Physiology of Aging

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The Geriatric (>65yo) Population

- Ancient Greece-life expectancy at birth = 20
- 1776-life expectancy at birth = 23
- 1900-life expectancy at birth = 47
- 2009-life expectancy at birth = 77.9
- Increased longevity primarily due to better health care and living conditions (80-100 y.o. limit).
- Maximum documented human = 122

13% 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) Theories/Mechanisms of Primary Aging
   Telomere attrition
   ROS

2) Theories/Mechanisms of Secondary Aging
   ROS

3) Organ System “Functional” Reserve
WHAT IS AGING?
WHAT IS AGING?

A Gordian Knot of Mechanisms
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”
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
- Sequelae are reduced tolerance to physiological stresses
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 DNA miscopying and failure of normal physiological function with reduced tolerance to physiological stresses

Genes 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
- Aging is an outcome of evolutionary selection

- EXAMPLE-gen genes for high testosterone levels good in young males but increase BPH risk over time
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

◆ Poorly understood biological phenomenon that reduces tolerance to physiological stresses
WHAT IS AGING?

Can we “un-tie” the Gordian Knot?
Primary Aging

Primary aging is defined as the universal changes occurring with age that are not caused by disease or environmental influences.
Secondary Aging

Secondary aging is defined as changes involving disease processes and environmental influences, such as smoking and exposure to ultraviolet radiation.
WHAT IS PRIMARY AGING?
(from the Cellular Perspective...)

Aging = Senescence

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

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What’s the clock?
Theories of 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 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 reach 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 Aging

“Telomere Theory of Aging”
- Germ/Stem cells have telomere length preserved by telomerase
- Somatic cells normally lack telomerase thus telomeres shorten with replication
- Syndromes of premature aging show accelerated telomere shortening with replication
Theories of Aging

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

- Shorter telomere length with advancing age in humans
Theories of Aging

Telomeres and Gender

- At birth, every individual has telomeres with an average length of 12 kb, at this stage there is no significant gender difference.

- Over time, telomeres shorten.

- Over time, telomeres in males shorten faster than in females.

- Men lose 67 base pairs per year, but women only 62. Therefore, a 50-year-old woman still has the same number of telomere base pairs as a 43-year-old man.
Theories of Aging

“Telomere Theory of Aging”

-increased numbers of senescent cells over time
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 SENESCE?
**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.

No senescence or apoptosis.
Telomeres as Mechanisms of Aging

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

TRF1 + TRF2 = telomere binding proteins
Theories of 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 Aging

“Free-Radical” Theory of Aging
- ROS can be generated by mitochondrial dysfunction and other endogenous sources
Theories of Aging

“Mitochondrial Theory of Aging”
- Variant of “Free Radical” theory
- Mitochondria function to generate ATP by transfer of electrons through the electron transport system (ETS).
- ROS can be formed by ETS resulting in mitochondrial DNA (mtDNA) damage
- Over time, ROS generation leads to progressive oxidative damage to mtDNA
- Damaged mtDNA results impaired ATP generation and cellular dysfunction
ROS + Telomeres as Mechanisms of Aging

PROBLEM with “ROS/mitochondrial theory” and primary aging

- Alteration of antioxidant defenses does not extend lifespan in aging models, but does improve tolerance to physiological stresses

**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>
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.
Can Aging Be Altered?

Mechanisms of aging are tractable!

• Caloric restriction extends lifespan
• Manipulation of Sirtuin proteins (deacetylates histones) extends lifespan
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”
SUMMARY: Primary and Secondary Aging

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

2) Secondary Aging
   - premature cellular senescence
   - ROS
Integrative Physiology of Aging
(from the Whole Animal Perspective…)

Involves both primary and secondary aging

Senescence is defined as the progressive deterioration during the adult period of life that underlies an increasing vulnerability to stresses and a decreasing ability of the organism to survive.
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”
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 rate of decline of "Functional Organ Reserve" with aging?

Appropriate Life-style Choices can delay 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