

## REVIEW

# Biology of ageing: principles, challenges and perspectives

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### Abstract

Living systems owe their survival and health to a series of complex biochemical pathways of maintenance and repair. These defense systems create the homeodynamic space of an individual, which is characterized by stress tolerance, molecular damage control and continuous remodeling. Ageing, age-related diseases and eventual death are the consequences of a progressive shrinkage of the homeodynamic space, due to the failure of maintenance and repair. Whereas longevity assurance genes do affect the essential lifespan of a species, there are no ageing-specific gerontogenes to cause ageing and to limit the lifespan of an individual. The challenge of preventing, managing or treating age-related chronic diseases and other health problems requires abandoning the traditional “one-target, one-shot” biomedical approach. Wholistic methods incorporating lifestyle-based hormetic interventions, including food, physical activity and mental engagement, appear to be potentially more successful in maintaining health and in extending healthspan and longevity.

**Keywords:** longevity, stress, homeostasis, homeodynamics, hormesis.

### Introduction

The scientific understanding of the evolutionary and mechanistic explanations for ageing, longevity and age-related diseases has come a long way during the last 50 years or so. Three major questions, when does ageing begins, why ageing happens, and how ageing proceeds, are more or less well resolved in modern biogerontology. Although some biodemographers would argue that human ageing begins even before birth [1], from birth or from the age of puberty [2], biogerontologists generally support the view that the physiologically impairing processes of ageing and senescence manifest primarily during the lifetime beyond the natural lifespan of a species, termed as the essential lifespan (ELS) [3–5]. This view has developed from the understanding of the evolutionary purpose of life in terms of reproduction and continuation of generations, and the biological understanding of the mechanisms of survival.

Survival of an organism is a dynamic tug between the occurrence of damage and the processes of maintenance and repair. These processes are also the main target of evolutionary investment, stability and selection [6–9]. Major categories of the maintenance and repair systems that comprise the longevity assurance processes during ELS are listed in Table 1.

**Table 1 – Major categories of maintenance and repair systems in biology**

1. Repair of nuclear and mitochondrial DNA.
2. Repair and turnover of normal and damaged RNA and protein.
3. Scavenging and removal of reactive oxygen and other free radical species.
4. Removal of damaged membranes and organelles.
5. Sensing and responding to intra- and extra-cellular stress.
6. Detoxification of chemicals, drugs and nutritional metabolites.
7. Innate and adaptive immune responses, including apoptosis.
8. Wound healing, tissue regeneration and other higher order processes, such as thermal regulation, tissue regeneration, neuro-endocrine balance, and chronic rhythms.

Another way of conceptualizing the ELS-assurance processes is the idea of homeodynamic space, which may also be considered as the “survival ability” or the “buffering capacity” of a biological system [10]. The term homeodynamics [11], meaning the same dynamics, is distinct from the classical term homeostasis, which ignores the reality of ever-dynamic living systems. Biological systems – cells, tissues, organs, organisms and populations – are never static. Therefore, the term homeodynamic space refers to the three main characteristics of the living systems that is the ability to respond to external and internal stress, the ability to control the levels of molecular damage, and the ability to constantly remodel and adapt in dynamic interactions.

At the species level, biological evolutionary processes have assured ELS, by optimizing for homeodynamic space, but the period of survival beyond ELS is characterized by the failure of homeodynamics [10]. At the biochemical level, the shrinkage of the homeodynamic space occurs primarily due to the stochastic occurrence and semi-stochastic accumulation of molecular damage, without any definitive programme behind it [4, 6, 12]. That is why the progression of ageing at the individual level is highly heterogeneous, with no two individuals ageing in the same way, and even within an individual, different organs, systems, tissues, cells, organelles and macromolecules undergo ageing and senescence at different rates and to different extent [4, 10, 13, 14].

### The challenge and perspectives

A major challenge for biogerontologists is to understand, define and modulate the highly individualistic and heterogeneous nature of ageing and of age-related diseases emerging because of the ageing process. Whether ageing is considered as a disease in itself or whether ageing is considered as an emergent phenomenon from life processes, which increases the chances of the onset of various diseases,

has serious implications with respect to interventional strategies [10, 14].

As discussed previously, “most of the biomedical research is so far dominated and supported by disease-directed thinking. Some biogerontologists have also succumbed to these pressures of disease-dominated world-view to the extent that they consider ageing as another disease. Although “ageing is a disease” kind of rhetoric may have some role to play in attracting the attention of big business and investors, it totally disregards the scientific history and understanding of biogerontology. Furthermore, a lack of interdisciplinary health discussion among scientists and other scholars has allowed the growth of numerous self-proclaimed anti-ageing specialists and longevity-gurus, generating a lot of confusion, false promises, muddled thinking, and impractical and even harmful interventions” [14].

When ageing is understood as an emergent phenomenon occurring progressively in each and every individual surviving beyond certain duration of life within the evolutionary framework, then ageing cannot be considered as a disease. Considering ageing as a disease that happens to everybody is an oxymoron. This viewpoint can transform our approach towards ageing interventions from the so-called anti-ageing treatments to abandoning an enemy-oriented rhetoric, such as the “war against aging”, “defeating aging”, and “conquering aging”, etc.

Optimal treatment and management of every disease, irrespective of age, is a social and moral imperative. Significant efforts and advances are being made in the management and treatment of all diseases, and these should and will continue. However, if we wish to intervene in the ageing process itself so that age-related diseases could be prevented or delayed, then that will require health-oriented and wholistic approaches. The traditional “one target, one shot” biomedical treatments, which have been highly successful against infectious and other diseases for which clear-cut causative agents could be identified, do not work successfully on age-related diseases. This is because the fundamental reason for the emergence of ageing and age-related diseases, including Alzheimer’s, Parkinson’s, sarcopenia, osteoporosis, cancer and others, is the imperfect processes of life beyond ELS.

Thus, biogerontological approaches towards intervention are influenced by the viewpoint as to whether one considers ageing as a disease or ageing as a process and a condition that increases the chances of onset of chronic diseases. Presently, there are four main streams of interventions towards prevention, treatment or management of ageing and age-related diseases: (1) wishful thinking, which often trivializes the complexity of biological ageing into an issue of intelligent redesigning and reverse- or forward-engineering of a machine; (2) piecemeal remedies, which are the most common and prevalent anti-ageing or anti-disease treatments with an aim to “fix what is broke”; (3) replenishing the loss or supplementation with one or more biochemicals; and (4) strengthening the homeodynamics based on the principles of hormesis.

Hormesis in ageing is defined as the life-supporting beneficial effects resulting from the cellular responses to single or multiple rounds of mild stress [15]. Moderate and repeated physical exercise is the best-documented

example of hormesis. Various other stressors that have been reported to modulate ageing and prolong longevity in cells and animals include heat shock, irradiation, heavy metals, pro-oxidants, acetaldehyde, alcohols, hypergravity, polyphenols, flavonoids, and short-term and long-term dietary restriction, including intermittent fasting [16, 17].

Within the field of hormetics, all such conditions that bring about biologically beneficial effects, by initially causing low-level damage that consequently stimulates various defense pathways, are termed as hormetins [15, 18, 19]. Hormetins are further categorized as: (1) physical hormetins, such as physical exercise, heat and radiation; (2) biological and nutritional hormetins, such as micro-nutrients, phytochemicals in spices and other natural and synthetic food sources, and fasting and calorie restriction; and (3) psychological or mental hormetins, such as increased brain activity through appropriate cognitive games and challenges, including solving puzzles, focused attention and meditation. However, at present, there are several issues regarding the dose, timing, frequency and specificity of various stresses that are yet to be resolved by proper research and careful testing [17, 20].

## ☐ Conclusions

Finally, biological research on life processes and lifestyle-related diseases has shown that the issues of ageing, quality of life and longevity need to be approached with wholistic health-oriented paradigms. Although there are some overlapping processes between ageing and age-related diseases [21], the traditional therapeutic approach of “one target at a time” often fails or has a limited effectiveness. The biological fact of inter-connectedness and trade-offs, and uncoupling of lifespan and healthspan must be incorporated in ageing research and interventions [22, 23]. Lifestyle-based and scientifically validated wholistic interventions, involving food consumption, physical activity, and social and mental engagement can maintain and strengthen homeodynamics and health.

## Conflict of interests

The author declares that there is no conflict of interests.

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