Inflammaging

Helping to Resolve Inflammation

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Vanessa Pavey, ND

Education Scientist

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What is Inflammaging?

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Advances in Geroscience: Impact on Healthspan and Chronic Disease Perspective

Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases

Claudio Franceschi[1,2] and Judith Campisi[3,4]

[1]DIMES, Department of Experimental, Diagnostic and Specialty Medicine and CIG, Interdepartmental Center "Luigi Galvani", University of Bologna, Italy.
[2]IRCCS Institute of Neurological Sciences, and CNR-ISOF, Bologna, Italy.
[3]Buck Institute for Research on Aging, Novato, California.
[4]Life Sciences Division, Lawrence Berkeley National Laboratory, California.

Address correspondence to Claudio Franceschi, MD, DIMES, Department of Experimental, Diagnostic and Specialty Medicine and CIG, Interdepartmental Center "Luigi Galvani", University of Bologna, Via S. Giacomo 12, 40126 Bologna, Italy. Email: claudio.franceschi@unibo.it

Human aging is characterized by a chronic, low-grade inflammation, and this phenomenon has been termed as "inflammaging." Inflammaging is a highly significant risk factor for both morbidity and mortality in the elderly people, as most if not all age-related diseases share an inflammatory pathogenesis. Nevertheless, the precise etiology of inflammaging and its potential causal role in contributing to adverse health outcomes remain largely unknown. The identification of pathways that control age-related inflammation across multiple systems is therefore important in order to understand whether treatments that modulate inflammaging may be beneficial in old people. The session on inflammation of the Advances in Geroscience meeting held at the National Institutes of Health/National Institute on Aging in Bethesda on October 30 and 31, 2013 was aimed at defining these important unanswered questions about inflammaging. This article reports the main outcomes of this session.

Key Words: Inflammaging—Biomarkers—IL-6.

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Decision Editor: Rafael de Cabo, PhD

"Inflammaging" describes the low-grade, chronic, systemic inflammation in aging in the absence of overt infection

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Why Care About Inflammation?

- **Chronic inflammation is associated with degenerative aging**
  - Cancer
  - Autoimmunity
  - Arthritis
  - Atherosclerosis
  - Dementia
- As we chronologically move forward, our ability to resolve inflammation diminishes

The Journals of Gerontology: Series A, Volume 69, Issue Suppl_1, 1 June 2014, Pages S4–S9
Frontiers in Immunology: 2018 Apr 9;9:586. doi: 10.3389/fimmu.2018.00586
The Journal of Immunologyg: 2014 Oct 15; 193 (8), doi: 10.4049/jimmunol.1401313

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What is Inflammation?

- Inflammation is an ***important & complex*** response to things that can harm us…
  - Infection
  - Trauma
  - Toxins / Irritants
- Inflammation is like a tornado
- Acute versus Chronic Inflammation
  - Acute lasts minutes to days
  - Subacute lasts two to six weeks
  - Chronic lasts months to years

Chronic Inflammation. Roma Pahwa; Anand Singh; Ishwarlal Jialal. StatPearls Publishing. 2019

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Acute Inflammation is GOOD Inflammation

Aulus Cornelius Celsus, Roman Encyclopedist of 1st century A.D, developed the "Celsus Tetrad of Inflammation"

Rubor (redness)

Calor (heat)

Dolor (pain)

Tumor (swelling)

Yale Journal of Biology and Medicine: 2011 Mar; 84 (1): 64-65

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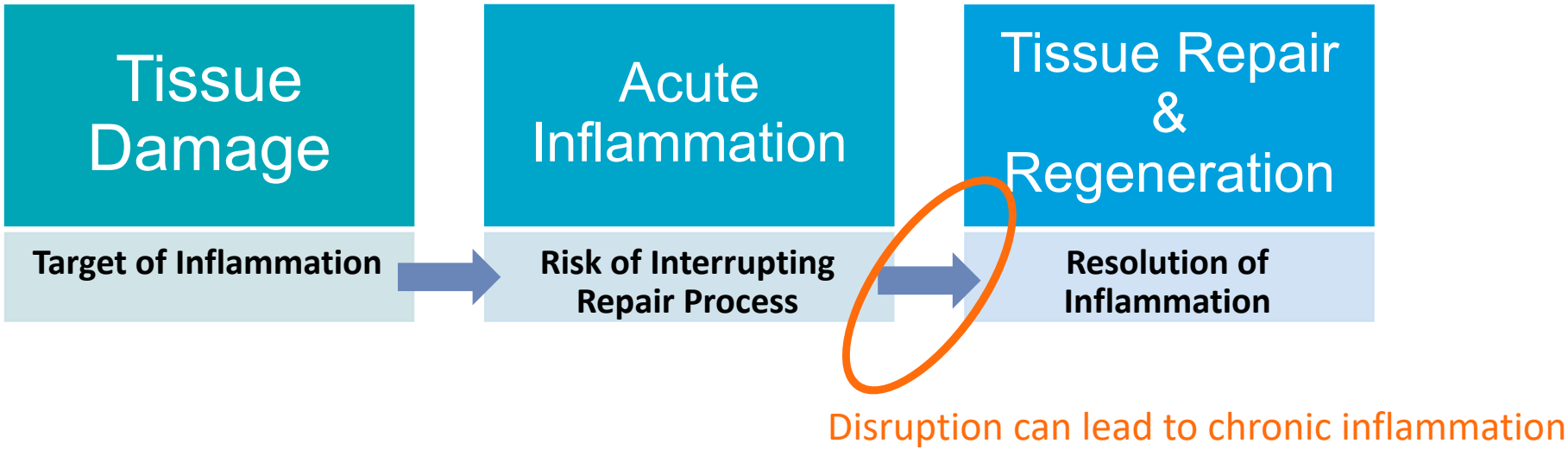
What About Chronic Inflammation?

- Chronic inflammation is similar to acute inflammation, **except…**
  - Persistent
  - Results in tissue damage
  - AND… Inflammaging



The Journals of Gerontology: Series A, Volume 69, Issue Suppl_1, 1 June 2014, Pages S4–S9, https://doi.org/10.1093/gerona/glu057
Journal of the American Society of Nephrology: February 2016, 27 (2) 371-379; DOI: https://doi.org/10.1681/ASN.2015030261

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Major Players in Inflammation

Eicosanoids

- Created from **FATS**
- Have a **LOCAL** effect
- Examples:
  - Prostaglandins, Leukotrienes, Thromboxanes

Cytokines

Created from **AMINO ACIDS** (protein)

- Have a **SYSTEMIC** effect
- Examples:
  - Interferons, Interleukins, TNF-a, NF-Kappa B, CRP

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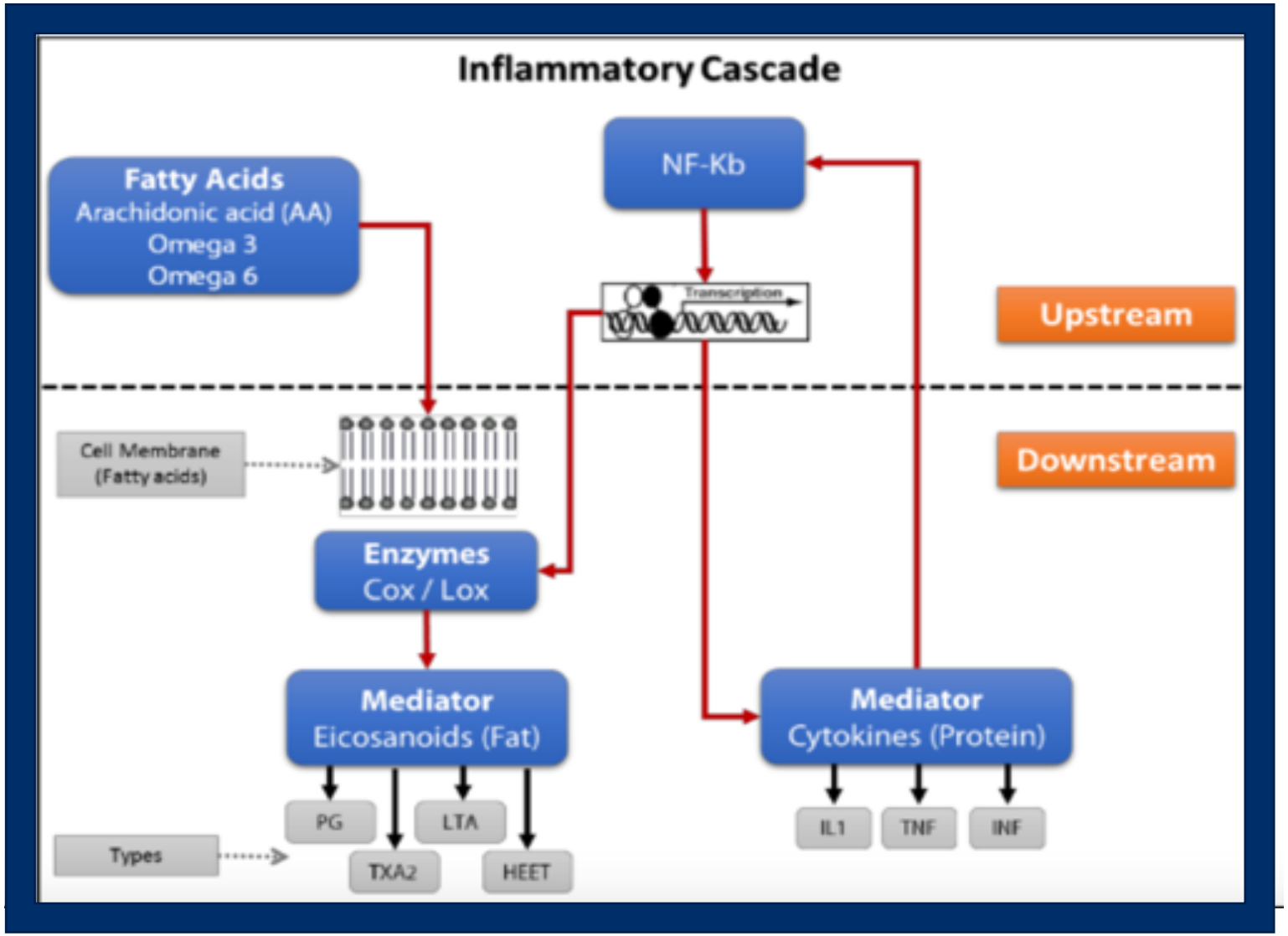
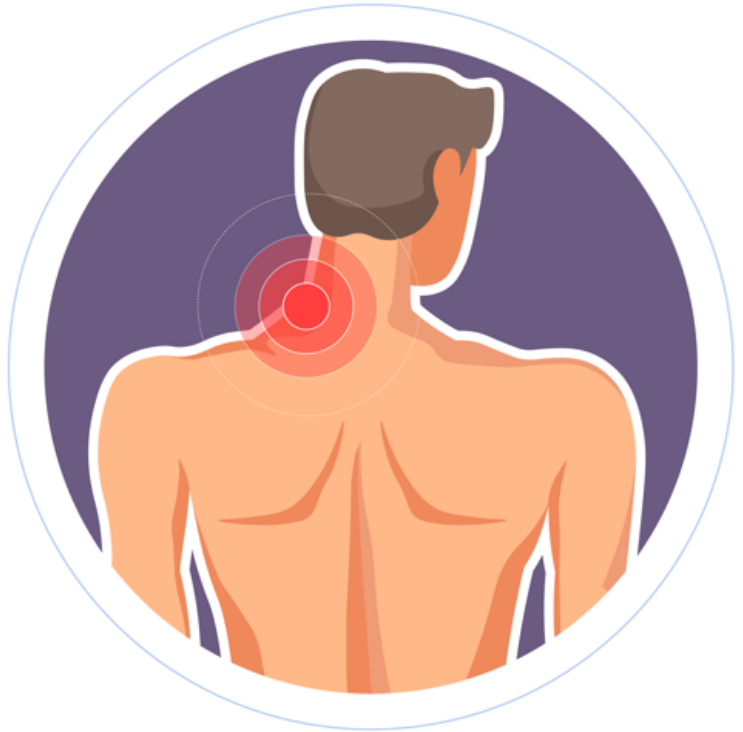
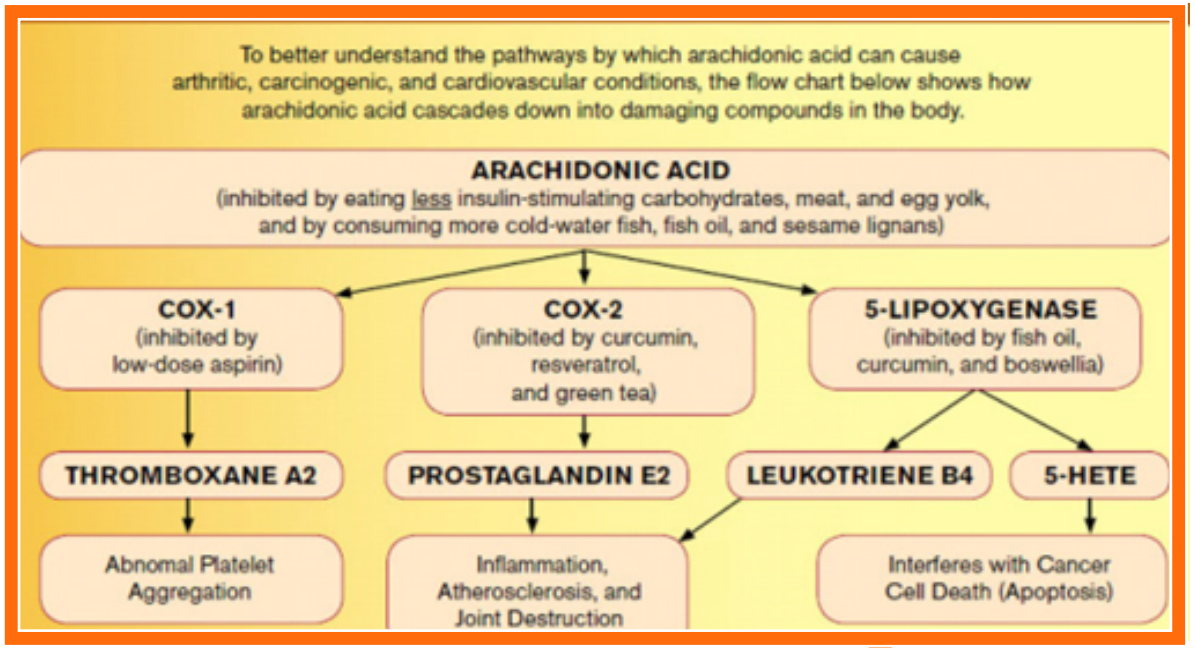
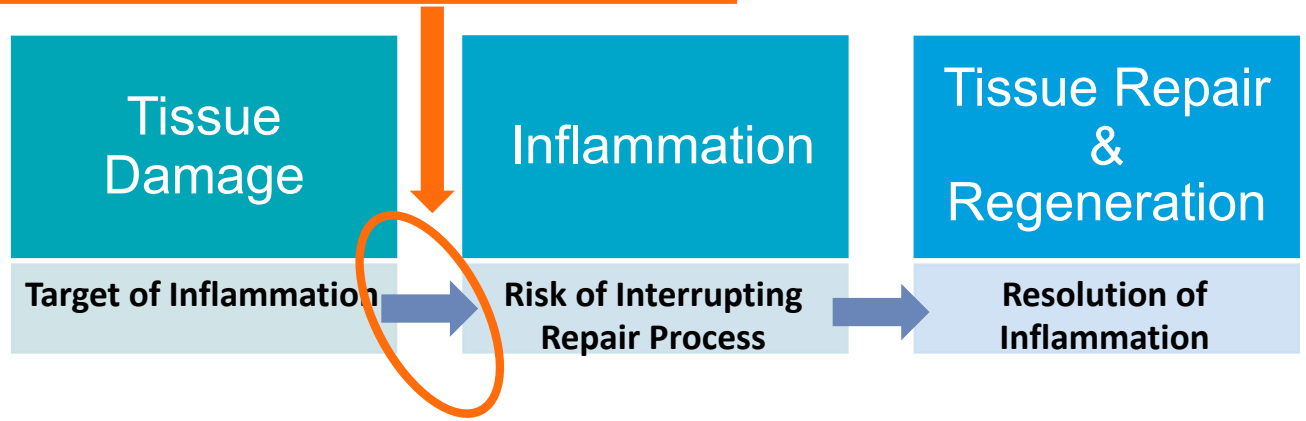
How it Works





But… I Take Curcumin





Journal of the American Society of Nephrology: February 2016, 27 (2) 371-379; DOI: https://doi.org/10.1681/ASN.2015030261

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Resolution of Inflammation

Tissue Damage	Acute Inflammation	Tissue Repair & Regeneration
Target of Inflammation	Risk of Interrupting Repair Process	Resolution of Inflammation

1. **Remove (Cleanup)**
Cellular debris left over from inflammation

2. **Restore (Balance)**
Maintain beneficial cytokine balance for whole-body health

3. **Renew (Rebuild)**
Support healthy tissue rejuvenation

Journal of the American Society of Nephrology: February 2016, 27 (2) 371-379; DOI: https://doi.org/10.1681/ASN.2015030261

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Specialized Pro-Resolving Mediators (SPMs)

The Missing Piece

Published in final edited form as:
Curr Opin Clin Nutr Metab Care. 2017 March ; 20(2): 145–152. doi:10.1097/MCO.0000000000000353.

Resolving Inflammation by using Nutrition Therapy: Roles for Specialized Pro-Resolving Mediators

Lucy V Norling[1], **Lucy Ly**[1,2], and **Jesmond Dalli**[1,2]

[1]The William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, United Kingdom

[2]QMUL Lipid Mediator Unit, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, United Kingdom

Structured Abstract

Purpose of Review—Inflammation is a unifying component of many of the diseases that afflict western civilizations. Nutrition therapy and in particular essential fatty acid (EFA) supplementation is one of the approaches that is currently in use for the treatment and management of many inflammatory conditions. The purpose of the present review is to discuss the recent literature in light of the discovery that essential fatty acids are converted by the body to a novel genus of lipid mediators, termed specialized proresolving mediators (SPM).

Recent findings—The SPM genus is composed of four mediator families, the lipoxins resolvins, protectins and maresins. These molecules potently and stereoselectively promote the termination of inflammation, tissue repair, and regeneration. Recent studies suggest that in disease, SPM production becomes dysregulated giving rise to a status of failed resolution. Of note, several studies found that omega-3 fatty acid supplementation, at doses within the recommended daily allowance, led to increases in several SPM families that correlate with enhanced white blood cell responses in humans and reduced inflammation in mice.

Summary—Given the potent biological actions of SPM in organ protection and promoting bacterial clearance, nutritional therapies enriched in omega-3 fatty acids hold promise as a potential co-therapy approach when coupled with functional lipid mediator profiling.

"Resolution of acute inflammation is a protective, highly coordinated cellular and biochemical process."
"This fundamental process orchestrated by a novel genus of lipid mediators, termed specialized pro-resolving mediators."

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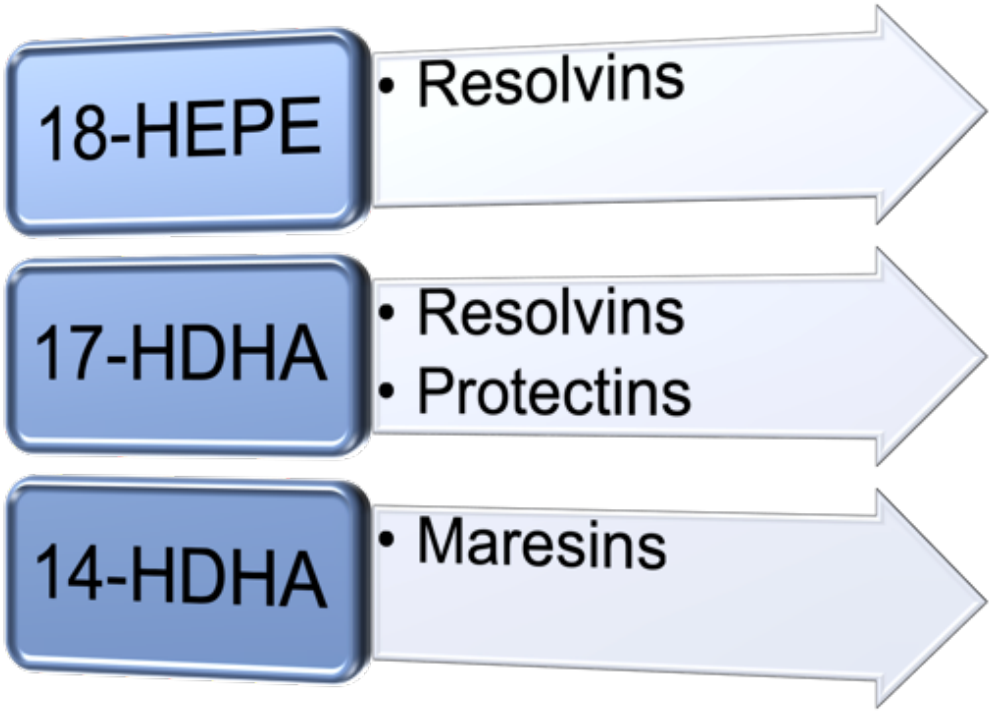
Meet the Mediators

Resolvins, Protectins, Maresins



- **Made when needed**
  - Precursors are required
- Precursors include:
  - 18-HEPE, 17-HDHA, 14-HDHA
- Precursors are metabolites of EPA & DHA

MAcrophage Mediator in **RES**olving **IN**flammation

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What Do They Do?

1. Remove (Cleanup)
Cellular debris left over from inflammation

SPMs support *activation* of **macrophage**.
The immune cells that **"clean up"** cellular debris.

2. Restore (Balance)
Maintain beneficial inflammation balance for whole-body health

SPMs inhibit pro-inflammatory **cytokines**
(IL-6, TNF-alpha, IL1beta, MCP-1)
to support **"balance"** to the inflammatory response

3. Renew (Rebuild)
Support healthy tissue rejuvenation

SPMs stimulate **endothelial nitric oxide** to enhance blood flow to support tissue **"rebuilding"**

Curr Opin Clin Nutr Metab Care: 2017 Mar;20(2):145-152. doi: 10.1097/MCO.0000000000000353

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Review of Studies

Arthritis, Atherosclerosis, Autoimmune, & Alzheimer‘s Disease

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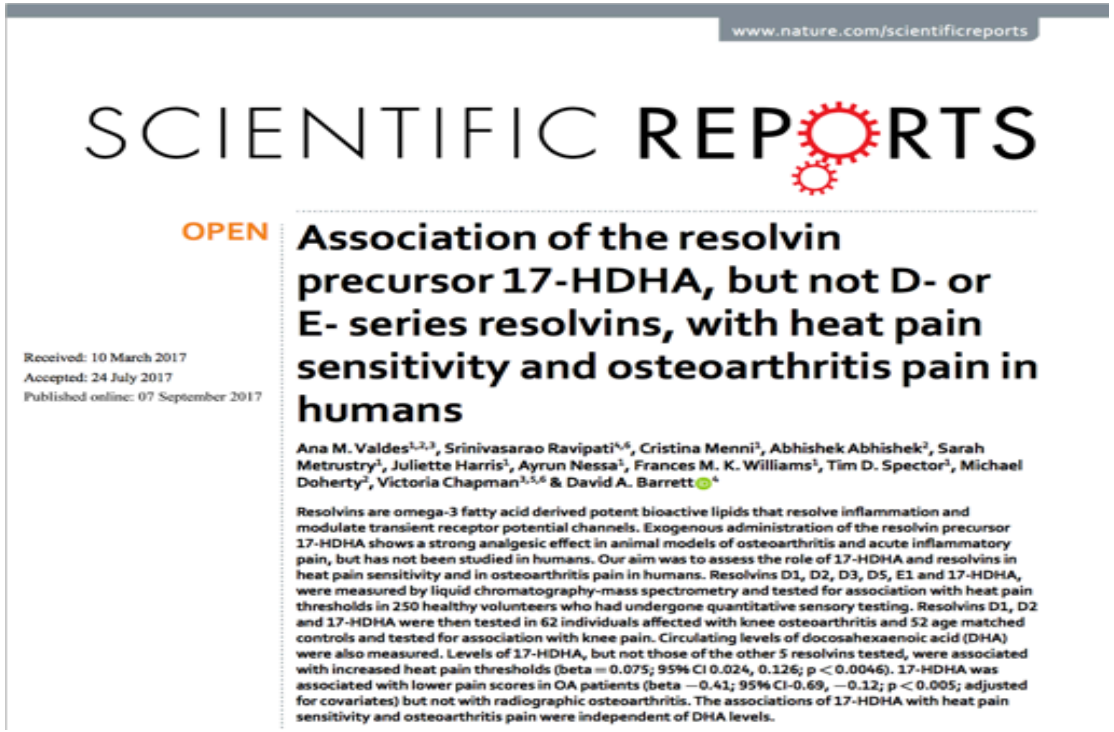
Arthritis (Osteoarthritis) Study

Human Study:

The researchers concluded:

"Our novel finding that 17-HDHA can modulate pain responses in humans suggest that exogenous administration of 17-HDHA in humans may also be analgesic."

"Another possibility is that the inhibitory effects of 17-HDHA are all due to RvD4."



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Association of the resolvin precursor 17-HDHA, but not D- or E- series resolvins, with heat pain sensitivity and osteoarthritis pain in humans

Ana M. Valdes[1,2,3], Srinivasarao Ravipati[4,6], Cristina Menni[1], Abhishek Abhishek[2], Sarah Metrustry[1], Juliette Harris[1], Ayrun Nessa[1], Frances M. K. Williams[1], Tim D. Spector[1], Michael Doherty[2], Victoria Chapman[3,5,6] & David A. Barrett[4]

Resolvins are omega-3 fatty acid derived potent bioactive lipids that resolve inflammation and modulate transient receptor potential channels. Exogenous administration of the resolvin precursor 17-HDHA shows a strong analgesic effect in animal models of osteoarthritis and acute inflammatory pain, but has not been studied in humans. Our aim was to assess the role of 17-HDHA and resolvins in heat pain sensitivity and in osteoarthritis pain in humans. Resolvins D1, D2, D3, D5, E1 and 17-HDHA, were measured by liquid chromatography-mass spectrometry and tested for association with heat pain thresholds in 250 healthy volunteers who had undergone quantitative sensory testing. Resolvins D1, D2 and 17-HDHA were then tested in 62 individuals affected with knee osteoarthritis and 52 age matched controls and tested for association with knee pain. Circulating levels of docosahexaenoic acid (DHA) were also measured. Levels of 17-HDHA, but not those of the other 5 resolvins tested, were associated with increased heat pain thresholds (beta = 0.075; 95% CI 0.024, 0.126; $p < 0.0046$). 17-HDHA was associated with lower pain scores in OA patients (beta −0.41; 95% CI-0.69, −0.12; $p < 0.005$; adjusted for covariates) but not with radiographic osteoarthritis. The associations of 17-HDHA with heat pain sensitivity and osteoarthritis pain were independent of DHA levels.

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Atherosclerosis Study

Mouse Study:

Atherosclerosis 250 (2016) 158–165

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Resolvin E1 attenuates atherosclerosis in absence of cholesterol-lowering effects and on top of atorvastatin

Kanita Salic [a, *], Martine C. Morrison [a], Lars Verschuren [b], Peter Y. Wielinga [a], Lijun Wu [c, 1], Robert Kleemann [a], Per Gjorstrup [c, **], Teake Kooistra [a]

[a] Department of Metabolic Health Research, Netherlands Organisation for Applied Scientific Research (TNO), Zernikedreef 9, 2333 CK, Leiden, The Netherlands
[b] Department of Microbiology and Systems Biology, Netherlands Organisation for Applied Scientific Research (TNO), Utrechtseweg 48, 3704 HE, Zeist, The Netherlands
[c] Resolvyx Pharmaceuticals, Inc., 222 Third Street, Cambridge, MA, 02142, United States

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Resolution
Statin

ABSTRACT

Background and aims: Besides LDL-cholesterol, local vascular inflammation plays a key role in atherogenesis. Efficient therapies to treat the inflammatory component of the disease have not been established. The discovery of specialized inflammation-resolving mediators, such as resolvins may provide new opportunities for treatment. This study examines whether the ω-3 fatty acid eicosapentaenoic acid-derived resolvin E1 (RvE1), can reduce atherosclerosis, when administered alone or in combination with a cholesterol-lowering statin.

Methods: ApoE*3Leiden mice were fed a hypercholesterolemic diet for 9 weeks and subsequently treated with RvE1-low (1 mg/kg/day), RvE1-high (5 mg/kg/day), atorvastatin (1.5 mg/kg/day) or the combination of atorvastatin and RvE1-low for the following 16 weeks.

Results: RvE1-low and RvE1-high reduced atherosclerotic lesion size to the same extent (−35%; $p < 0.05$), attenuated the formation of severe lesions, also seen as a proportional increase in the presence of mild lesions, but did not alter plasma cholesterol levels. Cholesterol-lowering atorvastatin reduced atherosclerosis (−27%, $p < 0.05$), and the combination of RvE1 and atorvastatin further attenuated lesion size (−51%, $p < 0.01$) and increased the content of mild lesions. RvE1 did not affect plasma SAA, E-selectin, VCAM-1 or MCP-1 but did reduce plasma FPHX4 and down-regulated the local expression of pro-atherogenic genes in the aortae, (e.g. *Cd74, Cd44, Ccl2, Ccr5* and *Adam17*) and significantly inactivated IFN-γ ($p < 0.001$) and TNF-α ($p < 0.001$) signalling pathways.

Conclusions: RvE1 attenuates atherogenesis both alone and on top of a statin. The local effects of RvE1 are demonstrated by the modulated aortic expression of genes involved in inflammatory and immune responses, without altering plasma cholesterol or circulating SAA.

"RvE1 attenuates atherogenesis both alone and on top of a statin. The local effects of RvE1 are demonstrated by the modulated aortic expression of genes involved in inflammatory and immune responses, without altering plasma cholesterol."

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Autoimmune (Sjogren's) Study

Mouse Study:

Published in final edited form as:
J Rheum Dis Treat. 2015 ; 1(4): .

Aspirin-Triggered Resolvin D1 Versus Dexamethasone in the Treatment of Sjögren's Syndrome-Like NOD/ShiLtJ Mice - A Pilot Study

Justin T Easley, Joel W Nelson, Rachel E Mellas, Salah Sommakia, Chunhua Wu, Bryan Trump, and **Olga J Baker***
School of Dentistry, University of Utah, Salt Lake City, UT 84108-1201, USA

Abstract

Resolvin D1 (RvD1) and its aspirin-triggered epimeric form (AT-RvD1) are endogenous lipid mediators (derived from docosahexaenoic acid, DHA) that control the duration and magnitude of inflammation in models of complex diseases. Our previous studies demonstrated that RvD1-mediated signaling pathways are expressed and active in salivary glands from rodents and humans. Furthermore, treatment of salivary cells with RvD1 blocked TNF-α-mediated inflammatory signals and improved epithelial integrity. The purpose of this pilot study was to determine the feasibility of treatment with AT-RvD1 versus dexamethasone (DEX) on inflammation (i.e., lymphocytic infiltration, cytokine expression and apoptosis) observed in submandibular glands (SMG) from the NOD/ShiLtJ Sjögren's syndrome (SS) mouse model before experimenting with a larger population. NOD/ShiLtJ mice were treated intravenously with NaCl (0.9%, negative control), AT-RvD1 (0.01–0.1 mg/kg) or DEX (4.125–8.25 mg/kg) twice a week for 14 weeks beginning at 4 weeks of age. At 18 weeks of age, SMG were collected for pathological analysis and detection of SS-associated inflammatory genes. The AT-RvD1 treatment alone did not affect lymphocytic infiltration seen in NOD/ShiLtJ mice while DEX partially prevented lymphocytic infiltration. Interestingly, both AT-RvD1 and DEX caused downregulation of SS-associated inflammatory genes and reduction of apoptosis. Results from this pilot study suggest that a systemic treatment with AT-RvD1 and DEX alone attenuated inflammatory responses observed in the NOD/ShiLtJ mice; therefore, they may be considered as potential therapeutic tools in treating SS patients when used alone or in combination.

"Both AT-RvD1 and DEX caused downregulation of SS-associated inflammatory genes and reduction of apoptosis. Results from this pilot study suggest that a systemic treatment with AT-RvD1 and DEX alone attenuated inflammatory responses observed in the NOD/ShiLtJ mice; therefore, they may be considered as potential therapeutic tools in treating SS patients when used alone or in combination."

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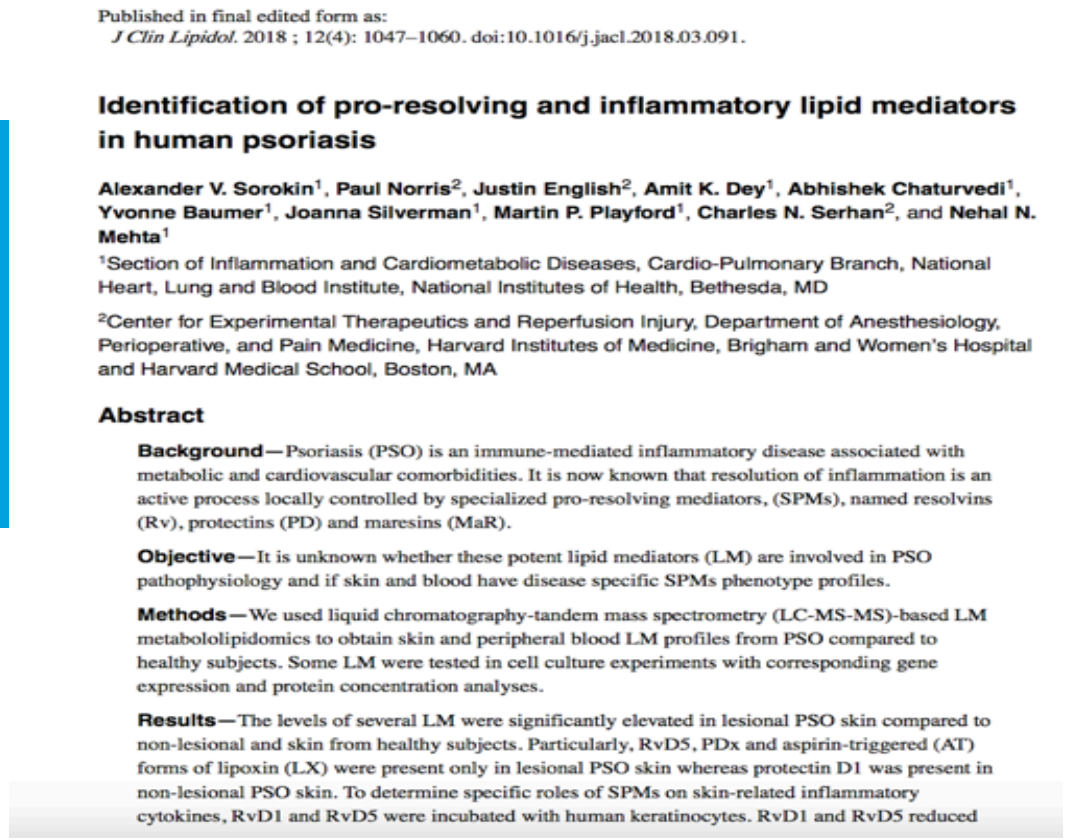
Autoimmune (Psoriasis) Study

The researchers concluded:

"The amounts of SPMs within psoriasis lesions were not produced in high enough concentrations to resolve the inflammation in the skin suggesting that increasing SPMs in psoriasis may represent a goal for new therapeutic interventions."

Human Study:



Published in final edited form as:
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Identification of pro-resolving and inflammatory lipid mediators in human psoriasis

Alexander V. Sorokin[1], **Paul Norris**[2], **Justin English**[2], **Amit K. Dey**[1], **Abhishek Chaturvedi**[1], **Yvonne Baumer**[1], **Joanna Silverman**[1], **Martin P. Playford**[1], **Charles N. Serhan**[2], and **Nehal N. Mehta**[1]

[1]Section of Inflammation and Cardiometabolic Diseases, Cardio-Pulmonary Branch, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD

[2]Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative, and Pain Medicine, Harvard Institutes of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Abstract

Background—Psoriasis (PSO) is an immune-mediated inflammatory disease associated with metabolic and cardiovascular comorbidities. It is now known that resolution of inflammation is an active process locally controlled by specialized pro-resolving mediators, (SPMs), named resolvins (Rv), protectins (PD) and maresins (MaR).

Objective—It is unknown whether these potent lipid mediators (LM) are involved in PSO pathophysiology and if skin and blood have disease specific SPMs phenotype profiles.

Methods—We used liquid chromatography-tandem mass spectrometry (LC-MS-MS)-based LM metabololipidomics to obtain skin and peripheral blood LM profiles from PSO compared to healthy subjects. Some LM were tested in cell culture experiments with corresponding gene expression and protein concentration analyses.

Results—The levels of several LM were significantly elevated in lesional PSO skin compared to non-lesional and skin from healthy subjects. Particularly, RvD5, PDx and aspirin-triggered (AT) forms of lipoxin (LX) were present only in lesional PSO skin whereas protectin D1 was present in non-lesional PSO skin. To determine specific roles of SPMs on skin-related inflammatory cytokines, RvD1 and RvD5 were incubated with human keratinocytes. RvD1 and RvD5 reduced

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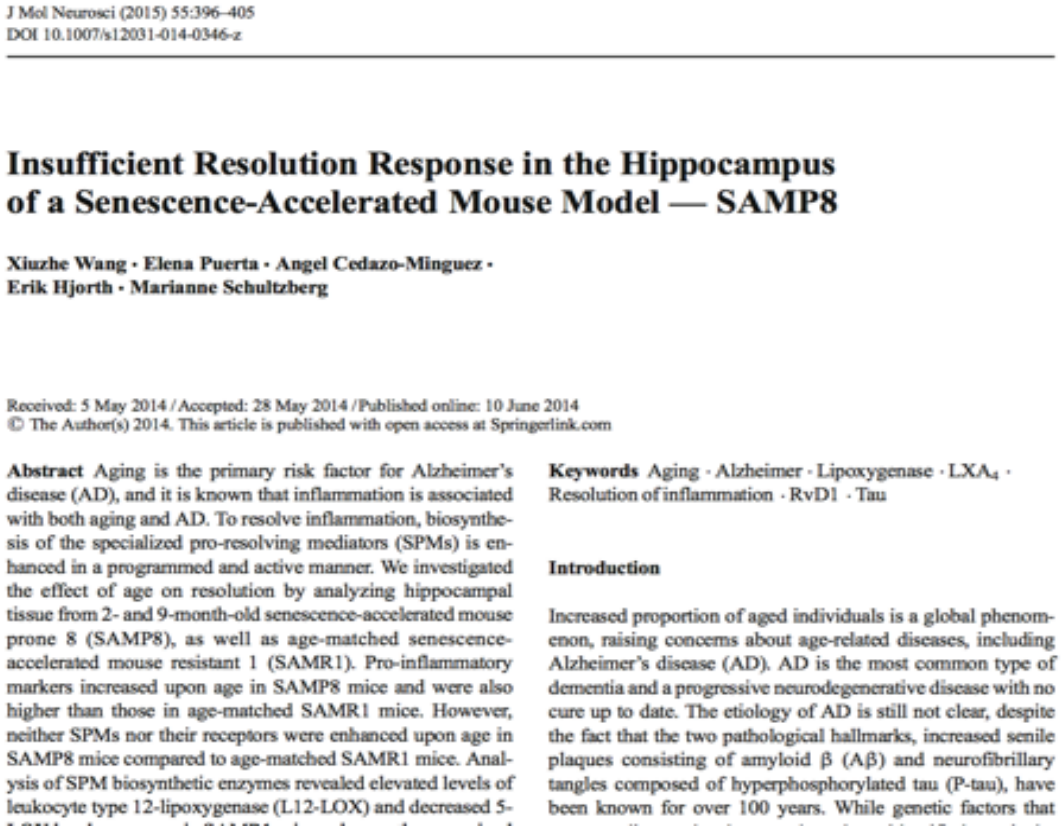
Alzheimer's Disease Study

Mouse Study:



J Mol Neurosci (2015) 55:396–405
DOI 10.1007/s12031-014-0346-z

Insufficient Resolution Response in the Hippocampus of a Senescence-Accelerated Mouse Model — SAMP8

Xiuzhe Wang · Elena Puerta · Angel Cedazo-Minguez · Erik Hjorth · Marianne Schultzberg

Received: 5 May 2014 / Accepted: 28 May 2014 / Published online: 10 June 2014

Abstract Aging is the primary risk factor for Alzheimer's disease (AD), and it is known that inflammation is associated with both aging and AD. To resolve inflammation, biosynthesis of the specialized pro-resolving mediators (SPMs) is enhanced in a programmed and active manner. We investigated the effect of age on resolution by analyzing hippocampal tissue from 2- and 9-month-old senescence-accelerated mouse prone 8 (SAMP8), as well as age-matched senescence-accelerated mouse resistant 1 (SAMR1). Pro-inflammatory markers increased upon age in SAMP8 mice and were also higher than those in age-matched SAMR1 mice. However, neither SPMs nor their receptors were enhanced upon age in SAMP8 mice compared to age-matched SAMR1 mice. Analysis of SPM biosynthetic enzymes revealed elevated levels of leukocyte type 12-lipoxygenase (L12-LOX) and decreased 5-

Keywords Aging · Alzheimer · Lipoxygenase · LXA_4 · Resolution of inflammation · RvD1 · Tau

Introduction

Increased proportion of aged individuals is a global phenomenon, raising concerns about age-related diseases, including Alzheimer's disease (AD). AD is the most common type of dementia and a progressive neurodegenerative disease with no cure up to date. The etiology of AD is still not clear, despite the fact that the two pathological hallmarks, increased senile plaques consisting of amyloid β (Aβ) and neurofibrillary tangles composed of hyperphosphorylated tau (P-tau), have been known for over 100 years. While genetic factors that

The researchers concluded:

"In summary, we provided data on how the resolution pathway in the brain is regulated to meet inflammation during normal aging using an animal model. Moreover, during abnormal aging, accompanied by AD-like pathologies, there was insufficient resolution to resolve the excessive inflammation compared to normal aging."

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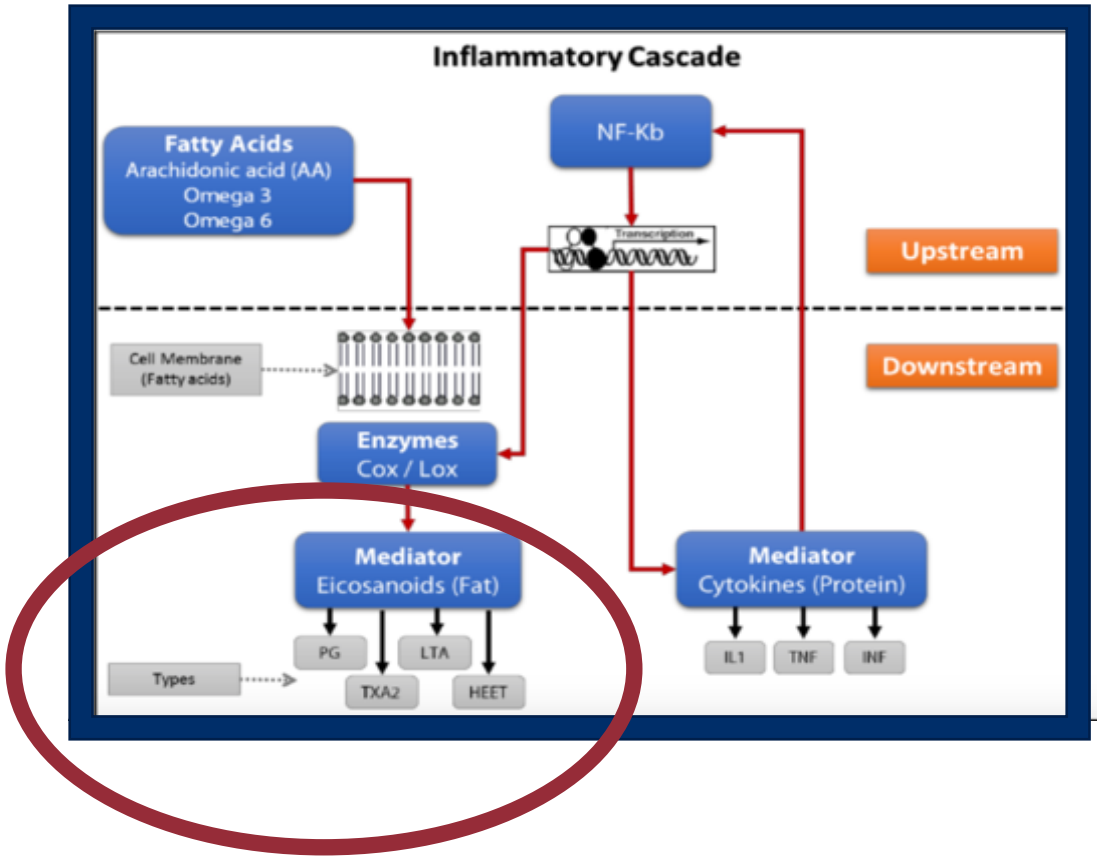
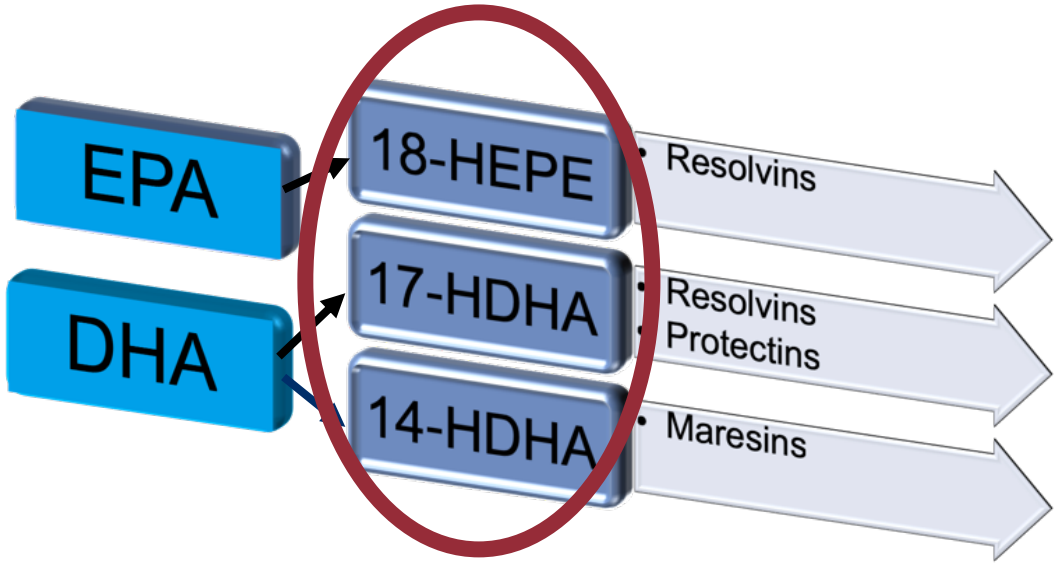
Is Taking Fish Oil Enough?

Inflammation Response



Post-Inflammation Response



SPMs are made
ON DEMAND
in the cells
during the resolution phase of inflammation. Do you have enough precursors?

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Thank You!

Questions?

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