Geroscience for Aging in Challenging Environments

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Trans-NIH Geroscience Interest Group

• Exposures and Latent Disease Risk
• Identifying Hallmarks and Key Characteristics

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Building a Conceptual Framework: Hallmarks of Aging
What is contained in each hallmark of aging?

- Transposons
- Metabolism
- Fibrosis
- Stem Cells
- Senescence
- Microbiome
- Telomeres
- Proteostasis
- Inflammation
- Proteome

Adapted from Niforou et al. (2014). Redox Biology. 2. 10.1016/j.redox.2014.01.017.
Building a Conceptual Framework: Hallmarks of Aging and Organ Systems
Building a Conceptual Framework: Aging as a risk factor …
Building a Conceptual Framework: Hallmarks of Aging

Aging Biology
- Epigenetics
- Damage
- Metabolism
- Molecular

Stress Response
Senescence
Proteostasis
Immunity
Inflammation

Clinical
- More Disease & Less Function
  - Cancer
  - Immunity
  - Frailty
  - COPD/IPF
  - CKD
  - CVD
  - Diabetes
  - Dementia
  - Neurodegeneration

Burdens of Chronic Disease
- Hearing
- Vision
- Mobility
- Arthritis
- Sarcopenia
- Osteoporosis
Multiple Chronic Conditions

• Age-Distribution of MCC

• Humans
  • Hypertension
  • Ischemic Heart Disease
  • Hyperlipidemia
  • Diabetes
  • Arthritis
  • Chronic Kidney Disease
  • COPD
  • Osteoporosis
  • …
# Multiple Chronic Conditions

<table>
<thead>
<tr>
<th>Human</th>
<th>Lab animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cancer</td>
<td>A. Cancer</td>
</tr>
<tr>
<td>2. Cardiac Hypertrophy</td>
<td>B. Cardiac Hypertrophy</td>
</tr>
<tr>
<td>3. Kidney Failure</td>
<td>C. Kidney Failure</td>
</tr>
<tr>
<td>4. Hypertension</td>
<td>D. Splenomegaly</td>
</tr>
<tr>
<td>5. Lung Function/Disease</td>
<td>E. Pneumonia</td>
</tr>
<tr>
<td>6. Bones</td>
<td>F. Bones</td>
</tr>
<tr>
<td>7. Joints</td>
<td>G. Joints</td>
</tr>
<tr>
<td>8. Muscles</td>
<td>H. Muscles</td>
</tr>
<tr>
<td>9. Skin</td>
<td>I. Skin</td>
</tr>
</tbody>
</table>
# Scoring Functions in Adults

<table>
<thead>
<tr>
<th>Function</th>
<th>Newborn</th>
<th>ML-Adult</th>
<th>LL-Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognition</strong></td>
<td></td>
<td>Response time, memory</td>
<td>Response time, memory</td>
</tr>
<tr>
<td><strong>Appearance</strong></td>
<td>Appearance/Complexion</td>
<td>blue or pale all over</td>
<td>BMI, skin tone, hair</td>
</tr>
<tr>
<td><strong>Pulse</strong></td>
<td>Pulse rate</td>
<td>0 to &gt;100</td>
<td>+/- exertion</td>
</tr>
<tr>
<td><strong>Grimace</strong></td>
<td>Reflex irritability</td>
<td>... when stimulated</td>
<td>Response to stimulation in periphery and centrally</td>
</tr>
<tr>
<td><strong>Activity</strong></td>
<td>Activity</td>
<td>Motion and resistance</td>
<td>Motion and Resistance</td>
</tr>
<tr>
<td><strong>Respiration</strong></td>
<td>Respiratory Effort</td>
<td>Irregular to regular</td>
<td>Lung function parameters</td>
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Geroscience: Aging in a Challenging Environment
Building a Conceptual Framework: Environment as a Risk Factor
Environmental Risk superimposed on age-related risk for breast cancer?

Adapted from Matsuno et al., Can Epidem Biomarkers & Prev 2007
The aging biology of age-related risk for breast cancer

Adapted from Matsuno et al., Can Epidem Biomarkers & Prev 2007

- Normal human mammary epithelial cells
- Age-emergent luminal cell subpopulations predict the chronological age
- Altered progenitor cell populations accumulate during aging
Individual susceptibility across the life span
Individual susceptibility across the life span: Outcomes for aging
For environmental exposures: sample collection mapped to the hallmarks of aging

- Bucal & Nasal Swabs
- Blood Cell Methycomes
- MRI Ultrasound
- Implied from lineages
- Transposons
- Fibrosis
- Stem Cells
- Senescence
- Microbiome
- Samples: Fecal & Nasal
- Leukocytes
- Telomeres
- Proteostasis
- Inflammation
- Metabolism
- MRI
- Ultrasound
- Fat Biopsies
- Blood Cells & Plasma
- Blood & Breath
- Plasma Proteome
Samples in a doctor’s visit
Combining Functional and Molecular Metrics in Adults

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Rates of Aging in Humans

Proteomics (SWATH-MS)
Metabolomics (untargeted LC-MS)
Cytokines (82-plex Luminex)
Transcriptome
Standard clinical blood tests

Stool microbial taxonomy
Stool microbial genes

Nasal microbial taxonomy
Nasal microbial genes

Conclusions for Aging

- Molecular hallmarks can be used to understand interactions between the environment and aging
  - Example from breast cancer
- Clinically useful information about the trajectories of human aging can be obtained in 2-3 years of doctor’s visits
  - Trajectories are individual
- Studies in laboratory animals establish principles and validate useful tools
  - Biology of aging and geroscience can be done in humans
Conclusions for Aging in Challenging Environments

• Explore how a variety of environmental factors influence the aging process and disease outcomes in aging populations

• Environmental effects that are chronic, acute, and combined

• **PAR-19-249** Aging Processes
  - (NIEHS, NIA, OBSSR)

• **PAR-19-250** Aging Populations
  - (NIEHS, NIA, NINR, NIMHD, OBSSR)