because the cell membrane and more specifically the phospholipid bilayer of cells are rich in PUFAs. Upon damage or disruption, there is a mobilization of PUFAs and lipids, which give rise to the production of a number of biological active metabolites, eicosanoids, and lipoxins regulating inflammatory and anti-inflammatory pathways. For example, cell damage and disruptions to the cell membrane result in the release of free ARA. An increase in free ARA (which is typically low under normal conditions) results in the generation of prostaglandins, prostacyclins, thromboxanes, and leukotrienes. Most commonly, prostaglandin E2 (PGE2), prostaglandin I2, (PGI2), and leukotriene B4 (LTB4) are generated and trigger a series of inflammatory pathways (Fig. 2). The generation of prostaglandins occurs when ARA is metabolized by COX-2 in cells around the site of injury or infection. Prostaglandins are considered to have a pro-inflammatory nature and lead to some of the classic symptoms of inflammation: redness (rubor), swelling (tumor), pain (dolor), and heat (calor). The recruitment of neutrophils to a site of inflammation and subsequent passage across the endothelial barrier has been linked to prostaglandins, specifically PGD2 (Marion-Letellier et al. 2015). Despite this, prostaglandins also paradoxically display an anti-inflammatory nature through the stimulation of lipoxin (LX) productions or the suppression of the adaptive immune system, namely, helper T-cells. The balance between pro-and anti-inflammatory properties can contribute to improved wound healing, whereas imbalance in these two pathways can lead to chronic injury states and nonoptimal wound recovery.

Another type of eicosanoid derived from ARA is thromboxane, which is largely produced by activated platelets. Platelets convert prostaglandin H2 into thromboxane A2 (THA2) which locally promotes vasoconstriction and platelet activation. Therefore, as ARA levels increase, one would expect a concomitant increase in platelet activation and clotting. Given that hypercoagulability is commonly observed after trauma, modulating the level of ARA could be used to regulate platelet

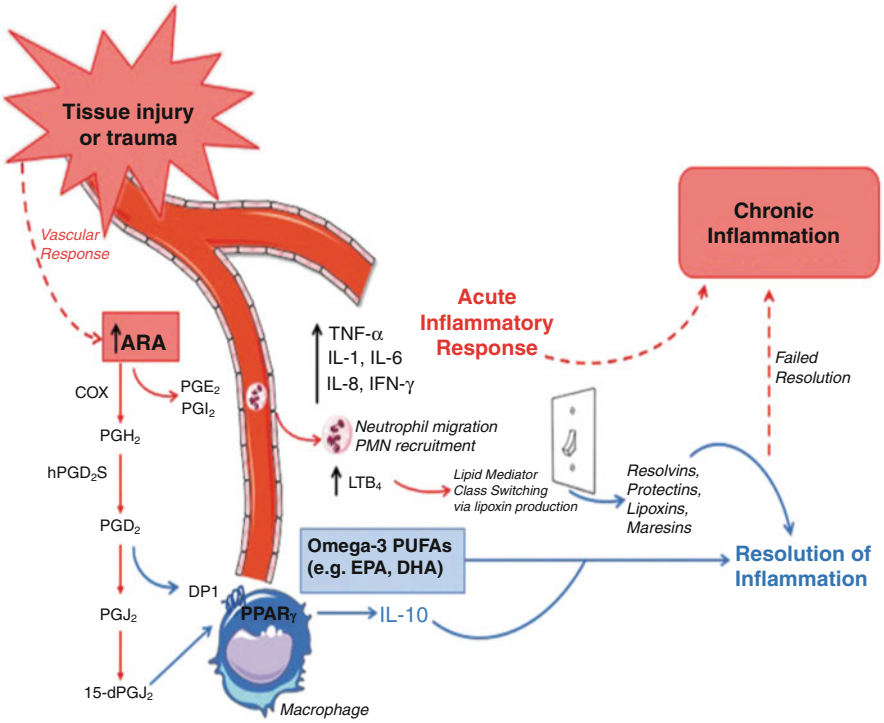

Fig. 2 Illustration of key n-6 and n-3 PUFAs, largely arachidonic acid (ARA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) pathways, involved in acute inflammation post-trauma and the role of lipid mediators in resolution or failure. Initiation of the acute inflammatory response after injury starts with the vascular response, often stimulated by PGE2 and PGI2, and LTB4, which are produced from ARA. The release of ARA from cell membranes is generally dependent on the extent of tissue damage. As ARA levels increase after trauma, there is a concomitant increase in interleukin (IL)-8 and IL-10 levels. IL-8 facilitates in the migration of neutrophils to the site of injury, whereas IL-10, often secreted by macrophages, inhibits inflammation and promotes a M2 phenotype. Therefore, a balance between both the acute inflammatory response and inflammation resolution phases is needed to ensure optimal wound recovery and tissue repair. (Reprinted with permission from Dr. Rahbar and Journal of Neurotrauma)

function. As mentioned earlier, dietary n-3 PUFAs are one possible method to attenuate the pro-inflammatory and pro-thrombotic response of ARA.

Freely circulating ARA can also be converted through LOX-mediated pathways into leukotrienes, a process that occurs primarily in leukocytes. Through the 5-lipooxygenase (5-LOX) pathway, leukotrienes are generated starting with the generation of leukotriene LTA4, leukotriene B4 (LTB4), and leukotriene E4 (LTE4). Leukotrienes are pro-inflammatory cytokines commonly produced by leukocytes and responsible for chronic inflammation in disease states such as asthma and heart disease (Peters-Golden and Henderson Jr 2007). In relation to trauma,

leukotrienes have been implicated in a number of post trauma/hemorrhagic shock states associated with poor patient outcomes such as acute kidney injury, ARDS, and neural inflammation (Corser-Jensen et al. 2014; Nunns et al. 2018; Stringham et al. 2014). Common anti-inflammatories such as NSAIDs or corticosteroids do not affect the 5-LOX pathway and have even been found to increase levels of leukotrienes when administered. Interestingly, dietary n-3 PUFAs have been shown to modulate leukocyte behavior and can be used to reprogram their response to inflammatory stimuli (Calder 2013; Calder 2006). This occurs either directly because n-3 long-chain PUFAs replace ARA as an eicosanoid substrate and inhibit ARA metabolism or indirectly via the change in expression of inflammatory genes through effects on transcription factor activation. Endothelial cells and neutrophils are also capable of producing leukotrienes and also responsive to dietary n-3 PUFAs; for example, DHA can inhibit neutrophil adhesion (Yates et al. 2011). Therefore, there is a delicate balance between n-6 and n-3 PUFA-derived metabolites that regulate the inflammatory and coagulopathic responses after injury. Table 1 provides a list of the ARA-derived eicosanoids and their primary functions in regulating inflammation and coagulation (Peters-Golden and Henderson Jr 2007; Yao and Narumiya 2019; Calder 2020; Braune et al. 2020; Innes and Calder 2018).

Table 1 ARA-derived eicosanoids and their primary functions

Eicosanoid family	Eicosanoid	Function
Prostaglandins	PGH_2	Precursor molecule to downstream PGs
	PGG_2	Precursor to PGH_2
	PGE_2	Endothelial permeability
		Inflammatory response (redness, swelling, pain)
	PGD_2	Produced mainly by mast cells in peripheral tissues
		Sleep regulation
		Allergic reactions
	PGI_2	Vasodilation
		Inhibits platelet aggregation
		Also referred to as prostacyclin
Leukotrienes	LTA_4	Starting molecule of LTx chain
	LTB_4	Immune cell recruitment and activation
		Increases vascular permeability
		Enhances leukocyte adhesion to endothelium
	LTE_4	Alternate product of LTA and most stable cysteinyl leukotriene
		Similar effects as LTB_4
		Upregulates COX-2 expression
		Increases production of PGE_2
Thromboxanes	TXA_2	Vasoconstriction
		Platelet aggregation
		Activation of endothelial inflammation
	TXB_2	Byproduct of TXA_2, inactive

Specialized Pro-Resolving Lipid Mediators (SPMs)

Converse to ARA, the n-3 long-chain PUFAs EPA and DHA are also release from cell membranes after cell damage and trauma. Release of EPA and DHA is subject to similar oxygenase pathways (i.e., COX and LOX) and generates a family of specialized pro-resolving lipid mediators (SPMs), including resolvins, maresins, protectins, and docasanoids.

Resolvins, derived from EPA (E-series) and DHA (D-series), are known to impact inflammation through downregulating the infiltration of macrophages and neutrophils (Abdolmaleki et al. 2020; Chiang and Serhan 2017). D-series resolvins are synthesized in neutrophils and macrophages through the formation of intermediates via COX-2. Specific to trauma, RvD1 has been demonstrated to be protective in the face of ischemia-reperfusion injury through the halting of neutrophil infiltration (Serhan and Levy 2018; Kasuga et al. 2008). Furthermore, the E-series resolving RvE2 is upregulated in hypoxic conditions (Serhan and Levy 2018). Maresins, or macrophage mediators in resolving inflammation, are derived from DHA via 12-LOX (Chiang and Serhan 2017). Marsin 1 (MaR1) has been identified as an activator of the LGR6 receptor, through which it stimulates phagocytosis and phosphorylation of downstream pathways (Chiang et al. 2019). Protectins are produced through 15-LOX oxidation of DHA and have been demonstrated to have neuroprotective effects in the face of TBI and ischemic stroke (Chiang and Serhan 2017). While the exact mechanisms by which n-3 PUFAs and their derived SPMs modulate inflammation are not clearly understood, we have evidence that they indirectly affect macrophage and leukocyte behavior through transcription factor changes and epigenetic modifications (e.g., hypomethylation of key CpG sites). There is a need for more studies to elucidate the exact mechanisms by which dietary PUFAs can be harnessed for immunomodulation.

It is also important to note that there are some byproducts of ARA that also have resolving properties, namely, lipoxins. A complete listing of SPMs has been provided in Table 2. Instead of inhibiting inflammatory action, SPMs actively contribute to the resolution of the inflammatory state and contribute significantly to the acute wound healing process. These and the SPMs produced from n-3 PUFAs are detailed in Table 2 (Serhan and Levy 2018; Innes and Calder 2018; Kwon 2020).

Effects of Dietary Supplementation with PUFAs in Trauma Populations

Traumatic injuries are the leading cause of mortality and morbidity in people between the ages of 1 and 45 years (Campbell et al. 2009; Kauvar et al. 2006). Common complications following a severe injury include acute respiratory distress syndrome (ARDS), sepsis, and multi-organ failure, often associated with a systemic inflammatory response. Therefore, it is not surprising that several attempts have been made to attenuate this inflammatory response via adjuvant and pharmacologic nutrition with n-3 PUFAs. Unfortunately, these clinical trials have led to mixed

Table 2 Specialized pro-resolving lipid mediators and their functions

PUFA precursor	SPM family	SPM	Function
EPA	E-series resolvins	RvE1	Inhibition of neutrophil migration
			Reduction of NF-κβ signaling
			Induces apoptosis of neutrophils
			Controls vascular inflammation
			Pain reduction
		RvE2	Upregulated during hypoxia
			Increases macrophage phagocytosis
			Inhibits neutrophil recruitment
		RvE3	Late-stage resolution
DHA	D-series resolvins	RvD1	Inhibits neutrophil infiltration through endothelium
			Stimulate macrophage phagocytosis
			Pain reduction
		RvD2	Inhibits neutrophil infiltration through endothelium
			Stimulates NO release
			Induces M2 macrophage phenotype
		RvD3	Blocking neutrophil migration
			Increases macrophage phagocytosis
		RvD4	Clot resolution
			Stimulate macrophage phagocytosis
		RvD5	Induces M2 macrophage phenotype
			Regulation of NF-κβ and TNF-α
	Maresins	MaR1	Increases macrophage phagocytosis of apoptotic neutrophils
			Neuroprotection
			Induces M2 macrophage phenotype
			Alleviation of inflammatory pain
	Protectins	PD1	Activated during ischemia-reperfusion injury
			Neuroprotective
			Renal protective
ARA	Lipoxins	LXA_4	Limits neutrophil infiltration and vascular adhesion
			Reduction of vascular inflammation during ischemia
			Modulates memory B-cell responses
		LXB_4	Limits neutrophil infiltration and vascular adhesion
			Stimulate monocyte recruitment and adhesion

findings and confusion (Garcia de Acilu et al. 2015; Li et al. 2015). In this section we summarize some of the main clinical trials that have investigated the use of dietary PUFAs in trauma populations and shed light on potential reasons for failure. We also provide some insights regarding the genetic contributions to PUFA metabolism and areas that future studies should focus on for trauma care.

Traumatic Brain Injury (TBI) and Concussions

Long-chain PUFAs have long been recognized to be essential for brain development and implicated to play a major role in memory and cognitive function (Barrett et al. 2014; Desai et al. 2014; Hasadsri et al. 2013; Cheatham et al. 2011). Long-chain PUFAs are an integral component of neuronal membrane phospholipids and have been shown to demonstrate anti-inflammatory effects. In particular, deficiencies in n-3 LC-PUFAs have been associated with impaired memory, inflammation, and delayed neuronal repair after mTBI (Barrett et al. 2014; Desai et al. 2014; Hasadsri et al. 2013; Wu et al. 2007; Schuchardt et al. 2016; Cooper et al. 2015). A metabolomic panel tested by Hogan et al. found that in the case of TBI within rodent models, free PUFA levels of ARA, DPA, and DHA were significantly higher compared to sham groups and that levels of oxidized PUFAs dropped (Hogan et al. 2018). This indicates that PUFAs have a notable role in the inflammatory and recovery process following TBI and could act as useful biomarkers in the diagnosis of TBI and mTBI.

LC-PUFAs have been recognized to be vitally important for brain development in early childhood. Data from the Rahbar research lab and others have shown that LC-PUFAs may continue to play a critical role in neuronal development and repair beyond these early years (Miller et al. 2016; Gow and Hibbeln 2014; Gow et al. 2009). Deficiencies in LC-PUFAs have been associated with several neuropsychiatric disorders, attention deficit disorders, lapses in memory, and impaired cognition (Strike et al. 2016; Eriksdotter et al. 2015; Agrawal and Gomez-Pinilla 2012; Boucher et al. 2011; Brookes et al. 2006). Alternatively, higher n-3 LC-PUFA levels have been shown to be associated with improved cognition, memory, reduced inflammation, and neuroprotective properties (Barrett et al. 2014; Hester et al. 2014; Cooper et al. 2015; Strike et al. 2016; Kulzow et al. 2016; Frensham et al. 2012).

As a result, the use of n-3 LC-PUFA supplements, such as DHA or fish oil, has been suggested for improving outcomes and mitigating post-concussion symptoms (PCS). Recently, Oliver et al. observed marked increases in circulating neurofilament light chain (NFLC) peptide levels in starting football college athletes and striking reductions in NFLC after taking n-3 LC-PUFA supplements over the duration of a single season (Oliver et al. 2016a; Oliver et al. 2016b). This data implies that LC-PUFAs and/or its metabolites may be linked to neuronal injury biomarkers and inflammation during mTBI recovery and PCS. A recent meta-analysis by Patch et al. found that in a number of rodent models ($n = 18$) that a diet supplemented with n-3 PUFAs led to statistically significant improvements in cognitive abilities and lowered signs of inflammation in rats with induced mTBI (Patch et al. 2021).

Conversely, there is literature reporting no effect of n-3 LC-PUFA supplements on patient outcomes and PCS (Rice et al. 2011; Phillips et al. 2015). There is even evidence that n-3 PUFA supplements may be detrimental to patient health when combined with prescribed blood thinners and could lead to excessive hemorrhage, but such cases are extremely rare and would require much more extensive investigation to indicate that PUFA supplements were the cause (Gross et al. 2017). A recent study by Fernandez et al. revealed that acyl-coA synthetase 6 (Acsl6) is

needed for the retention of DHA within the rodent brain (Fernandez et al. 2021). Hence, we believe these mixed findings from the clinical trials are due to our rudimentary understanding of the complex metabolic and lipidomic responses to concussive injuries and mTBIs and often the exclusion of genetic/epigenetic factors. It is likely that a "one-size-fits-all" approach is not sufficient. This is explained in greater detail at the end of this chapter.

Acute Respiratory Distress Syndrome (ARDS)

Acute lung injury (ALI) and its more severe form acute respiratory distress syndrome (ARDS) are inflammatory disorders characterized by decreased lung compliance, hypoxemia, capillary leakage, and pulmonary edema (Butt et al. 2016; Parekh et al. 2011; Rubenfeld and Herridge 2007). This disorder develops as a result of trauma, sepsis, pneumonia, and a number of other local or systemic factors and is associated with a high rate of morbidity and mortality in patients who develop the disorder. In the United States, roughly 150,000 patients develop ARDS per year, and despite improvements in treatment focused on continuous positive end-expiratory pressure (PEEP) and the administration of corticosteroids, the mortality rate for patients with ARDS is still high at roughly 40% (Butt et al. 2016; Parekh et al. 2011; Rubenfeld and Herridge 2007; Zhou et al. 2017). In patients suffering from ARDS and those at risk of developing ARDS, Kumar et al. found that circulating n-3 and n-6 PUFA levels were significantly lower compared to controls (Kumar et al. 2000). Omega-3 PUFAs have repeatedly demonstrated immunomodulatory and anti-inflammatory effects. Due to these properties, they have been investigated as possible treatments for patients with ALI or ARDS to mixed results.

The OMEGA trial was a large Phase 3 clinical trial with 44 enrolling hospitals of the NHLBI ARDS Clinical Trials Network. They hypothesized that enteral supplementation of n-3 PUFAs EPA and DHA, n-6 PUFA gamma-linolenic acid (GLA), and antioxidants would improve patient outcomes and reduce time on the ventilator (i.e., improvement in VENT-free days) (primary outcome) in ARDS patients. However, the study was terminated when an interim analysis showed no difference in VENT-free days between the treatment and placebo groups ($N = 272$ enrolled). Plasma, urine, and DNA samples from this trial are available for secondary analysis and currently stored at the NIH BioLINCC repository.

In some cases, it was found that supplementation of n-3 PUFAs was actually detrimental to favorable patient outcomes (Rice et al. 2011; Stapleton et al. 2011). These studies did note however that the methods of delivery for their dietary supplements differed compared to those that found more favorable results. These studies utilized a bolus delivery method as opposed to continuous enteral feeding. The possible difference in application of PUFA supplements for patients with ARDS could be a contributing factor to the mixed results characterizing the past decade of research into PUFA-based dietary treatment of ARDS. Different types and rates of deliveries could disrupt the balance of pro- and anti-inflammatory markers within the patient, both of which are important to recovery.

Despite these findings, research into possible mechanisms and applications using PUFA dietary supplements for patients with ALI and ARDS is continuing. Numerous studies have found that n-3 PUFA diets have decreased mortality compared to controls in murine models simulating sepsis-induced ARDS (Rice et al. 2011; Chang et al. 2017; Zhu et al. 2020). Zhu et al. found that in the case of intestinal reperfusion injury, pretreatment with n-3 PUFAs led to higher survivability in murine models. Perhaps the addition of n-3 PUFA supplements as a treatment for patients with ALI/ARDS is time-sensitive and possibly more effective based on the form of fatty acid and lipid emulsion provided. There is a need for more focused studies on better identifying the optimal timing, dosing, and method of administration of dietary PUFAs for ALI/ARDS patients. Additionally, other studies have found that in order to gain anti-inflammatory effects, proper ratios of n-6 and n-3 PUFAs need to be maintained rather than just supplementing with n-3 PUFAs alone (Chang et al. 2017). Considering that a large fraction of ARDS cases are caused as a secondary effect of sepsis, this could make sense. Unnecessary suppression of the immune response could limit the body's ability to combat the infection. Conversely, allowing rampant inflammation within the lungs could lead to ARDS. These conflicting findings between animal models and clinical studies are most likely due to different genetic factors within the observed populations and we discuss this in greater detail in the subsequent sections.

Orthopedic Trauma and Arthritis

Dietary PUFAs have also been investigated is bone health and repair following fracture. A 2015 study by Harris et al. concluded that n-3 PUFA consumption in late life corresponded to a decrease in fracture risk in older men as well as women in the middle stages of their lives (Harris et al. 2015). More recently, PUFA ratios and concentrations have been investigated as biomarkers in patients undergoing surgery to repair femoral neck fractures. It was found that both n-6 and n-3 PUFA levels were lower compared to controls within hours following both the initial fracture and surgery (Arsic et al. 2020a). The decrease in n-6 levels is thought to result from the increased generation of prostaglandins which are released in response to injury and are created as previously discussed. Specifically, PGE2 is important in regulating bone resorption and formation depending on the circulating levels of the molecule. N-3 PUFAs are important in the generation of SPMs which play a role in mitigating prostaglandin activity as well as in the promotion of insulin-like growth factors and in calcium absorption, a key process in bone repair.

Genetic and Epigenetic Determinants of PUFA Biosynthesis and Metabolism

One potential explanation for the mixed results regarding the efficacy of dietary PUFAs in human clinical trials is the lack consideration of genetic variants. Over the past two decades, there is growing evidence that the production of long-chain

PUFAs is considerably affected by genetic variants located within the fatty acid desaturase (*FADS*) gene cluster (11q12–13.1) and elongation of very long-chain fatty acids 2 (*ELOVL2*) (6p24.2) and *ELOVL5* (6p12.1) (Hester et al. 2014; Chilton et al. 2014; Mathias et al. 2014; Cormier et al. 2013; Sergeant et al. 2012; Glaser et al. 2010). These FADS and ELOVL variants have been shown to be associated not only with circulating and tissue levels of PUFAs but also complex diseases (Mathias et al. 2014; Cui et al. 2016; Mathias et al. 2011a; Howard et al. 2014).

The desaturase enzymes encoded by the *FADS* gene cluster have long been recognized as the rate-limiting steps in long-chain PUFA biosynthesis. Comprising of three genes (*FADS1*, *FADS2*, and *FADS3*), this is a region of high linkage disequilibrium (LD) (Mathias et al. 2014; Rahbar et al. 2017). There have been ~25 studies (Malerba et al. 2008; Martinelli et al. 2008; Rzehak et al. 2009; Schaeffer et al. 2006; Mathias et al. 2011b; Mathias et al. 2010; Sergeant et al. 2012; Xie and Innis 2008; Xie and Innis 2009; Porenta et al. 2013; Hong et al. 2013; Harsløf et al. 2013; Li et al. 2013; Morales et al. 2011; Gillingham et al. 2013; Freemantle et al. 2012; Lattka et al. 2013; Lattka et al. 2011; Steer et al. 2012; Koletzko et al. 2011; Kwak et al. 2011; Rzehak et al. 2010; Bokor et al. 2010) confirming that *FADS* variants account for large variation in circulating and cellular long-chain PUFA levels. New studies from the Rahbar lab and others indicate that the methylation status of specific CpG sites within the *FADS* cluster (specifically within the *FADS2* promoter and a region with between *FADS1* and *FADS2* with an enhancer signature) impacts the transcription of *FADS* cluster genes, PUFA metabolism, and, in one study, both immediate and delayed memory performance in toddlers (Cheatham et al. 2015; Hoile et al. 2014; Lupu et al. 2015). Taken together, these studies suggest that *FADS* genetic and epigenetic factors may not only contribute to differential levels of PUFAs and metabolites but also inadvertently be associated with altered inflammatory and physiologic responses. Moreover, these differential PUFA levels and genetic variants and epigenetic modifications may be important confounding variables impacting the efficacy of n-3 PUFA supplements, particularly in ethnically diverse populations where the allele frequencies are drastically different.

The most prominently studied of these variations is the single-nucleotide polymorphism (SNP) rs174537, which is located downstream of FADS1 on chromosome 11. There are three genotypes associated with rs174537, GG, GT, and TT and the frequency with which each genotype appears in the population is dependent on racial/ethnic background and geographical location, as illustrated in Fig. 3 (Mathias et al. 2014). For example, within those of European ancestry, the G allele frequency is 0.651, while the T allele frequency is 0.349. For those of African ancestry, the G and T allele frequencies are 0.975 and 0.025, respectively, while those of American ancestry display frequencies of 0.412 and 0.588, respectively (Mathias et al. 2011b). Genotype at rs174537 has been linked to circulating and tissue PUFA levels, as well as eicosanoid formation. Specifically, individuals who carry the major allele (i.e., GG and GT) are rapid metabolizers of n-6 PUFAs and convert DGLA to ARA at a faster rate than those homozygous with the minor allele (i.e., TT), and therefore we hypothesize that they may be more susceptible to a pro-inflammatory response due to elevated levels of ARA. As genotype is highly dependent upon race and

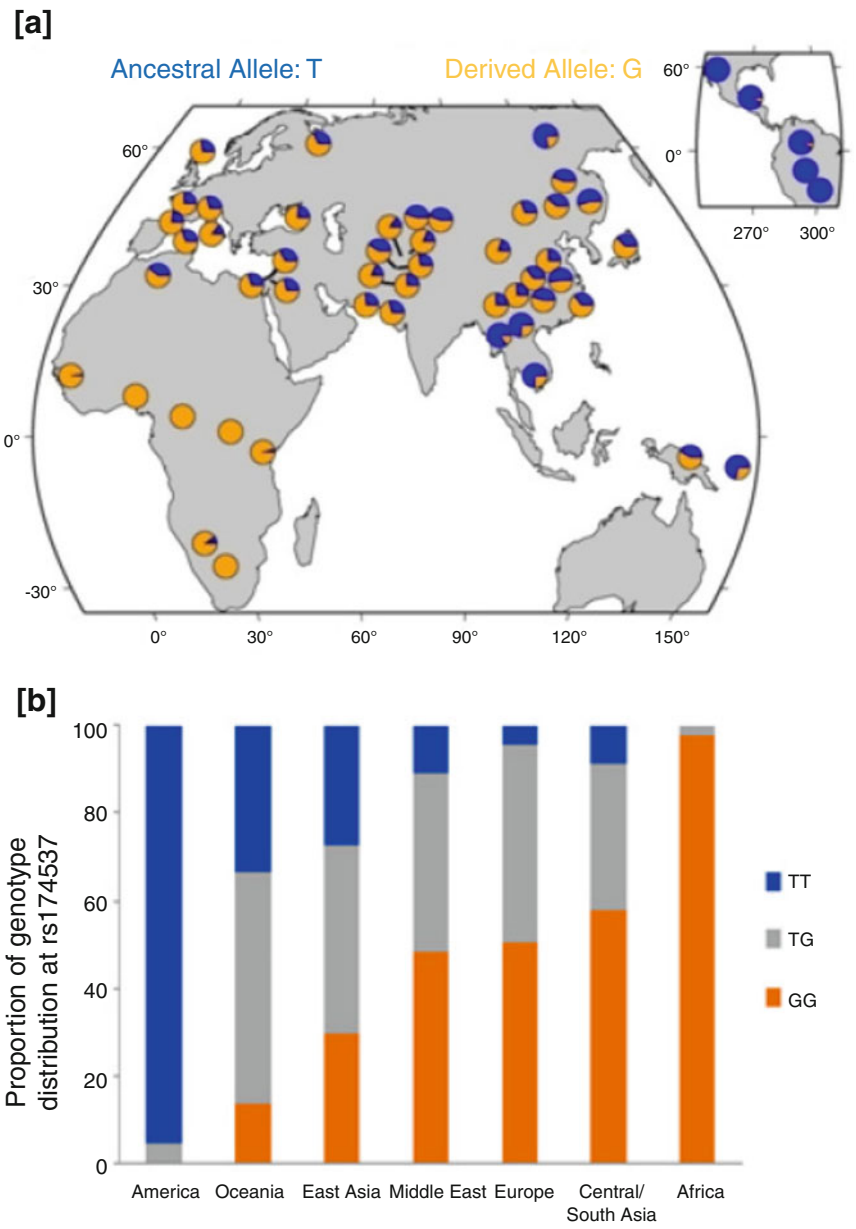

Fig. 3 Allele frequency of SNP rs174537 globally. The allele frequency of rs174537 varies tremendously by geographic and racial/ethnic populations. Individuals with African ancestry are predominantly homozygous with the major allele (i.e., GG), whereas individuals from Peru and South American ancestry are largely homozygous with the minor allele (i.e., TT). Caucasian and European ancestral populations tend to exhibit a more balanced allele frequency distribution. The reason for this variation is presumed to be an evolutionary trait from the population's primary diet,

geographical location, this is one mechanism through which race-based health disparities could be exacerbated (Chilton et al. 2014).

In particular, the OMEGA randomized clinical trial evaluated the effect of enteral dietary PUFA blend (GLA + EPA + DHA) in a cohort of critically ill patients with ARDS and was terminated early due to futility (Rice et al. 2011). One potential explanation for these unsatisfactory results may be due to the genetic variability within a population impacting their PUFA metabolic conversion capacities since both n-6 and n-3 PUFA was included in the blend. Given that *FADS* variants contribute to differential PUFA levels, we postulate that they may also inadvertently be associated with altered responses to dietary supplements and subsequent inflammation and coagulation after injury via the generation of PUFA-derived bioactive metabolites. In a secondary analysis of the OMEGA trial, Dosso et al. discovered that rs174537 had a significant impact on circulating DHA levels and urinary isoprostane levels (Dosso et al. 2020). While they were unable to detect a statistically significant effect of genotype at rs174537 on patient outcomes due to the relatively small patient population, they did observe some differences between African American and Caucasians warranting the need for larger ethnically diverse studies that can investigate the gene-diet interactions on inflammatory outcomes.

Another confounding factor influencing the mixed results in clinical studies is the use of dietary n-3 PUFAs in isolation vs. in dietary blends that include n-6 PUFAs like gamma-linolenic acid (GLA). A recent prospective clinical trial performed by the Chilton group has provided additional validation to these gene-diet interactions in healthy subjects. Supplementation with the n-6 PUFA GLA results in highly variable responses, and the varied efficiency of *FADS1* associated with genotype at rs174537 is proposed as the reason for this inconsistency. Upon supplementation with GLA, the PUFA is converted rapidly into DGLA through the ELOVL5 enzyme; FADS1 converts DGLA to the pro-inflammatory ARA at variable rates. The Chilton group explored the variable effects of GLA supplementation by feeding soybean oil (50% LA) or borage oil (37% LA and 23% GLA) to a cohort of healthy non-Hispanic white individuals genotyped at rs174537. After 4 weeks of dietary supplementation, analysis of circulating PUFA levels indicated that GLA feeding altered circulating levels of ARA and DGLA in a genotype-dependent manner; TT individuals had increase fold changes of DGLA in response to 4 weeks of GLA supplementation, which is consistent with decreased *FADS1* activity. Additional study is necessary to identify the links between this variability in PUFA levels and eicosanoid production, which directly impacts the inflammatory response (Sergeant et al. 2020).

Fig. 3 (continued) such that those who primarily eat fish and vegetables are prone to be more TT rather than those who eat red meat and favor a GG genotype. This genetic variation may potentially explain some of the health disparities in drug studies (e.g., COX inhibitors) and chronic diseases that are dependent on ARA and PUFA metabolism. (Reprinted with permission from Drs. Sergeant, Chilton and BMC Genomic Data)

Future Directions

As we look to the future, there is a need for larger clinical studies that include multi-omic biomarkers inclusive of genomic, metabolomic, lipidomic, and proteomic data. Clinical trials that consider evaluating the use of dietary PUFAs must perform their analyses stratified by race and adjust for genetic variation. For too long, we have ignored the role of ethnicity and gender on the effectiveness of nutritional supplements. While randomized clinical trials will continue to be a gold standard to evaluate efficacy of these dietary supplements, there is a need for alternative platforms that can assess the human response to PUFAs after injury.

A major contributor to our poor understanding of the complex human PUFA metabolic pathway and its implications on inflammation and immunity is the heavy reliance on single cell in vitro systems, or in vivo animal models, that have failed to translate to humans. For example, studies that evaluate PUFA exposure on isolated macrophages or in mouse models do not replicate human metabolism (Gutierrez et al. 2019; Kiecolt-Glaser et al. 2016). We suggest that using 3D tissue engineering and organoid-based platforms where primary human cells or inducible pluripotent stem cells (iPSCs) are cultured can be used to study the underlying mechanisms by which dietary PUFAs exert protective effects.

It is also important to consider that PUFAs and dietary supplements may also be affected by other factors such as age, obesity, diabetes, and other concomitant diseases. Thus, there is a need for future basic science and translational studies to consider the effects of these comorbidities in the altered response not only to trauma but dietary PUFA supplementation after injury. For example, the OXBIO trial was designed to study the effects of marine- and plant-sourced n-3 PUFAs on inflammation in female obese populations (Rodway et al. 2021; Hatchimonji et al. 2020).

Finally, while there have been over 25 studies (Malerba et al. 2008; Martinelli et al. 2008; Rzehak et al. 2009; Schaeffer et al. 2006; Mathias et al. 2011b; Mathias et al. 2010; Sergeant et al. 2012; Xie and Innis 2008; Xie and Innis 2009; Porenta et al. 2013; Hong et al. 2013; Harsløf et al. 2013; Li et al. 2013; Morales et al. 2011; Gillingham et al. 2013; Freemantle et al. 2012; Lattka et al. 2013; Lattka et al. 2011; Steer et al. 2012; Koletzko et al. 2011; Kwak et al. 2011; Rzehak et al. 2010; Bokor et al. 2010) confirming that fatty acid desaturase (*FADS*) variants account for a large variation in circulating and cellular PUFA levels in humans, highlighting the variability in PUFA metabolism not only by genetic variants but also racial/ethnic backgrounds, there are variants within *ELOVL* that may be just as important. Based on the current state of literature, differential PUFA levels (especially ARA and DHA levels) are driving the chronic inflammatory processes. Thus, genetic variants influencing these PUFA levels may be important confounding variables impacting the efficacy of n-3 PUFA supplements in human studies, especially in ethnically diverse populations. Ultimately, we need more multidisciplinary teams that can bridge the gaps between nutrition, metabolism, inflammation, coagulation, and trauma to identify new treatment and management strategies for trauma populations.

Applications to Prognosis, Other Diseases, and Conditions

In this chapter we discuss how circulating and tissue levels of PUFAs can be used to monitor the inflammatory and coagulopathic response to traumatic injuries. One of the primary proposed uses for PUFAs in terms of disease prognosis is measuring their relative balance following trauma. As we will discuss, measuring the levels of n-3, n-6, and the n-3/n-6 PUFA ratio in a patient's blood has been found to be a useful metric in predicting outcomes for a variety of different trauma-induced states (Colas et al. 2014; Chang et al. 2017; Arsic et al. 2020b). An imbalance toward the n-6 PUFA side could be indicative of a chronic inflammatory state, whereas a more n-3 heavy or balanced ratio of circulating PUFAs could be a sign of better outcomes and less chance of recurrent disease and comorbidity. Analysis of PUFAs as biomarkers is still a relatively new field, so there is no definitive guide to how to interpret circulating PUFA levels. This is further complicated by the fact that n-6 PUFAs do not fit neatly into an exclusively pro-inflammatory state. For instance, ARA predominantly generates prostaglandins which are pro-inflammatory but is also capable of being converted into the lipoxin molecule class which serves in an anti-inflammatory role. More in-depth metabolomic and lipidomic analyses are needed to determine which PUFA-derived biomarkers are most predictive of patient status and outcomes.

In terms of applications outside of trauma, PUFAs have been identified as important biomarkers in evaluating heart disease, neurodegenerative disorders, and cancer. The importance of chronic inflammation in the development of several chronic disease states has begun to be researched more extensively within the past 10 years and has been hypothesized to contribute to higher incidence of these chronic disease states. Higher circulating of n-3 PUFAs and their subsequent role in the generation of anti-inflammatory biomolecules generally correlates with lower incidence of chronic illness (Marventano et al. 2015; Calder 2006; Gu et al. 2015).

Glossary: Mini-Dictionary

Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) – inflammatory illness group categorized by inflammation in the alveoli and decreased oxygen exchange. These conditions occur in response to sepsis or traumatic injury.

Arachidonic acid (ARA, 20:4n-6) – a long-chain omega-6 polyunsaturated fatty acid containing 20 carbons. It is synthesized from linoleic acid and acts as a precursor molecule for several proinflammatory molecules, namely, prostaglandins, thromboxanes and leukotrienes.

Cyclooxygenase pathway (COX) – pathway that converts ARA into prostaglandins. A common target for anti-inflammatory drugs.

Docosahexaenoic acid (DHA, 22:6n-3) – a long-chain omega-3 polyunsaturated fatty acid consisting of 22 carbons. Can be synthesized from α-linolenic and is a precursor molecule for several anti-inflammatory biomolecules.

Eicosanoids – A family of biomolecules derived from arachidonic acid and other similar 20 carbon PUFAs. Eicosanoids serve primarily as signaling molecules multiple pathways such as inflammation, immune responses, pain, and many more.

Eicosapentaenoic acid (EPA, 20:5n-3) – a long-chain omega-3 polyunsaturated fatty acid consisting of 20 carbons. Can be synthesized from α-linolenic acid and is a precursor molecule for several anti-inflammatory biomolecules.

Fatty acid desaturase (FADS) – enzymes responsible for creating double bonds in fatty acids.

Leukotrienes (LTEs) – inflammatory molecules derived from ARA processed by the LOX pathway.

Lipoxins – an abbreviation of lipoxygenase interaction products. Lipoxins are biomolecules within the specialized pro-resolving mediator family. They act as signaling molecules and exhibit an anti-inflammatory effect.

5-Lipoxygenase pathway (5-LOX) – pathway by which ARA is synthesized into leukotrienes.

Polyunsaturated Fatty Acid (PUFA) – any fatty acid with more than one double bond within their backbone structure.

Prostaglandins – a family of ARA-derived biomolecules. Generally act as pro-inflammatory molecules.

Single nucleotide polymorphism (SNP) – the substitution of a single nucleotide at a specific point in the genome.

Thromboxanes – an eicosanoid family molecule. Thromboxanes play an important role in platelet activation and vasoconstriction.

Key Facts of PUFAs

- PUFAs are significant components of cellular membranes and important substrates in the synthesis of numerous signaling molecules.
- Dietary PUFAs, namely, ARA, EPA, and DHA play a critical role in early development of cell and brain tissues (e.g., maternal and prenatal health).
- The liver is the primary organ responsible for PUFA biosynthesis and metabolism.
- Omega-6 (n-6) PUFAs are generally pro-inflammatory and are precursors of biologically active metabolites that exert pro-inflammatory and pro-thrombotic effects.
- Omega-3 (n-3) PUFAs are generally anti-inflammatory and are precursors of biologically active metabolites that aid in the resolution of inflammation.
- ARA and associated pathways are common targets for anti-inflammatory drugs.
- Disruptions in the PUFA metabolism and biosynthesis can lead to serious chronic diseases and impairments in cellular function.

Summary Points

- PUFAs are a relatively new and promising field of investigation for biomarkers and are hypothesized to play an important role in multiple conditions and disease states.
- PUFAs play a significant role in the onset and resolution of inflammation, immune response, and clotting following trauma.
- Treatments using dietary n-3 PUFAs have shown promise in the treatment of injury following trauma in animal models and some clinical trials but have remained inconclusive in clinical trials.
- Balancing ratios of n-3 to n-6 PUFAs may be more important than just supplementing one and removing the other for the resolution of inflammation.
- Investigation into the role of genetic variants in the processing of PUFAs in different populations could explain the variation in effectiveness of treatment using n-3 PUFA supplements. This investigation could help unlock potential health disparities in response to PUFA supplementation.
- Genotype at rs174537 is associated with variable clinical outcomes in response to treatment using dietary PUFA supplementation. This is due to differing levels of enzymatic efficiency based on haplotype and how that affects downstream production of either pro- or antiinflammatory biomolecules.

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