

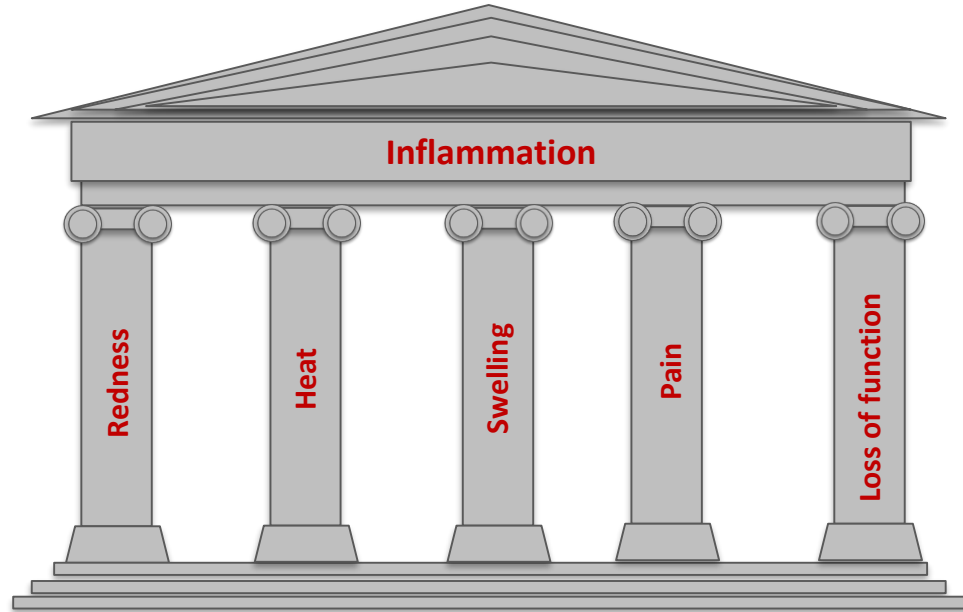
Specialized Pro-resolving Mediators (SPMs) and Inflammation Resolution

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Objectives

1. Understand and compare the two distinct phases of the inflammation response: initiation versus resolution
2. Discuss requirement for specialized pro-resolving mediators in inflammation resolution, and highlight areas where lipid mediator synthesis is dysregulated and may require additional support
3. Review emerging areas of clinical pro-resolution options, and discuss practice-based research results with specialized pro-resolving mediators

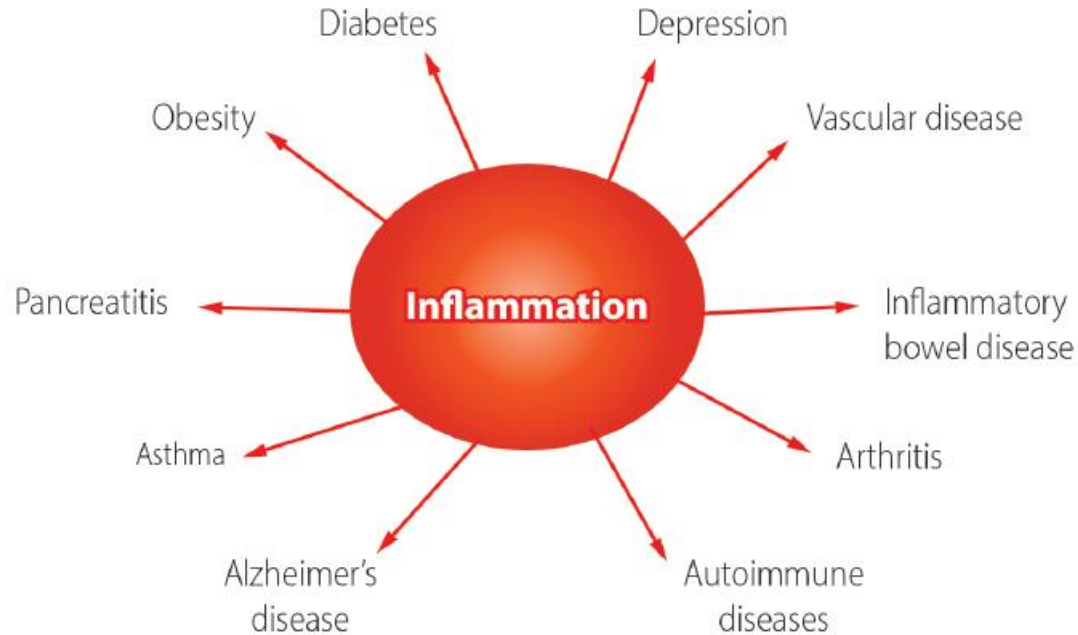
Cardinal signs of inflammation



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

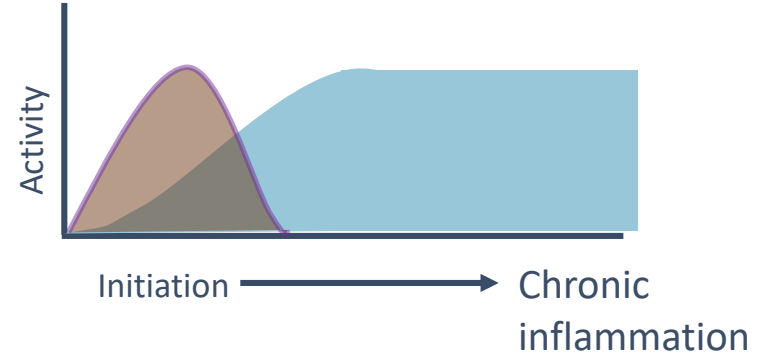
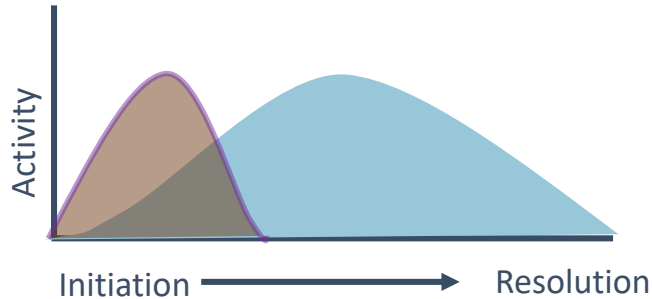
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Uncontrolled chronic inflammation is linked to many chronic diseases

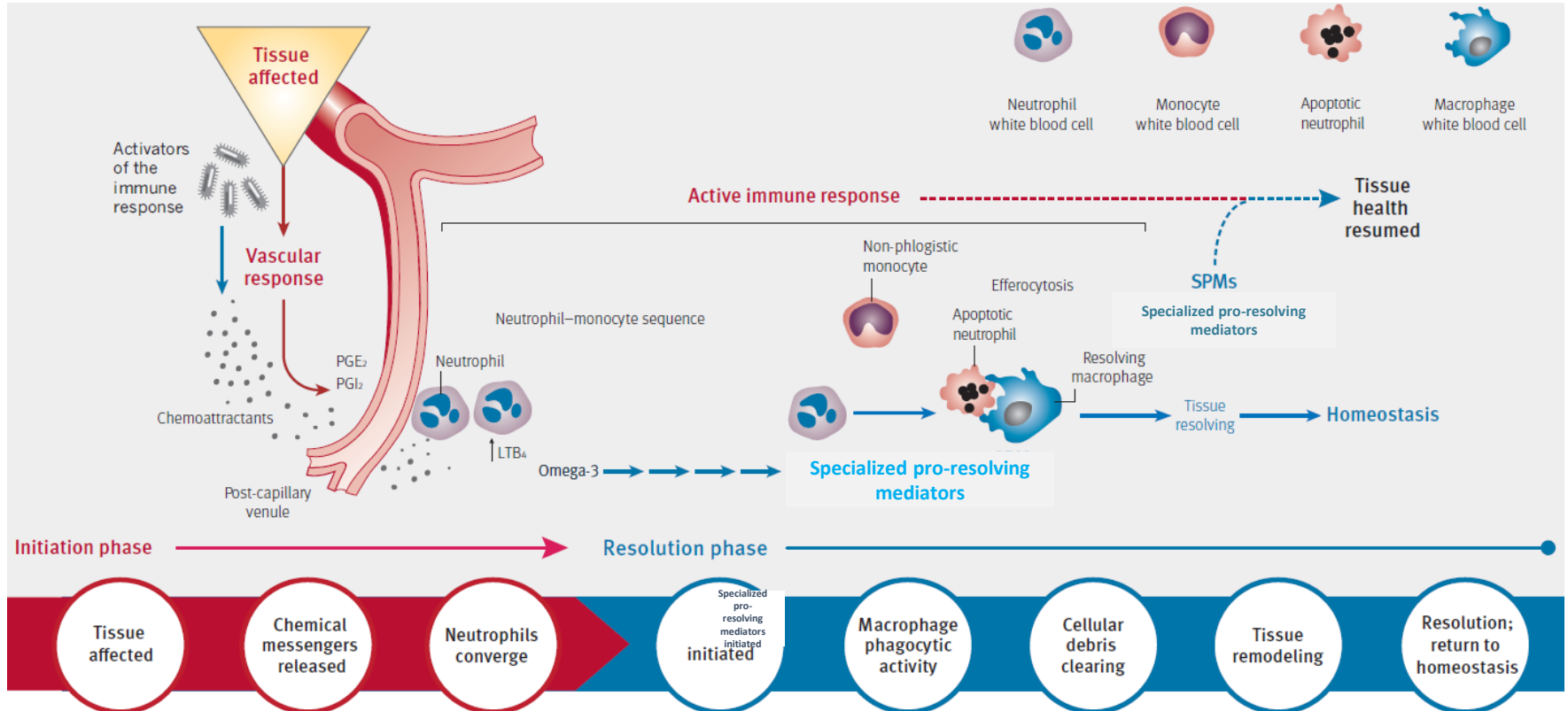


The innate inflammatory response has two distinct and active phases

1. Initiation
2. Resolution



Inflammation initiation and resolution activities



Adapted from 1) Serhan CN. *Nature*. 2014;510:92-101; 2) Serhan CN et al. *Semin Immunol*. 2015;27:200-215; 3) Lopez-Vicario C et al. *Eur J Pharmacol* 2016.785:133-143.

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Hallmarks of specialized pro-resolving mediator activity and inflammation resolution

- Limit PMN tissue infiltration, cessation
- Reduce collateral tissue damage by phagocytes
- Enhance macrophage phagocytosis, and efferocytosis
- Shorten R_i resolution interval
- Counter-regulate pro-inflammatory chemical mediators (e.g. LTs, PGs)
- Increase anti-inflammatory mediators (IL-10 and others)
- Increase microbial killing and clearance by innate immune cells
- Enhance tissue regeneration



Charles Serhan first published on specialized pro-resolving mediator identification¹

Continued identification of SPMs and characterization in models of self-limiting inflammation

Concept of resolution interval introduced²
SPMs in models of IBD³
Lower SPMs in AD brain tissue identified⁴

SPMs in models of obesity, diabetes, atherosclerosis, arthritis⁵⁻⁸

SPMs enhance B-cell response⁹

SPMs linked to tissue regeneration¹⁰

SPMs enhance uptake + killing of microbes and reduce Abx requirement in mice¹¹

Cohort studies highlight imbalance in lipid mediators in several conditions

Current main-stream clinical focus

Previous Perspective

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

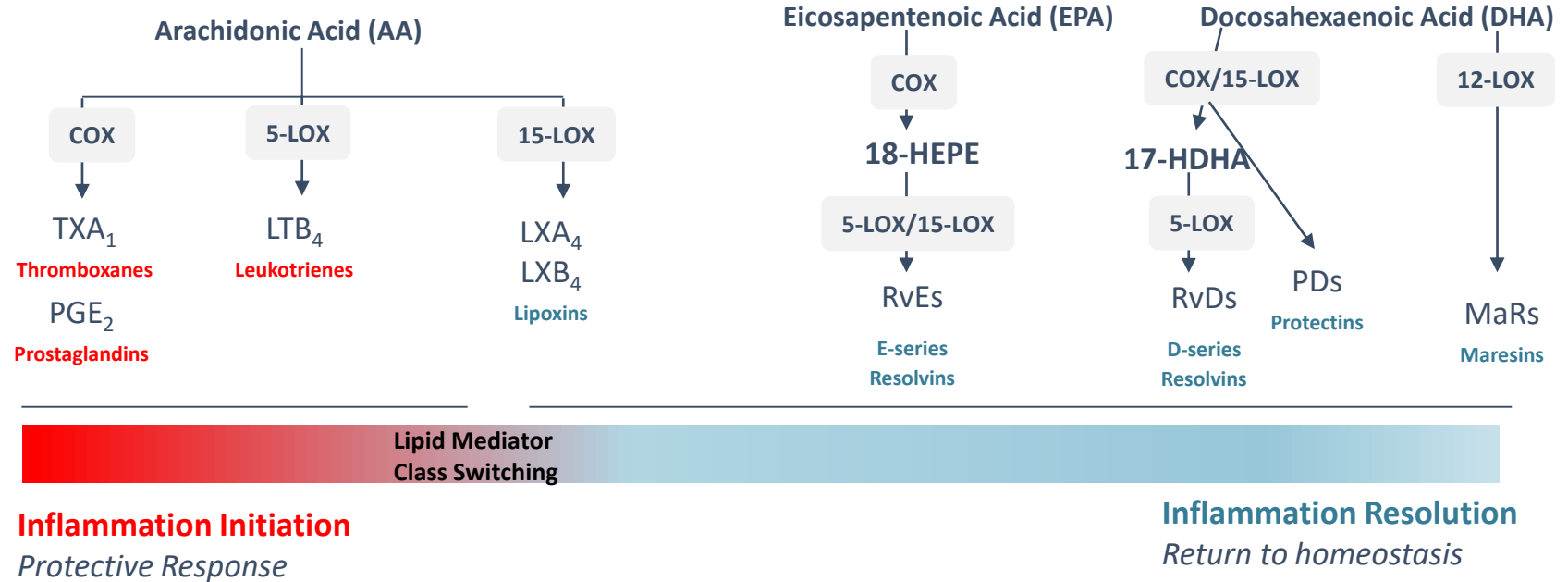
Current Perspective

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

1) Serhan et al. *J Exp Med*. 2000;192:1197–204.
2) Bannenberg et al. *J Immunol*. 2005;174:4345–4355.
3) Arita M et al. *Proc Natl Acad Sci USA*. 2005.
4) Lukiw WJ et al. *J Clin Invest*. 2005. 115(10):2774–83.
5) Gonzalez-Periz. *FASEB J*. 2009;23:1946–1957.
6) Hellman et al. *FASEB J*. 2011;25:2399–2407.
7) Ho et al. *Am J Pathol*. 2010;177:2116–2123.

8) Lima-Garcia et al. *Br J Pharmacol*. 2011;164(2):278–93.
9) Ramon et al. *J Immunol*. 2012;189(2):1036–42.
10) Serhan et al. *FASEB J*. 2012;26:1755–1756.
11) Chiang et al. *Nature*. 2012;484:524–528.
12) Titos et al. *J Immunol*. 2016;197:3360–3370.
13) Fredman et al. *Nat Commun*. 2016;7:12859.

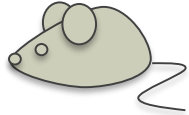
Pathways of lipid mediator biosynthesis



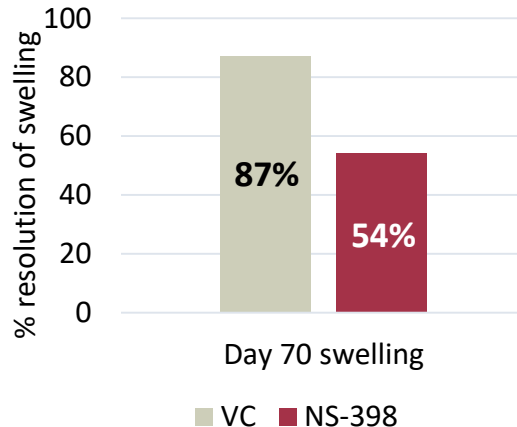
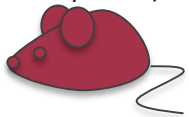
Blocking inflammation and resolution toxicity

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’

Induced arthritis model

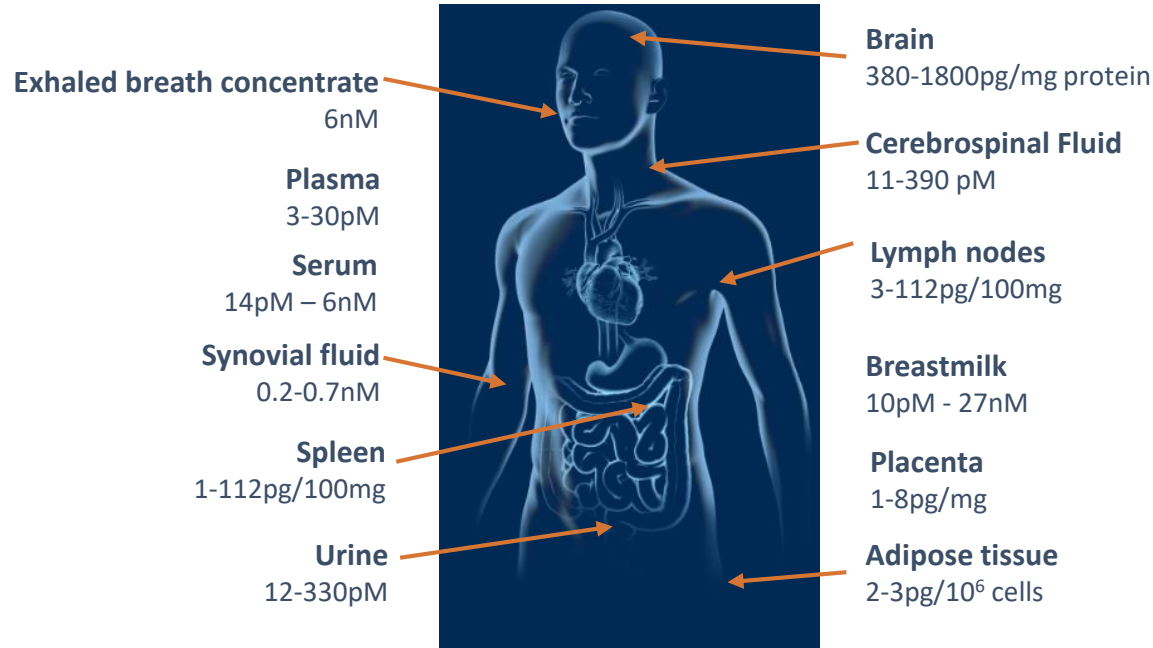


Induced arthritis
+ COX-2 inhibitor
(therapeutic)



- TNF α 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
- **PGE₂ analogue treatment helped restore resolution**

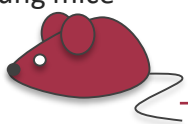
Specialized pro-resolving mediators have been identified at bioactive levels across human tissues



Aging delays resolution of acute inflammation



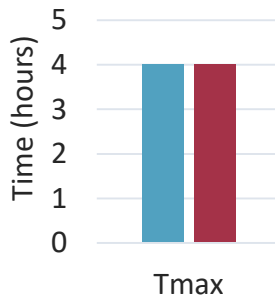
Young mice



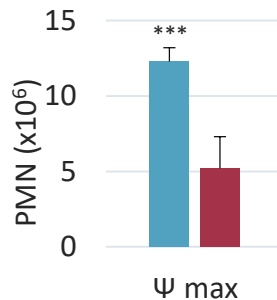
Peritonitis model
(Zymosan; i.p.)

Peritoneal exudates
assessed over 24-
hours

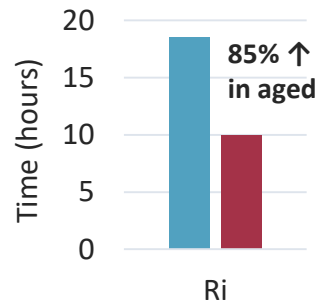
T_{max}
(PMN infiltration)



Magnitude at 4hrs
(PMN infiltration)



Resolution interval



- 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 ability to clear PMNs**

*** p<0.001 versus young mice

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

Accelerated resolution of local inflammatory challenge in women

Participants and study design

16 healthy premenopausal women and 16 healthy men

Local application of cantharidin with assessment of resulting blister formation at 24 and 72hrs

Results

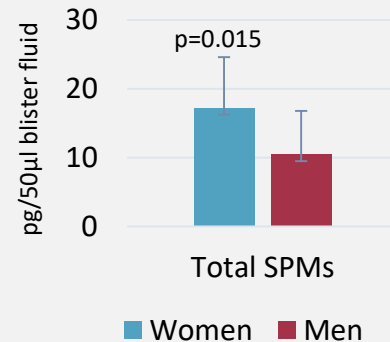
24 hours

- Blisters had formed within 24 hrs in both men and women
- No difference in recruited neutrophils in blister fluid between men and women at 24 hrs

72 hours

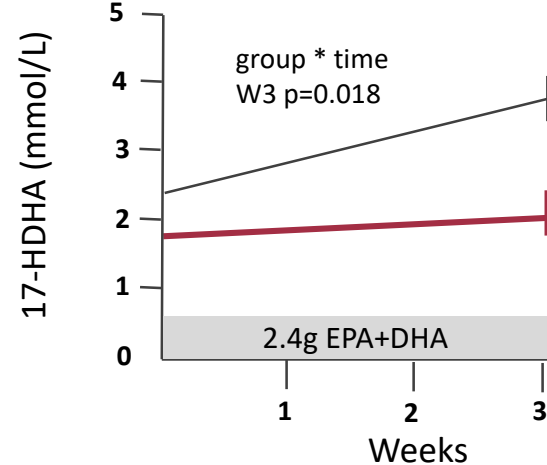
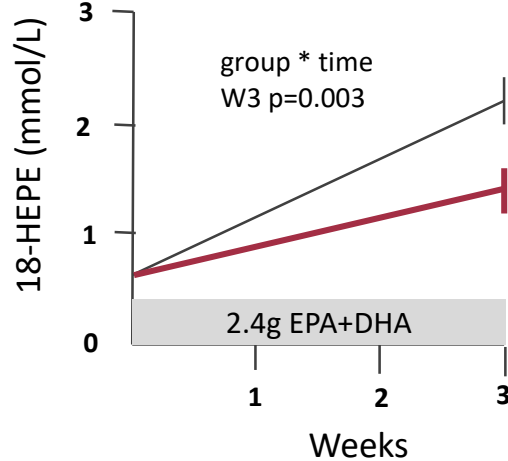
- Blister resolution in 70% of women compared to 30% of men
- Reduced leukocyte number and activation in women
- Greater total SPMs in women
- Distinct clustering of lipid mediators in men and women
 - Men enriched for LTB4
 - Women enriched for RvE1 and RvE3

Greater total SPMs in blister fluid of women versus men

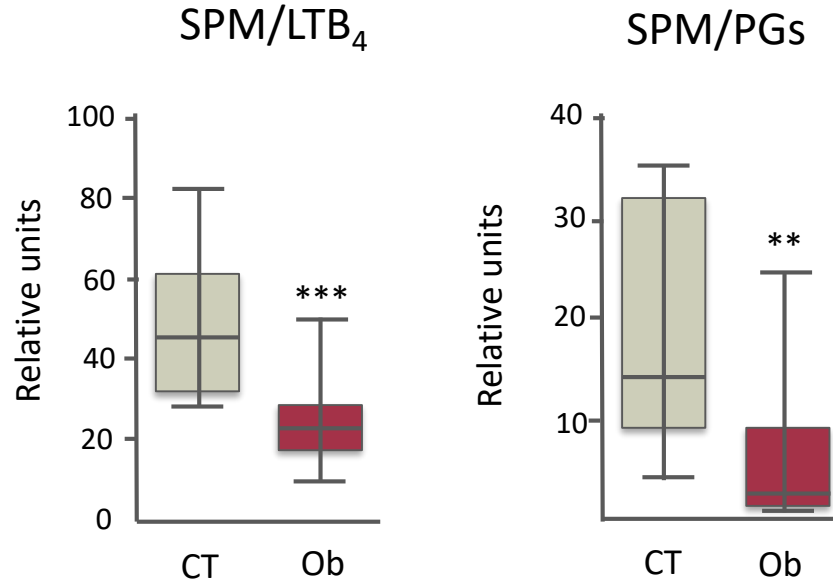


Metabolic syndrome blunts increase in 17-HDHA and 18-HEPE following EPA + DHA supplementation

Control —
MetSyn —

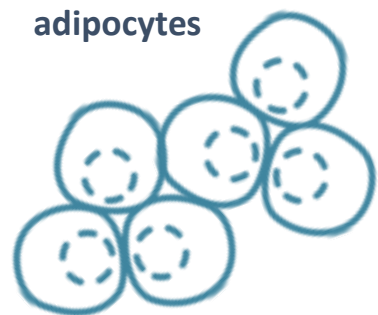


Obese subjects have a different lipid mediator profile than lean controls



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

Emerging area: Resolution in obesity and metabolic disease



RvD1, RvD2, RvE1, LXA₄^{1,2}

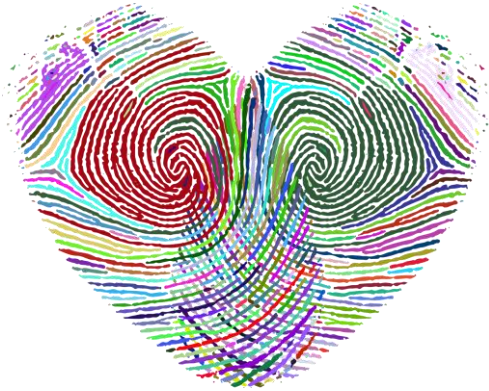


- Decrease secretion of pro-inflammatory adipokines
- Increase adiponectin secretion
- Increase macrophage phagocytosis
- Promote anti-inflammatory/pro-resolving M2 macrophage phenotype
- Reduce monocyte adhesion to adipocytes and reduce crown-like structures

1) Claria et al. *Mol Aspects Med.* 2017;58:83-92.

2) Spite et al. *Cell Metab.* 2014;19(1):21-36.

Emerging area: Resolution in vascular disease



- Primary human vascular cells produce SPMs and express SPM receptors^{8,3}
- Ratio of SPMs to pro-inflammatory leukotriene B4 (LTB4), are significantly decreased in the vulnerable compared with stable atherosclerotic plaque lesions⁷

**RvD3 and
RvD6**



Promote
macrophage
phagocytosis
of blood clots¹

RvE1



Reduced
smooth
muscle cell
migration³⁻⁵



Reduced
atherosclerotic
lesion size in
ApoE*Leiden mice⁶

- 1) Elajami et al. *FASEB J.* 2016;30(8):2792-2801.
- 2) Claria et al. *Am J Physiol Cell Physiol.* 2013;304:C1141-C1149.
- 3) Ho et al. *Am J of Pathol* 2010;177(4):2116-2123.
- 4) Hiram et al. *Am J Physiol Heart Circ Physiol.* 2014;307:H1547-H1558.
- 5) Akagi et al. *FASEB J.* 2015;29(6):2504-13
- 6) Salic et al. *Atherosclerosis* 2016;250:158-165
- 7) Fredman et al. *Nat Commun* 2016;23;7:12859
- 8) Chatterjee et al. *FASEB J.* 2017;31(8):3393-3402.

Emerging area: Resolution and arthritis



- Osteoarthritis (OA) is characterized by an increase in inflammatory cells and biomarkers in affected joints¹
- In patients with arthritis, lower levels of Rvs, 17-HDHA, and 18-HEPE were correlated with higher erythrocyte sedimentation rate and pain²
- In animal models, treatment with Rvs reduced joint inflammation, ameliorated arthritis symptom and severity, and stimulated chondrocyte matrix production³⁻⁵

1) Sellam J et al. *Nat Rev Rheumatol*. 2010;6(11):625-35.

2) Barden AE et al. *Prostaglandins Leukot Essent Fatty Acids*. 2016;107:24-9.

3) Norling LV et al. *J Cl Insight*. 2016. 1(5):e85922.

4) Lima-Garcia JF et al. *Br J Pharmacol*. 2011;164(2):278-93.

5) Arnardottir HH et al. *J Immunol*. 2016;197(6):2362-8.

Emerging area: Resolution and the brain



- 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 scores⁵

1) McGeer PL et al. *J Leukoc Biol.* 1999;65(4):409-15.

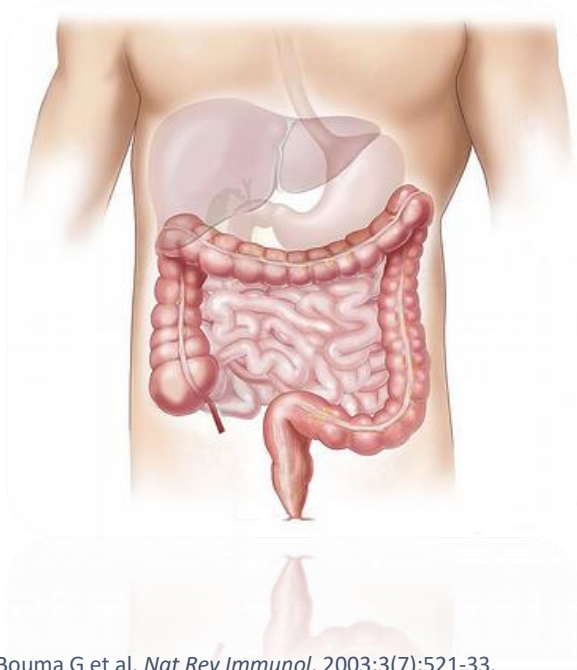
2) Yaffe K et al. *Neurology.* 2003;61(1):76-80.

3) Lukiw WJ et al. *J Clin Invest.* 2005;115(10):2774-83.

4) Zhu M et al. *Mol Neurobiol.* 2016;53(4):2733-49.

5) Wang X et al. *Alzheimers Dement.* 2015;11(1):40-50e1-2.

Emerging area: Resolution and inflammatory bowel disease



- Crohn's disease and ulcerative colitis are IBD that lead to long-term and occasionally irreversible impairment of gastrointestinal structure and function¹
- In animal models, Rvs, Mar, and 17-HDHA have been shown to help reduce tissue damage, reduce inflammation and neutrophil infiltration, maintain body weight, and increase survival²⁻⁵

1. Bouma G et al. *Nat Rev Immunol.* 2003;3(7):521-33.
2. Arita M et al. *Proc Natl Acad Sci USA.* 2005;102(21):7671-6.
3. Bento AF et al. *J Immunol.* 2011;187(4):1957-69.
4. Chiu CY et al. *Inflamm Res.* 2012;61(9):967-76.
5. Marcon R et al. *J Immunol.* 2013;191(8):4288-98.

Summary

- Two distinct phases of the inflammatory response – initiation and resolution
- Inflammation resolution is actively coordinated by a group of lipid mediators known as specialized pro-resolving mediators
- Lipid mediators class switching (from pro-inflammatory to pro-resolving) is critical for inflammation resolution to occur
- Several chronic conditions have been associated with reduced levels of specialized pro-resolving mediators in circulation or in tissues
- Mechanistic data points to potential therapeutic benefit for various specialized pro-resolving mediators

Cardinal signs of inflammation initiation and resolution

