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Healthy human ageing

Brian F.C. Clark, bfcc@mb.au.dk

Definition of ageing

Ageing involves a decrease in the ability of an organism to cope with living in a particular environment. The deleterious age-related changes are cumulative. Ageing is therefore an intrinsic property of living organisms. Ageing is natural and should not be considered as a disease. It cannot be cured but maybe in future, depending on the state of knowledge, the changes might be reversed or be prevented or delayed.

How to understand ageing

It is difficult to give a common precise definition of ageing especially in molecular and cellular terms, since we are only at the beginning of building a knowledge base on ageing in these terms. The problem is compounded since organisms may age with different detailed mechanisms. Especially human ageing is complex, because different humans can age differently and organs or cellular components within one body can age differently. Nevertheless, technology has advanced so rapidly in the past 50 years for researchers to be able to try to elucidate the mysteries of ageing, which touches all humanity, defining one of the outstanding human challenges with a need for understanding in molecular and cellular terms to clarify and alleviate medical and social problems.

Healthy ageing is something that everyone wishes for. It can be considered to consist of wellness (describing physical fitness) and well-being (describing mental state), both of which need to be kept functional with age. This functional integrity of ageing is all-important so that it could be maintained by the prevention of defects and/or reversed by interventions.

This concept requires society in future to consider functional age and not chronological age. The impact on politics and society's habits, particularly with respect to working life and retirement, needs to be restructured as soon as possible. To describe functional age, we need new knowledge on how to establish biomarkers of age and function. Thus, we need to invest in establishing a knowledge-based society to increase our understanding of healthy ageing and to ensure it for our society in the next 25 years. With this understanding, we shall automatically influence the prevention and intervention of age-related diseases. Such a knowledge base in understanding ageing will clearly have great potential for technology transfer into commercial applications for the fundamental improvement of health, usefulness, mobility and independence of the increasing proportion of the elderly in the population. Increasing political support for high-quality innovative research in this area will improve the commercialisation potential for increasing the quality of life in Europe.

Technologies needed for us to progress in the understanding of ageing and to allow direct intervention and modulation within the next 25 years are molecular and cell biology as the knowledge base for molecular medicine and medical biotechnology, systems biology or metabolomics, and human development including tissue regeneration. General details for personalised medicine will come from new diagnostics and therapies arising from developments in genomics and functional genomics. Indeed the first step in the analysis of an individual will probably be a standard genome analysis by the general practitioner. The present goal of our genome analysis is for a total genome to cost US$ 1000 and seems no more than a few years away.

One example should be raised to illustrate the changes of lack of knowledge in developing new applications in medicine. The use of stem cells has great potential in treating human bodily deficiencies if the technology is under control. At present there is too much hype without a proper knowledge base, which could result in unexpected detrimental results as has already happened in some instances. For example, also compare what happened in gene therapy treatments. For 2020 we should plan to modulate any type of cell to behave as we wish not just stem cells. This will come from an understanding of how to control gene expression, especially from an understanding of epigenetics focusing on modification of genes or proteins.

Background information

The significant increase in human life expectancy during the past three generations, achieved primarily by reducing birth-related parturient deaths and infant deaths, is however not matched by an equivalent improvement in the health span in old age. There may or may not be any further significant gains in life expectancy in the economically developed countries, but the socio-economic costs of large numbers of unhealthy and frail old people are unsustainable in any society. As a biosocial issue, ageing is the underlying basis of almost all major human diseases, such as atherosclerosis, cancer,

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cardiovascular defects, cataract, diabetes, dementia, macular degeneration, neurodegeneration, osteoporosis and sarcopenia. 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 and its dignity in old age.

Biogerontology, the study of the biological basis of ageing, has so far unveiled mysteries of ageing by describing age-related changes in organisms, organs, tissues, cells and macromolecules. The large body of published data clearly shows that ageing has many facets. The progression and rate of ageing is highly variable in different species, in organisms within a species, in organs and tissues within an organism, in cell types within a tissue, in sub-cellular compartments within a cell type, and in macromolecules within a cell. Thus, there is neither a single way of defining ageing, nor is there a single cause. Most importantly, these observations have led most biogerontologists to abandon the notion of ageing being genetically programmed and to consider it as being stochastic and individualistic. A combination of genes, environment and chance appear to determine the course and consequences of ageing and the duration of survival of an individual (longevity).

Some principles of ageing

Although the descriptive data about ageing suggest that there are no universal markers of ageing, some general principles can still be derived, which can be useful for future research and intervention.

First, ageing is considered as an emergent phenomenon seen primarily in protected environments which allow survival beyond the natural lifespan in the wild. The natural lifespan of a species has also been termed 'essential lifespan' (ELS), or the 'warranty period' of a species. ELS is defined as the time required to fulfil the Darwinian purpose of life, which is successful reproduction for the continuation of generations. Species undergoing fast maturation and early onset of reproduction with large reproductive potential generally have short ELS. By contrast, slow maturation, late onset of reproduction and small reproductive potential of a species is concurrent with its long ELS. For example, the ELS of *Drosophila* is less than a week as compared with that of about 50 years of *Homo sapiens*, even though in protected environments (laboratories and modern societies), a large proportion of

populations of both species can and do live for much longer than that. Therefore, the period of extended survival beyond ELS is also the period of enhanced ageing.

Second, ageing is characterised by a progressive accumulation of molecular damage in macromolecules, that is nucleic acids, proteins and lipids. The inefficiency and failure of maintenance, repair and turnover pathways is the main cause of age-related accumulation of damage. Since homeostasis or homeodynamic ability of a living system is primarily because of its maintenance and repair processes, it is the progressive failure of maintenance and repair mechanisms which is the universal biochemical basis of ageing and age-related diseases.

Third, unlike development, which is a highly programmed and well-coordinated genetic process in the evolutionary life history of an organism, there is no genetic programme which determines the exact duration of survival of an organism. Furthermore, studies on establishing an association between genes and longevity have reported that the genetic heritability of variance in lifespan is less than 35%. The evolutionary theories of ageing and longevity have developed sophisticated and convincing arguments against the existence of genes that may have evolved specifically to cause ageing and to determine the lifespan of an organism.

Genes that do influence longevity are those that have evolved in accordance with the life history of a species. Several lines of evidence support the view that natural survival and longevity of a species is a function of its maintenance and repair capacities. For example, positive correlations between species lifespan and the ability to repair DNA, to defend against reactive oxygen species, to react to and counteract stress, and to proliferate and facilitate turnover of cells have been reported. By contrast, there is a negative correlation between longevity and the rate of damage accumulation, including mutations, epimutations, macromolecular oxidation and aggregation. A lack of specific gerontogenes responsible for ageing does not imply that genes do not or cannot influence survival, longevity and the rate of ageing.

Molecular mechanism

A generalised definition of ageing as the failure of homeodynamics still requires mechanistic explanation(s) as to why such a failure occurs in the first place and what controls the rate of failure in different species. Over the past 50 years, researchers have proposed a large number of hypotheses which attempt to explain how the observed age-related changes in

macromolecules, cells, tissues, organs and systems may occur. Main examples of such hypotheses include altered gene regulation, somatic mutation accumulation, protein errors and modifications, reactive oxygen species and free radicals, immune-remodelling and neuroendocrine dysfunctioning. At the cellular level, the so-called telomere loss theory, and epimutation theory of progressive loss of DNA methylation are other examples of providing mechanistic explanations for the loss of proliferative potential of normal, differentiated and diploid cells *in vitro* and *in vivo*.

Currently many people – particularly in the US – consider ageing to be a disease. This certainly helps fund-raising proposals in medical research where one applies to cure a disease. Perhaps a more realistic view sees ageing as a collection of predictable diseases arising from deterioration of the body and its function in a time-dependent manner. Thus, ageing and age-related diseases can be two facets of the same process. It is still important to distinguish between the molecular mechanism of ageing and age-related diseases, contrasting basic research and medical research, which is a more European view. Clearly there is a need for new, sophisticated biomarkers of ageing as a basis for analysis to determine appropriate interventions.

Some priority research areas
- Explaining cellular components controlling gene expression which are involved in ageing.
- Determining the extent and biological relevance of various types of molecular damage.
- Determining the efficiency and effectiveness of specific maintenance and repair pathways.
- Unravelling the interactive networks among various survival and longevity assurance mechanisms, especially molecular turnover, stress response and inter-cellular communication.
- Post-translational modifications in proteins.
- Identifying functional markers of biological age, ageing and survival potential, which may be amenable to monitoring during intervention in modulation attempts.
- Defining and delimiting the scope of the concept for humans.
- Social, economic and environmental determinants of healthy ageing.
- Healthy ageing considered as individual behaviour and choices, including self-care.
- Interactions among genetic-biological markers, the environment and health behaviour.
- Nutritional status and ageing: nutrigenomics.
- Tissue regeneration and renewal: stem cells and reprogramming.

- Psychosomatic effects; psychosocial determinants of healthy ageing.

With the investment of the US at around 1 billion dollars a year in the National Institute on Aging and of the order of 100 million dollars being spent by European research funding agencies it is probable that new leads in understanding ageing mechanisms will come from the US unless things change in Europe.

Modulation: intervention therapy or prevention therapy

Unlike some other fields of research, it is central to biogerontology that effective means of intervention are found, developed and applied for modulating human ageing to prevent the onset of age-related diseases and improving the quality of life in old age. This is because, whatever its academic and intellectual importance, ageing is a highly emotive health issue for human beings. It has been argued that the experience of ageing and age-related diseases may be one of the bases for the origin of human cultural aspects including religion and moral codes of conduct.

According to the three principles of ageing and longevity described above, having the bodies that we have developed after millions of years of evolution, occurrence of ageing in the period beyond ELS and the onset of one or more diseases before eventual death appears to be the 'normal' sequence of events. This viewpoint makes modulation of ageing different from the treatment of one or more specific diseases. In the case of a disease, such as a cancer of any specific kind, its therapy will, ideally, mean the removal and elimination of the cancer cells and restoration of the affected organ/tissue to its original disease-free state. What will be the 'treatment' of ageing and to what original 'age-free' stage would hope to be restored – to day 1, year 1, 10, 30, 50 or what? Considering ageing as a disease and then trying to cure that disease is unscientific and misguided. Similarly, though piecemeal replacement of nonfunctional or half-functional body parts with natural or synthetic parts made of more durable material may provide a temporary solution to the problems of age-related impairments, it does not modulate the underlying ageing process as such.

Scientific and rational anti-ageing strategies aim to slow down ageing, to prevent and/or delay the physiological decline, and to regain lost functional abilities. However, the history of anti-ageing research and therapy is replete with fraud, pseudoscience and charlatanism, and has often given a bad name to the whole field. Claims for miraculous remedies and promises for extremely long lifespan are prevalent even today. Recently, highly crucial analyses of such approaches have been made by biogerontologists with a view to educate and inform people about the science and nonsense of much ageing-intervention research.

Clearly an investment in this area will stimulate the development of analytical tools, preventive medicine and therapy potentially in new biomedical technology industry.

Conclusion

The aim of the new approach, called 'personalised ageing', using personalised medical approaches to assess functional age, centres on increasing the independence of the elderly individual. Progress in allowing the individual to escape from dependence upon the health system to gain a better life of higher quality will be a necessity to prevent an unsustainable health cost burden for the society as people live longer in frail and debilitated states. An increasing interdisciplinary approach to solve the problems of an increasingly powerful section of the society in electoral terms will be a prerequisite for preventing enormous future tensions in our society. The approaches will cover better design of residences, travel and retraining possibilities, thus taking care of wellness and well-being components in enhancing the future quality of life. Since the present human preoccupation with physical appearance already has spawned over a $7 billion cosmetic industry, it is clear that there is also an increasing chance of a new industrial explosion to satisfy the elderly sector with respect to medical applications in prevention and intervention of what they see as disadvantages of living longer.

Indeed our group in Aarhus has been involved in the skin-care field through developments of the British company Senetek PLC and its subsidiary in Denmark. The discovery of the use of plant growth factors delaying human ageing skin characteristics by my colleague Suresh Rattan and myself has created a new field for the application of what can be called phytocosmeceuticals. Naturally you are what you eat and breathe, so more useful food and a less polluted environment will add to the new industrial developments for healthy ageing. I trust that European researchers and the EFB will play significant roles in new exciting developments in areas of biogerontology, and its supporting medical, food and environmental technologies.

Further reading

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Brian F.C. Clark
Department of Molecular Biology, Aarhus University, Gustav Wieds Vej 10, 8000 Århus, Denmark

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