The Aging Immune System and the Physiology of the Inflammatory Response

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The Clinical Questions

- Why do older people get sick all the time?
- Why do diseases cluster together late in life?
- Is there something biological that makes some people more vulnerable?
Introduction

• What is chronic inflammation?
• What triggers and sustains it?
• What are the consequences to the health of older adults?
• Can it be diagnosed and treated?
Chronic Inflammation

Age-related, multifactorial, low-grade activation of the innate immune system that leads to the chronic production of inflammatory mediators
Acute Vs. Chronic Inflammation Timeline

Stress/Infection  |  Response  |  Healing

IL-6  |  CRP

IL-6 Response  
CRP  
Healing
Inflammatory Response

**ACUTE INFLAMMATION**
- Vascular changes
- Neutrophil recruitment
- Mediators

**RESOLUTION**
- Clearance of injurious stimuli
- Clearance of mediators and acute inflammatory cells
- Replacement of injured cells
- Normal function

**INJURY**
- Infarction
- Bacterial infections
- Toxins
- Trauma

**Progression**

**INJURY**
- Viral infections
- Chronic infections
- Persistent injury
- Autoimmune diseases

**CHRONIC INFLAMMATION**
- Angiogenesis
- Mononuclear cell infiltrate
- Fibrosis (scar)

**FIBROSIS**
- Loss of function

**Pus formation (abscess)**

**Healing**

**Healing**
Inflammatory Gateway: NFkB

TNF  IL-1  LPS  H$_2$O$_2$

NFkB

IL-6  IL-8  MCP-1  COX-2

fibrosis  neutrophils  apoptosis  prostaglandins
Measuring Chronic Inflammation in Humans

- Usually done with serum markers
- Hundreds of association studies using mostly inflammatory cytokines as markers.
- Most tied to NFkB pathways
Inflammatoty Biomediators and Muscle Strength

- In CHIANTI, n=1020, age 65-100
- CRP, IL-6, IL-1RA correlated with decreased performance and strength
- IL-6 most consistent biomediator

Cesari M, et al., J Geront 2004
IL-6, CRP & Mortality

- IL-6 & CRP alone and in combination associate with mortality in healthy older adults.
  - IL-6 (>3.19 pg/ul)  RR 2.1, (CI 1.3,3.4)
  - CRP (>2.78 mg/L)  RR 1.7, (CI 1.1,2.6)
  - IL-6 & CRP   RR 3.5, (CI 1.4-5.4)
- All cause and cardiovascular mortality rates not different

C-Reactive Protein and Frailty

Walston, et al. Archives of Internal Medicine, 2002
Inflammatory Biomediators and Muscle Strength

- Health ABC, n=3071, age 70-79
- Consistent relationship in all groups between IL-6 and lower strength
- TNF-α also significantly related to declines in strength in women

Visser M, et al., J Geront 2002
Best Serum Inflammatory Markers of Vulnerability

- IL-1 RA
- IL-6
- TNF-alpha R1
- IL-18
- CRP
Inflammation Index and Mortality

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
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<tbody>
<tr>
<td>logCRP</td>
<td>72</td>
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<tr>
<td>logIL6</td>
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<td>&lt;.0001</td>
<td>1.44</td>
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<td>logTNFRI</td>
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<td>logIL18</td>
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<td>1.12</td>
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<td>logIL1RA</td>
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<tr>
<td>IIS</td>
<td>433</td>
<td>&lt;.0001</td>
<td>1.64</td>
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</table>

Each predictor is adjusted by age, except age by its own
IL-6 and Multisystem Dysregulation

- ↓ Appetite
- ↓ Lean body mass
- Anemia
- Polyclonal expression & autoantibodies
- Increased clotting
- HPA axis activation
- Localized CNS inflammation

Chronic IL-6 Signaling

- Contributes to declines muscle satellite and blood stem cells
- Remodels immune system with senescent immune cell proliferation
- Drives mitochondrial dysfunction and fibrotic tissue changes
- Accelerates chronic disease
IL-6 and Multisystem Dysregulation

- Rhesus monkeys injected with low dose IL-6 developed multisystem changes
  - 10% lean body mass decline by DEXA within 30 days
  - Anemia & osteopenia
  - Decreased albumin & cholesterol
  - Increased CRP, alkaline phosphatase

Binkley, NC, et al. 1994 and Ershler & Keller, 2000
Chronic TNF-Alpha R1

• Contributes to apoptosis and necroptosis signaling, and to accelerating cell loss
• Drives further inflammatory pathway activation and disease
What Triggers and Sustains It

- Senescent Fibroblasts/stromal cells
- Increased Fat Mass
- Damaged Mitochondria
- Altered Microbiome + Leaky Gut
- Diet, Lack of Exercise, Genes
- Chronic Disease and Chronic Infection
<table>
<thead>
<tr>
<th>Dietary and Lifestyle Factors Associated with Inflammation</th>
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<tbody>
<tr>
<td>Increase Inflammation</td>
</tr>
<tr>
<td>Trans fatty acids</td>
</tr>
<tr>
<td>Saturated fatty acids</td>
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<tr>
<td>High glycemic index foods</td>
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<tr>
<td>Excessive alcohol</td>
</tr>
<tr>
<td>Smoking</td>
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<tr>
<td>Excessive exercise</td>
</tr>
<tr>
<td>Reduce Inflammation</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
</tr>
<tr>
<td>Low cholesterol diets</td>
</tr>
<tr>
<td>Low glycemic index foods</td>
</tr>
<tr>
<td>Dietary fiber</td>
</tr>
<tr>
<td>Arginine-rich foods (fish, nuts)</td>
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<tr>
<td>Moderate alcohol intake</td>
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<tr>
<td>Physical activity</td>
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</table>
Do Stress Response Systems Underlie Vulnerability?

- Inflammation
- SNS
- HPA Axis
- RAS
Key Stress Response Systems

- Inflammation
- HPA Axis
- SNS
- RAS
Stress Response Systems and Vulnerability
Stress Response Systems and Vulnerability

Organ and tissue specific changes

Angiotensin System

Inflammation

SNS

HPA Axis

Disease

Disability

Depression
Stress Response Systems and Vulnerability

Tissue specific changes

Angiotensin System

Inflammation

SNS

HPA Axis

Chronic Disease

Depression

Disability
Model Pathway to Frailty and Adverse Outcomes in Older Adults

**Potential Triggers**
- Molecular Aging
- Mitochondrial decline
- DNA Methylation
- Apop/Necroptosis
- ↑ Senescent Cells
- ↑ Altered autophagy

- Genetic Variation
- Environment

**Physiology**
- ↑ Inflammation
- ↑ HPA Axis
- ↑ Sympathetic nervous system
- ↑ Angiotensin system action
- ↓ Energy production
- Altered Anabolic Hormones

**Clinically Apparent**
- Weakness
- Fatigue
- Weight loss
- Slowness

**Outcomes**
- Dependence
- Disability
- Chronic Diseases
- Mortality

**Model Pathway to Frailty and Adverse Outcomes in Older Adults**

Walston J, 2016
Tried and True Interventions that Reduce Inflammation

- EXERCISE
- EXERCISE
- EXERCISE
- GOOD NUTRITION
- Ongoing research looking into best types of activities and into optimal nutritional needs of older adults (i.e. types of protein that may be of most benefit).
Novel Interventions to Reduce Inflammation

- Angiotensin Receptor Blockers Being studied (Hopkins OAIC and ENERGISE)
- Other drugs such as NSAIDs not safe to utilize in chronically ill older adults
- Dietary supplements
  - Omega 3 fatty acids
  - Antioxidant derivatives of ‘superfoods’
  - Lactoferrin
Losartan Improves Muscle Remodeling and in vivo Function in Older Mice

• Burks T N et al. Sci Transl Med 2011
Future Directions

- Development of Best Clinical Measurement for Diagnostic and Treatment Monitoring Purposes
- Identify Specific ‘Upstream’ or causal measurements
- Determine ‘Downstream’ or reactive measurements and their impacts
‘Upstream’ or Causal Measures

- Specific Need for
  - Leaky Gut Markers
  - Mitochondrial Dysfunction Markers
  - Senescent Cell Markers
  - Altered Microbiome Markers
  - Early and stable inflammasome activation detection
‘Downstream’ Measures with Consequences

- Kyneurinine and neurotoxic derivatives
- Energy Metabolism (mitochondrial) Measures
- Remodulated or senescent immune system markers
- Altered Mitochondrial Function Markers
- (metabolomic and/or proteomic approaches may be helpful here)
Acknowledgments

J O H N S  H O P K I N S  U N I V E R S I T Y

OLDER AMERICANS INDEPENDENCE CENTER

• http://www.jhsph.edu/research/centers-and-institutes/johns-hopkins-center-on-aging-and-health/oaic/