Biomarkers of Aging

Luigi Ferrucci
National Institute on Aging
Discrepancy Between Biological and Chronological Age

Where is Biological Aging?

Metrics of aging

Age (yrs)

The Force Of Mortality
Phenotypic Change Over Time

Chronological age

0?

100?
Domains in the Causal Pathway to Cognitive and Physical Frailty

AGING and DISEASES

Aging Phenotype
- Changes in Body Composition
- Energy Imbalance Production/Utilization
- Homeostatic Dysregulation
- Neurodegeneration

Disease Susceptibility
- Reduced Functional Reserve
- Impaired Stress Response and Healing Capacity
- Unstable Health
- Failure to Thrive

Physical and Cognitive FRAILTY

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Aging is associated with up-regulation of immune function genes. Transcriptome-wide meta-analysis of genes whose expression differs by age in 7,257 individuals of European ancestry. Findings replicated in another 8,009 individuals. 1,497 genes were differentially expressed with age. The major cluster of positively age-correlated genes (GeneNetwork pathway, 77 genes) was related to innate and adaptive immunity, suggesting that dysregulation of the immune leading to a pro-inflammatory state is an hallmark of aging.
Interleukin-6 Serum Levels Predict Incident Disability
A Case Cohort Study Nested in the EPESE

Probability of Mobility Disability

2.5 pg/ml

Adjusted probability

95% CI

Ln (IL-6)

Ferrucci et al. JAGS 1999;47: 639-44
Systemic Effects of Localized Inflammation

Harmful stimuli:
- Damaged cells
- Irritant chemicals
- Pathogens

INFLAMMATION attempts to remove damaged cells, irritants or pathogens

Effective
Eliminates the cause of inflammation

“Switch off” inflammation

Healing

G.I. System
- Reduces food absorption
- Causes insulin resistance
- Stimulates glycogenolysis
- Down-regulates somatostatin

Muscle
- Inhibits muscle growth
- Down-regulates IGF-1 signaling

Bone
- Stimulates osteoclasts
- Down-regulates Osteocalcin

Bone Marrow
- Inhibits Hematopoiesis
- Down-regulates EPO signaling

Brain
- Activates microglia
- Inhibits Neurogenesis
- Down-regulates BDNF

Arteries
- Stimulates atherosclerosis
- Inhibit endothelial reactivity
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 Ratio for the development of high IL-6**

<table>
<thead>
<tr>
<th>Age</th>
<th>Development of Elevated IL-6 (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (581)</td>
<td>20.0%</td>
<td>0.145</td>
</tr>
<tr>
<td>Men (245)</td>
<td>15.7%</td>
<td></td>
</tr>
<tr>
<td>Women (336)</td>
<td>27.0%</td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td>28.1%</td>
<td></td>
</tr>
<tr>
<td>75–84</td>
<td>33.8%</td>
<td></td>
</tr>
<tr>
<td>≥ 85</td>
<td>40.2%</td>
<td></td>
</tr>
<tr>
<td>0 (109)</td>
<td>10.0%</td>
<td>0.001</td>
</tr>
<tr>
<td>1 (224)</td>
<td>16.0%</td>
<td></td>
</tr>
<tr>
<td>2 (167)</td>
<td>21.3%</td>
<td></td>
</tr>
<tr>
<td>≥ 3 (87)</td>
<td>25.8%</td>
<td></td>
</tr>
</tbody>
</table>

**Odds-Ratio for the development of high IL-6 by BMI and waist circumference (WC)**

<table>
<thead>
<tr>
<th>BMI</th>
<th>Normal WC</th>
<th>High WC</th>
<th>n*</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5–24.9</td>
<td>9.53</td>
<td>1.00</td>
<td>140</td>
</tr>
<tr>
<td>25–29.9</td>
<td>7.14</td>
<td>1.00</td>
<td>158</td>
</tr>
<tr>
<td>≥ 30</td>
<td>10.04</td>
<td>1.00</td>
<td>24</td>
</tr>
</tbody>
</table>

Surgery

- Bariatric surgery
- Proven to prevent diabetes
- Weight loss ~ 30%
- Several studies
- Consistently reduces markers of inflammation before any weight loss

- Liposuction
- Fewer reports
- Even with 10 kg liposuction, no change in metabolic parameters and inflammatory markers

eg. Klein et al, NEJM 2004
The Fast Food Study

Change Over Time in IL-6 According to Meal Type

Log(IL-6, pg/mL) vs. Time (min)

- Fast-Food Like Meal
- Healthy Meal

* p<.05
# p<.01
Chronic intestinal inflammation alters hippocampal neurogenesis


DSS=Dextran Sodium Sulphate; DCX=cytoplasmic marker doublecortin; Ki-67= nuclear, green
Periodontal disease associates with higher brain amyloid load in normal elderly

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Physical and Cognitive FRAILTY

Genetics: APOE Genotype Affects Baseline Amyloid Burden But Not Rate of Change

Susan Resnick, LBN/NIA
A Buffer against Chronic Stress:
Positive Aging Self-stereotypes Predict Reduced Cortisol over Time
Becca R. Levy, Scott Moffat, Susan M. Resnick, Martin D. Slade, and Luigi Ferrucci

Association of Age Stereotypes with AD Neuropathology at Autopsy

Association of Age Stereotypes with Hippocampal-Volume Decline over Time
What are the mechanisms by which aging and disease affect aging phenotypes and longevity?

**AGING and DISEASES**

- Stem Cells Exhaustion
- Altered Intercellular Communication
- Genomic Instability
- Telomere Attrition
- Epigenetic Alterations
- Loss of Proteostasis
- Deregulated Nutrient Sensing
- Mitochondrial Dysfunction
- Cellular Senescence

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Ferrucci L, Studenski S. Clinical Problems of Aging. In: Harrison's Principles of Internal Medicine, 18th Ed. – 2011

The Hallmarks of Aging
DNA methylation age of human tissues and cell types
Steve Horvath at http://genomebiology.com//14/10/R115

B Training data cor=0.92, p<1e-200
C Test data cor=0.92, p<1e-200

InCHIANTI Baseline (n=499)
InCHIANTI 9-year Followup (n=499)
BLSA (n=1105)
DNA methylation age of blood predicts all-cause mortality in later life


Riccardo E Marioni, Sonia Shah, Allan F McRae, Brian H Chen et al.
I am so lucky!!