Aging and Inflammation
What we know (little) and don't know (a lot)
Meta-analysis of age-related gene expression profiles identifies common signatures of aging
João Pedro de Magalhães\textsuperscript{1,*},\textsuperscript{†}, João Curado\textsuperscript{2} and George M. Church\textsuperscript{1}

### Table 1. Top functional annotation clusters of significant differentially expressed genes

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Enrich. score</th>
<th>No. of annot.</th>
<th>No. of genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overexpressed genes ($n = 236$ with $Q &lt; 0.5$)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune response, complement activation</td>
<td>6.88</td>
<td>41</td>
<td>86</td>
</tr>
<tr>
<td>Lysosome</td>
<td>6.48</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Plasma, extracellular region</td>
<td>5.41</td>
<td>5</td>
<td>37</td>
</tr>
<tr>
<td>Signal, glycoprotein</td>
<td>4.55</td>
<td>6</td>
<td>80</td>
</tr>
<tr>
<td>Negative regulation of apoptosis</td>
<td>2.75</td>
<td>16</td>
<td>53</td>
</tr>
<tr>
<td><strong>Underexpressed genes ($n = 141$ with $Q &lt; 0.5$)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondrion</td>
<td>5.49</td>
<td>52</td>
<td>70</td>
</tr>
<tr>
<td>Oxidative phosphorylation</td>
<td>3.57</td>
<td>79</td>
<td>82</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>3.19</td>
<td>5</td>
<td>108</td>
</tr>
<tr>
<td>Hydroxylysine, hydroxylation, collagen</td>
<td>2.83</td>
<td>43</td>
<td>47</td>
</tr>
</tbody>
</table>

Clusters from DAVID with an enrichment score above 2.5 are displayed. Cluster titles were selected based on the broadest of the top annotations in the cluster.
The Mild Pro-Inflammatory State of Aging

Age-Associated Increase in Cytokine Production During Systemic Inflammation: Adipose Tissue as a Major Source of IL-6

Marlene E. Starr,¹ B. Mark Evers,¹,² and Hiroshi Saito¹,²

A

Young LPS-stimulated C57BL/6 male mice (n=5)

Old LPS-stimulated C57BL/6 male mice (n=5)

IL-6 (short exposure)

IL-6 (long exposure)

B

Relative IL-6 mRNA Levels

0 0.2 0.4 0.6 0.8 1.0 1.2

Brain Lung Heart Liver Kidney Spleen Stomach Jejun Colon Fat Muscle Blood

Journal of Gerontology: BIOLOGICAL SCIENCES
Age-Associated Increase in Cytokine Production During Systemic Inflammation: Adipose Tissue as a Major Source of IL-6

Marlene E. Starr,¹ B. Mark Evers,¹,² and Hiroshi Saito¹,²

Journal of Gerontology: BIOLOGICAL SCIENCES
Predictors of Interleukin-6 Elevation in Older Adults

Shuhan Zhu, BS,* Kushang V. Patel, PhD, MPH,† Stefania Bandinelli, MD,‡ Luigi Ferrucci, MD, PhD,§ and Jack M. Guralnik, MD, PhD⁺

Odds-Ration for the development of high IL-6
Interleukin-6 Serum Levels Predict Incident Disability
A Case Cohort Study Nested in the EPESE

Ferrucci et al. JAGS 1999;47: 639-44
Inflammation, Muscle Strength, and Physical Performance
The Women's Health and Aging Study

Walking Speed

Walking Speed Adjusting for Hip Flexor Strength

Higher Inflammatory Marker Levels in Older Persons: Associations With 5-Year Change in Muscle Mass and Muscle Strength

Laura A. Schaap, Saskia M. F. Pluijm, Dorly J. H. Deeg, Tamara B. Harris, Stephen B. Kritchevsky, Anne B. Newman, Lisa H. Colbert, Marco Pahor, Susan M. Rubin, Frances A. Tylavsky, Marjolein Visser, for the Health ABC Study
Targeted ablation of IKK2 improves skeletal muscle strength, maintains mass, and promotes regeneration

Foteini Mourkioti, Paschalis Kratsios, Tom Luedde, Yao-Hua Song, Patrick Delafontaine, Raffaella Adami, Valeria Parente, Roberto Bottinelli, Manolis Pasparakis, and Nadia Rosenthal

**RelA (p65)**

**NF-κB1 (p105/p50)**

**IKKγ**

**IKKβ**

**IKKα**

**Nucleus**

**LPS**

**Proteasome-Degradation**

**Virus**

**Growth Factors Mitogens**

**Inflammatory Cytokines**

**Bacterial Products**

**Stress Signals**

**Mitogens**

**Inflammatory Cytokines**

**Bacterial Products**

**Signals**

**Proteasome-Degradation**
**Inflammation - Immunity**
(Chemokines, Cytokines, Immune Receptors, Adhesion Molecules)

**IKKγ**

** IKKβ**

**IKKα**

**Nucleus**

**RelA (p65)**

**NF-κB1 (p105/p50)**

**Cell Proliferation**
Cyclin D1, c-myc

**Angiogenesis**
Regulation of VEGF, TNF, IL-1 and IL-8

**Cell Survival and Cell Death**
Antia apoptotic (i.e. Bcl-xl, hs-20) and pro-apoptotic gene expression (i.e. Fas)

**LPS**

**Stress Signals**

**Virus**

**Growth Factors Mitogens**

**Inflammatory Cytokines**

**Bacterial Products**

**Signals**

**Proteins ubiquitin-proteasome involved in muscle protein degradation**

**IκB**

**Synthesis**
Age-Associated Inflammation and Toll-Like Receptor Dysfunction Prime the Lungs for Pneumococcal Pneumonia

Ernesto Hinojosa, Angela R. Boyd, and Carlos J. Orihuela

Data collected 1 day after intranasal challenge with $1 \times 10^7$ colony-forming units of S. pneumoniae.

The Journal of Infectious Diseases 2009;200:546–54
Age-Associated Inflammation and Toll-Like Receptor Dysfunction Prime the Lungs for Pneumococcal Pneumonia

Ernesto Hinojosa, Angela R. Boyd, and Carlos J. Orihuela

Data collected 2 days after intranasal challenge with $1 \times 10^7$ colony-forming units of S. pneumoniae.
Age-Associated Inflammation and Toll-Like Receptor Dysfunction Prime the Lungs for Pneumococcal Pneumonia

Ernesto Hinojosa, Angela R. Boyd, and Carlos J. Orihuela
Study of the early effects of NF-κB induction

- Cytapheresis
  - 5*10⁹ WBC
- Ficoll Separation
- PBMC
- Magnetic Bead Cell Sorting (CD4+)
- Lymphocytes CD4+

Controls (no Anti-CD3)
- 4 h
  - Proteins
  - RNA
  - Cytoplasm
  - Nuclear

Anti-CD3 2 µg/mL
- 2 h
  - Proteins
  - RNA
  - Cytoplasm
  - Nuclear

Anti-CD3 2 µg/mL
- 4 h
  - Proteins
  - RNA
  - Cytoplasm
  - Nuclear

Anti-CD3
- Rabbit
- Anti-Mouse IgG

Overnight Rest
Age-associated dysregulation of NF-κB function in human CD4+ T Lymphocytes

Arsun Bektas, Yongqing Zhang, Gertrude C. Kokkonen, William H. Wood.
Kevin G. Becker, Karen Madara, Luigi Ferrucci and Ranjan Sen

Unpublished (please, do not cite)
Age-associated dysregulation of NF-κB function in human CD4+ T Lymphocytes


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RNA Pathway Analysis (microarray for 22K genes)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>2-h Activation</th>
<th>4-h activation</th>
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<tr>
<td>IL-6</td>
<td>3.17</td>
<td>1.61</td>
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<td>IL-8</td>
<td>4.32</td>
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<td>MMP9</td>
<td>3.20</td>
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<td>-0.41</td>
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<td>TNF</td>
<td>3.53</td>
<td>1.79</td>
<td>1.63</td>
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<tr>
<td>Colony stimulator factor 2</td>
<td>0.4</td>
<td>-1.62</td>
<td>-10.27</td>
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<tr>
<td>Macrophage Inflamm. Protein-3</td>
<td>1.85</td>
<td>-3.65</td>
<td>-7.65</td>
</tr>
</tbody>
</table>
Resistance exercise-induced changes of inflammatory gene expression within human skeletal muscle

Thomas W. Buford · Matthew B. Cooke
Darryn S. Willoughby

* 3 sets of 10 repetitions at 80% of 1RM on each of the three exercises (24 women).
Exercise-Induced Activation of STAT3 Signaling Is Increased with Age
Muscle Stem Cells and Exercise

* Fusion with Existing Myofibers (nucleous donation)

- **Activation**: TNF-alpha, Nitric Oxide, Hepatocytes Growth Factor, Mechanogrowth Factor?

- **Differentiation**: IGF-1, TGF-β

- **Proliferation**: Hepatocytes Growth Factor, IGF-1, FGF, IL-6 and other cytokines

- **Muscle Repair (Hypertrophy)**

**Exercise**

**Muscle Damage**

**Notch**
Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression

STEWART H. LECKER, R. THOMAS JAGOE, ALEXANDER GILBERT, MARCELLO GOMES, VICKIE BARACOS, JAMES BAILEY, S. RUSS PRICE, WILLIAM E. MITCH, AND ALFRED L. GOLDBERG

<table>
<thead>
<tr>
<th>Clone</th>
<th>Unigene</th>
<th>Primary Sequence Name</th>
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<tr>
<td>3137251</td>
<td>Hs.183842</td>
<td>UBB</td>
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<td>2730250</td>
<td>Hs.183704</td>
<td>UBC</td>
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<td>2132619</td>
<td>Hs.3297</td>
<td>RPS27A</td>
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<td>4157922</td>
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<td>UBA52</td>
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<td>1723142</td>
<td>Hs.61661</td>
<td>FBXO32</td>
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<td>751477</td>
<td>Mm.32920</td>
<td>Atrogin-1/MAFbx</td>
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<td>747318</td>
<td>Mm.21634</td>
<td>Ube4b</td>
<td>-5</td>
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<td>2195309</td>
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<td>Mm.2287</td>
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<td>2123183</td>
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<td>Proteasome 19S subunit, ATPase, 4</td>
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<td>113452</td>
<td>Hs.90744</td>
<td>PSMD11</td>
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<td>833508</td>
<td>Mm.28571</td>
<td>Proteasome 19S subunit, non-ATPase, 11</td>
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<td>448976</td>
<td>Hs.112396</td>
<td>PA200</td>
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<td>1707220</td>
<td>Hs.75981</td>
<td>USP14</td>
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<tr>
<td>315082</td>
<td>Mm.930</td>
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<td>2935790</td>
<td>Hs.87417</td>
<td>CTSL2</td>
<td>-5</td>
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</table>

Fold increase is graded by intensity of red staining to the key: F, Fasting; T, tumor bearing; U, uremia; D, diabetes mellitus.
Mechanisms for Inhibition of Atrophy and Growth Promotion by Muscle Activity

Repeated Muscle Contraction

Insulin → PI3K → AKT → mTOR → TORC1 → Protein Synthesis

Local IGF-1

TNF-α → IKK → NF-κB → Caspase-3

FoxO - P

Ca++

mTORC1

Autophagy-Lysosome and Ubiquitin-Proteasome Systems

Atrogenes

PGC-1α

Mitochondria Slow Fibers

Aerobic Capacity

Protein

Fiber Size (quality?)
Nuclear factor-kappa B signaling in skeletal muscle atrophy

Hong Li • Shweta Malhotra • Ashok Kumar

Aging, Denervation, Unloading, Diabetes, CHF, COPD, Sepsis, Cancer, Duchenne Muscular Dystrophy

NF-κB

Ubiquitin
Proteasome System

Inflammation

Myogenesis

Maintenance of Skeletal Muscle Mass and Quality
Influence of low-grade inflammation impaired postprandial stimulation of muscle protein synthesis in old rats

Balage\textsuperscript{a,b}, Julien Averous\textsuperscript{a,b}, Didier Rémond\textsuperscript{a,b}, Cécile Bos\textsuperscript{c}, Estelle Pujos-Guillot\textsuperscript{a,b}, Isabelle Papet\textsuperscript{a,b}, Laurent Mosoni\textsuperscript{a,b}, Lydie Combaret\textsuperscript{a,b}, Dominique Dardevet\textsuperscript{a,b,*}

**Muscle fractional synthesis rate (FSR %/d)**

- **Non-Inflamed** (\(a2\)-macroglobulin \(\leq 100\) mg/L)

- **Low Grade Inflammation** (\(a2\)-macroglobulin 101-800 mg/L)
Influence of low-grade inflammation impaired postprandial stimulation of muscle protein synthesis in old rats

* Balage\textsuperscript{a,b}, Julien Averous\textsuperscript{a,b}, Didier Rémond\textsuperscript{a,b}, Cécile Bos\textsuperscript{c}, Estelle Pujos-Guillot\textsuperscript{a,b}, Isabelle Papet\textsuperscript{a,b}, Laurent Mosoni\textsuperscript{a,b}, Lydie Combaret\textsuperscript{a,b}, Dominique Dardevet\textsuperscript{a,b,*}

** Muscle Total Proteolysis **

<table>
<thead>
<tr>
<th></th>
<th>n mole tyrosine/mg protein/h</th>
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<tbody>
<tr>
<td>Non-Inflamed</td>
<td></td>
</tr>
<tr>
<td>(α2-macroglobulin≤100 mg/L)</td>
<td></td>
</tr>
<tr>
<td>Low Grade Inflammation</td>
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<tr>
<td>(α2-macroglobulin 101-800 mg/L)</td>
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</tbody>
</table>
Effect of Protein Intake on Change in Muscle Strength in Older Persons: Does Inflammation Matter?

Bartali B. et al. InCHIANTI Study – Unpublished (please, do not cite)

![Graph showing the relationship between protein intake and baseline IL-6 levels. The x-axis represents protein intake (g/day) ranging from 40 to 105, and the y-axis represents baseline IL-6 levels ranging from -3.0 to 2.0 pg/mL. The graph includes three lines, each representing different baseline IL-6 levels: 0.02-1.07 pg/mL (red), 1.08-1.89 pg/mL (blue), and 1.95-7.80 pg/mL (green).]
The genetics of chronic inflammatory diseases

Graham A. Heap and David A. van Heel

Centre for Gastroenterology, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Whitechapel, London E1 2AT, UK

Chronic Inflammatory Disease Gene Loci Identified by Genome Wide Association Study

No. of Loci Identified

Amyotrophic lateral sclerosis, Asthma, Celiac disease, Coronary disease, Crohn's disease, Dry AMD, Idiopathic pulmonary fibrosis, Juvenile idiopathic arthritis, Knee osteoarthritis, Multiple sclerosis, Psoriasis, Rheumatoid arthritis, Systemic lupus erythematosus, Type 1 diabetes, Type 2 diabetes, Ulcerative colitis, Wet AMD

1. Number of loci identified for chronic inflammatory diseases (2008). The sum of the number of loci identified from individual GWAS. Data was obtained from The National Human Genome Research Initiative Catalogue of Genome Wide Association Study Variants, available at http://www.genome.
The genetics of chronic inflammatory diseases

Graham A. Heap and David A. van Heel*

Centre for Gastroenterology, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Whitechapel, London E1 2AT, UK
Abnormal Body Composition Phenotypes in Older Rheumatoid Arthritis Patients: Association With Disease Characteristics and Pharmacotherapies

JON T. GILES,1 SHARI M. LING,2 LUIGI FERRUCCI,2 SUSAN J. BARTLETT,1 ROSS E. ANDERSEN,1 MARILYN TOWNS,1 DENIS MULLER,2 KEVIN R. FONTAINE,1 AND JOAN M. BATHON1

Figure 1. Adjusted odds of sarcopenia, overfat, and sarcopenic obesity for rheumatoid arthritis (RA) subjects compared with non-RA controls, by sex. Adjusted for current smokers and menopausal women. Values are shown as the odds ratio (95% confidence interval). Solid triangles = female; solid squares = male.
In producing cells and biological activities of IL-6.
IL-6R is present in cells sensible to IL-6 associated with a signal-transducing membrane protein gp130.
IL-6 Signaling

IL-6R is present in cells sensible to IL-6 associated with a signal-transducing membrane protein gp130.

The complex IL-6/IL-6R induces theimerization of the gp130 signal-transducing membrane and initiation of signaling.
The IL-6r is shedded from the membrane of the IL-6 sensible cell and becomes sIL-6r.
The IL-6r is shedded from the membrane of the IL-6 sensible cell and becomes sIL-6r. A soluble IL-6/sIL-6r complex is created.
The IL-6r is shedded from the membrane of the IL-6 sensible cell and becomes sIL-6r. A soluble IL-6/sIL-6r complex is created. The IL-6/sIL-6r complex initiates gp130 merization of a cell type lacking IL-6R expression and triggers cellular activation.
Discriminative Power for RA (n=136) vs. Age- and BMI-matched Controls (BLSA) for Different Inflammatory Markers

The IL-6 Pathway

The IL-6 Pathway

\[ P < 0.001 \]

N.S.

AUC

IL-6  sgp130  sIL-6r  sIL6r+IL6  sIL6r+IL6 +sgp130

N.S.

N.S.
IL-6, sIL6r and Parameters of Body Composition in 136 RA Patients

![Graph showing the relationship between IL-6, sIL6r, and parameters of body composition.](image-url)

- Adj-r=0.51; p<0.001
- Adj-r=0.08; p=0.19

**Percent Lean Body Mass (LBM)**

current weight-body fat mass/current weight * 100
Treatment of Rheumatoid Arthritis With Humanized Anti–Interleukin-6 Receptor Antibody

A Multicenter, Double-Blind, Placebo-Controlled Trial

Norihiro Nishimoto, Kazuyuki Yoshizaki, Nobuyuki Miyasaki, Kazuhiko Yamamoto, Shinichi Kawai, Tsutomu Takeuchi, Jun Hashimoto, Junichi Azuma, and Tadamitsu Kishimoto

▲ Controls
○ 4 mg/kg humanized anti–interleukin-6 receptor antibody (MRA)
● 8 mg/kg humanized anti–interleukin-6 receptor antibody (MRA)
Serum Interleukin-6 Receptor in Polymyalgia Rheumatica: A Potential Marker of Relapse/Recurrence Risk

LIA PULSATELLI, LUIGI BOIARDI, ELETTTRA PIGNOTTI, PAOLO DOLZANI, TANIA SILVESTRI, PIERLUIGI MACCHIONI, FABRIZIO CANTINI, CARLO SALVARANI, ANDREA FACCHINI, AND RICCARDO MELICONI

Figure 3. Kaplan-Meier curve. Cumulative rate of relapse-free survival (RFS) for the different subsets of patients with polymyalgia rheumatica divided according to both soluble interleukin-6 receptor (sIL-6R) levels and hemoglobin (Hb) values at diagnosis.
The surprising link between inflammation and heart attacks, cancer, Alzheimer’s and other diseases. What you can do to fight it.
The following only used eventually to address questions.
inflammatory status of the elderly: The intestinal contribution

Eduardo J. Schiffrin\textsuperscript{a}, John E. Morley\textsuperscript{b}, Anne Donnet-Hughes\textsuperscript{a}, Yves Guigoz\textsuperscript{a,}\textsuperscript{*}

\[\uparrow\text{Anaerobic Lactobacilli}\]
\[\uparrow\text{Bifidobacteria}\]
\[\uparrow\text{Enterobacteriaceae}\]
\[\uparrow\text{Gram Negative Bacteria}\]

\[\uparrow\text{Endotoxin}\]

\[\downarrow\text{Intestinal Barrier}\]

\[\text{Toll-Like Receptors}\]

\[\text{NF-kB}\]

\[\text{INFLAMMASOME}\]

\[\text{Caspase-1}\]

\[\text{Proinflammatory Cytokines}\]

\[\text{C-Reactive Protein}\]
Cytokine loops driving senescence

Jiri Bartek, Zdenek Hodny and Jiri Lukas

EC

...IL-1, IL-6, IL-8, TGFβ

Paracrine effects
Cell clearance

IL-6
IL6R

IL-8
CXCR2

TGFβ
TGFβR

DNA damage signalling

...NF-κB, C/EBPβ, STAT3...

Autocrine effects
Cell cycle block
Senescence phenotype

ROS
Anti-inflammatory drugs reduce age-related decreases in brain volume in cognitively normal older adults

K. Walther\textsuperscript{a}, B.B. Bendlin\textsuperscript{b,c}, E.L. Glisky\textsuperscript{a}, T.P. Trouard\textsuperscript{d}, J.R. Lisse\textsuperscript{e}, J.O. Posever\textsuperscript{f}, L. Ryan\textsuperscript{a,*}
Cytokines sing the blues: inflammation and the pathogenesis of depression

Charles L. Raison, Lucile Capuron and Andrew H. Miller