Age-Associated Cytokine Dysregulation (Not Inflammatory Disease) at the Root of Frailty

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Aging, Cytokines and Frailty

- Aging and frailty
- Cytokine profiles and aging
- Regulation of IL-6
- Influence of Estrogens and Androgens
- Frailty without inflammatory disease

Tenets of Geriatric Medicine

- There are highly variable age-associated changes in organs, tissues and cells that diminish functional reserve and confer vulnerability to stressors and/or disease.
- Aging is not a disease.

Features of Frailty

- Osteopenia
- Sarcopenia
- Low grade anemia
- Inflammatory profile
- Functional impairment
- Cognitive impairment
- Vulnerability
- Can occur without Disease

Aging Heterogeneity

- Threshold for Disability
- Threshold for Clinical Detection
- Homeostatic Maintained
- Entropic Forces

Frailty
Candidate Entropic Force: Dysregulated Inflammation

• Clinical picture of frailty resembles chronic inflammation
• Epidemiological studies have demonstrated an association of inflammatory markers and frailty

IL-6 and Age

The IL-6 Response

• Stimulates catabolic processes, providing energy for acute inflammation
• Stimulates calcium mobilization from bone
• Induces hepcidin thereby paralyzing GI iron absorption and mobilization from macrophages
• Stimulates marrow neutrophil and megakaryocyte progenitors, inhibits erythropoietin

But, why?

• Age-associated development (accumulation) of inflammatory processes.
• Increased relative adiposity
• Endocrine senescence (menopause and andropause)
1. NF-κB is maintained in the Cytoplasm by the Ikβ
2. In the absence of stimulation the IKK complex is inactive

3. Different type of stimuli can activate the IKK complex
4. IKK phosphorylates the Ikβ protein
5. Phosphorylation is a tag for ubiquitinization
6. NF-κB translocates into the nucleus, binds to κB elements in gene promoters and enhancers
7. Activates all sort of genes

8. The Synthesis of Ikβ is a feed-back time-dependent component to NF-κB response. Feedback inhibition can be rapid, or slow, and can be altered by physiological states, such as age, stress or inflammation.
Inhibition of NFκB Activity through Maintenance of IκBα Levels
Contributes to Dihydrotestosterone-mediated Repression of the Interleukin-6 Promoter

DHT inhibits NFκB complex formation on the IL-6 promoter

Androgens and IL-6
Keller et al., JBC 1996; 271:26267
DHT inhibits IL-6 production in LNCaP cells
DHT decreases steady state IL-6 mRNA levels in LNCaP cells
DHT inhibits transcriptional activation of the IL-6 promoter in LNCaP cells
Androgen receptor (AR) required for DHT inhibition, but did not bind IL-6 promoter
DHT treatment was associated with maintenance of IκBα when cells after PMA activation
In Vitro

In Vivo

Hormonal regulation of pro-inflammatory and lipid peroxidation processes in liver of old ovariectomized female rats


Biogerontology, 2009

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Intact animals (20 months)</th>
<th>Ovariectomized animals (20 months)</th>
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<tbody>
<tr>
<td>TNFα</td>
<td>57.2 ± 0.85</td>
<td>84.1 ± 6.8a</td>
</tr>
<tr>
<td>IL-1α</td>
<td>103.7 ± 2.5</td>
<td>126.9 ± 7.1a</td>
</tr>
<tr>
<td>IL-6</td>
<td>15.1 ± 1.5</td>
<td>32.8 ± 3.0a</td>
</tr>
<tr>
<td>IL-10</td>
<td>269.6 ± 16.7</td>
<td>148.7 ± 17.3a</td>
</tr>
</tbody>
</table>

-effects indicated by '*' compared to intact animals
-effects indicated by 'a' compared to intact animals + treatment
-effects indicated by 'b' compared to intact animals without treatment + GH
-effects indicated by 'c' compared to intact animals without treatment + GH + Eos + Phyt
-effects indicated by 'd' compared to intact animals without treatment + GH + Eos + Phyt + GH
-effects indicated by 'e' compared to intact animals without treatment + GH + Eos + Phyt + GH + Eos

Effects of oestrogen deprivation on interleukin-6 production by peripheral blood mononuclear cells of postmenopausal women

D Rakowska, J Miodowska, K Stokbocka-Kaczka, J Węglicki

Department of Hygiene and Technology of the Health Sciences of Lublin, 22-400 Lublin, Poland

Table 1: Characteristics of the volunteers studied

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Body mass index</th>
<th>Waist: Hip ratio</th>
<th>Number of volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>25-35</td>
<td>20.1-25.0</td>
<td>0.8-1.0</td>
<td>10</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>50-60</td>
<td>25.1-30.0</td>
<td>0.9-1.1</td>
<td>20</td>
</tr>
</tbody>
</table>

-effects indicated by '*' compared to postmenopausal women
-effects indicated by 'a' compared to young women
Conclusions

- Inflammatory pathways are activated with advancing age.
- There is evidence that this occurs to some extent in association with menopause (or andropause).
- Both estrogen and testosterone inhibit NFκB activation of IL-6 gene expression by maintaining IkB levels and reducing NFκB nuclear translocation.
- The proinflammatory pathway to frailty does NOT necessarily require the presence of coexisting inflammatory disease.