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REVIEW ARTICLE

Biogerontology: from here to where? The Lord Cohen Medal Lecture-2011

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Abstract Ageing is a progressive shrinkage of the homeodynamic space and, at the molecular level, it is associated with the stochastic occurrence and progressive accumulation of molecular damage. Imperfection of the maintenance and repair systems results in the failure of homeodynamics characterized by increased molecular heterogeneity, altered cellular functioning, reduced stress tolerance and reduced remodeling and adaptation, which lead to increased probability of diseases and eventual death. Although, several types of molecular damages have been shown to accumulate and increase molecular heterogeneity during ageing, its relevance and significance with respect to the physiology, survival and longevity remains to be determined. Such studies are essential for establishing biomarkers of health, frailty, remodeling and adaptation, and for developing effective methods for the prevention and reversion of age-related changes. A promising strategy for ageing intervention and modulation is that of strengthening the homeodynamics through repeated mild stress-induced hormesis by physical, biological and nutritional hormetins. Because a number of ethical, social, and personal implications emerge by the development and use of anti-ageing and life-extending technologies, biogerontologists should incorporate these elements while developing their research agenda in biogerontology.

Keywords Gerontogenes · Macromolecular damage · Stress · Homeostasis · Homeodynamics

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Introduction

Among the previous recipients of the Lord Cohen of Birkenhead Medal, awarded by the British Society for Research on Ageing (BSRA), Robin Holliday and Leonard Hayflick, have boldly stated that ageing was no longer an unsolved problem in biology (Hayflick 2007; Holliday 2006). This assertion underlines the fact that biological basis of ageing are well understood and a distinctive framework has been established, based on which general principles of ageing and longevity can be formulated, and those can be the basis for developing interventions towards achieving a healthy old age. These biological principles of ageing and longevity are summarized in Table 1.

Thus, ageing is an emergent, epigenetic and a meta-phenomenon, which is not controlled by a single mechanism. Although, individually no tissue, organ or system becomes functionally exhausted even in very old organisms, it is their combined interaction and interdependence that determines the survival of the whole. The evidence that genes have a limited

Table 1 Biological principles of ageing and longevity derived from biogerontological research

1. *Evolutionary principle:* Ageing is an emergent phenomenon observable primarily in conditions which allow survival of the organisms beyond the natural lifespan of a species, termed 'essential lifespan' (ELS), (Carnes 2011; Rattan 2000a, b; Rattan and Clark 2005).
2. *Non-genetic principle:* There is no fixed and rigid genetic programme, which determines the exact duration of survival of an organism, and there are no real gerontogenes whose sole function is to cause ageing and to determine precisely the lifespan of an organism (Rattan 1985; Rattan 1995; Rattan and Singh 2009).
3. *Differential principle:* The progression and rate of ageing is different in different species, organisms within a species, organs and tissues within an organism, cell types within a tissue, sub-cellular compartments within a cell type, and macromolecules within a cell.
4. *Molecular mechanistic principle*: Ageing is characterized by a stochastic occurrence, accumulation and heterogeneity of damage in macromolecules, leading to the shrinkage of the homeodynamic space and the failure of maintenance and repair pathways (Rattan 2006).

(about 25%) influence upon lifespan in human beings has mainly come from the studies performed on centenarians and their siblings, twins and long living families (Herskind et al. 1996). A combination of genes, milieu and chance determine the course and consequences of ageing and the duration of survival of an individual (Rattan 2007b).

Homeodynamic space and its shrinkage as the phenotype of ageing

All living systems have the intrinsic ability to respond, to counteract and to adapt to the external and internal sources of disturbance. The traditional conceptual model to describe this property is homeostasis, which has dominated biology, physiology and medicine since 1930s. However, advances made in our understanding of the processes of biological growth, development, maturation, reproduction, and finally, of ageing, senescence and death have led to the realization that homeostasis as an explanation is incomplete. The main reason for the incompleteness of the homeostasis model is its defining principle of "stability through constancy", which does not take into account the themes, such as cybernetics, control theory, catastrophe theory, chaos theory, information and interaction networks, which comprise and underline the modern biology of complexity (Rattan 2007a). Since 1990s, the term homeodynamics is being increasingly used to account for the fact that the internal milieu of complex biological systems is not permanently fixed, is not at equilibrium, and is a dynamic regulation and interaction among various levels of organization (Yates 1994).

Survival of an organism is a constant struggle between the occurrence of damage and the mechanisms of maintenance and repair. There are three major sources of damages within a cell: (1) reactive oxygen species (ROS) and free radicals (FR) formed due to external inducers of damage (for example ultra-violet rays), and as a consequence of cellular metabolism involving oxygen, metals and other metabolites; (2) nutritional components such as glucose and its metabolites, and their biochemical interactions with FR; and (3) spontaneous errors in biochemical processes, such as DNA duplication, transcription, post-transcriptional processing, translation, and post-translational modifications. Millions and millions of damaging events occur in cells constantly, but a wide range of molecular, cellular and physiological pathways of repair counteract them and assure survival. These maintenance, repair and defense systems range from multiple pathways of nuclear and mitochondrial DNA repair to FR-counteracting mechanisms, protein turnover and repair, detoxification mechanisms, and other processes including immune- and stress-responses. All these processes involve numerous genes whose products and their interactions give rise to a "homeodynamic space" or the "buffering capacity", which is the ultimate determinant of an individual's chance and ability to survive and maintain a healthy state (Holliday 2007; Rattan 2006).

An organism is born with certain extent of homeodynamic space, which undergoes expansion during growth, development and maturation, and reaches a level in accordance with the evolutionary life history and ELS of the species (Fig. 1). An effective homeodynamic space or buffering capacity has three major

characteristics: (1) stress response (Singh et al. 2007); (2) the ability for damage prevention, repair and removal (Holliday 2006); and (3) the ability for continuous remodeling and adaptation (Franceschi et al. 2000). However, there is a "vulnerability zone" around this protective homeodynamic space, the extent of which can vary among individuals depending on factors such as genetic polymorphism, prenatal exposures, and early growth and developmental conditions (Bocklandt et al. 2011; Tacutu et al. 2010). One way of conceptualizing ageing is the progressive shrinkage of the homeodynamic space during the period of survival beyond ELS (Fig. 2).

Molecular basis of ageing

The mechanistic theories of biological ageing have often focused on a single category of inducers of molecular damage as an explanation for possible mechanisms of ageing (Rattan 2006). For example, the free radical theory of ageing (FRTA), proposed in 1954, arose from a consideration of the ageing phenomenon from the premise that a single common biochemical process may be responsible for the ageing and death of all living beings (for an update, see (Harman 2006; Harman 2009)). There is abundant evidence to show that a variety of ROS and other FR are indeed involved in the occurrence of molecular damage, which can lead to structural and functional disorders, diseases and death. The chemistry and biochemistry of FR is very well worked out, and the cellular and organismic consequences are well documented (Sitte and von Zglinicki 2003).

However, the main criticisms raised against FRTA are with respect to its lack of incorporation of the essential and beneficial role of FR in the normal functioning and survival of biological systems (Gruber et al. 2008; Halliwell 2009; Howes 2006; Sanz and Stefanatos 2008). Additionally, FRTA presents FR as the universal cause of damage without taking into account the differences in the wide range of FR-counteracting mechanisms in different species (Barja 2008; Perez et al. 2009). Furthermore, a large body of data showing the contrary and/or lack of predictable and expected beneficial results of antioxidant and FR-scavenging therapies have restricted the FRTA to being only a partial explanation of some of the observed changes during ageing (Doonan et al. 2008; Gems and Doonan 2009; Gruber et al. 2008; Keaney and Gems 2003; Keany et al. 2004; Le Bourg 2005; Le Bourg and Fournier 2004; Pun et al. 2010). Studies performed on the naked mole-rats also question the role of oxidative damage in ageing, where higher levels of lipid peroxidation, protein carbonylation, and DNA oxidative damage are present even at a young age without having any obvious adverse effects (Perez et al. 2009).

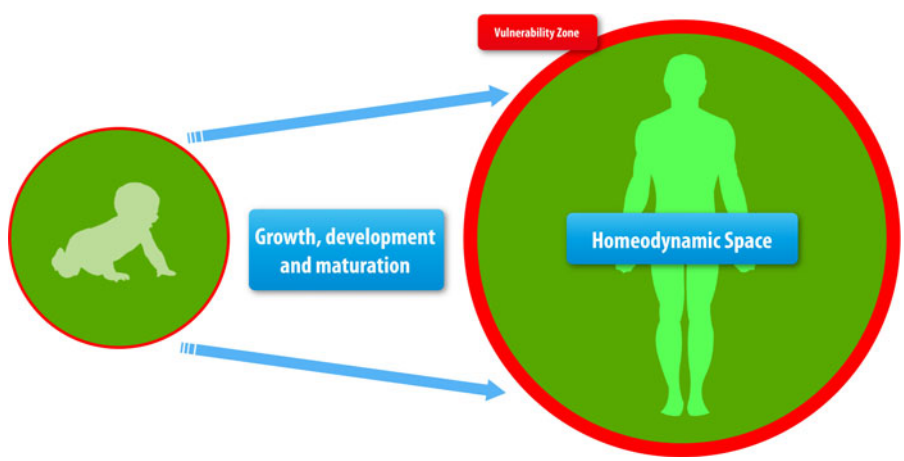

Fig. 1 Homeodynamic space is the ability of the living systems to respond and counteract stress, to repair and remove the damage, and to undergo constant remodelling and adaptation. Genetic polymorphism and epigenetic factors including prenatal exposures and lifestyle establish a personalised functional homeodynamic space during growth, development and maturation, within the evolutionary constraints of essential lifespan (ELS) of the species. Due to the imperfections of the maintenance and repair systems, there is always a small vulnerability zone even at a young age

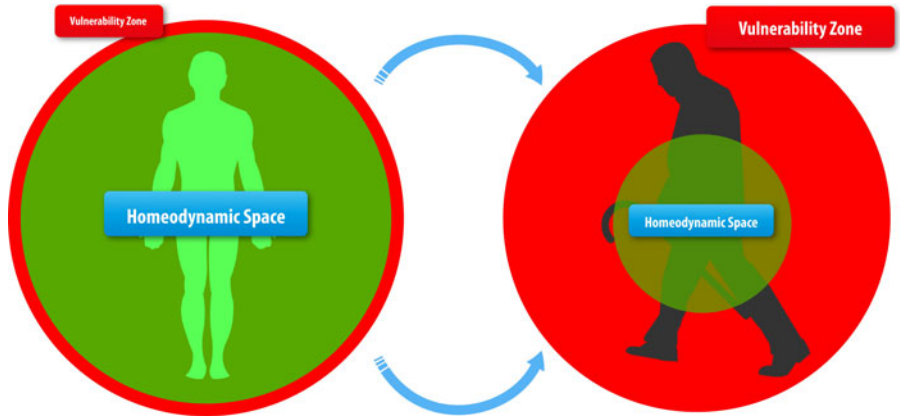

Fig. 2 Ageing is the progressive shrinkage of the homeodynamic space, resulting in an increase in the vulnerability zone and in the probability of emergence of age-related diseases and the eventual death

The other mechanistic theory of biological ageing, the so-called protein error theory of ageing (PETA), also known as the error catastrophe theory, has generated much controversy and debate (Holliday 1996; Rattan 1996; Rattan 2003; Rattan 2010). Since the spontaneous error frequency in protein translation is generally several orders of magnitude higher than that in DNA replication and RNA transcription, the role of protein errors and their feedback in biochemical pathways has been considered to be a crucial one with respect to ageing. Several attempts have been made to determine the accuracy of translation in cell-free extracts, and most of the studies show that there is an age-related increase in the mis-incorporation of nucleotides and amino acids (Holliday 1996; Rattan 1996; Rattan 2003). It has also been shown that there is an age-related accumulation of aberrant DNA polymerases and other components of the transcriptional and translational machinery (Fukuda et al. 1999; Holliday 1996; Rattan 1996; Rattan 2003; Srivastava and Busbee 2002; Srivastava et al. 2000). Further evidence in support of PETA comes from experiments which showed that an induction and increase in protein errors can accelerate ageing in human cells and bacteria (Holliday 1996; Nyström 2002a; Nyström 2002b; Rattan 1996; Rattan 2003). Similarly, an increase in the accuracy of protein synthesis can slow ageing and increase the lifespan in fungi (Holbrook and Menninger 2002; Silar and Picard 1994; Silar et al. 2000). Therefore, it is possible that errors in various components of protein synthetic machinery and in mitochondria do have long-term effects on cellular stability and survival (Hipkiss 2003; Holliday 2005; Kowald and Kirkwood 1993a; Kowald and Kirkwood 1993b). However, almost all these methods to determine the error levels have relied on indirect in vitro assays, and so far direct, realistic and accurate estimates of age-related changes in errors in cytoplasmic and mitochondrial proteins, and their biological relevance, have not been made. It will be necessary to combine several methods, such as electrophoresis, mass-spectrometry, protein–protein interactions and antibody-based detection of molecular heterogeneity to find out the extent of protein errors and their biological role in aging.

Both the FRTA and PETA provide molecular mechanisms for the occurrence of molecular damage. Furthermore, it has been realized that the nutritional components, specially the sugars and metal-based micronutrients, can induce, enhance and amplify the molecular damage either independently or in combination with other inducers of damage (Schaffer et al. 2011). Additionally, interest in the role of epigenetics as the molecular basis for age-related changes has resurged (Kahn and Fraga 2009).

Molecular heterogeneity and challenges for biogerontology

The biological consequences of increased levels of molecular damage can be wide ranging, including altered gene expression, genomic instability, mutations, loss of cell division potential, cell death, impaired intercellular communication, tissue disorganization, organ dysfunctions, and increased vulnerability to stress and other sources of disturbance. However, a common mechanistic basis for all these consequences is the increased molecular

heterogeneity. Since there is an extremely low probability that any two molecules become damaged in exactly the same way and to the same extent, an increase in molecular heterogeneity is inevitable. For example, if there are a thousand protein molecules freshly translated from a newly transcribed mRNA, and all these molecules are equally prone to post-translational stochastic damage as a function of their dwell time, very soon molecular heterogeneity will emerge within the molecular population. Furthermore, the nature, site and extent of damages will give rise to a population of that specific protein with alterations in structure and function ranging from being fully active to totally inactive molecules.

Among the thousands of types of proteins in a cell, some proteins may become preferentially damaged in a particular context. For example, it has been reported that among 1,000–2,000 proteins inside the mitochondria, aconitase is detected as being preferentially oxidatively damaged (Das et al. 2001; Yan et al. 1997). Some other proteins known to be more prone to oxidation include Hsp70, protein elongation factors, glutamine synthetase, glutamate synthetase, vimentin and pyruvate kinase (Ahmed et al. 2010; Kueper et al. 2007; Nyström 2002b; Stadtman and Levine 2003). The resulting increase in molecular heterogeneity and dysfunctionality has the following two major consequences:

(1) *Interrupted networks* Since biological macromolecules generally work in scale free networks with some proteins having a large number of interacting partners and the others having a few partners (Barabasi and Bonabeau 2003; Barabasi and Oltvai 2004), increased molecular heterogeneity is bound to lead to differential network perturbations and interruptions. Such interruptions may first happen at the weak links followed by disorganization, congestion and collapse of strong links and high degree central hubs (Budovsky et al. 2007; Csermely 2006; Szalay et al. 2007; Tacutu et al. 2010). Some of the major consequences of interrupted networks will include inhibition of signaling cascade and transcription factor-regulated gene expression, dysregulation of feedback control leading to metabolic instability, and increased sensitivity to stress and other damaging agents (Rattan 2008b).

(2) *Illegitimate networks* Occurrence of damage in macromolecules often leads to their altered structure, function and stability, such as altered folding, mistargetting, and altered epitope exposure. This can result in the formation of novel interactions, hubs and network structures (Budovsky et al. 2007; Szalay et al. 2007; Tacutu et al. 2010), which will bring about new biological phenotypes and altered hierarchy of various mediators of the network, for example the mediator ranking in the immune system (Tieri et al. 2005). Illegitimate networks can also lead to the activation, translocation and binding of transcription factors and other responsive elements resulting in the unwarranted gene expression, which was otherwise kept under strict regulation.

One of the challenges for biogerontologists is to design experiments and to develop analytical methods for determining the consequences of interrupted and illegitimate networks. For further progress in biogerontology, it is extremely important to: (i) determine the relevance and significance of different types and levels of molecular damage in physiological terms; and (ii) establish the profiles of young versus old, and healthy versus unhealthy molecular networks. Such studies are essential with respect to establishing biomarkers of health, frailty, remodeling and adaptation; and have wide ranging implications in the prevention and reversion of age-related changes.

Anti-ageing, healthy ageing and hormesis

According to the principles of ageing and longevity described above, occurrence of ageing in the period beyond ELS and the onset of one or more diseases before eventual death, appear to be the evolutionary sequence of events. This viewpoint makes modulation of ageing by prevention very much different from the treatment of a specific disease (Carnes 2011; Holliday and Rattan 2010). The scientific and rational interventional strategies aim to achieve "healthy ageing" by strengthening the homeodynamics, which has the potential to slow down the rate of ageing and prevent or delay the physiological decline (Rattan 2005).

A critical component of the homeodynamic space is the so-called stress response (SR). In this context, the term "stress" is defined as a signal generated by any physical, chemical or biological factor (stressor), which in a living system initiates a series of events in order to counteract, adapt and survive. The consequences of SR can be both harmful and beneficial depending both on the intensity, duration and frequency of the stress, and on the price paid in terms of energy utilisation and other metabolic disturbances. But the most important aspect of SR is that it is not monotonic with respect to the dose of the stressor, rather it is almost always characterized by a nonlinear biphasic relationship. Several meta-analyses performed on a large number of papers published in the fields of toxicology, pharmacology, medicine, and radiation biology have led to the conclusion that the most fundamental shape of the dose response is neither threshold nor linear, but is U- or inverted U-shaped, depending on the endpoint being measured (Calabrese 2008; Calabrese et al. 2007). This phenomenon of biphasic dose response was termed as hormesis (Southam and Ehrlich 1943). The terminology for hormesis has been further refined to specify the nature of the hormetic responses, such as physiological hormesis, pre-conditioning hormesis, and post-exposure conditioning hormesis (Calabrese et al. 2007).

Hormesis in ageing is defined as the life supporting beneficial effects resulting from the cellular responses to single or multiple rounds of mild stress (Rattan 2004; Rattan 2008a). Various mild stresses that have been reported to delay ageing and prolong longevity in cells and animals include thermal shock, irradiation, heavy metals, pro-oxidants, electromagnetic field, hypergravity, exercise and food restriction (Le Bourg and Rattan 2008; Rattan and Demirovic 2009; Rattan and Demirovic 2010a). Hormesis is also an explanation for the health beneficial effects of various foods and their components, including spices, flavanoids and polyphenols (Demirovic and Rattan 2011; Hayes 2007; Hayes 2010; Lima et al. 2011; Wiegant et al. 2009).

Various intracellular pathways of SR can be used as the screening platform for discovering, testing and monitoring the effects of hormesis-inducing conditions and compounds, termed hormetins (Rattan 2008a; Rattan and Demirovic 2010b). Such hormetins may be categorized as: (1) physical hormetins, such as exercise, heat and radiation; (2) biological and nutritional hormetins, such as microbial exposure, micronutrients, spices and other sources; and (3) psychological hormetins, such as mental challenge and focused attention or meditation. Understanding the hormetic and interactive mode of action of natural and processed foods is a challenging field of research, and has great potential in developing nutritional and other life style modifications for ageing intervention and therapies. For example, it may be possible to develop multi-hormetin formulations whose mode of action is through specific SR pathways resulting in the hormetically strengthened homeodynamic space.

Incorporating psycho-social realities of ageing in biogerontology

As a biomedical issue, the biological process of ageing underlies all major human diseases. Although, the optimal treatment of each and every disease, irrespective of age, is a social and moral necessity, preventing the onset of age-related diseases by intervening in the basic process of ageing is the best solution for improving the quality of human life in old age (Farrelly 2010; Rattan 2005). However, the personal and professional attitudes towards ageing interventions and life extension vary widely (Blagosklonny 2009; Underwood et al. 2009), and a number of ethical, social, and personal implications emerge by the development and use of anti-ageing and life-extending technologies (Partridge et al. 2009; Seppet et al. 2011; Wilson 2009). For example, it has been suggested that the realities of the social, political and economic constraints make it necessary to prioritize research areas in accordance with the proximate and distant needs of the elderly (Olshansky et al. 2011). However, others have argued against the user-led design strand of argument concerning older people as experts on their own ageing (Faragher 2009). Biogerontologists must become aware of these psycho-social issues and elements, and incorporate them into their research agenda. This will help to establish the future direction for biogerontology in "shifting the existing reference point of the medical sciences to one that is shaped by the findings of evolutionary biology and biodemography" (Farrelly 2010).

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