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EDITORIAL

Seven knowledge gaps in modern biogerontology

Suresh I. S. Rattan

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Abstract About a year ago, members of the editorial board of *Biogerontology* were requested to respond to a query by the editor-in-chief of the journal as to what one question within their field of ageing research still needs to be asked and answered. This editorial is inspired by the wide range and variety of questions, ideas, comments and suggestions received in response to that query. The seven knowledge gaps identified in this article are arranged into three main categories: evolutionary aspects of longevity, biological survival and death aspects, and heterogeneity in the progression and phenotype of ageing. This is not an exhaustive and exclusive list, and may be modified and expanded. Implications of these knowledge gaps, especially in the context of ongoing attempts to develop effective interventions in ageing and longevity are also discussed.

Keywords Health · Lifespan · Health-span · Geroscience · Evolution · Hormesis

More than 15 years ago, two of the well-known pioneers of biogerontology, Robin Holliday and Leonard Hayflick, boldly declared that ageing was no longer an unsolved problem in biology (Holliday 2006; Hayflick 2007a). This declaration was their rebuttal to a much earlier paper by the Nobel Laureate Peter Medawar that ageing was the last unsolved problem in biology (Medawar 1952). Both Holliday and Hayflick had based their proclamations on the assumption that, by the end of the twentieth century, a detailed description of the ageing phenotype at all levels of the biological organization was already achieved, possible molecular-genetic processes of longevity assurance were understood, and that explanations for the evolution of ageing and longevity were generally accepted.

Since then, a tsunami of ageing interventional research publications and associated industry news has been dominating the biogerontological scene, often with naïve extrapolations, overhyped claims and empty promises. Several biogerontologists, demographers and ethicists have repeatedly drawn the attention of scientists and the general public to the pros and cons, hype and reality, fact and fiction of the so-called "anti-ageing" industry (Le Bourg 2013, 2022; Faragher 2015; Olshansky 2017; Litterst et al. 2018; Kostick et al. 2019; Rattan 2020b; Brenner 2022).

Why such a situation has arisen that many scientists feel the need to raise such concerns and cautions? Do we still miss some critical pieces of information and knowledge in biogerontology, which will be necessary to develop genuinely effective strategies, and to make trustworthy and practical claims and recommendations for ageing interventions in humans?

S. I. S. Rattan (✉)
Department of Molecular Biology and Genetics, Aarhus University, 8000 Aarhus C, Denmark
e-mail: rattan@mbg.au.dk

It is in the above context that at the end of 2022, I, in my capacity as the Editor-in-Chief of *Biogerontology,* wrote a common email to all members of the editorial board of the journal with a query: *"In your expert opinion, what is the one question that still needs to be asked and answered in basic biological research on ageing within your field of research and interest?"*.

During the following couple of months, a majority of the editorial board members responded with their precise, and sometimes not-so-precise, questions, ideas and opinions. Based on those responses, this editorial article is my attempt to identify and compile a list of knowledge gaps in the biology of ageing research, and these are arranged under three main and general categories: (1) evolutionary aspects of longevity; (2) biological survival and death aspects; and (3) heterogeneity in ageing progression and phenotype. The implications of these knowledge gaps in biogerontology, especially in the context of ageing interventions for human health and longevity, are also discussed.

Evolutionary knowledge gaps

Of the three life-history strategies encountered in evolution (negligible senescence, rapid senescence and death, and progressive ageing and senescence), as described by Caleb Finch (Finch 1990), it is the third one that modern biogerontological research has been mostly concerned about. However, in more recent times, attention is also being given to the other two life-history strategies to unravel and explain why there is more than a thousand-fold variation in longevity within phyla, domains, species, genera and orders (Nussey et al. 2013; Austad 2022).

The average limited lifespan of a species in the wild natural conditions, as opposed to the maximum recorded lifespan of a single individual in any condition, is often termed as the essential lifespan (ELS) or the warranty period of the species (Rattan 2000; Carnes et al. 2003). Genes and genetic pathways that assure the species-specific ELS have been termed "longevity assurance genes" (LAG) and are mostly those that are involved in the repair and maintenance pathways from the molecular and metabolic to the organ and system-level processes (Turturro and Hart 1991; Jazwinski 1998; Holliday 2006, 2009). Even the genes and processes involved in the programmed cell death or apoptosis are basically the developmental-, survival- and ELS-assurance processes (Lockshin and Zakeri 1990; Munoz-Espin et al. 2013; Tower 2015). Furthermore, differences in the duration of ELS among species are often explained by introducing the idea of evolved public (universal) and private (species-specific) genetic pathways (Martin 2007; Martin et al. 2007). However, the nature of such public and private LAG is still obscure, and is the first major knowledge gap in biogerontology.

As for the proximate and ultimate distal reasons for the death of an individual, evolutionary theories generally discount the notion of an adaptive nature of ageing and death, and of its selection as an advantageous trait (Rose and Graves 1990; Kirkwood and Rose 1991; Rose 1991; Kowald and Kirkwood 2016). However, from time to time, old and new arguments are put forward in support of the adaptive and programmed nature of ageing, senescence and death (Kloeden et al. 1993; Lawler 2011; Trindade et al. 2013; Dong et al. 2016; Pamplona et al. 2023). Such arguments about the possibility of a genetically controlled ageing and death are often based on the observations that: (1) there is some heritability of lifespan as evident from studies on human twins (Tan et al. 2013); (2) there are several genetic mutants of premature ageing syndromes (Kipling et al. 2004; Martin et al. 2007); (3) genome wide association studies (GWAS) have identified some genes and gene-families associated with longevity; and (4) many spontaneous or induced genetic mutants with extended lifespan have been reported, mostly in experimental model systems (de Magalhaes 2014). However, none of these can be considered as real gerontogenes with the specific and evolved purpose and function of causing ageing and death of an individual (Rattan 1995; Holliday and Rattan 2010; Le Bourg 1996, 2013, 2020).

Therefore, the evolutionary explanations for the ELS of the species and the limited lifespan of an individual reside in the universal imperfections of nature, as envisioned by the quantum physics and the principles of entropy (Holliday 1997; Baynes 2000; Hayflick 2007b; Demetrius 2004, 2013; Demetrius and Legendre 2013; Gladyshev 2013; Chmielewski 2017). Our limited understanding of the nature and extent of imperfections, and their consequences in the growth,

development and survival of biological systems, is the second major knowledge gap in biogerontology.

Survival and the passage of biological time

The second category of knowledge gaps in biogerontology are similar to those in our understanding of the mechanisms of healthy survival during early growth, development and maturation, but with an added complexity of the ageing process and the ageing phenotype.

Metabolic systems of all life forms have the evolved ability to respond, to counteract and to adapt to the external and internal sources of disturbance. The traditional conceptual model to describe this survival ability is "homeostasis", meaning maintenance of the same state (Cannon 1929, 1939). However, the homeostasis model is incomplete, outdated and obsolete. This is because homeostasis is mainly an engineering-based concept of the body as a machine, and it presumes certain design and functional stability through constancy (Nicholson 2019). Furthermore, homeostasis does not take into account various biological themes, such as information and interaction networks, cybernetics, control theory, catastrophe theory, chaos theory, emergent properties and adaptation and compensation, which comprise and underline the modern biology of complexity (Wolf et al. 2018).

In comparison, the concept of homeodynamics, put forward almost 30 years ago (Yates 1994), accounts better 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 the organization. Similarly, another term, allostasis, underlies "stability through change" as the most realistic situation for biological systems (Sterling 2004; Sterling and Eyer 1988). Allostasis model also considers characteristics, such as reciprocal trade-offs between various cells, tissues and organs, accommodative sensing and prediction with respect to the severity of a potential stressor, and the final cost of making a response and readjustment to bring about the necessary change (Sterling 2004; Sterling and Eyer 1988). Every act of allostasis adds to the allostatic load in terms of unrepaired molecular damage, reduced energy deposits and progressively less efficient or less stable structural and functional components. Sometimes, another term "adaptive homeostasis" is also used to essentially describe above ideas of dynamicity and interaction in the context of biological survival and longevity (Davies 2016). The notions of adaptive homeostasis, homeodynamics and allostasis have been further integrated into the concept of homeodynamic space with its three main characteristics—stress, response, damage control and constant remodelling—as a measure of the survival ability, duration and health of an organism (Rattan 1998, 2007, 2020a). The factors that affect the development, maturation, success and stability of the homeodynamic space include internal and external factors, including prenatal and early-life exposures (Vaiserman 2019), circadian rhythms (Mattson et al. 2014; Jagota 2023) and the microbiome (Marotta 2023).

The duration of survival of an organism (both in the context of ELS of the species and the maximum lifespan potential of an individual within a species) is a representative of the passage of biological time in the context of the evolutionary life history of the species (Nathan 2021). For example, whereas the physical times required for any specific biochemical and molecular process(es) in the metabolic pathways of most eukaryotic organisms are almost identical, their biological times, in the sense of progressing from one biological stage to the next in a sequential, interactive and irreversible manner, is hugely variable. This can be seen in the differences in cell divisional, gestational, developmental, maturational and reproductive time-scales, that are evolutionarily programmed and well-regulated (Wolpert 2019). Therefore, if we compare the rates of passage of biological time from one stage to the next, using the man-made physical time units (seconds, minutes, hours and so on), it gives the illusion of slow and fast life-processes in different species (Lestienne 1988; Nathan 2021). With almost identical physical-time scale at the level of metabolic processes, how is the passage of biological-time regulated from one biological stage to the next through the life cycle, and until death?

Heterogeneity of the ageing phenotype

Conceptually, the emergence of the ageing phenotype has been characterized as a progressive failure of maintenance and repair processes of life (Holliday and Rattan 2010; Holliday 2009, 2007), or a

progressive shrinkage of the homeodynamic space (Rattan 2012, 2014). Such a change is mainly attributed to the imperfections of the maintenance, repair and other survival mechanisms, which allow an exponential accumulation of damage during the period of survival beyond ELS (Gavrilov and Gavrilova 2001; Rattan 2006; Gladyshev 2013). This is also in line with the framework of the second law of thermodynamics of increasing entropy (Hayflick 2007b; Demetrius 2013; Demetrius and Legendre 2013; Chmielewski 2017; Kim and Guan 2019). A progressive and exponential accumulation of molecular damage is one of the widely recognized phenotypes of ageing (Rattan 2008; Martinez-Miguel et al. 2021). So far, numerous different types of damages in DNA, RNA, proteins and other macromolecules, including epimutations, and post-transcriptional—and post-translational modifications have been identified, and only some of them have been studied in relation to ageing (Holliday 1998; Rattan 2010; Jorgensen et al. 2014).

Overall, the ageing phenotype is observed to be highly heterogenous at all levels of biological organization—from the species and population level to the levels of individuals, systems, organs, tissues, cells and molecules (Rattan 2008, 2012; Lowsky et al. 2014; Mitnitski et al. 2017; Rattan et al. 2018; Palmer et al. 2021; Tian et al. 2023; Burns et al. 2023). Especially at the molecular level, increased molecular heterogeneity, with its consequent interruptions and alterations in the nature of strong and weaker links, nodes, interactions and regulation, is still poorly understood (Csermely 2006; Rattan 2008; Spiro et al. 2008). Therefore, unravelling, quantifying, explaining and realizing the causes and consequences of heterogeneity of the ageing phenotype is perhaps the most challenging knowledge gap.

Another knowledge gap in biogerontology is how to differentiate among the possible adaptive, beneficial and harmful effects of the observed age-related changes at all levels. This is because, one of the characteristics of the homeodynamic space—constant remodelling—is indicative of the biological ability of adaptation, compensation and bypassing disturbances in metabolic processes for continued survival, even at the cost of increased allostatic load (Franceschi et al. 1995; Sterling 2004; Sterling and Eyer 1988; Lenart and Bienertova-Vasku 2017). It is not yet fully understood as to what extent a biological system can tolerate any specific molecular change, without showing any harmful and significant effects on the physiological functioning and performance of cells, tissues, organs and the whole body. For example, various age-related changes, such as reduced levels of several hormones and growth factors, a decline in protein synthesis, and various immunological changes seem to be health-beneficial and longevity-promoting (Arbeev et al. 2016; Hirokawa et al. 2016; Basisty et al. 2018; Fulop et al. 2018; Vitale et al. 2019; Eiriksdottir et al. 2021). Similarly, low levels of induced molecular damages are known to induce one or more stress responses, resulting in the stimulation of various maintenance and repair systems that can lead to potential health-benefits. This is the biphasic dose response phenomenon of hormesis, critical for almost all biological outcomes (Rattan and Le Bourg 2014; Rattan and Kyriazis 2019; Calabrese et al. 2023).

Some conclusions and implications

To recount, the major knowledge gaps identified and discussed above are listed in Table 1. It goes without saying that in each of the listed gaps, further specific questions can be raised as regards the nature of the species-specific regulatory genes, sex-specific differences, gene copy number issues, differential metabolic regulators, cell type-specific similarities and differences, organelle-heterogeneity and other macromolecular and metabolic specificities. Furthermore, in the case of human beings, other areas of knowledge gaps include the interdependence of mental health and biological- and social- health, well-being and longevity (Steptoe et al. 2015; John et al. 2023), which are beyond the scope of this article.

The seven knowledge gaps, arranged in three categories above, have significant implications for both the basic research in biogerontology and for the success of interventional strategies being pursued for healthy ageing and longevity of human beings. Of course, each of the listed knowledge gaps can be further expanded to the specific context of the species, sexes, bodily-systems, organs, cell types, organelles, and macromolecules. Yet, some general implications of these knowledge gaps can be envisioned as follows:

Table 1 Main categories and examples of knowledge gaps in biogerontology

Evolutionary issues:

1. What are the evolved public (universal) and private (species-specific) longevity assurance genes for the essential lifespan of a species?
2. What is the nature of imperfections that limit the optimal functionality of the longevity assurance processes, and are they sex-specific?

Biological survival and its limits:

3. With almost identical physical-time scales at the level of metabolic processes, how is the passage of biological-time regulated from one biological stage to the next through the life-cycle and until death?
4. What are the quantitative and qualitative features of the homeodynamic space in terms of the health and survival ability of a biological system?

Heterogeneity of the ageing phenotype:

5. What determines heterogeneity in the rate and extent of age-related changes at various levels of biological organization, from molecules to the whole body and population levels?
6. How to distinguish between harmful, useful, and neutral changes occurring during ageing?
7. How to identify and quantify the ability to tolerate, adapt, compensate and bypass age-related changes?

1. Since ageing is primarily a progressive loss of health, the focus of interventional strategies requires a shift from the treatment and prevention of diseases to the maintenance, recovery and enhancement of health. Such trends can already be seen emerging and being adopted (Kaeberlein et al. 2015; Cohen et al. 2020; Ramsey et al. 2021)
2. Whatever the specific therapeutic merits of single-target-oriented interventional approaches, healthy longevity strategies need to focus on the qualitative and quantitative measures of the complex and interactive metabolic, physiological and psycho-social markers of health (Sholl and Rattan 2019).
3. Potential health and ageing modulators at the level of prevention, repair or removal of any molecular damage need not aim for absolute efficiency, but should consider the homeodynamics of tolerance and adaptation concerning biological age and sex. The importance of taking into account the biphasic dose response hormetic curves for any interventions is also integral to this (Rattan and Kyriazis 2019; Calabrese and Agathokleous 2022).
4. While initial testing and screening of potential geroprotectors, using short-lived and convenient experimental model systems can be useful, biogerontologists must resist the temptation of making naïve extrapolation, overhyped claims and empty promises.

Finally, this short editorial aimed to take the status of biogerontology by identifying major knowledge gaps in our understanding of the phenomena, processes and proximate and distal mechanisms of ageing and limited lifespan. The list of knowledge gaps is in no way exhaustive and exclusive. Yet, it is hoped that this will initiate and inspire further contemplation, expansion and discussion as to how we could, should and would address such knowledge gaps in a much bigger scenario.

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