The Biology of Aging: An Overview

Robert J. Pignolo, M.D., Ph.D.
Assistant Professor of Medicine
Division of Geriatric Medicine
Fellow, Institute on Aging
Biology of Aging: An Overview

- General Concepts
- Theories of Aging
- Aging at the Cellular and Molecular Level
- Interventions in the Aging Process
Biology of Aging: An Overview

- General Concepts
- Theories of Aging
- Aging at the Cellular and Molecular Level
- Interventions in the Aging Process
Aging v. Senescence

Beneficial  Neutral  Deleterious
Universality of Aging

- Prokaryotes undergo senescence
- Populations of single-celled eukaryotic organisms are immortal, but single cells are not
- In multicellular organisms, senescence occurs in those that undergo somatic cell differentiation
Rates of Senescence

- **RAPID**: occurs abruptly after maturation (e.g., nematodes, flies) or soon after reproduction (e.g., annual plants, Pacific salmon)
- **GRADUAL**: slow but persistent deterioration after maturation in all placental mammals
- **NEGLIGIBLE**: no clear evidence for postmaturational increases in mortality rate (e.g., clams, trees, fish, reptiles)

Which of the following is true with regard to primary aging processes?

1. They are deteriorative changes over time in the relative absence of disease or injury.

2. Protection against premature death underlies survival increases that would otherwise be reduced secondary to primary aging processes.

3. They do not influence maximum life span.

4. They are not thought to be the underlying cause of senescence across species.
Primary Aging Processes

• Deteriorative changes over time in the relative absence of disease or injury
• Influence maximum life span
• Thought to be the underlying cause of senescence across species
Primary aging processes occur in the absence of disease

Bill Collins
World’s Fastest 50 Year Old

Age 17
Age 52

World Records: 5,000 M Run

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Speed (m/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>60</td>
<td>150</td>
</tr>
<tr>
<td>80</td>
<td>200</td>
</tr>
<tr>
<td>100</td>
<td>250</td>
</tr>
<tr>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>300</td>
<td>350</td>
</tr>
<tr>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>500</td>
<td>450</td>
</tr>
</tbody>
</table>

- Men
- Women
Median Length of Life

- Age at which there are as many individuals with shorter life spans as there are with longer ones
- Protection from premature death underlie survival increases
- Thought NOT to reflect primary aging processes
Maximum Life Span

• Age of the longest-lived survivors of a cohort or population
• For humans, operationally considered to be the oldest age reached by 1 in 100 million people
• Considered to be inversely proportional to the rate of aging of a population
All of the following resulted in a dramatic increase in average life span in the early 1900s except:

1. Sanitation  
2. Immunization  
3. Better nutrition  
4. Antibiotics
Human Survivorship through History

Increase in average life span (black arrows), but not maximum life span, is the result of protection from premature death.
# Life Expectancy List by the United Nations (2005-2010)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Life expectancy at birth (years)</th>
<th>Life expectancy at birth (years)</th>
<th>Life expectancy at birth (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Overall</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>1</td>
<td>Japan</td>
<td>82.6</td>
<td>78.0</td>
<td>86.1</td>
</tr>
<tr>
<td>2</td>
<td>Hong Kong</td>
<td>82.2</td>
<td>79.4</td>
<td>85.1</td>
</tr>
<tr>
<td>3</td>
<td>Iceland</td>
<td>81.8</td>
<td>80.2</td>
<td>83.3</td>
</tr>
<tr>
<td>4</td>
<td>Switzerland</td>
<td>81.7</td>
<td>79.0</td>
<td>84.2</td>
</tr>
<tr>
<td>5</td>
<td>Australia</td>
<td>81.2</td>
<td>78.9</td>
<td>83.6</td>
</tr>
<tr>
<td>6</td>
<td>Spain</td>
<td>80.9</td>
<td>77.7</td>
<td>84.2</td>
</tr>
<tr>
<td>7</td>
<td>Sweden</td>
<td>80.9</td>
<td>78.7</td>
<td>83.0</td>
</tr>
<tr>
<td>8</td>
<td>Israel</td>
<td>80.7</td>
<td>78.5</td>
<td>82.8</td>
</tr>
<tr>
<td>9</td>
<td>Macau</td>
<td>80.7</td>
<td>78.5</td>
<td>82.8</td>
</tr>
<tr>
<td>10</td>
<td>France (metro)</td>
<td>80.7</td>
<td>77.1</td>
<td>84.1</td>
</tr>
<tr>
<td>11</td>
<td>Canada</td>
<td>80.7</td>
<td>78.3</td>
<td>82.9</td>
</tr>
<tr>
<td>12</td>
<td>Italy</td>
<td>80.5</td>
<td>77.5</td>
<td>83.5</td>
</tr>
<tr>
<td>36</td>
<td>United States</td>
<td>78.3</td>
<td>75.6</td>
<td>80.8</td>
</tr>
</tbody>
</table>
Life Expectancy at birth
Longest-lived Humans

Jeanne Calment (France)
Lived to age 122

Christian Mortensen
(Danish-American)
Lived to age 115

Examples of long-lived human populations point to which of the following pro-longevity factor(s):

1. Genetic pre-disposition
2. Dietary practices
3. Spirituality
4. Conformity to beneficial health practices
5. All of the above
The places where people live the longest

- Okinawa, Japan
- Ovodda, Sardinia (Italy)
- Loma Lida, CA (USA)
Keys to longevity - Okinowawa

- “hara haci bu”
- Rainbow diet
- Diet: soy > fish, meat, eggs, dairy
- BMI 20.4
- ~1200 cal diet
- DHEA levels decline more slowly
Keys to longevity - Ovodda, Sardinia

• As many men live to 100 as women
• Sardinians who emigrated at 20, 30 or 40 years of age still manage to reach 100
• Descended from only a few original settlers – isolated, interbreeding
• G6PD deficiency, other genetic traits?
Keys to longevity- Loma Linda, CA

- Seventh Day Adventists
- Members live 5-10 years longer than fellow citizens
- No drinking or smoking
- Many adhere to a vegetarian diet the church advises
- Spiritual life
- Regular churchgoers – of whatever faith - live longer
- Significantly lower levels of stress hormones
Keys to longevity

“How long would you live if you were a Sardinian 7th Day Adventist who moved to Okinawa at 20 years of age?”
Female life-expectancy in Japan has risen for 160 years at a steady pace of almost 3 m/yr!

Compression of Morbidity

Which is true regarding morbidity with increased life span as reflected by disability trends?

1. Morbidity increases with life extension.
2. Morbidity remains the same with increased life span.
3. Morbidity is compressed.
Which of the following is **true** regarding the onset of age-related disease in centenarians?

1. Age-related disease is delayed by almost one decade.
2. Age-related disease occurs at about the same time in centenarians as in individuals with average life expectancy.
3. Age-related disease does not occur in centenarians.
4. Age-related disease may occur at about the same time as in individuals with average life spans, may be delayed or even absent in centenarians.
Who are centenarians?
<table>
<thead>
<tr>
<th>Characteristics of Aging</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased mortality after maturation</td>
<td>Survival curves showing exponential increase in mortality with age</td>
</tr>
<tr>
<td>Changes in biochemical composition of tissues</td>
<td>Increases in lipofuscin or age pigment</td>
</tr>
<tr>
<td></td>
<td>Increased cross-linking in extracellular matrix molecules such as collagen</td>
</tr>
<tr>
<td>Progressive, deteriorative physiologic changes</td>
<td>Declines in glomerular filtration rate, maximal heart rate, vital capacity</td>
</tr>
<tr>
<td>Decreased ability to adaptively respond to environmental changes</td>
<td>Decreased &quot;first past&quot; hepatic metabolism</td>
</tr>
<tr>
<td></td>
<td>Blunted maximal cardiac responses to exercise</td>
</tr>
<tr>
<td>Increasing incidence of many diseases</td>
<td>Ischemic heart disease, type II diabetes, osteoporosis, Alzheimer's disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics of Aging</th>
<th>Exceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased mortality after maturation</td>
<td>Human age-specific mortality rates do not continue to increase exponentially at very advanced ages</td>
</tr>
<tr>
<td>Changes in biochemical composition of tissues</td>
<td>Changes are quite heterogeneous from organ to organ within a specific individual and also from individual to individual (&quot;usual&quot; and &quot;successful&quot; aging)</td>
</tr>
<tr>
<td>Progressive, deteriorative physiologic changes</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>Decreased ability to adaptively respond to environmental changes</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>Increasing incidence of many diseases</td>
<td>Elimination of atherosclerosis and cancer as causes of death would only add about ten years to average life span and would not affect maximum life span potential</td>
</tr>
</tbody>
</table>
“Who you calling old?”
Biology of Aging: An Overview

• General Concepts
• Theories of Aging
• Aging at the Cellular and Molecular Level
• Interventions in the Aging Process
Theories of Aging

Stochastic or Random Error Theories

Genetic/Developmental Theories

Evolutionary Theory

Theories of Aging
Cumulative Oxidative Damage during Aging

All of the following evidence supports a genetic basis for longevity, except:

1. Common polymorphisms in the APOE gene have a modest effect on life span.
2. There is high conservation of maximum life span seen between species.
3. There are examples of exceptional longevity within families.
4. Twin studies demonstrate that genetic differences likely account for about 50% of the variance in adult human life span.
Genetic Basis of Aging Theories

- High conservation of maximum life span between species
- Similarity of attained age between monozygotic twins compared to dizygotic twins or nontwin siblings
- Examples of exceptional longevity within families
- Subsets of aging features in human genetic syndromes of premature aging
### Most commonly described human segmental progeroid syndromes.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Incidence (per live birth)</th>
<th>Inheritance</th>
<th>Mean life-span (years)</th>
<th>Progeroid features</th>
<th>Genome maintenance defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchinson-Gilford</td>
<td>~1/1,000,000</td>
<td>Unknown</td>
<td>~13</td>
<td>Alopecia, sclerosis, wrinkling, soft tissue, cachexia, arteriosclerosis, diminished fat</td>
<td>Laminin</td>
</tr>
<tr>
<td>Werner</td>
<td>&lt;1/100,000</td>
<td>Autosomal recessive</td>
<td>~50</td>
<td>Alopecia, osteoporosis, malignancies, arteriosclerosis, diabetes, cataracts, telangiectasia, skin atrophy, graying of hair</td>
<td>DNA helicase (RecQ-like), exonuclease</td>
</tr>
<tr>
<td>Rothmund-Thomson</td>
<td>&lt;1/100,000</td>
<td>Autosomal recessive</td>
<td>Normal ?</td>
<td>Alopecia, malignancies, poikiloderma, cataracts, osteoporosis, graying of hair</td>
<td>DNA helicase (RecQ-like)</td>
</tr>
<tr>
<td>Cockayne</td>
<td>~1/100,000</td>
<td>Autosomal recessive</td>
<td>~20</td>
<td>Thin hair, cachexia, retinal degeneration, hearing loss, neurodegeneration (cerebellar ataxia), cataracts</td>
<td>Transcription-coupled DNA repair</td>
</tr>
<tr>
<td>Trichothiodystrophy</td>
<td>&lt;1/100,000</td>
<td>Autosomal recessive</td>
<td>~10</td>
<td>Cachexia, osteoporosis, cataracts, fragile hair, neurodegeneration (cerebellar ataxia)</td>
<td>DNA repair, basal transcription</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>~1/60,000</td>
<td>Autosomal recessive</td>
<td>~20</td>
<td>Skin atrophy/sclerosis, telangiectasia, immunodeficiencies, malignancies, graying of hair, poikiloderma, neurodegeneration (cerebellar ataxia)</td>
<td>DNA damage signaling protein kinase</td>
</tr>
<tr>
<td>Down</td>
<td>~1/1,000</td>
<td>De novo</td>
<td>~60</td>
<td>Cataracts, graying of hair, alopecia, diminished subcutaneous fat, vision loss, neurodegeneration (Alzheimer-like), thyroid dysfunction</td>
<td>Trisomy</td>
</tr>
</tbody>
</table>

Evolutionary Theory

- Risk of mortality increases with time after reproduction
- Genes that confer early benefits on reproductive fitness are selected, even if they cause deleterious effects later in life
- No selective pressure against genes that confer negative effects later in life
- Strong pressure to retain genes that diminish vulnerability in young and old alike
Biology of Aging: An Overview

- General Concepts
- Theories of Aging
- Aging at the Cellular and Molecular Level
- Interventions in the Aging Process
Replication Potential of Normal Human Cells

Soma

- Post-mitotic cells (e.g., neurons)
  - No division

- Quiescent, Replication-competent Somatic cells (e.g., fibroblasts)
  - Finite division

- Stem cells (e.g., early hematopoietic precursors, gut-lining cells)
  - Potentially unlimited cell division

Germ Line

- Primative germ cells (e.g., spermatogonia)
Some characteristics associated with replicative senescence include all of the following except:

1. Apoptosis resistance
2. Finite replicative life span
3. Altered pattern of gene expression
4. Promotion of intrinsic aging in all cell types
5. Essentially irreversible growth arrest
Cellular (Replicative) Senescence

Stages in the in vitro life history of normal human diploid fibroblasts

Adapted from Cristofalo, V.J. and Pignolo, R.J. Handbook of the Physiology of Aging, Oxford University Press, 1995.
Telomere Shortening with Cellular Aging

Telomere dysfunction/uncapping

Persistent DNA damage Response
Replication Potential of Normal Human Cells

**Soma**
- Post-mitotic cells (e.g., neurons)
  - Telomerase -
  - No division
- Quiescent, Replication-competent Somatic cells (e.g., fibroblasts)
  - Telomerase -
  - Finite division
- Stem cells (e.g., early hematopoietic precursors, gut-lining cells)
  - Telomerase +
  - Potentially unlimited cell division

**Germ Line**
- Primative germ cells (e.g., spermatogonia)
  - Telomerase +
Aging in Telomerase-deficient mice

- Age-dependent telomere shortening
- Genomic instability
- Shortened life span
- Reduced capacity to respond to stressors
- Increased spontaneous malignancies
- Villi atrophy of small intestine

### Aging in Telomerase-deficient Humans

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Cells expressing telomerase</th>
<th>Defect in dyskeratosis congenita</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair</td>
<td>Hair follicle</td>
<td>Alopecia</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>Squamous epithelium</td>
<td>Leukoplakia (precancerous oral lesions)</td>
</tr>
<tr>
<td>Skin</td>
<td>Basal layer of epidermis</td>
<td>Abnormal pigmentation Nail dystrophy</td>
</tr>
<tr>
<td>Lungs</td>
<td>Type 2 alveolar epithelial cells</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Liver</td>
<td>?</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Intestine</td>
<td>Intestinal crypts</td>
<td>Gut disorders</td>
</tr>
<tr>
<td>Testes</td>
<td>Spermatogonia</td>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Progenitor stem cells</td>
<td>Failure to produce blood cells</td>
</tr>
</tbody>
</table>

Replication Potential of Normal Human Cells

Soma

- Post-mitotic cells (e.g., neurons)
  - Telomerase -
  - No division

- Quiescent, Replication-competent Somatic cells (e.g., fibroblasts)
  - Telomerase -
  - Finite division

- Stem cells (e.g., early hematopoietic precursors, gut-lining cells)
  - Telomerase -
  - Potentially unlimited cell division

Germ Line

- Primative germ cells (e.g., spermatogonia)
  - Telomerase +
  - Potentially unlimited cell division

aging
Replication Potential of Normal Human Cells

**Soma**
- Post-mitotic cells (e.g., neurons)
  - Telomerase -
  - No division
  - Aging
- Quiescent, Replication-competent Somatic cells (e.g., fibroblasts)
  - Telomerase -
  - Finite division
- Stem cells (e.g., early hematopoietic precursors, gut-lining cells)
  - Telomerase -
  - Potentially unlimited cell division

**Germ Line**
- Primative germ cells (e.g., spermatogonia)
  - Telomerase +
  - Dyskeratosis congenita
Aging, Cancer, and p53

Interactions between p53/p21 and p16/Rb
Which one of the following statements most accurately describes immune senescence?

1. It is associated with altered production of inflammatory cytokines.
2. There is an increase in T and B cell diversity with age.
3. It is similar in humans and mice.
4. T memory cells decrease and T naïve cells increase with age.
5. With aging, the response to new antigens remains intact.
Immune Senescence
(Perturbation of adaptive immune system with age)

• Altered/diminished immune responsiveness
  – Decreased response to new antigens
  – Decreased vaccine efficiency (e.g., influenza)
  – Compromised immune surveillance (?)

• Altered immune system physiology
  – Thymic involution
  – Decreased production of lymphocytes
  – Inversion in proportional representation of memory vs naïve cells (T memory cells increase and T naïve cells decrease with age)

• Altered immunoregulation
  – Increase in autoimmune syndromes (SLE, RA, SS, others)
  – Oligoclonal expansion of T- and B-cells (decrease in diversity with age)
  – Monoclonal gammopathies
Biology of Aging: An Overview

- General Concepts
- Theories of Aging
- Aging at the Cellular and Molecular Level
- Interventions in the Aging Process
Interventions in the Aging Process

• Cell-based therapies
• Hormonal therapies
• Genetic manipulations
• Dietary therapies
• Other: hypothermia, exercise
Clearance of p16Ink4a–positive senescent cells delays ageing–associated disorders

Darren J. Baker1,2,3, Tobias Wijshake1,4, Tamar Tchkonia1, Nathan K. LeBrasseur3,5, Bennett G. Childs1, Bart van de Sluis4, James L. Kirkland1 & Jan M. van Deursen1,2,3
Dietary Therapies

• Caloric Restriction
  – Extends average and maximum life spans by 30-40% if initiated in early adulthood, and by 20% if started in early middle age
  – Usually 30-60% reduction in calories with adequate content of essential nutrients
  – Effect preserved in a variety of species, including rodents, fish, flies, and worms
Effect of Dietary Restriction on Life Span

Caloric Restriction in Non-human Primates

A&B, 27 year old control; C&D, 27 year old CR
Caloric Restriction in Non-human Primates

• Altered Growth, Development or Metabolism
  – Lower body temperatures
  – Later sexual development
  – Later skeletal maturation

• Improved Health
  – Lower weight
  – Less abdominal fat
Caloric Restriction in Non-human Primates

- Reduced Risk for Age-related Diseases
  - Greater insulin sensitivity
  - Lower fasting insulin and glucose levels
  - Lower cholesterol and triglyceride levels
  - Higher HDL levels
  - Lower IGF-I levels
  - Slower decline in DHEAS

- Effects in Rodents but Still under Investigation in Monkeys
  - Later onset of age-related diseases (including cancer)
  - Longer average life span
  - Longer maximum life span
Caloric Restriction in Non-human Primates
Caloric Restriction in Non-human Primates
Explaining mixed results of calorie restriction in non-human primates

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled young animals (7-14 years)</td>
<td>Enrolled young (1-14 years) &amp; old (16-23 years) animals</td>
</tr>
<tr>
<td>Increased survival when non-aging related deaths are removed</td>
<td>No increased survival</td>
</tr>
<tr>
<td>Delay in cancer and DM in CR group</td>
<td></td>
</tr>
<tr>
<td>Increase in non-aging related deaths with CR (bloat, anesthesia)</td>
<td></td>
</tr>
<tr>
<td>Similar carbohydrate, protein, and fat content of diet</td>
<td></td>
</tr>
<tr>
<td>Sucrose, 28.5% of diet</td>
<td>Sucrose, 3.9% of diet</td>
</tr>
<tr>
<td>Control group fed ad libitum</td>
<td>Control group fed apportioned diet to prevent obesity</td>
</tr>
<tr>
<td>DM in 40% of controls</td>
<td>DM in 12.5% of controls</td>
</tr>
</tbody>
</table>

Austad, S Nature 2012, doi:10.1038/nature11484
Caloric Restriction in Humans

- Okinawans
- Biosphere 2 Project
- Short-term studies in humans
Caloric Restriction in Humans

Common to both CR nonhuman primates & long-lived males

- Lower levels of plasma insulin
- Lower body temperature
- Maintenance of higher plasma DHEA levels

25% CR in humans × 6 months

Prototype Caloric-Restriction Mimetic
Sirtuins (protein deacetylases): mediators of caloric restriction?
Resveratrol, a sirtuin activator, improves health and survival of mice on a high-calorie diet

Effects of resveratrol

- Extends lifespan of diverse lower species:
  - S. Cerevisiae
  - C. elegans
  - D. melanogaster

- Changes parameters associated with longer lifespan:
  - Increased insulin sensitivity
  - Reduced IGF-I levels
  - Increased mitochondrial number
  - Improved motor function
Dietary Therapies

• Antioxidant supplementation
  – Does not significantly change median or maximum life span
  – Except for vitamin E (and possibly vitamin C) being able to lower lipid oxidative damage, no evidence to support reduction in oxidative damage in humans
  – A compound with catalase and SOD activities (EUK-134) extends longevity in nematodes
  – Foods with a high oxygen radical absorbance capacity (ORAC) may be more protective than other antioxidant preparations
  – Antioxidants may help reduce the incidence of ARMD

Pharmaceuticals that have potential to extend life span

- National Institute of Aging has organized a multi-site study of in genetically heterogenous mice
- Of the agents being tested, aspirin and nordihydroguaiaretic acid have been found to lead to significant increases in life span in males
- Rapamycin leads to an increase in maximum longevity in both males and females
- Other compounds currently being tested as part of this initiative can be found at http://www.nia.nih.gov/ResearchInformation/ScientificResources/CompoundsInTesting.htm.
Rapamycin:
-- extended median and maximal lifespan of both male and female mice
-- led to an increase in lifespan of 14% for females and 9% for males
-- reproducible extended life span at three independent test sites in genetically heterogeneous mice
-- did not affect disease patterns compared to control mice

Harrison DE et al., Nature 2009
Other dietary manipulations that extend maximum life span

• Low-methionine diets
• Brief, but early nutritional deprivation

Strong, R et al, Aging Cell (2009)
Sun, L et al., J. Gerontol. (2009)