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

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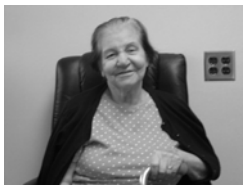
Aging, Cytokines and Frailty

- Aging and frailty
- Cyokine 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.**



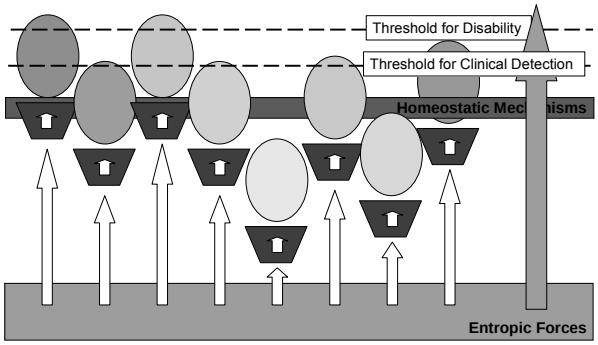
Aging Heterogeneity

Features of Frailty

- **Osteopenia**
- **Sarcopenia**
- **Low grade anemia**
- **Inflammatory profile**
- **Functional impairment**
- **Cognitive impairment**

- ***Vulnerability***
- ***Can occur without Disease***

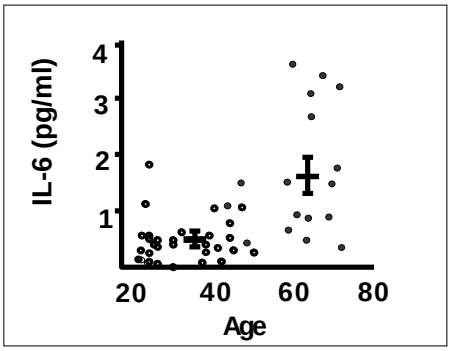
Frailty



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



IL-6 and Aging

- EPESE
- WHAS
- CHS
- BLSA
- InChianti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medical hypotheses

Correspondence

Interleukin-6 (IL-6) is still the leading biomarker of the metabolic and aging related disorders

Aging as well as some chronic medical disorders are characterized with chronic low-grade inflammation. Increased plasma levels of TNF-α, IL-6, and CRP have been demonstrated during aging. Plasma concentration of IL-6 has been shown to predict all-cause of mortality as well as cardiovascular mortality [1].

IL-6 is a pleiotropic cytokine with a key impact on the immune system and is released from immune cells during inflammation. However, in the absence of inflammation, about 10–35% of circulating IL-6 may be derived from adipose tissue particularly from the omental depot, which produces 3-fold more IL-6 than subcutaneous adipose tissue [2]. IL-6 may be the reason for the increased cortisol turnover of the obese state, because IL-6 directly stimulates adrenal cortisol secretion in addition to stimulating hypothalamic CRH and pituitary ACTH release [2]. IL-6 also induces hepatic insulin resistance, and particularly suppresses hepatic glycogen synthesis. Increased plasma IL-6 concentration accelerates the development of the metabolic syndrome and insulin resistance leading

there seems to extrapolate that IL-6 is an anti-inflammatory mediator. However, in contrast to these acute effects, persons who are chronically physically active tend to have lower levels of IL-6 and other inflammatory markers. A combination of diet and exercise regulation significantly reduces IL-6 level [1].

In acute and short-term strenuous exercise-increased IL-6 level generates protective effect while long term IL-6 exposure is injurious. IL-6 may contribute to sarcopenia causing a direct interference with insulin signal transduction and inhibition of the production of insulin-like growth factor-1. Harmful consequences of sarcopenia explain many disabilities of old age: loss of strength, inducing itself loss of mobility, falls, and equilibrium disorders. Supporting evidences came from the very recent InCHIANTI Study, indicating that pro-inflammatory cytokines, particularly IL-6 play a key role in the development of sarcopenic obesity, which leads to diminished mobility [4].

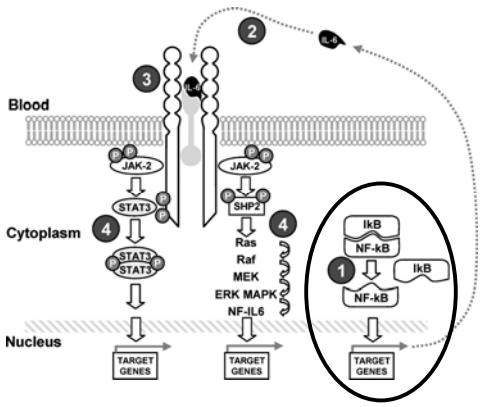
From a simplistic physiologic point of view, it seems rational that large quantities of IL-6 re-

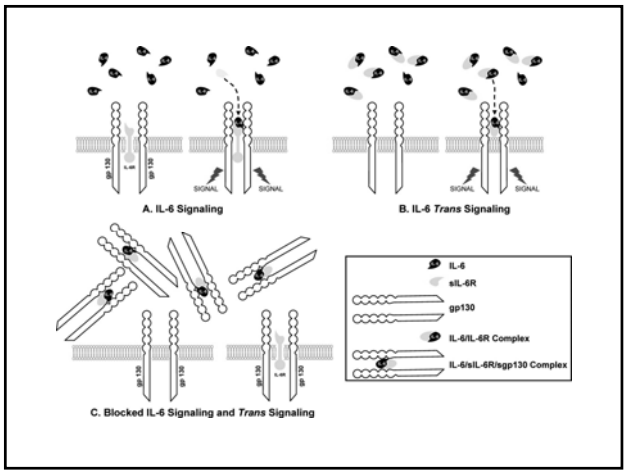
The IL-6 Response

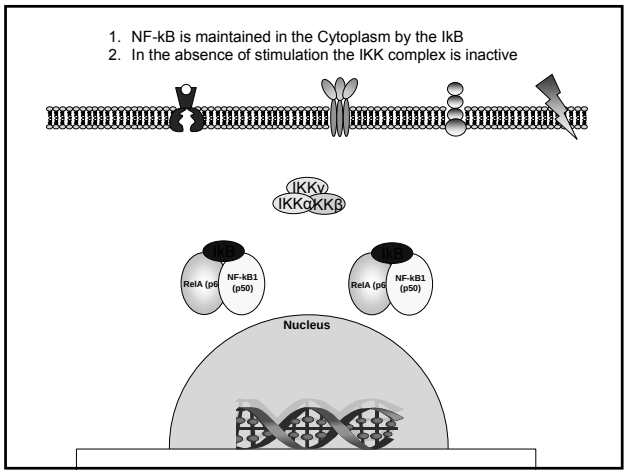
- **Stimulates catabolic processes, providing energy for acute inflammation**
- **Stimulates calcium mobilization from bone**
- **Induces hepcidin thereby paralyzing GI iron absorption and mobilization from macrophages**
- **Stimulates marrow neutrophil and megarkaryoctye progenitors, inhibits erythropoietin**

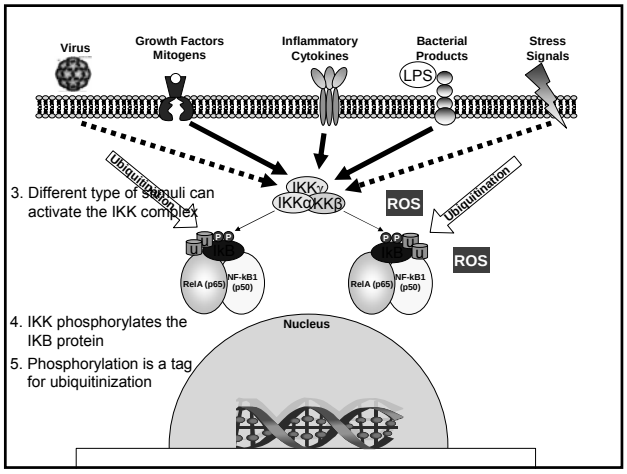
But, why?

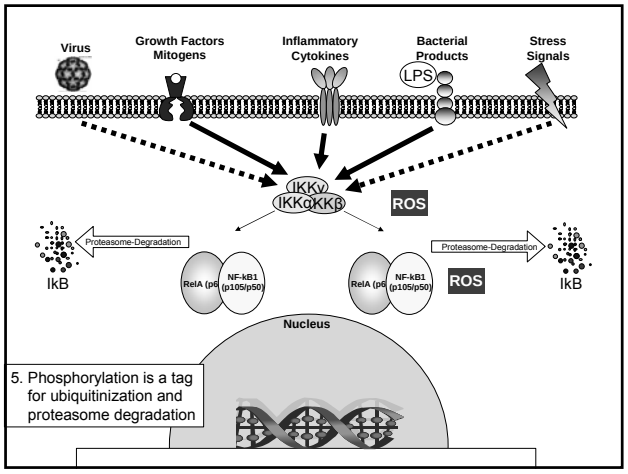
- **Age-associated development (accumulation) of inflammatory processes.**
- **Increased relative adiposity**
- **Endocrine senescence (menopause and andropause)**

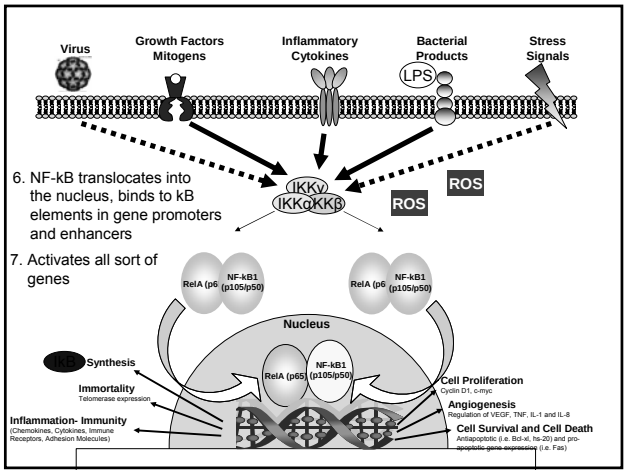


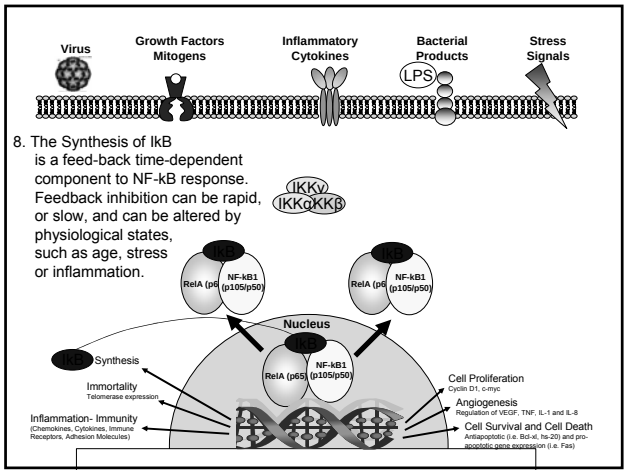

A. IL-6 Signaling
B. IL-6 Trans Signaling
C. Blocked IL-6 Signaling and Trans Signaling
IL-6
sIL-6R
gp130
IL-6/IL-6R Complex
IL-6/sIL-6R/sgp130 Complex


1. NF-kB is maintained in the Cytoplasm by the IkB
2. In the absence of stimulation the IKK complex is inactive
IKKγ
IKKαKKβ
IkB
RelA (p65)
NF-kB1 (p50)
Nucleus


Virus
Growth Factors Mitogens
Inflammatory Cytokines
Bacterial Products
Stress Signals
LPS
Ubiquitination
IKKγ
IKKαKKβ
ROS
3. Different type of stimuli can activate the IKK complex
4. IKK phosphorylates the IKB protein
5. Phosphorylation is a tag for ubiquitinization
RelA (p65)
NF-kB1 (p50)
Nucleus


Virus
Growth Factors Mitogens
Inflammatory Cytokines
Bacterial Products
Stress Signals
LPS
IKKγ
IKKαKKβ
ROS
Proteasome-Degradation
IkB
RelA (p65)
NF-kB1 (p105/p50)
Nucleus
5. Phosphorylation is a tag for ubiquitinization and proteasome degradation


Virus
Growth Factors Mitogens
Inflammatory Cytokines
Bacterial Products
Stress Signals
LPS
IKKγ
IKKαKKβ
ROS
6. NF-kB translocates into the nucleus, binds to kB elements in gene promoters and enhancers
7. Activates all sort of genes
RelA (p65)
NF-kB1 (p105/p50)
Nucleus
IkB Synthesis
Immortality
Telomerase expression
Inflammation- Immunity
(Chemokines, Cytokines, Immune Receptors, Adhesion Molecules)
Cell Proliferation
Cyclin D1, c-myc
Angiogenesis
Regulation of VEGF, TNF, IL-1 and IL-8
Cell Survival and Cell Death
Antiapoptotic (i.e. Bcl-xl, hs-20) and pro-apoptotic gene expression (i.e. Fas)


Virus
Growth Factors Mitogens
Inflammatory Cytokines
Bacterial Products
Stress Signals
LPS
8. The Synthesis of IkB is a feed-back time-dependent component to NF-kB response. Feedback inhibition can be rapid, or slow, and can be altered by physiological states, such as age, stress or inflammation.
IKKγ
IKKαKKβ
IkB
RelA (p65)
NF-kB1 (p105/p50)
Nucleus
IkB Synthesis
Immortality
Telomerase expression
Inflammation- Immunity
(Chemokines, Cytokines, Immune Receptors, Adhesion Molecules)
Cell Proliferation
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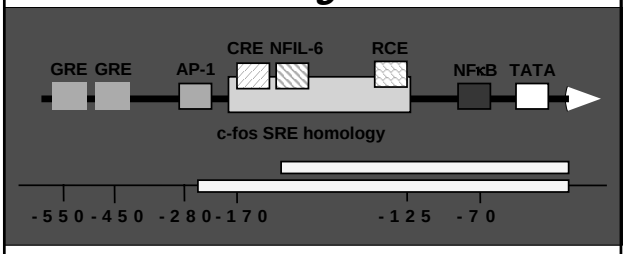
Regulation of VEGF, TNF, IL-1 and IL-8
Cell Survival and Cell Death
Antiapoptotic (i.e. Bcl-xl, hs-20) and pro-apoptotic gene expression (i.e. Fas)

Promoter Region of IL-6



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Inhibition of NFκB Activity through Maintenance of IκBα Levels Contributes to Dihydrotestosterone-mediated Repression of the Interleukin-6 Promoter*

(Received for publication, April 3, 1996, and in revised form, July 24, 1996)

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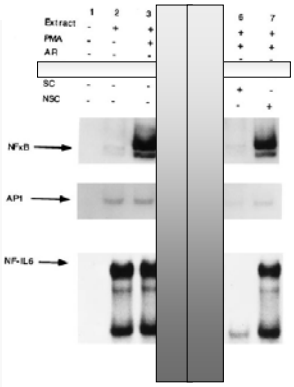
Androgens repress expression of many genes, yet the mechanism of this activity has remained elusive. The cytokine, interleukin-6, is active in a variety of biological systems, and its expression is repressed by andro-

activation, DNA binding, nuclear localization, dimerization, and ligand binding domains (reviewed in Ref. 21). The AR activates gene transcription by specific binding to a DNA sequence, the androgen response element (ARE), in a ligand-

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 IkBa when cells after PMA activation



DHT inhibits NFkB complex formation on the IL-6 promoter

Laboratory Investigations

Orchiectomy Increases Bone Marrow Interleukin-6 Levels in Mice

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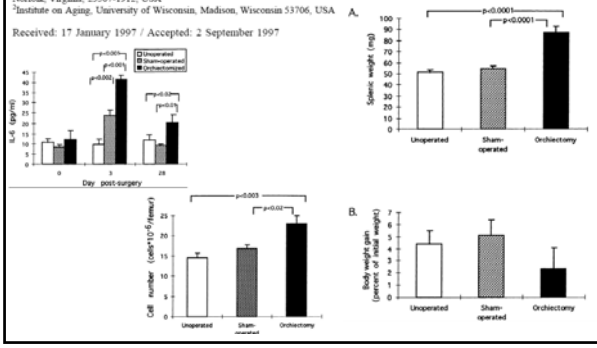

BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 244, 691–695 (1998)
ARTICLE NO. RC988324

Estrogen Inhibits Phorbol Ester-Induced IκBα Transcription and Protein Degradation

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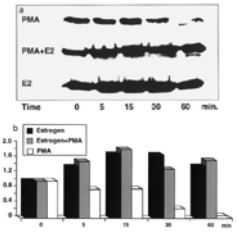

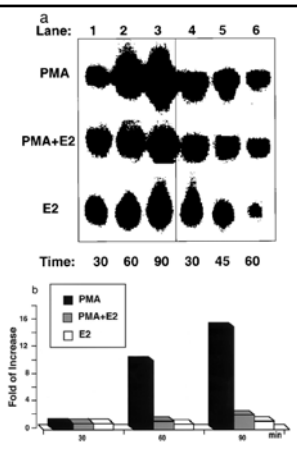

Effects of oestrogen deprivation on interleukin-6 production by peripheral blood mononuclear cells of postmenopausal women

D Rachoń, J Mysliwska, K Suchecka-Rachoń[1], J Więckiewicz and A Mysliwski

Department of Histology and Immunology of the Medical University of Gdańsk, 80 210 Gdańsk, ul. Dębinki 1, Poland
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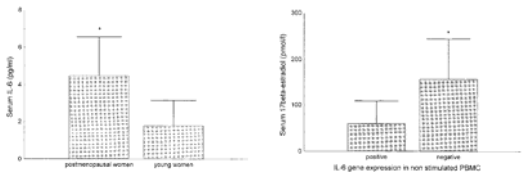
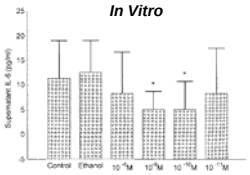
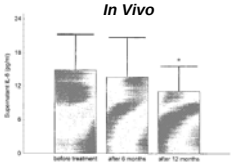
(Requests for offprints should be addressed to D Rachoń; Email: drachon@amedec.amg.gda.pl)



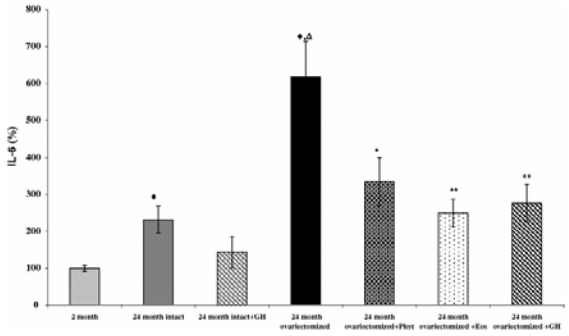




Hormonal regulation of pro-inflammatory and lipid peroxidation processes in liver of old ovariectomized female rats

R. A. Kireev , A. C. F. Tresguerres,
C. Garcia, C. Borras, C. Arriznavarreta,
E. Vara, J. Vina , J. A. F. Tresguerres

Biogerontology, 2009



Cytokines (pg/mg tissues)	2 Months	Intact animals (24 months)		Ovariectomized animals (24 months)			
		Without treatment	+GH	Without treatment	+GH	+Eos	+Phyt
TNFα	57.2 ± 0.85	84.1 ± 6.8[a]	59.6 ± 1.5[b]	95.2 ± 2.7[a]	55.4 ± 2.2[c]	61.4 ± 1.9[c]	54.2 ± 2.7[c]
IL-1β	103.7 ± 2.5	126.9 ± 7.1[a]	122.4 ± 9.7	141.1 ± 4.3[a]	112.6 ± 8.3[c]	116.2 ± 4.2[c]	111.9 ± 9.5[c]
IL-6	15.1 ± 1.5	32.8 ± 3.0[a]	25.5 ± 2.3	69.8 ± 8.1[a,d]	19.0 ± 1.7[c]	21.7 ± 2.9[c]	39.9 ± 2.1[c]
IL-10	269.6 ± 16.7	148.7 ± 17.3[a]	302.7 ± 39.8[b]	126.5 ± 12.1[a]	284.8 ± 23.5[c]	291.5 ± 17.8[c]	278.1 ± 19.5[c]

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

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Table 1 Characteristics of the subjects studied

	Postmenopausal women	Young women
No. of subjects	22	16
Age (years)	52·77 ± 4·59*	26 ± 3·09
Years since menopause	4·48 ± 4·26	—
Serum FSH levels (IU/l)	68·23 ± 21·17*	17·63 ± 8·25
Serum 17β-estradiol levels (pmol/l)	85·66 ± 76·33*	259·77 ± 132·89

*P<0·05.

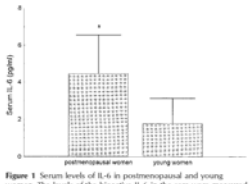

Figure 1 Serum levels of IL-6 in postmenopausal and young women. The levels of the bioactive IL-6 in the sera were measured using a B9 cell-proliferation assay. The postmenopausal women (n=22) had significantly higher levels of bioactive IL-6 than the young ones (n=16) (4·44 ± 2·10 pg/ml vs 1·76 ± 1·38 pg/ml) (*P<0·05).

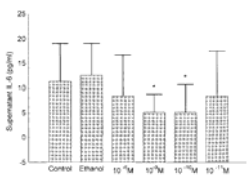

Figure 5 *In vitro* effects of 17β-oestradiol on the spontaneous IL-6 production by the PBMC of postmenopausal women. PBMC isolated from postmenopausal women (n=22) were incubated for 24 h with different concentrations of 17β-oestradiol. After the incubation period, the bioactive levels of IL-6 were measured in the supernatants using the B9 hybridoma proliferation assay. 17β-Oestradiol at the concentrations of 10^{-9} M and 10^{-10} M significantly decreased the spontaneous IL-6 production into the culture supernatants by the PBMC of postmenopausal women (*P<0·05).

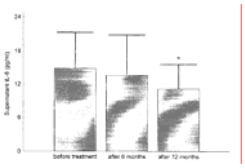

Figure 6 *In vivo* effects of 17β-oestradiol on the spontaneous IL-6 production by the PBMC of postmenopausal women. Seventeen out of twenty-two postmenopausal women were treated with 50 µg 17β-oestradiol/day transdermally (Estraderm 50MX). After 6 and 12 months of treatment, PMBC were isolated from venous blood and incubated for 24 h in a medium supplemented with FCS in a humidified atmosphere with 5% CO_2. After the incubation period, the bioactive levels of IL-6 were measured in the supernatants using the B9 hybridoma proliferation assay. PBMC of postmenopausal women treated with 17β-oestradiol released significantly smaller amounts of bioactive IL-6 into the culture media after 12 months of treatment than at baseline (11·11 ± 4·44 pg/ml vs 14·83 ± 6·37 pg/ml (*P<0·05).

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 NFkB activation of IL-6 gene expression by maintaining IkB levels and reducing NFkB nuclear translocation
- The proinflammatory pathway to frailty does NOT necessarily require the presence of coexisting inflammatory disease.