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Human ageing, longevity and evolution: can ageing be programmed?

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ABSTRACT: Understanding the proximate and ultimate causes of ageing is one of the key challenges in current biology and medicine. These problems are so important that they are sometimes referred to as the Holy Grail of biology and the Great Conundrum in biogerontology. From an evolutionary perspective, ageing is due to a failure of selection that is caused either by declining strength of selection after the onset of sexual reproduction (Medawar's theory and Charlesworth's model) or pleiotropic constraints (Williams' theory). According to the disposable soma theory, which was proposed by Kirkwood and Holliday, ageing is driven by the accumulation of damage during life and failures of defensive and repair mechanisms as the more an animal expends on sexual reproduction, the less it can expend on bodily maintenance, and vice versa. Although these standard models rule out the possibility that ageing is programmed, there is no consensus about the nature of ageing within the life history in current biogerontology. Interestingly, empirical studies show that there are molecular instructions for ageing and evolutionarily conserved mechanisms for ageing, which seems inconsistent with the idea that ageing is a matter of neglect or a consequence of a failure of selection due to pleiotropic constraints. Here, selected arguments for programmed (i.e. either determined and adaptive or prearranged but non-adaptive) and non-programmed ageing are discussed. Recent advances in biogerontology that cast new light on these problems are outlined here in the context of the idea that the pace of ageing can act as an adaptation in nature, even though ageing is non-programmed and non-adaptive.

KEY WORDS: ageing, evolution, longevity, senescence, theories of ageing

Introduction

In a dialogue between Scipio and Cato, the latter says: *I follow nature as the best guide and obey her like a god. Since she has carefully planned the other parts of the drama of life, it is unlikely that she would be a bad playwright and neglect the final act. This last act must take place, as surely as the fruits of trees and the earth must someday wither and fall. But a wise person knows this and accepts it with grace. Fighting against nature is as pointless as the battles of the giants against the gods* (Cicero, about 44 BC; after Freeman 2016). From such remote beginnings, philosophy and science have made

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great advances in the understanding of senescence from both evolutionary and mechanistic perspectives (da Costa et al. 2016; Reichard 2017; Flatt and Partridge 2018). Cato's response expresses the universal truth that we are pilgrims on this earth or, as one of the evolutionary theories of ageing suggests, 'disposable carriers' for genes that use our bodies to propagate themselves. According to Professor Jacek Witkowski (2009), this text written by Cicero more than two thousand years ago is still inspiring and it can be a message to young researchers in the field of ageing, presumably because we can draw upon the wisdom of nature.

In our endeavour to understand all aspects of human senescence, there are still more questions than answers and we need new answers to old questions. These perennial questions are: 'What are the evolutionary origins of ageing?', 'What is the nature of human ageing within the life history?', 'How did evolutionarily conserved mechanisms for ageing evolve if ageing is a "matter of neglect" or a failure of selection due to pleiotropic constraints' and 'How to effectively postpone ageing?'. Although the majority of researchers do not share the idea that ageing is programmed, current biogerontology is not confined to traditional models. We can hear that: falling selection pressure does not explain why senescence evolves (Baudisch and Vaupel 2012; Wensink et al. 2014), ageing might be avoidable (Jones and Vaupel 2017; Mitteldorf and Fahy 2018), ageing is easily treatable (Blagosklonny 2018) or even that ageing is a disease (Bulterijs et al. 2015; Gems 2015; Stambler 2017), so we can use drugs to delay ageing and prevent age-related diseases (Campisi et al. 2019; Dönertaş et al. 2019). All these claims go against a long tradition in science and they must be surprising or even shocking to some authors and researchers. It is highly questionable whether reductionist or disease-oriented approaches are applicable to human ageing (Hayflick 2004; Holliday 2007; Chmielewski 2019). Ageing is too broad and too complex to be reduced to a disease.

In this mini-review, selected arguments for programmed (either determined and adaptive or prearranged but non-adaptive) and non-programmed ageing are discussed. Recent advances in biogerontology that cast new light on these problems are outlined here in the context of the idea that the pace of ageing can act as an adaptation in nature, even though ageing itself is non-programmed and non-adaptive (Lenart and Bienertová-Vašků 2017).

What is ageing?

There are mortality-based and functional-based definitions. In scientific writing, combined definitions are often used. Ageing can be tentatively defined as a 'persistent decline in the age-specific fitness components of an organism due to internal physiological deterioration' (Rose et al. 2012) or a 'process that converts physiologically and cognitively fit healthy adults into less fit individuals with increasing vulnerability to injury, illness and death' (Warner et al. 2010). The latter definition focuses on two aspects: (1) the age-dependent loss of physiologic integrity that can be observed after reproductive maturity and (2) the increasing susceptibility to a variety of morbid conditions that can be observed after 'essential lifespan' (ELS), i.e. the natural duration of life that is necessary for individuals to grow, develop and reproduce, which is also referred to

as the time that is required to fulfil the 'Darwinian purpose of life'.

Evolutionary theories of ageing

Theories of ageing fall into two categories: evolutionary and mechanistic. As we have explained in our previous articles (Chmielewski and Borysławski 2016; Chmielewski et al. 2016; Chmielewski 2016, 2017), standard evolutionary models rule out the possibility that ageing is programmed, adaptive or altruistic. Nevertheless, empirical data are inconsistent with some of these older theories. Therefore, new and alternative models are possible (e.g. Baudisch 2005; Mitteldorf and Pepper 2009; Kenyon 2010, 2011; Baudisch and Vaupel 2012; Mitteldorf and Martins 2014; Werfel et al. 2015; Lenart and Bienertová-Vašků 2017; Mitteldorf 2016, 2017, 2018).

Before Darwin and Wallace, ageing was commonly understood as a natural process of deterioration that is due to entropy. All objects deteriorate slowly over time, including celestial bodies, cars, watches and organisms. The theory of evolution through natural selection was a major breakthrough in our thinking about life. Organisms are not like non-living objects as they have evolved and they have maintenance mechanisms responsible for prevention and repair of damage and organisms can reproduce themselves. Biological ageing must be different from ageing of non-living objects. Over the decades, the biology of ageing has made great advances (Holliday 2007; Rattan 2012, 2018, Chmielewski 2019). Nevertheless, ageing continues to be a paradox from an evolutionary perspective (Burger and Missov 2016) as it appears costly to fitness (Kowald and Kirkwood 2016), might be avoidable (Jones and Vaupel 2017; Mitteldorf and Fahy 2018) and yet it is nearly ubiquitous in the wild (Nussey et al. 2013; Lemaître et al. 2015).

August Weismann was the first to reinterpret Darwinian natural selection in light of Roux's idea to introduce a concept of 'programmed death' of an organism that might act as an adaptation in nature. According to Weismann, somatic cells and tissue accumulate damage and this fact contributes to ageing and death (Mikuła-Pietrasik et al. 2015). Reproduction is indispensable in the world that invariably causes degradation of mortal individuals. Older members of a given species are expected to die in old age by death mechanisms of natural selection so that they would no longer compete with younger generations for food and other resources (Ljubuncic and Reznick 2009). Therefore, not immortality but reproduction and a turnover of generations must have been secured by nature. In accordance with this tentative model, ageing through 'programmed death' might act as an adaptation. These death mechanisms can help eliminate older and worn-out individuals from a given population. Towards the end of his life, Weismann tried to moderate this idea and he suggested that it might be defective due to a number of reasons. Nevertheless, the most important concepts provided by Weismann were the idea that there are two lines of cells (somatic and germ cells) and the idea that reproduction, unlike immortality of individuals, must have been secured by evolution. Interestingly, Weismann's idea has survived to modern times as a concept of programmed and adaptive ageing (e.g. Longo et al. 2005; Mitteldorf 2017; 2018; Skulachev and Skulachev 2017), even though the majority of researchers do not share this view

(Chmielewski et al. 2016; Kowald and Kirkwood 2016; Chmielewski 2017).

In 1941, Haldane presented a mathematical model (for Huntington's disease) that shows that strength of natural selection declines with age, which also suggests that evolution simply does not care if we age or not. From an evolutionary perspective, only survival and reproduction have 'high priority', and ageing results from a failure of selection. Haldane was struck by the fact Huntington's disease is an inherited and dominant trait. According to the older models of evolution, this gene that causes this condition should have been eliminated a long time ago. Haldane was the first to present an early mathematical model and a plausible explanation. Huntington's disease cannot be eliminated by means of natural selection because this condition has symptoms that do not appear until the postreproductive period of life when the force of natural selection is drastically weakened because the parent has already passed on this gene to the offspring. In other words, such genes can survive because they reside in the 'selection shadow'. The selection shadow means that selection pressures are high when we are young but after the onset of sexual reproduction they decline with age, and there is a 'shadow of time' where evolution through natural selection becomes 'blind' and does not care what happens because the genes have been passed on to the next generations. This is beyond ELS, so this is when ageing begins (Rattan 2014; Chmielewski 2017).

This mathematical model was developed by Peter Medawar in 1952. Medawar argued that ageing is a by-product of natural selection that is driven by the fact that diminishing selection leads to the accumulation of mutations or late-acting harmful genes (Medawar 1952; Ljubuncic and Reznick 2009). In particular, the accumulation of mutations is the real cause of ageing. Medawar suggested that all animals are prone to predators, starvation and disease. In the wild, there is a very low probability to survive to advanced ages and suffer from the effects related to senescence. From an evolutionary standpoint, there is not much reason why the body should stay fit for the long haul as the strength of selection is very low in old ages and older individuals will die soon anyway. In accordance with this important theory, ageing is a matter of neglect and a by-product of natural selection. Senescence is not ubiquitous but rare in the wild. Medawar's concept is popular and remains valid. It is one of the three main evolutionary theories of ageing. This theory is often used by advocates of non-programmed and non-adaptive ageing to show that ageing results from random causes and, therefore, cannot be programmed. Nevertheless, there are at least three problems with this theory. The first problem was noted a long time ago. If the accumulation of mutations that drives ageing proceeds faster in old age and these mutations are harmful after reproductive maturity, then we should observe a dramatic increase in mortality rates when selection pressures reach zero, i.e. in the postreproductive period. In other words, these mortality rates that we observe after reproductive maturity in humans should be steeper and they should increase monotonically after sexual maturity. In particular, late-life mortality plateaus should not be observed. In humans and many other species, a different pattern is observed: (1) the equilibrium frequencies of deleterious alleles affecting late life are lower than predicted, (2) the

mortality rates after sexual maturity are less steep and (3) there are late-life mortality plateaus. Therefore, Charlesworth (2001) presented a modified model of the accumulation of mutations. Nonetheless, there are several other problems. One problem is that today we know how genes act and how they are expressed in different stages of ontogeny. They are expressed differentially in progressive and regressive ontogeny because of epigenetic mechanisms for ageing (Lui et al. 2010; Somel et al. 2010). The model of 'epigenetic clocks' for ageing (Mitteldorf 2015, 2016) and 'molecular instructions' for ageing (de Magalhães 2012), either in its current form or in a more sophisticated future form, might be a tentative and plausible explanation. Another problem is that we observe different patterns of sustenance and negative senescence (Baudisch and Vaupel 2012), which seems inconsistent with the idea that ageing is a matter of neglect and it is driven by the accumulation of mutations. The last problem is that recent studies show that the idea that senescence is rare in nature might be specious as senescence is nearly ubiquitous in the wild (Nussey et al. 2013; Lemaître et al. 2015; Burger and Missov 2016; Lenart and Bienertová-Vašků 2017). These findings also suggest that strength of natural selection does not have to decline with age and does not have to reach zero when sexual reproduction ceases (Baudisch 2005). In opposition to Hamilton's model, alternative mathematical models show that the selection shadow can be a dynamic state in which the strength of natural selection can even increase for a while. Furthermore, a number of other theoretical problems with Hamilton's model have been recognised (Baudisch 2005).

Another evolutionary model for ageing was proposed by George Williams in 1957. According to this theory, ageing is due to the pleiotropic effects of genes that are beneficial early in life but harmful in late life (Williams 1957; Ljubuncic and Reznick 2009). These genes which have these opposite effects, for example they are associated with higher levels of testosterone in young males (this is adaptive as higher masculinity is associated with greater physical strength, dominance, violence and reproductive success) but eventually contribute to cancer or cardiovascular disease in older males or those that are associated with higher inflammatory responses in young individuals (this is adaptive because the inflammatory response is the basic protective mechanism to tissue damage that is activated by pathogens, disease or trauma) but higher levels of systemic inflammation in older individuals, are termed pleiotropic genes. There are not many good examples of pleiotropic genes that might contribute to the ageing process in humans. Moreover, there are some potential theoretical problems with this theory. Williams' model posits that preadult mortality does not matter to the evolution of senescence and higher adult death rates select for shorter length of life and earlier senescence, which was interpreted as predicting that ageing should be caused by extrinsic mortality. From a mathematical standpoint, this model is wrong. Some authors discuss these and other flaws of Williams' model (Moorad et al. 2019). Nonetheless, the idea that pleiotropic constraints might be a driver of ageing seems reasonable from an evolutionary standpoint (Austad and Hoffman 2018; Mitteldorf 2018). This theory has been discussed in our previous article about modern theories of ageing (Ch-

mielewski 2017). Here, we want to stress the main differences between Medawar's theory and Williams' theory. The main difference is that the latter predicts that genes, including genes for ageing or rather 'virtual gerontogenes' as there are no true gerontogenes (Rattan 2014; de Grey 2015, are actively kept in the gene pool by natural selection because they cannot be selected against so ageing is due to a failure of selection that consists in pleiotropic constraints, whilst the former predicts that mutations or genes with negative effects at old ages accumulate passively from one generation to the next because of a failure of selection that consists in the fact that the strength of selection diminishes with age. In other words, the latter does not preclude the possibility that ageing is prearranged, predetermined or quasi-programmed, although any purposeful or altruistic programme for ageing cannot exist. The former puts an emphasis on random causes of ageing and the fact that evolution is 'blind' and ageing is due to random damage that cannot be programmed or prearranged by nature.

In 1979, Kirkwood and Holliday presented a model for ageing known as the Disposable Soma Theory (DST). Two years earlier, Kirkwood had published his first article in Nature and he had introduced this new concept. Today, this is the third mainstream theory of ageing. This theory remains popular and influential amongst researchers, even though several weak points and possible problems with this theory have been recognised by other authors (e.g. Le Bourg 2007; Blagosklonny 2010; Mitteldorf 2010). According to Kirkwood and Holliday (1979), ageing occurs because of the accumulation of random molecular and cellular damage. In brief, maintenance mechanisms and reproduction are energetically costly, and the body has finite resources. The more an animal expends on reproduction, which is costly from both physiological and behavioural perspectives, the less it can expend on bodily maintenance, and vice versa. In other words, even though this is against popular belief, this theory explains that it is not easy to stay alive. And this is definitely true. To survive, the body ('soma') must be continuously repaired and renewed. This is very costly. If the body expends its finite resources on maintenance (e.g. prevention and repair of damage), it cannot expend them on sexual reproduction. If the body expends its resources on reproduction, it cannot expend them on maintenance. This model predicts that sexual reproduction is costly in terms of human longevity (Kirkwood and Holliday 1979; Westendorp and Kirkwood 1998). This theory has been discussed in our previous article (Chmielewski 2017). Numerous studies have corroborated this model in both laboratory experiments and anthropological investigations (Jasienska et al. 2017; Ziomkiewicz et al. 2016, 2019). In this view, ageing cannot be programmed, adaptive or altruistic (Kirkwood 2005; Kirkwood and Melov 2011; Kowald and Kirkwood 2016). Nevertheless, this theory has several weak points. For example, molecular and cellular mechanisms to which an organism shifts energy to somatic repair over reproduction should be recognised and studied but this theory does not postulate any such mechanisms. There are also other theoretical problems with the modern version of the DST (cf. Blagosklonny 2010, 2012). Moreover, calorie restriction should not have beneficial effects in long-lived species, such as dogs and primates, but it seems that some beneficial effects have

recently been observed (Colman et al. 2009; Campisi et al. 2019). Furthermore, other analyses show that increased reproduction does not have to decrease longevity in humans, especially in men, as data for women are mixed (Le Bourg 2007; Mitteldorf 2010).

Mechanistic theories of ageing

From a biochemical perspective, ageing can be attributed to slow poisoning of the body, which might be an atavistic process. In this view, there are many causes of ageing, both extrinsic and intrinsic (de Magalhães 2012; da Costa et al. 2016). For example, side-effects of metabolism and reactive oxygen species (ROS) can cause oxidative damage (Harman 2006; Barja 2014; Schöttker et al. 2015), which together with chronic systemic inflammation and its pleiotropic effects (Ferrucci and Fabbri 2018) might be one of the main causes of ageing and selected age-related diseases (Franceschi and Campisi 2014; Chmielewski and Strzelec 2018).

According to the theory of phenoptosis, which was formulated by Vladimir Skulachev, ageing is determined from a biochemical perspective and age-related problems with mitochondria and cells are responsible for the ageing process (Skulachev 1997; Longo et al. 2005; Skulachev and Longo 2005; Skulachev 2013; Skulachev and Skulachev 2017). When we are young our mitochondria do not 'kill' us yet but when we are old poisoning of the whole body is advanced and this process can eventually assassinate the body. In accordance with this concept, we can use 'anti-ageing' drugs to fight with 'phenoptosis' or we can remove defective mitochondria and senescent cells that contribute to chronic low-grade systemic inflammation. Although the theory of phenoptosis posits that ageing is biochemically determined and evolutionarily programmed, this is not necessarily true and it depends on our point of view whether we interpret ageing as an atavistic, evolutionarily conserved and mitochondria-mediated programme, a developmentally prearranged 'quasi-programme' that is a consequence of developmental programmes but is non-adaptive or a non-programmed and non-adaptive metaphenomenon.

According to theories of errors and damage-induced ageing, including the free radical/oxidative stress theory (Harman 2006; Kirkwood and Kowald 2012; Barja 2014; Schöttker et al. 2015), the mitochondrial free radical theory (de Grey 1999), the theory of cross-linking (Bjorksten and Tenhu 1990), the theory of molecular entropy (Hayflick 2007) and the reliability theory of ageing (Gavrilov and Gavrilova 2001), errors and damage occurring at different levels of biological organisation, from the molecular, cellular, tissue to organ level, is the main cause of ageing. For example, DNA damage, but especially double-strand breaks, might play a key role in ageing and is often studied. This damage also occurs in mechanisms that are responsible for prevention and repair of damage because of genomic instability, mutations and various stochastic factors and processes (Jin 2010). Therefore, ageing can be attributed to the escalating loss of molecular fidelity that exceeds repair capacity. Ageing results from the intrinsic, progressive and age-related deterioration of the homeodynamic (homeostatic) capabilities of the body, leading to a constantly increasing risk of death.

According to the theory of hyperfunction, ageing does not result from the ac-

cumulation of random molecular damage. Instead, mTOR signalling is a master driver of ageing, the grand 'conducTOR' and 'moTOR' of ageing (Blagosklonny 2012). Next to other signalling pathways, such as growth hormone/insulin/ IGF-1 signalling, mTOR (mechanistic/mammalian target of rapamycin) contributes to so-called 'hyperfunction' that inevitably kills the body, even though ageing is non-programmed and non-adaptive. In this view, ageing is 'programme-like' or 'quasi-programmed, and mTOR is an extremely important signalling pathway and the signalling 'hub' in cell survival that is the universal molecular 'hypothalamus'. We have discussed this theory in our previous articles (Chmielewski and Borysławski 2016; Chmielewski et al. 2016; Chmielewski 2016, 2017). However, it remains unclear what 'hyperfunction' really means. Is everything that is not caused by random molecular damage but the increased activity of mTOR hyperfunction? Moreover, it is not clear what drives ageing: the accumulation of random molecular and cellular damage (caused by ROS, electrophiles and stochastic factors and processes) or mTOR and its hyperfunction (cf. Blagosklonny 2012; Zimniak 2012). Some authors suggest that the theory of hyperfunction can help explain why we must die (i.e. why our lifespan is finite) but cannot explain why we age (since this can be explained only by the accumulation of damage occurring over time at different levels of biological organisation).

The neuroendocrine theory of ageing stresses the role of neuronal and endocrine mechanisms in the ageing process (Diggs 2008), although this does not mean that ageing is genetically programmed as hormones that regulate reproduction act in an antagonistic pleiotropic manner to control ageing via cell cycle signalling (Atwood and Bowen 2011). According to theories of programmed longevity, genes are differentially expressed in different stages of ontogeny, and some genes are switched on and off to drive ageing (Jin 2010). With ageing, multiple hormone and neuronal changes occur, which suggests that multiple genes must be differentially expressed. These changes might result from alterations in overarching biological mechanisms that gradually switch on and off selected genes for hormonal axes in the body (e.g. the somatotropic axis, the lactotropic axis, the thyrotropic axis, the corticotropic axis etc.). These axes play a key role in mammalian metabolism, and decreased sensitivity of hypothalamus and peripheral receptors can cause: (1) energy misbalance through the hypothalamus-pituitary-thyroid axis, (2) weakening of the immune system through immunesenescence, (3) decrements of physiological adaptability through the hypothalamus-pituitary-adrenal axis and (4) weakening of reproductive ability through the hypothalamus-pituitary-gonadal axis, which contributes to ageing. Some proponents of this theory suggest that improved sensitivity of hypothalamus and peripheral receptors should enhance longevity in mammals. On the other hand, we know that increased activity of hormones, such as GH, insulin and IGF-1, might contribute to ageing and some age-related diseases such as cancer. For example, reduced GH/insulin/IGF-1 signalling can be a protective mechanisms in humans. It has been hypothesised that GH/insulin/IGF-1 signalling is one of the evolutionarily conserved mechanisms for ageing. In general, insulin has beneficial effects on the body and these effects result from evolution-

arily conserved mechanisms. Empirical data suggest that decreased activity of the somatotropic axis (GHRH/GH/IGF/IGF-BP3) along with reduced GH/insulin/IGF-1 signalling can slow down the ageing process in model animals. Nevertheless, increased insulin levels can accelerate ageing in some tissues.

Network theories of ageing

There is compelling evidence that ageing is a highly complex and multifaceted phenomenon that is a by-product of natural selection. Multiple different mechanisms at many different levels of biological organisation might contribute to the ageing process. Therefore, both programmatic aspects of longevity (e.g. side-effects of metabolism, a consequence of growth and development etc.) and the accumulation of random and non-programmed damage might be responsible for ageing. Although some of those older theories that were presented by Medvedev in 1990 are no longer current, various theories from different groups can be true.

To understand ageing, multiple connected processes, both intrinsic and extrinsic, that contribute to the biology of ageing should be carefully studied. An early network model called MARS (mitochondria, aberrant proteins, radicals, scavengers) was presented by Kirkwood and Kowald in 1994 and 1996. In this model, the key variable is the free radial production rate that depends on various factors and processes such as the kinetics of the production of free radicals by the mitochondria and their destruction by various antioxidants (Kowald and Kirkwood 1994; Arking 2019). The network theory of ageing puts an emphasis on interactions, synergism and antagonism of different biological processes that might shape senescence. The production of free radicals depends on the level of energy that is provided by the mitochondria as well as on the synthesis, turnover and degradation of these organelles. Some new network models posit that the production of free radicals is molecularly regulated by mTOR and probably other molecular 'conductors' of ageing. These integrative models that are based on systems biology and new data from empirical studies are extremely important as they can help understand the complexity of the ageing process. Their implications include studying ageing at many different levels of biological organisation and the development of data bases for the biology of ageing. Interestingly, data from genomics and proteomics suggest that there is a relationship between the genetics of development and the genetics of ageing (de Magalhães et al. 2009; de Magalhães 2012).

Arguments in favour of programmed or prearranged ageing

Proponents of non-programmed ageing have argued that a single gene mutation cannot extend lifespan. Today, there is compelling evidence that a single gene mutation can enhance longevity in model organisms such as nematodes, fruit flies and mammals (Kenyon 2010, 2011). Interestingly, evolutionarily distant organisms share the same molecular basis and evolutionarily conserved mechanisms for ageing (Kim 2007; Campisi et al. 2019; Dönertaş et al. 2019). There are signalling pathways that modulate stress response and affect ageing and longevity in evolutionarily distant model organisms (Kim 2007; Kenyon 2010, 2011). These

evolutionarily conserved pathways play a crucial role in the link between ageing and age-related diseases. For example, GH/insulin/IGF-1 signalling might be involved in the link between ageing and cancer in humans.

Empirical data from modern genetics, genomics and proteomics suggest that the idea of programmed (molecularly orchestrated) ageing is not without some merit. In brief, multiple genes and microRNA (miRNA) are differentially expressed during ontogeny because of overarching epigenetic mechanisms (Mitteldorf 2016; Chmielewski 2019). There are intrinsic mechanisms at the molecular level that can be described as signatures and 'instructions' for ageing (de Magalhães 2012). It has been hypothesised that there is an epigenetic clock that controls this transition from the state of high somatic maintenance and normal bodily functioning to the state of low somatic maintenance and increasingly abnormal functioning (Mitteldorf 2015; 2016). Interestingly, partial reprogramming ameliorates hallmarks of ageing and erases markers of ageing, thereby extending lifespan in human and mouse cells (Ocampo et al. 2016). Furthermore, various atavistic processes of self-destruction, such as apoptosis (programmed cell death) and autophagy, might play an important role in ageing at the organismal level (Terman et al. 2007; Barbosa et al. 2019). On balance, empirical data show that ageing is molecularly orchestrated and hormonally regulated (van Heemst et al. 2005; Atwood and Bowen 2011; Chmielewski 2019).

In most species, including humans, ageing can be observed after ELS, which means that all-cause mortality increases with age (Warner et al. 2010; Rattan 2014). In humans, mortality doubles every eight years between ages 30 and 80 (Kirkwood 2015), which results from homeostenosis, i.e. the intrinsic and progressive decline in physiologic integrity of the body (Rattan 2014; Cohen 2015, 2016). Surprisingly, there are some species that have a different pattern of age-related changes in mortality rates. In desert tortoises (*Gopherusagassizii*) and white mangroves (*Avicennia marina*), the likelihood of survival increases with age (Jones et al. 2014). Interestingly, some authors argue that the likelihood of survival increases with age in human populations since 'death rates decelerate with age' (cf. Vaupel et al. 1998; Hayflick 1998). In my view, this argument is misleading. In human populations with high rates of extrinsic mortality, when selection pressures are high, newborns, infants and mothers are more likely to die due to complications associated with delivery, lack of medical care and other causes such as starvation, predation etc. In these populations, adults who survived to age 30 or 40 are fit and healthy, and those who survived to age 60 or 70 are extremely successful, e.g. they have more resources than other tribe members. Therefore, they can outlive younger individuals. But these findings do not provide any insight into the intrinsic biology of ageing.

While life expectancy increases in human populations around the world, there is a limit that is known as the maximum lifespan (MLS) and this limit remains unchanged (Lenart and Bienertová-Vašků 2017). Therefore, many authors suggest that there is a genetic programme for longevity in every species, and longevity, unlike ageing, is genetically determined. Humans grow, develop, reproduce and age following a relatively similar pattern. Therefore, those researchers who

identify ageing with longevity (but especially those who assert that there are 'genes for ageing', e.g. Mitteldorf), suggest that ageing, like longevity, must be programmed (either determined or predetermined by nature).

According to proponents of programmed and adaptive ageing, several 'biological clocks' have been identified to date, including mitotic and epigenetic clocks for ageing (Mitteldorf 2015; 2016; 2017; 2018) as well as the thymus that functions continuously throughout life (Haynes et al. 2000) and the suprachiasmatic nucleus (SCN) that interacts with many other parts of the brain. These systems are believed to be 'biological clocks' that act through hormones to control the pace of ageing (Jin 2010). At least two groups of mechanistic theories seem related to this concept, i.e. the theory of slow poisoning of the body through slow phenoptosis and the neuroendocrine theory of ageing (cf. Mitteldorf 2018).

Arguments in favour of non-programmed (damage-induced) ageing

It is often argued that most of the arguments for programmed and adaptive ageing are based on circumstantial evidence and circular reasoning. Moreover, valid mathematical models and simulations show that standard theories of programmed ageing are defective and predictions of their proponents are wrong (Kowald and Kirkwood 2016). Standard evolutionary models rule out the possibility of programmed, adaptive and altruistic ageing because ageing is non-adaptive at the individual level. Furthermore, the majority of authors and researchers do not support the view that ageing is programmed and adaptive. Ageing arises from progressive fall in Hamilton's forces of natural selection and this process does not have any biological function or purpose (Rauser et al. 2009; Cohen 2015).

Evolutionary conserved mechanisms for ageing are sometimes described as arguments against non-programmed (damage-induced) ageing. For example, Blagosklonny (2012, 2013) and other authors suggest that ageing is quasi-programmed, which means that it is driven by signalling pathways such as mTOR and GH/insulin/IGF-1, and there are no studies showing that prevention of damage can extend lifespan. These signalling pathways can be evolutionarily conserved mechanisms for the evolutionary trade-offs between growth, development, reproduction and ageing. In this view, signalling pathways do not actively drive the ageing process but they are important for growth and development. It is well known that ageing can be viewed as a developmental process that consists in retrograde changes over time, including the age-related loss of physiologic integrity of the body. Therefore, these signalling pathways, including the insulin/IGF-1 pathway, might play a critical role in the link between ageing and age-related diseases.

According to Kirkwood (2005), any genetic programme for ageing, assuming that ageing and metabolism are not intertwined phenomena as ageing is against survival, would be eliminated by natural selection. In other words, if there is a 'programme for ageing', we should observe non-ageing mutants. Since there are no such mutants, ageing cannot be genetically programmed. Additionally, if ageing were genetically programmed, genetically identical organisms should age in a very similar way. Noteworthy,

genetically identical monozygotic twins living in the same environment have different life trajectories associated with the age-related loss of functional capacity and they differ in lifespan (Finch and Kirkwood 2000), which shows that there is no genetic programme for ageing.

Modern evolutionary theories of ageing are part of life history theory. This theory explains how natural selection has shaped rates and patterns of ageing as well as the relation between ageing and reproduction in humans and other species (Flatt and Partridge 2018). It can explain why some species have unusual patterns of age-related changes in mortality. Interestingly, recent studies confirm that there are physiological and cognitive costs of increased reproduction in humans (Jasienska et al. 2017; Ziomkiewicz et al. 2016, 2019), which corroborates the DST. This theory can help understand that ageing is non-adaptive at the individual level and, therefore, is cannot be programmed by nature.

Negligible senescence

Some eminent proponents of programmed ageing argue that negligible senescence, which can be observed in some species, might be an argument for programmed ageing because these is no ageing programme in these animals. According to some traditional models of non-programmed ageing, including the entropic model that was proposed by Hayflick (2007), all organisms should age and the very idea that some animals do not undergo senescence seems preposterous. At one anatomical conference, I said during my speech: 'Today, we know that not all organisms undergo ageing. Ageing researchers have discovered negligible senescence. This term was coined by Caleb Finch. For example, Hydra can live more than 10000 years in protected environments'. One Professor of Anatomy from Łódź responded: 'This is impossible. You must be wrong. So why do these organisms die?'. 'Because of extrinsic mortality, for example predators', I replied. He did not believe me, and he should have asked why these organisms do not age. According to proponents of non-programmed ageing, the answer is this: Hydra does not have a 'true soma' and other answers are possible for different species because of different life history strategies. According to proponents of programmed ageing, the answer is: an ageing programme might not work in these species. This answer can tentatively explain why other species that have a 'true soma' do not suffer from age-related diseases. For example, naked mole-rats (*Heterocephalus glaber*) do not suffer from cancer, atherosclerosis, cardiovascular disease or immunodeficiency (Skulachev 2013; Ruby et al. 2018) and these rodents die of unknown causes at the age of 28–32 years in protected environments. Since they have a different pattern of age-related changes in gene expression than those mammals that undergo ageing, Skulachev (2013) argues that an ageing programme 'seems to be not operative in these mammals'.

Conclusions

The discussion concerning the nature of human ageing within the life history (programmed/quasi-programmed/non-programmed) involves controversial and potentially arbitrary interpretations. Standard evolutionary models, according to which ageing cannot be programmed, are dominant in current biology. These standard theories rule out the possibili-

ty that ageing is programmed, adaptive or altruistic. Nevertheless, proponents of programmed and quasi-programmed (non-adaptive) ageing might present their own models.

Conflict of interest

The author declares that there are no conflicts of interest regarding the publication of this paper.

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