Inflammation and Targeted Nutrition

Nutrition Masters Course

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Learning Objectives

1. Understand the two distinct phases of inflammation: initiation and resolution.
2. Learn how inflammation initiation can be modulated with select nutritional bioactives EPA, DHA, curcumin, xanthohumol, *Boswellia serrata*, ginger, and THIAA.
3. Review the science behind specialized pro-resolving mediators (SPMs), their biosynthesis, the essential role they play in inflammation resolution, and the rationale for supplementation.
4. Discuss an integrated view of up-to-date research supporting the clinical management of inflammation in practice.

Inflammation Overview

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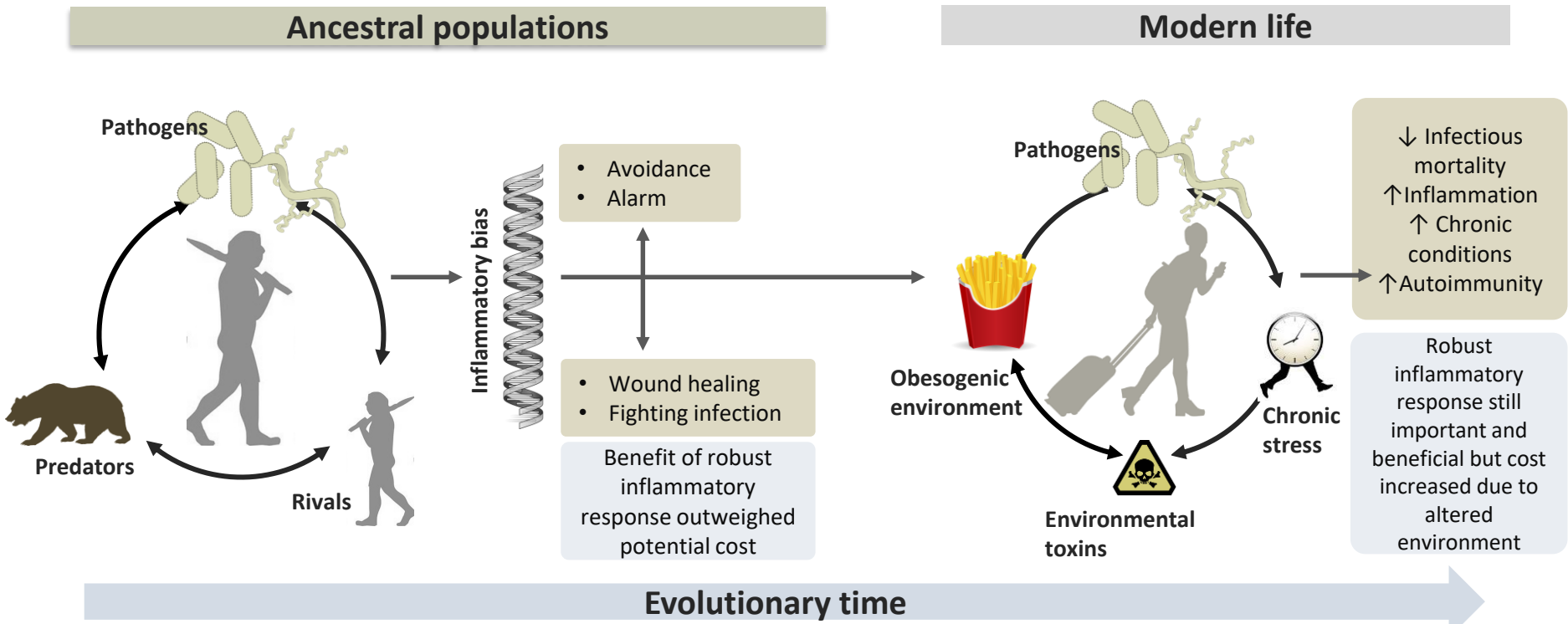
Inflammation: Friend or Foe?

Inflammation is critical for survival, but excessive inflammation is linked with disease.



Adapted from: Miller AH, Raison CL. *Nat Rev Immunol*. 2016;16(1):22–34.
Okin D, Medhitov R. *Curr Biol.* 2012;22(17):R733-R740.

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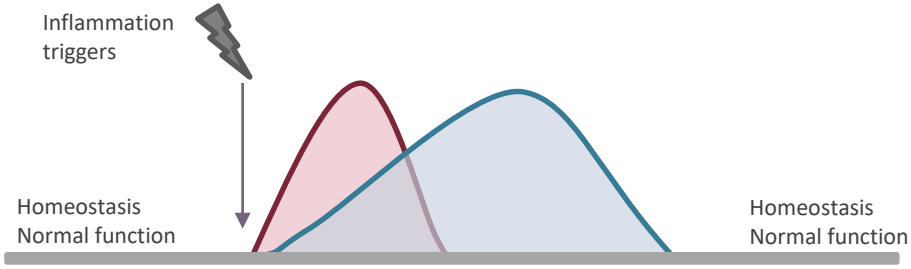
What Is Normal Inflammatory Process?



	Inflammation initiation	Inflammation resolution
Goal	Localize and eliminate trigger of inflammation	Counter-regulate initiation; subsidence of inflammation, tissue regeneration, and return to normal function
Predominant immune cells	Neutrophils, monocytes, PMNs	Resolving macrophages
Chemical mediators	Pro-inflammatory lipid mediators—e.g., PGs, LTs, chemokines, and pro-inflammatory cytokines)	Specialized pro-resolving mediators (SPMs)

Adapted from: Serhan CN. *Nature*. 2014;510:92-101.

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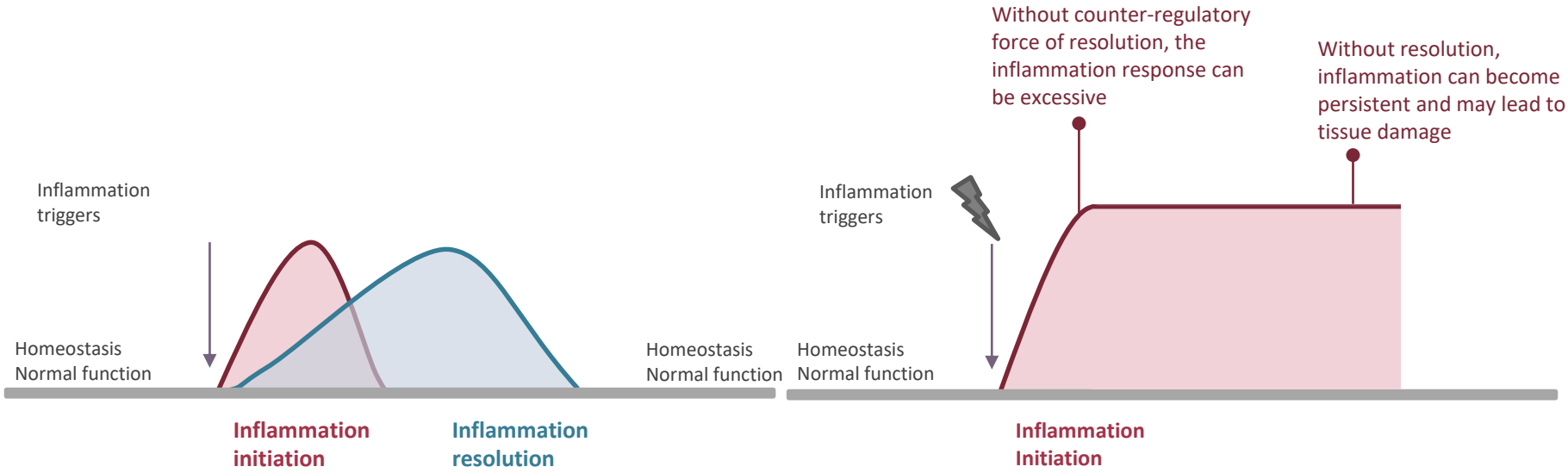
Without Robust Resolution, Inflammation Can Become Persistent—Preventing Return to Normal Function



Adapted from: Serhan CN. *Nature*. 2014;510:92-101.

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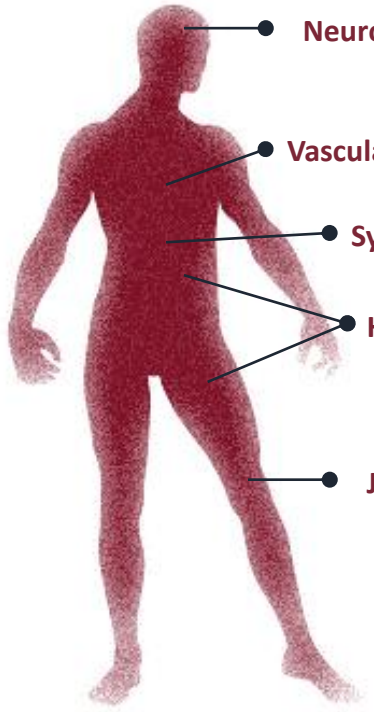
Inflammation Within Tissues Is at the Core of Chronic Disease



Neuroinflammation—Linked with Alzheimer's disease, Huntington's disease, Parkinson's disease

Vascular inflammation—Core for development of atherosclerosis

Systemic and local inflammatory environment

Hepatic and adipose inflammation—Linked with insulin resistance and type 2 diabetes

Joint inflammation—Arthritis development

Handschin C & Spiegelman BM. *Nature*. 2008;454:463-469.

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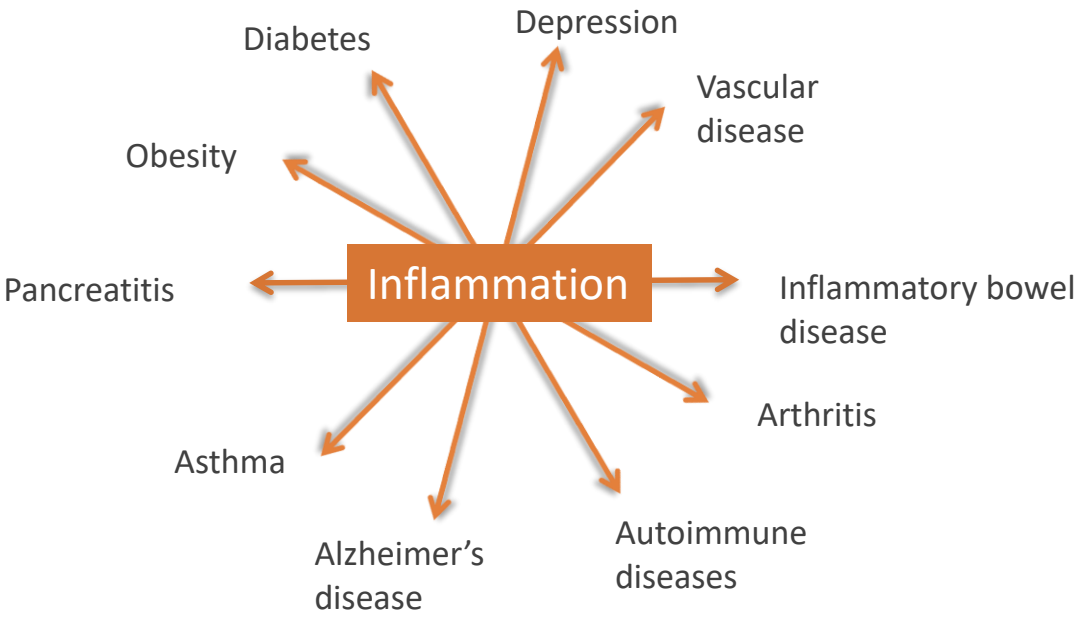
Uncontrolled Chronic Inflammation Is Linked to Many Chronic Diseases



Serhan CN et al. *Nat Immunol*. 2005;6(12):1191-1197.
Nathan C et al. *Cell.* 2010;140(6):871-882.

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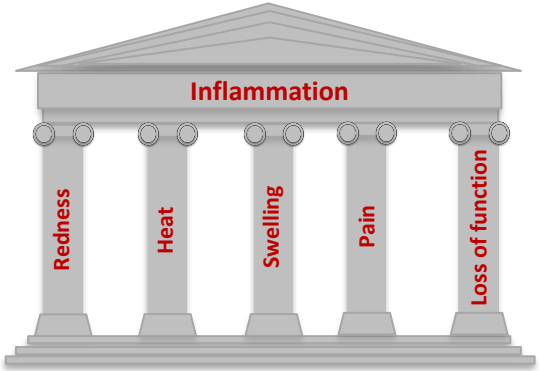
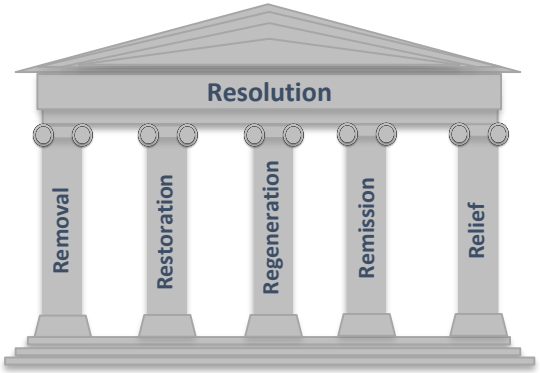
Cardinal Signs of Inflammation Initiation and Resolution



Protective response



Resolution response

Adapted from: Basil MC, Levy BD. *Nat Rev Immunol*. 2016;16(1):51–67.

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Inflammation Initiation Mechanisms

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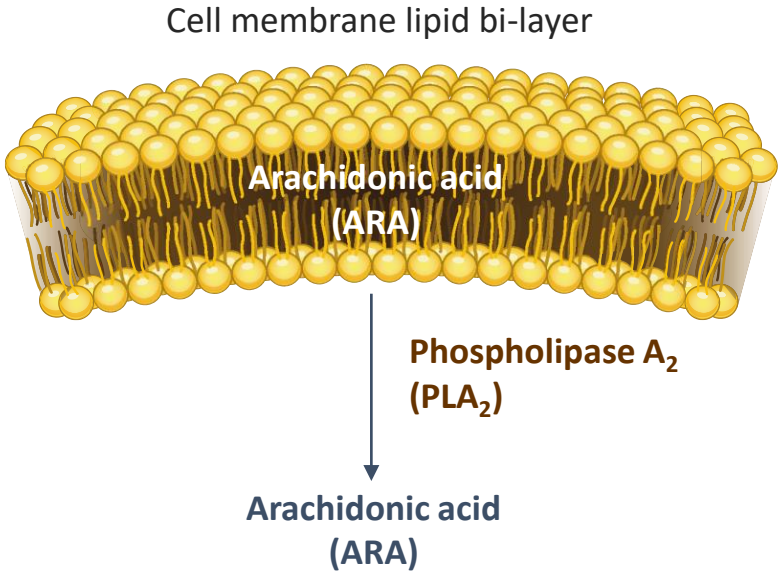
Inflammation & Pain: Key Enzymes

Phospholipase A_2 (PLA_2)

- Liberates arachidonic acid (ARA) from the cell membrane
- ARA is then available as a substrate for **COX-1**, **COX-2**, and **LOX** (as well as other enzymes)



Dennis EA et al. *Chem Rev*. 2011;111(10):6130-6185.

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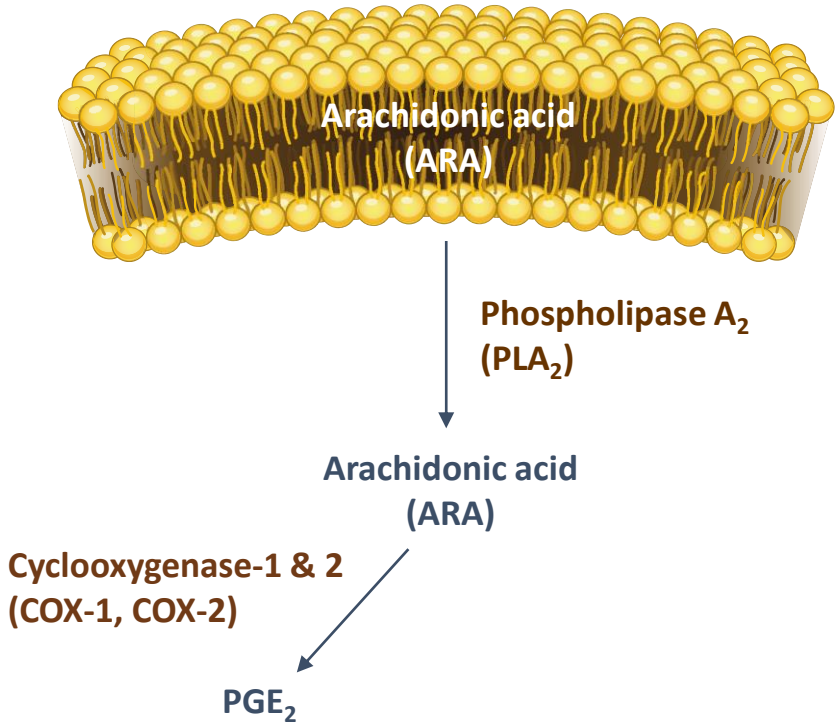
Inflammation & Pain: Key Enzymes

- **Cyclooxygenase (COX-1 and COX-2)**
  - Converts ARA to prostaglandins (including PGE_2)
  - **PGE_2**
    - Increases pain perception
    - Contributes to the destruction of cartilage in arthritic joints in both **rheumatoid arthritis (RA)** and **osteoarthritis (OA)**



Dennis EA et al. *Chem Rev*. 2011;111(10):6130-6185.
Lee A et al. *Gene*. 2014;527(2):440-447.

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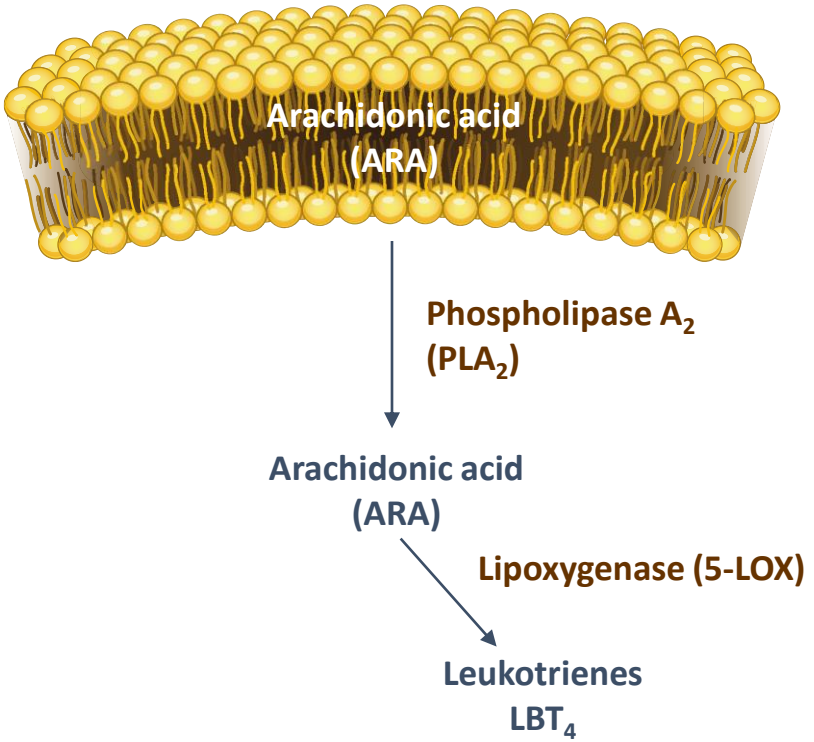
Inflammation & Pain: Key Enzymes

- **Lipoxygenase (LOX)**
  - Converts ARA to leukotrienes (including LTB4)
  - Leukotrienes are active during inflammation initiation
  - Overproduction of **leukotrienes** plays a role in inflammatory conditions like **asthma** and **allergic rhinitis**
  - Commonly used LOX inhibitors include medications used as analgesics for **OA** and **RA** and treatments for **asthma**



Coffey M, Peters-Golden M. *Curr Opin Allergy Clin Immunol*. 2003;3(1):57-63.
Çobanoğlu B et al. *Curr Allergy Asthma Rep*. 2013;13(2):203-208.

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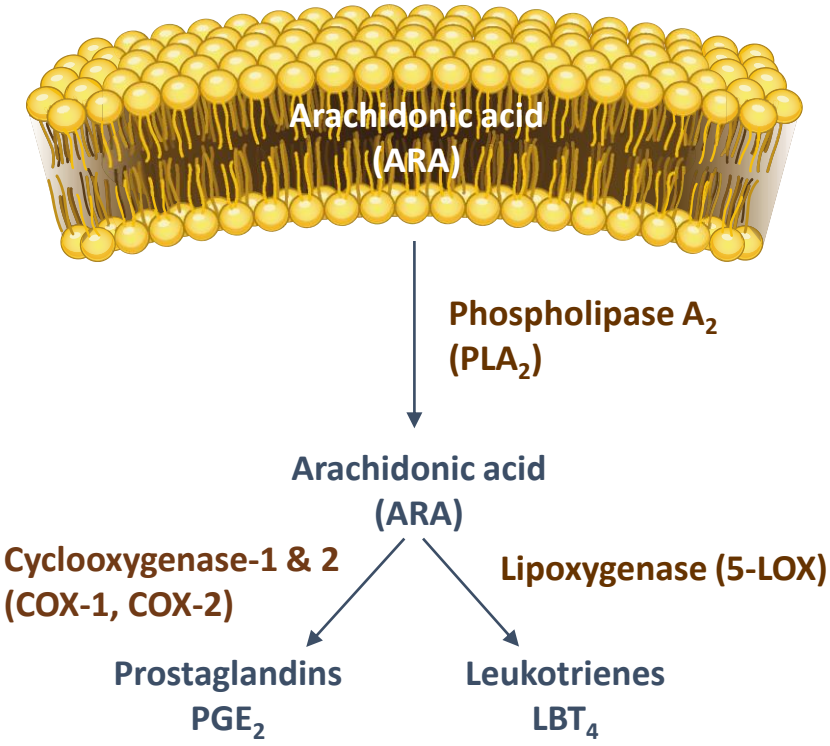
Inflammation & Pain: Key Enzymes

1. ARA is released from the cell membrane through the action of PLA_2.
2. Through the actions of COX and LOX enzymes, ARA is converted to the pro-inflammatory lipid mediators such as prostaglandins and leukotrienes.
3. These pro-inflammatory lipid mediators are key drivers of inflammation initiation, and they enhance vasodilation, attract pro-inflammatory immune cells to the affected tissue, and—in the case of prostaglandins—contribute to pain.



Dennis EA et al. *Chem Rev*. 2011;111(10):6130-6185.

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Inflammation & Pain: Key Regulator of Gene Expression

- Nuclear factor-kappa B (NF-κB)
  - Protein complex that controls DNA transcription/genetic expression
  - When activated, controls/regulates the expression of ~500 genes, including:
    - Pro-inflammatory enzymes: PLA_2, COX-1, COX-2, LOX
    - Pro-inflammatory cytokines: IL-1β, IL-6, IL-12, TNFα
    - Chemokines: CXCL8 (aka IL-8), MCP-1

Shih R et al. *Front Mol Neurosci.* 2015;8:77.

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Nuclear Factor-Kappa B (NF-κB)

Upstream **NF-κB (inactive)**

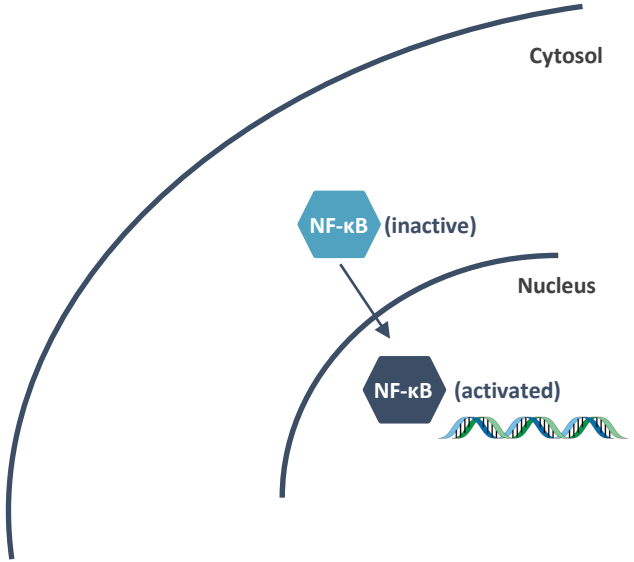
↓

NF-κB (activated)

↓

Downstream **Increased expression of:**

- **PLA_2**
- **COX-1**
- **COX-2**
- **LOX**
- **TNFα, IL-1β, IL-6, IL-12**
- **CXCL8 (IL-8)**
- **MCP-1**



Shih R et al. *Front Mol Neurosci.* 2015;8:77.

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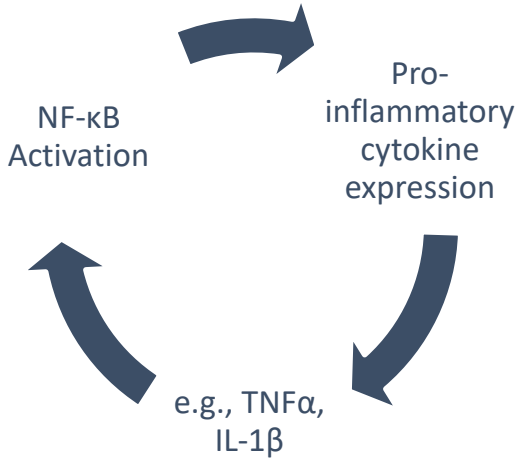
Inflammation & Pain:
NF-κB & Pro-Inflammatory Cytokines

- Not only does NF-κB increase the **expression** of pro-inflammatory cytokines
- Some pro-inflammatory cytokines increase the **activation** of NF-κB
  - e.g., TNFα, IL-1β
- Chronic inflammation persists



Hayden MS, Ghosh S. *Semin Immunol.* 2014;26(3):253-266.

TNFα Activates NF-κB

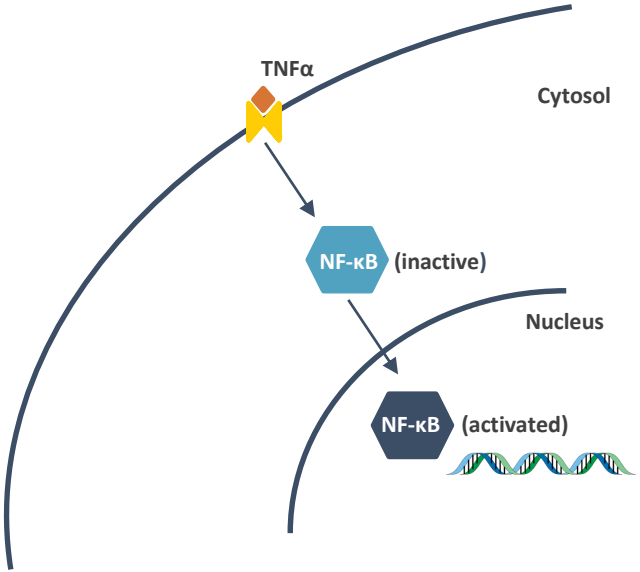
Upstream **TNFα**

NF-κB (inactive)

NF-κB (activated)

Downstream **Increased expression of:**

- **PLA_2**
- **COX-1**
- **COX-2**
- **LOX**
- **TNFα, IL-1β, IL-6, IL-12**
- **CXCL8 (IL-8)**
- **MCP-1**



Hayden MS, Ghosh S. *Semin Immunol.* 2014;26(3):253-266.
Shih R et al. *Front Mol Neurosci.* 2015;8:77.

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Inflammation & Pain: Chemokines

- Examples of inflammatory chemokines
  - Chemokine ligand 8 (CXCL8, aka IL-8)
  - Monocyte chemoattractant protein 1 (MCP-1)
  - Interferon-γ activated protein (IP-10)
- Recruit white blood cells to local sites of inflammation
  - Promote **joint pathology** in patients with arthritis

Szekanecz Z et al. *Front Biosci*. 2010;146(614):41-46.
Kapoor M et al. *Nat Rev Rheumatol*. 2011;7(1):33-42.

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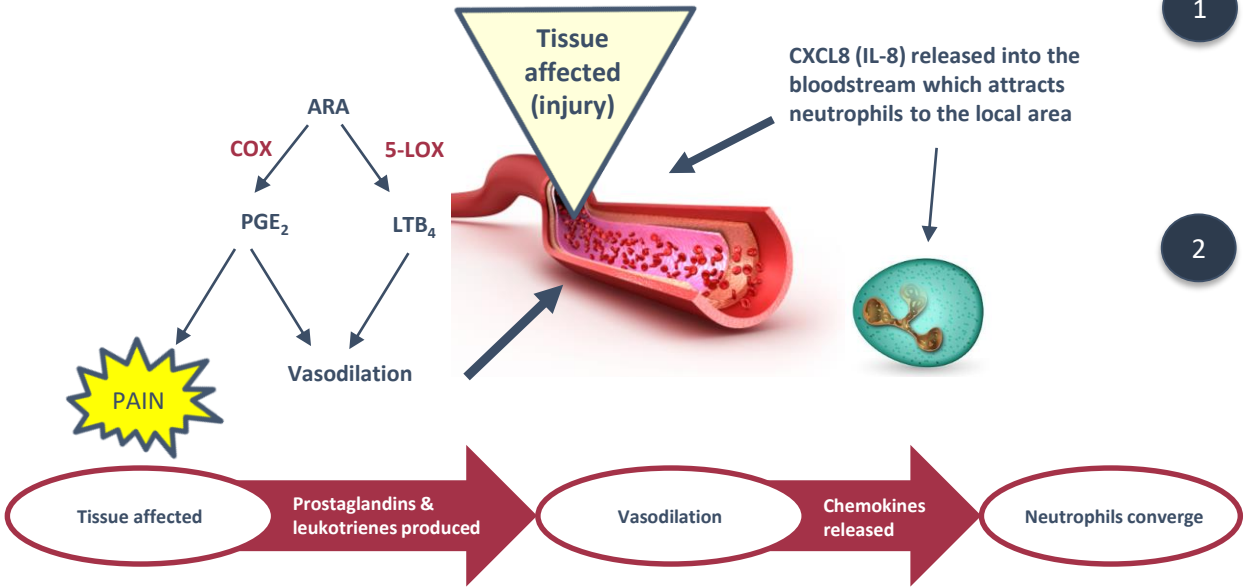
Immune Response Causing the Initiation of Inflammation & Pain



1. ARA is released from the cell membrane through the action of PLA2 and pro-inflammatory lipid mediators are produced through the actions of COX and LOX enzymes.

2. These lipid mediators in combination with other pro-inflammatory chemokines and cytokines act to enhanced vasodilation and attract pro-inflammatory cells to the affected tissue with a goal of containing the source of inflammation.

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Focus on Nutritional Bioactives with Inflammation Initiation Modulating Activity

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Key Nutritional Bioactives for Modulation of Inflammation Initiation

- Omega-3 fatty acids EPA and DHA
- Tetrahydro-iso-α acids (THIAA)
- Curcumin
- Xanthohumol
- *Boswellia serrata*
- Ginger

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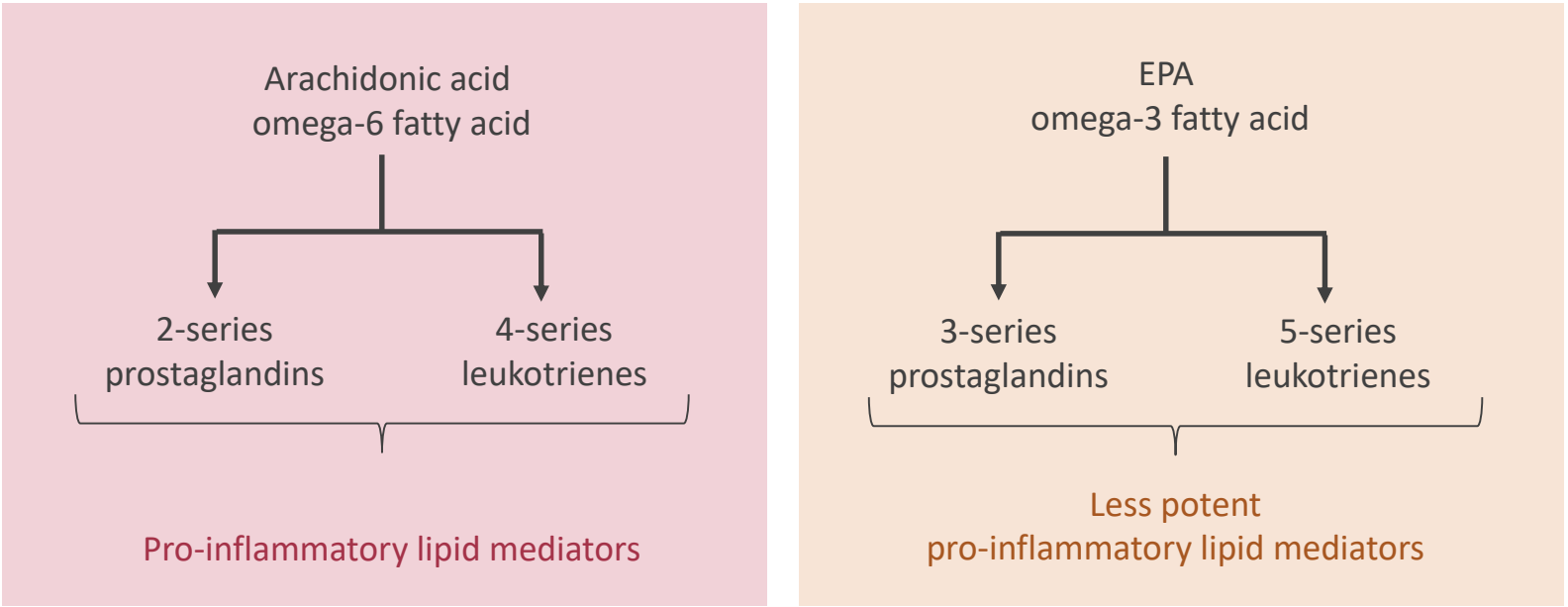
Omega-3 Fatty Acids EPA and DHA



Adapted from: Calder PC. *Nutrients.* 2010;2(3):355-374.

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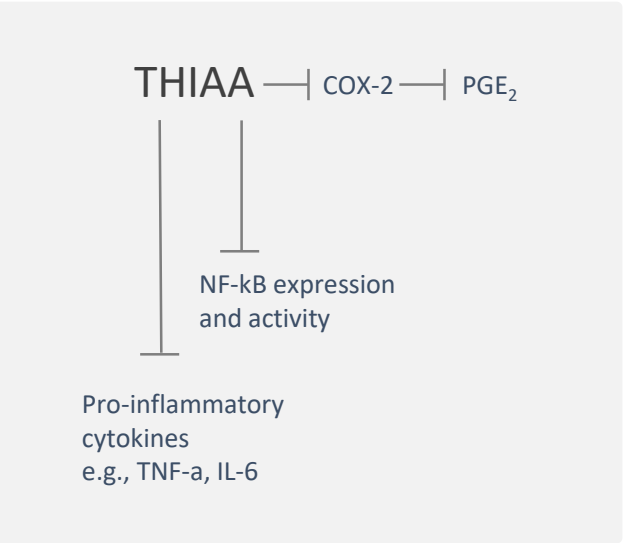
Tetrahydro-iso-α acids (THIAA) from Hops Have Anti-Inflammatory Properties



Mechanistic studies in endothelial cells, monocytes, macrophages, and human rheumatoid arthritis synovial fibroblasts indicate anti-inflammatory activities of THIAA.

Desai A et al. *Inflamm Res.* 2009;58(5):229-34.
Konda VR et al. *Arthritis Rheum.* 2010;62(6):1683-1692.
Desai A et al. *Atherosclerosis.* 2012;223:130-136.

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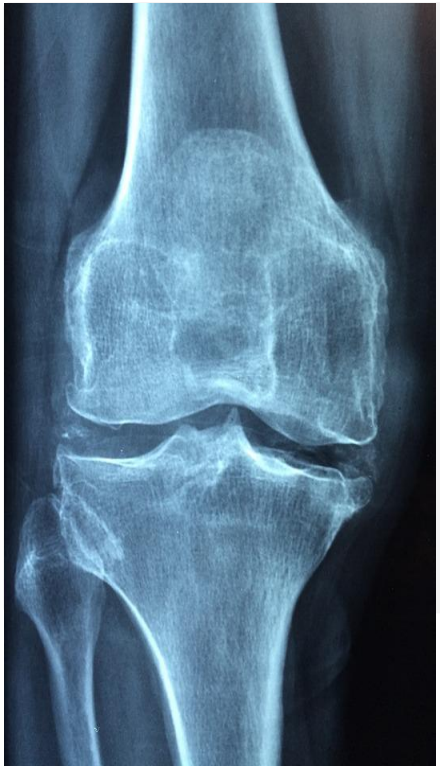
Tetrahydro-iso-α acids (THIAA) from Hops Have Anti-Inflammatory Properties



In a mouse model of induced arthritis, treatment with THIAA

- ✓ Reduced paw swelling
- ✓ Reduced arthritis index
- ✓ Reduced extent of joint damage
- ✓ Reduced cartilage degradation
- ✓ Reduced bone erosion
- ✓ Reduced IL-6 levels

Konda VR et al. *Arthritis Rheum.* 2010;62(6):1683-1692.

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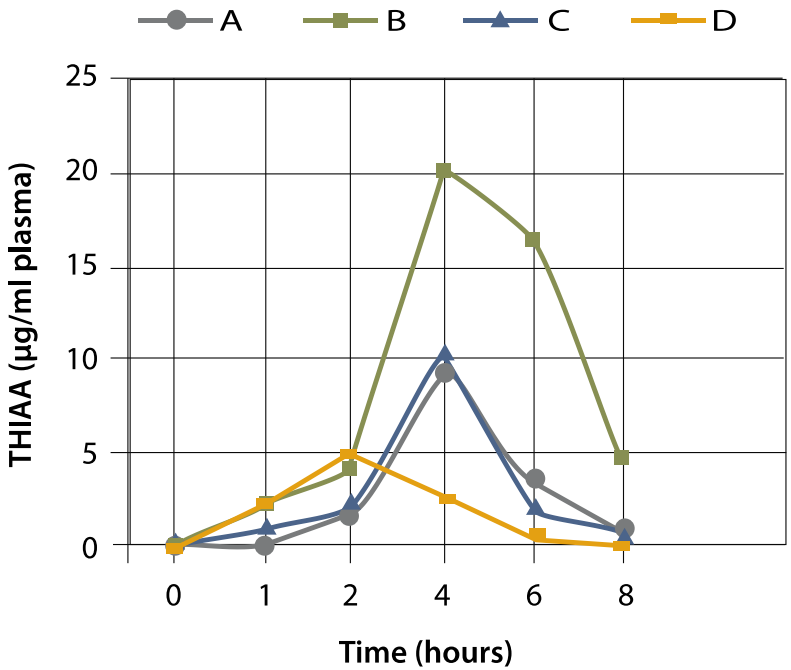
Tetrahydro-iso-α acids (THIAA) Increase in Plasma Postconsumption

In a study of healthy men and women (n=4), plasma levels of THIAA were seen to increase after consumption of 940 mg.



Adapted from: Desai A et al. *Inflamm Res.* 2009;58(5):229-234.

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Curcuminoids: Isolated Constituents

- Primary active constituents in turmeric root (*Curcuma longa*)
- Turmeric has culinary and potential therapeutic uses
- **Properties**
  - **Analgesic**: Reduces pain including neuropathic pain in mouse models[1-2]
  - **Anti-arthritic**: e.g. Reduces joint inflammation and matrix metalloproteinase expression in mice[3]
  - **Anti-inflammatory**[4]
  - **Antioxidant**[4]
  - Other: Inflammatory bowel disease (animal models and pilot human data),[5] antidepressant (clinical data),[6,7] antidiabetic (clinical data),[8-10] cardiovascular risk markers (clinical data)[11,12]

1. Banafshe HR et al. *Eur J Pharmacol.* 2014;723:202-206.
2. Zhu X et al. *PLoS One.* 2014;9(3):e91303.
3. Mun SH et al. *J Pharmacol Sci.* 2009;111(1):13-21.
4. Shezhad A et al. *J Food Sci.* 2017;82(9):2006-2015.
5. Vecchi Brumatti L et al. *Molecules.* 2014;19(12):21127-21153.
6. Sanmukhani J et al. *Phytother Res.* 2014;28(4):579-585.
7. Lopresti AL et al. *J Affect Disord.* 2014;167:368-375.
8. Maradana MR et al. *Mol Nutr Food Res.* 2013 ;57(9):1550-1556.
9. Na LX et al. *Mol Nutr Food Res.* 2013;57(9):1569-1577.
10. Chuengsamarn S et al. *Diabetes Care.* 2012;35(11):2121-2127.
11. Khurana S et al. *Nutrients.* 2013;5(10):3779-3827.
12. Chuengsamarn S et al. *J Nutr Biochem.* 2014;25(2):144-150.

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Curcumin Bioavailability Considerations

- Poor bioavailability
  - Not well absorbed
  - Animal studies have shown that the majority of curcumin (up to 85%) passes through the GI tract
- Absorption improves slightly when consumed with lipids/fat or piperine (in peppercorns)

Natural Medicines. Turmeric. https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=662. Accessed August 27, 2018.

Curcumin as CGM

- Curcumagalactomannoside (CGM)
- Combines curcumin with galactomannan fibers (from fenugreek seeds)
- Bioavailability[1,2]
  - Enhanced absorption of curcuminoids into the bloodstream
  - Exceptional delivery to target tissues

1. Sudheeran SP et al. *J Clin Psychopharmacol.* 2016;36(3):236-243.
2. IM K et al. *J Funct Foods*. 2015;14:215-225.

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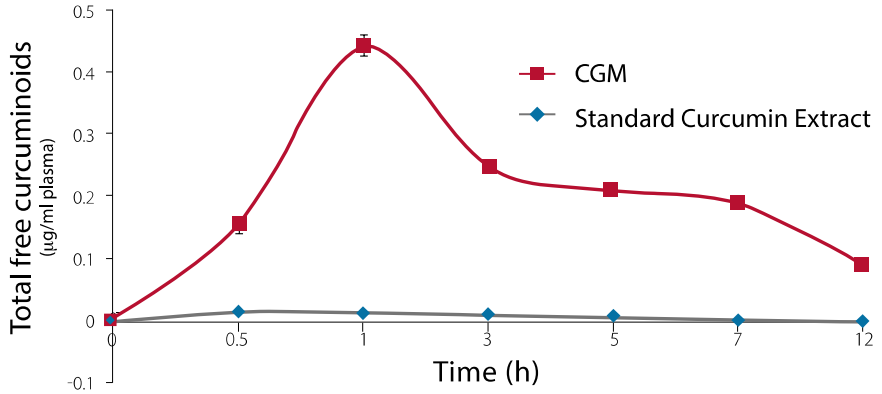
Circulating Free Curcuminoids in Human Plasma Are Higher with CGM Compared to Standard Curcumin Extract

- Studies have shown that CGM is exceptionally well-absorbed compared to standard curcumin
- Plasma curcuminoids were assayed after a single 500 mg dosage



In a randomized, crossover study of 50 subjects, the CGM group demonstrated 45.5-fold more bioavailability of free curcuminoids in plasma (AUC) as per HPLC-PDA detection method. Subjects were given a single dose of 500 mg of curcumin in each group, and curcumin levels were measured over 12 hours. No glucuronidase enzyme was used for the treatment of blood to convert the glucuronides to free curcumin; therefore, the quantification is mainly for the free curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin). Data represented as mean±SEM.

Adapted from: Sudheeran P et al. *J Clin Psychopharmacol.* 2016;36(3):236-243.

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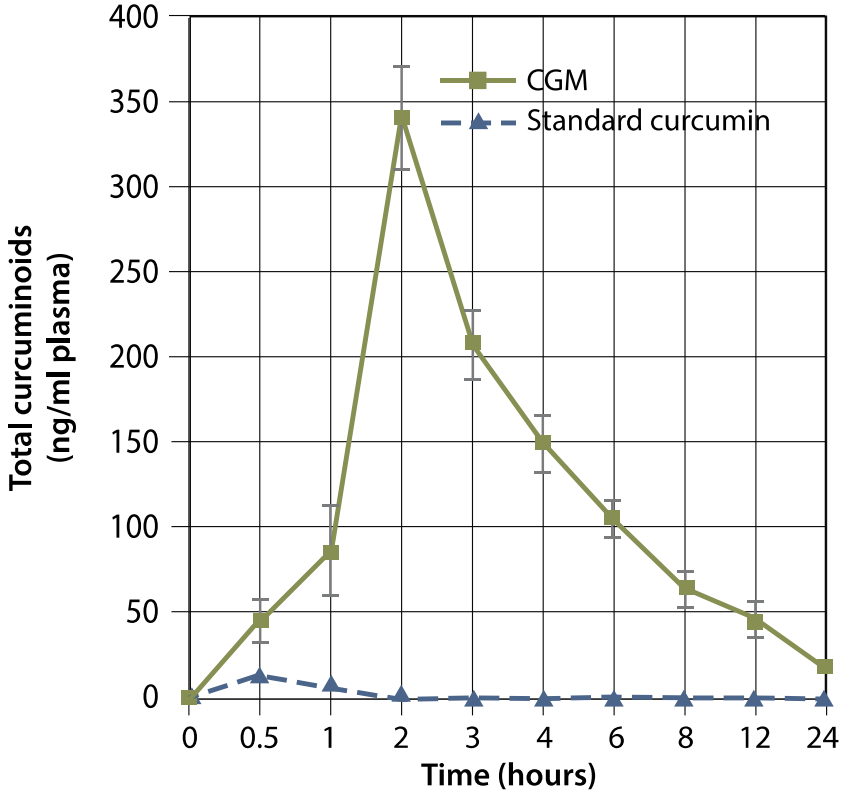
Circulating Free Curcuminoids in Rat Plasma Are Higher with CGM Compared to Standard Curcumin Extract

CGM leads to higher total curcuminoids in circulation compared to standard curcumin



Total free curcuminoids in plasma of Wistar rats orally administrated with standard curcumin or CGM. Data presented as mean ± SD.

Adapted from: IM K et al. *J Funct Foods*. 2015;14:215-225.

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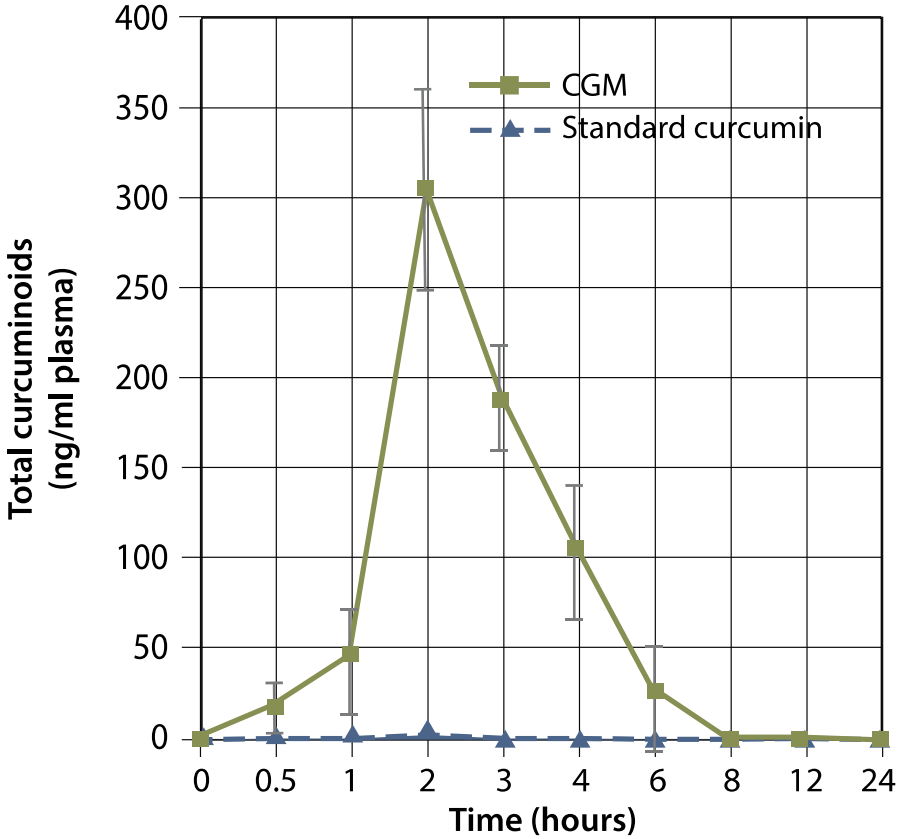
Circulating Free Curcuminoids in Rat Brain Tissue Are Higher with CGM Compared to Standard Curcumin Extract

CGM effectively crosses the blood-brain barrier in a preclinical animal study (BBB)



Total free curcuminoids in brain tissue of Wistar rats orally administrated with standard curcumin or CGM. Data presented as mean ± SD.

Adapted from: IM K et al. *J Funct Foods*. 2015;14:215-225.

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Circulating Free Curcuminoids Across Rat Plasma Are Higher with CGM Compared to Standard Curcumin Extract

Differences in Curcuminoid AUC in Rat Tissue Following CGM Compared with Standard Curcumin Preparation

Tissue	Standard curcumin (200mg dose)	CGM (200mg dose)	CGM compared to standard
	AUC	*AUC*	*Fold Increase*
Plasma	70.18	1,758.00*	25.05
Liver	7.77	867.60*	111.6
Kidney	12.21	882.20*	72.25
Heart	8.7	476.90*	54.82
Spleen	9.87	543.00*	55.02
Brain	2.41	838.50*	347.93
Intestine	351,277	4,396,000*	12.51

AUC, area under the curve. Data as mean ± SD (n=3).
* denotes $p < 0.001$ of CGM compared with standard curcumin preparation.

Adapted from: IM K et al. *J Funct Foods*. 2015;14:215-225.

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Curcumin/CGM—Key Takeaways

- Properties of curcumin:[1-4]
  - **Analgesic** (reduced neuropathic pain in animal models)[1,2]
  - **Anti-arthritic** (reduced production of MMP1 and 3 in mouse model of arthritis)[3]
  - **Anti-inflammatory signaling**[4]

- CGM is highly bioavailable[5,6]
  - Readily enters the blood and tissues

1. Banafshe HR et al. *Eur J Pharmacol.* 2014;723:202-206.
2. Zhu X et al. *PLoS One.* 2014;9(3):e91303.
3. Mun SH et al. *J Pharmacol Sci.* 2009;111(1):13-21.
4. Shezhad A et al. *J Food Sci.* 2017;82(9):2006-2015.
5. Sudheeran SP et al. *J Clin Psychopharmacol.* 2016;36(3):236-243.
6. IM K et al. *J Funct Foods.* 2015;14:215-225.

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Xanthohumol: An Isolated Constituent

- Xanthohumol is one of many active constituents in hops flowers (*Humulus lupulus*)
- Hops flowers have commercial uses (to flavor and preserve beer) and medicinal uses
- **Properties**[1]
  - **Anti-inflammatory**
  - **Antioxidant**
- Evidence:
  - Anti-arrhythmic and anti-atherosclerotic properties in animal models,[2-4] reduced platelet activation (human *ex vivo*),[5] anti-obesity and glucose lowering effect in animal models,[6] reduced DNA damage (clinical study)[7]

1. Liu M et al. *Molecules.* 2015;20(1):754-779.
2. Arnaiz-Cot JJ et al. *J Pharmacol Exp Ther.* 2017;360(1):239-248.
3. Liu et al. *J Nat Prod.* 2017;80(7):2146-2150.
4. Hirata et al. *PLoS One.* 2012;7(11):e49415.
5. Lee YM et al. *Evid Based Complement Alternat Med.* 2012;2012:852362.
6. Legette LL et al. *Phytochemistry.* 2013;91:236-241.
7. Ferk F et al. *Mol Nutr Food Res.* 2016;60(4):773-786.

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Xanthohumol—Key Takeaways

- Properties:[1,2]
  - **Anti-inflammatory**
  - **Antioxidant**
- Xanthohumol delivered through a hops-protein matrix:
  - Increased bioavailability[3]

1. Liu M et al. *Molecules.* 2015;20(1):754-779.
2. Ferk F et al. *Mol Nutr Food Res.* 2016;60(4):773-786.
3. O'Connor A et al. *Mol Nutr Food Res.* 2018;62(6):e1700692.

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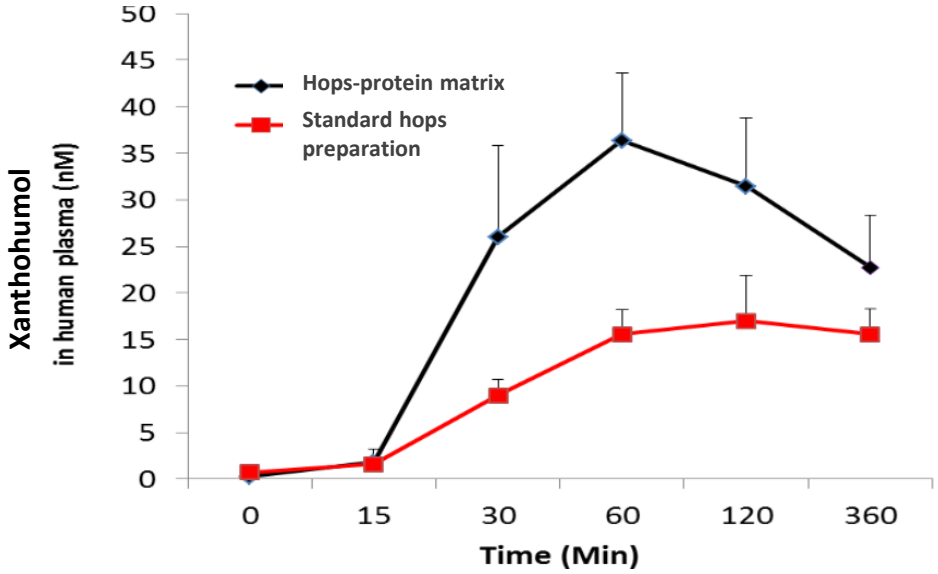
Xanthohumol Availability Is Enhanced by Delivery Through a Hops-Protein Matrix

- Xanthohumol is generally not well absorbed
- Xanthohumol given as part of a hops-protein matrix shows enhanced bioavailability compared to standard hops-xanthohumol preparations



Adapted from: O'Connor A. *Mol Nutr Food Res*. 2018;62(6):e1700692.

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Boswellia Serrata

- Also known as Indian Frankincense
- A “gum resin” from the *Boswellia serrata* tree
- Contains a few active constituents:
  - Beta-boswellic acids
  - Alpha-boswellic acids
  - Essential oils
  - Flavonoids—quercetin
- **Properties**
  - **Analgesic** (increased pain threshold in healthy subjects)[1]
  - **Anti-arthritic** (reduced inflammatory markers and arthritis score in mouse models and reduced knee pain in subjects with OA)[2,3]
  - **Anti-inflammatory and anti-oxidant signaling**[4]

1. Prabhavathi K et al. *Indian J Pharmacol.* 2014;46(5):475-479.
2. Umar S et al. *Phytomedicine.* 2014;21(6):847-856.
3. Kimmatkar N et al. *Phytomedicine.* 2003;10(1):3-7.
4. Du Z et al. *Planta Med.* 2015;81(4):259-267.

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Ginger Root

- Contains several constituents:
  - Gingerol
  - Gingerdione
  - Shogaol
  - Sesquiterpene and monoterpene volatile oils
- Properties[1,2]
  - **Analgesic**
  - **Anti-inflammatory**
  - **Antioxidant**

1. Semwal RB et al. *Phytochemistry.* 2015;117:554-568.
2. Rayati F et al. *Dent Res J.* 2017;14(1):1-7.

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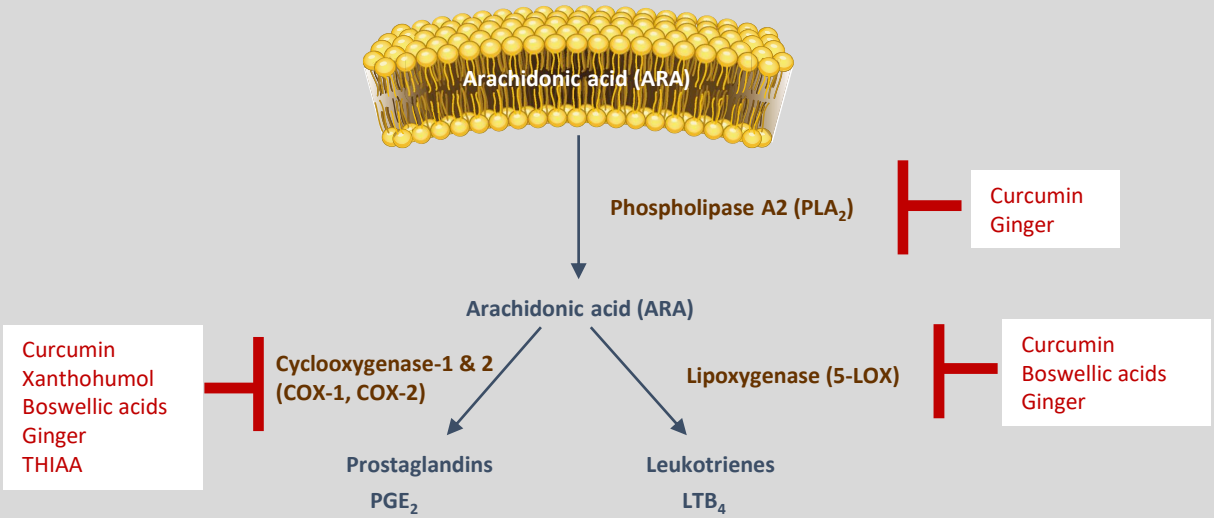
Inflammation & Pain: Key Enzymes



Perrone D et al. *Exp Ther Med.* 2015;10(5):1615-1623.
Zhou H et al. *Curr Drug Targets*. 2011;12(3):332-347.
Nievergelt A et al. *J Immunol.* 2011;187(8):4140-50.
Kunnumakkara AB et al. *Br J Pharmacol.* 2017;174(11)1325-1348.
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Abdel-tawab M et al. *Clin Pharmacokinet*. 2011;50(6):349-369.
Grzanna R et al. *J Med Food*. 2005;8(2):125-132.
Desai A et al. *Inflamm Res.* 2009;58:1-6.
Konda VR et al. *Arthritis Rheum.* 2010;62(6):1683-1692.
Desai A et al. *Atherosclerosis.* 2012;223:130-136.

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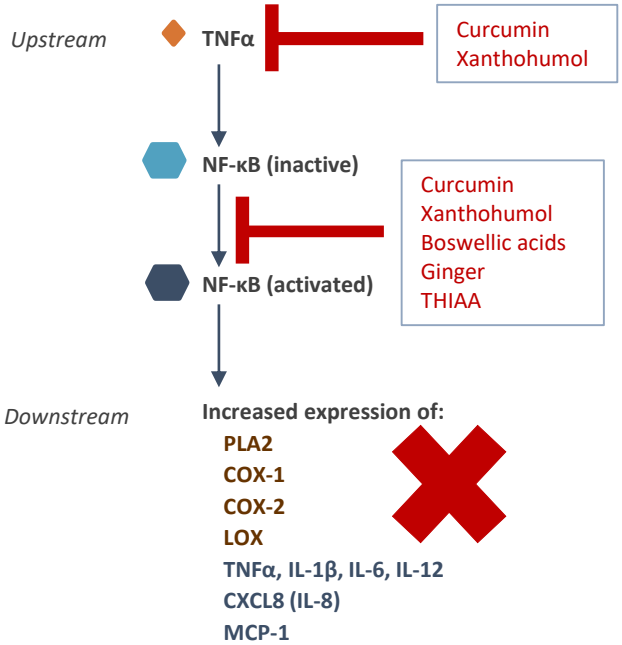
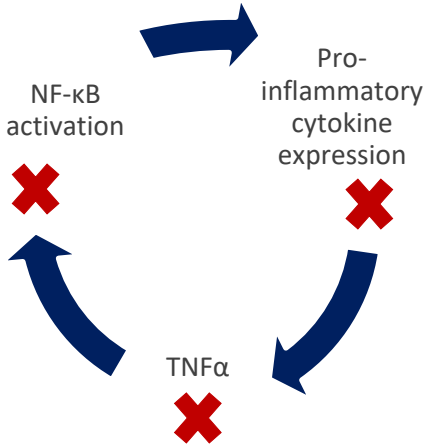
Phytonutrients Shown to Modulate Inflammatory Cascade





Panahi Y et al. *Biomed Pharmacother*. 2016;82:578-582.
Lupinacci EL et al. *J Agric Food Chem*. 2009;57(16):7274-7281.
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Liu M et al. *Molecules*. 2015;20(1):754-779.
Khan MA et al. *Molecules*. 2015;20(1):754-779.
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Desai A et al. *Atherosclerosis.* 2012;223:130-136.

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Inflammation & Pain: Chemokines

- Curcumin
  - Reduces serum levels of MCP-1[1]
  - Reduces chondrocyte production of CXCL8[2]
- Xanthohumol
  - Reduces macrophage production of MCP-1[3]
- Ginger
  - Reduces IP-10, specifically in activated human synoviocytes[4]

1. Karimiana MS et al. *Cytokine Growth Factor Rev*. 2017;33:55-63.
2. Panahi Y et al. *Biomed Pharmacother*. 2016;82:578-582.
3. Lupinacci EL et al. *J Agric Food Chem.* 2009;57(16):7274-81.
4. Phan PV et al. *J Altern Complement Med.* 2005;11(1):149-154.

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Mechanism of Action Summary

	Curcumin	Xanthohumol	*Boswellia serrata*	THIAA	Ginger
Moderation of pro-inflammatory cytokines, chemokines, and transcription factors associated with inflammation and pain	✓ Moderates NFkB ✓ Reduces serum levels: TNFα, IL-1β, IL-6, MCP-1 ✓ Diminishes chondrocyte production of CXCL8 (IL-8)	✓ Moderates NF-κB ✓ Reduces WBC production of TNFα, IL-12, MCP-1	✓ Moderates NF-κB	✓ Moderates NF-κB expression and activity ✓ Reduces serum levels of IL-6 ✓ Reduces immune cell production of pro-inflammatory cytokines	✓ Moderates NF-κB ✓ Diminishes synoviocyte production of IP-10
Moderation of enzymes and prostaglandins associated with inflammation and pain	✓ Moderates PLA2 ✓ Moderates COX-2 ✓ Moderates 5-LOX	✓ Moderates COX-1 & COX-2	✓ Moderates COX-1 & COX-2 ✓ Moderates 5-LOX	✓ Moderates COX-2	✓ Moderates PLA2 ✓ Moderates COX-1 & COX-2 ✓ Moderates LOX

Mathy-Hartert M et al. *Inflamm Res*. 2009;58(12):899-908.
Karimiana MS et al. *Cytokine Growth Factor Rev*. 2017;33:55-63.
Panahi Y et al. *Biomed Pharmacother*. 2016;82:578-582.
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Lee T et al. *Biochem Biophys Res Commun.* 2009;382(1):134-139.
Lee HY et al. *Br J Pharmacol.* 2012;167(1):128-140.
Ganjali S et al. *Scientific World J.* 2014;2014:898361.
Desai et al. *Inflamm Res.* 2009;58:1-6.
Konda et al. *Arthritis Rheum.* 2010;62(6):1683-1692.

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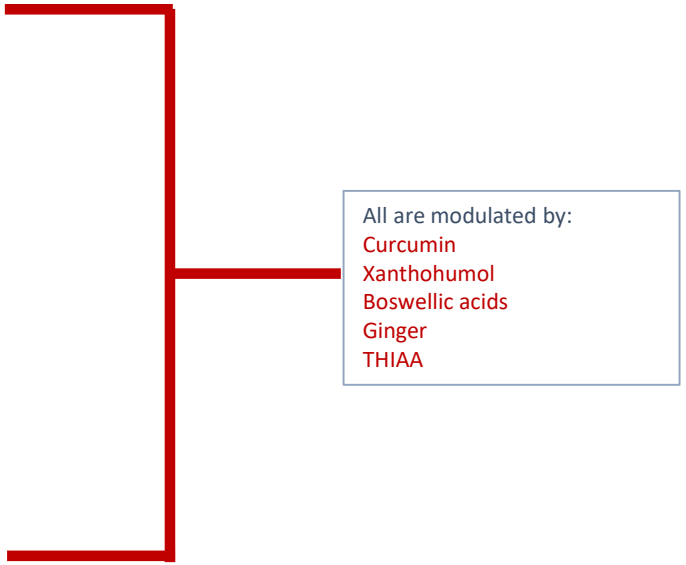
Key Mediators of Inflammation & Pain Modulated by Curcumin, Xanthohumol, Boswellic Acids, & Ginger

- Enzymes
  - Phospholipase A2 (PLA_2)
  - Cyclooxygenase (COX-1 and COX-2)
  - Lipoxygenase (LOX)
- Gene expression regulators
  - Nuclear factor-kappa B (NFkB)
- Pro-inflammatory cytokines
  - TNFα
  - IL-1β
  - IL-6
  - IL-12
- Chemokines
  - Neutrophil chemotactic factor (CXCL8, aka IL-8)
  - Monocyte chemoattractant protein 1 (MCP-1)
  - Interferon-γ activated protein (IP-10)



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Mechanistic Takeaways

- There are several nutritional bioactives that modulate inflammation initiation, including curcumin, xanthohumol, *Boswellia serrata,* ginger, and THIAA:
  - **Moderate several key mediators** of inflammation & pain
    - NF-κB—Upregulates cytokines, chemokines, and pro-inflammatory enzymes
    - Pro-inflammatory cytokines
    - Chemokines—WBC recruitment
    - Enzymes involved in prostaglandin and leukotriene production
  - **Act upstream and downstream** on inflammation & pain pathways

Panahi Y et al. *Biomed Pharmacother*. 2016;82:578-582.
Lupinacci EL et al. *J Agric Food Chem*. 2009;57(16):7274-7281.
Kunnumakkara AB et al. *Br J Pharmacol.* 2017;174(11)1325-1348.
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Konda VR et al. *Arthritis Rheum.* 2010;62(6):1683-1692.
Desai A et al. *Atherosclerosis.* 2012;223:130-136.

Other Key Takeaways

THIAA

Has anti-inflammatory properties, and has demonstrated anti-arthritic action in animal model of arthritis[1-3]

Curcumin

Has anti-inflammatory and analgesic action in pre-clinical models.[4-6] Shown to have anti-arthritic properties in rodent models of arthritis[7]

Xanthohumol

Activates anti-oxidant and anti-inflammatory signaling pathways.[8] Preclinical studies have demonstrated anti-arrhythmic and anti-atherosclerotic properties,[9-11] anti-obesity and glucose lowering effect in animal models.[12] Human studies showed reduced platelet activation (*ex vivo* model)[13] and reduced DNA damage (clinical study)[14]

Boswellia serrata

Analgesic and anti-arthritic action in human studies,[15,16] and modulate anti-inflammatory and anti-oxidant signaling pathways[17]

Ginger

Demonstrated anti-inflammatory anti-oxidant signaling effects,[18] and analgesic effects[19]

1. Desai A et al. *Atherosclerosis.* 2012;223:130-136.
2. Desai A et al. *Inflamm Res.* 2009;58(5):229-234.
3. Konda VR et al. *Arthritis Rheum.* 2010;62(6):1683-1692.
4. Banafshe HR et al. *Eur J Pharmacol.* 2014;723:202-206.
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16. Kimmatkar N et al. *Phytomedicine.* 2003;10(1):3-7.
17. Du Z et al. *Planta Med.* 2015;81(4):259-257.
18. Semwal RB et al. *Phytochemistry.* 2015;117:554-568.
19. Rayati F et al. *Dent Res J.* 2017;14(1):1-7.

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Inflammation Resolution Mechanisms and the Role of Specialized Pro-Resolving Mediators (SPMs)

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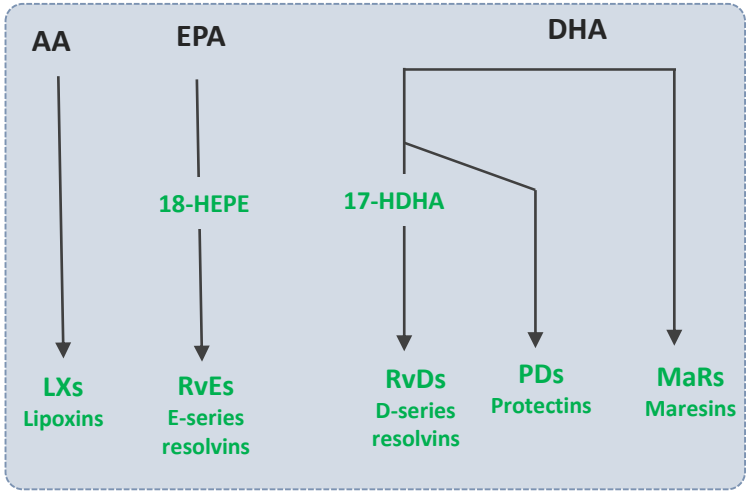
What are Specialized Pro-Resolving Mediators?



Specialized Pro-Resolving Mediators

1. Specialized pro-resolving mediators (SPMs) are a group of lipid mediators that drive the resolution of inflammation.
2. SPMs can be produced endogenously in the body from precursor polyunsaturated fatty acids (AA, EPA, and DHA)
3. SPMs are required for inflammation resolution to occur and for effective return to homeostasis or previously normal conditions
4. There are several classes of SPMs (lipoxins, resolvins, protectins and neuro-protectins, maresins) that all work together to resolve inflammation
5. Key hydroxylated precursor SPMs such as 18-HEPE and 17-HDHA can give rise to an array of downstream SPMs that have been identified to date. 18-HEPE can be converted into 4 distinct E-series resolvins (RvE_{1-4}) and 17-HDHA can be converted into 6 distinct D-series resolvins (RvD_{1-6})

Adapted from: Serhan CN. *FASEB J.* 2017;31(4):1273-1288.

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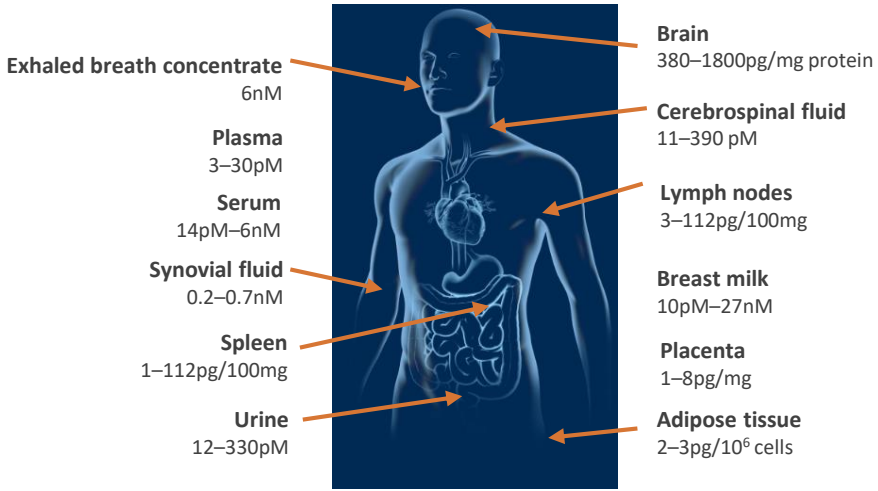
SPMs Have Been Identified at Bioactive Levels Across Many Human Tissues and Fluids



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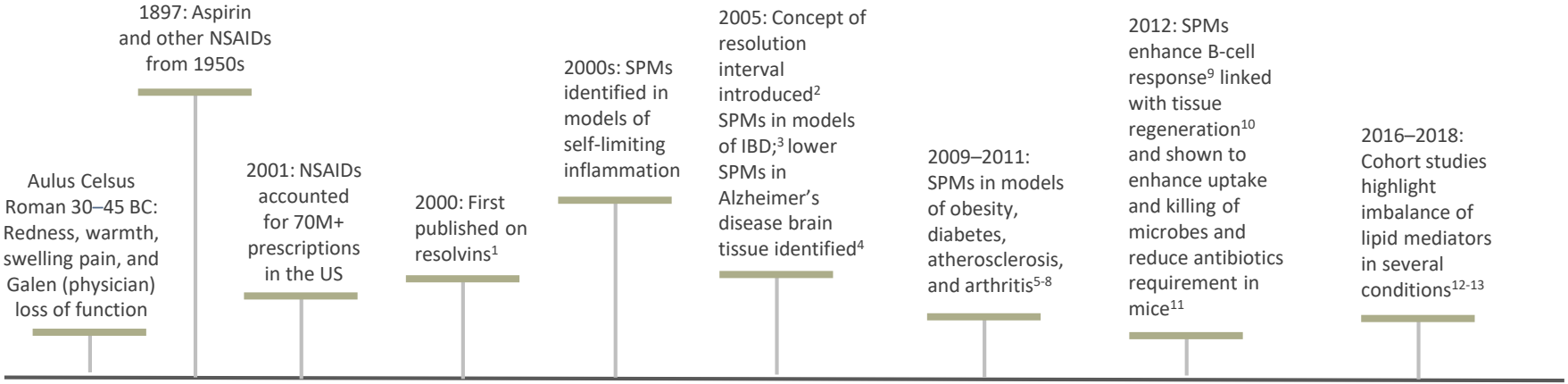

Previous science perspective

- Inflammation faded out by itself
- Blocking inflammation was the goal

Current perspective

- Inflammation resolution is an active process required for homeostasis
- Resolution is coordinated by specialized pro-resolving mediators

1. Serhan CN et al. *J Exp Med*. 2000;192:1197–1204.
2. Bannenberg GL et al. *J Immunol.* 2005;174:4345-4355.
3. Arita M et al. *Proc Natl Acad Sci* USA. 2005;201:7671-7676.
4. Lukiw WJ et al. *J Clin Invest*. 2005;115(10):2774-2783.
5. Gonzalez-Periz A et al. *FASEB J.* 2009;23:1946-1957.
6. Hellman J et al. *FASEB J.* 2011;25:2399-2407.
7. Ho KJ et al. *Am J Pathol.* 2010;177:2116-2123.
8. Lima-Garcia JF et al. *Br J Pharmacol.* 2011;164(2):278-293.
9. Ramon S et al. *J Immunol*. 2012;189(2):1036-1042.
10. Serhan CN et al. *FASEB J* 2012;26:1755-1765.
11. Chiang N et al. *Nature.* 2012;484:524-528.
12. Titos E et al. *J Immunol.* 2016;197:3360-3370.
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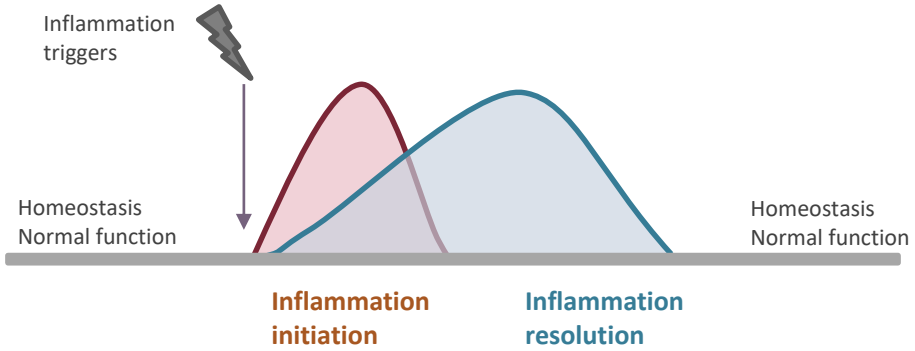
Hallmarks of SPM Activity and Inflammation Resolution



SPMs actively promote inflammation resolution

- Enhance macrophage phagocytosis and efferocytosis, which clears up dead or dying cells and cellular debris
- Shorten the time to resolution
- Increase the production of anti-inflammatory mediators
- Increase the killing and clearance of microbes
- Enhance tissue regeneration

SPMs act to curtail excessive inflammatory response

- Limit further pro-inflammatory PMN cells coming to the site of inflammation
- Counter-regulate pro-inflammatory mediators
- Limit tissue damage from excessive or persistent inflammation

Adapted from: Serhan CN. *FASEB J.* 2017;31(4):1273-1288.

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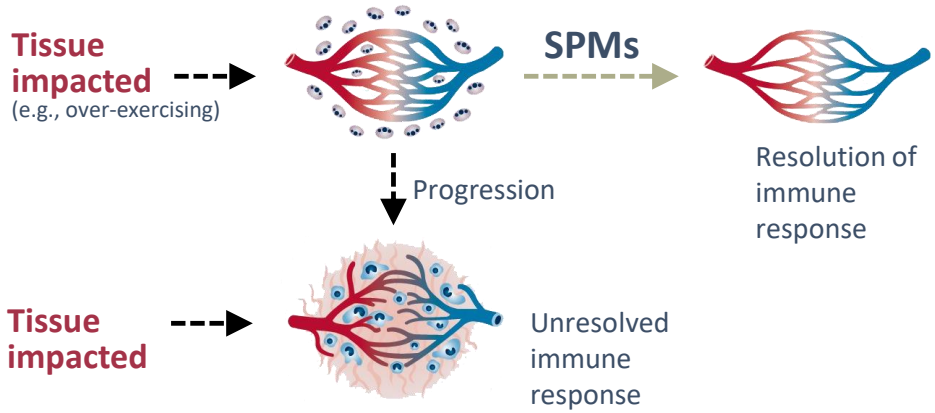
Resolution is Necessary to Prevent Tissue Damage—Associated with Chronic Inflammation



Kumar et al. *Robbins & Cotran Pathologic Basis of Disease*. 8th ed. Saunders;2009.

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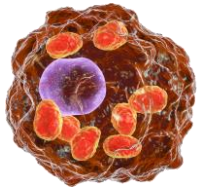
Pro-Resolving Versus Pro-Inflammatory Macrophages

Pro-inflammatory
- M1 phenotype
- Classically activated macrophages

Functions:
- Anti-microbial activity
- ROS production
- Engulfs pathogens



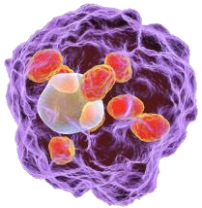
Secretes:
- Free radicals
- Pro-inflammatory cytokines e.g. TNF-α, IL-6
- MHC-II

End result = inflammation

SPMs promote pro-resolving phenotype

Pro-resolving
- M2 phenotype
- Alternatively activated macrophages

Functions:
- Anti-inflammatory
- Engulfs dead and dying cells and other cell debris



Secretes:
- IL-10
- TGF-β
- VEGF
- PDGF

Resolution of inflammation and tissue regeneration

Adapted from: Das A et al. *Am J Pathol.* 2015;185(10):2596-2606.

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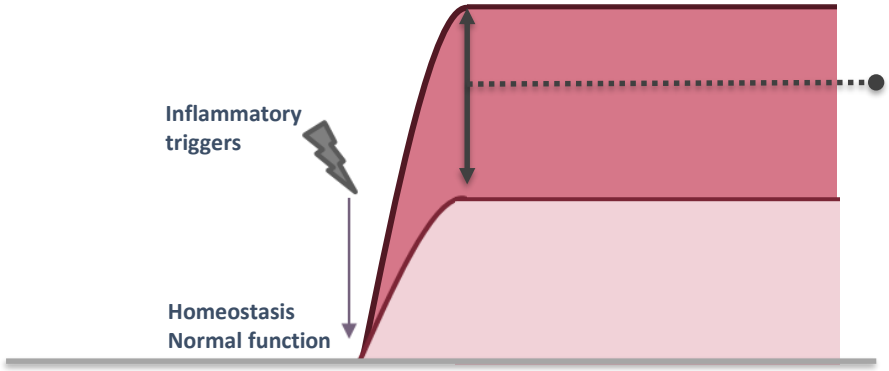
Why Use Anti-Inflammatory Agents?



Anti-inflammatory agents may be important to help reduce the magnitude of the inflammation initiation response.

Most anti-inflammatory agents do not address inflammation resolution.

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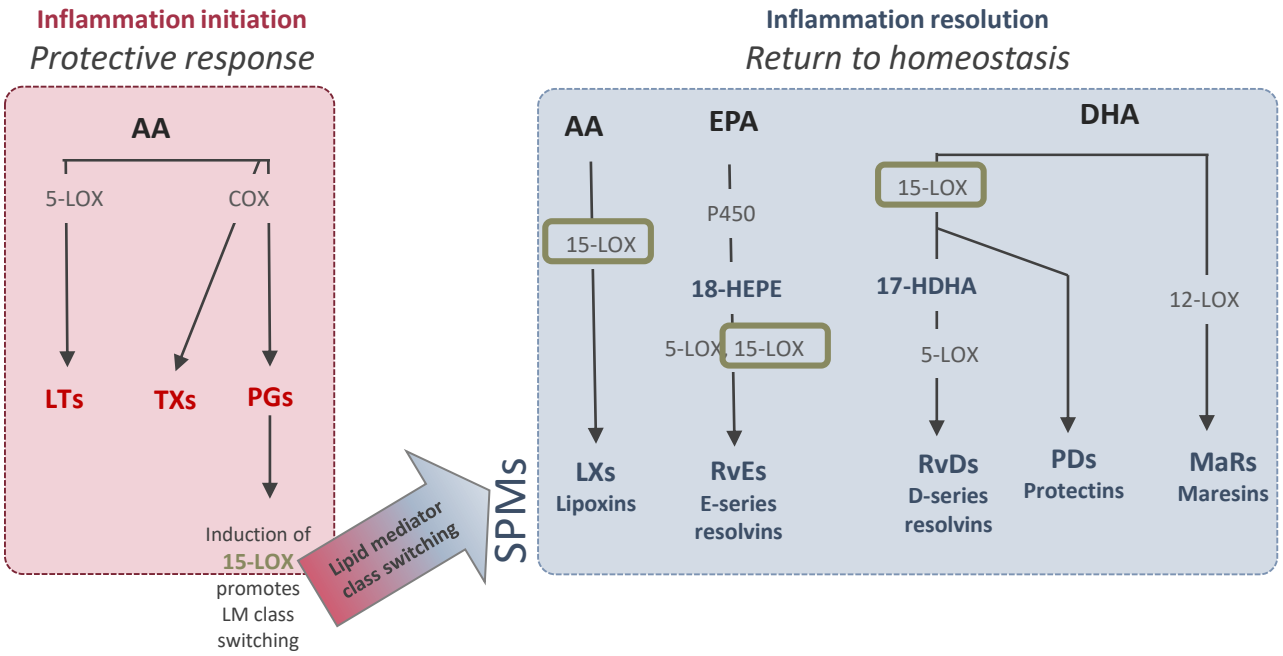
Lipid Mediator Biosynthesis



1. During initiation, pro-inflammatory lipid mediators such as LTs and PGs are predominant.
2. PGs promote 15-LOX induction. 15-LOX is an enzyme important for SPM production.
3. Lipid mediator class switching occurs when SPM synthesis increases. SPMs promote inflammation resolution.
4. During resolution, SPMs are predominant.

Lipid mediators involved in inflammation initiation
Lipid mediators involved in inflammation resolution

Adapted from: Serhan CN. *FASEB J.* 2017;31(4):1273-1288.

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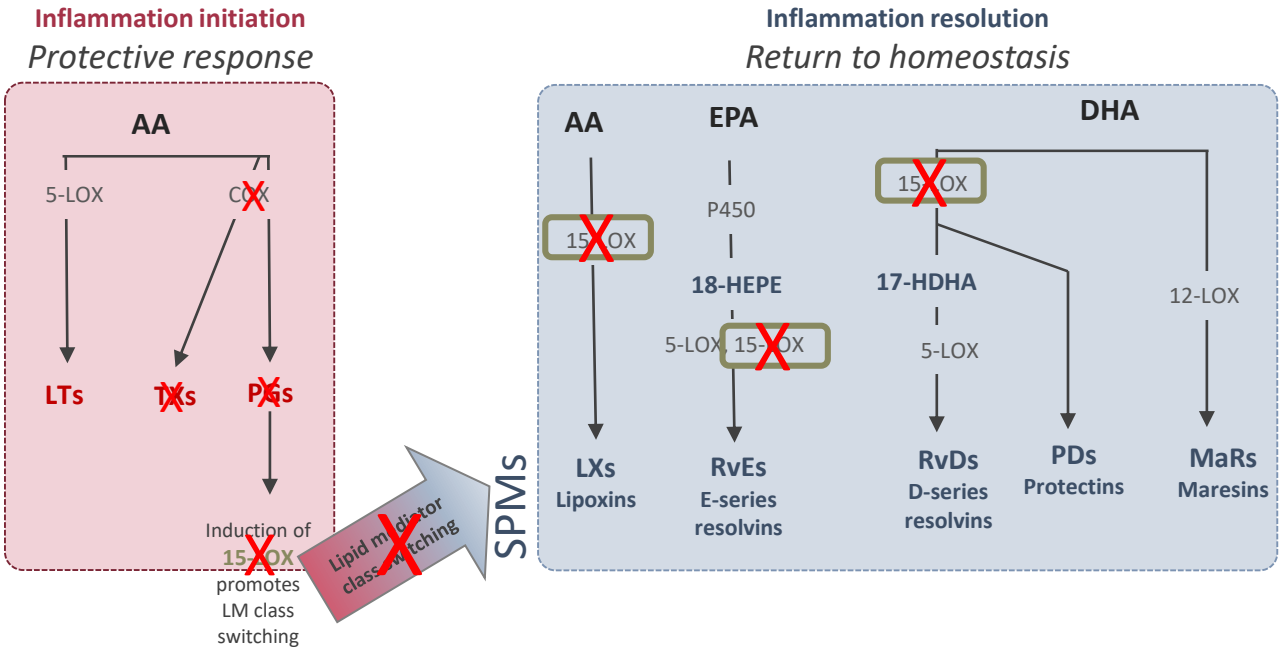
Impact of COX-2 Inhibitors on Lipid Mediator Biosynthesis



1. COX-2 inhibitors block the production of PGs.
2. Because PGs promote the induction of 15-LOX needed for production of SPMs, SPM production can be reduced.
3. Lipid mediator class switching is impaired.
4. COX-2 inhibitors are considered "resolution toxic."

Lipid mediators involved in inflammation initiation
Lipid mediators involved in inflammation resolution

Adapted from: Serhan CN. *FASEB J.* 2017;31(4):1273-1288.

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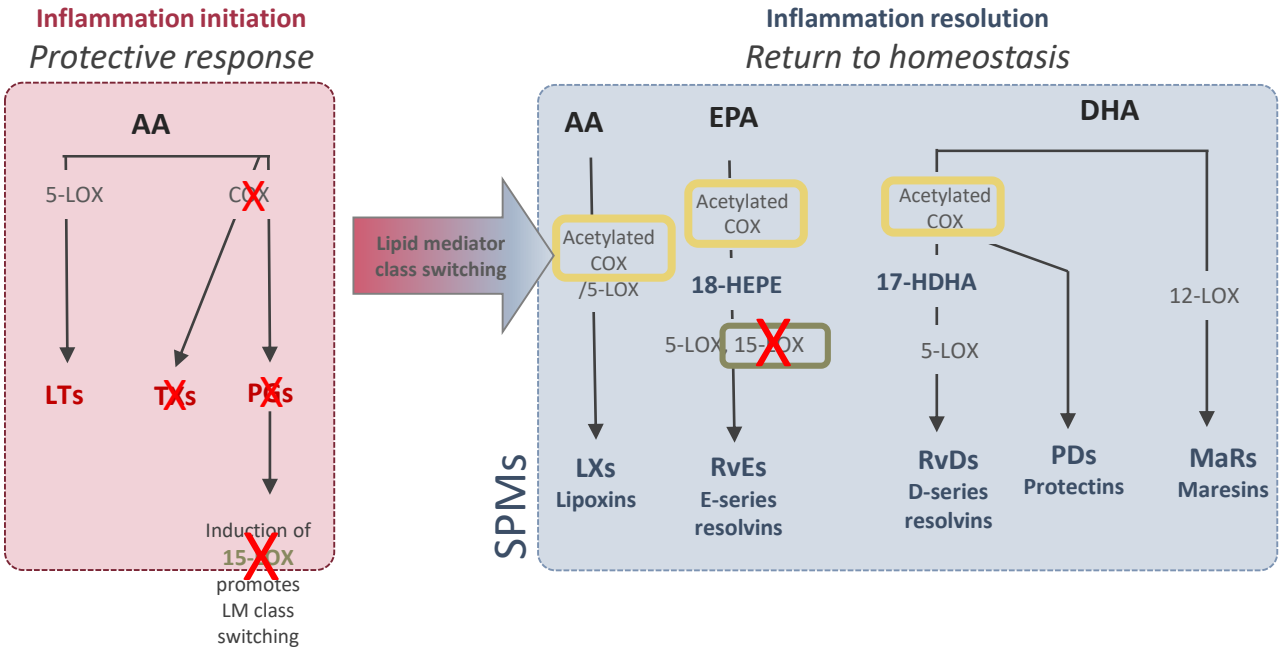
Impact of Low-Dose Aspirin on Lipid Mediator Biosynthesis



1. Low-dose aspirin blocks the activity of COX that leads to PG production.
2. But low-dose aspirin changes the COX catalytic domain. Acetylated COX is involved in the production of aspirin-triggered SPMs.
3. Lipid mediator class switching can occur.
4. Low-dose aspirin is considered "resolution friendly."

Catalytic domain: the region where the chemical reaction takes place

Lipid mediators involved in inflammation initiation

Lipid mediators involved in inflammation resolution

Adapted from: Serhan CN. *FASEB J.* 2017;31(4):1273-1288.

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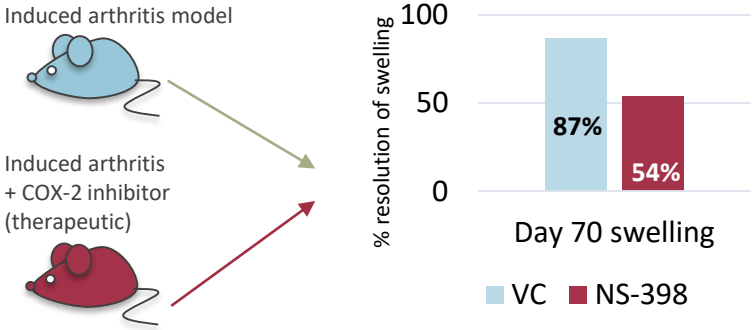
Blocking Inflammation and Resolution Toxicity

Alpha signals omega—prostaglandin biosynthesis is critical to resolution, because PGEs stimulate induction of lipoxygenases necessary for LX and Rv synthesis. Blocking this cascade (e.g., COX-2 inhibitors) can be “resolution toxic.”



- TNFα and IL-17mRNA increased in NS-398
- Radiography showed greater degree of soft tissue swelling, digital misalignment, ankyloses ,and loss of bone density in NS-398
- Histological staining showed pannus of knee joint was proliferative and cartilage and bone more severely damaged in NS-398
- **PGE_2 analogue treatment helped restore resolution**

Adapted from: Chan MM et al. *J Immunol.* 2010;184:6418-6426.

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SPMs Are Not Considered Immunosuppressive

In a range of preclinical mouse models of infection, SPMs have been shown to improve outcomes—highlighting that SPMs do not reduce the protective inflammatory response and are therefore not considered immunosuppressive.

Infection	Model	SPM Tested	Outcome in SPM Group
Candida albicans	Mouse candidiasis	RvE1	Stimulated clearance of the fungus from circulating blood
Sepsis	Mouse CLP	RvD2	Reduced mortality
Escherichia coli	Mouse pneumonia	RvE1	Reduced mortality
Herpes simplex virus	Mouse keratitis	RvE1	Reduced lesion severity
Escherichia coli	Mouse peritonitis	RvD1	Reduced mortality
Escherichia coli	Mouse peritonitis	RvD1 RvD5	Protections from hypothermia and enhanced antibiotic effectiveness
Staphylococcus aureus	Mouse skin infection	RvD1 RvD5	Reduced bacterial titers and enhanced antibiotic effectiveness
Sepsis	Mouse double injury of burn and sepsis	RvD2	Increased survival

Adapted from: Chiang N et al. *Mol Aspects Med*. 2017;58:114-129.

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Factors Impacting Levels of Endogenous Specialized Pro-Resolving Mediators (SPMs)

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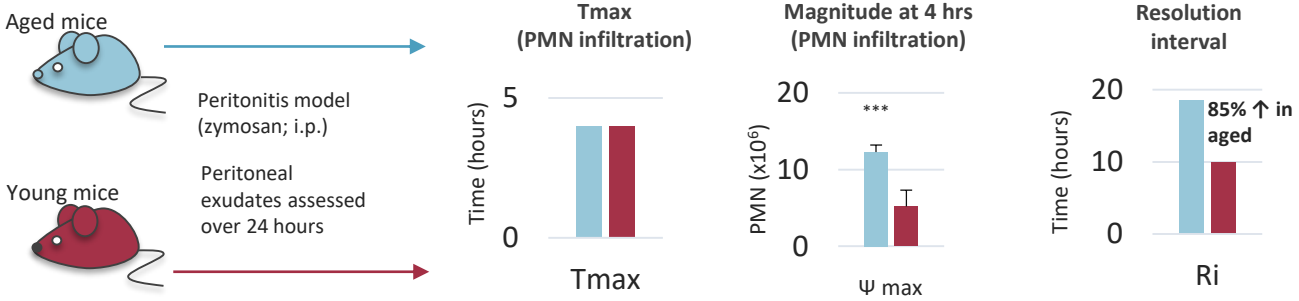
Aging Delays Resolution and Alters the Balance of Pro-Inflammatory : Pro-Resolving Mediators



- IL-6 ↑ in exudates from aged mice
- Macrophages from aged mice had reduced ability to clear apoptotic PMNs
- Distinct lipid mediator profile in young versus aged mice: reduced lipoxins and DHA-derived SPMs and increased PGs/TXs
- **RvD3 shorted Ri, reduced PMN, and enhanced ability of macrophage to clear PMNs**

*** p<0.001 versus young mice

Adapted from: Arnordottir HH et al. *J Immunol.* 2014;193:4235-4244.

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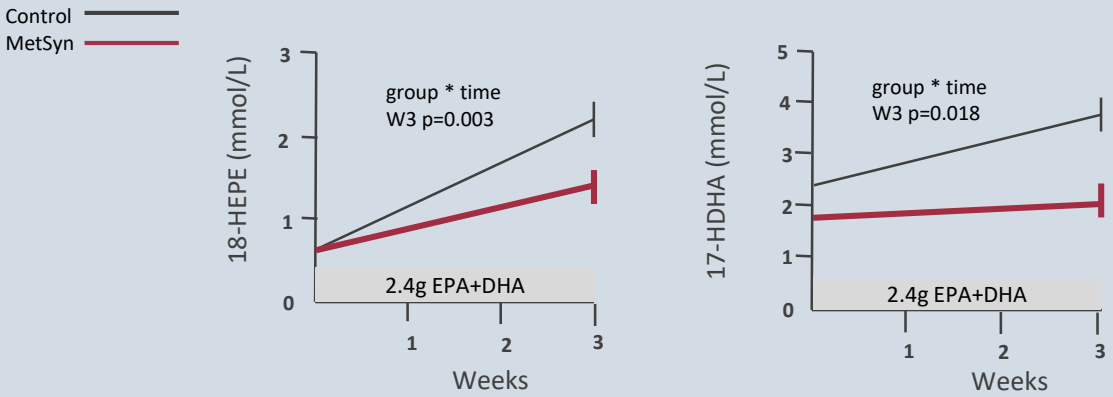
Less SPMs in Circulation Following Fish Oil in Metabolic Syndrome vs. Healthy



Metabolic syndrome blunts increase in 17-HDHA and 18-HEPE following EPA + DHA supplementation

Adapted from: Barden AE et al. *Am J Clin Nutr.* 2015;102:1357-1364.

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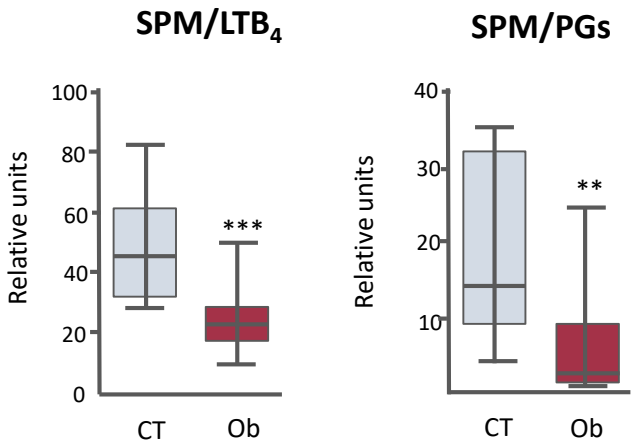
People with Obesity Have a Lower Ratio of SPMs: Pro-Inflammatory Mediators Compared to People with Lower Body Weight



- The ratio between SPMs and pro-inflammatory markers is lower in obese adipose tissue.
- Subjects with obesity (Ob) scheduled for bariatric surgery (n=41) and lean controls (CT) (n=7) scheduled for cholecystectomy. Omental adipose tissue samples collected at time of surgery.

Data are mean ± SEM
**p< 0.005 vs. CT subjects
***p<0.001 vs. CT subjects

Adapted from: Titos E et al. *J Immunol.* 2016;197:3360-3370.

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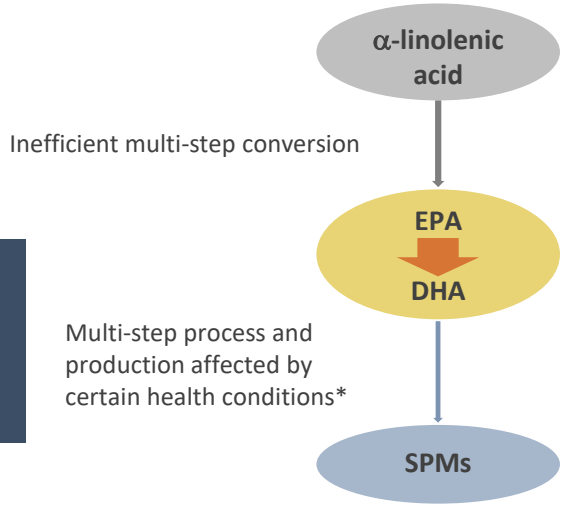
Conversion of Parent Fatty Acids to SPMs May Not Be Optimal in All Individuals

Inefficient conversion to meet needs in the face of inflammation, particularly in an already compromised host



Essential fatty acids
Must be acquired through diet

Conditionally essential fatty acids support:
- Cell membrane integrity
- Brain and eye health
- Healthy triglycerides level
- Heart health

Unique role in supporting the resolution of the immune response and inflammation—necessary for healthy aging and active living
- Neutrophil activity is curtailed
- Macrophages remove dead neutrophils, bacteria, and debris
- Tissue is remodeled
- Return to homeostasis (cells' previous normal conditions)

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Potential Groups Who May Benefit from SPM Supplementation

- Research has described areas in which SPM levels and the balance between the pro-inflammatory and pro-resolving lipid mediators are related. For example:
  - In a preclinical mouse model of aging, SPM levels were lower and pro-inflammatory mediators were higher following an inflammatory challenge compared with younger mice, and giving exogenous SPMs could rescue this.[1]
  - Circulating SPM (17-HDHA and 18-HEPE) levels increased to a lesser magnitude in people with metabolic syndrome vs. healthy controls following fish oil supplementation- indicating a potential need for more direct supplementation with SPMs.[2]
  - In people with obesity, a lower level of SPMs and a higher level of pro-inflammatory lipid mediators is seen indicating some dysregulation of lipid mediators.[3] Animal research in obesity has also shown that this occurs in diet-induced and genetic models of obesity,[4,5] and that DHA-rich diets are less effective in raising tissue SPM levels in obese animals compared with leaner controls.[5]

1. Arnordottir HH et al. *J Immunol.* 2014;193:4235-4244.
2. Barden AE et al. *Am J Clin Nutr.* 2015;102:1357-1364.
3. Titos E et al. *J Immunol.* 2016;197:3360-3370.
4. Claria et al. *J Immunol.* 2012;189:2597-2605.
5. Neuhofer A et al. *Diabetes.* 2013;62:1945–1956.

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Emerging Areas of Specialized Pro-Resolving (SPMs) Research

- Preclinical and human observational cohort data highlights potential areas of interest for resolution science

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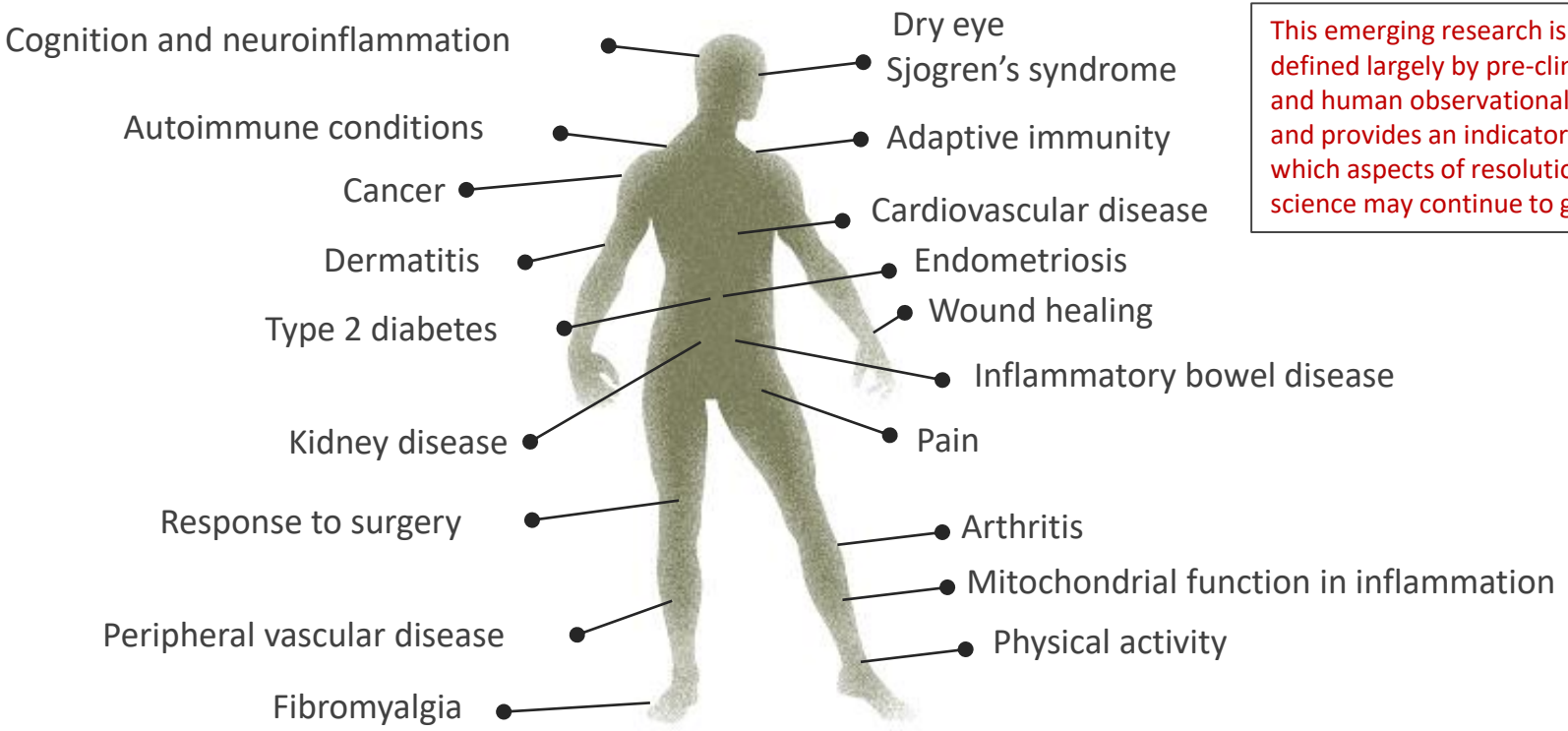
Emerging Areas of Specialized Pro-Resolving Mediator Research



This emerging research is defined largely by pre-clinical and human observational data and provides an indicator of which aspects of resolution science may continue to grow

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Emerging Area: Adaptive Immunity

B-cell differentiation and function[1,2]

- RvD1 and 17-HDHA promote the differentiation of IgG-secreting B cells and enhance antibody-mediated immune responses.
- RvD1 and 17-HDHA inhibit IgE production by human B cells and suppress the differentiation of naïve B cells into IgE-secreting cells by specifically blocking epsilon germline transcript.

T-cell response[3,4]

- Data suggests that RvD2 inhibits systemic and gingival Th1-type adaptive responses known to mediate alveolar bone loss in a mouse model of periodontitis.
- In human peripheral blood lymphocytes, RvD1, RvD2, and Mar1 reduced cytokine production by activated CD8(+) T cells and CD4(+) T helper 1 (TH1) and TH17 cells and prevented naïve CD4(+) T cell differentiation into TH1 and TH17 cells.

1. Kim N et al. *Eur J Immunol*. 2016;46(1):81-91.
2. Ramon S et al. *J Immunol*. 2012;189(2):1036-1042.
3. Mizraji G et al. *Front Immunol*. 2018;9:785.
4. Chiurchiu V et al. *Sci Transl Med*. 2016;8(353):353ra111.

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Emerging Area: Endometriosis

Objective: To study the effects of two resolvins of D series, RvD1 and 17(R)-RvD1, on inflammatory signs associated with endometriosis, in a rat model of endometriosis.

Design:
Intravenous or intraperitoneal injections of RvD1 (300 ng/kg) or 17(R)-RvD1 (300 and 900 ng/kg) in rats with surgically induced endometriosis.

Results:
Both resolvins, but not vehicle control (placebo), significantly decreased vascular permeability in ectopic endometrial tissue. 17(R)-RvD1 also significantly alleviated severity of vaginal hyperalgesia.

Conclusion:
RvD1 and 17(R)-RvD1 can be considered for further investigation of their therapeutic potential for treating endometriosis.

Dmitrieva N et al. *Fertil Steril.* 2014;102(4):1191-1196.

Emerging Area: Dermatitis

Objective: To study the effects of resolvin E1 (RvE1) in a mouse model of psoriatic dermatitis.

Design: Mice with imiquimod-induced psoriasis treated with daily IV injections of E1 (RvE1) and ear swelling (site of psoriasis) and epidermal hyperplasia, as well as T-cell populations, neutrophil levels and immune markers assessed as psoriasis severity-related outcomes.

Conclusion:
RvE1 reduced inflammation and leads to improvements in psoriatic skin in mice.

Results:

- RvE1 suppressed the inflammatory cell infiltration and epidermal hyperplasia in the psoriatic skin.
- RvE1 decreased the mRNA expression of IL-23 in the skin.
- RvE1 inhibited migration of IL-17-producing cells *in vivo.*

Sawada Y et al. *Sci Rep*. 2018;8(1):11873.

Emerging Area: Dermatitis

Objective: To determine the protective effects and the underlying mechanisms of RvD1 in a mouse model of induced psoriatic dermatitis.

Design:
Mice were pretreated intraperitoneally (i.p.) with or without RvD1, and severity of induced dermatitis graded using a modified Psoriasis Area and Severity Index (PASI), histopathology, and cytokine analysis.

Conclusion:
RvD1 can improve skin inflammation in mice with induced psoriasiform dermatitis.

Results:
- RvD1 treatment alleviated induced psoriasis form dermatitis and improved skin pathological changes.
- RvD1 treatment inhibited pro-inflammatory signaling in this model.

Xu J et al. *J Dermatol Sci*. 2018;89(2):127-135.

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Emerging Area: Wound Healing

Objective: To explore sex differences in wound healing in lipid mediator profile over time-course of blister formation and resolution.

Design:
Skin blister was induced by cantharidin in 16 men and 16 pre-menopausal women. Inflammatory exudate was collected and lipid mediators and cellular recruitment was measured at 24 and 72 hours.

Conclusion: Pre-menopausal women appear to have greater capacity for resolution in this blister model than men, and this may be mediated by an elevation of the D-resolvin pathway.

Results:

- At 24 hours, cantharidin formed blisters of similar volume in both sexes; however, at 72 hours, blisters had only resolved in women.
- Monocyte and leukocyte counts were reduced, and the activation state of all major leukocytes was lower in blisters of females.
- This was associated with enhanced levels of the resolving lipids, particularly D-resolvin.

Rathod KS et al. *J Clin Invest*. 2017;127(1):169-182.

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Emerging Area: Wound Healing

Objective: Compare the effects of resolvins D1 (RvD1), D2 (RvD2), and E1 (RvE1) on their abilities to inhibit neutrophil migration *in vitro* and to promote wound healing *in vivo* in a mouse model.

Design:

- The impact of vD1, RvD2 and RvE1 on neutrophil migration was assessed in vitro (Transwell system).
- RvD1, RvD2, RvE1 and vehicle control (placebo) were then applied topically to mice with an excisional wound (1 cm x 1 cm), and time to wound closure was measured.

Conclusion:

Topical application of specific resolvins shows promise for supporting wound healing.

Results:

- All three resolvins inhibited neutrophil migration, with RvE1 being the most effective.
- Topically applied Rvs accelerated wound closure. RvE1-treated wounds healed within 19.4 ± 1.5, RvD2-treated within 22.8 ± 1.8 days, and RvD1-treated within 24.4 ± 2.2 days. All resolvin-treated groups healed significantly faster than placebo (within 28.6 ± 1.5 days).
- There was a strong linear correlation (R^2=0.9384) between each resolvin's potency in inhibiting neutrophil migration *in vitro* versus accelerating wound healing *in vivo.*

Mennon R et al. *Nano Life*. 2017;7(1).pii:1750002.

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Emerging Area: Mitochondrial Function in Inflammation

Objective: To investigate the impact of omega-6 (arachidonic acid) and omega-3 (EPA, DHA) fatty acids, and specialized pro-resolving mediators (18-HEPE and RvE1) on mitochondrial function in experimental inflammation.

Design:

- Peripheral blood mononuclear cells (PBMCs) were isolated from healthy individuals, pre-treated with TNF-a, and then treated with fatty acids (EPA, DHA, linoleic acid) or the SPMs (18-HEPE or RvE1).
- Pro-inflammatory mediators were measured, as were markers of mitochondrial function including respiration, membrane potential, and reactive oxygen species.

Conclusion:

These results suggest a novel functional mechanism for the beneficial effects of 18-HEPE and RvE1 in inflammatory reactions.

Results:

- The results revealed that, in contrast to n-6 and n-3 fatty acids, both 18R-HEPE and RvE1 possess anti-inflammatory and anti-apoptotic properties.
- Both mediators are able to restore inflammation-induced mitochondrial dysfunction, which is characterized by a decrease in mitochondrial respiration and membrane potential as well as an imbalance of mitochondrial fission and fusion.

Hecker M et al. *Biochim Biophys Acta*. 2018;1863(9):1016-1028.

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Emerging Area: Post-Surgery

Objective: To characterize the changes in interleukin-6 (IL-6), cortisol, and the specialized pro-resolving mediators lipoxin A4 and resolvin D in patients who underwent oncologic liver resection.

Design:

- Blood samples were collected before surgery and on the mornings of postoperative days 1, 3, and 5 from 41 patients undergoing liver resection.
- Interleukin-6, cortisol, lipoxin-A4, and resolvin D were measured in plasma.

Conclusion: Following surgery, circulating lipoxin A4 and resolvin D are low and IL-6 and cortisol are high. The impact of this on recovery from surgery should be tested in future studies.

Results:

- The most common reason for liver resection was colorectal metastatic disease.
- Plasma concentrations of IL-6 were highest on day 1 after surgery and remained higher than the baseline up to postoperative day 1. Cortisol concentrations spiked on postoperative day 1.
- The concentrations of lipoxin A4 and resolvin D were lowest on day 1 after surgery.
- Postoperative complications occurred in 14 (24% of total) patients.

Cata JP et al. *World J Surg Oncol*. 2017;15:152.

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Emerging Area: Cancer

Objective: To determine the impact of tumor debris on cancer progression and assess whether this could be modulated by treatment with resolvins.

Design:

- Tumor debris was generated by treating tumor cells *in vitro* with chemotherapy or targeted therapy (e.g., cetuximab).
- Debris was then injected into an *in vivo* mouse debris-stimulated tumor models.

Conclusion:

Enhancing endogenous clearance of tumor cell debris may be a valuable complement to cytotoxic cancer therapies.

Results:

- Tumor cells killed by chemotherapy or targeted therapy ("tumor cell debris") stimulate primary tumor growth.
- RvD1, RvD2, and RvE1 inhibited debris-stimulated tumors and cancer progression by enhancing clearance of debris via macrophage phagocytosis in multiple tumor types.

Sulciner ML et al. *J Exp Med*. 2018;215(1):115-140.

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Emerging Area: Fibromyalgia

Objective: To determine if spinal or systemic treatment with specialized pro-resolving mediators impacted the behavioral and neurochemical changes seen in a mouse model of fibromyalgia.

Design:
Mice with induced fibromyalgia were treated with resolvin D1 (RvD1), aspirin-triggered resolvin D1 (AT-RvD1), and resolvin D2 (RvD2).

Conclusion:
D-series resolvins AT-RvD1, and mainly RvD2, reduced painful and depressive symptoms of fibromyalgia in mice.

Results:

- Acute administration of AT-RvD1 and RvD2 significantly inhibited mechanical allodynia and thermal sensitization.
- Chronic treatment with AT-RvD1 and RvD2 prevented depressive-like behavior (assessment of immobility time).
- RvD2 prevented 5-HT reduction in total brain, and AT-RvD1 led to a recovery of dopamine levels in cortex and 5-HT in thalamus.

Klein CP et al. *Neuropharmacology.* 2014;86:57-66.

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Emerging Area: Sjögren's Syndrome

Objective: To determine the feasibility of treatment with AT-RvD1 versus dexamethasone (DEX) on inflammation in submandibular glands of NOD/ShiLtJ Sjögren's syndrome (SS) mouse model.

Design:
Mice were treated intravenously placebo, AT-RvD1, or DEX twice a week for 14 weeks, and then submandibular glands were collected for pathological analysis and detection of SS-associated inflammatory genes.

Conclusion:
This pilot results suggest that treatment with AT-RvD1 and DEX both attenuated inflammatory responses observed this SS mouse model.

Results:

- AT-RvD1 treatment alone did not affect lymphocytic infiltration seen in this mouse model, while DEX partially prevented lymphocytic infiltration.
- Both AT-RvD1 and DEX caused downregulation of SS-associated inflammatory genes and reduction of apoptosis.

Easley JT et al. *J Rheum Dis Treat*. 2015;1(4):pii:027.

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Emerging Area: Obesity and Metabolic Disease

Adipocytes

RvD1, RvD2, RvE1, LXA_4 [1,2]

- Decrease secretion of pro-inflammatory adipokines
- Increase adiponectin secretion
- Increase macrophage phagocytosis
- Promote anti-inflammatory/pro-resolving M2 macrophage phenotype
- Reduce monocyte adhesion to adipocytes and reduce crown-like structures

1. Claria J et al. *Mol Aspects Med.* 2017;58:83-92
2. Spite M et al. *Cell Metab.* 2014;19(1):21-36.

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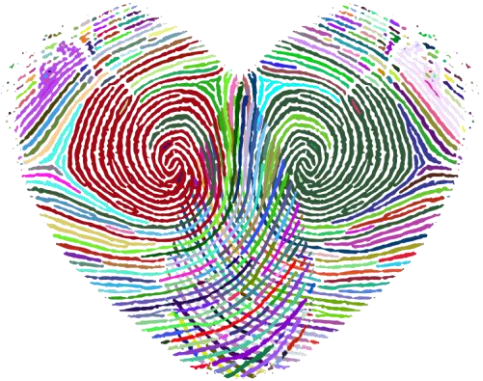
Emerging Area: Vascular Disease



RvD3 and RvD6

Promote macrophage phagocytosis of blood clots[1]

RvE1

Reduced smooth muscle cell migration[2-5]

Reduced atherosclerotic lesion size in ApoE*Leiden mice[6]

- Ratio of SPMs to pro-inflammatory leukotriene B4 (LTB4), is significantly decreased in the vulnerable compared with stable atherosclerotic plaque lesions.[7]
- Primary human vascular cells produce SPMs and express SPM receptors.[3,8]

1. Elajami TK et al. *FASEB J*. 2016;30(8):2792-801.
2. Claria J et al. *Am J Physiol Cell Physiol*. 2013;304:C1141-C1149.
3. Ho KJ et al. *Am J of Pathol.* 2010;177(4):2116-2123.
4. Hiram R et al. *Am J Physiol Heart Circ Physiol.* 2014;307:H1547-H1558.
5. Akagi D et al. *FASEB J.* 2015;29(6):2504-2513.
6. Salic K et al. *Atherosclerosis.* 2016:250:158-165.
7. Fredman G et al. *Nat Commun.* 2016;23;7:12859.
8. Chatterjee A et al. *FASEB J.* 2017;3393-3402.

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Emerging Area: Arthritis

- Osteoarthritis (OA) is characterized by an increase in inflammatory cells and biomarkers in affected joints.[1]
- In patients with arthritis, lower levels of Rvs, 17-HDHA, and 18-HEPE were correlated with higher erythrocyte sedimentation rate and pain.[2]
- In animal models, treatment with Rvs reduced joint inflammation, ameliorated arthritis symptom and severity, and stimulated chondrocyte matrix production.[3-5]

1. Sellam J et al. *Nat Rev Rheumatol*. 2010;6(11):625-635.
2. Barden AE et al. *Prostaglandins Leukot Essent Fatty Acids*. 2016;107:24-29.
3. Norling LV et al. *JCI Insight*. 2016;1(5):e85922.
4. Lima-Garcia JF et al. *Br J Pharmacol*. 2011;164(2):278-293.
5. Arnardottir HH et al. *J Immunol*. 2016;197(6):2362-2368.

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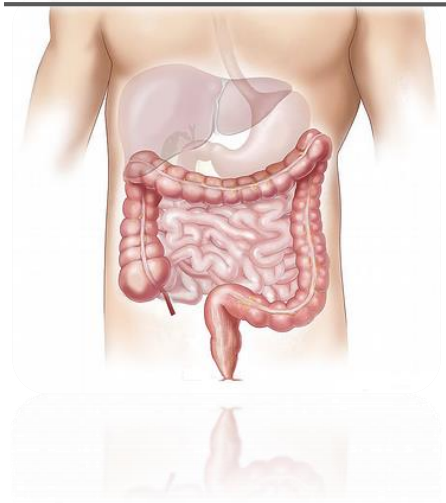
Emerging Area: Neurodegeneration

- Neuroinflammation has been associated with cognitive decline.[1,2]
- Measured in the postmortem brain tissues, lower levels of specific neuroprotectin and Rv in the brain and cerebrospinal fluid were seen in Alzheimer's disease (AD)-related neurodegeneration.[3,4]
- Levels of lipoxin and Rv, measured in the postmortem brain tissues from AD patients, were positively correlated with cognitive function as determined by Mini-Mental State Examination scores.[5]

1. McGeer PL et al. *J Leukoc Biol.* 1999;65(4):409-415.
2. Yaffe K et al. *Neurology*. 2003;61(1):76-80.
3. Lukiw WJ et al. *J Clin Invest*. 2005;115(10):2774-2783.
4. Zhu M et al. *Mol Neurobiol*. 2016;53(4):2733-2749.
5. Wang X et al. *Alzheimers Dement*. 2015;11(1):40-50.e1-2.

Emerging Area: Inflammatory Bowel Disease



- Crohn's disease and ulcerative colitis are IBD that lead to long-term and occasionally irreversible impairment of gastrointestinal structure and function.[1]
- In animal models, Rvs, Mar, and 17-HDHA have been shown to help reduce intestinal tissue damage, reduce inflammation and neutrophil infiltration, maintain body weight, and increase survival.[2-5]

1. Bouma G et al. *Nat Rev Immunol*. 2003;3(7):521-533.
2. Arita M et al. *Proc Natl Acad Sci U S A*. 2005;102(21):7671-7676.
3. Bento AF et al. *J Immunol*. 2011;187(4)1957-1969.
4. Chiu CY et al. *Inflamm Res*. 2012;61(9):967-976.
5. Marcon R et al. *J Immunol*. 2013;191(8):4288-4298.

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Metagenics Institute: Educational Resources on SPMs

Access a discussion on emerging areas of SPM research with Charles Serhan, PhD, DSc.

From the 15th International Conference on Bioactive Lipids in Cancer, Inflammation and Related Diseases, October 2017 in Puerto Vallarta, Mexico

Metagenics Institute. SPMs Now: Therapeutic Research Areas. https://www.metagenicsinstitute.com/video/spms-now-therapeutic-research-areas/. Accessed August 27, 2018.

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Metagenics Institute: Educational Resources on SPMs

Access a discussion on the emerging link between SPMs and adaptive immunity with Charles Serhan, PhD, DSc.

Metagenics Institute. SPMs Now: Newly Discovered Role in Adaptive Immunity. https://www.metagenicsinstitute.com/video/spms-now-newly-discovered-role-adaptive-immunity. Accessed August 27, 2018.

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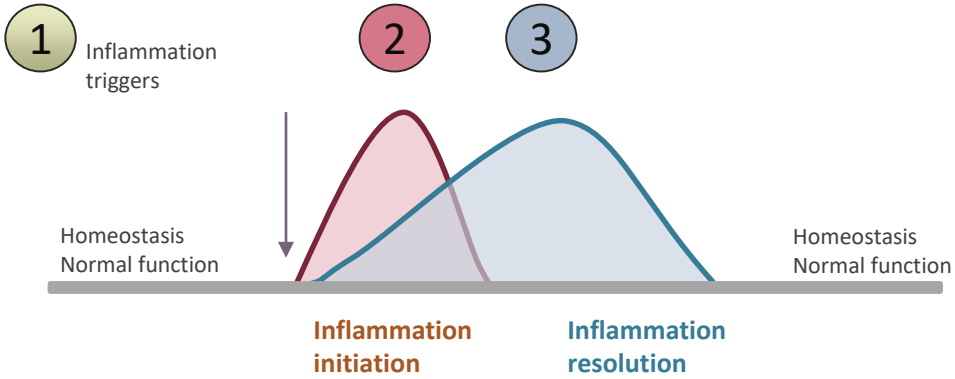
Clinical Management of Inflammation: A Question of Balance

1. **Address underlying triggers**
   Reduced inflammation triggers by addressing obesity, body composition, glucose control, diet, intestinal permeability and microbiome, allergy, and infection

2. **Modulate initiation**
   Utilize phytonutrients and long-chain omega-3 fatty acids that act on inter-cellular inflammatory signals that impact NF-κB, oxidative stress, and pro-inflammatory eicosanoid production

3. **Push for resolution**
   Utilize specialized pro-resolving mediators and emerging science of inflammation resolution



Adapted from: Serhan CN. *Nature*. 2014;510:92-101.

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