Effect of Malnutrition on Resistance to Infection

Charles B. Stephensen, Ph.D.
USDA Western Human Nutrition Research Center
Department of Nutrition, UC Davis
The Immune Response to Infection

Pathogenesis of Infectious Disease. Cedric Mims.

Innate Immunity ......... Adaptive Immunity
Chapter 3: Effect of Malnutrition on Resistance to Infection

1968
- Synergism & antagonism of nutrition and infection
  - Little mechanistic data
- Observational clinical & community studies
- Animal studies
  - Many species
  - Clinical, pathological, & microbiological endpoints

2008
- A focus on mechanisms
  - Some nutrients “modulate” immune response (vitamin A, ω3/ω6 fatty acids)
- Randomized, controlled trials
- Animal studies
  - Mice (± gene of interest)
  - Immunologic endpoints
Chapter 4: Determinants of the Effects of Nutrition on Infection

1968
- Immune mechanisms
  - Antibody formation
  - Phagocytic activity
- Protein energy malnutrition impairs protective immunity
- Infectious disease

2008
- Adaptive immune system
  - B cells, CTL, Th1, Th2, Th17, Treg, γ/δT, NK, NKT
- Innate immune system
  - Pattern-recognition receptors, anti-bacterial peptides, antigen-presenting cells
- Dietary restriction in a “calorie rich” environment enhances immunity
- Inflammatory disease
Fat Does More Than Provide Energy: Fatty Acids Modulate Inflammation
Bacterial LPS stimulates transcription of proinflammatory genes by activation of toll-like receptor 4 (TLR4)
Saturated fatty acids stimulate and unsaturated fatty acids inhibit TLR4 activation


Cyclooxygenase 2 (COX2) promotes inflammation by metabolizing arachidonic acid (AA) to produce prostaglandins.
Relative dietary intake of AA and EPA determines membrane AA:EPA ratio

Arachidonic Acid (AA) 20:4 ω6

- COX
- 5LOX

2-series prostaglandins
4-series leukotrienes

INFLAMMATION

Eicosapentaenoic Acid (EPA) 20:5 ω3

- COX
- 5LOX

3-series prostaglandins
5-series leukotrienes

less inflammation
Arthritic Joint

LTB4 (enhance inflammation)

X ↔ EPA

LTB4

TNF-α, IL-1β

Protein-Energy Malnutrition, Dietary Restriction and Adaptive Immunity

T cell

Innate Immunity ........ Adaptive Immunity
Protein-energy malnutrition impairs thymic function, diminishing T cell-mediated immunity.

Thymic functions recover rapidly on refeeding.

Mechanism?

DTH skin test (*Candida*) in children with malnutrition (severe, moderate, control)

Neumann et al., Am J Clin Nutr 28:89-104, 1975
T-cell immune deficiency is induced by starvation and reversed by leptin

Leptin is produced by adipose tissue, reflects energy reserves and is lower in PEM. Mice without leptin or its receptor have thymic atrophy. T cells have leptin receptors. Leptin promotes T-cell survival, proliferation and differentiation.

Gambian infants born in hungry season have impaired thymic function and greater mortality as adults than children born during the harvest season.


**Thymic Function** - 8 wk old infants born in harvest season have a significantly higher % of recent thymic emigrant T-cells in their blood than do infants born in the hungry season (2.12 v. 0.92 per 100 T-cells, P = 0.006)
T-cell senescence is delayed by caloric restriction in long-lived nonhuman primates

Messaoudi et al. PNAS 103:51 2006

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**Male**

<table>
<thead>
<tr>
<th>% Naïve T-cells</th>
<th>Recent Thymic Emigrants (per 1000 cells)</th>
<th>T-cell Receptor Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>/</td>
<td></td>
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</tbody>
</table>

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**Female**

<table>
<thead>
<tr>
<th>% subset</th>
<th>% subset</th>
<th>TREC/1000 cell</th>
<th>% polyclonal Vβ families</th>
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</thead>
<tbody>
<tr>
<td>CD8</td>
<td>CD4</td>
<td>CD4</td>
<td>CD8</td>
</tr>
</tbody>
</table>

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*P-values:*

- Male: Naïve T-cells (P=0.003), TREC/1000 cells (P=0.027)
- Female: Naïve T-cells (P=0.009), TREC/1000 cells (P=0.029)

- Control vs. calorie-restricted

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**T-cell senescence is delayed by caloric restriction in long-lived nonhuman primates**

Messaoudi et al. PNAS 103:51 2006
Vitamin A, Community Intervention Trials, Nuclear Receptors and Adaptive Immunity

Innate Immunity .......... Adaptive Immunity
Vitamin A supplementation decreases early childhood mortality in community-based RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Aceh, Indonesia</td>
<td>0.73</td>
<td>0.024</td>
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<tr>
<td>Ghana</td>
<td>0.82</td>
<td>0.0005</td>
</tr>
<tr>
<td>Hyderabad, India</td>
<td>0.94</td>
<td>0.817</td>
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<tr>
<td>Jumla, Nepal</td>
<td>0.74</td>
<td>0.058</td>
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<tr>
<td>MSG, Indonesia</td>
<td>0.70</td>
<td>0.001</td>
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<tr>
<td>Sarlahi, Nepal</td>
<td>0.71</td>
<td>0.003</td>
</tr>
<tr>
<td>Sudan</td>
<td>1.04</td>
<td>0.756</td>
</tr>
<tr>
<td>Tamil Nadu, India</td>
<td>0.50</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td><strong>0.775</strong></td>
<td><strong>3 x 10^{-9}</strong></td>
</tr>
</tbody>
</table>
Vitamin A supplementation decreases mortality from measles

Subjects
- 189 children < 13 y of age admitted to hospital for measles

Treatment
- 200,000 IU vit. A on admission and d 2

Results
- Reduced mortality and severity
Vitamin A supplementation slows recovery in children hospitalized with pneumonia

*Stephensen et al, Pediatrics 101:e3-10, 1998*

**Hypothesis**
- Vitamin A will decrease duration and severity of pneumonia

**Results**
- No change in duration of hospitalization
- Vit. A slowed normalization of clinical indicators of severity
- Vit. A decreased prevalence of subclinical deficiency
1968: What is the active metabolite of vitamin A in the immune system?

Retinoic Acid

1987: P. Chambon, R. Evans Labs

RAR:RXR
Vitamin A promotes Th2 responses

RA = Retinoic Acid

Defense against intracellular pathogens
- cytotoxic T-cells
- IgG2a
- Macrophage activation

Defense against extracellular pathogens
- IgA, IgG1, IgE
- (α4β7 integrin)
- eosinophils

Impaired by vitamin A deficiency
Vitamin A deficiency decreases and high vitamin A increases influenza-specific salivary IgA response by decreasing number of flu-specific plasma cells.
Th2 Response Promotes Asthma Development

allergen

Airway IL-4 (mast cell)

Th0

Th1

Th2

“IASTHMA”

IL-4
IL-5
IL-13

eosinophil

Impaired by vitamin A deficiency?
Vitamin A deficiency decreases & high vitamin A increases severity of eosinophilic pulmonary inflammation (“asthma”) in mice.


Inhalation Treatment (Methacholine)

Baseline Saline

Airway Resistance

VAD-OVA

4IU-OVA

250IU-OVA

High VA

Control

VA Deficient
Vitamin A Requirements

- Infection Risk
- Th2 Response
- Asthma Risk?
- CNS, liver, bone toxicity
Summary

1968

• Nutritional deficiencies are definitively associated with increased severity of infectious disease

2008

• Treating micronutrient deficiencies with supplements decreases morbidity and mortality in randomized, controlled trials

• Detailed mechanistic data on impact of some nutrient deficiencies on specific aspects of immunity from mouse models

• MISSING LINK: Mechanistic studies in humans with nutritional deficiencies in appropriate populations and geographic settings