Physiology of Aging

Dean L. Kellogg, Jr, MD. Ph.D
Departments of Physiology and Medicine
Disclosures
Disclosures
Disclosures
Disclosures
Physiology of Aging

Dean L. Kellogg, Jr, MD. Ph.D
Departments of Physiology and Medicine
The Geriatric (>65yo) Population

- Ancient Greece-life expectancy at birth = 20
- 1776-life expectancy at birth = 23
- 1900-life expectancy at birth = 47
- 2007-life expectancy at birth = 77.9
- 2008-life expectancy at birth = 77.8

- Maximum documented human lifespan = 122

Increased longevity primarily due to better healthcare and living conditions (80-100
2011-
13% of US
count is in Geriatric Age Group

2030-20% of US population!
Physiology of Aging

1) What is Aging?

2) Theories/Mechanisms of Aging
   - Primary Aging
   - Secondary Aging

3) Organ System “Functional” Reserve
WHAT IS AGING?
1967-age 36

Youthful space travelers
2011-age 80

Aged Earthmen
WHAT IS AGING?

“a confusing mess of mechanisms”
WHAT IS AGING?

“the post-maturational deterioration of cells and organisms with the passage of time leading to an increased vulnerability to stresses, an increased prevalence of age-related diseases, and a decreased ability to survive.”

MULTIPLE THEORIES
Theories of Aging
Mechanisms
Early concept-body is a machine

“Wear and Tear” Theory
- Cells are damaged by toxins in diet and environment
- Repair processes gradually lost over time
- “Older” individuals become more susceptible to physiological stresses because they cannot repair cellular “wear and tear”
Theories of Aging
Mechanisms
Genes and Extrinsic Factors involved in aging

“Somatic Mutation” Theory
- Based on observations that effects of radiation exposure were similar to aging
- “Aging hits” damage chromosomes
- Chromosomal damage accumulates over time leading to failure of normal physiological function with reduced tolerance to physiological stresses
Theories of Aging
Mechanisms

Aging is an outcome of genetic effects of evolutionary selection

“Antagonistic Pleiotropy” Theory
(application of evolutionary mechanisms to aging)
- Genes are pleiotropic – they can control more than one trait
- Genes that increase reproductive success early in life are selected for even though they may be deleterious later in life

EXAMPLE – genes for high testosterone levels good in young males but increase BPH in older males
WHAT IS AGING?

Multiple Theories attest that aging is:

✓ Complex, integrated process that is universal
✓ Universal nature of aging implies that aging is encoded in the genome
  (suggests that genes determine maximum lifespan under ideal conditions)
✓ Extrinsic factors (such as environmental stressors) can modify aging

◆ Incompletely understood biological phenomenon that reduces tolerance to physiological stressors.
WHAT IS AGING?
Can we “sort out” the mess of multiple aging theories?

Primary Aging
Secondary Aging
Primary Aging

Primary aging is defined as the universal changes occurring with the passage of time due to **intrinsic** biological processes that are **not** caused by disease or environmental influences.
Secondary Aging

Secondary aging is defined as changes that occur over time that involve *extrinsic* processes such as disease processes and environmental influences, such as smoking and exposure to ultraviolet radiation.
Theories of Primary Aging

“Free-Radical” Theory

Reactive Oxygen Species = superoxides, free radicals, peroxides that are HIGHLY REACTIVE

- ROS react with biological molecules
- ROS reactions with DNA, lipids, and proteins lead to cellular dysfunction
- Aging is due to accumulation of cellular damage by reactions with ROS over time
Theories of Primary Aging

“Free-Radical” Theory of Aging
- ROS can be generated by mitochondrial dysfunction and other endogenous sources
- Increased ROS leakage from mitochondria with aging
- Impaired antioxidant defense against ROS with aging
ROS + Theories of Primary Aging

PROBLEM with “ROS/mitochondrial theory” and primary aging
- Genetic augmentation of antioxidant defenses does not extend lifespan in primary aging models

Antioxidant Defense

<table>
<thead>
<tr>
<th>ROS Scavenging Agents</th>
<th>ROS Protective enzymes</th>
<th>Sequestration of transition metal ions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutathione</td>
<td>Superoxide dismutase</td>
<td>Transferrin</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Catalase</td>
<td>Ferritin</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Glutathione peroxidase</td>
<td>Metallothioneins</td>
</tr>
<tr>
<td>Albumin</td>
<td>Glutathione reductase</td>
<td>Ceruloplasmin</td>
</tr>
</tbody>
</table>
Theories of Primary Aging

“Aging Clock” Theory
- Based on observation that human fibroblasts can only divide a finite number of times ("Hayflick limit")
- Somatic cells with replicative potential have a “mitotic clock” that determines their maximum lifespan
- Aging due to progressive increase in number of cells reaching Hayflick limit over time
Theories of Primary Aging

“Aging Clock” Theory

- Based on observation that human fibroblasts can only divide a finite number of times ("Hayflick limit")
- Somatic cells with replicative potential have a “mitotic clock” that determines their maximum lifespan
- Aging due to progressive increase in number of cells reaching Hayflick limit over time

What’s the clock?
Theories of Primary Aging

“Telomere Theory of Aging”
- Telomeres are the “Aging Clock”
- Telomere = specialized DNA/protein “cap” that protect ends of chromosomes to promote genome stability
- Telomere = thousands of base pairs and associated proteins
Theories of Primary Aging

“Telomere Theory of Aging”

- Cell replication results in progressive loss of base-pairs from telomeres so that telomeres shorten with each cell division.

- When telomeres shorten to a critical length, protective function is lost.

- Short telomeres cause cell to exit cell cycle (senescence) or undergo apoptosis (programmed cell death) = protective against DNA replication errors.
Theories of Primary Aging

**Human Evidence for “Telomere Theory of Aging”**

- Shorter telomere length with advancing age in humans
What is the outcome of telomere attrition vis-à-vis primary aging?

1) **Cell Death** (apoptosis)
2) **Cell Senescence**
What is the outcome of telomere attrition vis-à-vis primary aging?

*Senescence limits the replicative potential of cells.*

- **Quiescent cells** = temporarily out of cell cycle
- **Senescent cells** = permanently out of cell cycle
Senescent Cells

• Not just passive “bystanders” in tissues
• Adopt a “pro-inflammatory” phenotype with altered gene expression
• Can alter tissue function by producing an array of paracrine signaling molecules (often pro-inflammatory)
• Paracrine signaling from senescent cells contributes to “aging”...for example cytokines and reactive oxygen species

Diagram: 
- TGF β1
- Quiescent Epithelial Cell
- Oxidative Stress
- Senescent Epithelial Cell
- Replication
- Hyperplasia
- FGF2
- FGF7
- IL-8
- IL-1α
WHY SENESCENCE?

Isn’t senescence make things worse?
Senescence and Antagonistic Pleiotropy

- Senescence is anti-tumorogenic in youth, thus enhancing reproduction.
- Cancer results from failure of senescence process.

Senescence prevents cells with damaged/defective DNA from replicating.
“Telomere Theory of Aging”

- increased numbers of senescent cells and reduced numbers of replicating cells over
Can Aging Be Altered?

Mechanisms of aging are tractable!
• Caloric restriction extends lifespan

Feeding
- Increase in plasma insulin and IGF-1
  - Decrease in glucagon
  - Inhibition of autophagy
  - Decreased degradation (and increased synthesis) of protein, membranes, and organelles
  - Reduced degradation of altered membranes and organelles
  - Loss of control of autophagy functioning
  - Accumulation of altered membranes, mitochondria, and peroxisomes
  - Higher levels of oxidative stress
  - Impaired maintenance of structure and functions of membranes
  - Impaired cell and tissue function

Fasting
- Decrease in plasma insulin and IGF-1
  - Increase in glucagon
  - Stimulation of autophagy
  - Increase in degradation (and decreased synthesis) of protein, membranes, and organelles
  - Maintained juvenile regulation of autophagy
  - Reduced number of altered membranes, mitochondria, and peroxisomes
  - Lower levels of oxidative stress
  - Maintenance of structure and functions of membranes
  - Maintenance of cell and tissue function
Can Aging Be Pharmacologically Altered?

Mechanisms of aging are tractable!

- Antagonism of mTOR by rapamycin (sirolimus) extends lifespan
Mice on Rapamycin are “Younger” in activity levels and coat appearance.

- Control Female
- RAPA Female
- Resveratrol Male
- RAPA Male

“Activity” level preserved in Males.
Mechanisms of aging are tractable!

- Extension of lifespan by pharmacological means is possible.
- Preserved activity level in males suggests that extension of ‘health span’ may also be possible.
- Presumed that RAPA alters primary, but may alter secondary aging.
On To Secondary Aging....

“it’s remarkable, Mr. Volmer. You have the clothes of a man half your age!”
Secondary aging is defined as changes involving interactions of primary aging processes with disease processes and environmental influences, such as smoking and exposure to ultraviolet radiation.

What mechanism do disease processes, UV, etc. have in common?
Oxidative Stress ........ ROS!

• Likely that ROS play an important role in secondary aging, i.e., age-related diseases.
Mechanisms of Secondary Aging

• High levels of ROS may mediate age-related disease processes of “secondary aging” by accelerating telomere attrition and thus premature cellular senescence leading to age-related diseases.
Can Secondary Aging Be Altered?

Initial attempts not encouraging:

• Genetic augmentation of endogenous ROS defenses (SOD) does not alter lifespan unless physiological stress added!
• In humans, exogenous anti-oxidants (Vit C, Vit E, etc) have done little or nothing to alter lifespan or promote “health” (may even be detrimental).
Can Secondary Aging Be Altered?

Resveratrol extends lifespan in lower organisms and in overfed mice (not in “normal mice”) probably by activating Nrf2-KEAP1-ARE pathway.

Nrf2=Nuclear factor (erythroid-derived 2)-like 2
KEAP1=Kelch-like ECH-associated protein 1
ARE=Antioxidant Response Element

Mechanisms of secondary aging are...
Sulforaphane activates Nrf2

Eat your broccoli!
Bardoxolone in T2DM with CKD

Bardoxolone:
- Activates Nrf2-KEAP1-ARE pathway
- Elicits sustained increases in GFR in T2DM (persisted for 4 weeks post-treatment)
Primary and Secondary Aging are closely interrelated...especially in the real world!
In the clinical setting, aging represents an integration of both primary and secondary aging that results in reduced physiological function.
AGE-RELATED CHANGES OF PHYSIOLOGICAL FUNCTION:

What are the ‘real world’ physiological consequences of primary and secondary aging?
IN GENERAL:
The ability to respond to physiological stress declines with advancing age.

WHY IS THAT?
IN GENERAL:

The ability to respond to physiological stress declines with advancing age.

WHY IS THAT?

Age-related attrition of “organ system functional reserve”
Age-related Changes of Physiological Function

- Organ system reserve capacity declines with age
- Decline occurs in all organ systems
- Clinically significant symptomatology occurs when "critical threshold" is reached

Graph:
- Asymptomatic
- Critical threshold
- Clinical signs and symptoms of failure

Point A: Asymptomatic
Point B: Critical threshold
Point C: Clinical signs and symptoms of failure
Physiological Systems: Effects of Age
What can be done to reduce rate of decline of "Functional Organ Reserve" with aging?

Appropriate Life-style Choices can delay rate of decline in "Functional"
CLINICAL POINT

- Incidence of clinically significant symptomatology increases as “critical threshold” of depleted functional reserve is approached.
- “Provocative stressors” (drugs, infections, etc.) can acutely deplete functional reserve to be below the “critical threshold” resulting in failure of the affected organ system(s).
EXAMPLE OF AGE-RELATED CHANGES OF PHYSIOLOGICAL FUNCTION
Clinical Example: CV-Baroreflex

- Baroreceptor Reflex Sensitivity Decreases with Age
  - reduced responses to blood pressure changes
Clinical Example: CV-Baroreflex

Ability to tolerate hypotensive stress declines with age and is worsened by non-selective Alpha 1 receptor blockade in geriatric patients.
BAROREFLEX challenge for a youthful space traveler?

Jumping up and fighting the Gorn!
BAROREFLEX challenge for an aged Earthman?

Standing up and walking off the beach!
Cerebrocortical System (Cognitive Function)

• Decline in Cognitive Function with age:
  – prevalence of moderate to severe dementia
    • 1 to 2% at ages 65 to 69 years
    • 2 to 5% at ages 70 to 79 years
    • 11 to 20% at ages 80 to 89 years
    • 39 to 60% at ages 90 to 99 years
    • 75 to 85% at ages >100 years

• 40% of ‘apparently normal’ 80 year olds show evidence of cognitive decline (executive function) on executive function tests (CLOX) that may be missed on “memory-based” tests (MMSE)
Cerebrocortical System (Cognitive Function)

CLOX: An Executive Clock Drawing Task

STEP 1: Turn this form over on a light colored surface so that the circle below is visible. Have the subject draw a clock on the back. Instruct him or her to “Draw me a clock that says 1:45. Set the hands and numbers on the face so that a child could read them.” Repeat the instructions until they are clearly understood. Once the subject begins to draw no further assistance is allowed. Rate this clock (CLOX 1).

STEP 2: Return to this side and let the subject observe you draw a clock in the circle below. Place 12, 6, 3, & 9 first. Fill in the rest of the numbers. Set the hands again to “1:45”. Make the hands into arrows. Make the hour hand shortest. Invite the subject to copy your clock in the lower right corner. Score this clock (CLOX 2).

<table>
<thead>
<tr>
<th>Organizational Elements</th>
<th>Point Value</th>
<th>CLOX 1</th>
<th>CLOX 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does figure resemble a clock?</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circular face present?</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimensions &gt;1 inch?</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All numbers inside the perimeter?</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No sectoring or tic marks?</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12, 6, 3, &amp; 9 placed first?</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spacing Intact? (Symmetry on either side of 12 and 6 o’clock?)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only Arabic numerals?</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only numbers 1-12 among the numerals present? (ignore notation)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequence 1-12 intact? No omissions or intrusions</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only two hands present? (ignore sectoring tic marks)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All hands represented as arrows?</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hour hand between 1 and 2 o’clock?</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minute hand obviously longer than hour?</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None of the following: 1) hand pointing to 4 or 5 o’clock?</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) “1:45” present?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) Any other notation (e.g. “9:00”)?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4) Any arrows point inward?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5) Intrusions from “hand” or “face” present?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6) Any letters, words or pictures?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7) Any intrusion from circle below?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TOTAL
Cognitive challenge for an youthful space traveler?

I can draw clocks for at least 237,000 different planetary systems without my tricorder.
Cognitive challenge for an aged Earthman?

I can’t draw a clock, but I can do this!
Coffee Activates Nrf2-KEAP1-ARE

Dark roast is best!

Time for coffee!
SUMMARY: Physiology of Aging

1) Primary Aging
   - telomere attrition leads to cell senescence
   - accumulation of senescent cells alters tissue function over time

2) Secondary Aging
   - driven by ROS
   - premature cellular senescence

3) Aging CAN be pharmacologically manipulated
   - rapamycin

4) Organ System Reserve Capacity
   - decline in reserve with age leads to reduced tolerance of