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
- 2010-life expectancy at birth = 78.2
- Increased longevity primarily due to better health care and living conditions (80-100 y.o. limit).
- Maximum documented human lifespan = 122

Today-13% of US population!
2030-20% of US population!
“Give it to me straight, Doc. How many more golden years would you say I have staring me in the face?”
Physiology of Aging

1) What is Aging?

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

3) Organ System “Functional” Reserve
WHAT IS AGING?
Before Friendship 7
In 1962
Before STS-95
In 1998
WHAT IS AGING?

A Gordian Knot 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

“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”

Early concept-body is a machine
Theories of Aging Mechanisms

“Neuroendocrine” Theory
- Variant of “Wear and Tear” theory
- Lower levels of hormones are produced over time
- Lower hormone levels result in alteration of normal physiological function with reduced tolerance to physiological stresses

Early concept-body is a machine
Theories of Aging Mechanisms

“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

- Genes involved in aging
- Extrinsic factors involved in aging
Theories of Aging Mechanisms

“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
- Aging is an outcome of evolutionary selection
WHAT IS AGING?

Multiple Theories attest that aging is:

✓ Integrative and complex process that affects essentially all body tissues
✓ Universal nature of aging thus implying that aging mechanisms are encoded in the genome (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 “un-tie” the Gordian Knot of multiple 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

“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”
- Explanation for “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

Human Evidence for “Telomere Theory of Aging”

- Shorter telomere length with advancing age in humans
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
WHAT IS THE OUTCOME of PRIMARY AGING?
(from the Cellular Perspective…)

1) Cell Death (apoptosis)
2) Senescence
WHAT IS THE OUTCOME of PRIMARY AGING?
(from the Cellular Perspective…)

Senescence is defined as a barrier that limits the replicative potential of cells.

Quiescent cells= temporarily out of cycle

Senescent cells= permanently out of 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!

• Resistant to apoptosis
WHY SENESCENCE?
Telomeres and Antagonistic Pleiotropy

• Senescence is anti-tumorogenic in youth, thus enhancing reproduction
• Cancer results from failure of senescence process
• Senescent cells have deleterious effects as they accumulate with age

Senescence prevents cells with damaged/defective DNA from further replication
Theories of Primary Aging

“Telomere Theory of Aging”

-increased numbers of senescent cells over time
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

![Diagram of mitochondrial electron transport chain and reactive oxygen species (ROS)]
Telomeres as Mechanisms of Aging

• Telomere attrition rate slowed by gender and telomerase.
• Telomere attrition rate increased by ROS.

TRF1 + TRF2 = telomere binding proteins
ROS + Telomeres as Mechanisms of Aging

PROBLEMS with “ROS/mitochondrial theory” and primary aging
- Few tissues reach Hayflick limit
- Alteration 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>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
WHAT IS SECONDARY AGING?

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 do these processes have in common?
ROS!
Mechanisms of Secondary Aging

- Likely that ROS play an important role in secondary aging
Mechanisms of Secondary Aging

- Exogenous and endogenous sources of increased ROS may contribute to secondary aging.
- High levels of ROS may mediate age-related disease processes of “secondary aging” by accelerating telomere attrition and thus premature cellular senescence.
Primary and Secondary Aging are closely interrelated.
Integrative Physiology of Aging
(from the Whole Animal Perspective…)

Involves both primary and secondary aging
Can Aging Be Altered?

Mechanisms of aging are tractable!
• Caloric restriction extends lifespan

Diagram:
- Feeding:
  - Increase in plasma insulin and IGF-1
  - Decrease in glucagon
  - Inhibition of autophagy
  - Decreased degradation (and increased synthesis) of protein, membranes and organelles
  - Loss of control of autophagy functioning
  - Reduced degradation of altered membranes and organelles
  - 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
  - Increased degradation of altered membranes and organelles
  - Reduction in 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 Altered?

Mechanisms of aging are tractable BUT

- Alteration of endogenous ROS defenses does not alter lifespan unless physiological stress added!
- In humans, exogenous anti-oxidants have done little or nothing to alter lifespan or promote “health”
Can Aging Be Altered?

Mechanisms of aging are tractable!

• Manipulation of Sirtuin proteins (deacetylates histones) extends lifespan in lower organisms and in overfed mice (not in “normal mice”)

Integration of the various findings to show the pathways by which caloric restriction and resveratrol enhance lifespan via stimulation of sirtuins. Cox-1, cyclooxygenase-1; IGF-1, insulin-like growth factor-1; NcoR, nuclear receptor co-repressor; SMRT, silencing mediator of retinoid and thyroid hormone receptors; FOXO, forkhead/winged helix box gene, group O; SOD, superoxide dismutase; PPAR, peroxisome proliferator-activated receptor.
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  Rapa Female
Res Lo Male  Res Hi Male  Rapa Male
Can Aging Be Pharmacologically Altered?
Mechanisms of aging are tractable!
- Extension of lifespan by pharmacological means is possible.
Autophagy (cellular self-eating)

- A catabolic mechanism whereby cells degrade protein for metabolic needs and simultaneously eliminate damaged or unnecessary cell constituents.

- Autophagy is suppressed by feeding and stimulated by fasting.

- Genetic studies show that autophagy-related genes are required for lifespan extension in various long-lived mutant nematodes and promote survival in worms and flies exposed to prolonged starvation.

These data implicate autophagy in the aging process.
Autophagy and Aging

✧ Inefficient removal (autophagy) may contribute to aging by failing to clear non-functional cell organelles generated by ROS
✧ General decline in “housekeeping” mechanisms may be critical in the progression of aging

✧ What was considered “aging” today may be reclassified as “disease” tomorrow.
SUMMARY: Primary and Secondary Aging

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

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

3) Aging CAN be pharmacologically manipulated
   - rapamycin
AGE-RELATED CHANGES OF PHYSIOLOGICAL FUNCTION: General Aspects
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

Decline of organ system functional reserve with age: clinically significant symptomatology occurs when “critical threshold” is reached.
Decline of organ system functional reserve with age recapitulates telomere attrition.
Physiological Systems: Effects of Age
What can be done to reduce the rate of decline of "Functional Organ Reserve" with aging?

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

- Incidence of clinically significant symptomatology increases as “critical threshold” is approached.
- Drugs or infections can act as “provocative stressors” and shift an organ system below the “critical threshold so that clinical signs and symptoms develop.
EXAMPLES OF AGE-RELATED CHANGES OF PHYSIOLOGICAL FUNCTION
Clinical Example: CV-Baroreflex

- Baroreceptor Reflex Sensitivity Decreases with Age
  - reduced responses to blood pressure changes
Baroreceptor challenge for an astronaut.....getting spun in a human centrifuge!
Baroreceptor challenge for a Geri-naut….getting up from a chair!
Clinical Example: CV-Baroreflex

HYPOTENSIVE STRESS
"There has been a sharp increase in his cantankerousness."
Clinical Example: Respiratory System

- Surface Area Decreases
- Compliance Increases
- Surface Area Decreases
Clinical Example: Respiratory System
"It's remarkable, Mr. Volmer. You have the clothes of a man half your age!"
Cerebrocortical System (Cognitive Function)

- Decline in Cognitive Function with age:
  - Prevalence of moderate to severe dementia
    - 1 to 2% at ages 65 to 70 years
    - 2 to 5% at ages 70 to 75 years
    - 11 to 20% at ages 80 to 85 years
    - 39 to 60% at ages 90 to 95 years
    - 75 to 85% at ages >100 years

- 40% of 80 year olds show evidence of cognitive decline (executive function) on standardized tests (CLOX) that may be missed on “memory-based” tests (MMSE)
Physiology of Aging

1) Theories/Mechanisms of Primary Aging
   Telomere attrition
   ROS

2) Theories/Mechanisms of Secondary Aging
   ROS leading to premature senescence

3) Organ System “Functional” Reserve
   Decline in reserve with age leads to reduced tolerance of stresses