Session 172 PD - Living to 100: The Biology of Aging

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2017 SOA Annual Meeting & Exhibit

Session 172: Living to 100: The Biology of Aging

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October 18, 2017
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Agenda

• Theories of aging
• Aging as a disease
• Latest on science of aging
• Genetic components of aging
• Other factors on mortality
• Some implications of an aging population
• Morbidity compression
• The future
The Biology of Aging – The Science
The Challenge

• Older age population is increasing
• Population is increasingly more frail with age
• Our current medical paradigm ensures better survival but not less frailty
• Unsustainable approach
• What is health? Vs What is frailty?
Aging as a disease?
Aging Phenotype

• Look at your high school graduation picture
Definition of disease

• Disease: a condition of the living animal or plant body or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms [Merriam-Webster]

• Syndrome: a group of signs and symptoms that occur together and characterize a particular abnormality or condition
Acute vs. Chronic Disease

- Infectious agent
- Infection
- Inadequate response
- Damage
- Environmental cause
- Susceptibility
- Inadequate response
- Damage
• Measuring aging: mortality rate doubling time
Classification of Aging Theories

• Why do we care? Why vs How...

• Three main idea schools:
  • Wear and tear
  • Non programmed
  • Programmed
Wear and Tear

• Rocks erode
• Machine deteriorate
• Humans wear out too

• Issues
  • Why does it happen only after a certain age?
  • Why such variance by species, even for superficially similar species?
Medawar’s Hypothesis

• 1952 extension of Darwin’s theory
• Underlying: nature is stingy
• No evolutionary benefit to combat aging after age of reproduction: no natural selection engine
• Strong evolutionary pressure to survive to age of sexual maturity and none thereafter
Non Programmed Aging

• No evolutionary pressure relevant to aging past reproduction
• Therefore no mechanisms
• Mutation accumulation that are only bad for increasing age (Like Huntington’s) (Medawar 1952). Only relevant for maintenance genes (that are not at play early in life)
Programmed Aging

• Some species live much longer than others - even if superficially similar (mouse vs naked mole rat)
• Aging and death are necessary part of evolution: no death -> no evolution
• Rate of living: so many heartbeats [Stibich]
• Salmon is “programmed” to die after reproduction
• Some species senesce rapidly (century plant)
Selection at Group Level

• Altruistic aging (old make room for new) (Weisman 1891)
• Antagonistic pleiotropy (Williams): some genes confer an early advantage in exchange for a later cost
  • Found genes with either no impact or only one sided impact
  • Disposable soma (Kirkwood 1977) postulate redistribution of energy from somatic cells to reproductive cells
• Group benefit of a limited lifespan: avoid all individuals to be subject to a catastrophic event (starvation, epidemic) at the same time (Mitteldorf)[Wikipedia]
Medical Models of Aging

• Yeast 0.04 year
• Worms (nematodes) 0.16 year
• Fruit fly 0.3 year
• Mice 4 years
• Human 122 years
Cellular Hallmarks of Aging
Genomic Instability  
 telomere attrition  
 epigenetic alteration  
 loss of proteostasis  
 deregulated nutrition sensing  
 mitochondrial dysfunction  
 cellular senescence  
 stem cell exhaustion  
 altered intercellular communication  
 from hallmarks of aging by Lopez-Otin et al, Cell 6/32013
Causes of Damage

From Hallmarks of Aging by Lopez-Otin et al, Cell 6/32013
Response to Damage

- Deregulated Nutrition Sensing
- Mitochondrial Dysfunction
- Cellular Senescence

From Hallmarks of Aging by Lopez-Otin et al, Cell 6/32013
Impact on Phenotype of Aging

Stem Cell Exhaustion

Altered Intercellular Communication

From Hallmarks of Aging by Lopez-Otin et al, *Cell* 6/32013
Genomic Instability
Genomic Instability

• Nuclear DNA
  • Many sources of damage
  • Poor repair promotes aging (mice and humans)
  • Better repair less aging (in mice)

• Mitochondrial DNA
  • Less sturdy repair, not protected by histones
  • More genomes
  • Accelerated aging in HIV patients on retroviral drugs which hinder mtDNA replication

• Nuclear architecture
  • Lamina is scaffold inside the nucleus
  • Some genetic premature aging syndrome linked to nuclear lamina defect
  • Progerin, which interfere with proper function, increases with age (and telomere shortening) and stress
  • Decreasing progerin delays aging (in mice)
Telomere

From Y Tambe Wikimedia Commons
Telomere Attrition

- Telomere are “cap” of chromosome necessary to replication
- Shortens at each replication (source of Hayflick’s limit)
- Especially vulnerable to damage as not repaired by normal DNA repair functions
- Repaired by telomerase produced by some cells
- Dysfunction increases aging (in mice and human)
- Lengthening increases lifespan (in mice)
Epigenetics

• Key to cell differentiation from stem cells
• Gene activation and deactivation
• Genes are turned on and off at reasonably predictable times
• Somewhat inherited
• In twins, epigenetic differences increase with age
Histones and Nucleosome

From Wikimedia Commons
Richard Wheeler
Chromatin

- DNA
- The Nucleosome
- "Beads-on-a-String"
- The 30nm Fibre

Isolated patches.

Genes under active transcription.

Less active genes.

Add core histones.

Add histone H1.

From Wikimedia Commons Richard Wheeler
Epigenetic Alterations

• Histone modification
  • Sirtuins, histones protectors, implicated in healthy aging in mammals
  • Sirt6 impacts IGF-1
• DNA methylation (inactivates genes)
• Chromatin remodeling
  • Can alter lifespan and overexpression delays muscular degeneration of aging (in flies)
  • Impacts telomere length
Epigenetic Alterations

• Transcriptional Alteration
  • Mediated by a special class of microRNA
  • miRNA are small non-coding RNA molecules involved in regulating gene expression

• Reversion of epigenetic changes
  • Epigenetic changes are theoretically reversible
Loss of Proteostasis

- Protein folding and stability
  - Protein shape is key to function
  - Folded into the right shape
  - Some causes of cellular stress can unfold them
  - Repair systems can refold or destroy them
  - Increasing repair ability preserves muscle function (in mice)
Loss of Proteostasis (cont)

• Proteolysis
  • Decreases with age
  • Improved cell autophagy increases longevity (in flies)
  • Rapamycin increase autophagy but not in humans
  • Human impact of rapamycin probably is through other mechanisms
Deregulated Nutrition Sensing

• Insulin and IGF-1 pathways
  • Sense glucose
  • Impact on growth hormone
  • Evolutionary conserved
  • Impacts mTOR complex and FOXO transcription factors (Kenyon, Barzilai)
  • Can impact longevity both ways
    • Decrease with aging
    • But protective if low
      • Slower cell growth minimizes damage amplification
  • This pathway impacted by dietary restriction (in flies)
• Other pathways (mTOR, AMPK, sirtuins)
Deregulated Nutrition Sensing

• mTOR complex
  • Downregulation increase longevity in mice
  • Mimics effect of dietary restriction
  • Impacted by rapamycin

• AMPK and sirtuins
  • Sensors of poor nutritional environment
  • Upregulation improves longevity
  • Impacted by metformin
  • Sirtuins also impact AMPK levels
Mitochondrial Dysfunction

• Mitochondria is energy generator of the cell
• Reactive oxygen species (ROS) (Free radicals)
  • Damages DNA
  • Unexpected results: increasing ROS improves longevity (in worms) or does not increase aging (in mice)!
  • Current theory: ROS signals difficult environment to trigger repair mechanisms but increases above a certain level is damaging
Mitochondrial Dysfunction

• Mitochondrial integrity and biogenesis
  • Mitochondrial dysfunction increases aging
  • Aging reduces biogenesis of mitochondria (mediated by telomeres and sirtuins)
  • Accumulation of mutation in mtDNA
  • Endurance training and alternate day fasting avoid mitochondrial degeneration

• Mitohormesis
  • Mild toxic treatment triggers damage repairs systems
  • May be pathways for metformin and resveratrol
Cellular Senescence

- Blocks proliferation of damaged cells
- Anti cancer
- Anti aging up to a threshold and then proaging (increase inflammation...)
- In liver, young mice have 8% senescent cells, old mice 17%
- Secreting impact on neighboring cells (Campisi)
Stem Cell Exhaustion

• Two possible causes
  • Loss of activity of stem cells
  • Depletion of stem cells reservoir
• But stem cell proliferation is deleterious!
• Is there some extra-cellular component?
  • Injection of muscle stem cells from young mice to old mice improves functioning even in tissue where no stem cells are present
  • Parabiosis
Altered Intracellular Communication

• Inflammaging
  • Tissue damage and poor defective cell clearance
  • Poor pathogen clearance
  • Senescent cell secretions
  • Connected with DM2, obesity, atherosclerosis

• Other types of communication
  • Aging contagion

• Restoring communication
  • Dietary restriction, aspirin, microbiome
Comparative Genomics

• Genealogical pedigrees of longevity (Perls)
• Interspecies comparison
  • a number of genetic pathways are conserved
  • Mouse have a lot of cancers, naked mole rats don’t
### Genes Affecting Longevity

<table>
<thead>
<tr>
<th></th>
<th># Genes</th>
<th># Genes +100%</th>
<th>Max impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker’s yeast</td>
<td>216</td>
<td>4</td>
<td>+600%</td>
</tr>
<tr>
<td>C. elegans</td>
<td>441</td>
<td>14</td>
<td>+1000%</td>
</tr>
<tr>
<td>Mouse</td>
<td>45</td>
<td>0</td>
<td>+46%</td>
</tr>
</tbody>
</table>

Personal calculations on GenAge data
Treatment

• All 9 hallmarks have been addressed in mouse models
• No major longevity revolution in mice so far
• We have been able to read
• We are starting to have dictionaries: Comparative genomics

• We can now write: CRISPR
Lifestyle

• Dietary restriction?
Genetic Component

• Aging varies by species
• In humans, can see familial clusters
• Single genes manipulation/dysfunction
  • Can extend longevity in C elegans
  • Can accelerate aging in humans (Werner Syndrome...)
    [Rodriguez]
• Genome comparison of different individual and different species (naked mole rat vs mice, sea urchins)[Sergiev]
Para Genetic Components of Aging

- Mitochondrial DNA (inherited solely from mother) is key component of a healthy cell
- Epigenetic
- Transcriptome
- Microbiome
Transcriptome

• Genome->Transcriptome->Proteome
• Set of all messenger RNA (mRNA) in a cell
• mRNA is itself controlled by micro RNA (miRNA) that inhibit message transcription and accelerate degradation
• Potential clues on hippocampal degeneration with aging (promoting cognitive impairment)
• Difference in transcriptome of centenarian vs septuagenarians (Borras)
Microbiome

• Eating young fish poo makes a fish live longer (Nature 2017)
Recap

• Aging phenotype
• Complex process
• Pleiotropy
• Interconnectedness of cellular hallmarks
• Importance of non-genetic micro factors
  • Epigenetics
  • Transcriptome
  • Microbiome
• We have the Rosetta stone
• We can write
The Biology of Aging
Other factors and implications
Other factors – Lifestyle (1)

• Obesity
  • Obesity is at an all-time high in most countries – U.S. (2015-2016)
    • Adults: 37.9% for males and 41.1% for females; 39.6% total, up from about 37.6% from 2013-2014 (the statistical between results of these two surveys)
    • Children: 18.5%, up from 17.0% (2013-2014)
  • Due to nutrition and physical activity, as well as genetics

source: various National Health and Nutrition Examination Surveys (NHANES)
Other factors – Lifestyle (2)

• Smoking
  • Gradually decreasing in overall prevalence
  • Even though rate of smoking is much less at ages over 65, the residual long-term effect at those ages can be deadly
  • Since recent population experience reflects significant dropoff, future improvement may not be as favorable

<table>
<thead>
<tr>
<th>Gender%</th>
<th>Males (%)</th>
<th>Females (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–24</td>
<td>28.0%</td>
<td>18.5%</td>
<td>20.7%</td>
</tr>
<tr>
<td>24–44</td>
<td>26.8</td>
<td>22.9</td>
<td>21.4</td>
</tr>
<tr>
<td>45–64</td>
<td>25.2</td>
<td>19.4</td>
<td>18.8</td>
</tr>
<tr>
<td>65+</td>
<td>8.9</td>
<td>9.8</td>
<td>8.3</td>
</tr>
<tr>
<td>Total</td>
<td>23.9</td>
<td>18.8</td>
<td>18.1</td>
</tr>
</tbody>
</table>

source: Centers for Disease Control and Prevention (CDC)
Other factors – Lifestyle (3)

• Frailty risk (reduction in strength, with little contingent bodily resource support)
  • Falls – direct deaths (many indirect)

Source: CDC
Other factors – Lifestyle (4)

• Drinking
  • Total, high-risk and disorders (AUD) increasing

<table>
<thead>
<tr>
<th>Age / Year</th>
<th>12-Month Alcohol Use 2001-02</th>
<th>12-Month Alcohol Use 2012-13</th>
<th>12-Month High-Risk Drinking 2001-02</th>
<th>12-Month High-Risk Drinking 2012-13</th>
<th>DSM-IV Alcohol Use Disorder 2001-02</th>
<th>DSM-IV Alcohol Use Disorder 2012-13</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29</td>
<td>73.1%</td>
<td>80.1%</td>
<td>16.9%</td>
<td>19.3%</td>
<td>16.2%</td>
<td>23.4%</td>
</tr>
<tr>
<td>30-44</td>
<td>71.9</td>
<td>79.5</td>
<td>10.3</td>
<td>14.8</td>
<td>9.7</td>
<td>14.3</td>
</tr>
<tr>
<td>45-64</td>
<td>64.3</td>
<td>71.9</td>
<td>7.5</td>
<td>11.2</td>
<td>5.4</td>
<td>9.8</td>
</tr>
<tr>
<td>65+</td>
<td>45.1</td>
<td>55.2</td>
<td>2.3</td>
<td>3.8</td>
<td>1.5</td>
<td>3.1</td>
</tr>
<tr>
<td>All</td>
<td>65.4</td>
<td>72.7</td>
<td>9.7</td>
<td>12.6</td>
<td>8.5</td>
<td>12.7</td>
</tr>
</tbody>
</table>

Other factors – Lifestyle (5)

- Other addictions, e.g., opioids
  - Dramatically affecting mortality at middle ages – millions now taking opioids
- Suicides and homicides
- Sleeping
- Limited social interactions
- Mental conditions
  - For example, forgetting medicine
- Poverty
  - Inability to afford or unwillingness to take drugs
Other factors – Environmental

• Air and water quality

• Natural disasters and climate change
  • Differential effect for vulnerable population (both in lesser developed countries and those in poverty in more developed countries)
Other factors – the individual

• Educational attainment
  • Some studies have shown this to be one of, if not the major characteristic that affects mortality

• Socio-economic characteristics

• Culture and race/ethnicity
  • Peculiar U.S. Hispanic mortality paradox

• Age and gender
  • The original actuarial mortality variables
Implications of aging – to the individual

• Increased health care and activities of daily living support needed
• Savings needed for longevity risk is increasing, while actual savings not keeping pace
  • Rate of working at older ages increasing
Implications of aging – to society

• Stagnating economy (although many other factors involved, especially relatively low fertility)
• Increased need for pre-retirement savings
• Dependency costs
• Increased need for caregivers
  • Family & friends
    • Reduced productivity and increased personal wear-and-tear
  • Paid – limitations on supply, low pay
• Price of housing
  • Some think of home equity as providing for retirement or LTC needs – but operating costs, especially of an older home, can upset those plans
Implications of aging – to institutions

• Cost of remaining defined benefit plans
• Social Security (U.S.), for example, funded primarily on a pay-as-you-go basis, will see increases in the cost per supporting worker
  • Problem won’t go away after baby boomers die off – a fertility/immigration problem
• Relative savings / investment
  • The poor and disabled haven’t had opportunity to save/invest
• Investments
  • Because longevity at typical retirement ages has lengthened, prior advice (a conservative portfolio) may no longer be as relevant
Morbidity compression

• Life expectancy minus healthy life expectancy
• Will net morbidity incidence improve as fast as mortality improves?
  • Differing results in various studies
    • Trend in cognitive/mental illnesses – prevalence
    • Due in part to studying different population segments given much higher rate of dementia in those of lower income
• Obesity
  • Obesity tends to lengthen disability period, while smoking tends to decrease it – since the former is increasing and latter decreasing = longer future disability period (Mehta and Myrskylä (2017 Health Affairs))
• Growth in those of older ages with multiple underlying conditions
  • Improved treatments in many areas have reduced effect on deaths, but as they accumulate in individuals, may increase risk of mortality and morbidity
Life expectancy (LE) and Healthy life expectancy (HLE) Changes between 2000 and 2013

Overall life expectancy growing faster than healthy life expectancy

Source: based on data from WHO
The future – the age gradient

• Historically, rates of improvement (multiplicative) have often been smaller at older ages
  • What can this be attributed to?
  • Incorporated in many actuarial projections of rates of improvement

• Calendar year versus cohort effects
  • Non-genetic factors have usually had a reduced effect at older ages
    • For example, socio-economic and lifestyle

• Recent increases in U.S. mortality in mid-life may change this differential
  • But it has gone in cycles
The future: non-genetic factors - summary

• Ever-improving understanding of our bodies (and minds)
• Areas of advancement to look forward to
  • New and better technologies
  • New and better diagnostics
  • New and better treatments and drugs

• But
  • Our bodies and minds wear down eventually
  • Evil things can happen
    • Such as antibiotic resistance and pandemics
    • Behaviors that may not progress as much as the science
  • High prevalence of multiple adverse conditions at older ages a risk
    • Due in part to improving overall longevity
The future – actuarial projections

- Challenges associated with the two primary improvement methodologies
  - Mathematical models
    - Statistical
    - Trend extrapolation of some kind
  - Cause-related
- Some consider causes in deriving the mathematical model used
- But none deals well with discontinuities, non-linearities and cycles and usually all assume multiplicative relationships
Questions?