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Contemporary views on human aging and longevity

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Abstract: Aging is currently stimulating intense interest of both researchers and the general public. In developed countries, the average life expectancy has increased by roughly 30 years within the last century, and human senescence has been delayed by around a decade. Although aging is arguably the most familiar aspect of human biology, its proximate and ultimate causes have not been elucidated fully and understood yet. Nowadays there are two main approaches to the ultimate causes of aging. These are deterministic and stochastic models. The proximate theories constitute a distinct group of explanations. They focus on mechanistic causes of aging. In this view, there is no reason to believe that there is only one biological mechanism responsible for aging. The aging process is highly complex and results from an accumulation of random molecular damage. Currently, the disposable soma theory (DST), proposed by Thomas Kirkwood, is the most influential and coherent line of reasoning in biogerontology. This model does not postulate any particular mechanism underpinning somatic defense. Therefore, it is compatible with various models, including mechanistic and evolutionary explanations. Recently, however, an interesting theory of hyperfunction of mTOR as a more direct cause of aging has been formulated by Mikhail Blagosklonny, offering an entirely different approach to numerous problems and paradoxes in current biogerontology. In this view, aging is quasi-programmed, which means that it is an aimless continuation of developmental growth. This mTOR-centric model allows the prediction of completely new relationships. The aim of this article is to present and compare the views of both parties in the dispute, based on the results of some recent experimental studies, and the contemporary knowledge of selected major aspects of human aging and longevity.

Key words: aging, hyperfunction theory, longevity, mTOR-centric model, quasi-programmed aging, senescence, signaling pathways

Introduction

"The idea is to die young as late as possible" Ashley Montagu (1905–1999).

The problem of aging has been stimulating intense interest of both researchers and the general public because of the continuously extending average human lifespan. In developed countries, there

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has been a steady rise in the number of elderly people as a proportion of the total population. In the United States, for example, the average lifespan has increased from 47 years in 1900 to about 75 years in the early 21st century (Ganong 2005). Similar trends can be observed in all developed countries across the world (Barbi et al. 2008). It has been estimated that human senescence has been delayed by around a decade (Vaupel 2010). Some authors state that the gain of about 30 years in life expectancy in the United States, Canada, Europe, and Australia, and even larger gains observed in Japan, stands out as one of the most important accomplishments of the 20th century (Christensen et al. 2009).

In addition to demographic, biological, and medical aspects of aging, there is another important reason why the aging process is such an interesting subject of research and attracts so much attention. Probably only human beings realize the inevitable passage of time and the fact of aging and dying. Therefore, since time immemorial people have searched for various life extension methods and rejuvenation strategies which would ensure the longest possible period of youth, fitness, and health (Gavrilov and Gavrilova 1991; Arking 2006; Kwiatkowska and Borysławski 2010; Karnaukhov et al. 2015; Kaeberlein and Martin 2016).

Aging can be viewed as a normal developmental process. That aging is a genetically programmed aspect of development. Cellular senescence is often described as a programmed response of cells to diverse stresses, including oxidative damage, telomere shortening, oncogene activation, and changes in chromatin structure (Kaeberlein and Martin 2016). There is no doubt that senescence is one of the fundamental physiological processes that can affect cells and systems made up of them, as well as their chemical components such as collagen and elastin (Ganong 2005; Arking 2006). Aging is arguably the most familiar aspect of human biology, although both its proximate causes and evolutionary explanations are not fully understood and remain open to misinterpretation. For example, the entropic view, according to which the aging process results from physical necessity determined by the changing, unstable nature of complex systems, described by the second law of thermodynamics, is very old, extremely widespread, and most likely defective. Although the analogy of an aging body and a car breaking down over time may be philosophically attractive and appealing, no convincing experimental evidence that would support such a model of organismal aging has been proposed to date (Arking 2006). In addition, living organisms are thermodynamically open biological systems that exchange matter and energy with the environment. This is a sufficient argument to challenge the theory of entropy with respect to mechanistic causes of organismal senescence. In late ontogeny, however, homeostatic mechanisms tend to falter and eventually allow entropy in biological systems (Chmielewski et al. 2015b). This problem highlights the fact that the process of aging is much more complex and multifaceted than it seems to be. The peculiarity of the aging process consists in its complexity (Kaczmarek and Szwed 1997; Borysławski and Chmielewski 2012a; 2012b; Borysławski et al. 2015).

According to another group of theories, commonly referred to as the deterministic models of aging, there is a biological program for destruction of the body. These views, as opposed to the

stochastic models that focus on random molecular damage, concentrate on the genetically programmed causes of aging such as phenoptosis (Skulachev 2011; 2012; Khalyavkin 2013). The proponents of such explanations argue that the process of structural and functional deterioration with age, manifested outwardly as non-adaptive, has evolved independently as a by-product of evolution. Thus, the process of organismal senescence has been favored for some reasons by natural selection due to its covert adaptive value. Therefore, "senescence occurs not because of trade-offs early or late in life but simply because the species reaches an evolutionary stable strategy for life span that would be less or as stable if longevity were increased" (Gonidakis and Longo 2009). Although there are some plausible arguments in favor of these theories (Longo et al. 2005; Prinzinger 2005; Mitteldorf 2006; 2010; 2016; Mitteldorf and Pepper 2009; Skulachev 2011; 2012; Khalyavkin 2013), they are inconsistent with contemporary population genetics and evolutionary biology, and therefore many authors maintain that they are invalid (Kirkwood 2005; 2008; Rose and Finch 2010; Kirkwood and Melov 2011; Blagosklonny 2013a; 2013d). Mikhail Blagosklonny (2013d) asserts that: "Aging is not and cannot be programmed. Instead, aging is a continuation of developmental growth, driven by genetic pathways such as mTOR. Ironically, this is often misunderstood as a sort of programmed aging". Currently, the majority of researchers and scholars do not share the deterministic view, and consequently the otherwise interesting idea of phenoptosis proposed by Skulachev and Longo remains controversial. It should be mentioned, however, that the model of programmed and altruistic aging is much more optimistic than the alternative stochastic model as it predicts the possibility of various therapeutic approaches and interventions known as the anti-aging medicine, while the stochastic model does not allow such a possibility.

The theories of evolutionary trade-offs were proposed several decades ago by Williams (1957) and Kirkwood (1977). According to the widely accepted models of evolutionary trade-offs, there is no genetic program that would actively and solely contribute to the aging process and destruction of the body. Since the body is not programmed to age and die, there is nothing in the human genome that specifies the lifespan or controls the rate of aging. There are no genes that activate any type of destruction, deterioration, and aging. Indeed, the opposite is true. The body is programmed for survival up to the last minute of our life. The activity of genes and their expression products, resulting from the process of natural selection, ensures the propagation of the genes in the gene pool of a population, and increases the likelihood of survival, not the likelihood of self-destruction of the body (Kirkwood 1999; 2002; 2005; 2008). In addition, there is also the well-known problem of "cheating" that challenges the theories of programmed and altruistic aging (Kirkwood 2005). Even if there were some genetic program responsible for destruction and aging, serious errors should be expected to occur in it at some time of evolution. For example, a single mutation or a set of mutations that would inactivate the aging program, which would be also beneficial to such mutants. Non-mutant organisms would continue to "sacrifice" themselves, while the mutants would benefit from the sacrifice of others, "enjoying any fitness advantage that might accrue

from immortality" (Kirkwood 2005). Such mutations would be beneficial in terms of adaptation and would therefore be expected to spread. They would be favored by any type of natural selection (Kirkwood 2002; 2005; 2008) because all or at least most of the morphological, physiological, biochemical, and behavioral aspects of aging are non-adaptive. Therefore, the elimination of the causes of aging and their phenotypic symptoms would increase the evolutionary adaptation of the mutants, and consequently such mutations would spread in the gene pool of the population. According to the models of evolutionary trade-offs, the real cause of aging is therefore either different activity of genes ensuring survival and fertility in young and old age, defined as the theory of antagonistic pleiotropy (Williams 1957), or the compromise in allocating resources for survival (i.e. for maintenance and repair), and reproduction, which is defined as the disposable soma theory (DST), proposed by Thomas Kirkwood (1977; 1999; 2002; 2005; 2008), and described by mathematical models (Drenos and Kirkwood 2005). Both these axioms consist in evolutionary trade-offs. Unlike the theory of antagonistic pleiotropy, the DST does not postulate any particular mechanism underpinning somatic defense, and therefore is compatible with various mechanistic theories and models of aging, including the free radical theory proposed by Harman (1956; 2006), the mitochondrial free radical theory (MFRTA), the theory of DNA damage and mutations (especially in mtDNA), the theory of accumulation of random molecular damage, and the accumulation of incorrect repair resulting in the defective structure and function (Kirkwood and Kowald 2012). Interestingly, this view also provides a framework for understanding the evolutionary mechanisms that have led to the existence of aging (Kirkwood 1999; 2002; 2005; 2008).

An increasing number of experimental data suggest that aging in evolutionary distant model organisms, such as nematodes, fruit flies, and some mammals, is regulated through evolutionary conserved signaling pathways such as the insulin/IGF-1 pathway (Kenyon 2011) and mTOR (Blagosklonny 2012), which stands for "mammalian target of rapamycin", formally referred to as "mechanistic target of rapamycin" (MTOR), informally known as the "M(o)TOR of aging", and biochemically described as serine/threonine kinase (Hands et al. 2009; Kapahi et al. 2009; Katewa and Kapahi 2011; Sharp 2011; Kaeberlein and Martin 2016). Based on this, the theory of hyperfunction has been latterly formulated, including the important mTOR quasi-program rival to the DST, offering a completely different approach to numerous problems and paradoxes in current biogerontology, and allowing the prediction of completely new relationships (Blagosklonny 2008; 2009; 2010a; 2010b; 2012; 2013a; 2013b; 2013c; 2013d; 2013e; 2013f). However, there were also some controversies. For example, serious reservations and criticisms were put forward as to the appropriateness of establishing such a new paradigm to replace the convenient and conceptually capacious theories of random molecular damage as proximate causes of aging which can include, according to some authors, also the hyperfunction of developmental programs (Zimniak 2012).

The purpose of this article is to present and compare the views of both parties in the dispute, based on the results of recent experimental biogerontological

studies and the contemporary knowledge of selected major aspects of human aging and longevity, as well as characterize the explanatory power of the new theory of hyperfunction in view of the existing theories of aging, particularly the DST proposed by Kirkwood (1977; 2005; 2008), mainly with regard to the recent findings on various factors and mechanisms of human aging and longevity.

Models of aging: solving the problem of conceptual dualism

Currently, there are two main theoretical approaches to the ultimate causes of aging. These two opposite concepts are deterministic and stochastic models, although the standard model is stochastic. It assumes that aging is a highly complex phenomenon that results from an accumulation of random molecular damage. According to the deterministic view (Severin and Skulachev 2009), the aging process consists in the activity of biological mechanisms that are evolutionarily programmed to bring about the death of an individual in later stages of the ontogenetic development. In this view, aging is adaptive, altruistic, teleological (purposeful), and increases the adaptation at the population level, because it is associated with the desired elimination of individuals that are older, weaker, and that require care (Skulachev 2011; 2012). Thus, it is possible to invent a remedy for aging, or even the "elixir of youth", simply by using inhibitors of the biological mechanisms responsible for the aging process (Longo et al. 2005; Mitteldorf 2006; 2010; 2016; Skulachev 2011; 2012).

On the other hand, the stochastic model of aging considers senescence as an aimless, non-programmed, and non-adaptive process of gradual and irreversible changes that lead to reduced regeneration capacity, adaptability, and reproductive potential. These changes also disturb the mechanisms responsible for homeostasis of the organism. This processes are neither adaptive nor altruistic, and not even genetically programmed (Kaczmarek and Szwed 1997; Kirkwood 2005; 2008). According to this view, there is no single cause of aging (Arking 2006) but rather an accumulation of random molecular damage, including various detrimental effects of reactive oxygen species (ROS), electrophiles, mutations, molecular damage in DNA and proteins that causes aging (Zimniak 2012). In this approach, achieving immortality through medical interventions or therapies is very unlikely. The aging process is a multifaceted, malleable, and highly complex phenomenon (Kaczmarek and Szwed 1997), involving all levels of biological organization, that is not directly controlled by any causative agent, and therefore cannot be easily eliminated by some sophisticated methods, even therapeutic ones. Interestingly, this dualism corresponds to the well-known problem of aging as a disease and aging as normal part of development. Thus, a number of multi-level structural and functional changes with age in numerous biological traits (Borysławski et al. 2015; Chmielewski et al. 2015a; 2015b) inevitably lead to death and determine lifespan. A variant of this approach is the widespread and popularized disposable soma theory proposed by Kirkwood (1977; 1999; 2002; 2005; 2008). Curiously, Kirkwood (1999) believes that his theory supports the stochastic models of aging rather than deterministic ones, although there is no full consensus among researchers, and some even claim that it is exactly the

opposite (Kołodziejczyk 2007). This may suggest that such classification is in fact arbitrary and artificial, and the aging process is neither genetically programmed nor completely passive but consists in quasi-program, which is an aimless continuation of developmental growth caused by the evolutionary conserved insulin/IGF signaling pathway (Kenyon 2011) and the hyperfunction of mTOR (Blagosklonny 2012; 2013a).

Blagosklonny (2010a) asserts that the DST, in its current form, implicitly contradicts the evolutionary theory, because it suggests that the aging process "is regulated by choosing not to repair in the time of plenty, or instead repair when resources are scarce in order to live longer (as if aging limits lifespan in the wild) and reproduce later". For example, according to the DST, menopause is programmed to benefit aging women, their children, and grandchildren (Chmielewski 2012), because such cessation of reproduction is associated with increased rate of repair due to the allocation of resources (Kirkwood 1999), which is beneficial to women's health and extends their longevity. According to the proponents of the mTOR-centric model, menopause (like other diseases, e.g. arteriosclerosis) is an aimless and quasi-programmed by-product or a consequence of the ontogenetic development that is definitely not beneficial to women's health. In this view, women cannot benefit from menopause mainly because most females in our evolutionary past did not live long enough to experience it. Therefore, menopause is simply another example of age-related conditions or diseases which occur in aging individuals.

Interestingly, the well-known dualism "aging caused by mistakes is non-programmed" vs. "aging caused by nature is programmed" is thus no longer current.

Table 1. Comparison of three models of aging, their premises, and central tenets (after Blagosklonny 2013a, modified).

Model of aging and its major premise	Is aging programmed?	Is aging purposeful?	Menopause is…	Link between aging and disease is…	Extra calories…
Stochastic aging is driven by random molecular damage caused e.g. by ROS	No, although in some organisms such as salmon it seems to be (a special case)	No	programmed and beneficial to women's health	vulnerability to diseases	are good for health via repair and should extend lifespan
Quasi-programmed hyperfunction of mTOR causes aging, not random molecular damage	Never, it results from developmental growth	No	a prototypical disease and is not beneficial to women's health	manifested by diseases	accelerate aging via mTOR, which can shorten lifespan
Deterministic aging is driven by non-random molecular damage caused e.g. by ROS	Yes, through phenoptosis	Yes	programmed	unspecified	unspecified

If aging is driven by molecular and cellular damage or errors that accumulate with age and are being made purposely by some innate program, senescence could be viewed as a programmed process that consists in mistakes. If aging results from an aimless continuation of developmental growth, which is known as the mTOR-centric model, then it is quasi-programmed, but it is still definitely not programmed (Blagosklonny 2013d). According to Blagosklonny (2012), the hyperfunction is not an example of random molecular damage. In this view, therefore, aging is not programmed and does not consist in mistakes. It is an aimless continuation or a consequence of developmental growth.

The current models of aging, including both mechanistic theories of non-programmed aging driven either by random molecular damage (the stochastic model) or the hyperfunction theory of aging (the mTOR-centric model of quasi-programmed aging), as well as the deterministic theory of programmed and altruistic aging driven by non-random molecular damage caused by the process of phenoptosis, are summarized in Table 1.

The quest for determinants of human longevity

Like the aging process, human lifespan is remarkably malleable and pliable. Factors affecting lifespan and longevity are of vital importance to researchers and society. It has long been known that there is clear heritability of human longevity. Nonetheless, the genetic factors involved in longevity are extremely complex, and the quest for genetic determinants of lifespan has a long history (Beekman et al. 2013).

It is important to understand that longer lifespan is largely attributed to the invention of antibiotics, the introduction of immunization, improved sanitary and living conditions, the progress in hygiene and prophylaxis, and above all, more effective treatment and prevention of infections or other causes of premature death. Therefore, more and more people have a chance to live to the age of 70 years. At the same time, the maximum lifespan (MLS) has probably not changed at all, and the longest-living person whose dates of birth and death were confirmed was a French supercentenarian Jeanne Calment (1875–1997) who lived to 122. It is not impossible, however, that in the future this figure will be higher since the steady and dramatic increase in the proportion of the most long-lived individuals, i.e. centenarians and supercentenarians, is being observed (Oeppen and Vaupel 2002; Robine and Caselli 2005; Robine et al. 2007; Weon and Je 2009).

The heritability of human lifespan has been estimated at about 20–25% (McGue et al. 1993; Herskind et al. 1996; Skytthe et al. 2003; Hjelmborg et al. 2006), but after age 60 this rate increases to approximately 25–32% (Christensen et al. 2006), and may be even higher after age 90 (Perls et al. 2002). This implies that around 70–75% of the variation in this trait depends on environmental conditions and lifestyle. The role of genetic factors in determining human lifespan is well documented, but in spite of extensive research in the field of gene polymorphism and the molecular background of longevity, these determinants have not been fully explained. It is known that the factors at the genetic level are not limited to mutations, the additive allele effect, the activity of many non-allelic cumulative genes, or the effect of gene pleiotropy, but also concern epigenetic regulation of gene expression (Tollefsbol 2010).

Human lifespan is a multifactorial trait which depends on the interaction of three groups of factors, i.e. the endogenous program, environmental factors, and lifestyle (Butler and Jasmin 2000; Arking 2006; Robine et al. 2007). Lifestyle is a strong factor that affects longevity. However, the effect of individual factors from each group on lifespan varies between individuals, and also changes in the course of the ontogenetic development (Vaupel et al. 1979; Weiss 1990). It should be noted, however, that terms like "lifespan", "length of life", and "longevity" can be ambiguous. Like aging, they can be understood and defined differently, depending on the context and the current research purpose (McDonald 2013). Therefore, to avoid confusion, gerontologists have made a distinction between such concepts as individual lifespan (ILS), average lifespan (ALS), maximum lifespan (MLS), and maximum achievable lifespan (MALS). Only MLS reflects to some extent the rate of aging, while ALS cannot be used for this purpose (Kowald 2002). Moreover, in distinction to most other quantitative biological characteristics (e.g. body height and weight, body temperature, blood pressure, etc.), lifespan can be measured only once (Gavrilov and Gavrilova 1991). This fact has important implications as it is impossible to study lifetimes at the organismal level, and therefore the individual dynamics of longevity cannot be investigated at all. In addition, the errors of once-only observations cannot be determined, and the only way to study lifespan is through the statistical investigation of the population, while genetic and environmental factors are varied.

The high variability in lifespan between individuals is one of the major methodological problems in gerontological research. It has been estimated that up to 70–80% of embryos die before the implantation of the blastocysts in the uterine wall or shortly after this stage of the prenatal development, when nobody even notices it (Diamond 1987). On the other hand, the record value of human lifetime is now 122 years, and there is a chance that it will be exceeded in future generations. The value of the MALS has not been finally established (Hayflick 2000; Weon and Je 2009), but some authors indicate it to be around 120–130 years. Even if these extremes were eliminated, the variability in lifespan is still considerable in each population, and significant differences exist even between monozygotic twins (Finch and Kirkwood 2000). Moreover, these statistically significant differences also occur under laboratory conditions, where the effects of genetic and environmental factors on lifespan in genetically identical individuals of *Caenorhabditis elegans* living in the very same conditions are strictly controlled (Herndon et al. 2002).

Because of improved living conditions, progress in hygiene, medicine, and technology (e.g. the invention of antibiotics, vaccines, new drugs, better prophylaxis, surgical procedures, etc.), which is accompanied by generally healthier lifestyle and diet, increased health awareness, more effective prophylaxis of many diseases, the reduction in perinatal mortality, etc., a dramatic increase in life expectancy at age x (e_x) is being observed. At birth, this measure is denoted as e_0. It is a statistical value, often used in demography, epidemiology, and gerontology, which expresses the remaining number of lifetime for an average person at a given age belonging to a particular birth cohort and living in a particular population. Thus, if the average lifespan changes due

to improved or deteriorated living conditions, the value of e_0 will also change.

The term "longevity" refers to a situation in which the individual lifespan is longer than the life expectancy at birth, i.e. ILS > e_0. It can also be assumed that it is the individual lifespan that is longer than the ALS in the population, i.e. ILS > ALS. According to other authors, longevity can refer to ILS longer than 80 or 85 years. WHO defines longevity as age over 90 years. Currently, in the Polish population, considering the value of e_0 estimated for men and women, it can be assumed that the long-lived people are those who live to be 85 years old or over (the group of the "oldest old"). Three methods are used to assess and compare longevity in different groups of people, i.e. populations or groups of individuals differing in a given trait (Samaras 2008). The first method involves a comparison of similar age groups in terms of their e_x value, the second compares mortality rates in a given unit of time (number of deaths/100,000 individuals/year), which is the inverse of longevity, and the third one is based on determining and comparing the percentage of the "oldest old" subgroup of the population (individuals aged 85 years and above) and usually also considers a percentage of centenarians and supercentenarians. The value of MLS is relatively constant for all populations and has probably not changed significantly since the origin of modern humans, i.e. in the Middle Paleolithic nearly 200,000 years ago (Bräuer 2015). Generally, the e_x value has been increasing since ancient times, although changes in the opposite direction also have occurred during that period (Barbi et al. 2008). It should be stressed that variations in the mortality of children and adults in a given population, reflected in the changes in ALS and e_x, depend on a set of biological, ecological, and socioeconomic factors taking effect in a specific place and time on specific populations (Butler and Jasmin 2000; Crews 2003; Knight 2010; Overton 2010). There are some important differences between individuals, generations, and populations in susceptibility and vulnerability to these factors. Therefore, some authors argue that the methods of evaluating and comparing the value of e_x for different and geographically (as well as genetically) distant populations, which are affected by different groups of factors determining and modifying lifespan, especially for the determination of the rate of aging or the impact of various morphological traits (e.g. body height) on longevity, seem to be inappropriate because they do not allow for genetic and environmental differences associated with various adaptations to different living conditions in these populations. More importantly, the differences in the rate of aging cannot be concluded based solely on data on the ALS because this value is not a measure or proxy of the rate of senescence (Kowald 2002). Similarly, the processes like graying of hair and wrinkle formation do not measure the rate of aging (Heward 2010). Nevertheless, the comparison of ALS or e_x for different groups of people may to some extent reflect the environmental welfare and the overall biological condition of individuals from given populations, especially if such populations live in similar and good environmental conditions.

The role of biosocial factors in human longevity

In biogerontology, factors influencing the aging process and lifespan are classified

as constant and variable (Gavrilov and Gavrilova 1991). The first group includes factors such as sex, genotype, age of the parents at the moment of the conception of the individual, birth order, family size, the number of siblings, environmental conditions, climate, conditions and factors affecting the development and health at the early stages of ontogeny, which have distant health effects, ethnicity, some psychological traits, including personality, character, and intelligence. The second group includes more variable or flexible factors that are more likely to change during ontogeny, and therefore they can be modified. These are, for example, exposure to ecological hazards (e.g. pathogens, parasites, toxins, radiation, pollution, trauma, accidents, etc.), lifestyle, stress level, emotional experiences, amount of sleep, diet and nutrition, use of stimulants, nutritional deficiencies, the level of physical activity, some diseases, social support, and marital status.

Both these groups of factors, i.e. determinants and modifiers of lifespan, form a complex network of mutual interactions or feedback (Fig. 1). Interestingly, some important factors which determine the chances of achieving longevity are to some extent involved in shaping the variability in body size. This refers especially to some genetic and environmental factors, conditions during the early stages of ontogeny, diseases, the level of stress, lifestyle, socioeconomic status (SES), and exposure to ecological hazards (Butler and Jasmin 2000; Wolański 2008; 2012). The old Jewish adage recorded in the Apocrypha, which reads: "If you would live long, choose your parents well", and used as the title of the article by Cournil and Kirkwood (2001), refers

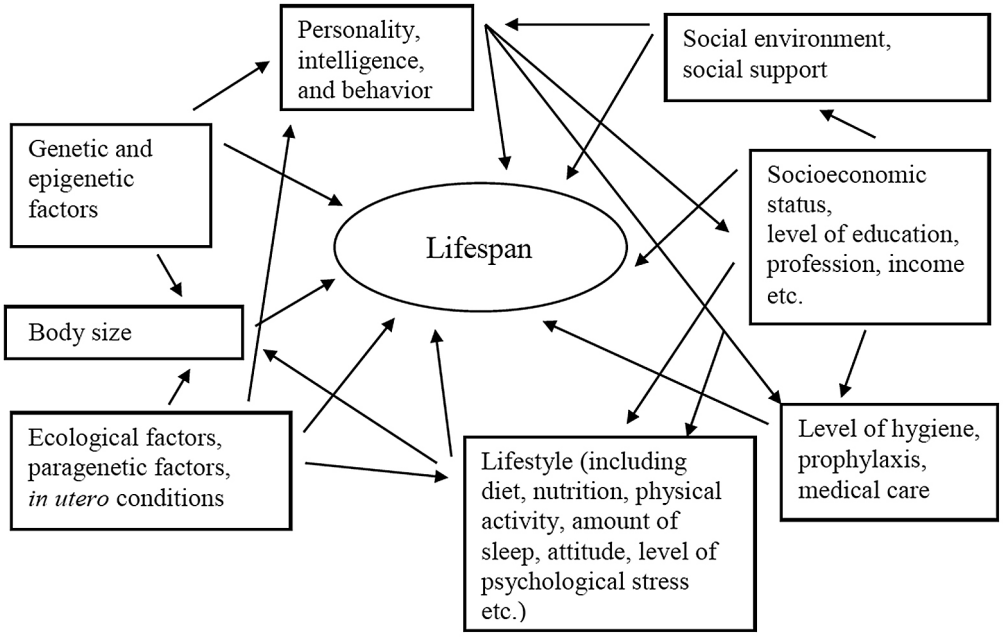

Fig. 1. Selected factors affecting human lifespan and some major interactions between them; based on the BOLSA model of longevity (Butler and Jasmin 2000, modified).

not only to genotype and inherited epigenetic control of gene expression, factors related to the mother's body, such as conditions during the prenatal development, the level of hormones, vitamins, and other biologically active substances, birth order, the number of siblings, family size etc., but also to the role of socioeconomic status (SES), such as the level of parental investment, wealth of the family, lifestyle of parents, and their level of education.

For example, to grow tall, the body requires optimal conditions for the development and growth, so it can be expected that factors promoting taller stature will also increase the chances of survival (cf. Butler and Jasmin 2000; Kirkwood 2010). Taller individuals usually do not have low birth weight (<2500 g). Moreover, they have a favorable socioeconomic status, which increases their chances of reaching longevity. The level of education, income, and thus the quality of life, diet, hygiene, living conditions, medical care, prophylaxis, etc., are in the case of taller individuals factors predisposing them to longer lifespan. Therefore, it is believed that body height is an important variable relevant to the epidemiology of growth, development, and various aspects of health (Bogaert and McCreary 2011).

According to some studies, body height is also positively correlated with IQ, mainly due to gene pleiotropy and the linkage of some factors associated with higher SES, and more beneficial conditions for growth and development (Marioni et al. 2014a; 2014b). On the other hand, it is known that individuals representing the Mongolian race, generally of a shorter stature, are regarded by some authors as the most intelligent race (Rushton and Jensen 2010). However, these views on differences in IQ can be considered controversial, mainly due to significant methodological problems concerning such a comparison. It should be stressed that there are different definitions and criteria for determining intelligence, and IQ tests measure only a small range of this trait. Moreover, there is no objective reason to prefer cognitive intelligence against creative, linguistic, musical, emotional, interpersonal, social, spatial or kinesthetic intelligence. Furthermore, comparatively little attention has been paid to the differences in age-related changes in the fluid and crystallized components of intelligence, which are believed to occur in opposite directions. Another likely factor is the fact that tests used to measure intelligence, being developed by and for people with a particular cultural background, may be less applicable to other groups of people.

It is well known that marital status is a very important biosocial factor with respect to health and longevity. Married people tend to be healthier and live longer than never married, separated, divorced, and widowed people at every age over 20 years, and mortality rates are as much as 50% higher in unmarried individuals (Smith 1993). Moreover, some studies have suggested that one effect of parental divorce may be decreased longevity among the children (Schwartz et al. 1995; Tucker et al. 1997). Presumably, parental divorce alters children's behaviors and eventually their physiology. Interestingly, a more recent study carried out in Tanzania showed that children who lost a father before the age of 15 tended to be shorter and lived shorter than their peers who had a father. Furthermore, those children who lost a mother were even shorter and lived shorter than their

peers who had both parents and than those who lost a father (Kirkwood 2010).

Taller men are less likely to stay lonely, and loneliness is associated with increased mortality rates in men but not in women (Kandler et al. 2007), as they marry more frequently and earlier in life compared with shorter men (Weitzman and Conley 2014). Taller men have also greater reproductive success mainly because women find them more attractive. On the other hand, shorter men tend to be in more stable marriages. In general, taller men are at higher risk of unstable marriage and divorce (Weitzman and Conley 2014). In general, taller men are healthier than shorter ones, and married men are generally healthier than single men, not only because of the "protective role of marriage", but also as a result of selection to marriage, in which women prefer men with better health, higher socioeconomic status, and lower testosterone level (Trivers 1985; Umberson 1992; Bereczkei et al. 1997). Men with lower testosterone level are often perceived as better partners as they are less violent, aggressive or dominant, and more affectionate, friendly, and faithful than men with greater masculinity and with higher testosterone level. Among men, tallness is associated with dominance, masculinity, and higher socioeconomic status (Bogaert and McCreary 2011).

In summary, it is worth noting that the better biological condition of tall individuals mainly depends on environmental factors and those associated with higher socioeconomic status, and not on biological determinants. Therefore, there is currently no reason to expect that genes associated with greater body height have a positive effect on lifespan (pleiotropic effect), and it is also unlikely that other biological factors (e.g. hormones) associated with tall stature could have a positive effect on lifespan. Nevertheless, there is some evidence of such relationships with respect to biological factors associated with short stature (Holzenberger et al. 1991; de Magalhães and Faragher 2008; Bartke 2012; He et al. 2014).

Molecular and cellular aspects of aging and longevity

In the 1960s, Leonard Hayflick and Paul Moorhead demonstrated that human somatic cells can divide *in vitro* for a limited number of times (the Hayflick limit). This finding was considered to be a major breakthrough because it was previously believed that somatic cells are inherently capable of multiplying and they will do so indefinitely. Later on, it was showed that telomeres, which are special repetitive DNA sequences wrapped in specific protein complexes, located at the ends of chromosomes, and required for proper chromosome segregation, play an important role as a buffer. Most importantly, they protect the ends of the chromosome from deterioration or undesirable fusion with neighboring chromosomes. In the 1970s, Olovnikov proposed a theory, which states that the length of telomeric DNA diminishes in dividing normal somatic cells at each cell doubling, and the loss of sequences containing important information could cause the onset of cellular senescence. In 2003, Boukamp asked whether telomere shortening is the causal event (the clock work) for aging or just a marker (the hand of the clock) of an as yet unidentified mechanism (Arking 2006).

There is a strong separation between normal somatic cells and other types of cells in the body, including germ cells,

pluripotent stem cells, and cancer cells, because telomere length is stabilized in almost every type of immortal or cancer cell line examined (Fig. 2), as a result of the activity of telomerase and other related molecular mechanisms. This observation has opened up a new line of inquiry for cancer diagnosis and therapies based on some sophisticated methods of genetic engineering. The increase in telomerase activity in cancer cells makes this enzyme a good target for chemotherapy. It seems that inhibited activity of telomerase in neoplastic cells should lead to telomere shortening, which could practically restore the ability of such cells to age and die (Bal 2013). It should be remembered, however, that telomerase is active in stimulated lymphocytes, germs cells, and in all types of stem cells. Therefore, permanent inhibition of telomerase would be deleterious.

Currently, there are a number of known genes whose mutations and expression products (proteins and transcription factors) can affect the rate of aging and lifespan in evolutionarily distant model organisms. There are certain important genes whose mutations significantly impact the aging process and extend longevity in different model organisms, particularly the *Age-1* gene, which is responsible for the activity of PI-3 kinase, the stress response gene *Amp-1, Chico*, determining the production of substrate for the insulin receptor, the *Daf-2* gene, encoding the insulin/IGF-1 receptor, the *Ghrhr* gene, encoding the somatoliberin receptor (GHRH), clock genes *CoQ*, involved in the synthesis of coenzyme Q, the *Hsp 70* gene, involved in the production of the heat shock protein, the *Pcmt* gene, encoding methyltransferase, and *Prop1*, which is essential for

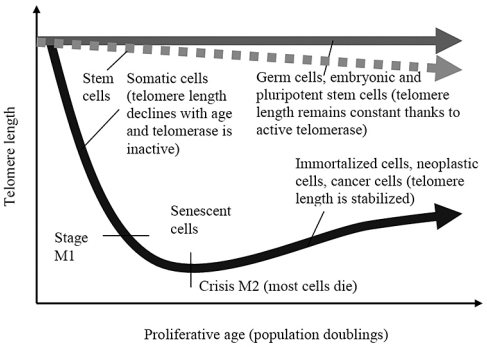

Fig. 2. The relationship between the length of telomeres and proliferative age of cells in various types of human cells (after Bal 2013; Borysławski et al. 2015, modified).

the development and activity of the pituitary gland.

In humans, numerous genes variants and mutations have been reported to be associated with exceptional longevity. These are, for instance, *AKT1*, *APOC3*, *APOE*, *CAT*, *CEPT*, *FOXO* variants, *GH1*, *IGF-1*, *IGF-2*, *IGF1R*, *INSR*, *MTT*, *P21 (CDKN1A)*, *PON1*, *SIRT* variants, *SOD1*, *SOD2*, and *TP53*. These genetic components, i.e. specific genes, their polymorphism, including single-nucleotide polymorphisms (SNPs), and mutations in mtDNA, that have been discovered to be associated with longevity in humans are summarized in Table 2.

APOE variants were found to play a role in the genetics of human longevity relatively early. It is known that the $\varepsilon 4$ allele frequency is positively correlated with low-density lipoprotein (LDL) cholesterol and is negatively correlated with longevity among elderly people. Similarly, the role of sirtuins, i.e. NAD^+-dependent deacetylases encoded by the *SIRT* genes and involved in the formation of chromatin structure, gene silencing, DNA repair, and the control of genome stability as well as cell survival

Table 2. Genes, their functions, and mutations in mtDNA which have been reported as being associated with human longevity.

Genes or mutations	Description	Protein name and/or function
AKT1	An intronic SNP in *AKT1* gene is associated with lifespan	Serine/threonine kinase PKB is involved in insulin/IGF-1 signaling
APOC3	*APOC3* gene belongs to the apolipoprotein gene family	Apolipoprotein C-III is a main component of very low density lipoprotein (VLDL)
APOE	The ε4 allele frequency is positively correlated with LDL cholesterol and is negatively correlated with longevity among older people (>60 years of age)	Apolipoprotein E (ApoE) transports lipoproteins, cholesterol, and fat-soluble vitamins, but is also has some functions beyond lipoprotein metabolism
CAT	This gene encodes catalase and is located on the eleventh chromosome (11p13)	Catalase is a key antioxidant enzyme that protects the cell from oxidative damage caused by ROS
CEPT	This gene is located on the sixteenth chromosome (16q21)	Cholesteryl ester transfer protein
FOXO1A	Its forkhead box is O1A	Involved in insulin/IGF-1 signaling
FOXO3A	Its forkhead box is O3A	Involved in insulin/IGF-1 signaling
GH1	Growth hormone 1 gene	Involved in insulin/IGF-1 signaling
IGF-1	Insulin-like growth factor 1 gene	Involved in insulin/IGF-1 signaling
IGF-2	Insulin-like growth factor 2 gene	Involved in insulin/IGF-1 signaling
IGF1R	It encodes the IGF-1 receptor	Involved in insulin/IGF-1 signaling
INSR	It encodes the insulin receptor	Involved in insulin/IGF-1 signaling
MTT	Its mutation is more prevalent among adults with mtDNA disease	Microsomal protein involved in the transport of cholesteryl esters and lipids
P21 (CDKN1A)	It encodes cyclin-dependent kinase inhibitor 1	This enzyme is a cell-cycle inhibitor
PON1	It encodes paraoxonase 1	Paraoxonase 1 enzyme has several functions, including the ability to scavenge free radicals
SIRT	Genes *SIRT1*, *SIRT2*, *SIRT3*, *SIRT4*, *SIRT5*, and *SIRT6*	Deacetylases involved in metabolism, inflammation, DNA repair, insulin secretion, and regulation of cell cycle
SOD	Genes *SOD1* and *SOD2*	Superoxide dismutase 1 and 2
TP53	The *TP53* gene is the most frequently mutated gene in cancer. It plays a role in preventing cancer formation.	TP53 is an important tumor suppressor
Mutations in mtDNA (C150T, Mt5178, Mt8414T, and Mt30310A)	They alter the production of energy by mitochondria, and the energy-producing capacity can be significantly changed	They alter the production of energy by mitochondria, and the energy-producing capacity can be significantly changed

is particularly interesting. Furthermore, the functioning of the GH/insulin/IGF-1 pathway, the mTOR pathway, and some other signaling pathways, in conjunction with the activity of *AKT1* and *FOXO* genes seems to be crucial (Bishop et al.

2010). Other noteworthy genetic factors include the *TP53* gene encoding the tumor suppressor protein, stress response genes, especially *SOD1* and *SOD2* encoding superoxide dismutase 1 and 2, respectively, the *CAT* gene encoding catalase, the *ACE* gene encoding angiotensin converting enzyme, the *MTTP* gene encoding microsomal triglyceride transfer protein, the *APOE* genes, and protein isoforms APOE2, APOE3, APOE4, certain genes associated with the immune response, anti-inflammatory cytokines, the regulation of their secretion, and specific mutations in mtDNA, haplotype J, as factors such as TNF-α and TGF-β. For example, recently published results of over 40-year-long studies indicate that in a population of U.S. residents with Japanese ancestry, shorter men live significantly longer than taller ones, and also have lower fasting insulin levels. In addition, they more frequently carry the *FOXO3* gene variant (He et al. 2014), which is characteristic for the most long-lived people such as centenarians. The transcription factor DAF-16/FOXO is involved, for instance, in gluconeogenesis, glycogenolysis, insulin signaling, inhibiting adipogenesis, protecting against heat and oxidative stress, and enhancing cell survival (Guarente et al. 2008; Lodish et al. 2008).

The proximate causes of aging: random molecular damage or hyperfunction?

Recent experimental biogerontological studies carried out on evolutionarily distant model organisms (yeast, fruit flies, nematodes, rodents) have shown that aging can be a consequence of programmed and evolutionarily conserved signaling pathways. These are the insulin/IGF-1 pathway and mTOR, which has two variants, i.e. rapamycin-sensitive mTORC1 and rapamycin-insensitive mTORC2 (Hands et al. 2009; Kapahi et al. 2010; Laplante and Sabatini 2009; Toschi et al. 2009; Katewa and Kapahi 2011; Sharp 2011). The term "quasi-program" or "pseudo-program" means that the process of aging is completely aimless and is driven by hyperactivation or hyperfunction of natural processes involved in developmental growth. However, it may seem "purposeful", "programmed", and even "altruistic", cf. the theory of phenoptosis proposed by Skulachev (2011; 2012) and the demographic theory of aging proposed by Mitteldorf (2006), but these theories of programmed and altruistic aging are sometimes considered as a misinterpretation of the quasi-program.

The mTOR-driven programmed growth and quasi-programmed aging integrate many processes and pathways inside the cell, whose activity is regulated by various important nutrients (glucose, amino acids, and fatty acids), oxygen, hormones (e.g. insulin), growth factors (IGF-1 and others), and cytokines. Moreover, mTOR is also a "sensor" of body nourishment in terms of energy value and quality of food. Basic functions regulated or controlled by mTOR include cell proliferation and motility, redox reactions, response to dietary restriction, metabolism of ROS, body growth, and gene expression along with protein synthesis by regulating transcription and translation.

According to the model of mTOR-driven quasi-programmed aging, known as the theory of hyperfunction, alternative to the DST proposed by Kirkwood (1977; 2002; 2005; 2008), aging is not the direct result of accumulated molecular damages – though they actually occur and have

deleterious consequences, but do not directly cause this aging process which leads earlier to illness and death (i.e. "aging as we know it"). Neither it is a consequence of allocation of resources and energy to reproductive and life-supporting processes, but results from "aimless continuation" of the developmental program (Blagosklonny 2012; 2013a; 2013b; 2013c). In other words, to stop aging the body would have to arrest all growth and developmental processes at the molecular and cellular levels. A young body which has finished its growth still continues to develop and the direct causes of developmental growth are causes of aging at later stages of ontogeny. Thus, the same mechanisms that determine growth (the function of mTOR) are the direct causes of aging in later life (the hyperfunction of mTOR). It is important to understand that the level of mTOR activity at progressive stages of ontogeny is closely related to the level of hyperfunction in late ontogenetic development.

The free-radical theory of aging proposed by Harman (1956; 2006), and the mitochondrial theory of aging now form a coherent model describing the causes of aging and differences in lifespan known as the mitochondrial free-radical theory of aging, MFRTA (de Grey 1999), although not all studies provide evidence supporting it. Currently, because of the great amount of experimental data, the causative role of free radicals in the induction of aging and the correctness of the MFRTA are increasingly often questioned (Miwa et al. 2004; Sanz et al. 2006; Sanz and Stefanatos 2008; Pérez et al. 2009), but MFRTA still applies to the standard model of the DST (Kirkwood and Kowald 2012).

It can be assumed that the theory of hyperfunction is a new version of the antagonistic pleiotropy theory proposed by Williams (1957), formulated recently, based on numerous genetic studies merging biogerontology, developmental biology and the molecular biology of aging (Blagosklonny 2012). Interestingly, the theory of hyperfunction can explain in an alternative way to the DST why women live longer than men, why the increased sexual activity of iteroparic animals does not adversely affect their lifespan, why smaller individuals of a given species live longer than larger ones, though interspecies comparisons generally show an inverse relationship, what the essential cause of the phenomenon of life extension through dietary restriction is, why antioxidants do not extend longevity (and some may be even detrimental to health), and why single-gene mutations, despite the skeptical predictions of evolutionary biologists, are able to significantly postpone aging and extend longevity in many species, at least under laboratory conditions. Moreover, the mTOR-centric model can be used to elucidate some other paradoxes and new discoveries in the field of biogerontology, so far unexplained by any of the existing theories of aging, and can also predict completely new relationships (Blagosklonny 2008; 2009; 2010a; 2010b; 2012; 2013a; 2013b; 2013c; 2013d; 2013e; 2013f).

For example, according to the DST, women live longer because they are "less disposable" from the evolutionary point of view, i.e. they are more involved in supporting the survival of our species than men, and more specifically, their reproductive success and role in reproduction are more dependent on their good health. They have higher levels of parental investment than men. Therefore, they should live longer to ensure the survival of offspring (Kirkwood 1999; 2010).

Blagosklonny (2010a) considers this explanation as a tautology, a repetitive argumentation that has no experimental basis. He also believes that the current version of the DST describes life and aging as if they were designed by an intelligent mathematician: nothing is wasted, aging is a completely passive and random process that consists in accumulation of molecular damage, and repair of damage is limited by the availability of energy resources, depending on the needs of the organism. But life was not designed by any intelligent designer. Instead, it was shaped by a "blind watchmaker" for immediate benefits. It wastes energy if in this way it can increase the chance of survival or reproduction, which is also reflected in the antagonistic activity of mTOR. For instance, extra-calories activate the mTOR pathway, which signals both growth and aging. According to this view, in our evolutionary past the fitness of young men depended more on their faster growth and development, because they had to develop greater muscle mass, strength, and endurance to successfully compete or fight for a sexual partner, survival, food, and resources. The level of mTOR activity had to be, therefore, established at a higher level than in women. The higher level of hyperfunction of mTOR after puberty and faster aging as well as shorter lifespan of men is therefore the cost of this "credit" drawn in youth (Blagosklonny 2010). Interestingly, the differences between shorter and taller or slimmer and stouter individuals can be explained in a similar fashion. For example, in shorter (and slimmer) individuals, the rate of developmental growth was lower (the activity of mTOR was also relatively lower) than in taller (and stouter ones), which directly results in weaker hyperfunction in old age. Interestingly, this theory also explains why in men the health span is relatively longer than in women. In men, the hyperactivity of mTOR is adaptive in youth, when it enhances their survival (good health), and non-adaptive in old age, when it accelerates aging (bad health), while in women the credit drawn in youth is relatively less pernicious to their health, and there are neither early benefits from it nor later costs (Blagosklonny 2010a; 2010b). Therefore, men benefit from early hyperactivation of mTOR, but women have lower mortality rates because their rate of activation of mTOR is more stable throughout ontogeny.

According to the DST, longer lifespan in women can be attributed to some extent to menopause, which also increases the chance of survival of their offspring and grandchildren (Kirkwood 1999; 2010; Chmielewski 2012). More importantly, women live longer because they are "less disposable" than men from an evolutionary point of view. In other words, their reproductive role is more directly dependent on their continued good health compared with men (Kirkwood 2010).

According to the mTOR-centric view, menopause can be interpreted in terms of the side-effects of developmental growth or age-related diseases. More specifically, it is a "prototypical disease", which results from the hyperfunction and is definitely not beneficial to women's health or lifespan. The same factors and mechanisms that initiated the menstrual cycle, hyperactivate ovarian function in the later stages of the development, which leads to the end of the reproductive period, which is accompanied by some distressing symptoms. Menopause is an evolutionarily new process, like cancer or atherosclerosis, and women

have been experiencing it since relatively recently, and therefore this is definitely not a universal biological "method" of life extension in humans (Blagosklonny 2010a; 2010b). Blagosklonny asserts that menopause has been of minor (if any) importance in our evolutionary past with respect to the evolution of lifespan. In this view, other aging-associated diseases (e.g. hypertension, cancer, and diabetes) also result from this hyperfunction. Thus, the links between aging and diseases are manifested by these diseases, and not by susceptibility and vulnerability to diseases.

The effect of caloric restriction on lifespan seems to be a paradox in terms of the DST. Reduced energy resources should mean less efficient repair of molecular damage, the same as higher investment in reproduction in women should correspond with shorter lifespan, but this is not observed in either of the cases (Mitteldorf 2010; 2016). Furthermore, the DST predicts that fertility is negatively related to lifespan, but this correlation is observed neither in animals nor in humans (Mitteldorf 2010). The effect of dietary restriction is usually explained by the fact that during the shortage of energy, the body ceases to invest in reproductive processes and is mainly focused on survival. Longer lifespan in women can be attributed to less disposable bodies and the positive effect of menopause on lifespan, which also increases the chance of survival of their offspring and grandchildren (Kirkwood 1999; 2010).

The mTOR-centric model of hyperfunction offers a completely different explanation. In this perspective, it is natural that if the caloric sensor (mTOR) receives a smaller amount of energy with food, then the activation of the whole "quasi-program" will be weaker. Diet is an example of an environmental factor which affects both health and aging. Numerous studies have demonstrated the phenomenon of life extension through caloric restriction (CR) or dietary restriction (DR) in short-lived animals, including nematodes, fruit flies, and mice. However, the results of studies on the effects of CR on health, mortality, and lifespan in long-lived primates remain mixed (Colman et al. 2009; Austad 2012). Interestingly, some authors assert that CR is very unlikely to delay aging and enhance longevity in long-lived primates, including humans (Shanley and Kirkwood 2006). Nevertheless, it is known that CR inhibits mTOR (Blagosklonny 2013c), and this fact raises hopes that the use of inhibitors of mTOR can be a strategy for postponing aging and extending longevity in humans.

According to some researchers and scholars, the positive effect of CR on health and lifespan, which was observed in many species, cannot be easily reconciled with the disposable some theory because food scarcity and CR should be closely linked to impaired maintenance and repair of the body (Blagosklonny 2010a; Mitteldorf 2016). Mitteldorf (2010) states explicitly that: "If the fundamental cause of aging were a compromise in the allocation of caloric energy, then it follows that caloric restriction should cause *shortening* of life span (…). When *less* food energy is available, each of the demands on that energy must share the burden, making do with a reduced share of the smaller total. Allocation for repair and maintenance must be smaller, and if the DS theory is correct then aging must proceed more rapidly. This is the opposite of what is observed. Reduced caloric intake reliably leads to slower ag-

ing and enhanced life span." Curiously, other authors assert that the opposite is true, and the effect of CR makes perfect sense in the light of the DST because the energy that is available for the organism is redirected from reproduction to maintenance and repair of the body due to the fact that the offspring's chance of survival is decreased by hardship and environmental challenge like CR (Książek and Bartosz 2009).

Be that as it may, it has been established that CR lowers blood pressure, increases insulin sensitivity of target cells, elevates the level of plasma adiponectin, stimulates the release of ghrelin, and most importantly enhances mitochondrial function, which decreases the production of ROS (Lanza and Nair 2010). Moreover, CR can significantly lower the risk of age-related diseases, including cardiovascular diseases, diabetes, and cancer (Colman et al. 2009). Other authors, however, argue that CR has its side-effects that can be harmful to health. It was earlier demonstrated that CR can lead to osteoporosis, impaired libido and potency, depression, and increased frailty especially in older people (Shanley and Kirkwood 2006; Marzetti et al. 2009).

It is well known that levels of insulin and IGF-1 in blood are associated with the lifespan of mammals and other animals whose growth and development depends on these factors. In nematodes cell receptors of insulin and insulin-like growth factors are encoded by the *daf-2* gene, and its inhibition impairs insulin signaling, resulting in life extension by about 200%. It was also shown that in humans low levels of insulin and IGF-1 in the blood are associated with increased longevity (He et al. 2014). Kirkwood's finding (2005) that: "The real paradox is why, in mammals, low insulin levels are associated with good health, but low insulin responsiveness with bad health", was commented on by Blagosklonny (2010a) in the following fashion: "Low insulin levels (by not activating mTOR) extend life span (good health), whereas low insulin responsiveness can be a feedback response to over-activated mTOR, which shortens lifespan (bad health)".

In conclusion, the theory of hyperfunction seems to be an attractive and promising explanation of many riddles and paradoxes in current biogerontology. This model, which does not necessarily contradict the free-radical theory of aging proposed by Harman (1956) and the original version of the DST proposed by Kirkwood (1977), is a mechanistic explanation concerning proximate or more direct causes of aging.

The gender gap in longevity: why women live longer than men

Considering historical and contemporary data, lifespan in women is on average about 50–60 months longer than in men (Eskes and Haanen 2007; Møller et al. 2009). However, in different countries there are distinct differences between the sexes caused by various reasons (Arking 2006). In Pakistan, the gender gap is 0.2 years (the lifespan in both sexes is short), and in Finland and post-Soviet countries this gap is about 9.8 years, but excess male mortality is the main cause of these differences only in the latter case. Among developed countries, the smallest differences have been observed in the United Kingdom (4.9 years), and Japan (5.6 years), while and the largest differences have occurred in Finland and France (8.2 years). In the United States, the differences are moderate (around 7 years). There are also countries where

women live shorter, especially due to high maternal mortality. In Bangladesh, men live 0.2 years longer than women, and in Nepal as much as 2.8 years longer (Arking 2006). The size of the gender gap in longevity in the Polish population amounts to 7.1 years, which is more than the threshold of 85 months. Thus, this is more than the average value, which reflects the phenomenon of excess male mortality in the Polish population.

In animals, the differences in lifespan between the sexes have been observed a long time ago. Females tend to live longer in most species (Gavrilov and Gavrilova 1991). In various cases, however, the reasons for the disparities or differences in longevity may be different. Similarly, various reasons and determinants of longer lifespan of women have been investigated (Charnov and Berrigan 1993; Kirkwood 1999; 2010; Stindl 2004; Viña et al. 2005; Arking 2006; Austad 2006; Eskes and Haanen 2007; Biecek and Cebrat 2008; Møller et al. 2009; Borysławski and Chmielewski 2012a; McDonald 2013).

Although there is no simple answer to the question "why do women live longer than men?", it turns out that important biological causes may be the differences in sex chromosomes and different pattern of gene expression. Males are heterogametic (XY), whereas females are homogametic (XX) with respect to allosomes. Because of lyonization, i.e. the inactivation of the additional X chromosome (either the maternal X^M or the paternal X^P), which is visible in the cell nucleus as the Barr body, both sexes have only one active X chromosome. Under normal conditions, the process of inactivation of the additional X chromosome is random (although the inactivation can be skewed, which can result from some external stress or genetic predisposition), so females have active copies of genes from both parents in their somatic cells, while in males the information stored on the X chromosome comes from the mother (the X^M). Thus, according to the heterogametic sex hypothesis, the lack of possibility for selecting which X chromosome should be inactivated is associated with greater genetic and developmental instability in males, which can lead to higher mortality rates. In other words, males can only express their X chromosome genes that come from the mother, while females have an advantage by selecting the "better" X chromosome, while inactivating the "worse" X chromosome. Some authors assert that this fact may be connected with the well-known greater genetic and developmental stability of the female sex (Smith and Warner 1989; Wolański 2008; 2012). Furthermore, approximately 15–20% of the genes on the inactivated X chromosome can be expressed (Carrel and Willard 2005; Austad 2006), and thus these genes escape inactivation to some degree, which may also provide an additional important survival advantage for females. Likewise, this process of selection for "better" genes is impossible in males. With age, the process of X inactivation gradually changes from being random in the early ontogenetic development to becoming biased toward either the X^M or the X^P.

In terms of developmental biology, women are the "passive" and "default" sex, which means that the creation of a male individual requires the sequence or cascade of events at a molecular level, which are initiated by the activity of the *SRY* gene located on the Y chromosome. This activity and change in the direction of development results in a greater number of disturbances and developmental

disorders, because the normal course of development requires many different factors and mechanisms, each of which must work properly and at a specific stage of the development. Furthermore, throughout ontogeny men are more vulnerable and susceptible to diseases and some harmful environmental and lifestyle-related factors (e.g. smoking and drinking), which is defined as the greater ecosensitivity of the male sex (Stini 1969; 1978; Stinson 1985). Recent immunological studies have shown that the activity and aging of the immune system are different in elderly people of both sexes. Men are more likely to contract viral and bacterial infections, and their immunity at the cellular and humoral level decreases significantly faster with age. Women are slightly more prone to autoimmune and inflammatory diseases such as rheumatoid arthritis, but generally immunosenescence is slower in women (Caruso et al. 2013; Hirokawa et al. 2013). In our recent study comparing longitudinal and cross-sectional changes with age in leukocyte count in men and women aged 45+, we demonstrated that men had continuously higher leukocyte count compared with women throughout the period under study (Chmielewski et al. 2016). More importantly, lower total leukocyte count within the normal range was a useful predictor of longevity. It is believed that high average but normal leukocyte count can serve as a crude indicator of increased systemic inflammation and probably a marker of subclinical illness, including cardiovascular disease, chronic heart failure, inflammation, cancer, etc., while low average yet normal leukocyte count is associated with good health and increased survival. This line of reasoning is supported by extensive data and results of numerous previous studies (Alexander 1994; Erlinger et al. 2004; Hansson 2005; Leng et al. 2005; Margolis et al. 2007; Ruggiero et al. 2007; Willems et al. 2010; Mochizuki et al. 2012; Nilsson et al. 2014).

Another important reason for the differences in lifespan between the sexes may be different hormonal profiles, especially the higher level of testosterone in men than in women, which translates into more frequent cardiovascular and immune disorders. On the other hand, the higher level of estrogens in the blood of women may have a protective effect on the heart and circulatory system (Viña et al. 2005). Estrogens also have antioxidant activity, thereby they more effectively protect against harmful effects of ROS and other free radicals, which damage cell components, cause their peroxidation, damage to genetic material, mutations, malignant transformations, and are in part responsible for the aging process. It has been generally estimated that differences in hormonal profile in both sexes determine about 18% of lifespan (Arking 2006).

Moreover, the level of testosterone (T) along with its various metabolites, especially dihydrotestosterone (DHT), converted from testosterone by 5-α-reductase, is responsible for some traits of the male phenotype (e.g. the development of genitals organs, physical stature, body hair, and androgenic pattern of baldness) as well as for male behavioral pattern (e.g. increased level of aggression, violence, more frequent risk taking, suicide, accidents, use of stimulants, including alcohol and tobacco use, etc.). It is well known that the set of behavioral and lifestyle-related factors is to some extent responsible for the shorter lifespan in men (Martin et al. 2011; Borysławski and Chmielewski 2012a; 2012b). In Poland

and post-Soviet countries, men choose more dangerous occupations, have unhealthy diet, use significantly more stimulants, and display other negative behaviors. However, it does not explain the complete picture because women have a relatively shorter health span than men, which means that for the relatively longer part of their lifetimes they experience various health problems (Eskes and Haanen 2007; Møller et al. 2009).

Moreover, despite the egalitarianism of both sexes in developed countries, these differences still exist, which suggests that some biological determinants and mechanisms are involved in these disparities (Kirkwood 2010; Borysławski and Chmielewski 2012a; 2012b). For example, some gerontologists attribute these differences in longevity between sexes to different patterns of gerontogenes, telomere length and attrition rate, the degree of mutations in mtDNA, different levels of ROS generated by the mitochondria, different cellular antioxidant activity, different levels of certain prostaglandins such as I2 (PGI2), and the activity of other specific molecules as well as epigenetic control of gene expression. These processes play important roles in the maintenance of the body, the repair of damage at the molecular and cellular level, and the control of gene expression (Cherif et al. 2003; Stindl 2004; Arking 2006).

Conclusions

A growing body of evidence suggests that in evolutionary distant model organisms, such as nematodes, fruit flies, and mammals, aging may be driven by evolutionarily conserved signaling pathways, including the insulin/IGF-1 pathway and mTOR. Based on this, the theory of hyperfunction of mTOR as a more direct cause of aging ("aging as we know it") than random molecular damage has been recently formulated. This m-TOR-centric model, which is rival to the disposable soma theory proposed by Kirkwood, predicts that aging is not and cannot be programmed but results from the quasi-program driven by these signaling pathways. In this view, aging is neither a completely passive process (the stochastic model) nor a programmed and altruistic process (the deterministic model) but consists in an aimless continuation of developmental growth. There are many aspects of such hyperfunction with age, and the link between aging and diseases is manifested by aging-associated diseases, including cancer, hypertension, and diabetes. In women, menopause is such a "prototypical disease" which is not beneficial to women's health and results from the hyperfunction. The theory of hyperfunction offers a completely different approach to numerous problems and paradoxes in current biogerontology and also allows the prediction of entirely new relationships.

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Authors' contributions

PC wrote the paper in collaboration with BS. KB and BS revised the article critically for important intellectual content. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that there is no conflict of interests.

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