The Biology of Ageing: Pathological Mechanisms and Future Directions

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Abstract : Ageing is a universal and multifaceted biological process marked by progressive decline in physiological integrity, heightened susceptibility to chronic diseases, and ultimately, mortality. Despite decades of intensive research, no single theory has been able to fully capture the complexity of ageing. This review provides a critical evaluation of the major evolutionary, systemic, and molecular theories of ageing, with a particular emphasis on pathological perspectives. We explore how evolutionary trade-offs such as antagonistic pleiotropy and disposable soma theory contribute to age-related degeneration, while also examining the role of systemic dysregulation in neuroendocrine, immune, and metabolic systems. At the molecular level, we discuss the accumulation of DNA damage, mitochondrial dysfunction, epigenetic alterations, and proteostasis failure as key contributors to tissue ageing. Histopathological changes across major organ systems are examined in the context of emerging geropathology concepts. We propose that ageing is best understood as a dynamic interplay between evolutionary constraints, systemic failures, and cumulative cellular injury. Future research should prioritize the development of robust, pathology-based biomarkers of biological age, the integration of multi-omics data with histological findings, and the translational application of geroscience insights from animal models into clinically viable human interventions.

Key Words

Geropathology; Cellular Senescence; Oxidative Stress; DNA Damage; Caloric Restriction

Introduction

Ageing is defined as the time-related deterioration of physiological functions necessary for survival and reproduction.[1] Senescence refers to the progressive decline in tissue homeostasis after reproductive maturity, increasing susceptibility to mortality.[2] Although ageing is influenced by both genetic and environmental factors, its underlying mechanisms remain incompletely understood. Classical evolutionary views—from Medawar's mutation-accumulation concept to Williams' antagonistic pleiotropy and Kirkwood's disposable soma theory—regarded ageing as a by-product of natural selection rather than an adaptive trait.[1, 4] However, recent evidence shows that genetic and epigenetic pathways influence lifespan and that dietary or pharmacological interventions can modify ageing trajectories. [5] This article reviews ageing theories and their relevance to pathology, summarising histopathological manifestations and potential interventions while identifying key knowledge gaps. An integrative and translational approach that bridges basic biology with clinical applications will be essential to advance effective interventions and improve health span.

Evolutionary Theories of Ageing

- **Mutation Accumulation Theory**
- Proposed by Medawar (1952),[1] this theory suggests that deleterious mutations expressed late in life persist because natural selection weakly acts beyond reproductive age. Examples include Huntington's disease, which manifests post-reproduction. While it explains persistence of harmful alleles, it does not account for variability in ageing rates among species. Recent genomic studies support this theory by identifying genes under positive selection for reproductive success that may harbour deleterious late-life effects, illustrating how early-life fitness advantages can result in genetic burdens later in life. [6]
- **Disposable Soma Theory**
- Kirkwood (1977)[4] proposed that organisms allocate finite resources between reproduction and somatic maintenance. Post-reproductive somatic

decline results from evolutionary prioritisation of reproduction. This theory highlights trade-offs but lacks detail on molecular pathways.

- **Antagonistic Pleiotropy**
- Williams (1957) [3] suggested that certain genes enhance early-life fitness but exert harmful effects in later life. For example, high sex hormone activity enhances reproduction but increases risk of prostate cancer in older males. Molecular evidence supports the role of pleiotropic genes in ageing. [6]

Critical Perspective:
Evolutionary theories explain the persistence of ageing traits but do not elucidate proximate molecular mechanisms. Integration with molecular biology is necessary for a complete understanding.

Systemic Theories of Ageing

- **Neuroendocrine Theory**
  This theory attributes ageing to dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, reducing stress adaptation.[5] Age-related declines in growth hormone and sex steroids support this view, although similar patterns of ageing in species with simpler neuroendocrine systems suggest this mechanism may be secondary (Dilman, 1994).[7]
- **Immunologic Theory**
  Walford (1969) [8] proposed that deterioration of the immune system with age leads to increased infections, cancer, and autoimmunity. Contemporary evidence, including T-cell decline and chronic low-grade inflammation (inflammageing), supports this theory.[9]

Critical Perspective:
Systemic theories emphasise regulatory dysfunction but often blur causality. Systems biology tools, such as omics integration and network modelling, are needed to delineate interactions across systems.

Molecular and Cellular Theories

- **Error Catastrophe Theory**
  Orgel (1963) proposed that transcriptional and translational errors accumulate over time, impairing proteins. However, this theory lacks robust empirical support. [10]
- **Free Radical/Oxidative Stress Theory**
  Harman (1956)[11] hypothesised that reactive oxygen species (ROS) cause cumulative molecular damage. While oxidative stress correlates with ageing, antioxidant therapies show inconsistent results, and ROS also serve important signalling functions. [12]
- **DNA Damage and Repair**
  Accumulation of DNA damage and failure of repair mechanisms contribute to genomic instability. Progeroid syndromes such as Werner's syndrome highlight this role.[13]
- **Telomere Attrition Theory**
  Progressive telomere shortening induces cellular senescence, leading to growth arrest.[14] However, cross-species correlations between telomere length and lifespan are inconsistent.

Critical Perspective:
Molecular theories offer mechanistic clarity but often examine isolated pathways. Cellular senescence, driven by multiple ageing triggers, appears to be a central unifying process. Senescent cells exhibit β-galactosidase activity and secrete pro-inflammatory mediators, contributing to "inflammageing".[15] Multi-omics approaches are essential to understand these interactions.

Histopathological Changes

Recognisable microscopic and gross features of ageing include:

- Nervous system: neuronal loss, neurofibrillary tangles, lipofuscin accumulation.[16]
- Cardiovascular: myocardial fibrosis, arterial stiffening. [17]
- Respiratory: alveolar elasticity loss, pigment deposition.[18]
- Renal: glomerulosclerosis, tubular atrophy. [18]
- Endocrine: thyroid follicular involution, adrenal cortical thinning. [18]
- Musculoskeletal: osteoporotic bone, cartilage degeneration. [18]

Geropathology and Biomarkers

Geropathology uses lesion scoring to assess organ-specific biological age. Combining histological findings with epigenetic clocks and proteomics offers a promising approach to measure biological age beyond chronological age. [19,20]

Prevention and Interventions

- Lifestyle: regular physical activity and antioxidant-rich diets preserve tissue function.[15]
- Caloric Restriction: shown to extend lifespan and reduce pathology in animal models.[21]
- Pharmacology: drugs like metformin,[22] rapamycin, [23] and senolytics[24] show promise but require more long-term human studies.

Future Directions

- Develop validated histopathological biomarkers of ageing. [20]
- Integrate molecular, imaging, and pathology data for predictive modelling. [5]
- Conduct longitudinal trials of geroprotective agents. [22,23]
- Investigate long-lived species like the naked mole-rat for resistance mechanisms. [25]

Conclusions

Ageing is a multifactorial process involving evolutionary trade-offs, systemic dysregulation, and cumulative molecular damage. Pathological changes across organ systems provide quantifiable markers for research and clinical applications. Integrating geropathology with systems biology will be essential to transform basic research into clinical interventions aimed at extending healthspan.

Declarations

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Approval

Not applicable. This article is a review and does not involve any studies with human or animal participants.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions Details

VVM was involved in Conceptualisation, Design, Definition of intellectual content, Data acquisition Data analysis, Manuscript preparation, editing and review of the manuscript.

VMP was involved in Conceptualisation, Definition of intellectual content, Literature search, Data acquisition, Manuscript editing and review

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