“Preventing Collateral Damage”
Clinical Relevance of SPM’s

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We have been lost in trying to prevent inflammation

we forgot resolution inflammation
Acute or Chronic Inflammation

Injury

Invading Organisms Infection

Chemical Mediators

Acute Inflammation

- Abscess formation
- Chronic inflammation
- Wound healing Scarring

Modified from: CN Serhan, Am J Pathology 2010
Acute, Chronic, or Resolution of Inflammation

Injury

Invading Organisms Infection

Chemical Mediators

Resolution

Abscess formation

Wound healing Scarring

Chronic inflammation

Periodontal disease
Rheumatoid arthritis
Cirrhosis
Valvular heart disease
Atherosclerosis
Etc etc etc

Modified from; CN Serhan, Am J Pathology 2010

Previously considered passive process ??
Case study

- 63 yo male relatively healthy male with mild HTN, untreated. Sustains hypertensive intracranial hemorrhage in thalamus at border of caudate nucleus.

CNS inflammation following bleed is significant.
Now What?
Multiple compounds now reported to be active in “resolution” of inflammation

- **SPM’s**
  - Lipoxins, resolvins, protectins, maresins

- **Proteins and peptides**
  - Annexin A1

- **Gaseous mediators**
  - NO, CO, H₂S

- **Adenosine**
  - Jacobson KA et al *Neuropharmacology* 2015

- **Vagal release of neuropeptides / HPA axis**
  - Boonen E et al *Int Care Med* 2015
EPA / DHA

Membrane Phospholipids

Eicosanoids

Signal transduction Pathways (NFkB)

SPM’s

Increase vagal tone

Enhance diaphragm function

TLR4
Receptor binding

ICAM 1
E-Selectin

Membrane Fluidity

Receptors

Enzymes

Cytokines

Inflammation and Immunity
Reported benefits of EPA and DHA in clinical settings

- Cardiovascular Ds
- Cardiac Arrhythmias
- Rheumatoid Arthritis
- Psoriasis
- IBD
- Renal Transplant
- Multiple Sclerosis
- Glucose tolerance
- Lupus
- ARDS
- Cystic Fibrosis
- Psychiatry
  - Depression, suicide
- etc etc etc etc ........

In excess of >4000 clinical trials showing benefits of fish oil or omega 3 fatty acids in clinical medicine !!!!
Intravenous fish oil blunts the physiological response to endotoxin in healthy subjects

Pluess TT et al Intensive Care Med (2007 33:789-797
Three short perioperative infusions of n-3 PUFAs reduce systemic inflammation induced by cardiopulmonary bypass surgery: a randomized controlled trial

- PRBCT Evaluation influence of FO infusion in immediate peri-operative period in CABG
  - N=28 equal groups
  - Three 2 hour infusion with/in 12 pre-op period
  - Results: FO showed;
    - Pilot study not powered for clinical outcome
      - No change in mortality, clinical outcome, endogenous glucose production
    - Trend toward decrease APACHE, SOFA
    - Improved glycemic control
    - Decrease in lactate
    - Decrease in IL-6

Berger M et al Am J Clin Nutr 2013
Not all the data is positive or consistent!

Fish Oils use in the ICU / Trauma:

Clinical Outcome Dependent on Several Factors:

- **ARDS / ALI (variable)**
  - Dependent upon;
    - Route of feeding (EN v PN)
    - Bolus versus continuous
    - Background nutrition

- **Cardiac rhythm stabilization (variable)**
  - Dependent upon
    - Timing of delivery
    - Background cardiac status

- **Prevention of hepatic steatosis**
  - Anytime

- **Early recovery after traumatic brain injury**
  - Well developed in animal studies
  - As early as possible following injury
  - Dependent on timing of injury
Macrophage Heterogeneity
(a cell with “split personality”)

M0

M1

M2

Inducers

Secreted Products & Markers

Type I Response

Pro-inflammatory

Microbicidal Activity

Tumor Resistance

Cytotoxicity

Type II Response

Immunoregulation

Matrix Deposition

Tissue Remodeling

Changing of neutrophil class

When macrophages ingest apoptotic neutrophil, the change phenotype from M1 to M2 (M2 macrophages resolution phase macrophage)

Efferocytosis-(Effere-Latin “to take to the grave”)
Dead cells are engulfed before cell membranes are breached

SPM: specific pro-resolving mediators
LM: Lipid mediators

Serhan C Nature 2014
Biological Systems: On and Off Signals

Radically changed concept of inflammation

- Concept stimulated by his own experience
  » Active vs passive resolution of inflammation
- 1984 Lipoxins – stopped inflammation
- 1992 ASA stimulated lipoxin
- 2000 mouse abscess model
  – Resolvins, Protectins and Maresins
- Actively stimulate cardinal signs of resolution, namely;
  - Cessation of leukocytic infiltration
  - Counter regulation of pro-inflammatory mediators
  - Stimulate the uptake of apoptotic neutrophils
  - Clearance of cellular debris
SPM’s present in most tissues tested to date

- Bioactive at levels of 20 to 200 picomolar
  - Serum in range of pg/ml (10^{-12})

- Serum (Serhan C et al Am J Physiol 2014)
- Human milk (Weiss et al 2013 Lipids in Health and Disease)
- Urine (Sasaki et al 2015 Annals Bioanal Chem)
- Lymph nodes (Colas et al 2014 Am J Physiology)
- Adipose tissue (Claria et al 2013 Am J Physiol Cell Physiol)

Serhan C et al Am J Physiology 2014
SPM: Resolvins, Protectins and Maresins in Disease

**Lungs** Human & Mouse
*ATL, RvE1, PD1, MaR1*
↓ Airway inflammation (asthma)

**Cardiovascular**
*RvE1, RvD1*
↓ Platelet aggregation
*PD1, RvD1*
↓ Atherosclerosis

**Eyes** Human & Mouse
*RvE1, PD1, RvD1*
↓ Vaso-obliteration and neovascularization (Retinopathy)
↑ Wound healing (Cornea)

**Kidney**
*ATL, PD1, RvD1*
↓ Renal ischemic injury

**Brain** Human & Mouse
*PD1, RvD1, RvD2*
↓ Stroke damage and PMN entry into the brain
↑ Neural cell survival

**Oral** Rabbit & Mouse
*ATL, RvE1*
↓ Inflammation-induced tissue and bone loss (Periodontitis)

**GI tract**
*RvD1, RvE1, RvD2*
↓ PMN and weight loss
– Survival (Colitis, sepsis)

**Liver**
*RvE1, PD1, RvD1*
↓ I/R injury
↑ Glucose and lipid homeostasis

Nanograms to micrograms
Human and Animal Disease Models

CN Serhan et al., *Nat Rev Immunol* 2008; 8: 349-361
What current data is available to support clinical use?

**Acute Inflammation**

- **Sepsis**

- **Infections**
  - **Bacterial**
    - Chiang N et al *Nature* 2012
  - **Virus**
    - Baille J et al *NEJM* 2013
  - **Other**

- **Stroke**
  - Marcheselli et al *JBC* 2003

- **Trauma**
  - Orr SK et al *Critical Care Med* 2015

- **Surgery**

- **Acute pain**
  - Xu Z et al *Nature Med* 2010
  - Lim JY et al *Biomed Res* 2015
Infection regulates pro–resolving mediators that lower antibiotic requirements

Nan Chiang, Gabrielle Fredman, Fredrik Bäckhed, Sungwhan F. Oh, Thad Vickery, Birgitta A. Schmidt & Charles N. Serhan

Antibiotics

SPM Resolvins

Bacteria

Host response

Phagocytosis, Containment, Killing, Clearance of Bacteria

E. coli, S. aureus skin

Resolvins Accelerate resolution of Infections
Enhance bacterial killing, reduce inflammation
Treating the host SPM lowers the required antibiotic doses
Demonstration: Human SPM Production & Assessment of Function

Blood sampling 19G needle Heparin

ASA (81mg)

0 h 2 h 4 h

1g EFA supplementation
EPA (50%) DHA (20%)

Plasma (1 mL)
Whole blood (20 μL)

Automated targeted LM metabollolipidomics

Bacterial phagocytosis assay

Fluorescent-labeled E. coli
Phagocytes in whole blood
Phagocytosis 37°C, 1 h
Phagocytes ingestion of E. coli measured by flow cytometry

Several Resolvins lower mortality in viral illness

Baillie JK et al *NEJM* 2013
Controlling Herpes Simplex Virus-Induced Ocular Inflammatory Lesions with the Lipid-Derived Mediator Resolvin E1

Naveen K. Rajasagi,* Pradeep B. J. Reddy,* Amol Suryawanshi,* Sachin Mulik,* Per Gjorstrup,† and Barry T. Rouse*

Rajasagi NK J Immunology 2011;186:1735
Formalin-induced Spontaneous Pain

RvE1, NS-398 (COX-2 inhibitor), Morphine

CFA-evoked heat hyperalgesia

Pain resolution?
Chronic

- Asthma
- Atherosclerosis
- Retinal angiogenesis
- Obesity
  - Claria et al. *J. Immunology* 2012
- Metabolic syndrome
- Alzheimer’s Disease
  - Wang X *Alzheimers Dementia* 2015
- Periodontitis
  - Cianci E et al *Stem Cells Transplantation* 2016
- Rheumatologic disorders
  - Headland SE et al *Seminar Immunology* 2015
- IBD
  - Corminboeuf O et al *J Med Chem* 2015
Other areas for SPM’s recently evaluated

- **Stem cells**
  - Das UN et al *Nutrition* 2011
  - Cianci E et al *Stem Cells Trans Med* 2016

- **Tissue regeneration**
  - Schlegel M et al *Hepatology* 2015
Conclusions

Resolution is an *active* process

Anti-inflammation is *not* equivalent to Pro-Resolution.

**SPM’s**

*Lipid compounds Isolated in many human tissue during inflammation*

1) Chemically synthesized in lab and in vivo
2) Injected into humans at physiologic doses
3) Inflammation resolves faster – mimics natural healing
4) Prevents transition to chronic inflammation
5) Increases bacterial and viral killing, decreases need antibiotics
6) In some tissues stimulates “regeneration”

Serhan CN, Dalli J et al *Immunology* 2015
Summary and Conclusion

• Current “fish oil” literature remains a bit confusing

• Where can the routine use be supported:
  • Preventing or resolving chronic inflammation
  • Surgical ICU setting:
    – Favorable modulation of inflammatory response shows consistent decrease in LOS, ICU days
      » TBI, hepatic steatosis, trauma, major surgery

• SPM physiology offer some explanation for the current confusion in the “clinical science” of fish oils

• Where can SPM’s be expected to show benefit:
  • Limitless potential
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- Current “fish oil” literature remains a bit confusing.
- Where can the routine use be supported:
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- SPM physiology offers explanation for some of the current confusion in the “clinical science” of fish oils.
- Where can SPM’s be expected to show benefit:
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