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The dynamic nature of ageing: novel findings, therapeutic avenues and medical interventions

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ABSTRACT: Ageing is one of the most complex and difficult problems for humans to face and for science to solve. Although human senescence was viewed as a passive and uncontrollable process of deterioration over time with little or no genetic regulation, the concept that ageing is caused by both genetic and environmental factors is now generally accepted, even though it remains difficult to distinguish between ageing *sensu stricto* and the effects of age-related diseases. Empirical data show that mechanisms of ageing are highly conserved during evolution. Moreover, it has been established that there are specific molecular 'instructions' for ageing, which suggests that a better understanding of the molecular biology of ageing will open new possibilities regarding future interventions. The complexity of ageing diminishes the possibility that any general theory will completely explain this metaphenomenon. Likewise, it is highly unlikely that any medication can stop or reverse human senescence. Nevertheless, ageing as a dynamic and malleable metaphenomenon can be modulated by a variety of influences. The concept of the shrinkage of the homeodynamic space with age, i.e. homeostenosis, is especially interesting and intriguing as it shows that novel therapeutic approaches and rational strategies can help delay the onset of the ageing-associated pathologies by enhancing the homeodynamic capabilities of the body. The aim of this article is to present current data from evolutionary and molecular gerontology and discuss them within the ambit of this review which is devoted to the dynamic, emergent and plastic nature of human ageing and implications for future interventions.

KEY WORDS: ageing, epigenetic clocks, epigenetic mechanisms, homeodynamics, human longevity, hyperfunction, senescence

Introduction

Ageing is arguably one of the most complex and difficult problems for humans to face and for science to solve (Kirkwood and Franceschi 1992; Kaczmarek and Szwed 1997; Chmielewski et al. 2016a; Cohen 2016; Muntané et al. 2018; Chmielewski 2019a, 2019b). At the same time, ageing is a fascinating phenomenon that has captivated philosophers and researchers for centuries (da Costa et al. 2016). The questions regarding human ageing and longevity, such as

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'Why is ageing inevitable?' and 'How to slow down the ageing process?', have intrigued humans since the dawn of time.

Human senescence used to be described as a passive, stochastic and uncontrollable process of deterioration over time with little or no genetic regulation. Today, the concept that ageing is a dynamic and malleable metaphenomenon (i.e. a mixture of processes) that is due to both molecular and environmental factors is generally accepted (Warner et al. 2010; DiLoreto and Murphy 2015; Rizzo et al. 2017; Campisi et al. 2019; Dönertaş et al. 2019), even though it remains difficult to distinguish between ageing *sensu stricto* and the effects of age-related diseases. It has been established that there are specific molecular signatures and 'instructions' for ageing at the molecular level, and a better understanding of the molecular biology of ageing will open new possibilities regarding rational strategies and interventions (López-Otín et al. 2013; Kennedy et al. 2014; DiLoreto and Murphy 2015; McHugh and Gil 2018; Campisi et al. 2019; Dönertaş et al. 2019). Nevertheless, the complexity of ageing diminishes the possibility that the problem of ageing can be solved using reductionist and disease-oriented approaches (Chmielewski 2017, 2019a, 2019b; Rattan 2019). To understand the nature of ageing, we must first understand life. Many researchers conclude that ageing and metabolism are intertwined phenomena, and answering the question: 'What is ageing?' is tantamount to answering the question: 'What is life?' (da Costa et al. 2016).

The aim of this paper is to present new findings from evolutionary and molecular gerontology and discuss them within the ambit of this article which is devoted to the dynamic, emergent and plastic nature of ageing. Here, an interpretation of human senescence as a dynamic and malleable metaphenomenon is introduced and briefly discussed. This model is especially useful in the context of rational strategies and interventions that can help delay the onset of the age-related physiological decline in humans.

Homeostenosis as a hallmark of ageing

It has been suggested that the intrinsic and progressive deterioration of the homeodynamic capabilities of the body, i.e. homeostenosis, is a hallmark of ageing (Witkowski 2009; Rattan 2014; Cohen 2016; Chmielewski 2017). In gerontology, the term 'homeostasis' is not particularly appropriate. Therefore, the term 'homeodynamics' has been adopted (Lloyd et al. 2001; Witkowski 2009; Rattan 2018; Chmielewski 2017, 2018, 2019a). Briefly, maintenance mechanisms operate through stress responses, damage control and constant remodelling (Rattan 2014) to keep the body alive in spite of stresses and challenges. Thus, there is nothing static in the body, including maintenance mechanisms, and the 'equilibrium' is not fixed. An ageing organism continuously reorganises itself in response to the environment, and ageing can be understood as a consequence of regulatory mechanisms that actively control how cells, tissues and organs respond to their environment (Rizzo et al. 2017; Chmielewski 2019a).

Based on novel findings, three principles of ageing have recently been formulated (Rattan 2014): (1) ageing does not start at birth but after essential lifespan

(ELS), i.e. the natural duration of life that is necessary for individuals to grow, develop and reproduce in order to fulfil the Darwinian purpose of life (Steinberg 2012); (2) human senescence as observed today is possible because humans live in protected environments that allow them to survive much longer that ELS; (3) ageing is a highly complex process that can be described as a metaphenomenon, which means that ageing is not a single process but there are many mechanisms and processes that contribute to ageing.

According to modern views, ageing and life, or at least metabolism, are intertwined phenomena (Warner et al. 2010; DiLoreto and Murphy 2015; Rizzo et al. 2017; Chmielewski 2017, 2019a; Campisi et al. 2019). Therefore, the notion that ageing is a passive and stochastic process is probably faulty (de Magalhães 2012). Life is possible because organisms have evolved to survive and reproduce themselves and they are adapted to their environment. To oppose changes in both intrinsic and extrinsic factors, organisms have adaptations that function constantly to keep them alive. At every level of biological organisation, including the sub-cellular, cellular, tissue, organ and organismal levels, there are consecutive developmental stages, i.e. infancy, childhood, adolescence, adulthood and senility (Fig. 1), even though these terms are preferably used for the organismal level (Kaczmarek and Wolański 2018). Nevertheless, similar stages can be observed at any level of biological organisation in the context of developmental processes (Witkowski 2009). For example, there are three main developmental stages in human enterocytes, i.e. 'cellular infancy', the stage of maximal functional capacity ('cellular adolescence and adulthood') and senescence. During progressive stages of development, these biological systems (cells, tissues, organs and organisms) develop to resist stresses and challenges thanks to various adaptations. Progressive development and survival are programmed and there are genes that ensure the viability and reproductive success. Before sexual maturity, there are two stages with suboptimal adaptability and faster or slower unfolding of optimal adaptive functions, i.e. infancy and childhood. Noteworthy, all life trajectories of the functional capacity of organisms are relatively similar at these stages, and there is no age-related decline in physiologic integrity that would increase the risk of death. In other words, infants and children follow a relatively similar pattern of growth and development, and ageing does not occur at early stages of ontogeny.

At the organismal level, the adaptability increases up to the stage of sexual maturity (the peak, see Fig. 1) when an organism produces progeny. After reproductive maturity, the intrinsic and pro-

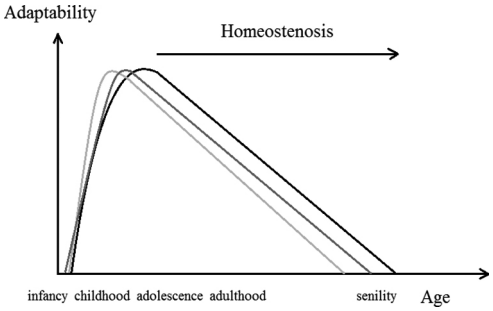

Fig. 1. Age-related changes in the functional capacity and adaptability in three different populations, i.e. short-lived, normal (grey lines) and long-lived (black line). Ageing occurs after essential lifespan as an intrinsic and progressive deterioration in the homeodynamic capabilities of the body, leading to a constantly increasing risk of death (see text for details)

gressive decline in maintenance mechanisms in complex biological systems (cells, tissues, organs and organisms) can be observed. This decreasing adaptability after ELS results from the intrinsic and progressive decline of the homeodynamic capabilities of complex biological systems, such as organs and organisms, which leads to a constantly increasing risk of death.

After reproductive age, organisms enter the 'selection shadow'. The functional capacity gradually diminishes and the decrease is pronounced in late ontogeny when senescence occurs. This means that all complex biological systems in the body (cells, tissues, organs) lose their functional capacity in the postreproductive period. A corollary is that ageing cannot be observed before the onset of sexual maturity. Noteworthy, the earlier the peak during progressive ontogeny is reached, the earlier the physiological decline can be observed (see Fig. 1). After ELS, everything in the body gets worse, including the homeodynamic capabilities and the likelihood of survival. Interestingly, ageing is heterochron in most biological systems, which means that sub-cellular systems, cells, tissues and organs begin to age at different times and have different rates and patterns of ageing (Rattan 2014; Muntané et al. 2018).

Noteworthy, this is a down-to-earth approach that is very practical and useful in terms of future interventions as it shows that various factors and conditions that enhance the homeodynamic capabilities of the body might slow down the ageing process. However, the question remains if it is really possible to postpone or reverse ageing in humans. Other authors assert that no intervention can stop or reverse ageing in humans (Hayflick 2004).

Atavistic mechanisms of self-destruction: programmed cell death and autophagy

The molecular orchestration of the ageing process involves mechanisms of self-destruction such as apoptosis (programmed cell death, PCD) and autophagy . The former is a consequence of a cascade of caspase activation, whilst the latter does not depend on caspases but consists in 'self-eating' because of the increased activity of autophagosomes. Apoptosis was first described in 1842 by Karl Vogt but its mechanism remained poorly studied for a long time. In 1965, this topic was resurrected and several decades later Brenner, Horvitz and Sulston won the Nobel Prize in Physiology or Medicine for the discovery concerning genetic regulation of PCD.

The term 'autophagy' was coined by de Duve in 1963. Autophagy is understood as a lysosomal catabolic pathway that plays key roles in intracellular quality control, cell survival, immunity and homeodynamics. The finding that these specific mechanisms of self-destruction play a major role in human ageing is incompatible with the traditional belief that ageing is a passive and uncontrollable process. In proliferating cells, oxidative stress causes DNA damage that induces apoptosis or cellular senescence. Postmitotic cells, such as neurones and cardiomyocytes, have other means of adapting to oxidative stress, which is essential for their survival. It turns out that autophagy, i.e. self-eating, might play a major role in their adaptive responses to stresses. These highly metabolic and postmitotic cells accumulate wastes such as lipofuscin. In fact, lipofuscin accumulation is often described as a hallmark of the ageing process and a biomarker of

reduced cellular turnover. Overarching problems resulting from reduced cellular turnover are another hallmark of ageing. In postmitotic cells, not only lipofuscin is accumulated but also other wastes and organelles that undergo age-related changes. With ageing, these aggregates and old organelles are stored as extremely large sub-cellular components that cannot be degraded through autophagy. They produce large amounts of ROS that cause molecular damage. Autophagy is induced by nutrient deprivation. For example, starvation leads to increased autophagy induction when degradation of aggregates and old organelles in autophagosomes produces ATP, thereby ensuring survival in harsh conditions. Autophagy can be triggered by metformin, which is an oral hypoglycaemic agent (De Santi et al. 2019). It has been hypothesised that autophagy might play a role in cancer prevention through the elimination of damaged proteins and organelles, and metformin might have anti-cancer properties through different mechanisms, independent of its hypoglycaemic effect (Potempa et al. 2016; Libby et al. 2009; De Santi et al. 2019). Noteworthy, calorie restriction (CR) triggers autophagy and leads to the purification of cells from their debris, which can enhance health and survival in model organisms. Thus, autophagy might play a major role in homeodynamics but its activity decreases with age, which can be interpreted as part of the overall pattern of ageing as a intrinsic and progressive deterioration in the homeodynamic capabilities of the body.

Regulatory mechanisms: mTOR as a master signalling pathway

According to the hyperfunction theory, ageing is driven be the evolutionarily conserved signalling pathways, including the insulin/IGF-1 pathway and the mechanistic (mammalian) target of rapamycin (mTOR), which is a master signalling pathway for the regulation of growth, development and the homeodynamic space of the organism (Blagosklonny 2008, 2012). It has been hypothesised that mTOR is a key sensor of various cellular signals, including energy level, oxygen, nutrients, stress and growth and a central hub of nutrient signalling and cell growth, which plays an active role in development and ageing and might contribute to age-related diseases (Kennedy and Lamming 2016; Campisi et al. 2019; Kim and Guan 2019). In late ontogeny, mTOR becomes 'hyperactive', which might contribute to ageing (Blagosklonny 2008; Chmielewski et al. 2016a). It is believed that also other factors that lead to an upregulation of protein translation and increased reactive oxygen species (ROS) production can contribute to ageing *sensu lato* (Zimniak 2012). Therefore, many authors believe that the real cause of ageing is the accumulation of random molecular damage (Kirkwood 2005) or molecular entropy (Hayflick 2007).

From an evolutionary perspective, mTOR is an indispensable factor for growth, development and survival. In late life, its hyperfunction contributes to ageing and age-related diseases as the antagonistic pleiotropy theory predicts. According to the hyperfunction theory, mTOR acts as a molecular hypothalamus, and the multidimensional hyperfunction is a direct cause of ageing, not random molecular damage (Blagosklonny 2013). This alternative view might seem refreshing and stimulating as it explains why hormesis is possible and why hormetins can modulate ageing and longevity by strengthening the homeodynamic space and the buffering

capacities whose main characteristics include stress responses, damage control and constant remodelling (Demirovic and Rattan 2013), which also proves that ageing is a dynamic and emergent process. Nonetheless, the question remains whether the use of rapamycin and rapalogs can slow down the ageing process in humans as the hyperfunction theory posits. Like calorie restriction (CR), these drugs – especially when used with other substances such as aspirin – can only act as a 'speed hump' (Cohen 2016) but they cannot cure or eliminate ageing, even though it is claimed that ageing is 'easily treatable' (Blagosklonny 2017, 2018).

Noteworthy, the inhibition of mTOR does not solve all problems associated with ageing (Zimniak 2012). The positive effects of CR on health and longevity in short-lived species results from this inhibition or allocation of biological resources as the standard version of allocation theory predicts. In long-lived species, CR has both positive and negative effects on health and is highly unlikely to postpone ageing (Le Bourg 2006; Shanley and Kirkwood 2006). Moreover, other authors suggest that mTOR is only one aspect of the molecular orchestration of ageing and the hyperfunction theory is too simplistic (Chmielewski 2017).

Regulatory mechanisms: GH/insulin/IGF-1 signalling

Insulin is a peptide hormone that is released by the β cells of the islets of Langerhans in the pancreas in two phases: the first phase is triggered by increased blood glucose levels, whereas the second phase does not depend on this factor but consists in slow release of newly formed vesicles peaking in a couple of hours. Insulin is one the principal hormones that regulate metabolism. Its main actions include: (1) transport of glucose from the blood into most tissues as it causes the insertion of the GLUT4 transporter in the cell membrane which allows glucose to enter the cell, (2) stimulation of glucose utilisation, (3) inhibition of gluconeogenesis and glycogenolysis, (4) stimulation of glycogenesis, (5) stimulation of fat synthesis, (6) inhibition of proteolysis, (7) inhibition of lipolysis and (8) inhibition of autophagy – postprandial levels inhibit autophagy completely (Bergamini et al. 2007).

The biochemical cascade initiated by the binding of insulin or insulin-like growth factor 1 (IGF-1) to the insulin receptor is summarised in Fig. 2. It is well known that the signal is amplified at several stages along this pathway. Since the activated insulin receptor is a protein kinase, each activated receptor can phosphorylate multiple insulin receptor substrate molecules. Activated enzymes further amplify the signal. Therefore, a small increase in the concentration of circulating insulin can produce a robust intercellular response. If not enough insulin is produced, for example when the β cells are destroyed by an autoimmune reaction, type 1 diabetes develops. If insulin receptors and cells fail to respond normally to insulin, insulin resistance and type 2 diabetes occur.

IGF-1 is produced by the liver and is homologous with pro-insulin. This factor is indispensable for growth and development but it is also important for the regulation of pathological processes (e.g. cancer). Growth hormone (GH)/insulin/IGF-1 signalling is often considered a major regulatory mechanism that controls stress resistance and longevity in evolutionarily distant model organ-

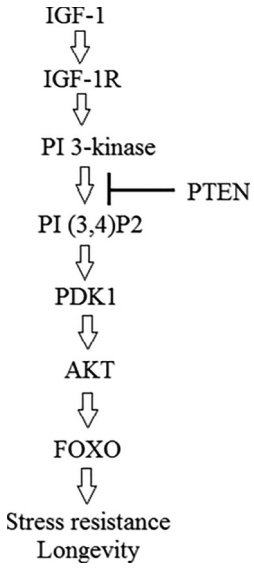

Fig. 2. The evolutionarily conserved insulin/IGF-1 pathway that regulates stress resistance and longevity in evolutionarily distant species. In mammals, insulin and two IGFs can activate this pathway. GH/insulin/IGF-1 signalling plays a critical role in the link between ageing and cancer, which opens new avenues for cancer prevention and treatment (see text for details)

isms (Warner et al. 2010). This type of signalling can also play a critical role in the link between ageing and cancer (Boffetta and Hainaut 2019). Kenyon (2010) argues that ageing 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 aspects of senescence in model organisms. Whilst this interpretation might explain, at least to some extent, the malleability of ageing in model organisms, it is still not clear what is 'programmed': ageing, longevity or both because it depends on arbitrary definitions (Chmielewski et al. 2016a; Chmielewski 2017, 2019a, 2019b).

Although much of the evidence that molecular factors play a key role in the regulation of ageing comes from studies on *Caenorhabditis elegans* and other model organisms, including mutant mice, the evolutionarily conversed insulin/IGF-1 signalling pathway might play a major role in the regulation of human ageing and longevity, and reduced GH/insulin/IGF-1 signalling can slow down the ageing process and reduce the risk of some age-related diseases. Currently, there are several lines of evidence that provide support for this statement. Patients with Laron syndrome have a longer life expectancy compared to the control, while patients with acromegaly are at a higher risk of premature death from the age-related conditions such as cancer, type 2 diabetes and cardiovascular disease (CVD). Moreover, shorter and slimmer people who follow a healthy diet tend to outlive their taller and stouter counterparts (Chmielewski 2016), even though the final results remain mixed because of several confounders such as BMI, socioeconomic status (SES) and educational attainment. Finally, long-term effects of growth hormone therapies in men include the increased risk of death from cancer and type 2 diabetes. Interestingly, the evolutionarily conserved insulin/IGF-1 pathway along with its signalling cascade, which includes PI3K, AKT, mTOR and AMPK, have been implicated in cancer development and progression in humans (Wang 2018; Boffetta and Hainaut 2019). Insulin can promote cancer as a mitogen. Insulin also decreases IGF-1 binding proteins and thus increases levels of bioactive IGF-1, which is a worse situation because the latter is important for the regulation of this pathological process.

Suppressors of the insulin/IGF-1 pathway include AMPK activators, such as metformin, and mTOR inhibitors,

such as rapamycin and resveratrol. These small molecules can protect against cancer and type 2 diabetes. On balance, new findings suggest that reduced GH/insulin/IGF-1 signalling can be a protective mechanism in humans (van Heemst et al. 2005; Warner et a. 2010). These findings are in line with several modern theories of ageing, including the antagonistic pleiotropy theory and the hyperfunction theory.

Targeting cellular senescence: how to harness the benefits?

Cellular senescence is an antagonistic hallmark of ageing that consists in cell cycle arrest after multiple cell doublings when the Hayflick limit is reached (Jeyapalan and Sedivy 2008; López-Otín et al. 2013; McHugh and Gil 2018). In general, there are two mechanisms, which are partly overlapping, that can induce cellular senescence. The first mechanism is associated with telomere shortening, and increased telomere erosion is associated with ageing, age-related mortality and diseases. Telomeres are specialised T-loop structures that protect the ends of the chromosomes but shorten after each round of replication. Eventually, cellular senescence is triggered by a DNA damage response that directly results from the telomere attrition. The p53 protein, acting as a transcription factor, induces the expression of p21, i.e. a potent cyclin-dependent kinase inhibitor (CKI). Proliferating cells accumulate not only p21 but also other CKIs, including $p16^{INK4a}$ that induces cell cycle arrest through RB1. Interestingly, there are four aspects of cellular senescence. Although this process is often described as one of the mechanisms by which tumour suppression occurs as senescent cells cannot divide, cellular senescence also promotes tissue repair, inflammation and cancer progression (Rodier and Campisi 2011), thereby participating in four different biological processes that have opposing effects. Thus, a deeper understanding of these mechanisms is indispensable to harness the benefits of cellular senescence while suppressing its drawbacks in future interventions.

Chronic systemic inflammation: a common denominator of age-related pathologies?

Chronic low-grade systemic inflammation (CLSI) can be tentatively defined as ageing-associated increments in the systemic concentration of tumour necrosis factor alpha (TNF-α), interleukins IL-1β and IL-6, C-reactive protein (CRP) as well as other pro-inflammatory and anti-inflammatory mediators that can contribute to the ageing phenotype and age-related diseases (Ortega et al. 2012; Franceschi and Campisi 2014; Fougère et al. 2017).

Although numerous studies use inflammatory markers as simple tools to predict chronic disease and mortality in older people (e.g. Nilsson et al. 2014; Proctor et al. 2015; Chmielewski et al. 2016b), inflamm-ageing does not simply reflect an age-related increase in the levels of pro-inflammatory markers. Recently, a clear and stable structure among these biomarkers has been identified (Morrisette-Thomas et al. 2014). To approximate this structure, two axes have been set up: the first axis is correlated with age and explains inflammatory activation (both pro- and anti-inflammatory markers), whilst the second axis explains

innate immune response but is not correlated with age. It turns out that both axes are more predictive than individual biomarkers.

Whilst CLSI is common among older people, not all suffer from age-related diseases. Some authors conclude that CLSI is a consequence of altered hallmarks but not a true hallmark of ageing (López-Otín et al. 2013). Nevertheless, all nine hallmarks and seven pillars of ageing are so intertwined phenomena that any consequence that is a driver of the ageing phenotype can be classified as an integrative hallmark (McHugh and Gil 2018) and a pillar of ageing (Kennedy et al. 2014)

Apart from the problem of classification, the causes of CLSI also remain unclear. It has recently been hypothesised that the sources of CLSI include: genomic instability, senescent cells and senescent-associated secretory phenotype (SASP), self-debris, increased gut permeability, dysregulation of immune cells, chronic infections, activation of nucleotide-binding domain, leucine-rich repeat, with N-terminal pyrin domain containing 3 (NLRP3) inflammasome, adipose tissue but especially central obesity, changes in microbiota composition and age-related mitochondrial dysfunction associated with increased oxidative stress (Ferrucci and Fabbri 2018; Mau and Yung 2018).

With age, senescent cells accumulate in the body. They secrete molecules that are collectively referred to as senescent-associated secretory phenotype (SASP) and these molecules have an extremely wide range of potential activities, including the stimulation of local and chronic systemic inflammation. Chronic systemic inflammation, which is often described as a common denominator of age-related diseases, such as cancer, CVD, autoimmune disease and type 2 diabetes (Franceschi and Campisi 2014; Fougère et al. 2017), is caused not only by pro-inflammatory cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor (TNF) but also by immunesenescence, pro-inflammatory processes associated with the adipose tissue, age-related mitochondrial dysfunction and changes in the gut microbiota (Chmielewski 2018). Interestingly, selected inflammatory markers can predict cardiovascular and all-cause mortality in humans (Nilsson et al. 2014; Proctor et al. 2015; Chmielewski et al. 2016b; Chmielewski and Strzelec 2018), which is an important finding because there is currently no genuine biomarker of ageing. The fact that there is no single biomarker that would measure the age-dependent loss of homeodynamic capabilities of the body, i.e. homeostenosis, and portend mortality also shows how complex and irreducible ageing is.

Epigenetic clocks for ageing: how to turn back the hands of time?

Although the field of ageing epigenetics is relatively new, it has already been established that epigenetic factors play a major role in both cellular senescence and organismal ageing (López-Otín et al. 2013; McHugh and Gil 2018). Epigenetic alterations include changes in DNA methylation, noncoding RNA, polycomb group proteins, histone modifications and other processes that control gene expression. Gene expression is precisely regulated by epigenetic mechanisms, i.e. heritable and reversible factors that do not change DNA or pro-

tein sequence. Epigenetic modifications have been extensively studied and they have been shown to be closely associated with numerous age-related diseases. For example, specific alterations in DNA methylation and changes in chromatin architecture and function might contribute to cancer, Alzheimer's disease and age-related immune defects and autoimmunity. Despite numerous studies, there is a paucity of information about the involvement of various intracellular epigenetic markers in normal ageing in humans. The field of ageing epigenetics is fraught with problems and obstacles because entirely new tools and types of analysis are needed in order to explore the full spectrum of epigenetics. Recently, it has been hypothesised that an epigenetic clock controls the transition from the state of high somatic maintenance and normal bodily functioning to the state of low somatic maintenance and increasingly abnormal bodily functioning (Mitteldorf 2013, 2016), raising hopes that reprogramming and other more sophisticated interventions might be useful in slowing down ageing and delaying the onset of age-related diseases in the future.

Can calorie restriction delay the onset of age-related disease?

Calorie restriction (CR)/dietary restriction (DR) is the most robust non-pharmacological intervention that slows down the ageing process in short-lived animals and reduces the risk of selected ageing-associated pathologies in humans and other primates (Campisi et al. 2019; Dönertaş et al. 2019). It has been well established that CR slows down ageing and extends lifespan in model organisms. From an evolutionary perspective, CR can be an effective method of life extension only if the allocation of resources is affected by nutrient availability, which can be observed in short-lived animals such as nematodes, fruit flies and mice. CR is believed to be much less effective in long-lived species such as primates (Le Bourg 2006; Mockett et al. 2006; Shanley and Kirkwood 2006), although not all authors agree that these evolutionary considerations are valid (Masoro 2006; Weindruch 2006; Yu 2006). Recently, it has been hypothesised that CR can suppress hyperfunction (Blagosklonny 2018) and can delay the onset of age-related chronic diseases (Campisi et al. 2019; Dönertaş et al. 2019). Nevertheless, CR is associated with side-effects such as psychological disturbances, behavioural changes and metabolic alterations (Redman et al. 2009). Unlike physical exercise, CR reduces bone mass, muscle mass, muscle size and strength and maximal aerobic capacity in proportion to the reduction in body weight (Villareal et al. 2006; Weiss et al. 2007). Moreover, there is compelling evidence that CR is linked to impaired glucose tolerance in subsequent generations (Zambrano et al. 2005).

It has been suggested that pharmaceuticals, known as 'CR mimetics', can be used instead of low-energy diets, which are extremely unpleasant to most humans, to postpone the ageing process. Nonetheless, different researchers have different opinions about whether and how CR can affect human healthspan and lifespan. It has been suggested that: (1) CR will not enhance longevity in long-lived species, including primates, because metabolic stability determines longevity, and different species have dif-

ferent life history adaptations (Demetrius 2005), (2) any beneficial effect of CR on longevity stems from the lowering of oxidative stress and the attenuation of inflammation (Yu 2006), (3) CR can work through the inhibition of mTOR (Blagosklonny 2010) and (4) the effects of CR on health might be partly attributed to the stimulation of autophagy (Terman et al. 2007; Barbosa et al. 2019). Unlike evolutionary explanations, points (2–4) refer to the mechanistic causes and have important limitations as they fail to provide a comprehensive understanding of CR effects on health and longevity in different species with different life history adaptations.

Can drugs delay the onset of ageing-associated pathologies?

It has been proposed that the hallmarks and 'pillars' of ageing (Kennedy et al. 2014) can be targeted by naturally occurring compounds or 'anti-ageing' drugs (Blagosklonny 2017, 2018; Fang et al. 2017; Wang 2018). Although disease-oriented approaches seem incongruous from a biological perspective as the ageing process is neither a disease nor a monolithic phenomenon that can be treated (Chmielewski 2019a; Rattan 2019), the idea that specific interventions can help delay the onset of age-related diseases through the activation of pathways that shift the physiology towards cell protection and maintenance is not without some merit (Kenyon 2010; Kennedy et al. 2014; Campisi et al. 2019; Dönertaş et al. 2019). Several drugs and interventions have been tested as 'anti-ageing' factors (Fig. 3).

Rapamycin (sirolimus) is an mTOR inhibitor that has been used as an immunosuppressant to prevent organ transplant rejection. Nevertheless, it has been shown to have a wider therapeutic range (Wang 2018), including some 'anti-ageing' effects. After numerous animal studies, rapamycin and rapalogs are considered drugs that might enhance longevity in humans. On the other hand, adverse effects of rapamycin include nausea, pain, impaired wound healing, hypertriglyceridemia, hypercholesterolemia, hypertension and diabetes-like symptoms. Some studies have suggested that the prolonged use of large doses of rapamycin might be associated with an increased risk of lymphoma in some patients.

Resveratrol is a SIRT1 activator and an mTOR inhibitor that can mimic the beneficial effects of CR (Fernández et al. 2011). This naturally occurring compound is a natural non-flavonoid polyphenol that is abundant in grapes, berries, peanuts and red wine. It has been demonstrated that resveratrol displays an extremely broad spectrum of anti-ageing effects (Ginés et al. 2017). Nevertheless, there is no evidence that it can slow down the ageing process or enhance longevity in humans.

Huperzine A (HupA) is a plant-based acetylcholinesterase inhibitor (AChEI) that is used in the treatment of Alzheimer's disease. HupA has been found to attenuate cognitive deficits in model animals. Some studies have shown that HupA has various anti-inflammatory and neuroprotective effects. Therefore, it has been suggested that HupA can help delay the ageing process in humans.

Metformin is an AMP-activated kinase (AMPK) activator that has been used as an inexpensive and relatively safe glucose-lowering drug in clinical practice. Although it is the first-line treatment for patients with type 2 diabetes,

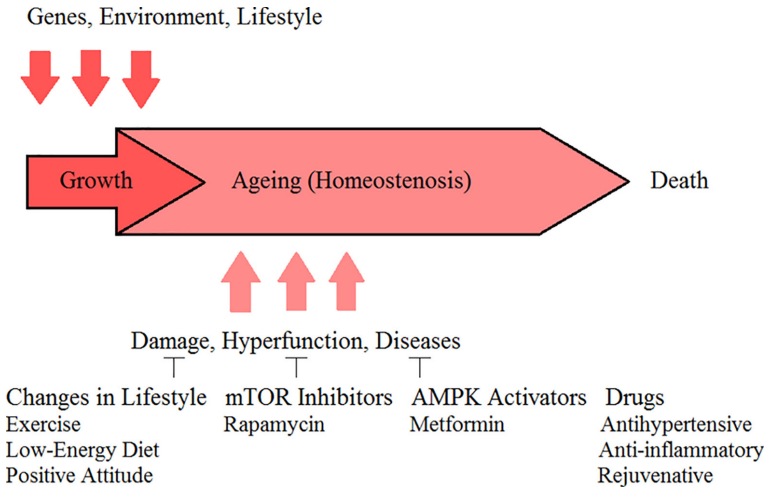

Fig. 3. Possible strategies and interventions that can suppress hyperfunction and extend lifespan in humans (after Blagosklonny 2017, modified). Growth depends on genes, epigenetic factors, environment and lifestyle, whereas ageing (homeostenosis) is driven by damage, stress and hyperfunction. The rate of ageing can be retarded under certain conditions. Although lifestyle changes should be pursued to combat damage and stress, specific drugs can be used to treat diseases and suppress hyperfunction. Nevertheless, it is questionable whether drugs can slow down the ageing process in humans (see text for details)

it also reduces the risk of CVD and various types of cancer (Gandiniet al. 2014; Kasznicki et al. 2014). Furthermore, it has anti-inflammatory pleiotropic effects that contribute to the reduction of levels of pro-inflammatory cytokines such as IL-6 and TNF-α (Fang et al. 2017). Remarkably, chronic metformin exposure extends both healthspan and lifespan in mice (Wang 2018). There are several potential anti-ageing mechanisms of metformin, including inhibition of the inflammatory pathway, activation of AMPK and stimulation of autophagy. Therefore, metformin has been tested as an 'anti-ageing' drug in several clinical trials. This oral hypoglycaemic agent triggers autophagy, i.e. a cellular mechanism by which cells degrade their intracellular components, such as damaged proteins or defective mitochondria, in lysosomes, maintaining cellular homeodynamics (De Santi et al. 2019). Side-effects of metformin include nausea, cramps, vomiting, flatulence and diarrhoea.

Antihypertensive and anti-inflammatory drugs are extremely important tools for the treatment of hypertension and various pathologies, including some ageing-associated diseases. Nevertheless, these drugs can delay the age of death but it is questionable whether they can slow down the ageing process. In the fight against ageing, only holistic, sophisticated and evidence-based strategies, e.g. systemic interventions like methods of rejuvenation of blood and therapies using stem cells and partial reprogramming, can be useful and effective tools.

Although these drugs are believed to be safe and have a wide therapeutic range, disease-oriented approaches are unsuitable for dealing with ageing (Chmielewski 2019a; Rattan 2019). In brief, ageing arises as a by-product from life history adaptations and is a highly com-

plex metaphenomenon that cannot be reduced to a single pathology. Furthermore, treatment of disease can delay the age of death but cannot slow down the ageing process (Carnes et al. 2013). The conceptualisation of healthy ageing as a treatable disease or 'predisease' has a number of serious disadvantages (Hayflick 2004, 2007; Rattan 2016; Chmielewski 2018). Likewise, the use of drugs in the fight against ageing has several significant limitations (Chmielewski 2019a; Rattan 2019). These theoretical problems notwithstanding, many researchers classify ageing as a disease (Bulterijs et al. 2015; Gems 2015; Stambler 2015, 2017) and promote 'anti-ageing' drugs (Blagosklonny 2017, 2018), even though most of these methods seem incongruous from an evolutionary standpoint. Nevertheless, it is possible that ageing as a dynamic and plastic process can be modulated using more sophisticated methods in the future (cf. Hayflick 2004, 2007; Ocampo et al. 2016; Campisi et al. 2019). This topic deserves to be investigated further in future research as it is very extensive.

Can future interventions slow down the ageing process?

Although some authors argue that no intervention will ever slow down, stop or reverse the ageing process in humans as ageing is a stochastic, passive and inevitable metaphenomenon (Hayflick 2004, 2007; Carnes et al. 2013), novel findings suggest that rational strategies and interventions can help delay the onset of age-related pathologies, acting as a 'speed hump' for ageing (Cohen 2016; Campisi et al. 2019; Dönertaş et al. 2019). For example, it has been hypothesised that inhibited mTOR, decreased hyperfunction, reduced chronic systemic inflammation, increased autophagy and ameliorated homeodynamic capabilities through reprogramming and modifications of epigenetic clocks (Mitteldorf 2013, 2016)along witha healthy lifestyle and 'anti-ageing' drugs (Blagosklonny 2017, 2018) can extend healthspan by enhancing the homeodynamic capabilities of the body (Fig. 3). Firstly, the number of genes that can enhance longevity is much larger than expected, which suggests that ageing is a dynamic and plastic process that is molecularly orchestrated (Campisi et al. 2019). Secondly, the genes for ageing are evolutionarily conserved across wide evolutionary distances. If targeting signalling pathways such as mTOR extends lifespan in model animals, then it is reasonable to predict that similar effects are possible in humans. Finally, partial reprogramming ameliorates hallmarks of ageing and erases cellular markers of ageing in human cells (Ocampo et al. 2016), which suggests that the age-related changes in gene expression and overarching epigenetic alterations originate in developmental programmes and are modifiable.

Nonetheless, human ageing is an irreducible metaphenomenon that arises as a by-product from life history adaptations. Thus, it is highly unlikely that the use of any drug, such as rapamycin, resveratrol, metformin, aspirin etc., can postpone or eliminate the ageing process (Chmielewski 2019a; Rattan 2019). Nevertheless, it is possible that rational strategies and future interventions, including the use of more sophisticated methods (e.g. reprogramming, epigenetic modifications etc.), can help delay the onset of ageing-associated diseases in the future (Kenyon 2010; Kennedy et al. 2014; Rattan 2014; Kennedy and Lamming 2016;

Ocampo et al. 2016; Wang 2018; Campisi et al. 2019).

The concept of hormesis is especially promising in this context (Rattan2008; Demirovic and Rattan 2013). Hormetins are natural factors and conditions that might enhance the homeodynamic capabilities of complex biological systems by affecting maintenance mechanisms, including compensatory and reparative processes. They can stimulate an adaptive and compensatory response to stresses, thereby extending healthspan and survival. In general, there are three types of hormetins, i.e. physical, biological and psychological, and new data show that they can improve important physiological parameters in both model organisms and humans (Schneider et al. 2006; Sikora et al. 2010; Fernández and Fraga 2011; Zając-Gawlak et al. 2016). Unlike disease-oriented approaches, these pro-longevity interventions and health-oriented approached are safe and have no side-effects. They can enhance the homeodynamic capabilities of the body. Noteworthy, they do not oppose nature, they do not fight with nature but only ameliorate physiological parameters for healthy ageing. Furthermore, they can reduce the economic burden of ageing and age-related conditions.

Conclusions

Recent studies indicate that human ageing is not a passive and uncontrollable process of deterioration over time but a dynamic, emergent and malleable metaphenomenon that can be affected by a variety of influences. The concept of the shrinkage of the homeodynamic space is especially interesting and intriguing as it shows that novel therapeutic approaches and rational strategies can help delay the onset of ageing-associated pathologies. Moreover, future interventions based on scientific research can help regain lost functional capabilities, thereby extending both healthspan and lifespan.

Conflict of interest

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

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