Biology of Aging

Chapter 488 | Part 18: Biology of Aging

KEY CLINICAL POINTS

1. Aging is a nonadaptive, progressive process involving deterioration in structure and function, leading to increased disease susceptibility.
2. Evolutionary theories (Mutation Accumulation, Antagonistic Pleiotropy) suggest aging is not shaped by selection.
3. The Disposable Soma Theory posits a trade-off between germ cell maintenance and somatic repair.
4. The 'Grandmother Effect' explains extended postreproductive survival in some species, including humans.
5. Demographic shifts show that the population ≥ 65 years now exceeds children under age 5.
6. Many noncommunicable diseases (NCDs) exhibit an exponential increase in incidence with age.
7. The 'Hallmarks of Aging' are 12 interconnected biological processes that drive aging and related pathologies.
8. Inflammaging refers to low-grade activation of the innate immune system (elevated IL-6 and TNF-α).
9. Caloric Restriction (CR) reduces nutrient-mediated release of growth factors and improves health span.
10. Pharmacological agents like Resveratrol, Rapamycin, Spermidine, and Metformin target key pathways like mTOR and AMPK to delay aging.

DEFINITION & OVERVIEW

- **Definition:** Aging is a progressive process associated with deterioration in structure and function, leading to increased susceptibility to disease and mortality, and often associated with impaired reproductive capacity.
- **Nature of Aging:** Generally considered nonadaptive; not shaped by evolution or genetically programmed.
- **Mechanism of Initiation:** Likely involves stochastic, nonprogrammed changes in nuclear maintenance that influence gene expression and repair.
- **Components of Definition:**
  - **Biological Component:** Encapsulated by the 12 hallmarks of aging (Figure 4A).
  - **Phenotypic Component:** Includes many chronic diseases and syndromes of aging (Figure 4B).
  - **Statistical Component:** In most species, involves an exponential (Gompertz) increase in the risk of mortality with age (Figure 4C).

EPIDEMIOLOGY

- **Demographic Trends:**
  - Significant shift: Population ≥ 65 years now exceeds children < 5 years (Table 1, Figure 2).

– Impact: Increased demand for health services and aged care; increased risk of iatrogenic burdens like polypharmacy.

- **Disease Incidence:**
  – Noncommunicable diseases (NCDs) show an exponential increase with age (Figure 3).
  – Age-related disorders: Dementia, sarcopenia, frailty, and osteoporosis are very rare below the age of 50 years (Table 2).

ETIOLOGY & PATHOPHYSIOLOGY

- **Hallmarks of Aging:** 12 interconnected processes that erode various pillars of health.
  – **Inflammaging:** Low-grade activation of the innate immune system; elevated IL-6 and TNF-α; often associated with increased C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and a lower lymphocyte-to-neutrophil ratio.
  – Potential drivers: SASP, chronic infection with cytomegalovirus (CMV), obesity, leaky gut, and activation of the nuclear factor κB (NF-κB) pathway.
- **The 12 Hallmarks (Table 3):**

1. Genomic Instability
2. Telomere Attrition
3. Epigenetic Alterations
4. Loss of Proteostasis
5. Disabled Macroautophagy
6. Deregulated Nutrient Sensing
7. Mitochondrial Dysfunction
8. Cellular Senescence
9. Stem Cell Exhaustion
10. Altered Intracellular Communication
11. Chronic Inflammation
12. Dysbiosis

- **Detailed Mechanisms:**
  – **Genomic Instability:** Vulnerable to exogenous (radiation, chemicals) and endogenous (oxidative stress) factors → point mutations, translocations, and chromosomal anomalies. Mitochondrial DNA is especially susceptible due to proximity to free radicals or lack of histones/repair mechanisms.
  – **Telomere Attrition:** TTAGGG sequence; telomerase present in germ/tumor cells; other cells stop dividing when telomeres are truncated.
  – **Epigenetic Alterations:** Changes in DNA methylation, histone modification, chromatin remodeling, and noncoding RNAs → altered transcription of genes for inflammation, mitochondrial function, and autophagy.
  – **Loss of Proteostasis:** Impaired autophagy-lysosomal and ubiquitin-proteosome systems → accumulation of aggregates (lipofuscin, Lewy bodies, neurofibrillary tangles, amylin).
  – **Disabled Macroautophagy:** Reduced sequestration/digestion of proteins and organelles; decline in age.
  – **Deregulated Nutrient Sensing:** Impacted by CR; involves insulin/IGF-1, mTOR, AMPK, SIRT1, FGF21.
  – **Mitochondrial Dysfunction:** Increased electron leak, decreased ATP production (impaired complex IV), and mitochondrial DNA damage.
  – **Cellular Senescence:** Stopped division due to telomere shortening or INK4/ARF system.

– **Stem Cell Exhaustion:** Reduced numbers due to replicative senescence and telomere shortening.

– **Altered Intracellular Communication:** Changes in insulin/IGF-1, dopaminergic, sex hormones, GDF11, and renin-angiotensin system.

– **Dysbiosis:** Complex changes in the gut microbiome with age.

CLINICAL FEATURES

• **Frailty:** Multisystem aging syndrome; aging changes present in most tissues → multiple deficits and impaired function.

• **Multimorbidity:** Aging changes more advanced in several tissues (rare < 50 years).

• **Longevity Dividend:** Concept where an intervention that slows the aging process is likely to delay a wide range of age-related diseases/syndromes and increase "health span".

• **Clinical Syndromes:** Dementia, sarcopenia, frailty, and osteoporosis are primarily age-related; rare below age 50.

DIFFERENTIAL DIAGNOSIS

• **Aging vs Disease:**

– Distinction: Often based on quantitative differences in the expression of hallmarks (e.g., inflammation, mitochondrial function) and the specific tissues affected.

– Clinical Presentation: Differences are often based on quantitative artifacts; chronic disease can be viewed as aging predominant in a particular tissue.

INVESTIGATIONS & DIAGNOSIS

1. **Biomarker Identification:**

• Epigenetic modifications serve as emerging targets for identifying age-related changes.

2. **Differentiation from Disease:**

• Tissue Specificity: Determine if the pathology is localized (disease) or systemic (aging).

• Quantitative Analysis: Assess the degree of hallmark expression (e.g., inflammation levels) to distinguish between normal aging and specific disease states.

MANAGEMENT & TREATMENT

1. **Caloric Restriction (CR):**

• Mechanism: Reduces nutrient-mediated release of growth factors → slows aging and reduces risk for metabolic, cardiovascular, and oncologic conditions.

• Evidence: Validated in multiple species including rodents, fish, insects, and non-human primates.

2. **Pharmacologic Interventions:**

• **Resveratrol:** Polyphenol; impacts SIRT1 pathways; potential to improve mitochondrial function and reduce inflammation.

• **Rapamycin:** mTOR inhibitor; used as an immunosuppressant/chemotherapeutic; targets the mTOR pathway to delay aging.

• **Spermidine:** Polyamine; promotes autophagy via inhibition of histone acetylases; protects against neurodegeneration.

• **Metformin:** Biguanide; inhibits hepatic gluconeogenesis and activates AMPK → inhibits mTOR; reduces oxidative damage and inflammation.

KEY PEARLS & HIGH-YIELD POINTS

• **Aging is nonadaptive:** It is not a programmed response but a result of stochastic, nonprogrammed changes in nuclear maintenance.

• **Inflammaging:** A key clinical concept where low-grade inflammation (IL-6, TNF-α) serves as a driver for multiple age-related diseases.

• **Longevity Dividend:** The primary goal of geroscience is to improve "health span" by targeting the 12 hallmarks of aging.

• **Rapamycin vs. Metformin:** Rapamycin targets mTOR; Metformin activates AMPK → inhibits mTOR. Both are key pharmacological tools in aging research.