Biomarkers of Aging and Chronic Inflammation

2015 New York Clinical Conference

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Key Immune Terminology:

- **Immunosenescence**: overall change to the immune system with age
  - greater susceptibility to pathology
  - reduced responsiveness and impaired communication between all cells
- **Inflammaging**: upregulation of the inflammatory response, resulting in low-grade chronic systemic proinflammatory state
  - raised levels **proinflammatory cytokines** interleukin-1 (**IL-1**), interleukin-6 (**IL-6**) & tumor necrosis factor (**TNF**)
  - involved in pathogenesis of most age-associated diseases

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Clinical Consequences

- Cardiovascular disease
- Alzheimer's disease
- Autoreactivity & Vaccine failure
- Increased vulnerability to infectious
- Frailty Syndrome
  - loss of muscle
  - weakness, slowing
  - decreased energy
  - unintended weight loss

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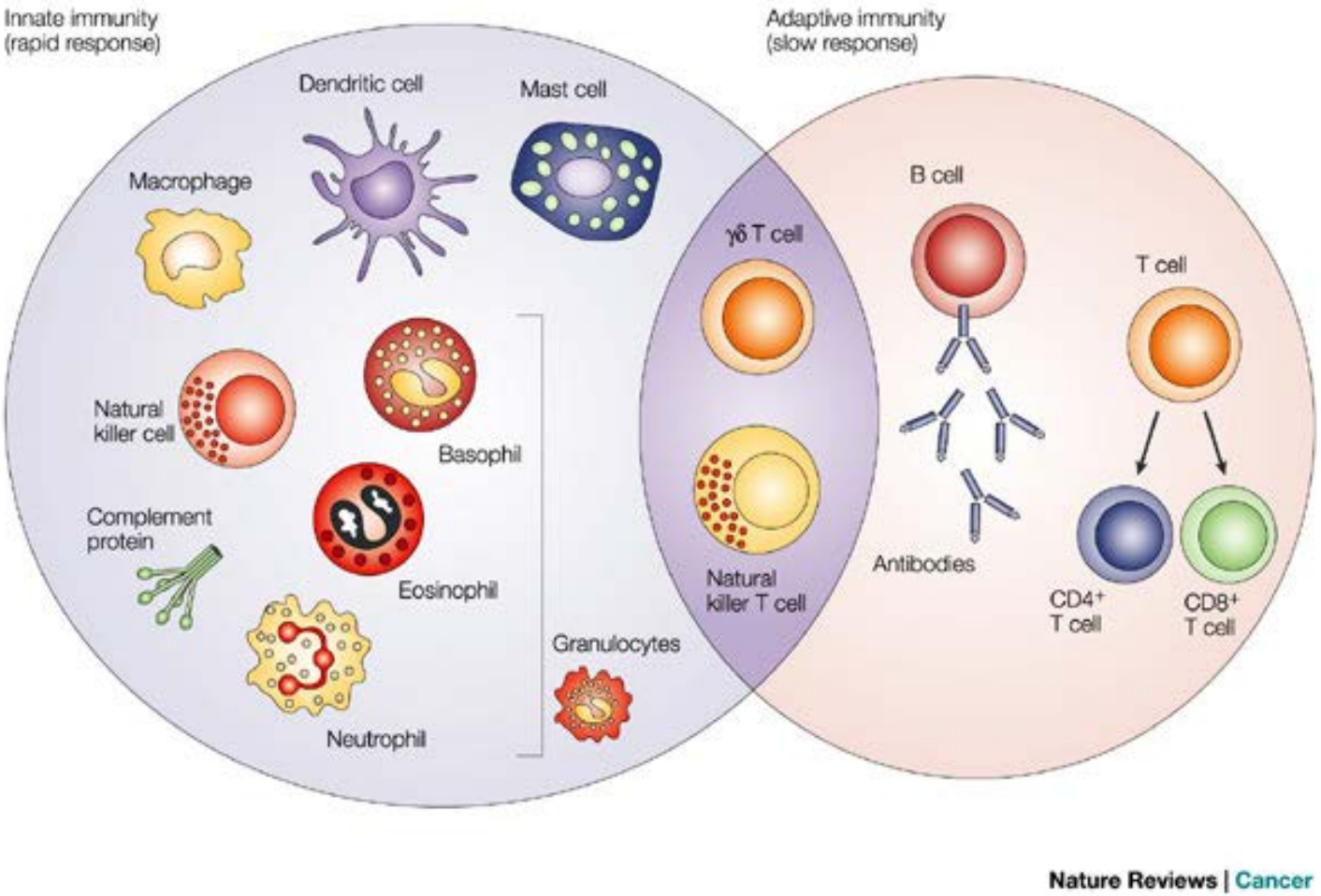
Innate versus Specific Immunity



Dranoff 2004

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Age-related **Innate** Changes

Cell Type	Age-related Changes
Neutrophils	Impaired phagocytosis, impaired superoxide production
Macrophages	Impaired phagocytosis, impaired superoxide production, lower MHC II
Dendritic cells	Impaired phagocytosis, impaired migration
NK cells	Reduced cytotoxicity

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Age-related **T-cell** Changes

- Thymus atrophy
- Reduced naïve cells
- Impaired expansion and differentiation
- Reduced IL-2, increased *proinflammatory* cytokines
- Increased memory and effector cells
- Impaired T help for B cells
- Reduced regulatory cells
- Expanded CD8+ clones for specificity to single antigens, particularly latent viral infections: dominating repertoire and limiting other responses

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Age-related **B-cell** Changes

- Reduced number of mature B’s leaving marrow
- Increased memory B cells, reduced naïve
- Reduced responsiveness to stimulatory molecules
- Impaired antibody response to vaccination

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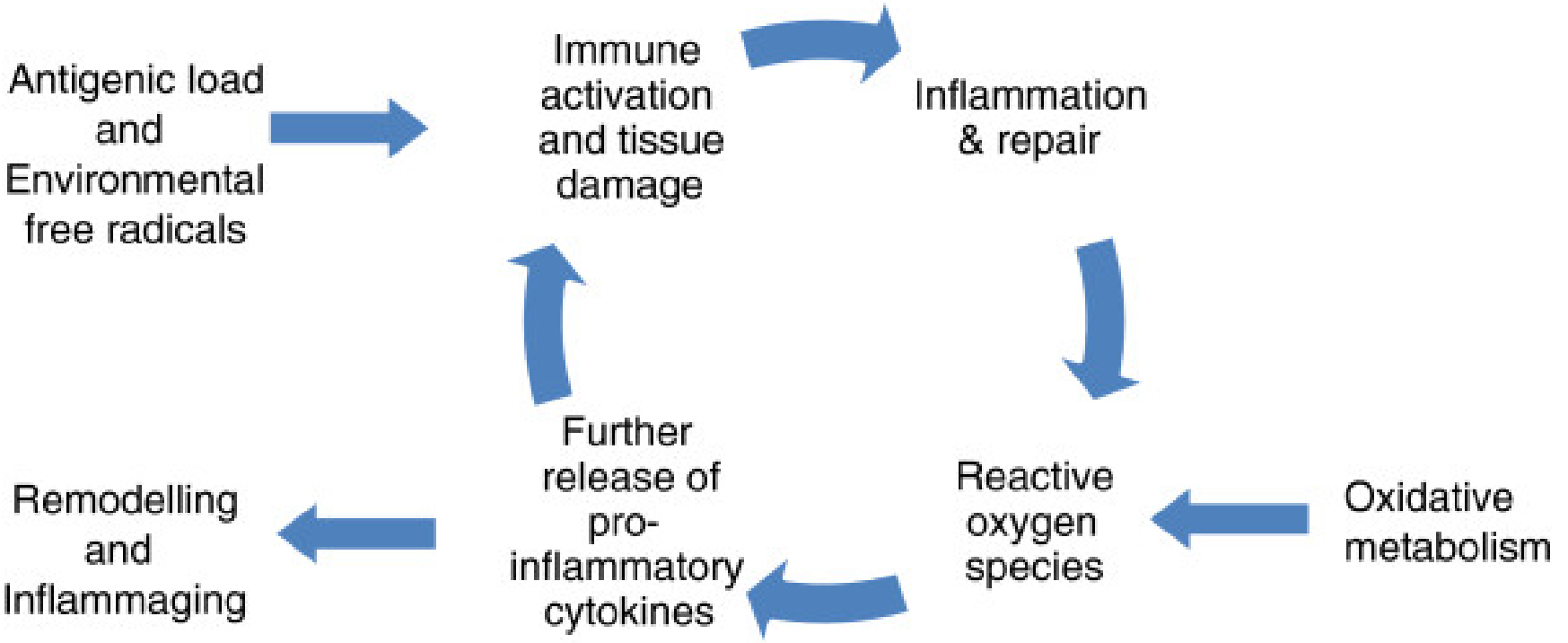
Cumulative lifetime exposure to antigenic load: Vicious Cycle



Baylis et al 2013

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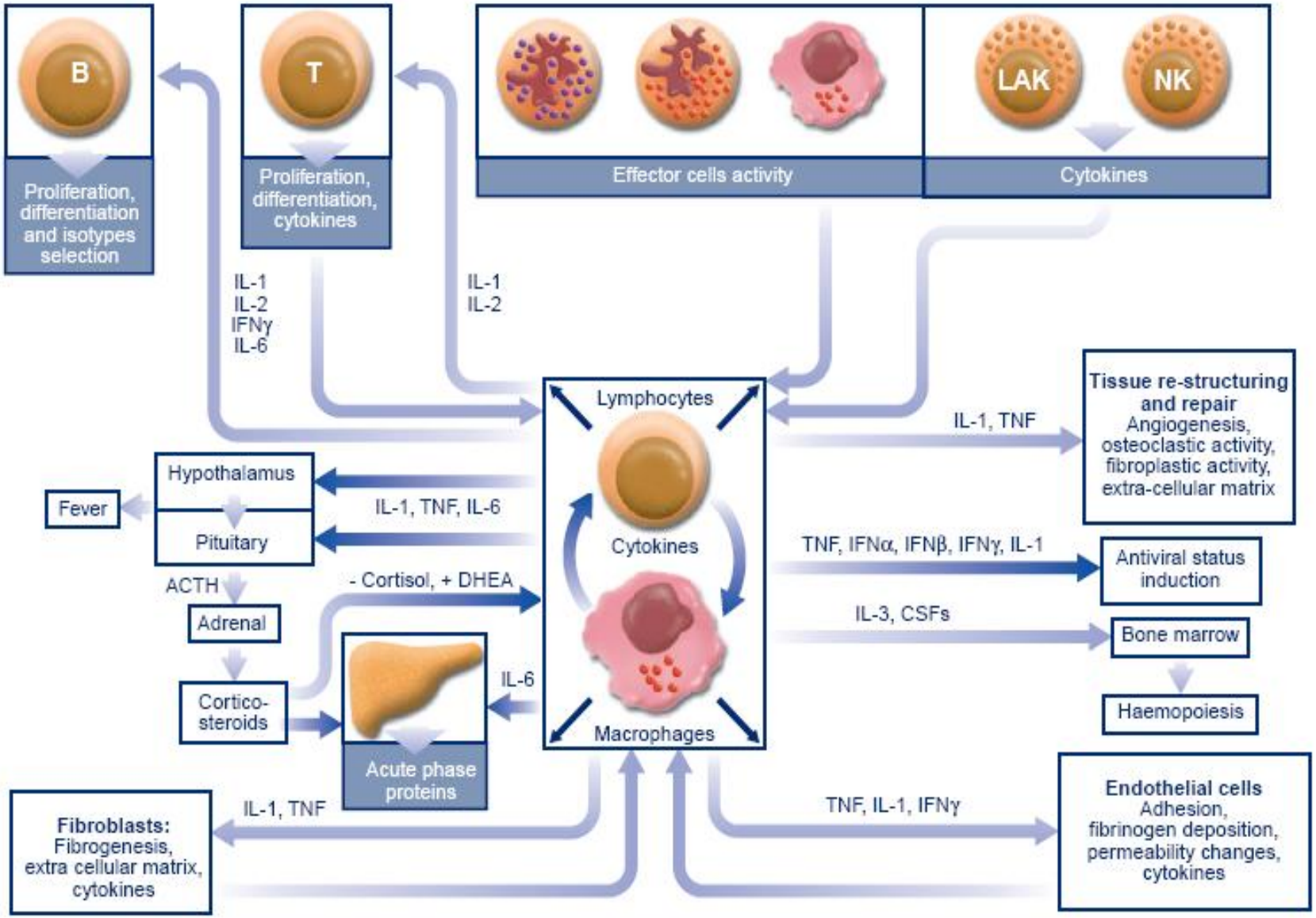
Major functions of cytokines



Inflammaging

- **Chronically increased** production of **inflammatory cytokines** and prolongation of the immune response
- Elevations in levels of **TNF**, **IL-6**, **IL-1** and **CRP**
- **Monocytes** and **macrophages** contribute most
- Strong independent risk factors for **morbidity and mortality** in older people
- Many **age-related diseases** are initiated or worsened by **systemic inflammation**
- Significant **associations** between inflammation **neurodegeneration, atherosclerosis, Alzheimer's disease, osteoporosis, dementia,** and **frailty syndrome**

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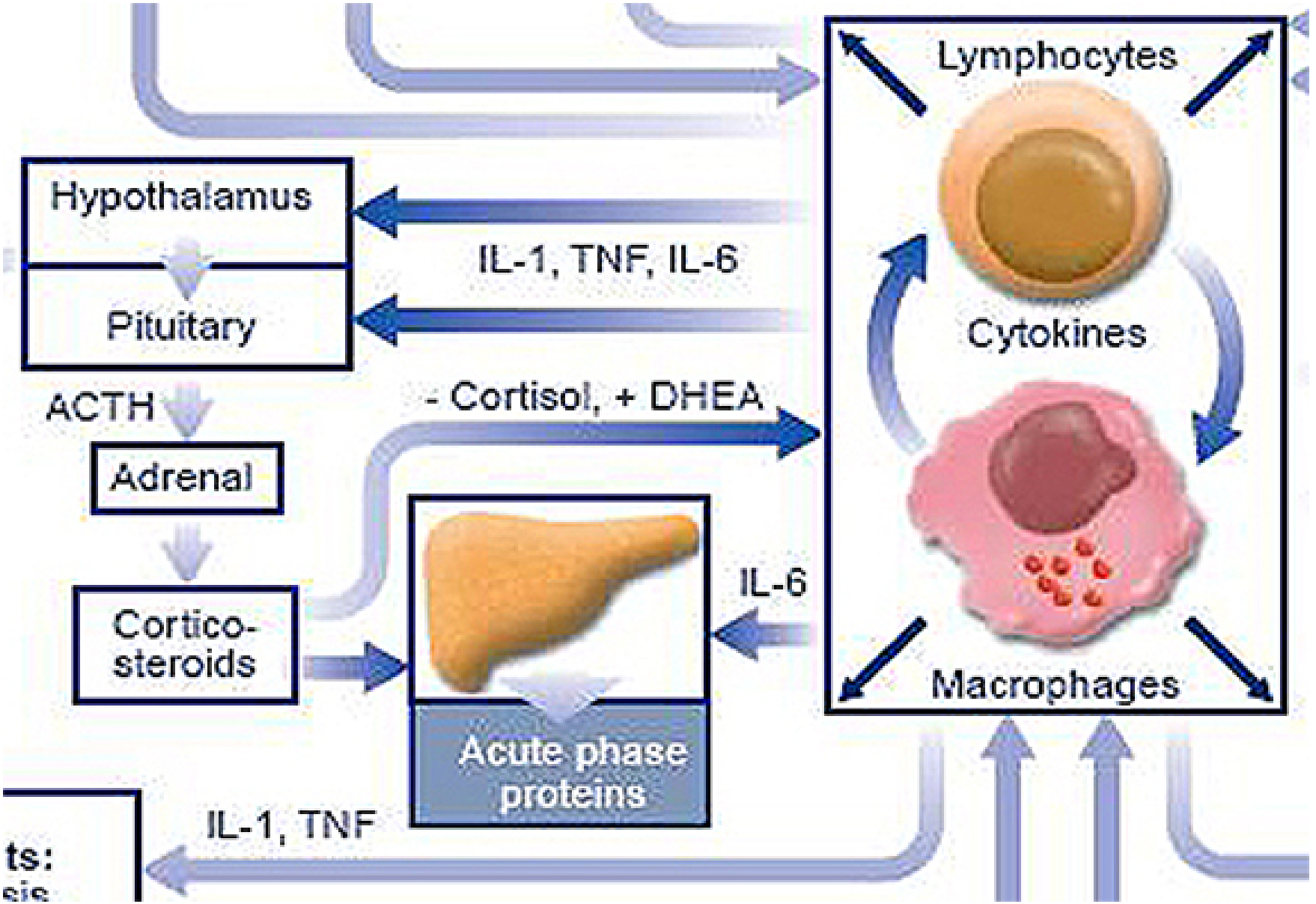
Lymphocytes
Hypothalamus
Pituitary
IL-1, TNF, IL-6
Cytokines
ACTH
- Cortisol, + DHEA
Adrenal
Cortico-
steroids
IL-6
Acute phase
proteins
Macrophages
IL-1, TNF
ts:

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Anti-inflammaging

- Inevitable physiological response to inflammaging is an **increase** in circulating **cortisol** levels
- Represents an appropriate **attempt to counter** the **inflammaging** process → negative implications: the **paradox** of both inflammaging and the global immunosuppression seen with increasing age
- Associations with **frailty** via **catabolic effects** on several tissue types: liver (gluconeogenesis), muscle (protein catabolism) and bone (resorption)

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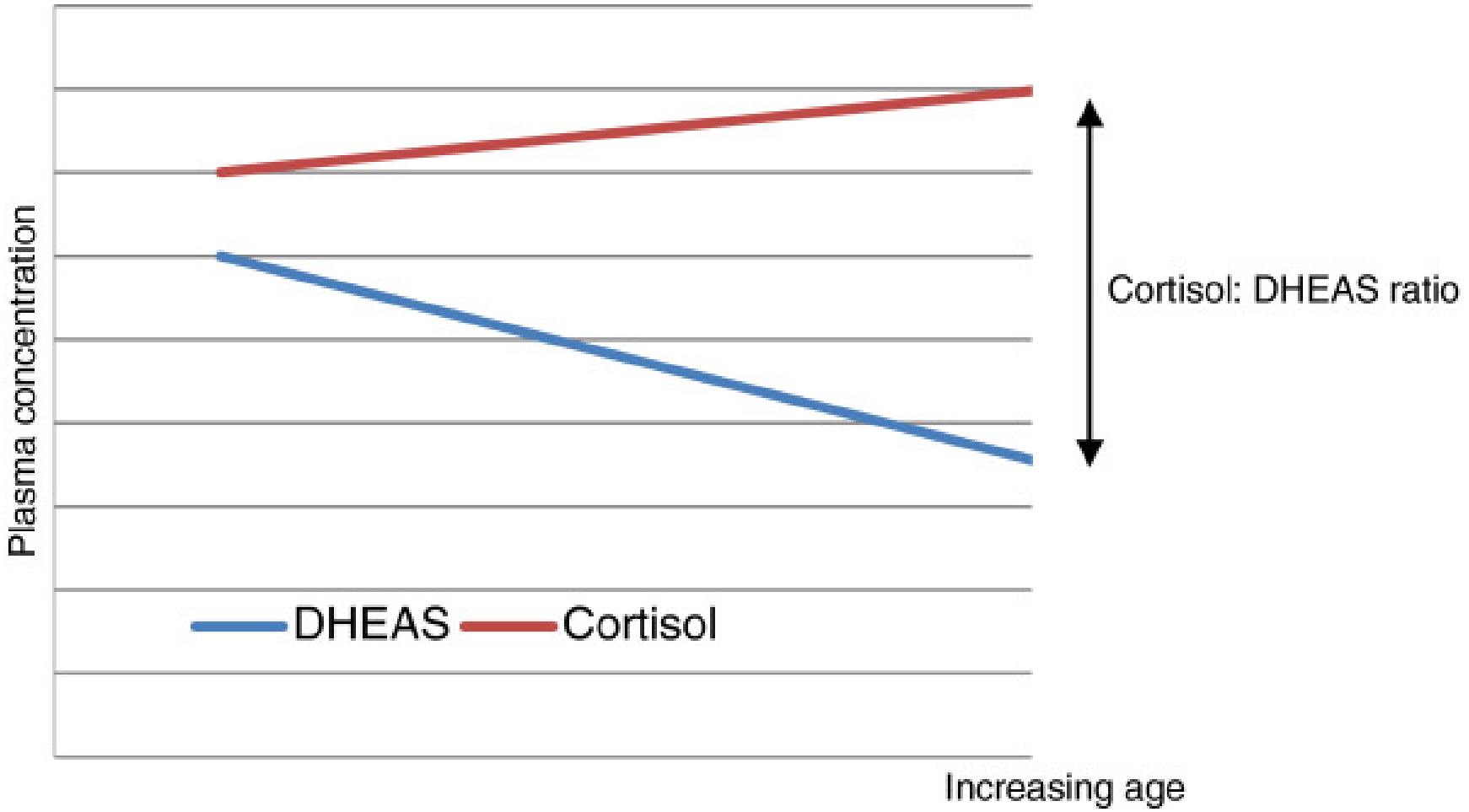
Anti-inflammaging (cont.)

- Dehydroepiandrosterone (DHEA) has opposing actions to cortisol and may protect individuals from negative effects of anti-inflammaging
- **Cortisol and DHEA have opposing effects** relating to the immune system
  - **Cortisol** causes immune-suppression and its concentration **increases with age**
  - **DHEA** antagonizes the effects of cortisol and is immune modulating, and its concentration **falls with age**

Anti-inflammaging



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Cortisol and DHEAS: Clinical

- **Higher cortisol** levels **associated** with **increased mortality** in patients with **stroke, sepsis, heart failure** and **sarcopenia**
- **Low levels of DHEA** have been demonstrated in patients with **chronic inflammatory diseases, including inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus , pemphigus, cardiovascular disease, sarcopenia, osteoporosis** and **all-cause mortality**

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The Bad Guys

- Over 40+ possible biological markers…
- Three of major significance:
  - IL-6
  - CRP
  - Telomeres

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Interleukin-6: **IL-6**

- Cytokine with **many activities**
- Functions in **regulation** of **immune** and **nervous** systems
- Involved in **liver** regeneration and in the **metabolic control** of the body

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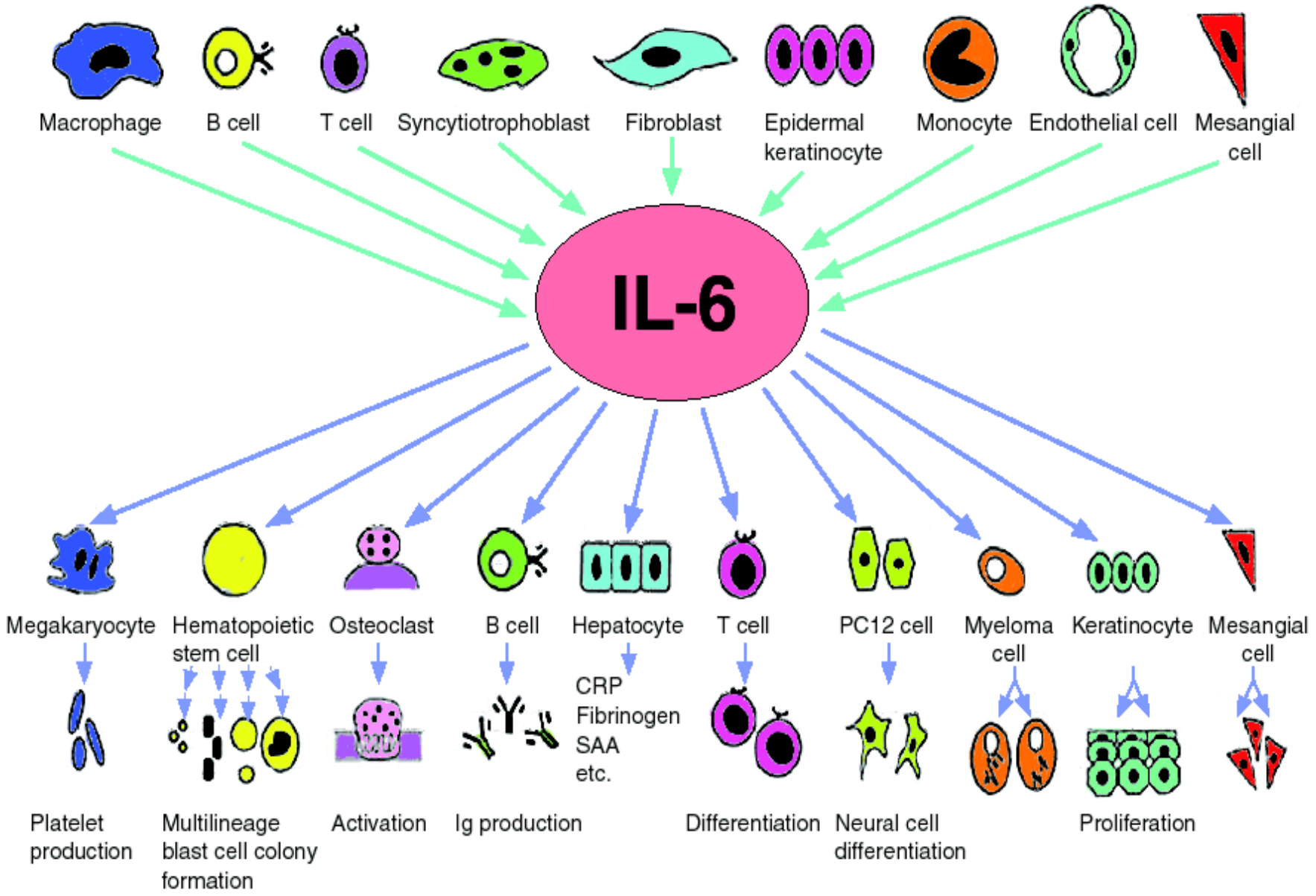
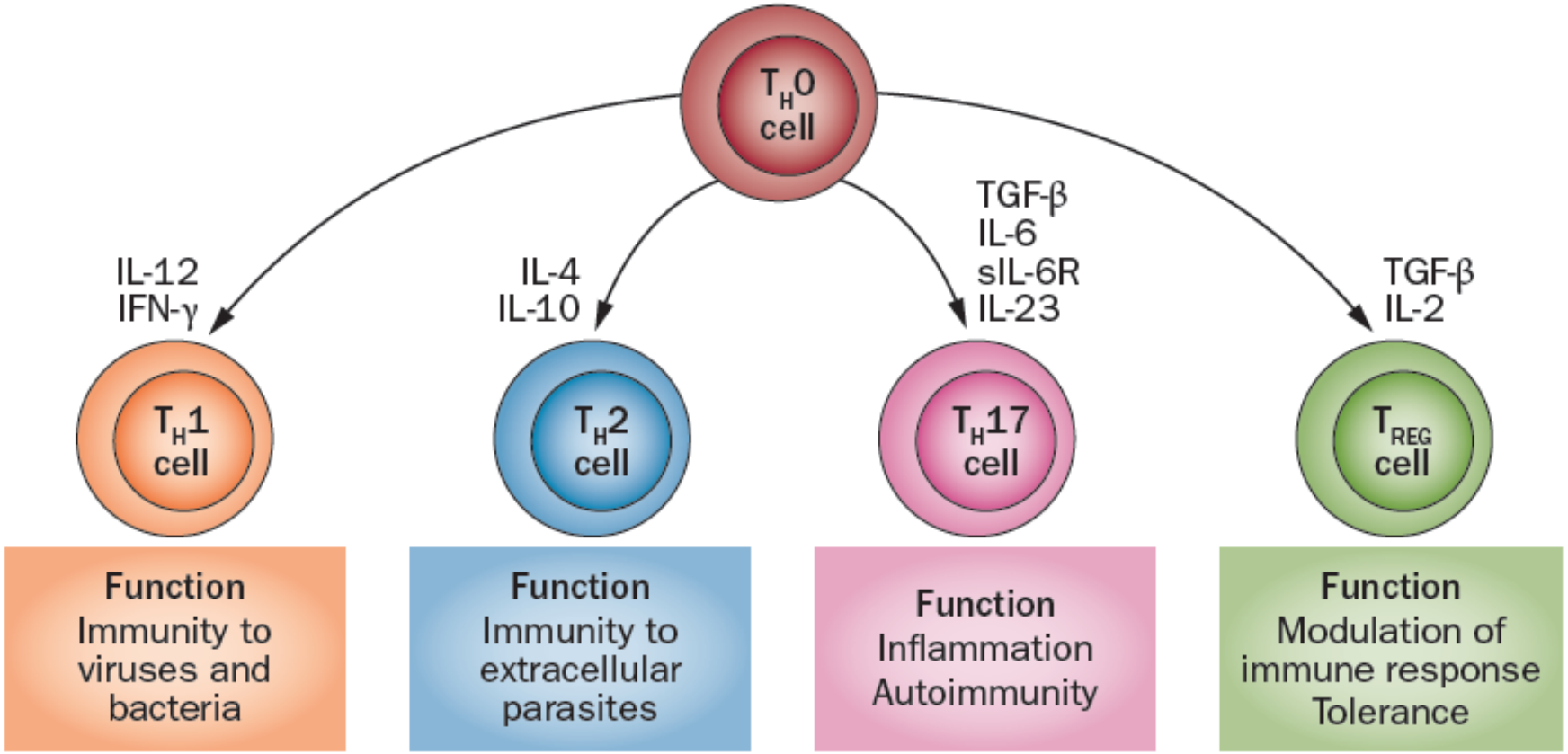


T_H17


T_H0 cell
IL-12
IFN-γ
IL-4
IL-10
TGF-β
IL-6
sIL-6R
IL-23
TGF-β
IL-2
T_H1 cell
T_H2 cell
T_H17 cell
T_{REG} cell
Function
Immunity to viruses and bacteria
Function
Immunity to extracellular parasites
Function
Inflammation
Autoimmunity
Function
Modulation of immune response
Tolerance

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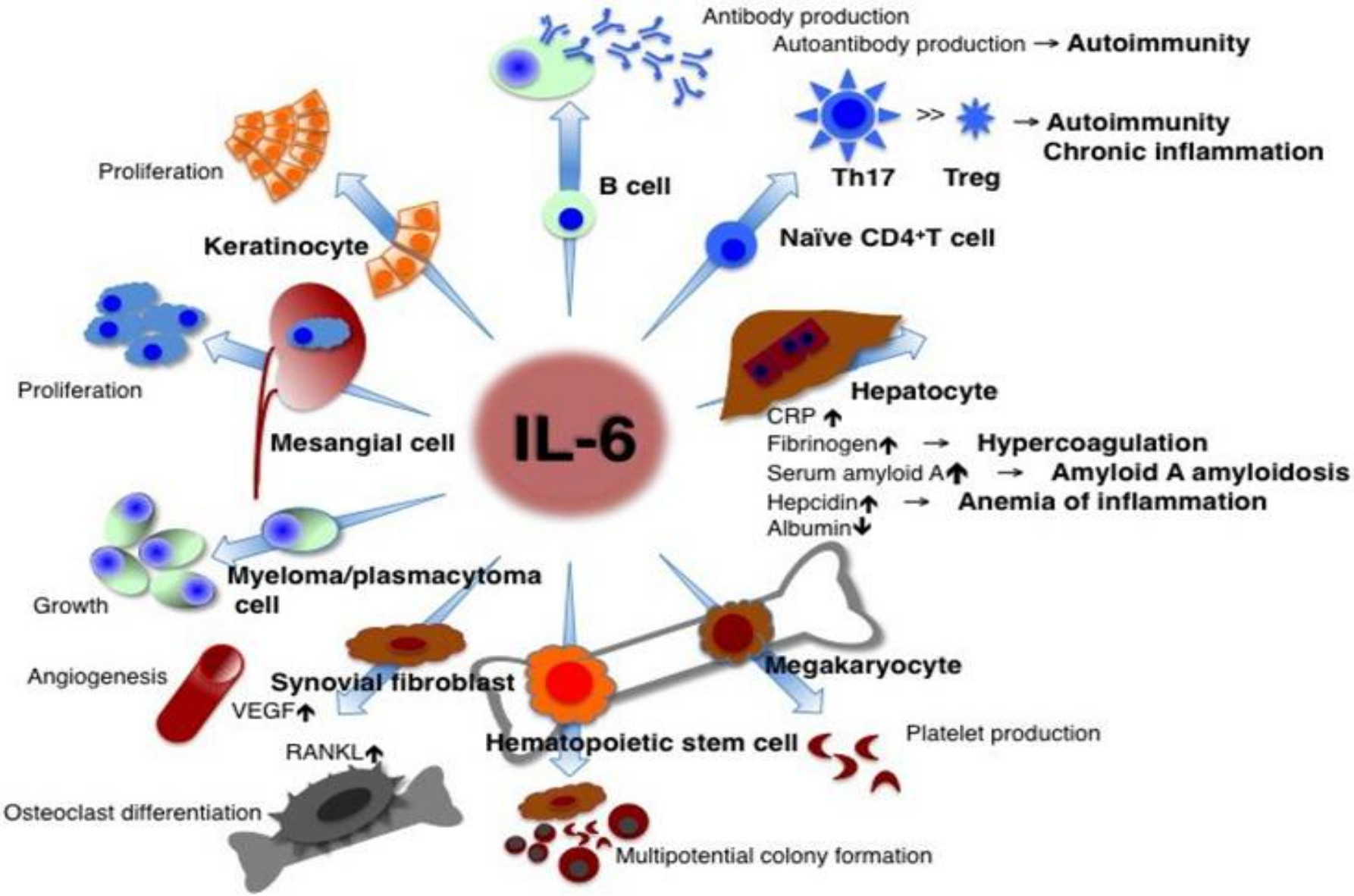
Antibody production
Autoantibody production → Autoimmunity
Th17
>>
Treg
→ Autoimmunity
Chronic inflammation
B cell
Naïve CD4+T cell
Proliferation
Keratinocyte
Proliferation
Mesangial cell
IL-6
Hepatocyte
CRP ↑
Fibrinogen↑ → Hypercoagulation
Serum amyloid A↑ → Amyloid A amyloidosis
Hepcidin↑ → Anemia of inflammation
Albumin↓
Growth
Myeloma/plasmacytoma cell
Angiogenesis
VEGF↑
Synovial fibroblast
Megakaryocyte
RANKL↑
Hematopoietic stem cell
Platelet production
Osteoclast differentiation
Multipotential colony formation

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Arthritis Care & Research

Original Article

Evaluation of serum IL-6 level as a surrogate marker of synovial inflammation and as a factor of structural progression in early rheumatoid arthritis: Results from the ESPOIR cohort

Athan Baillet[1,8], Laure Gossec[2], Simon

Issue

Serum IL-6 Level and the Development of Disability in Older Persons

Journal of the American Geriatrics Society - Volume 47, Issue 6 (June 1999) - Copyright © 1999 American Geriatrics Society -
About This Journal

Interleukin-6: a new therapeutic target in systemic sclerosis?

Steven O'Reilly, Rachel Cant, Marzena Ciechomska and Jacob M van Laar

Hepatogastroenterology. 2014 Jul-Aug;61(133):1196-200.

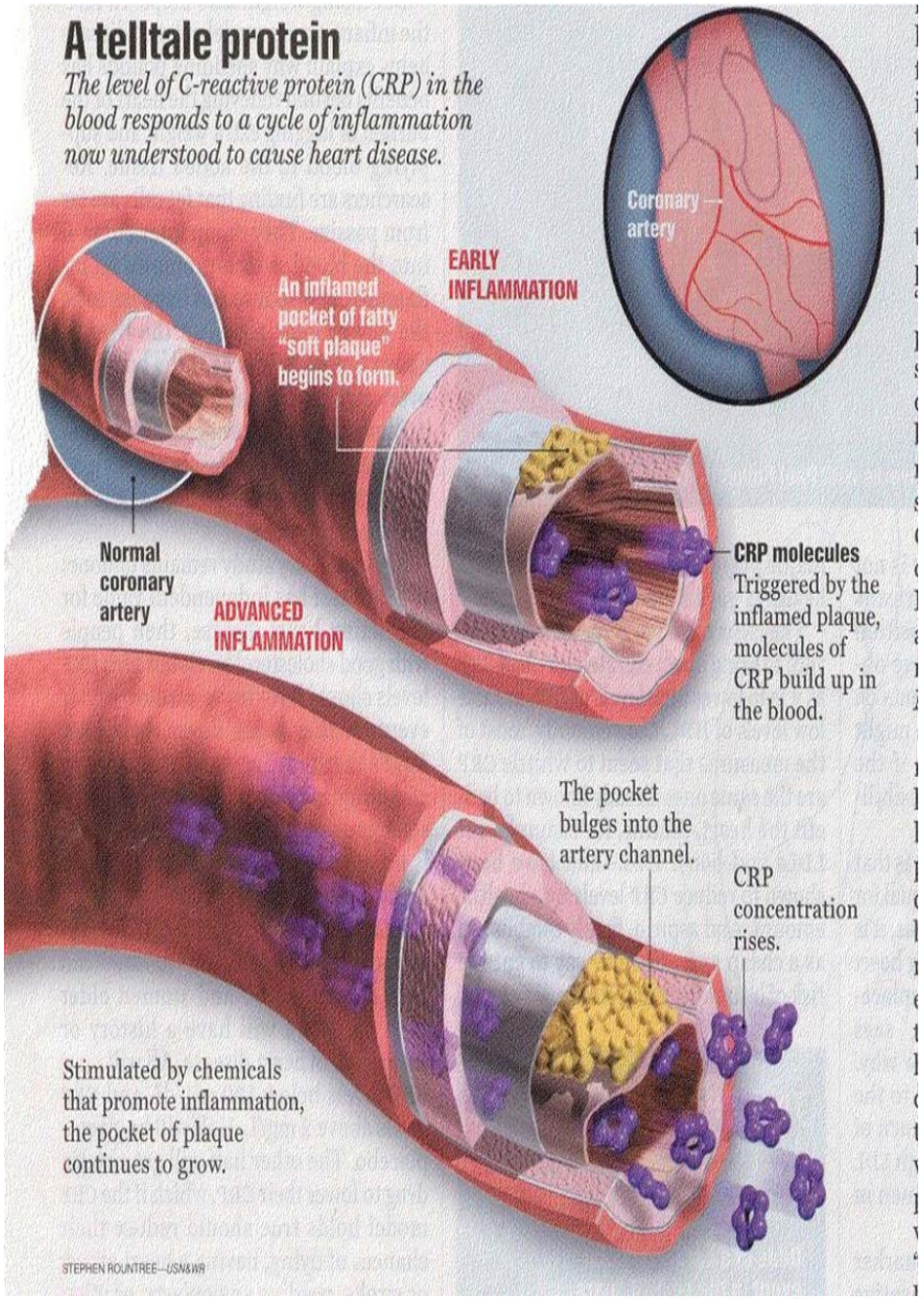
Evaluation of the relationship between serum ghrelin, C-reactive protein and interleukin-6 levels, and disease activity in inflammatory bowel diseases.

Cekic C, Arabul M, Alper E, Pakoz ZB, Saritas E, Yuksel, Ünsal B.

CRP

C-reactive protein

- **Acute phase protein** produced by the **liver** in response to **IL-6**
- Useful **marker** of **inflammaging**
- Commonly used in **clinical practice**
- Robust **predictor** of risk for **cardiovascular** and other diseases



American Heart Association: Risk of Developing Cardiovascular Disease

- Low
  - hs-CRP level is lower than 1.0mg/L
- Average
  - levels are between 1.0 and 3.0 mg/L
- High
  - level is higher than 3.0 mg/L

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Positive Test = Inflammation

- Cancer
- Connective tissue disease
- Heart attack
- Infection
- Inflammatory bowel disease
- Lupus
- Pneumococcal pneumonia
- Rheumatoid arthritis
- Rheumatic fever
- Tuberculosis

This list is not all inclusive

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Nord J Psychiatry. 2014 Dec 10:1-8. [Epub ahead of print]

Levels of C-reactive protein (CRP) in patients with schizophrenia, unipolar depression and bipolar disorder.

Wysokiński A[1], Margulska A, Strzelecki D, Kłoszewska I.

Arq Bras Cardiol. 2014 Dec 9;0:0. [Epub ahead of print]

Correlation between C-Reactive Protein in Peripheral Vein and Coronary Sinus in Stable and Unstable Angina.

[Article in English, Portuguese]

Leite WF[1], Ramires JA[1], Moreira LF[1], Strunz CM[1], Mangione JA[2].

Contemp Clin Dent. 2014 Oct;5(4):484-8. doi: 10.4103/0976-237X.142816.

Comparative evaluation of serum C-reactive protein levels in chronic and aggressive periodontitis patients and association with periodontal disease severity.

Goyal L[1], Bey A[1], Gupta ND[1], Sharma VK[1].

Int J Radiat Oncol Biol Phys. 2014 Dec 5. pii: S0360-3016(14)04256-4. doi: 10.1016/j.ijrobp.2014.10.005. [Epub ahead of print]

High-Sensitivity C-Reactive Protein Complements Plasma Epstein-Barr Virus Deoxyribonucleic Acid Prognostication in Nasopharyngeal Carcinoma: A Large-Scale Retrospective and Prospective Cohort Study.

Tang LQ[1], Li CF[2], Chen QY[1], Zhang L[1], Lai XP[3], He Y[3], Xu YX[3], Hu DP[3], Wen SH[3], Peng YT[3], Chen WH[4], Liu H[1], Guo SS[1], Liu LT[1], Li J[4], Zhang JP[5], Guo L[1], Zhao C[1], Cao KJ[1], Qian CN[1], Zeng YX[4], Guo X[1], Mai HQ[1], Zeng MS[6].

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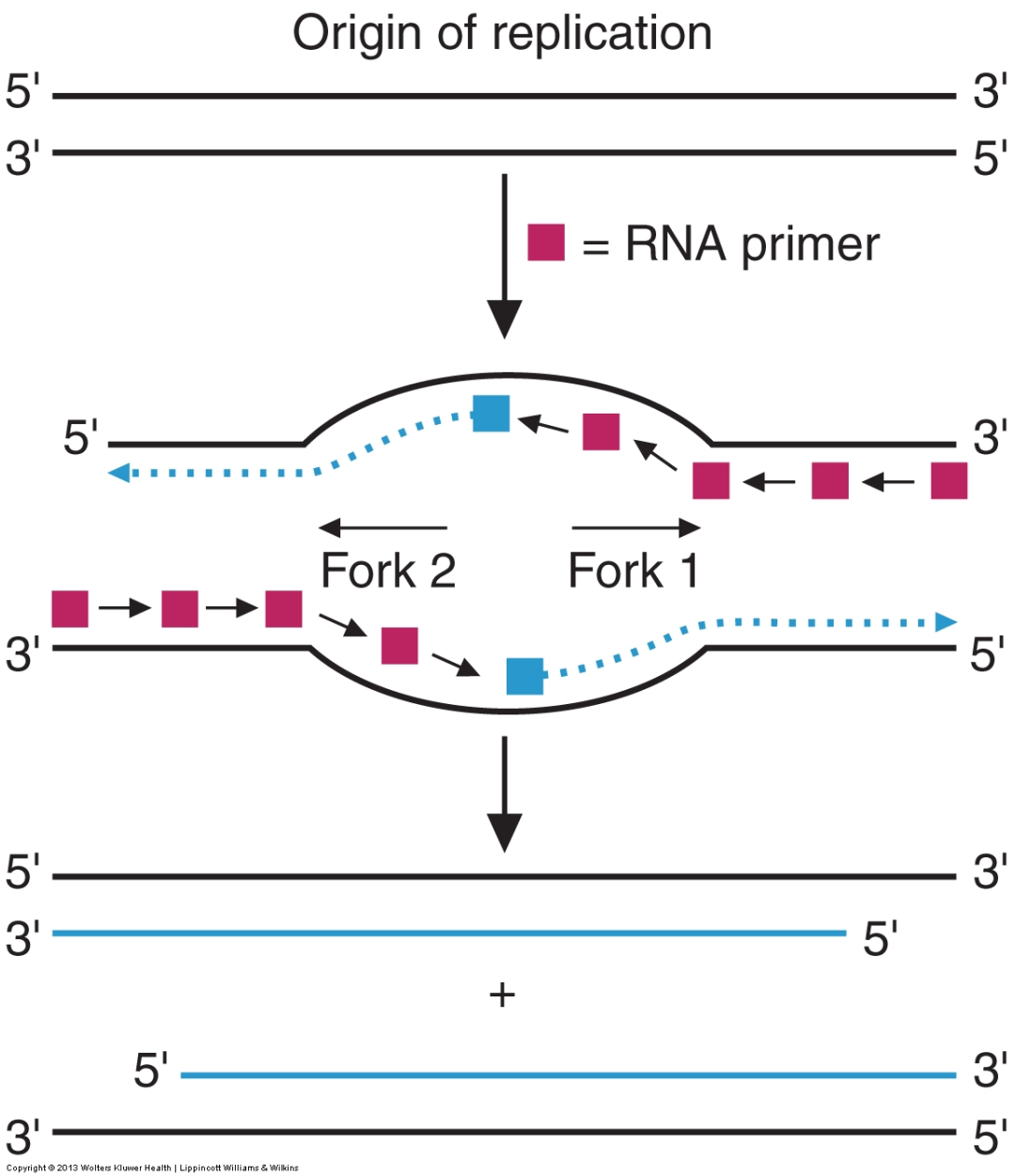
Telomeres

- End of linear chromosomes
- **Problem** develops during **DNA replication** → new strand is shorter at 5’ end, with **3’** overhang
- Solution: telomeres created by enzyme **telomerase**



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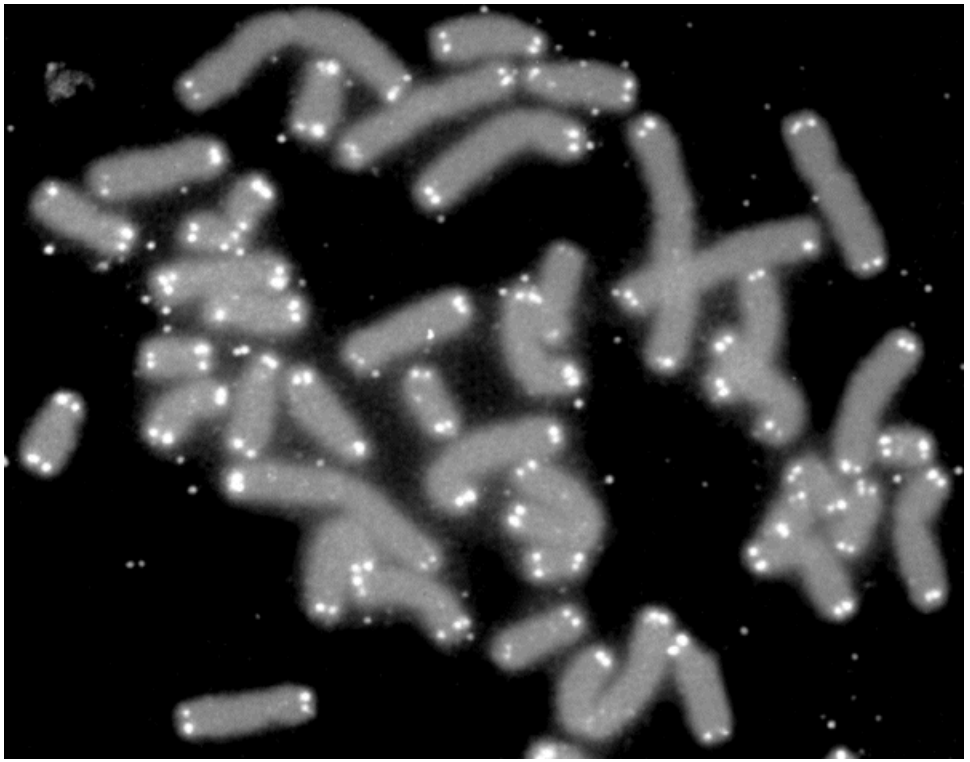
Telomeres

- Telomere lengths predict life expectancy
- Many cancers have shortened telomeres, including pancreatic, bone, prostate, bladder, lung, kidney, and head and neck.



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Ann N Y Acad Sci. 2009 August ; 1172: 34–53. doi:10.1111/j.1749-6632.2009.04414.x.

Can meditation slow rate of cellular aging? Cognitive stress, mindfulness, and telomeres

Elissa Epel, PhD.[1,*], **Jennifer Daubenmier, Ph.D.**[1], **Judith T. Moskowitz, Ph.D.**[2], **Susan Folkman, PhD.**[2], and **Elizabeth Blackburn, PhD.**[3]

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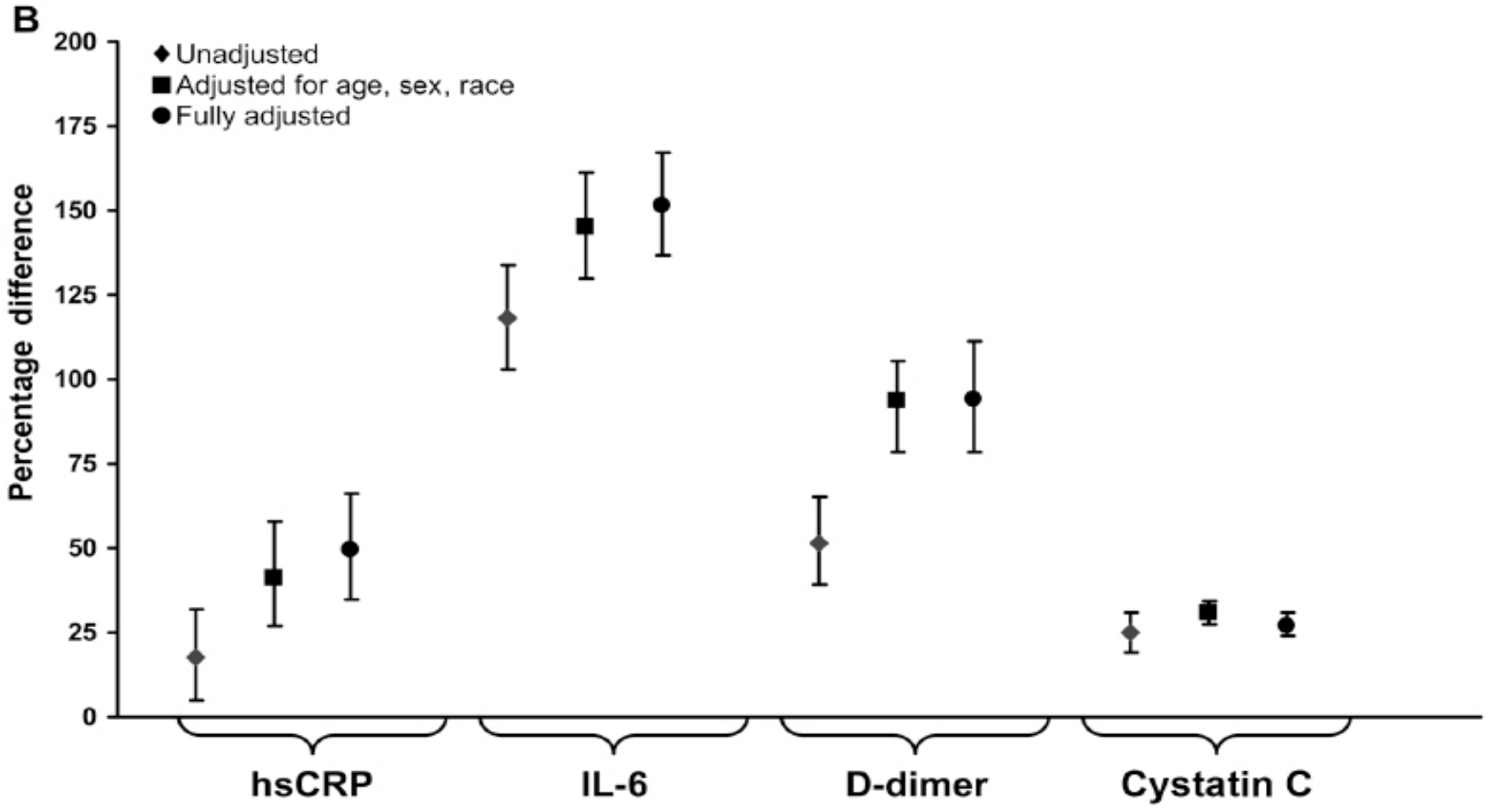
[3]UCSF Department of Biochemistry & Biophysics, 3333 California Street, Suite 465, San Francisco, CA 94143

Adults with HIV Infection



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- Indicators of “Healthy Aging” in older women (65-69 years of age). A data-mining approach based on prediction of long-term survival. Swindell et al. BMC Geriatrics 2010, 10:55
- Markers of Inflammation, Coagulation, and Renal Function Are Elevated in Adults with HIV Infection. Neuhaus et al, The Journal of Infectious Diseases 2010; 201(12)
- *Marks’ Basic Medical Biochemistry: A Clinical Approach*, 4th*Edition;* Michael Lieberman and Allan D. Marks**,** Wolters Kluwer/Lippincott Williams & Wilkins, 2013

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