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Rethinking modern theories of ageing and their classification: the proximate mechanisms and the ultimate explanations

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ABSTRACT: For a very long time, ageing has been an insurmountable problem in biology. The collection of age-dependent changes that render ageing individuals progressively more likely to die seemed to be an intractable labyrinth of alterations and associations whose direct mechanisms and ultimate explanations were too complex and difficult to understand. The science of ageing has always been fraught with insuperable problems and obstacles. In 1990, Zhores Medvedev presented a list of roughly 300 different hypotheses to illustrate this remarkable complexity of the ageing process and various approaches to understanding its mechanisms, though none of these hypotheses or aspect theories could be the general theory of senescence. Moreover, in the light of current data some of these ideas are obsolete and inapplicable. Nonetheless, the misconception that there are hundreds of valid theories of ageing persists among many researchers and authors. In addition, some of these obsolete and discarded hypotheses, such as the rate of living theory, the wear and tear theory, the poisoning theory, or the entropy theory still can be found in today's medical textbooks, scientific publications aimed at the general public, and even in scientific writing. In fact, there are only several modern theories of ageing supported by compelling evidence that attempt to explain most of the data in current gerontology. These theories are competing to be a general and integrated model of ageing, making it unlikely that all of them could be true. This review summarises briefly several selected modern theories of senescence in the light of the contemporary knowledge of the biological basis for ageing and current data.

KEY WORDS: ageing, gerontology, programmed ageing, quasi-programmed ageing, senescence, stochastic ageing, theories of ageing

Introduction

Traditionally, theories of biological ageing have been classified into two categories, i.e. those which explain the evolutionary origin of senescence (i.e. the ultimate explanations), thereby addressing the question "Why did ageing evolve?" and those which concentrate on proximate mechanisms, such as genes and other molecular factors, that directly drive the ageing process (i.e. the proximate explanations), thereby answering

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the question "How do we age?". The first group of theories was divided into deterministic models that explain ageing as an atavistic, programmed, and altruistic process that is driven by hundreds or thousands of genes and molecular factors to purposefully eliminate older individuals from the population through higher levels of natural selection, chiefly group selection and evolvability at the population level (Skulachev 1997; Longo et al. 2005; Skulachev and Longo 2005), and stochastic models that explain ageing as a completely passive and non-programmed process that is driven by the gradual accumulation of random molecular and cellular damage that is non-adaptive and not programmed since it is definitely non-adaptive at the levels where natural selection takes place according to the selfish gene theory (Kirkwood 2005).

Some of the proponents of deterministic models of ageing opine that Dawkins' theory is definitely specious, but some of these deterministic theories are based on flimsy argumentation (e.g. entropy cannot be the real cause of ageing, hence the theory of molecular entropy is definitely invalid, while molecular entropy is caused by the fact that living systems have built-in mechanisms that actively resist entropy which tend to falter and fail in late ontogeny, and thus the causes of molecular entropy are of different nature) and highly speculative models of the evolution of senescence such as group selection and evolvability. The vast majority of researchers and scholars do not support such a view on the evolution of senescence, which does not mean that it is utterly meaningless and without some merit.

Although the above-mentioned categorization of theories of ageing into programmed and stochastic models is no longer current (Rattan 2006), this dualism lingers on as it illustrates the core of the long-running dispute among gerontologists, which is known as the great conundrum in gerontology (cf. Kirkwood and Melov 2011; Skulachev 2011; 2012; 2013). Interestingly, some authors suggest that these two fiercely competing theories "are not necessarily mutually exclusive" (Sergiev et al. 2015) as real ageing can vary across species and the build-up of random molecular damage or the decreased capacity for repair and maintenance of the body can be accelerated by programmed aspects of senescence whose traces and signalling pathways become more and more evident thanks to recent research into the genetics and epigenetics of ageing.

Unlike in the case of evolutionary explanations or at least the milestones (Weismann 1889; Medawar 1952; Williams 1957; Kirkwood 1977), a surprisingly large number of hypotheses related to the proximate mechanisms and aspects of ageing have been put forward. Indeed, ageing used to be an insurmountable problem in biology for a long time (Holliday 2006; Hayflick 2007) since the collection of age-dependent changes that render ageing individuals progressively more likely to die seemed to be an intractable labyrinth of alterations and associations whose direct mechanisms and ultimate explanations were too complex and difficult to follow. Thus, the science of ageing has always been fraught with insuperable problems and obstacles. Edward Schneider, a distinguished American gerontologist, quipped: "If you think that cancer is complicated, look at ageing". Indeed, the ageing process is immensely complex and multifaceted. It is far more complex than cancer. It was a Russian biogerontologist, Zhores Medvedev (1990), who compiled

a list of over 300 different hypotheses of varying kinds to illustrate this remarkable complexity of the ageing process and various approaches to understanding its mechanisms, though none of these working hypotheses or aspect theories could be labelled as the theory of ageing (Rattan 2006). Moreover, some of them are now obsolete in the light of current data on the biological basis for ageing. Nevertheless, the misconception that there are more than 300 valid theories of ageing or numerous valid theories and the science of ageing has not made any progress since this list was presented still persists among many authors and researchers. In addition, some of these outdated and discarded hypotheses, such as the rate of living theory proposed by Pearl, the early version of the wear and tear theory, Rubner's theory, Mechnikov's theory, the poisoning theory, the entropy theory, and so forth still can be found in today's medical textbooks, scientific publications aimed at the general public, and scientific writing.

In fact, there are only several modern theories of ageing supported by compelling evidence that attempt to explain most of the data in current gerontology, including findings from the genetics and epigenetics of ageing and longevity, the underlying causes of sex differences in healthspan and lifespan, the effects of calorie restriction in animal models, the effects of antioxidants on health and longevity, the mysterious effect of hormesis, and the links with age-related diseases like cancer, cardiovascular disease (CVD), and type 2 diabetes (for a review, see Harman 2006; Rattan 2006; Jin 2010; Sikora 2014; Kochman 2015; Lipsky and King 2015; Sergiev et al. 2015; Chmielewski and Borysławski 2016; Chmielewski et al. 2016). These modern theories are competing to be a general and integrated model of ageing, making it unlikely that all of them could be true. This review summarises briefly some of these modern theories of biological ageing in the light of new data and the contemporary knowledge of the biological basis for ageing.

Programmed ageing: altruistic suicide through slow "phenoptosis"

Ageing is arguably the most familiar aspect of ontogenetic development and the latter process is tightly controlled and programmed. Moreover, the ageing process involves a predictable regularity and reproducibility of age-dependent changes in numerous morphological and physiological characteristics which occur with advancing age in all ageing individuals within a given species, which makes it rather improbable that all these alterations depend on random, i.e. stochastic, factors. Therefore, since time immemorial ageing has been perceived as programmed. This group of explanations is very old and extremely widespread, especially among non-specialists and newcomers to the field of biogerontology.

It was August Weismann (1889) who first introduced the idea that a group of ageing and dying organisms would have a fitness advantage over a group of non-ageing and immortal organisms because older, ill, and worn-out individuals are not only valueless but also harmful to the group from an evolutionary point of view. Therefore, although death was not a primary necessity, it has become a secondarily acquired adaptation to eliminate worn-out and harmful individuals from a given population, thereby increasing its fitness at the species level. By the end of

his life, Weismann became more sceptic and recanted or at least moderated this idea. However, it still persists among some authors and new findings suggest that it could be valid in some circumstances, or at least it has been interpreted so by the proponents of programmed and altruistic ageing (Longo et al. 2005; Mitteldorf 2010; 2016; 2017; Skulachev 2011; 2012; 2013).

Vladimir Petrovich Skulachev, an eminent Russian biochemist, developed the theory of phenoptosis and "the Samurai law of biology" based on this concept (Skulachev 1997; 2001). According to these views, biological systems at different levels of organisation have built-in mechanisms of self-destruction as "it is better to die than to be wrong" from an evolutionary point of view. Thus, these atavistic processes and mechanisms are evolutionarily conserved and they are adaptive as they can accelerate evolution (Skulachev 2011; 2013). For example, the process of apoptosis, i.e. programmed cell death (PCD) eliminates unnecessary and damaged cells in order to ensure the proper development of the organism as well as to defend the body against, for example, tumour cells. Skulachev asserts that the process of destruction of some organelles, such as mitochondria, is tightly controlled by some molecular factors and, therefore, it is an example of "mitoptosis". Likewise, "organoptosis" is a programmed death of an organ of the body such as the heart. Similarly, an organism is subject to programmed death known as "phenoptosis". Normal ageing consists in slow phenoptosis. In some circumstances, however, this process can be very fast and spectacular such as the phenomenon of instant death after reproduction in semelparous organisms. In humans, it can be observed in individuals with progeroid syndromes, like progeria, or during sepsis. Skulachev suggests that the process of slow phenoptosis (as observed during normal senescence) is possible because cells are subordinate to the organism – they are relatively cheap and less important. Therefore, it is better to eliminate unnecessary, abnormal, or damaged cells than to leave them alone since it may bring about a situation in which the survival of the whole body is menaced by these relatively unimportant cells. Therefore, various mechanisms have evolved to ensure the survival of the more important biological systems. For example, the gene p53 at the cellular level is such a "guard of the genome". When DNA damage is increased, its protein is more active and it is involved in DNA repair, arrest of cell cycle, and PCD. Mutations that decrease the activity of the p53 protein are closely related to increased risk of cancer. Conversely, mutations increasing its activity decrease significantly the risk of cancer. Since old individuals are more likely to develop cancer and then die from this condition, it is reasonable to expect that mutations increasing the activity of the p53 protein would increase the lifespan of model organisms. Surprisingly, it is the other way round (Garcia-Cao et al. 2002; Tyner et al. 2002). Moreover, if the protein p53 is much more active, the lifespan decreases threefold (Scrable et al. 2009). Skulachev (2013) interprets these results in the light of the phenoptosis theory and suggests that "this protein is likely to become too active in discarding cells with certain genome damage. As a result, it is not only malignant cells (whose genome was seriously damaged) that die because of apoptosis, but also those whose genome was damaged but slightly". Thus, his standpoint is that the increased rate

of apoptosis results in decreased lifespan of the organism since apoptosis contributes to organismal senescence, an explanation that is not commonly accepted among gerontologists.

Although many authors and researchers argue that the theory of programmed and altruistic ageing through phenoptosis is outdated and invalid, it seems that it is still alive and not without some merit. From an anthropological perspective, there are at least several reasons why it is so attractive and seductive. First, it seems logical and straightforward – probably most people feel that ageing is somehow determined by nature and therefore it must be programmed. Second, this view is very optimistic and allows the possibility to slow down the ageing process using different rejuvenation techniques and strategies known as anti-ageing medicine. Third, it may offer many concepts or ideas that seem refreshing, edifying, and stimulating since the advocates of this theory update it continuously using new data from current research into the biochemistry, genetics, and epigenetics of ageing to defend it against severe criticism. Furthermore, evidence is accumulating that the molecular determinants of the ageing process are much more robust than it was previously suggested by the proponents of non-programmed ageing, i.e. ageing as a completely passive process that has nothing to do with molecular and cell biology. For example, it has been demonstrated that ageing is molecularly orchestrated and hormonally regulated by some evolutionarily conserved mechanisms such as mTOR and insulin/IGF-1 signalling pathways (van Heemst et al. 2005). Also, recent findings from functional genomics, proteomics, and molecular biology of ageing suggest that there are specific instructions for ageing in our genome (de Magalhães 2012), which seems incompatible with the idea of non-programmed and purely stochastic ageing as well as the contemporary understanding of evolutionary mechanisms and population genetics. It is important to understand that these new discoveries do not challenge or disprove the evolutionary theory or the evolutionary theories of senescence, as some have claimed (Heininger 2012); rather, they show that our understanding of nature is still limited and incomplete. Moreover, it appears that they do not necessarily challenge the disposable soma theory proposed by Kirkwood or other theories of non-programmed ageing, such as the theory of antagonistic pleiotropy formulated by Williams that can be also interpreted as an early version of quasi-programmed models of senescence, but rather show that there is also a possibility that some age-dependent changes are to some degree controlled by specific molecular factors or even instructions in order to drive the ageing process in some circumstances. Therefore, the ultimate answer to the question: "Is there a programme for ageing?" depends on our point of view. Specifically, it appears that it depends on whether our interpretation of senescence is more simplistic and teleological or more sophisticated and naturalistic. Robin Holliday, an eminent British molecular biologist and biogerontologist, asserted that the idea of programmed ageing is far too simplistic. He often used the example of the ageing of teeth as an illustration of the limitations of the idea of programmed ageing. It is known that the ontogenetic development of teeth is genetically controlled and programmed. There is even a precise timetable with respect to the ontogenetic development of the teeth, according to which dental

age of a given individual can be estimated, and "teeth are indeed programmed to last a lifetime" (Holliday 2007). However, if a given person follows a liquid diet and takes care of the teeth for a long time, they can survive much longer as if they were younger. Conversely, if they are misused or used properly but too often, the process of wear and tear can destroy them at a relatively young age. Holliday contended that the same mechanism is applicable to the whole body. Therefore, the ageing process is definitely much more stochastic than deterministic. Nevertheless, the question remains whether the teeth of an old individual who followed a liquid diet and took care of them for a long time could be biologically younger and developmentally the same as the teeth of a young individual. It seems that the answer is no since apart from the forces acting upon the teeth during the process of mastication, there are also other harmful factors, programmed and non-programmed, that cause tooth decay over time, including bacteria, plaque, un unhealthy diet, mineral and vitamin deficiencies, poor hygiene, genetic determinants, and so forth. Thus, even such an edifying and brilliant example of limitations of the idea of programmed and altruistic ageing seems to be inconclusive.

Programmed ageing: nutrient sensing and response to nourishment

As shown in Figure 1, there are currently more than one modern and valid theory of programmed ageing. Apart from the theory of phenoptosis, the idea of nutrient sensing and response to nourishment, proposed by Cynthia Kenyon, is often discussed in the literature. Other deterministic models include the theories of biological clocks, such as the epigenetic clock for ageing, and the demographic theory proposed by Mitteldorf (2016; 2017).

It was Ilya Mechnikov who first introduced the idea that senescence may result from response of the organism to waste products of metabolism, chiefly toxic substances produced by bacteria in the gut. His theory proposed that diet supplements rich in lactic acid bacteria, such as sour milk or yogurt, can increase life expectancy and slow down the ageing process. Although the consumption of these dairy products has been shown to have some important health benefits with respect to ageing-associated conditions, such as having ameliorating effects on the function of the digestive system, lowering blood pressure, reducing the risk of hypertension and type 2 diabetes (Soedamah-Muthu et al. 2012; Gao et al. 2013; Wang et al. 2015; Díaz-López et al. 2016; Gijsbers et al. 2016), especially in women, Mechnikov's hypothesis that human senescence results from toxic substances produced by intestinal bacteria and dairy food consumption could postpone the ageing process is invalid.

According to the modern theory of response to nourishment, the existence of single genes whose mutations can extend lifespan several-fold in certain model organisms, such as *Caenorhabditis elegans*, a possibility which was ruled out by the proponents of stochastic and non-programmed ageing on the basis of the standard evolutionary theories, weighs in favour of the belief that ageing is programmed and heavily influenced by molecular factors, such as the insulin/IGF-1 signalling pathway, that control its pace (Kenyon 2001; 2005; 2010; 2011). According to Kenyon (2010), or-

ganismal senescence could have evolved as an adaptation to nutrient conditions, and the biology of insulin/IGF-1 provides a particularly interesting context for understanding the evolutionary basis and origin of senescence. Thus, she argues that: "the finding that lifespan can be increased by pathways that shift the physiology towards cell protection and maintenance provides an explanation that does not invoke selection for longevity per se, as these pathways could have evolved simply to allow animals to survive harsh, life-threatening environments. Once these protective pathways were in place, however, they would naturally have the potential to extend lifespan by counteracting internal metabolic wear and tear that accelerates ageing. Moreover, mutations that augment the basal activity levels of these cell-protective pathways, through changes in regulators or downstream targets, might have increased lifespan during evolution." She also suggests that these mechanisms of the evolution of ageing might explain why the ageing process is so malleable and why some age-dependent changes prove to be reversible, contrary to the prediction of the stochastic and non-programmed models of senescence.

This explanation seems compelling and evidence is accumulating that it is relevant to organismal senescence in various evolutionarily distant groups of organisms. It also recognises the importance of TOR signalling in the ageing process as TOR inhibition increases resistance to environmental stress and extends lifespan independently of DAF-16/FOXO, which suggests that TOR inhibition activates a pathway that is distinct from the insulin/IGF-1 pathway (Kenyon 2010) and is a primary cause of life extension through dietary restriction in model animals. To date, calorie restric-

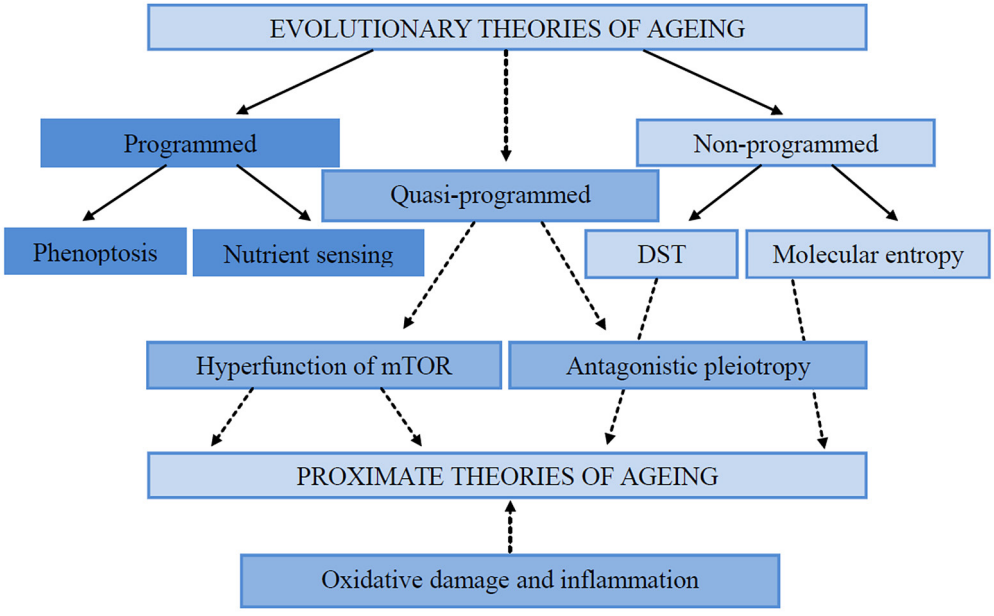

Fig. 1. Classification of modern theories of ageing (after Sikora 2014, modified)

tion (CR) or dietary restriction (DR) is the most effective way of slowing down the ageing process and extending life expectancy. The TOR kinase plays a key role in the regulation of cell proliferation and metabolism, and its activity is regulated by various factors, including oxygen, nutrients (e.g. glucose, amino acids, and fatty acids), hormones and growth factors (insulin, IGF-1), and cytokines (Chmielewski et al. 2016). Interestingly, the TOR kinase is activated by these factors and inhibited by a shortage of these factors or by some TOR inhibitors such as PP242 and Torin1 (Leontieva et al. 2015; Chmielewski and Borysławski 2016). Mutations that inhibit the TOR pathway extend lifespan in numerous evolutionarily distant model organisms such as nematodes, fruit flies, and mammals. Moreover, CR does not further extend the lifespan of these mutants, which suggests that the primary cause why dieting organisms live longer compared to ad libitum fed organisms is TOR inhibition.

Quasi-programmed ageing: antagonistic pleiotropy

In 1957, George Williams proposed a theory according to which ageing has evolved due to antagonistic pleiotropy, i.e. the phenomenon where a given gene controls for more than one phenotypic trait, and its effects are beneficial to survival and reproductive success at young age but become costly and detrimental to these fitness components at old age. It was favoured by natural selection because its early benefits (e.g. taller stature, higher level of testosterone in men, greater reproductive success, greater activity of the p53 protein, more frequent apoptosis, autophagy, greater inflammation, etc.) outweigh its late costs (e.g. higher risk of testicular cancer, neoplasms, cardiovascular disease, greater chronic low-grade inflammation, type 2 diabetes, decreased life expectancy, etc.), chiefly because even small positive effects early in life can be strongly selected for, while even large negative effects in late life are in selection shadow and hence cannot be selected against. This process has several negative consequences such as homeostenosis, i.e. reduced adaptive responses to environmental stresses, which is a hallmark of ageing.

Williams (1957) pointed to the example of a gene that codes for calcium deposition in bones, which promotes survival at early stages of ontogeny. Such a gene should be favoured by natural selection. Yet, if the same gene promotes calcium deposition in the arteries, causing atherosclerosis later in life, it cannot be selected against by natural selection because this organism had better chances of survival early in life when the forces of selection were stronger and could have greater reproductive success. Thus, it already produced its offspring. Such a stage is referred to as selection shadow because the genes were already passed on to the next generation and the selection pressures are now significantly diminished. Even a trait that has large negative effects on health and survival cannot be selected against. Huntington's disease is often given as an illustration of this concept. Some later investigations suggest that the process of antagonistic pleiotropy is underappreciated and of fundamental importance to the maintenance of the polymorphic disease alleles and the evolution of senescence (Blagosklonny 2010; Carter and Nguyen 2011). Genes that act in this way have been termed "antagonistically pleiotrop-

ic genes" and they are responsible for fitness trade-offs, for example increased risk of testicular cancer in taller and more masculine men compared to shorter and less masculine ones (Dieckemann et al. 2008). Other examples of antagonistically pleiotropic genes include the IGF genes, the clk-1 gene (in *C. elegans*), and genes regulating apoptosis, including the p53 gene. For instance, an adequate level of IGF-1 (as well as GH and insulin) is indispensible to normal growth and development during progressive stages of ontogeny. However, its elevated level in adulthood and later in life is associated with higher risk of cancer and premature death. Interestingly, this type of trade-off can be involved in shaping the mysterious inverse relationship between adult height and longevity which has been reported by some authors, though it can be tenuous or can even disappear after controlling for several confounders, especially in women (Chmielewski 2016).

Quasi-programmed ageing: mTOR as a "molecular hypothalamus"

On the basis of the theory of antagonistic pleiotropy and the concept of quasi-programmed ageing, Mikhail Blagosklonny developed the idea of hyperfunction of certain molecular mechanisms of growth and development, such as mTOR, as more proximate causes of organismal ageing (Fig. 1) than the accumulation of random molecular damage (Blagosklonny 2010; 2012; 2013). In this view, although the body was not programmed to age and die, there are some intrinsic and inevitable processes and mechanisms that eventually kill the body. For example, the process of cell division and developmental growth, which depend on some molecular factors, prove to be costly and harmful to the body in the long run.

According to this theory, the TOR kinase and TOR signalling are indispensable for the growth and development of the body (it is their function in early life) and they play a key role in the process of controlling ageing and its pace (it is their hyperfunction in late life) as a universal "molecular hypothalamus" (Blagoskonny 2013), which is also known as the "mTOR-centric model" of ageing. This model provides alternative explanations for many unsolved problems and paradoxes in current gerontology (for a review, see Chmielewski and Borysławski 2016; Chmielewski et al. 2016), and, for instance, hormesis does not make sense except in the light of the hyperfunction theory and the mTOR-centric model (Blagoskonny 2011). However, some authors suggest that this view is far too simplistic and the accumulation of random molecular damage is the more proximate cause of ageing, so the paradigm of gerontology should not be changed (Zimniak 2012).

Non-programmed ageing: the disposable soma theory

In 1977, Thomas Kirkwood, a young British biologist, came up with an idea that the ageing process has something to do with the energy budget of the organism and the necessity to economically distribute resources for two energetically competitive processes, i.e. the maintenance of the body and the reproduction. From an evolutionary perspective, the propagation of genes to the next generations was the overriding priority in our evolutionary past when the selection pressures were extremely high, hence it

was never a high enough priority to invest in a body that could last forever or at least much longer than the limit of essential lifespan (35-45 years in humans), and shortly afterwards things get ugly with respect to health and life expectancy since from an evolutionary point of view it would be unreasonable to predict that the organism is still alive after this limit. Senescence is just the continuation of these unplanned events that involve homeostenosis, i.e. a non-programmed reduction in adaptive capacity of the organism with advancing age that results mainly from the gradual accumulation of random molecular and cellular damage and manifests itself in distorted response to environmental stresses. In the light of this simple and testable theory, it is clear that ageing cannot be programmed (Fig. 1) by any intrinsic mechanisms, such as gerontogenes, because when the resources were allotted to the reproduction at the expense of the maintenance and repair of the body, evolution through natural selection could not have further limit the survival by any programme for ageing, or at least it does not make any sense from an evolutionary point of view.

Nevertheless, it is conceivable that the programme for ageing was already there and could have act as an atavistic and primary mechanism that has controlled the metabolism of the organism, irrespective of further evolutionary events. It appears that Kirkwood's theory suggests that ageing is of secondary origin compared to the mechanisms of survival and reproduction, as the standard model of evolution predicts which is not necessarily true. For example, Kirkwood (2005) asserts that even if there were some programme responsible for ageing and destruction of the body, errors, such as mutations, should be expected to occur in it at some time of evolution. As a result, non-mutant organisms would continue to sacrifice themselves to the good of the population or species, whilst these mutant organisms would benefit from the sacrifice of others, thereby enjoying any fitness advantage that may accrue from the cessation of ageing and virtual immortality. He does not consider the possibility that the cessation of ageing through mutations that inhibit its genetic programme could have a sinister side or could have semi-lethal or lethal effects in the wild. Although it may seem improbable, it is conceivable that the inhibition of TOR and insulin/IGF-1 signalling, or the knock-out of genes controlling metabolism and ageing can concurrently lead to, for instance, severe impairment of growth and development, disadvantageous changes in the phenotype or metabolism of these mutants, and altered responses to nourishment that were pernicious to their survival in nature. For example, it is known that dieting model organisms are very often significantly smaller and physically weaker than their ad libitum fed counterparts, and it seems that virtually all methods of life extension, such as the inhibition of TOR and insulin/IGF-1 signalling, stem cell therapies, and other forms of epigenetic reprogramming, have some side-effects. However, to my knowledge none of the authors has ever suggested that these side-effects could have been responsible, to some extent, for the limitations of natural selection with respect to the elimination of the process of ageing through mutations or other mechanisms that are likely to distort the programme for ageing, probably because they seem too small and unimportant and life extension is very often perceived as the most desired effect.

Moreover, it is not clear why human sexual activity and fertility are usual-

ly not inversely related to longevity, a finding that is contradictory to the disposable soma theory. Some studies have shown that there is such a negative relationship in humans (Westendorp and Kirkwood 1998), but most studies have demonstrated that there is a lack of any association or there is even a positive relationship between these life history parameters, which flies in the face of Kirkwood's theory (Mitteldorf 2010; 2016). However, the studies on the costs of reproduction are well advanced. These biological costs, such as greater oxidative stress, as assessed by 8-OHdG and some other biomarkers, in women who had more children compared to those with lower gravidity and parity, have been confirmed by recent investigations (Ziomkiewicz et al. 2016). On the other hand, other authors suggest that the costs of reproduction in women are not so important with respect to general health and longevity (Gurven et al. 2016).

Non-programmed ageing: molecular entropy

It is known that the idea of entropy as a direct cause of organismal ageing is obsolete and discarded. This theory, also referred to as the standard version of the wear and tear theory, predicted that the accumulation of some kind of damage at the physical level is responsible for ageing and the human body is breaking down over time just in the same way a car does.

If this were the case, organisms should be thermodynamically closed systems, and we know that this is definitely not true because "to put it bluntly, we have a hole at each end" (Kirkwood 1999). Moreover, from its beginning life would also be subject to some kind of deterioration with time, which shows that this is a specious argument. Some authors (e.g. Mitteldorf 2010) put forward some arguments to disprove the valid theory of molecular entropy, which seems unjustified as the entropic view is very different from the theory of molecular entropy. The latter holds that evolution only took care of the growth and development of the organism. These processes are tightly controlled at the molecular and cellular level and they are genetically programmed. However, evolution did not take care of the events following the growth and development due to, for instance, the selection shadow. With ageing, the built-in mechanisms that normally resist entropy early in life tend to falter and fail in the long run. Therefore, the ageing process involves a progressive deterioration in homodynamic mechanisms and the adaptive capacity of the organism to respond to environmental stresses, which is often referred to as homeostenosis, which is a hallmark of ageing. Thus, these homeodynamic (but not "homeostatic" since this term is erroneous and should not be used anymore in the scientific literature as there is nothing static in the organism) mechanisms resist entropy, but they falter and fail in late ontogeny and eventually allow molecular entropy, which is a consequence of deterioration in these mechanisms resisting entropy. This theory predicts that molecular entropy is the most proximate cause of ageing, but the very explanation for the origin and mechanisms of evolution of senescence through molecular entropy could also be classified as a non-programmed model of ageing (Fig. 1).

Conclusions

Currently, the science of ageing offers at least several theories which are compet-

ing to be a general and integrated model of senescence, making it unlikely that all of them could be true. These theories can be categorised into three groups, i.e. programmed, quasi-programmed, and non-programmed models of ageing. The deterministic views include the theory of phenoptosis proposed by Skulachev, the theory of nutrient sensing and response to nourishment proposed by Kenyon, and some other explanations, including the demographic theory and the theory of epigenetic clock that controls senescence. Quasi-programmed models include the antagonistic pleiotropy theory proposed by Williams and the theory of TOR-driven ageing proposed by Blagosklonny. These two views can also be considered the same general theory. The disposable soma theory formulated by Kirkwood is very similar to these models, but ageing cannot be programmed or quasi-programmed according to Kirkwood's theory since the resources were allocated to the process of reproduction at the expense of the processes of maintenance and repair of the body. Thus, it would be not reasonable to predict that some types of selection pressures could have further limit the survival through some unnecessary programmes for ageing, as if the problem was too long lifespan in the wild. On the contrary, since the resources were scarce the problem was to ensure the survival in order to propagate the genes to the next generation. Another model of non-programmed ageing, known as the theory of molecular entropy, postulates that evolution could have taken care of the growth and development of the organism but the events following the limit of essential lifespan in late ontogeny result from the gradual accumulation of molecular and cellular damage because of homeostenosis which is caused by the gradual deterioration in homeodynamic mechanisms that resist entropy earlier in life. Thus, this theory is different from the theory of wear and tear or the entropic view and should not be considered equivalent to them.

Conflict of interest

The author declares that there is no conflict of interests regarding publication of this paper.

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References

Blagosklonny MV. 2010. Revisiting the antagonistic pleiotropy theory of aging: TOR-driven program and quasi-program. Cell Cycle 9(16):3171–6.

Blagosklonny MV. 2011. Hormesis does not make sense except in the light of TOR-driving aging. Aging 3(11):1051–62.

Blagosklonny MV. 2012. Answering the ultimate question "What is the proximal cause of aging?". Aging 4(12):861–77.

Blagosklonny MV. 2013. M(o)TOR of aging: MTOR as a universal molecular hypothalamus. Aging 5(7):490–4.

Carter AJ, Nguyen AQ. 2011. Antagonistic pleiotropy as a widespread mechanism for the maintenance of polymorphic disease alleles. BMC Med Genet 12:160.

Chmielewski P. 2016. The relationship between adult stature and longevity: tall men are unlikely to outlive their short peers – evidence from a study of all adult deaths in Poland in the years 2004–2008. Anthropol Rev 79(4):439–60.

Chmielewski P, Borysławski K. 2016. Proksymalne przyczyny starzenia się człowieka: przypadkowe uszkodzenia molekularne czy hiperfunkcja programów rozwojowych? Kosmos 65:339–49.

Chmielewski P, Borysławski K, Strzelec B. 2016. Contemporary views on human aging and longevity. Anthropol Rev 79:115–42.

de Magalhães JP. 2012. Programmatic features of aging originating in development: aging mechanisms beyond molecular damage? The FASEB Journal 26(12):4821–6.

Díaz-López A, Bulló M, Martínez-González MA, Corella D, Estruch R, Fitó M, Gómez-Gracia E, Fiol M, García de la Corte FJ, Ros E, Babio N, Serra-Majem L, Pintó X, Muñoz MÁ, Francés F, Buil-Cosiales P, Salas-Salvadó J. 2016. Dairy product consumption and risk of type 2 diabetes in an elderly Spanish Mediterranean population at high cardiovascular risk. Eur J Nutr 55(1):349–60.

Dieckmann KP, Hartmann JT, Classen J, Lüdde R, Diederichs M, Pichlmeier U. 2008. Tallness is associated with risk of testicular cancer: evidence for the nutrition hypothesis. Br J Cancer 99(9):1517–21.

Gao D, Ning N, Wang C, Wang Y, Li Q, Meng Z, Liu Y, Li Q. 2013. Dairy products consumption and risk of type 2 diabetes: systematic review and dose-response meta-analysis. PLoS One 8(9):e72965.

Garcia-Cao I, Garcia-Cao M, Martin-Caballero J, Criado LM, Klatt P, Flores JM, Weill JC, Blasco MA, Serrano M. 2002. ''Super p53'' mice exhibit enhanced DNA damage response, are tumor resistant and age normally. EMBO J 21:6225–35.

Gijsbers L, Ding EL, Malik VS, de Goede J, Geleijnse JM, Soedamah-Muthu SS. 2016. Consumption of dairy foods and diabetes incidence: a dose-response meta-analysis of observational studies. Am J Clin Nutr 103(4):1111–24.

Gurven M, Costa M, Ben Trumble, Stieglitz J, Beheim B, Eid Rodriguez D, Hooper PL, Kaplan H. 2016. Health costs of reproduction are minimal despite high fertility, mortality and subsistence lifestyle. Sci Rep 6:30056.

Harman D. 2006. Free radical theory of aging: an update. Increasing the functional life span. Ann N Y Acad Sci 1067:10–21.

Hayflick L. 2007. Biological aging is no longer an unsolved problem. Ann N Y Acad Sci 1100:1–13.

Heininger K. 2012. The germ-soma conflict theory of aging and death: obituary to the "evolutionary theories of aging". WebmedCentral AGING 3(4):WMC003275.

Holliday R. 2006. Aging is no longer an unsolved problem in biology. Ann N Y Acad Sci 1067:1–9.

Holliday R. 2007. Aging: the paradox of life. Why we age. New York: Springer.

Jin K. 2010. Modern biological theories of aging. Aging Dis 1(2):72–4.

Kenyon C. 2001. A conserved regulatory system for aging. Cell 105(2):165–8.

Kenyon C. 2005. The plasticity of aging: insights from long-lived mutants. Cell 120(4):449–60.

Kenyon CJ. 2010. The genetics of ageing. Nature 464:504–12.

Kenyon C. 2011. The first long-lived mutants: discovery of the insulin/IGF-1 pathway for ageing. Philos Trans R Soc Lond B Biol Sci 366(1561):9–16.

Kirkwood TBL. 1977. Evolution of ageing. Nature 270:301–4.

Kirkwood T. 1999. Time of our lives. The science of human aging. New York: Oxford University Press.

Kirkwood TBL. 2005. Understanding the odd science of aging. Cell 120(4):437–47.

Kirkwood TB, Melov S. 2011. On the programmed/non-programmed nature of ageing within the life history. Curr Biol 21(18):R701–7.

Kochman K. 2015. New elements in modern biological theories of aging. Folia Medica Copernicana 3(3):89–99.

Leontieva OV, Demidenko ZN, Blagosklonny MV. 2015. Dual mTORC1/C2 inhibitors suppress cellular geroconversion (a senescence program). Oncotarget 6:23238–48.

Lipsky MS, King M. 2015. Biological theories of aging. Disease-a-Month 61:460–6.

Longo VD, Mitteldorf J, Skulachev VP. 2005. Programmed and altruistic ageing. Nat Rev Genet 6:866–72.
Medawar PB 1952. An unsolved problem of biology. London: HK Lewis and Co.
Medvedev ZA. 1990. An attempt at a rational classification of theories of ageing. Biol Rev Camb Philos Soc 65:375–98.
Mitteldorf J. 2010. Evolutionary origins of aging. In: Fahy GM, editor. The future of aging. Pathways to human life extension. New York: Springer.
Mitteldorf J. 2016. An epigenetic clock controls aging. Biogerontology 17(1):257–65.
Mitteldorf J. 2017. Aging is a group-selected adaptation: theory, evidence, and medical implications. New York: Taylor & Francis Group.
Rattan SIS. 2006. Theories of biological aging: genes, proteins, and free radicals. Free Radic Res 40(12):1230–8.
Scrable H, Burns-Cusato M, Medrano S. 2009. Anxiety and the aging brain: stressed out over p53? Biochim Biophys Acta 1790:1587–91.
Sergiev PV, Dontsova OA, Berezkin GV. 2015. Theories of aging: an ever-evolving field. Acta Naturae. 7(1):9–18.
Sikora E. 2014. Starzenie i długowieczność. Postępy Biochemii 60(2):125–37.
Skulachev VP. 1997. Aging is a specific biological function rather than the result of a disorder in complex living systems: biochemical evidence in support of Weismann's hypothesis. Biochemistry 62(11):1191–5.
Skulachev VP. 2001. The programmed death phenomena, aging, and the Samurai law of biology. Exp Gerontol 36(7):995–1024.
Skulachev VP. 2011. Letter to the editor: Aging as a particular case of phenoptosis, the programmed death of an organism (a response to Kirkwood and Melov "On the programmed/non-programmed nature of ageing within the life history". Aging 3(11): 1120–3.
Skulachev VP. 2012. What is "phenoptosis" and how to fight it? Biochemistry 77(7):689–706.
Skulachev VP. 2013. Concept of aging as a result of slow programmed poisoning of an organism with mitochondrial reactive oxygen species. In: VP Skulachev, AV Bogachev, FO Kasparinsky, editors. Principles of bioenergetics. New York: Springer.
Skulachev VP, Longo VD. 2005. Aging as a mitochondria-mediated atavistic program: can aging be switched off? Ann NY Acad Sci 1057:145–64.
Soedamah-Muthu SS, Verberne LD, Ding EL, Engberink MF, Geleijnse JM. 2012. Dairy consumption and incidence of hypertension: a dose-response meta-analysis of prospective cohort studies. Hypertension 60(5):1131–7.
Tyner SD, Venkatachalam S, Choi J, Jones S, Ghebranious N, Igelmann H, Lu X, Soron G, Cooper B, Brayton C, Hee Park S, Thompson T, Karsenty G, Bradley A, Donehower LA. 2002. p53 mutant mice that display early ageing-associated phenotypes. Nature 415:45–53.
van Heemst D, Beekman M, Mooijaart SP, Heijmans BT, Brandt BW, Zwaan BJ, Slagboom PE, Westendorp RGJ. 2005. Reduced insulin/IGF-1 signalling and human longevity. Aging Cell 4:79–85.
Wang H, Fox CS, Troy LM, Mckeown NM, Jacques PF. 2015. Longitudinal association of dairy consumption with the changes in blood pressure and the risk of incident hypertension: the Frmanigham Heart Study. Br J Nutr 114(11):1887–99.
Weismann A. 1889. Essays upon heredity and kindred biological problems. Oxford: Claderon Press.
Westendorp RG, Kirkwood TB. 1998. Human longevity at the cost of reproductive success. Nature 396(6713):743–6.
Williams G. 1957. Pleiotropy, nautral selection, and the evolution of senescence. Evolution 11:398–411.
Zimniak P. 2012. What is the proximal cause of aging? Front Genet 3:189.
Ziomkiewicz A, Sancilio A, Galbarczyk A, Klimek M, Jasienska G, Bribiescas RG. 2016. Evidence for the Cost of Reproduction in Humans: High Lifetime Reproductive Effort Is Associated with Greater Oxidative Stress in Post-Menopausal Women. PLoS One 11(1):e0145753.