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From gerontology to geroscience: a synopsis on ageing

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ABSTRACT: Biological ageing can be tentatively defined as an intrinsic and inevitable degradation of biological function that accumulates over time at every level of biological organisation from molecules to populations. Senescence is characterised by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death. With advancing age, all components of the human body undergo these cumulative, universal, progressive, intrinsic and deleterious (CUPID) changes. Although ageing is not a disease *per se*, age is the main risk factor for the development of a panoply of age-related diseases. From a mechanistic perspective, a myriad of molecular processes and components of ageing can be studied. Some of them seem especially important and they are referred to as the hallmarks of ageing. There is compelling evidence that senescence has evolved as an emergent metaphenomenon that originates in the difficulty in maintaining homeodynamics in biological systems. From an evolutionary perspective, senescence is the inevitable outcome of an evolutionarily derived equilibrium between the amount of resources devoted to somatic maintenance and the amount of resources devoted to sexual reproduction. Single-target, single-molecule and disease-oriented approaches to ageing are severely limited because they neglect the dynamic, interactive and networking nature of life. These limitations notwithstanding, many authors promote single-target and disease-oriented approaches to senescence, e.g. repurposed drugs, claiming that these methods can enhance human health and longevity. Senescence is neither a disease nor a monolithic process. In this review, the limitations of these methods are discussed. The current state of biogerontology is also summarised.

KEY WORDS: age, ageing, age changes, biogerontology, gerontology, health, senescence

Introduction

In The Seventh Seal by Ingmar Bergman, Death asks Antonius: 'Have you tricked me?', and the knight replies: 'Of course. You fell into the trap'. On another occasion, Antonius knocks the chess pieces over and says: 'I forget where the pieces were', but Death restores them to their place saying: 'But I haven't forgotten' and 'No one escapes me'.

These excerpts express fundamental truths about human life and existence. Death is inevitable. Nature carefully keeps its secrets, allowing us to wonder

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at its wonders. Like Antonius, we will never stop asking questions. Playing chess with death, we can win a single battle, but does this mean that human ageing is not inevitable?

In this review, I summarise the current knowledge of ageing based on my research and experience (Chmielewski and Borysławski 2012, 2016; Chmielewski et al. 2015, 2016a, 2016b, 2017; Chmielewski 2016, 2017, 2018, 2019, 2020a, 2020b; Chmielewski and Strzelec 2018, 2020). Currently, the world of biogerontologists is divided into two parties: one group believes that human ageing is something similar to a disorder that can be treated with drugs, whereas the second group considers ageing as a continuum of life that is neither a treatable condition nor a monolithic process. Many biogerontologists believe that ageing is treatable (de Grey et al. 2002; Blagosklonny 2018) or curable (Skulachev 2011; Skulachev and Skulachev 2017). In this article, arguments in favour of the opposite viewpoint are presented.

Ageing, lifespan and longevity

Biological ageing can be defined as an 'intrinsic and inevitable degradation of biological function that accumulates over time at every level of biological organisation from molecules to populations' (Carnes 2011) or a 'progressive loss of function and fitness, which occurs during the extended period of survival beyond the essential lifespan (ELS)'. Lifespan is defined as an individual's observed duration of life. Life expectancy at birth (e_0) is a key term that denotes the average number of years newborns may be expected to live under the death rates that prevail at different ages in a given population. Life expectancy is an important measure of mortality. Longevity is a long duration of life or just the length of life (Carnes 2011; Chmielewski et al. 2016b). Longevity is considered a multifactorial trait that is determined by genetic background, epigenetic alterations, the environment and lifestyle-related factors such as diet, nutrition and behaviour.

When human ageing begins

There has been considerable debate on when biological ageing begins: at birth, conception or parental gamete formation (Milne 2006; Kinzina et al. 2019; Cohen et al. 2020b). Biochemists and geneticists often consider ageing as the result of the accumulation of molecular and cellular damage. The idea that the ageing process commences early in ontogeny is grounded in the view that DNA damage accumulation most likely begins at parental gamete formation (Bocklandt et al. 2011; Horvath 2013; Kinzina et al. 2019). Furthermore, senescent cells accumulate in the body throughout ontogeny and they can contribute to organismal senescence (Franceschi and Campisi 2014; Sikora et al. 2018). On the other hand, meaningful impacts of cellular senescence are primarily later in life, i.e. after ELS. Moreover, critical arguments have posited that growth, development and maturation cannot be understood as ageing (Kaczmarek and Szwed 1997; Rattan 2006; Carnes 2011; Chmielewski 2017; Kaczmarek and Wolański 2018; Arking 2019).

Thus, making a distinction between developmental changes, which are programmed and adaptive, and age-changes, which are non-programmed and non-adaptive, would further our understanding of ageing dynamics. In 1959, Strehler proposed five criteria, i.e. cumu-

lative, universal, progressive, intrinsic and deleterious (CUPID) changes, that must all be satisfied in order to assign a given change in biological structure or function to senescence (Carnes 2011; Arking 2019). Nevertheless, it is of note that physiological decline commences early in human ontogeny. Therefore, it is reasonable to predict that the accumulation of molecular damage starts early (Kinzina et al. 2019; Cohen et al. 2020b). Ageing is *heterochron*, meaning that different biological systems begin to age at different times. The ageing process also bears similarities with *heterotrop*, as age changes in different biological systems may follow different patterns. For example, the skin, vasculature and kidneys begin to age relatively early, whereas physiological brain ageing occurs at later stages of ontogeny. In fact, older adults experience ageing at different rates, and even in the same person different organs age at varying rates.

Understanding ageing: the concept of homeodynamics

Unlike non-living objects, living organisms are able to respond, to counteract and to adapt to the internal and external factors. The internal conditions of biological systems are not permanently fixed and they are not 'at equilibrium'. The notion of 'stability through constancy' does not sufficiently take into account the dynamic nature of information and interaction networks that underlie the inherent complexity of biological systems. Given that living organisms are dynamic entities in constant flux, it can be argued that the biological term *homeostasis* is problematic (Witkowski 2009). Therefore, it would be more judicious to use the term *homeodynamics* (Lloyd et al. 2001). It is important to note that terms like 'dynamic homeostasis' are erroneous as they imply that there is also 'static homeostasis', while homeostasis (in all biological systems) is understood as the *dynamic* interplay between external influences that may contribute in altering an organism's internal environment and the internal control mechanisms that oppose such changes. Thus, adding the adjective 'dynamic' to the term that refers to a dynamic process makes little sense (Cohen 2016).

Healthy ageing: from disease-oriented to health-oriented approaches

Biological ageing occurs in spite of complex processes and mechanisms for somatic maintenance, repair and defence (Rattan 2013). Since all molecular processes in biological systems are regulated by genes and gene products, discovering 'genes for ageing', i.e. gerontogenes *sensu stricto*, has been a popular theme in gerontology. To date, hundreds of putative gerontogenes have been identified. Nevertheless, it has been established that gerontogenes *sensu stricto* do not exist, and there is no genetic programme specifically to cause ageing (Kirkwood 2005; Kowald and Kirkwood 2016). If ageing were genetically programmed, or at least quasi-programmed, it could be treated like a disease (Skulachev 2011; Blagosklonny 2018). Instead, ageing is an emergent metaphenomenon. Although 'ageing as a disease' label can attract the attention of investors, it totally disregards the accumulated research in the field. Numerous sound arguments have been advanced against the idea that age-

ing is a disease (Hayflick 2016; Rattan 2016; Chmielewski and Strzelec 2020).

Although ageing is not a disease *per se*, age is a major risk factor for the development of a wide spectrum of age-related diseases (ARDs). The rate of human ageing can be accelerated by an unhealthy diet and lifestyle (Kirkwood 2005). Many authors suggest that human senescence can be effectively postponed in the future (López-Otín et al. 2013; Kennedy et al. 2014; Longo et al. 2015; Campisi et al. 2019), as the rate of senescence can be modulated, at least to some extent (Cohen 2016), by genetic, dietary, biochemical and pharmacological methods, although other researchers have challenged this claim (Hayflick 2003, 2004, 2007a, 2007b; Carnes et al. 2013; Hayflick 2016). The empirical data show that ageing is not an immutable process, but a dynamic and malleable phenomenon that can be affected by a variety of influences.

It is worth recalling that single gene mutations can extend lifespan in worms (Kenyon 2010, 2011). Cynthia Kenyon discovered that mutations in a gene called *daf-2* double lifespan in *Caenorhabditis elegans* (in hermaphrodites). In the other sex, the same mutation increases longevity more than 6-fold. In human terms, this is equivalent to 500 years. It has also been demonstrated that reprogramming erases cellular markers of ageing in human cells (Ocampo et al. 2016). This amelioration of age-associated features of the ageing phenotype highlights the role of epigenetic dysregulation as a driver of mammalian ageing. These unexpected findings indicate that ageing is a dynamic and plastic process that is amenable to intervention. Moreover, there are a number of potential methods that could be employed in order to extend human lifespan. These include: (1) gene therapy, (2) epigenetic reprogramming, (3) stem cell therapies, (4) elimination of senescent cells and dysfunctional mitochondria and (5) CR mimetics and repurposed drugs such as rapamycin and metformin. However, it is health that should be enhanced, not just lifespan (Chmielewski et al. 2016b; Olshansky 2018). Ageing studies focus on improving lifespan. Currently, our arsenal of possible interventions and methods for life extension is brimming with promising candidates. Nevertheless, improving healthspan in parallel is crucial for reducing chronic disease burden (Kennedy et al. 2014). Furthermore, one of the greatest challenges in current biogerontology is to translate the information gathered from studies performed on animal models to humans (Rattan 2020). Other biogerontologists assert that human longevity cannot be effectively enhanced (Hayflick 2003, 2004, 2007a, 2007b, 2016).

From gerontology to geroscience

Gerontology is the study of the biological, social, psychological, cognitive and anthropological aspects of ageing. This term was coined by Ilya Mechnikov in 1903. Biogerontology, which is also referred to as the biology of ageing, is the study of the physiological mechanisms of ageing and the evolutionary aspects of senescence.

Geriatrics is a branch of medical science concerned with the prevention, diagnosis and treatment of diseases in older people. Recently, a new interdisciplinary subfield called geroscience has emerged. This subfield is at the interface

of biogerontology and geriatrics. Like biogerontology, geroscience is based on the functional understanding of ageing as the risk factor for the development of a panoply of ARDs and geriatric syndromes. Geroscience aims to understand the links between normal ageing and the wide spectrum of ARDs based on experimental data and epidemiological research (Kennedy et al. 2014; Franceschi et al. 2018). This subfield is focused on the molecular biology of ageing. Many biogerontologists argue that a deeper understanding of these cell-molecular mechanisms of ageing will be crucial in the development of therapeutic approaches for the widespread panorama of ARDs.

Ageing is a fascinating topic that has captured the interest of many researchers from a diverse range of disciplines, ranging from biochemistry, genetics, cell biology, bioinformatics, biophysics, medicine, endocrinology, epidemiology, evolutionary biology, ecology, systems biology and biodemography. A fundamental challenge has been to integrate both empirical data and theoretical constructs that have emerged from these different subfields and perspectives, as well as to establish a common language and definitions. The science of ageing has made great advances in the understanding of physiological and evolutionary aspects of senescence. Although biogerontology has matured as a scientific discipline and our knowledge has advanced (Holliday 2006, 2009; Rattan 2006; Hayflick 2007a, 2007b), the diverse nature of ageing has not been fully understood. One possible reason for this is due to the heterogeneity and complexity of mechanisms and processes contributing to ageing (Jones et al. 2014; Cohen 2018; Cohen et al. 2020a, 2020b).

Furthermore, there is marked disagreement on the most fundamental questions in the field such as: (1) when ageing begins, (2) how to measure its rate, (3) how to retard the ageing process, (4) how to prevent ARDs, as well as several other pressing issues (Chmielewski 2020a; Cohen et al. 2020a). Based on own research and experience, I have compiled a list of fifteen questions that can be considered to be the most fundamental issues in current biogerontology (Table 1). The possible answers have been divided into three groups: 'yes' (to express total agreement), 'partly/in a sense' (to express the idea that the question is complex or imprecise, or that we are not ready to provide a straight answer to the question) and 'no' (to express strong disagreement). The authors that have been treated as respondents are noted biogerontologists, biochemists, geneticists and researchers who have published hundreds of scientific articles on ageing. Two methods have been employed in order to increase the reliability of such a juxtaposition of possible answers that can be considered too arbitrary or subjective: these authors have already provided tentative answers and they are strident advocates of their own views.

For example, Question No. 1, i.e. 'Can ageing be programmed?' has two possible answers: *Yes* and *No*, and only the strident advocates of these two rival theories are cited (Longo et al. 2005; Skulachev and Longo 2005; Skulachev and Skulachev 2017) for 'yes' and (Kirkwood and Melov 2011; Kowald and Kirkwood 2016) for 'no', even though it is generally agreed that the standard theoretical models of ageing rule out the possibility that ageing is programmed. Therefore, the answer to this question is skewed towards

Table. 1. Big names and the odd science of ageing. There is marked disagreement on the most fundamental questions in the field

Yes	Partly/In a sense	No
1. Can ageing be programmed?		
Longo et al. 2005; Skulachev and Skulachev 2017		Kirkwood and Melov 2011; Kowald and Kirkwood 2016
2. Can ageing be programmed through hormonal cascades in some species as a rare exception from the general rule?		
Cohen 2018		
3. Is it true that many animals do not age?		
Finch 2009; Sikora 2014; Cohen 2018		Hayflick 2007b, 2016; Holliday 2009
4. Can evolution favour ageing in sexually reproducing animals?		
Lenart et al. 2018		Kirkwood 2005
5. Is mammalian ageing molecularly orchestrated?		
van Heemst et al. 2005	Blagosklonny 2008	
6. Is ageing driven by genes and/or biochemical pathways for ageing, e.g. mTOR and insulin/IGF-1 signalling?		
Longo et al. 2005; Blagosklonny 2008	Bartke et al. 2002	Kirkwood 2005
7. Are there 'enemies within the body' that can contribute to human senescence?		
Longo et al. 2005; Blagosklonny 2008	Franceschi and Campisi 2014	Rattan 2006
8. Is the Theory of Molecular Entropy of Ageing fundamentally wrong?		
Kirkwood 1999; Mitteldorf 2010		Hayflick 2007a, 2016; Demetrius 2013
9. Is the Free Radical Theory of Ageing (FRTA) specious?		
Piotrowska and Bartnik 2014		Kirkwood and Kowald 2012
10. Does human ageing begin early in ontogeny, e.g. at conception or at parental gamete formation?		
Bocklandt et al. 2011; Horvath 2013	Cohen et al. 2020b	Rattan 2006
11. Is the distinction between senescence and age-related pathologies artificial and elusive?		
Holliday 2006, 2009; Kirkwood 2011		Hayflick 2016; Rattan 2016
12. Is human ageing an inevitable process (a stochastic process that cannot be postponed with drugs)?		
Hayflick 2003, 2004; Carnes et al. 2013		Kennedy et al. 2014
13. Can human ageing be effectively postponed in the future?		
Kirkwood 1999; Rose 1999; de Grey et al. 2002; Kennedy et al. 2014	Cohen 2016	Hayflick 2003, 2004; Carnes et al. 2013
14. Is there a biological limit to human longevity?		
Carnes et al. 2003; Dong et al. 2016		
15. Is our understanding of biological ageing almost complete?		
Holliday 2006, 2009; Hayflick 2007a, 2007b		da Costa et al.2016a, 2016b; Cohen 2018

the negative, as there is neither a rigid programme for ageing nor gerontogenes *sensu stricto*, i.e. genes that cause ageing. The idea of 'quasi-programmed ageing' is omitted for two reasons: firstly, it is too simplistic (Zimniak 2012; Rattan 2020); secondly, the author of this paradigm states that ageing is 'quasi-programmed' and 'non-programmed' simultaneously. Thus, it can be argued that this author has considerably diminished the value of his own work.

Question No. 3 refers to the idea that 'many animals do not age', which is a direct quote from Cohen (2018). In fact, many noted biogerontologists share this idea (Austad 2009; Sikora 2014; Kowald and Kirkwood 2016). The concept of negligible senescence was introduced by Caleb Finch (2009). Finch's idea included other animals and became one of the most promising discoveries in the field of ageing (Austad 2009). Many evolutionary biologists believe that human ageing can be arrested at a given age, at least in theory (Kirkwood 1999; Rose 1994, 1999), as human senescence naturally ceases at approximately 95 years of age (Rose, personal communication; Mueller et al. 2011). However, it is obvious that human ageing does not stop (Finch 2009). Nearly all known animals undergo ageing which cannot be postponed, stopped or reversed (Hayflick 2003, 2004, 2007a, 2007b, 2016). Holliday (2009) contended that 'there is no mystery in the fact that all animals age' (page 226).

Question No. 13, i.e. 'Can human ageing be effectively postponed in the future?', has three different answers: *Yes*. 'In theory, it certainly can' (Kirkwood 1999; Rose 1999; da Costa et al. 2016a, 2016b)' and yes since 'all the key components of mammalian ageing are indeed amenable to substantial reversal' (de Grey et al. 2002); *Not exactly* as 'there is little hope that rejuvenation therapies will be able to do much more than serve as a speed bump during the ageing process' (Cohen 2016); and *Definitely not* as 'No intervention will slow, stop, or reverse the ageing process in humans' (Hayflick 2004). It can be argued that authors who use phrases such as 'it certainly can' and 'no intervention will ever do something', already know the answers. These authors approach the problem from very different perspectives, i.e. evolutionary and mechanistic.

Question No. 14, i.e. 'Is there a biological limit to human longevity?' has one direct answer, which is based on the hypothesis that human longevity is predetermined and limited, which has received empirical support (Carnes et al. 2003; Dong et al. 2016). Nonetheless, other authors argue that human lifespan can be indefinite, at least in theory (Rose 1999), as maintenance mechanisms of the body and human physiology can be optimised (Kirkwood 1999). For example, da Costa and associates (2016b) claim that: 'an optimization of these processes could, in theory, make life indefinite'. Thus, the idea that humans can become virtually immortal persists in the scientific literature, despite compelling evidence to the contrary (Dong et al. 2016). Holliday (2009) argues that the idea that human ageing can be effectively postponed thanks to anti-ageing drugs and interventions is scientifically ungrounded. Both the empirical data and theoretical models have proved the sceptics right (Hayflick 2003, 2004; Carnes et al. 2008, 2013; Cohen 2016; Dong et al. 2016; Chmielewski 2020a; Rattan 2020).

It is of note that all these answers are definitely not true as they contradict each other. Ageing research has burgeoned in

the last decade. Consequently, biogerontology has made remarkable progress in understanding the physiological mechanisms of ageing (Holliday 2006, 2009; Hayflick 2007a, 2007b). However, despite the growing knowledge of these mechanisms, there are still a number of questions that remain unanswered. Therefore, some authors argue that the science of ageing is 'very much at its inception' (da Costa et al. 2016a) as ageing is 'poorly understood' (Cohen 2018). In fact, little is known about how these mechanisms interact to shape the trajectory of senescence and the onset of ARD. Furthermore, the scientific literature offers 'surprisingly little' insight into the key mechanisms of ageing, especially in the context of geroscience (Melov 2016). Thus, more research is needed in order to understand how to enhance human healthspan, not just lifespan (Olshansky 2018; Chmielewski 2020a). With this in mind, the general theory of health needs to be developed, and the science of ageing awaits such a theoretical framework. For many biogerontologists, ageing is an inevitable phenomenon that cannot be effectively postponed or reversed (Hayflick 2003, 2004, 2007a, 2007b, 2016; Carnes et al. 2008, 2013; Carnes 2011; Cohen 2016; Chmielewski 2019, 2020a).

Theories of biological ageing: an ever-evolving field

In order to understand the nature of ageing, a number of theoretical frameworks have been developed. In general, the theories of ageing fall into two categories: mechanistic theories address questions of *how* ageing and death occur in different species, whilst evolutionary theories explain *why* ageing evolved. Thus, the latter focus on the evolutionary explanations and resolve the apparent paradox that a phenomenon has evolved that is non-adaptive at the individual level. It has been hypothesised that ageing might be a more fundamental aspect of cellular organisms than assumed thus far (Ackermann et al. 2007), as the mechanisms of ageing are expected to operate in a wide range of organisms, suggesting that ageing evolved early in the history of life.

Several years ago, a modern classification of these theories was presented and discussed (Sikora 2014; Chmielewski 2017). An alternative classification, proposed by Trindade et al. 2013 and da Costa et al. 2016a, is summarised in Fig. 1. Causality theories consist of three types of explanations: (1) entropy-based theories, (2) stochastic damage theories, such as the Free Radical Theory and the DNA Damage Theory and (3) sudden death phenomena, which include accidents, cannibalism, fatal reproduction, semelparous reproduction, as well as apoptosis in unicellular organisms.

However, it should be remembered that other classifications of ageing and death theories exist (Kaczmarek and Szwed 1997; Kirkwood 2005; Mikuła-Pietrasik et al. 2014; Sikora 2014; Chmielewski 2017), with marked disagreement on the most fundamental issues in the field (Table 1). Given that the hallmarks of ageing are intertwined processes (López-Otín et al. 2013; Kennedy et al. 2014; Mikuła-Pietrasik et al. 2014), a network theory of ageing is a more progressive idea than an aspect theory of senescence. Recently, a unified theory of senescence encompassing genes, proteins, free radicals and the performance of maintenance and repair systems has gained general acceptance (Rattan 2006).

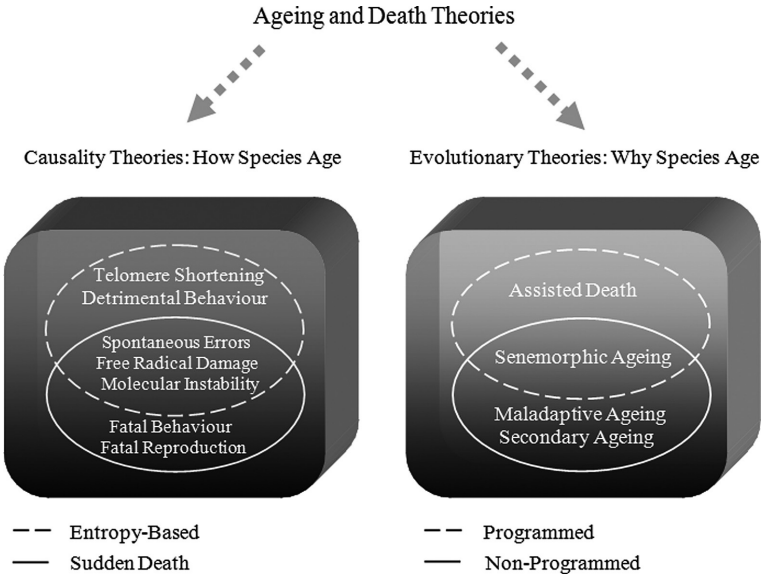

Fig. 1. An alternative classification system for ageing and death theories (after Trindade et al. 2013 and da Costa et al. 2016a, modified). In general, the theories fall into two categories: causality and evolutionary. Causality theories consist of three types of explanations: (1) entropy-based theories, (2) stochastic damage theories and (3) sudden death phenomena. Stochastic damage theories propose that ageing is caused by the intrinsic and progressive accumulation of molecular damage over time, leading to an increasing risk of death. The standard models predict that ageing is due to the summation of randomly acquired deleterious effects, i.e. CUPID changes. Accordingly, ageing results from the gradual lifelong accumulation of molecular damage. These standard theories include the Mutation Accumulation Theory, the Antagonistic Pleiotropy Theory and the Disposable Soma Theory (DST). Nevertheless, other classification systems include the Developmental Theory of Ageing (DTA), the Theory of Molecular Entropy and the Theory of Phenoptosis

Programmed ageing: phenoptosis revisited

The concept of programmed ageing was developed as early as 1889 by August Weismann. In brief, this hypothesis states that: (1) ageing corresponds with an adaptation in nature, (2) evolution favours ageing individuals over non-ageing individuals and (3) ageing fulfils a biological function because it eliminates aged, ill and worn-out individuals from the group, thereby providing living space, food and other resources for the offspring. At the end of his life, Weismann became sceptical and recanted this idea.

The concept that biological ageing is programmed and determined, or at least predetermined, is so attractive and appealing that it persists among researchers in spite of compelling evidence to the contrary. Many authors argue that it is still a matter of debate whether biological ageing is a programmed process, a quasi-programmed (non-adaptive) phenomenon, or merely a consequence of the accumulation of random molecular damage (Sikora 2014; da Costa et al. 2016b; Lenart et al. 2018; Schmeer et al. 2019).

According to the theory of phenoptosis, which was formulated in 1999 by

Vladimir Skulachev, ageing is an atavistic and mitochondria-mediated programme that consists in gradual degeneration and self-destruction of the body. In this view, ageing resembles a programmed phenomenon that results from the accumulation of detrimental changes, damage and toxins generated by the same maintenance mechanisms that sustain life. Mitochondria are the key energy-producing organelles. These organelles play a crucial role in a variety of biochemical processes. With advancing age, however, mitochondrial dysfunction occurs, and this decline has been associated with both normal ageing and the development of a wide range of ARDs. Hence the idea of quasi-programmed ageing, i.e. predetermined ageing, is not without merit if we understand it from a mechanistic perspective.

According to some authors, phenoptosis could be an evolutionarily programmed mechanism that culls out aged, ill and damaged individuals, which is analogous to apoptosis, i.e. programmed cell death (PCD). In brief, cells are cheaper, less important and subordinate to the body. Such biological entities are described as units of a lower order. According to the Samurai law of biology, a lower order units should be eliminated to secure the survival of units of a higher order. In particular, abnormal, damaged or cancer cells should be killed as they threaten the survival of the whole body. With age, all somatic cells accumulate damage, which can be understood as a consequence of metabolic processes. Similarly, a single organism seems less important at a group level, often subordinating to the group, just like cells are subordinate to the body.

Proponents of programmed ageing often argue that evolution, which is understood as a process of nature, 'wants us to die' because we generate more costs than benefits as we age. This statement sounds similar to the idea that 'the force of gravity wants us to fall over a precipice', which is obviously false and hardly anybody would espouse that idea. At the same time, the concept of programmed ageing is popular due to its parsimony. Many authors argue that it is still a matter of debate whether ageing is a programmed phenomenon or merely a stochastic process (Sikora 2014; Schmeer et al. 2019). Although a vast majority of biogerontologists do not share the idea that ageing evolved for its own sake (Kirkwood and Melov 2011; Kowald and Kirkwood 2016), alternate views exist. At one extreme, Skulachev and associates claim that ageing is an atavistic programme that fulfils a biological function (Longo et al. 2005; Skulachev and Longo 2005; Skulachev and Skulachev 2017). While other eminent researchers assert that ageing is not an adaptation, it is definitely an inherent biological programme (Declerck and Vanden Berghe 2018) or at least a quasi-programme (Blagosklonny 2008, 2018). Recently, the Developmental Theory of Ageing (DTA) has been reintroduced (Maklakov and Chapman 2019).

Let us hypothesise that biological ageing is genetically programmed and the genes for ageing exist. This view might seem optimistic as sophisticated interventions can interfere with the underlying mechanisms that appear to be common to multiple symptoms. In this view, ageing can be treatable or curable just like a disease. However, if a 'cure' for ageing were developed in the near future, the concern of rising population would not amount to a marked increase for a considerable period. However, overcrowding would eventually become

detrimental to the human population, showing that evolution really 'wanted us to die'.

Nonetheless, there have been many critiques of the idea of adaptive and altruistic ageing. Firstly, special circumstances need to exist for this strategy, i.e. adaptive and altruistic senescence, to be an evolutionarily stable strategy (ESS), let alone the only ESS (Kirkwood and Melov 2011; Kowald and Kirkwood 2016). This argument derives from Evolutionary Game Theory and disproves the idea of adaptive and altruistic ageing. Secondly, organismal senescence 'is, *prima facie*, quite different from other programmed biological processes such as development and apoptosis' (Cohen 2015). Cohen (2015) argues that ageing is too heterogeneous across individuals to be a programme and the ageing process takes too long to be a programme. 'Development is also slow, but making an organism is difficult. Making it die is, biologically, a simple task'. A simple task cannot take several decades. Thirdly, there is no empirical evidence that gerontogenes exist (Kowald and Kirkwood 2016) or that ageing fulfils a biological function (Rauser et al. 2009; Cohen 2015). Finally, in humans and in other sexually reproducing species, the survival of offspring depends upon the survival of their parents and alloparents. If ageing were an adaptation or a phenomenon resembling an adaptation (Lenart et al. 2018), then it would have the effect in limiting the longevity of older individuals, thereby increasing the likelihood of death of their offspring. In other words, if programmed death mechanisms operate to kill the mother, then the survival of her progeny is also endangered. This suggests that the idea of programmed, adaptive and altruistic ageing is flawed.

Non-programmed ageing: molecular entropy

Traditionally, ageing was understood as an inevitable outcome of chemical damage and entropy. In fact, the idea that biological ageing is due to entropy is very old and widespread. It is noteworthy that all organisms are thermodynamically *open* systems, whereas the Second Law of Thermodynamics is concerned with *closed* systems. Moreover, all organisms must be liberated from the Second Law of Thermodynamics in order to exist. Failure to resist entropy ensures death. Since biological organisms have the ability to escape entropy during their life cycle, it is unclear why entropy is relevant. Although the theory of entropy can explain the complex processes of decay and death of organic matter, it cannot explain why humans age.

Biogerontologists argue that if entropy were a real cause of biological ageing, life from its beginning would be subject to deterioration with time, which indicates that the theory of entropy is specious and invalid (Kirkwood 1999). Furthermore, it can be argued that no convincing arguments or theoretical models have been presented in order to verify role of entropy in biological ageing (Chmielewski and Borysławski 2016).Thus, it seems that the theory of entropy is more suitable for explaining the degradation of dead organic matter (Mitteldorf 2010). Surprisingly, several modern classifications of ageing and death theories embrace the idea that senescence is due to molecular entropy (Trindade et al. 2013; Sikora 2014, da Costa et al. 2016a, 2016b). Many noted biogerontologists argue that molecular entropy is the real cause of biological ageing (Hayflick 2003, 2004, 2007a, 2007b, 2016; Demetrius 2013),

which is rather surprising as it is generally agreed that entropy has no bearing on biological ageing (Kirkwood 1999; Mitteldorf 2010). Are there any hidden arguments in favour of this theory?

It may seem that ageing is due to increasing disorder (entropy) as all biological systems move towards increasing disorder with time. Even if we have a perfect system to start with, molecules and cells become damaged and disordered due to the complex interaction between genes and the environment. Biological organisms are affected by external forces and energy that can damage molecules and cells. Samaras (1974) points out that the human body is a complex system that is composed of subsystems, i.e. molecules, cells, tissues, organs, and processes. The human body has an optimum configuration of parts and interrelationships that involve roughly 10^{14} cells (Kłyszejko-Stefanowicz 1998; Bianconi et al. 2013). Although, the human body share similarities with inanimate systems, it is more than a configuration of subsystems. Moreover, biological systems are different from non-living object.

The theory of molecular entropy predicts that internally and externally caused disorder is never fully corrected by our internal repair and defence systems. In a closed system without an intake of restorative energy from an external source, life would quickly become disordered and die. However, the human body is not a closed system, and we obtain ordered energy from the physical world. Human bodies are also capable of removing dead or damaged cells and associated waste products. Thus, humans are able to restore much of our internal disorder for approximately 100 years (Dong et al. 2016). Unfortunately, this process is not perfect and we gradually accumulate damaged cells and lose our ability to replace them with new cells. Interestingly, the sheer number of cells in the human body can predict the relation between body size and cancer with no need to suggest additional factors (Nunney 2018). Although cells are constantly repairing and maintaining themselves via intake of free chemical energy from food and by dumping their waste entropy back into the surroundings, individuals within the same species that have a considerable amount of extra cells are more prone to DNA damage and cancer. This is because more cells in the body increase the risk factor for DNA damage and mutations.

Disposable Soma Theory: an update

The Disposable Soma Theory (DST) constitutes a physiologically based evolutionary model that describes ageing as a stochastic process that occurs as a result of evolved limitations in somatic maintenance (Kirkwood 1977, 2005). Recently, this prominent theory has been expanded to all unicellular lineages (Teulière et al. 2020), thereby falsifying the claim that ageing can be programmed because bacteria undergo bacterial senescence (cf. Mitteldorf 2010). Thus, the arguments in favour of programmed ageing are nebulous and implausible.

According to DST, ageing occurs as a result of evolved limitations in somatic maintenance, as the more an animal expends on sexual reproduction and growth, the less resources it can invest in somatic maintenance, and *vice versa* (Kirkwood and Holliday 1979; Kirkwood and Rose 1991; Kowald and Kirkwood 2016). Thus, there are evolutionary trade-offs between the allocation of re-

pairing mechanisms and somatic maintenance, and the allocation of resources for sexual reproduction. Maintenance mechanisms and reproduction use the same resources, and the body (soma) is merely a 'disposable carrier' for genes that use the body to propagate themselves. After sexual reproduction has taken place, the body becomes redundant, whereas the genetic material lives. Several studies have corroborated this theory in both laboratory experiments and anthropological investigations (Ziomkiewicz et al. 2016; Jasienska et al. 2017).

It is generally accepted that sexual reproduction is costly from both physiological and behavioural perspectives. DST provides an elegant theory for explaining the phenomenon known as 'negligible senescence'. For example, the Hydra is a cnidarian that does not have a true 'soma'. Therefore, it is virtually immortal in protected environments, but this is true only for its asexual form (Austad 2009; Cohen 2018). In sexually reproducing animals, there are evolutionary trade-offs between growth and reproduction early in life and resources that are available for somatic maintenance at later stages of ontogeny. This is why ageing evolves. According to DST, ageing cannot be programmed as it is non-adaptive at the individual level (Kirkwood 2005; Kowald and Kirkwood 2016). Standard evolutionary models explain that ageing is tuned by relaxation of natural selection, which means that ageing does not occur in species that rely exclusively on symmetrically fissile reproduction (Rose 1994). Interestingly, DST enables us to understand why humans are long-lived primates. It should be noted that resources that are available for somatic maintenance are surplus to requirements (Kirkwood 1977), and health costs of reproduction are relatively low in humans (Gurven et al. 2016).

However, some critiques of DST have been raised. According to other authors, DST cannot explain the effects of caloric restriction (CR) on lifespan in animal models as it predicts that energy shortage should result in a shorter lifespan as resources available for somatic maintenance are significantly reduced (Kyriazis 2020). In fact, the opposite is true. DST is useful here as it predicts that: (1) the allocation of resources is affected by nutrient availability in short-lived animals; (2) the shortage of energy in the form of food signals a situation that will result in lower offspring survival; and consequently, (3) resources are redirected from reproduction to somatic maintenance and repair, as the probability of the survival of these offspring is significantly reduced due to physical hardships and environmental challenges (Kirkwood et al. 2000; Chmielewski et al. 2016b).

According to these standard models, CR and CR mimetics will not enhance longevity in long-lived species such as humans and other primates (Demetrius 2005; Le Bourg 2006; Shanley and Kirkwood 2006). It has been established that CR extends lifespan in multiple species (Zid et al. 2009), including long-lived species. According to Kirkwood, there are very good grounds to believe that any effect of CR on lifespan in non-human primates is likely to be extremely modest, if it exists at all (cf. Austad 2012); for humans, an even more extreme statement could be made. According to other researchers, CR can enhance human health and longevity, but its effect is likely to be minor compared with the effects observed in short-lived animals. Moreover, CR is problematic in humans due to numerous side-effects. Therefore, some

researchers believe that a future drug could imitate the benefits of CR, thereby by-passing this physiological hurdle (Ingram and Roth 2011, 2015). However, other biogerontologists are sceptical as to the therapeutic usefulness of CR mimetics and other ageing-modulating drugs (Olshansky et al. 2002; Hayflick 2003, 2004; Carnes et al. 2013).

Another critique of DST is that if sexual reproduction is costly in terms of human longevity, the theory should identify the molecular mechanisms to which an organism shifts energy to somatic repair over reproduction. This is because this transition should be understood in order to improve health in people with high lifelong reproductive effort. Nevertheless, it is generally accepted that sexual reproduction is a costly mechanism. Increased reproduction can unfavourably alter the metabolism of lipids (Hansen et al. 2013) and is associated with greater oxidative stress (Ziomkiewicz et al. 2016). Other arguments against DST seem problematic and invalid (Kowald and Kirkwood 2016).

Limitations of single-target and disease-oriented approaches to human ageing

The dream of fending off old age and natural death is as old as recorded history. The science of ageing is linked to the idea that various pharmacological and dietary interventions can help effectively postpone ageing and delay the onset of ARDs (López-Otín et al. 2013; Kennedy et al. 2014; Franceschi et al. 2018). However, biogerontologists are becoming increasingly aware of the limitations of single-target and disease-oriented approaches to ageing (Chmielewski 2020a; Rattan 2020). 'Anti-ageing' medicine has the following limitations that should be acknowledged: (1) single-target and disease-oriented approaches to senescence, such as repurposed drugs, are severely limited as they neglect the dynamic, interactive and networking nature of life; in other words, biological entities, such as cells, do not operate as machines; (2) ageing is not driven by any underlying mechanism, hence the effectiveness of a single method for slowing down ageing, such as CR/DR, CR mimetics, senolytics or mTOR inhibitors, is likely to be extremely modest, if it exists at all; (3) although the rate of ageing can be accelerated by single gene mutations, epigenetic alterations or an unhealthy diet and lifestyle, no such interventions have yet been identified which effectively postpone human senescence; (4) the idea that physiological processes can be optimised to make life indefinite is probably specious; (5) single-target and disease-oriented approaches can delay the age at death but they cannot effectively postpone senescence; (6) current 'anti-ageing' medicine is fraught with naive assumptions and extrapolations (Rattan 2020) that are unrealistic and fraudulent (Holliday 2009).

Conclusions

Biological ageing is considered an inherent, dynamic and emergent metaphenomenon, i.e. the collection of CUPID changes, that leads ageing organisms towards eventual mortality. The concept of ageing as a single, monolithic, well defined and treatable process has hindered progress in biogerontology. Thus, it can be argued that ageing *sensu stricto* does not exist (cf. Cohen et al. 2020b). Moreover, mechanisms and processes contrib-

uting to the diversity of ageing across the tree of life are highly complex and heterogeneous. There is neither a common underlying mechanism nor a genetic or epigenetic programme for ageing. What can be observed is a collection of CUPID changes. Ageing is distinct from development. Ageing cannot be understood as a pathological process, such as cancer or type 2 diabetes, even though it is the main risk factor for the development of a wide spectrum of ARDs. Ageing is not a uniform process that can be treated with single-target or disease-oriented approaches. Biogerontologists are increasingly realising that 'anti-ageing' therapies , such as repurposed drugs, are severely limited, because they ignore the highly dynamic and complex mechanisms inherent in biological organisms (Cohen 2016).

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