Emerging Molecular Biomarkers of Aging

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Disclosures

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Have you ever...

1. Adjusted for “age” in your statistical models?
2. Conducted gene-pathway enrichment analysis and thought, “That makes sense,” but it really doesn’t?
3. Questioned why so many of the diseases share the same exposures or biological pathways?
What is “Aging?”

Genetic/developmental susceptibility

Accumulation of bad things (or loss of healthful things)

Toxins

Damage/Repair

Impaired maintenance

Age-correlated exposures or diseases

Body “weathering”
(D) All of the above
Molecular biomarkers = “canary in the mine”

- Molecular dysfunction + adaptation (Functionally normal)
- Physiological dysfunction + adaption (Functionally normal)
- Sub-clinical (Functional decline)
- Clinical disease (impaired)
- Too late

Age (years)

Primary Prevention

Secondary Prevention

Tertiary Prevention

Too late

Death
The Hallmarks of Aging
Genome
- Genomic instability
- Telomere attrition

Proteome
- Epigenetic alterations
- Loss of proteostasis
- Deregulated nutrient sensing
- Mitochondrial dysfunction

Cellular
- Cellular senescence
- Stem cell exhaustion

Extracellular
- Altered intercellular communication

Primary hallmarks
Causes of damage

Antagonistic hallmarks
Responses to damage

Integrative hallmarks
Culprits of the phenotype

Conditions of Aging

- Cancer
- Cardiovascular disease
- Type 2 Diabetes
- Dementia/Alzheimer's
- Osteoporosis
- Wound healing

Conditions of Aging:

- Genomic instability
- Telomere attrition
- Epigenetic alterations
- Loss of proteostasis
- Deregulated nutrient sensing
- Mitochondrial dysfunction
- Cellular senescence
- Stem cell exhaustion
- Altered intercellular communication
<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Genomic instability</td>
<td>Leukocyte telomere length</td>
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<tr>
<td>Telomere attrition</td>
<td>DNA methylation, miRNA</td>
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<td>Epigenetic alterations</td>
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<td>Loss of proteostasis</td>
<td>insulin insensitivity, GH, IGF1</td>
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<td>Deregulated nutrient sensing</td>
<td>Bioenergetics (Oroboros), Reactive Oxygen Species, mtDNA deletions</td>
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<td>Mitochondrial dysfunction</td>
<td>p16&lt;sup&gt;INK4a&lt;/sup&gt;, SASP (proinflamm cytokines, matrix metalloproteinases, interleukins, growth factors)</td>
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<tr>
<td>Cellular senescence</td>
<td>Cytokines, neuroendocrine systems (eg, renin-angiotensin system, insulin-IGF response)</td>
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<td>Stem cell exhaustion</td>
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Example: Epigenetics
Range of epigenetic time scales

Air pollution (minutes/hours)

Cell identity (lifetime)

Low

High

Permanence of epigenetic marks

Age (years)

Epigenetic Age (years)

Chronological Age (years)
1. Are we examining the relevant tissue?

- Tissue-agnostic
  - e.g., Epigenetic clock

- Tissue-specific
  - e.g., Cell identity mark

Does it matter?

- For prediction: No, as long as it works.
- For mechanism: Yes, but this should be part of any effort to understand mechanism (molecular, cellular, tissue, organismal, societal contexts).
2. Confounding by cellular heterogeneity

- Solution: Purified cells, single-cell analysis, or cell counting
3. Single vs Bulk cells

Unmethylated (0%) + Methylated (100%) = Methylated (50%)

(Average across thousands of cells)

Solution: Cell sorting and cryopreservation
4. Cell-free DNA (‘liquid biopsy’) as window into other tissues

Current trends in sample collection

1. Addressing cellular heterogeneity
   a. Cell counting
      i. Flow cytometry (HRS)
      ii. Cryopreservation (UK Biobank, All Of Us, CARDIA)
   b. Purify cells
      i. FACS (GESTALT)
      ii. Monocytes (MESA)
      iii. CD4+ T-cells (GOLDN)

2. Tissues Cell compartments
   a. Non-blood tissues
      i. GTEx Project
      ii. Animal studies + small human validation studies
   b. cfDNA
   c. Exosomes
Conclusions

1) Opportunity for early detection

- Prediction: Molecular biomarkers may serve as early signs of biological dysfunction, preceding physiological and clinical detection.
- Mechanism: Provide deeper understanding of biology

2) Match stored samples to emerging technology

- Need longitudinal studies to confirm clinical utility of biomarkers.
- New sample collection (tissues and sample prep) needs to start now.