Ageing: The Emerging Area of Bio-gerontology - A Review

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Received Date: 09-03-2022, Accepted Date: 25-03-2022, Published Date: 01-04-2022

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Abstract

Ageing is linked to a progressive loss of physical function and fitness, imperfect maintenance and repair systems. Many theories, such as evolutionary (mutations), telomere shortening, linked to a system (neuroendocrinologic, immunologic) appear to be the molecular and cellular hallmarks of ageing. The ultimate causes of ageing remain not yet elucidated, but they seem to be multifactorial. However, the consequences of ageing are better identified and leading to adapted gerodontologic therapies. Geroscience involves mostly all oral pathologies, focusing on endocrine and infectious disorders of periodontal diseases, involving the dental pulp and carious lesions, syndromes (e.g. trisomy 21 syndrome), salivary dysfunctions, burning mouth syndrome and tumor pathogenesis. With the increasing number of patients over 80+, gerodontology pave the way for a domain oriented toward therapeutic dentistry, leading to an extended lifespan. The future of ageing therapies involves selective elimination of senescent cells (SNSs), also known as senolysis, which prevents various age-related diseases. Most pathologies are implicated on the effects of ageing without exerting undesirable side effects.

Keywords

Ageing; Geroscience; Senescence; Telomeres Shortening; Geriatric Pathologies; Periodontitis; Caries; Oral Cancer; Dental Pulp; Salivary Glands; Senolysis
Introduction

People over 60 make up 12.3% of the global population and that number will rise to 16 - 22% by 2050. The world population is ageing and therefore, the needs for health care are increasing for the growing older population. The number of persons aged 80 years or over is projected to triple, from 143 million in 2019 to 426 million in 2050 (data from the United Nations) [1,2].

The phenotype of ageing is linked to a progressive loss of physical function and fitness, imperfect maintenance and repair systems. The Essential Lifespan (ELS) for a human being is 122 years [3-9]. Ageing is determined by biological, psychological and social factors. Three major questions arise from biological and epidemiological studies, 1) “when does ageing begins”, 2) “why ageing happens” and 3) “how ageing proceeds”. The biology of ageing implicates a series of answers, more or less clarified in modern biogerontology. These questions implies the following answers 1) ageing begins before birth, 2) ageing starts from birth up to the adult life and 3) ageing and senescence happens beyond the Essential Lifespan of a Species (ELS).

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Categories</th>
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<tbody>
<tr>
<td>1</td>
<td>Repair of nuclear and mitochondrial DNA</td>
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<tr>
<td>2</td>
<td>Repair and turnover of normal and damaged RNA and protein</td>
</tr>
<tr>
<td>3</td>
<td>Scavenging and removal of reactive oxygen and other free radical species</td>
</tr>
<tr>
<td>4</td>
<td>Removal of damaged membranes and organelles</td>
</tr>
<tr>
<td>5</td>
<td>Sensing and responding to intra- and extra-cellular stress</td>
</tr>
<tr>
<td>6</td>
<td>Detoxification of chemicals, drugs and nutritional metabolites</td>
</tr>
<tr>
<td>7</td>
<td>Innate and adaptive immune responses, including apoptosis</td>
</tr>
<tr>
<td>8</td>
<td>Wound healing, tissue regeneration and other higher order processes, such as thermal regulation, tissue regeneration, neuro-endocrine balance and chronic rhythms</td>
</tr>
</tbody>
</table>

Table 1: Major categories of maintenance and repair systems in biology [5].

Theories of ageing

The stochastic and developmental-genetic theories of ageing are not mutually exclusive. Increasing evidences suggest that cellular and organismic senescence prevent malignant transformation.

The theories of ageing in humans implies:

- Programmed and damaged theories, implicating three sub-categories
  1. Programmed longevity
  2. Endocrine theory
3. Immunological theory

This is leading to an increased vulnerability and therefore, to ageing and death

- Error theories

The biological theories include damages or errors, rate of living, cross-linking and free radicals. While most damages are repaired, some others accumulate, such as the DNA Polymerases and other repair mechanisms which cannot correct defects as fast as they are produced and deteriorations and malfunctions of cells.

<table>
<thead>
<tr>
<th>Biological Level/Theory</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Evolutionary</strong></td>
<td></td>
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<tr>
<td>Mutation accumulation*</td>
<td>Mutations that affect health at older ages are not selected against.</td>
</tr>
<tr>
<td>Disposable soma*</td>
<td>Somatic cells are maintained only to ensure continued reproductive success; after reproduction, soma becomes disposable.</td>
</tr>
<tr>
<td>Antagonistic pleiotropy*</td>
<td>Genes beneficial at younger age become deleterious at older ages.</td>
</tr>
<tr>
<td><strong>Molecular</strong></td>
<td></td>
</tr>
<tr>
<td>Gene regulation*</td>
<td>Ageing is caused by changes in the expression of genes regulating both development and ageing.</td>
</tr>
<tr>
<td>Codon restriction</td>
<td>Fidelity/accuracy of mRNA translation is impaired due to inability to decode codons in mRNA.</td>
</tr>
<tr>
<td>Error catastrophe</td>
<td>Decline in fidelity of gene expression with ageing results in increased fraction of abnormal proteins.</td>
</tr>
<tr>
<td>Somatic mutation</td>
<td>Molecular damage accumulates, primarily to DNA/genetic material.</td>
</tr>
<tr>
<td>Dysdifferentiation</td>
<td>Gradual accumulation of random molecular damage impairs regulation of gene expression.</td>
</tr>
<tr>
<td><strong>Cellular</strong></td>
<td></td>
</tr>
<tr>
<td>Cellular senescence-Telomere theory*</td>
<td>Phenotypes of ageing are caused by an increase in frequency of senescent cells. Senescence may result from telomere loss (replicative senescence) or cell stress (cellular senescence).</td>
</tr>
<tr>
<td>Free radical*</td>
<td>Oxidative metabolism produces highly reactive free radicals that subsequently damage lipids, protein and DNA.</td>
</tr>
<tr>
<td>Wear-and-tear</td>
<td>Accumulation of normal injury.</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Programmed cell death from genetic events or genome crisis.</td>
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</tbody>
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DOI: http://dx.doi.org/10.46889/JCMR.2022.3108
System

<table>
<thead>
<tr>
<th>Neuroendocrine*</th>
<th>Alterations in neuroendocrine control of homeostasis results in ageing-related physiological changes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunologic*</td>
<td>Decline of immune function with ageing results in decreased incidence of infectious diseases but increased incidence of autoimmunity.</td>
</tr>
<tr>
<td>Rate-of-living</td>
<td>Assumes a fixed amount of metabolic potential for every living organism (live fast, die young).</td>
</tr>
</tbody>
</table>

**Table 2**: Classification and brief description of main theories of ageing [10,11].

The ultimate causes of ageing remain unknown. The ageing process is multifactorial and complex. The human cells ability to divide is limited to approximately 50-times, after which they simply stop dividing (Hayflick limit theory of ageing). According to telomeres theory, they have been shown to shorten with each successive cell division [12,13].

**Ageing in-vitro: the telomeres length**

Hayflick reported three successive cellular phases. At the start, the primary culture was named "phase one". Phase two the time of "luxuriant growth". Then, cells reach phase three, named "senescence". The Hayflick limit correlates with the length of the telomeric region at the end of chromosomes. During the process of DNA replication of a chromosome, small segments of DNA within each telomere are lost. This is due to the uneven nature of DNA replication which are not replicated symmetrically. The telomeric region of DNA is simply a repeated code on the end region of linear eukaryotic chromosomes. The telomeres reach a critical length and the cell becomes senescent. It is the Hayflick limit.

Telomeres protect DNA every time a cell divides and the telomeres become shorter and they can no longer replicate. Most cells replicate 50 times before the telomeres become too short. Cancer cells activate telomerase. Some people had not shortening of telomeres (telomerase inhibitors), making the aging phenomenon more complicated.

Organismal ageing: Some of these variable results are attributable to the mosaicism of cell replication numbers at different body sites where cells were taken.

**Molecular and cellular hallmarks of ageing**

Based on Maintenance and Repair Systems (MARS), some of the main MARS are nuclear and mitochondrial DNA repair. They are anti-oxidative enzymes and free radical scavengers. Lopez-Otin, et al., propose a series of metabolic "hallmarks" of ageing in various organisms
Telomere shortening, due to telomerase add the telomere onto the chromosome attach cell division and inflammageing.

Biogerontological studies have repeatedly shown that numerous age-induced changes hormone levels and other proteins and enzymes are the sign of constant remodeling and adaptation for survival and health. Biologically beneficial effects by initially causing low level stress, are termed as hormetins. Hormetins are further categorized as physical (physical exercise, heat and radiation); biological and nutritional (micronutrients, phytochemicals in natural and synthetic food sources); psychological or mental (increased brain activity through cognitive games and challenges, including solving puzzles, social engagement, focused attention and meditation).

Loss of (stem) cells via telomere attrition provides strong selection for abnormal and malignant cells, a process facilitated by the genome instability and aneuploidy triggered by dysfunctional telomeres. The crucial role of telomeres in cell turnover and ageing is highlighted by patients with 50% of normal telomerase levels resulting from a mutation in one of the telomerase genes. These combined approaches will allow a detailed understanding of the mechanisms underlying the hallmarks of ageing and will facilitate future interventions for improving human health span and longevity [17].

Geriatric pathologies: including “pathophysiology of periodontitis”

Ageing phenomena include decreases in memory, muscle strength and mass, manual dexterity, cardiac output, hearing loss and cataracts, loss of hairs, increase body fat, risk of cancer, diabetes, infections, chronic obstructive osteoarthritis, osteoporosis and decrease in high due to decreased intervertebral space. They include frailty, urinary incontinence, falls, delirium and pressure ulcers.

Accumulating evidences suggest that ageing is implicated in the impairment of periodontal homeostasis and the pathophysiology of periodontitis. Indeed, persistent bacteria-derived lipopolysaccharide stimulation influences cellular senescence in osteocytes, driving alveolar bone resorption. Lastly, senotherapy directly target the mechanisms of ageing at the periodontal level ageing when still at “subclinical” stages toward ageing-related diseases.

Ageing of Senescent Patients - Dental and Oral Therapies

The elderly is including caries and periodontitis, tooth loss, erythematous lesions and/or angular cheilitis. Local and systemic effects/implications may have an impact on the oral health. The ageing population is growing and older adults have more oral problems than did analysis of previously studied cohorts of patients [18-22].
**Ageing and oral mucosa (cancers)**

With aging, the oral epithelium becomes thinner, with a reduced elasticity. Thinning and decreased keratinization of the gingival epithelium have been reported. Gingival recession occurs, with in parallel a decrease of cells producing collagen fibers, vascularization and a decrease in alveolar bone density [23].

Epithelial cells tended to become larger and flatter with age according three main age groups 1) from 0 to 20 years, 2) adult life (21-50 years) and 3) the ageing group (50-90 years). Oral epithelial cells display decreased cell density, decreased mitotic activity, a slowdown in tissue regeneration and healing rate. A progressive atrophy of the oral mucosa is detected in the epithelium, characterized by less prominent epithelial ridges, epithelial atrophy, reduction of cell density and mitotic activity [23]. Loss of elastin and adipose tissue in the submucosa, reduction in the filiform papillae, increase of fibrous connective tissue, degenerative changes in the collagen, are slowing tissue regeneration [24].

The dorsum of the tongue displays a deficit of iron and B-complex vitamins. In the ventral zone of the tongue, the development of sublingual varicosities increases.

A reduction of Langerhans Cells (LC) density was found in human gingival epithelium. LC appeared with long and branched cytoplasmic processes. In older patients, the LC network was deteriorated and the reduction of the network was age-related.

**Precancerous lesions**

Leukoplakia is considered as precancerous condition. Most of the oral carcinomas are squamous cell carcinomas and the common sites observed are lower lip, tongue, gingivae and floor of the mouth. Oral Sub-Mucous Fibrosis (OSMF) is a chronic, insidious, disabling disease involving oral mucosa, the oropharynx and rarely the larynx.

Potential Malignant Lesions (PML) and diets low in fruits and vegetables increase the number of malignant cancers. The Human Papillomavirus (HPV) immunosuppression, is also implicated in this types of cancer.

**Enamel senescence**

Post-eruptive maturation is occurring, which leads to greater mineral contents over time. In older individuals, cracks are often observed during clinical examination of the enamel surface [21]. Post-eruptive maturation content is seen on the outer enamel surface.
Dentin aging

The teeth look more yellow than white. Secondary dentin is produced continuously. Tubules become sclerotic (dental sclerosis). Calcification of the pulp with root canals narrowing increase in frequency, leading to decreased sensitivity to stimuli (cold and sweet foods). Tertiary dentin is deposited, including reactionary and reparative dentines.

Senescence of cementum

There is no known mechanism regulating the thickening of cementum with age. Correlation between the age and incremental lines (incremental lines of Salter). Dark layers stand for 1 year of age each and do not exceed 2.5 years (hypermineralization, followed by layers of hypomineralization). The reliability of counting lines in root cement seems to be questionable.

Senescence of the dental pulp

Human DPSCs differentiate and display self-renewal capability. They differentiate into adipocytes and neural-like cells [25,26]. CD 44, integrin β1, VCAM-1, α-SM actin, collagen -1, collagen III, osteocalcin, osteonectin, osteopontin are also identified. Alkaline Phosphatase and FGF-2 are expressed by pulp cells. Osteocalcin expression is reduced in aged human dental pulp [27].

When the cell density of a 70-year-old patient is compared to that in a 20-year-old individual, the cell number of old individuals is nearly half that of younger individuals. Increased diffuse mineralization is observed in the pulp root (dystrophic calcification). Tertiary dentin is deposited under pathologic stimuli. The pH of lysosomal β-galactosidase is about 4, whereas that of SA-β-gal in lysosomes is about 6.

In older individuals, pulp stones narrow the pulp chamber space and diffuse calcification is found in radicular pulp. Schwann cells form a network at the dentin-pulp interface expressing of S100, SOX10, while these markers are expressed in non-myelinating Schwann cells from young adult teeth. These markers decline significantly in old adult teeth. Myelinated axons are mainly present in the Raschkow plexus and within nerve bundles in the dental pulp, but their density is reduced in old versus young teeth [29]. To summarize, the pulp chamber volume is reduced [30]. There is a decreased vascular supply and modifications of the stem cells niches.
Pulp side population

Side Population (SP) cells constitute 0.40% in young rats and 0.11% in aged rats, whilst p16 mRNA expression indicated an increase in cell senescence [29]. Fibrosis and calcospherites are associated with parameters such as changes in telomere length, microarray and RT-PCT. Cell apoptosis, pulp stones and pulp calcification occur in various physiopathological conditions [30,31].

The key roles of TNAP are in the mineralization of hard tissue (providing free phosphate for the creation of hydroxyapatite crystals and hydrolysing pyrophosphate, an inhibitor of bone matrix formation. It's role is a key role in the metabolism of vitamin B6 and thus in the metabolism of neurotransmitter γ-Aminobutyric Acid (GABA). Therefore, the depletion or recessive mutation of TNAP leads to defects in both the mineralization of hard tissue and the development of the nervous system [32,33].

Salivary glands ageing

Three major salivary glands (parotid, submandibular and sub-ligual) produce most of the saliva in the oral cavity (92-95% of saliva). The minor salivary glands are found in almost any part of the mouth (except gingiva and anterior part of the palate). Their secretion is mainly mucous. In the dorsal surface of the tongue, Von Ebner glands are found open in the circumvallate papillae (involved in the production of serous fluid and taste perception). Ageing produces structural changes: the connective tissue and intralobular ducts are increased, together with a decrease of acinar tissue. Saliva becomes thicker. Medications like anti-hypertensives, antipsychotics, anxiolytics etc. lead to xerostomia and the absence of the protective influences of saliva in the oral cavity increases the predisposition to oral disease. There is a link between dry mouth (one fifth of the group of aged persons). Comorbidities, such as diabetes, Alzheimer or Parkinson diseases are frequent, as well as general dehydration. Caries, cracked lips, fissured tongue and oral mucositis are also seen. These alterations impact heavy on the patient quality of life, taste, speaking and ingestion of food. Changes include a general thinning over time.

Figure 1: Young and aged teeth - therapies for age-related diseases [31].

Goldberg M | Volume 3, Issue 1 (2022) | JCMR-3(1)-052 | Review Article


DOI: http://dx.doi.org/10.46889/JCMR.2022.3108
The healing rate is lower. Geriatric patients develop oral cancer starting on the side of the tongue, floor of mouth or lips.

Benign salivary gland tumors include pleomorphic adenoma, Warthin’s tumor and myoepithelioma and a series of minor tumors. Pleomorphic and monomorphic adenomas, acini cell carcinoma, adenoid cystic carcinoma constitute the revised WHO histologic classification of salivary glands tumours (Table 3).

<table>
<thead>
<tr>
<th>1. Adenomas</th>
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<tr>
<th>2. Carcinomas</th>
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<tr>
<td>Acinic cell carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, polymorphous slow grade adenocarcinoma (terminal duct adenocarcinoma), epithelial-myoepithelial carcinoma, basal cell adenocarcinoma, sebaceous carcinoma, papillary cyst adenocarcinoma, mucinous adenocarcinoma, oncocytic carcinoma, salivary duct carcinoma, adenocarcinoma, malignant myoepithelioma (myo epithelial carcinoma), carcinoma in pleomorphic adenoma (malignant mixed tumour), squamous cell carcinoma, small cell carcinoma, undifferentiated carcinoma and other carcinomas.</td>
</tr>
</tbody>
</table>

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<tr>
<th>3. Non-epithelial tumors</th>
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<tr>
<th>4. Malignant lymphomas</th>
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<th>5. Secondary tumors</th>
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<tr>
<th>6. Unclassified tumors</th>
</tr>
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</table>

| 7. Tumor-like lesions, sial adenosis, oncocytosis, necrotizing sialometaplasia (salivary gland infarction), benign lymphoepithelial lesion, salivary gland cysts, chronic sclerosing sialadenitis of submandibular gland cystic lymphoid hyperplasia in AIDS. |

**Table 3:** Classification of salivary glands tumors [35,36].
**The Burning Mouth Syndrome (BMS)**

Burning mouth syndrome is characterized by a burning sensation in the tongue or other oral sites, usually in the absence of clinical findings, (over 50 years of age), with a female to man ratio as much as 33 to 1 [37]. In most studies published to date, oral burning appears to be most prevalent in postmenopausal women (Table 3) [38].

| Deficiency of iron, folic acid or various B vitamins (glossitis e.g. due to anemia), or zinc. |
| Neuropathy, e.g. following damage to the chorda tympani nerve, hypothyroidism, medications ("scalded mouth syndrome", unrelated to BMS), protease inhibitors and angiotensin-converting-enzyme inhibitors. True xerostomia, caused by hypo salivation (e.g. Sjögren's syndrome), parafunctional activity, nocturnal bruxism or a tongue thrusting habit, restriction of the tongue by poorly constructed dentures. Geographic tongue. Oral candidiasis. herpetic infection (herpes simplex virus), fissured tongue, lichen planus, allergies and contact sensitivities to foods, metals and other substances, hiatal hernia, human immunodeficiency virus and multiple myeloma. |

**Table 4:** A list of causes of an oral burning sensation is given here.

In the 30 to 39 years old patients the prevalence was 0.6% and increased to 12.2% in the oldest age group. In individuals with BMS, the most prevalent site with burning sensations was the tongue (67.9%).

Understanding ageing allow us to better treat and prevent ageing-related degenerative diseases of incorrect senescence or failure to senesce and slow ageing itself, improving with age [7].

**Periodontitis and biological ageing**

Accelerated biological ageing is part of the geroscience approach [39]. Shortened telomeres are encountered in populations affected by severe periodontitis. Further advancements provide the chance to intercept ageing at a “subclinical” stage [40,41].

**Senolytics and Senotherapies**

Senolytics and senotherapies are potential therapies for Age-Related Disease (ARDs) [42-45]. Senolytics drugs prevent diseases, neuro psychiatric alterations, liver, kidney, musculo skeletal and radiations. Early pilot trials of senolytics drugs suggest that they decrease the number of senescent cells. Clinical trials are underway or beginning. They can be administered
intermittently. The Senescence-Associated Phenotype (SASP) includes inflammation, chemokines, TGFβ family members contributing to fibrosis, causing blood clotting, bioactive lipids that contribute to inflammation and tissue dysfunction (Fig. 2).

As the target of senolytics drugs is obviously senescent cells, they appear to delay, prevent or alleviate multiple age-related conditions and enhance health span and lifespan. Therefore, these agents could lead to interventions on humans, as treatment of age-related conditions, if clinical trials continue to demonstrate effectiveness and low toxicity. However, unless and until such clinical trials are completed, demonstrate safety, tolerability and effectiveness, senolytics drugs should not be prescribed or used for general populations. Up to now, they should only be administered in the course of carefully monitored clinical trials.

![Figure 2: Senolytics drugs: a class of drugs that selectively clear senescent cells.](image)

**Conclusion**

The phenomenon of ageing is not yet elucidated, but the consequences of ageing are better identified. Caries and periodontal diseases, infections due to bacterial invasion, early stages of cancer and related tumors, xerostomiae, burning mouth syndrome, are the targets of gerodontological practice.

Geriatric dentistry (or gerodontology) is an increasing field of dental practice, mostly associated with the growing group of patients over 80+ years. Elderly people lose manual dexterity as a result of arthritis, injury, stroke, aging itself and they are likely to have poor oral hygiene. Elderly people are unlikely to seek dental treatment but receive treatments that result in the utilization of approximately 25% of the national total of drugs prescription.
Medications such as antidepressants, antihistamines, antihypertensives and diuretics, cause a reduction in salivary flow. Elderly people may be deficient in salivary flow (an intrinsic cleansing mechanism), combined with diminished oral hygiene practices (extrinsic cleansing mechanism). This leads to heavy plaque accumulation on the tooth and denture surfaces, to caries and periodontal diseases. Elimination of senescent cells, known as senolysis, extends median lifespan and prevents or attenuates various features of aging and age-related diseases. In order to eliminate senescent cells senolytic drugs were developed. Clinical success is the next critical milestone for the development of treatments that can extend longevity to elderly people.

**Conflict of Interest**

The author declares no conflict of interest.

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