Omega-3 and its impact on immune health:
exploring the potential of omega-3

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Session: Capitalising on the immunity 'super' trend
Objectives

Omega-3: A central role in the inflammatory response

Understanding the actions of long chain omega-3 poly-unsaturated fatty acids (LC omega-3 PUFA) in the immune system:
  - formation and actions omega-3-derived lipid mediators

Evolution in the field and why food matters
“Omega-3” - a structural descriptor of a functional group

LC omega-3 PUFA:

EPA eicosapentaenoic acid (C20:5)

DHA docosahexaenoic acid (C22:6)

EPA and DHA can be considered “conditionally” in/dispensable essential fatty acids

Omega-3 and its impact on immune health

Is there a role for EPA and DHA in the immune system and do LC-omega-3 PUFA support immune health?

Historical perspectives on the impact of n-3 and n-6 nutrients on health.
The New England Journal of Medicine

THE EFFECT OF DIETARY SUPPLEMENTATION WITH n-3 POLYUNSATURATED FATTY ACIDS ON THE SYNTHESIS OF INTERLEUKIN-1 AND TUMOR NECROSIS FACTOR BY MONONUCLEAR CELLS

Stefan Endres, M.D., Reza Ghorbani, B.S., Vicki E. Kelley, Ph.D., Kostis Georgilis, M.D., Gerhard Lonnewann, M.D., Jos W. M. van der Meer, M.D., Joseph G. Cannon, Ph.D., Tina S. Rogers, Ph.D., Mark S. Klemper, M.D., Peter C. Weber, M.D., Ernst J. Schaefer, M.D., Sheldon M. Wolff, M.D., and Charles A. Dinarello, M.D.
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The inflammatory response: time course - leukocytes and exudate protein

Zymosan A-stimulated peritonitis in mouse (1 mg i.p.)

Pro-inflammatory phase  Resolution phase

<table>
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<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>12</th>
<th>24</th>
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<td>6</td>
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<td>2</td>
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<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
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</tbody>
</table>

- Total exudate cells
- PMN
- Mononuclear cells

Molecular circuits of resolution: formation and actions of resolvins and protectins.

Anti-inflammatory lipid mediators and insights into the resolution of inflammation.
Neutrophil infiltration

**Neutrophil**

- Microbial infection
- Endothelial cell
- Monocyte
- Macrophage

- Neutrophil adhesion to endothelium, adhesion, chemotaxis, diapedesis & activation
- Neutrophil phagocytosis of microbes
- Neutrophils die by apoptosis
- Monocyte migration and differentiation to macrophages
- Non-phlogistic phagocytosis of apoptotic neutrophils
- Macrophage egress to lymph nodes or undergo apoptosis

**Time**

- **Inflammation** (pro-inflammatory phase)
- **Resolution** (removal of neutrophilic exudate)
The resolution of acute inflammation; A definition in operative and quantitative terms by the following Resolution Indices

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Molecular circuits of resolution: formation and actions of resolvins and protectins.
Temporal profiles of cytokines and chemokines

resolution

- IFN-γ *
- RANTES *
- IL-13 *
- GM-CSF **
- IL-4 **
- IL-10 **

IL-6 **

- IL-6 **

IL-12 **

- IL-12 **

- JE (MCP-1)*
- KC (IL-8) **
- MIP-2 **

IL-13 *

- IL-13 *

IFN-γ *

- IFN-γ *

GM-CSF **

- GM-CSF **

IL-10 **

- IL-10 **

MIP-1α **

- MIP-1α **

TGF-β

- TGF-β
Temporal profiles of DHA-derived lipid mediators

Omega-3 and its impact on immune health


Prostanoids:
PGE2
PGI2
PGF2α
PGD2
Thromboxane A2
12-HHT

Leukotrienes:
Leukotriene B4
Cysteinyl-leukotrienes

Lipoxins:
Lipoxins (LXA4 / LXB4)

"3-series" Prostanoids:
PGE3
PGI3
PGF3α
PGD3
TXB3
Leukotriene B5

E-series resolvins:
RvE1
RvE2
RvE3

12-OH-17,18-EpETE

D-series resolvins:
RvD1
RvD2
RvD3
RvD4
RvD5
RvD6

Maresins (MaR1, MaR2)
14-Hydroxy-sulfido-conjugates
14,20-diHDHA

Specialized Pro-resolving lipid Mediators - SPMs
Specific SPMs are formed at defined time intervals during resolution.

Lipoxin biosynthesis

Arachidonic acid

- 15-lipoxygenase
  - Epithelia or monocytes

- 5-lipoxygenase
  - PMN

15S-H(p)ETE

- 5-lipoxygenase
  - PMN

Eicosanoids:
Prostaglandins
Leukotrienes
Thromboxane

Cyclooxygenase

Leukotriene A₄

- 12-lipoxygenase
  - Platelets

Lipoxin A₄

- Lipoxin B₄

Stable lipoxin analogs

ATLa 15-epi-16-(p-fluoro)-phenoxy-LXA₄-methyl ester
Formation of Resolvin E1

Aspirin

\[ \text{Eicosapentaenoic acid (EPA; C20:5)} \]

\[ \text{acetylated-COX2 / cytochrome P} \_450 \]
(unknown endogenous/microbial)

\[ \text{5-lipoxygenase (PMN)} \]

\[ \text{5S-hydroperoxy-18R-hydroxy-EPE} \]

\[ \text{Epoxide formation and rearrangement with incorporation of water} \]

\[ \text{5S,12S,18R-EPE (Resolvin E1; RvE1)} \]

Serhan, J. Exp. Med. 192, 2000
More than 30 ω3-derived metabolites have been identified.
Modulation of inflammation and resolution

**Acute Inflammation**

- **Lipoxin A4 stable analogue (ATLa)**
  - $\Psi_{\text{max}} = 13.2 \times 10^6$
  - $T_{\text{max}} \sim 12$ hr
  - $T_{50} \sim 24$ hr
  - $R_{50} = 8.25 \times 10^6$

- **RVE1**
  - $\Psi_{\text{max}} = 12 \times 10^6$
  - $T_{\text{max}} \sim 8$ hr
  - $T_{50} \sim 20$ hr

- **Protectin D1**
  - $\Psi_{\text{max}} = 10 \times 10^6$
  - $T_{\text{max}} \sim 5$ hr
  - $T_{50} \sim 11$ hr

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**Important indications**

1. Resolution of inflammation is not a passive process

2. Resolution can be activated

3. Anti-inflammation is not the same as pro-resolution

LC omega-3-derived lipid mediators play an important role in endogenous anti-inflammation and the resolution of inflammation
SPMs are lipid mediators which actively regulate a concerted set of cellular actions that promote the resolution of inflammation.
LC omega-3 and omega-6 derived anti-inflammatory lipid mediators function as endogenous receptor ligands.

Cash et al, Drug Discovery Today 2014

Bannenberg & Serhan, BBA 2010
Redefining the importance of food and dietary components as anti-inflammatory and/or pro-resolving for immune health

- Which foods, nutrients, and diets are pro-resolving and drive resolution of inflammation?
- Which compounds or conditions interfere with resolution?
- Can we ascribe chronic inflammatory disease to defects in resolution?
SPMs stimulate phagocytosis

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SPMs stimulate clearance of infections

N. Chiang, G Fredman, F Bäckhed, S h, T Vickery, B Schmidt & CN Serhan.
SPMs are tissue protective in inflammatory disease

Resolvin E1, an endogenous lipid mediator derived from omega-3 eicosapentaenoic acid, protects against 2,4,6-trinitrobenzene sulfonic acid induced colitis.

M Arita et al. PNAS 2005
Eosinophils control the resolution of inflammation and draining lymph node hypertrophy through the proresolving mediators and CXCL13 pathway in mice. Tani, et al. FASEBJ 2014.


SPM formation upon oral intake of its precursors EPA and DHA

Formation of lipid mediators from a single oral dose of EPA/DHA

Activation of whole blood phagocytic activity after a single oral dose of EPA/DHA

Increase of EPA-derived hydroxy, epoxy and dihydroxy fatty acid levels in human plasma after a single dose of long-chain omega-3 PUFA. *Prostaglandins Other Lipid Mediat.* 2014. Schuchardt JP, Schneider I, Willenberg I, Yang J, Hammock BD, Hahn A, Schebb NH.

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Omega-3-derived lipid mediators in the inflammatory response

- Transcellular biosynthesis permits local biosynthesis under specific conditions (context-dependent cell-cell interactions)
- Receptor-mediated anti-inflammatory and resolution-activating actions
- Endogenous agonists for regulating the inflammatory response
Lipid mediators have oral bio-availability and/or systemic actions

The lipoxin analogue ATLa stops leukocyte infiltration in zymosan A-stimulated peritonitis

Lipoxins and novel 15-epi-lipoxin analogs display potent anti-inflammatory actions after oral administration.
Thank you!

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GOED – Global Organization for EPA and DHA
PUFA Newsletter – August 2014

Editorial
The Essential Fats of Life – Unabated

Cardiovascular Health
Insight into the Variations in the Individual Response to Supplemental EPA/DHA Intake
Correcting VLDL Kinetic Abnormalities in Obesity and Insulin-Resistance

Maternal and Infant Health
Towards Faster Weaning from Parenteral Nutrition in Neonates with Short Bowel Syndrome

Immune Function
Reference Profiles for PUFA-derived Lipid Mediators in Human Plasma and Serum

Brain and CNS
Facilitating Transport of DHA into the Brain

Mental Health and Cognition
Addressing Depression in Maintenance Hemodialysis Patients
EPA/DHA – Perspectives for Neuropsychological Improvement in Malnourished Pre-adolescent Children

Guest Article
Omega-3 PUFAs: Who Could Have Predicted?

Invited Opinion
Clinical Studies on the Effect of Omega-3 Fatty Acids on Cardiovascular Outcomes