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Near-to-Perfect Homeostasis: Examples of Universal Aging Rule Which Germline Evades

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ABSTRACT

Aging is considered to be a progressive decline in an organism's functioning over time and is almost universal throughout the living world. Currently, many different aging mechanisms have been reported at all levels of biological organization, with a variety of biochemical, metabolic, and genetic pathways involved. Some of these mechanisms are common across species, and others work different, but each of them is constitutive. This review describes the common characteristics of the aging processes, which are consistent changes over time that involve either the accumulation or depletion of particular system components. These accumulations and depletions may result from imperfect homeostasis, which is the incomplete compensation of a particular biological process with another process evolved to compensate it. In accordance with disposable-soma theory, this imperfection in homeostasis may originate as a function of cell differentiation as early as in yeasts. It may result either from antagonistic pleiotropy mechanisms, or be simply negligible as a subject of natural selection if an adverse effect of the accumulation phenotypically manifests in organism's post-reproductive age. If this phenomenon holds true for many different functions it would lead to the occurrence of a wide variety of aging mechanisms, some of which are common among species, while others unique, because aging is the inherent property of most biological processes that have not yet evolved to be perfectly in balance. Examples of imperfect homeostasis mechanisms of aging, the ways in which germ line escapes from them, and the possibilities of anti-aging treatment are discussed in this review. J. Cell. Biochem. 113: 388–396, 2012. © 2011 Wiley Periodicals, Inc.

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Multiple pathways are known to be involved in the aging of organisms. A massive accumulation of genomic and functional data has expanded the number of known aging mechanisms revealing more and more biological processes that affect aging rates and lifespans [Troen, 2003]; see also Bostock et al. [2009] and Cluett and Melzer [2009] for reviews and de Magalhães et al. [2009] and Wieser et al. [2011] for bioinformatics resources across different species. Because of this complexity, there is still no universal model has been developed to describe how multiple functions of almost any eukaryotic organism ubiquitously diminish over time. Some mechanisms and pathways that affect aging in one species are less relevant in others, indicating that it is represented by a set of different processes rather than by one common mechanism.

However, what is common for all aging mechanisms is the fact that some quantitative change occurs over time that involves either progressive accumulation or loss of some biological structure or system components. One may hypothesize that such accumulations or losses may result from an incomplete balance between biological processes such that one process is not perfectly compensated for by another. This failure to compensate may be defined as imperfect or near-perfect homeostasis because the deviations from ideal compensation can be relatively small, and are normally enough to allow an organism to live out its lifespan.

Indeed, the achievement of perfect balance for an entire biological system including all of its processes, if it were possible, would require high energy expenditures and become problematic for the formation of complex and specialized structures. Presumably, the difficulty of achieving the perfect balance should be proportional to the complexity of the system and the need of its different components to perform specialized functions, in accordance with the recently proposed concept of aging as a price of complexity [Kiss et al., 2009]. Accordingly, most prokaryotes and some simple eukaryotes (e.g., euglena, hydra, and some sea urchins) show fewer signs of aging [Martínez, 1998; Ebert, 2008; Goto and Beneragama, 2010], indicating that they are able to achieve better homeostasis and that aging phenomenon develops later in evolution. It is possible that those primitive organisms achieve their homeostatic perfection because they avoid any situations that are difficult to balance. Also, unicellular organisms are subjects of a quick clonal selection filtering out every genome that is not

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supportive of perfect homeostasis. In multicellular systems, the disadvantageous genomes are filtered out, but every genome that is able to provide selective advantage is also filtered out to protect against clonal growth. The remaining systems achieved a near-perfect balance, and even a slight but consistent homeostatic shift toward one side would be negligible early in life (or may be advantageous), but critical over a long period of time, which is consistent with the theory of antagonistic pleiotropy [Williams, 1957].

For this reason, evolution headed toward dividing every species into two lineages: the complex, specialized, multicellular, and mortal soma and the simple, primitive, clonal, but basically immortal germline that evades the aging rule as was brilliantly proposed more than a century ago by Dr. August Weismann and was applied to create one of the first explanation of aging known as the "disposable soma" theory by Dr. Thomas Kirkwood [Kirkwood, 1977; Kirkwood, 2005]. The purpose of this review is to summarize the known mechanisms of near-perfect homeostasis with regard to aging and to discuss the ways in which germ line/ embryonic stem cells succeed in achieving a better balance.

ACCUMULATION AND LOSS DISEASE: EXAMPLES AND MEANS OF AVOIDANCE

This section includes some examples of aging mechanisms that result from incomplete homeostasis.

LOSS OF TELOMERES

Loss of telomeres may be the classical example of incomplete homeostasis. It is currently well known that the ends of chromosomes, called telomeres, become shorter with every cell division and finally cause cell cycle exit after a certain number of replications. This phenomenon arises because of the physical structure of the DNA replication complex, which is not able to replicate the terminus of one strand of the DNA helix. This was first theoretically predicted by Dr. Alexey Olovnikov [Olovnikov, 1971] and by Dr. James Watson [Watson, 1972]. Alexey Olovnikov also predicted that telomere shortening may be responsible for the cell division limit (Hayflick limit) that is observed during culturing and may be related to organismal aging [Olovnikov, 1973]. Further, he hypothesized that a specialized enzyme that is called telomerase exists to build up telomeres in germline cells and to make them divide indefinitely [Olovnikov, 1971].

Currently, it is generally accepted that telomerase is expressed in somatic cells (mostly in adult stem cells), although on a lower level than in germline. This somatic expression is not enough to compensate for telomere loss, and telomeres are consumed slightly more quickly than they are generated by the enzyme. As a result, telomere shortening is observed over time in somatic cells, which finally causes growth arrest and senescence [Herbig et al., 2004; Jacobs and de Lange, 2004]. The rate of telomeric DNA loss is found to be either consistent throughout the life of an organism [Vaziri et al., 1993; Aikata et al., 2000] or higher in an early life when most active replication occurs [Frenck et al., 1998; Baerlocher et al., 2003; Hall et al., 2004], depending on the species and cell type studied. This example of incomplete homeostasis results from the internal guard against clonal growth, that is required in multicellular organisms. When the somatic expression of telomerase is artificially enhanced in mice, early death has been observed to occur due to tumor formation [González-Suárez et al., 2002], indicating that the shift in telomeric homeostasis automatically dysregulates the process of anti-cancer protection and ultimately decreases the lifespan of an organism.

This question was brilliantly addressed in the recent work by Drs. Montecino Serrano and Maria Blasco [Tomás-Loba et al., 2008], aiming to improve both telomere and anti-cancer homeostasis. By concomitantly elevating the expression of telomerase and two tumor suppressor genes, p16 and p53, in mouse epidermal tissues (Super-Tert-Super-p53-Super-p16 mice), they achieved postponed aging in these tissues and prolonged lifespan of the animals. Species specificity remains an interesting issue in these experiments because telomeric attrition was not thought to be a problem in mice until recently. Unlike humans and some other higher primates, in which telomere shortening clearly contributes to aging phenotypes and losses of regenerative abilities in a majority of tissues, mice have longer telomeres, and knocking out telomerase leads to preliminary aging phenotype only after ~3–4 generations [Herrera et al., 1999; Rudolph et al., 1999]. The main cause of death in mice is the formation of tumors, indicating that anti-tumor homeostasis plays a rate-limiting role in the aging of this species and manifests earlier than the imperfection in telomere homeostasis. However, in a strengthened tumor-suppressive background, it is possible that telomeric homeostasis becomes rate-limiting.

To sustain immortality, both germ cells and the embryonic stem (ES) cells they originate from retain high telomerase activity [Thomson et al., 1998; Wright et al., 2001]. The recent discovery of the re-programming of normal human fibroblasts to ES-like primitive states (iPS cells) has shown that these cells acquire immortality and reactivate telomerase expression in the process of reprogramming [Takahashi et al., 2007; Marion et al., 2009]. At the same time, both ES and iPS are capable of unlimited clonal growth and form teratomas when introduced to the body. Most prokaryotes, with a few exceptions, avoid telomere problems due to their circular genomes.

ACCUMULATION OF DAMAGED STRUCTURES

The accumulation of mutations in the genome, in addition to the accumulation of damaged proteins and other biological structures was shown to take place almost ubiquitously in different organisms over a period of time (see Sinclair and Oberdoerffer [2009], Bogenhagen [2010], and Møller et al. [2010] for recent reviews). Accumulation of damage has long been proposed to be an aging mechanisms in a popular aging theory known as "Error's Catastrophe" [Orgel, 1963]. Damage to biological systems as to any other system is caused by variety of interfering factors, environmental as well as intrinsic. In biological systems, damage normally occurs due to oxidative stress, natural radioactivity and toxins, errors in nuclear and mitochondrial DNA replication and transcription and protein misfolding. If this damage occurs even slightly faster than is corrected by reparation systems, it will have an impact on the functioning of the organism (including the repair system itself), causing the state of "Catastrophe of errors." The most

prominent phenotypic effect of mutations accumulation is significant increase in tumor formation after certain age, which manifests earlier in mice than in humans, as mentioned above.

Damage is a stochastic process, and the capacity of repair systems to maintain homeostasis is limited in somatic cells. There may be two explanations as to how germline and simple organisms survive this deterioration. One is that they develop much more efficient repair systems than the somatic cells at the cost of a lack of specialized (''social'') functions. For example, there are evidences that ES cells are more resistant to genotoxic stress than somatic cells [Vinoth et al., 2008]. Another possibility is that a perfect repair homeostasis mechanisms have not yet been developed in nature, and germline/bacteria are accumulating the ''garbage'' at approximately same rate as other somatic cells. Nevertheless, on unicellular stage cells with the damaged structures are quickly filtered out by natural selection and replaced by the clonal outgrowth of their healthy counterparts, which is prohibited within multicellular structures because of their strict limitations on clonal growth.

ACCUMULATION OF SENESCENT CELLS

Senescence is a special cellular state that is characterized by irreversible cell cycle arrest, an enlarged morphology, slow metabolism and the expression of several markers (beta-galactosidase, senescence-associated heterochromatin foci, telomere dysfunction-induced foci, etc.). Senescence predominantly results from the derepression of p16INK/p14(19)ARF locus, likely through the deactivation of BMI1 polycomb repressor [Bracken et al., 2007], which is triggered by several factors, such as telomere attrition, accumulation of mutations, oxidative, and other types of damage (see Jeyapalan and Sedivy [2008] and Beltrami et al. [2011] for reviews). In addition, senescence was found to be triggered by p21 tumor suppressor [Herbig et al., 2004]. It has been shown that senescent cells accumulate in many tissues with age [Dimri et al., 1995; Ressler et al., 2006], and are gradually increasing in number throughout the lifespan of an organism starting from an early age [Jeyapalan et al., 2007; Wang et al., 2009]. Although they occupy some space in tissues, they are not yet known to perform any specialized functions. Along with apoptosis, senescence is one of the most powerful mechanisms of anti-cancer protection. Cells from p16/p19 knock-out mice are not able to go to senescence, and, like telomerase knock-ins, these mice die early from multiple tumors [Serrano et al., 1996].

The fact that senescent cells accumulate over time indicates that the formation of senescent cells prevails over the process of their slow death, although a mechanism of active senescent cells removal from the body is not yet precisely known and is an intriguing biological problem.

In ES cells and iPS cells p16/p19 locus is stably repressed through epigenetic mechanisms [Li et al., 2009]; therefore they do not go through senescence [Evans and Kaufman, 1981; Thomson et al., 1998].

LOSS OF FUNCTIONAL ADULT STEM CELLS

Unlike any other physical objects, living bodies have developed the unique ability to regenerate and self-renew almost all of their structures. The regeneration and self-renewal of all the different tissues in multicellular organisms occur through their re-population by adult stem cells. These cells usually retain some degree of pluripotency, although pre-committed to one particular lineage or to the several lineages. They are slow to divide, and a pool of them resides in a particular space, called a niche, within every tissue structure. They can self-renew through the cells division to produce other stem cells, and some of their progenies commit and differentiate to certain cell types.

It has been observed that the abilities of tissues to regenerate and self-renew gradually decline with age. Moreover, they are almost completely lost with advanced age. For some cell lineages, the exhaustion of adult stem cell pools over time has been clearly shown, for example, for melanocyte stem cells of hair follicles, causing graying of hair [Nishimura et al., 2005] and for mesenchymal stem cells of bone marrow [Bellantuono et al., 2009]. For other tissues, however, stem cells do not change or even increase in number, but rather their ability to divide and to respond to differentiation stimuli decreases dramatically (see Geiger and Rudolph [2009] for a review of hematopoetic stem cells). The characteristics of hematopoetic stem cell pool exhaustion, however, vary between mouse strains with different genetic backgrounds. The third category of stem cells is able to divide and differentiate normally, but the cells do no receive adequate stimuli from their microenvironment, and therefore, remain quiescent; for example, muscle satellite cells [Conboy et al., 2005].

The exhaustion of functional stem cell pools over time results from a combination of several accumulation and depletion mechanisms. Some of them have already been listed above, such as all dividing cells in the body are subject to telomere attrition (recently reviewed in Flores and Blasco [2010] in relation to adult stem cells), mutations accumulation and senescence (recently reviewed in Beltrami et al. [2011]). In addition, there are changes in external signaling cues from other cells and gradual biochemical and physical changes in the niche in which stem cells reside. Another reason that adult stem cells diminish in number over time may be due to slightly shifted self-renewal homeostasis (determined by both cell and niche). If stem cells of particular tissue tend to differentiate at a slightly, but consistently faster rate than they self-renew, this difference will become apparent over a long period of time and cause the depletion of the entire tissue. The delicate balance between stem cells self-renewal and differentiation is regulated at several levels by signaling molecules of the niche microenvironment, classic examples of which are Notch and Wnt signals, as well as by special mechanisms of asymmetric cell division [Sawa, 2010; Charville and Rando, 2011; Williams et al., 2011]. However, because 100% accuracy is not possible for homeostasis, and deviations do occur, it would likely be dangerous for an organism if adult stem cells self-renew at a slightly faster rate than that at which they differentiate. Therefore, the imperfection in adult stem cell self-renewal homeostasis could be another powerful mechanism of anti-cancer protection.

Some evidence supporting the depletion mechanism may include the fairly consistent decline in the regenerative abilities of many tissues during an organism's lifespan, starting from early childhood. Also, it has been observed that in advanced age some people have experienced reopening of burn scars that had been completely

healed, which may indicate more rapid stem cells exhaustion in previously injured sites of the body [Holavanahalli et al., 2010].

Therefore, the type and speed of stem cells exhaustion are highly species- and tissue-specific, and even mouse-strain specific; in each particular case, they are determined by different, earliest manifesting and worst-balanced, and therefore rate-limiting biological process.

The problem of progressive loss of functional stem cells does not exist in bacteria, ES, and iPS cells by definition.

ACCUMULATION OF ALTERNATIVELY SPLICED LAMIN A

Premature aging syndromes, or progerias, are powerful tools in the study of aging. Usually rare diseases, they show how single gene mutation can cause aging phenotypes to appear significantly earlier in life. One example is Hutchinson–Gilford progeria syndrome, which is characterized by multiple aging symptoms that start to develop as early as at two years of age; these people rarely survive to the age of thirteen.

The Progeria Research Foundation was established by Dr. Leslie Gordon to find the cause of disease of her own son, a single nucleotide mutation in the Lamin A gene [Eriksson et al., 2003]. Continued research in collaboration with Dr. Francis Collins has shown that this synonymous mutation increases the efficiency of an alternative splicing site, producing a different variant of pre-Lamin A protein, which they named Progerin. When farnesylated, it accumulates in the nuclear lamina but cannot be properly cleaved by specific proteases and significantly disrupts the nuclear architecture [Capell et al., 2005].

Interestingly, the use of alternative splicing site and the accumulation of Progerin in the nuclear lamina over time was recently found to occur in many tissues, indicating that it may be one of the normal mechanisms of aging [Scaffidi and Misteli, 2006; McClintock et al., 2007]. Although, the physiological role of the alternative form of lamin is not yet clear, its accumulation represents another example of the homeostasis failure to remove it from the membrane or degrade it in a timely manner.

It is known that naturally immortal organisms and cells (e.g., germ, ES, and iPS cells) do not produce Lamin A and therefore avoid this problem. Instead, they use Lamin B, which undergoes a more balanced metabolism [Constantinescu et al., 2006].

ACCUMULATION OF AMYLOID AND TAU: PROTEOSTASIS

Alzheimer's disease is a fatal, degenerative brain disorder that is characterized by progressive dementia followed by the significant impairment of brain functions based on neuronal loss in the cerebral cortex. Along with some other forms of dementia, Alzheimer's disease is an age-related disorder. With the exception of a few genetic forms, it manifests late in life with the number of affected individuals dramatically increasing with age; one-fourth of the human population over the age of 75 and one-third of the population over 80 are affected, according to the Alzheimer's Drug Discovery Foundation. Therefore, Alzheimer's disease is a part of physiological aging.

The primary cause of the disease is thought to be the accumulation of two neurotoxic protein deposits: extracellular plaques consisting of amyloid (Aβ) peptides and intracellular tangles composed of hyperphosphorylated tau protein. There is no consensus regarding the reasons for Aβ and tau accumulation in the brain over time, but they may share common mechanisms with other aging processes. For example, there may be a slightly faster synthesis of the involved proteins as compared to their clearance throughout life, accumulation of mutations and oxidative damage in Aβ and tau pathways, but it is also very likely to be due to the malfunction of cells responsible for protein clearance homeostasis, such as the glia cells and neurons. This malfunction, in its turn, may result from the exhaustion of the neuronal stem cell population that is responsible for the replacement of aging brain cells. Such a possibility, largely unexplored until now, may have been demonstrated by the transplantation of exogenous neuronal stem cells in an animal model of Alzheimer's disease.

Alzheimer's disease is specific to mammals with highly developed brains, such as humans, other primates, cats and dogs. In simpler animals, such as rodents, there are no signs of spontaneous Alzheimer's disease. Therefore, poor amyloid and tau homeostasis may likely be the consequences of the additional layer of complexity that gives an advantage in the form of high intelligence. The neurons of slow-aging/immortal organisms (e.g., hydra) do not express amyloid peptides, and neither bacteria, germ, ES nor iPS cells contain these specialized proteins.

Alzheimer's disease is an example of a more extensive problem that is known as inefficient proteostasis, which is a significant component of aging. Other age-related disorders result from the accumulation of particular proteins; for example, alpha-synuclein in Parkinson's disease (see Balch et al. [2008] and Douglas and Dillin [2010] for recent reviews on aging-related proteostasis).

ACCUMULATION OF MOBILE GENETIC ELEMENTS: THE FORGOTTEN HYPOTHESIS

Some of the recent discoveries in the aging field are somewhat reminiscent of a forgotten hypothesis from the mid-1980s regarding the activation and accumulation of transposons. Such accumulation with age was demonstrated in some works and not supported in others [Gaubatz and Flores, 1990; Murray, 1990]. Twenty years later, Dr. David Sinclair at MIT researched extrachromosomal elements that play critical roles in the aging process in yeast. As mentioned earlier, yeasts were some of the first organisms that are separated into immortal germ cells and aging somatic cells. In yeasts, cell division is asymmetric and produces a slowly aging mother cell representing the soma, which is capable of a limited number of further divisions, and a young daughter cell that divides indefinitely. The yeast histone deacetylase Sir2 maintains the particular repression status of the repetitive ribosomal RNA locus. This ribosomal locus produces circular DNA elements through the amplification of its genes. These elements usually do not recombine back into the genome but have their own replication origins and therefore are able to multiply and exist independently, similar to transposons. By maintaining the preferential distribution to the mother cell, these circular elements slowly but consistently accumulate and eventually cause the mother cell's functions to deteriorate [Sinclair and Guarente, 1997].

The discovery of this mechanism leads to two interesting possibilities. One is that primary differentiation may originate (as a

way of performing specialized functions) along with and tightly linked to the process of getting rid of any structures and functions that are problematic to regulate by simply relocating them to the mortal soma: for example, damaged structures [Aguilaniu et al., 2003]. The second assumption is that similar DNA elements may be produced with age in other species from repetitive sequences, transposons, endogenous retroviruses, and other regions of the genome. Although the accumulation of transposons with age has not been proven, the large-scale and powerful system of anti-transposon protection is expressed preferentially in germline cells. It consists of more than a million unique small RNA species called piRNA [Aravin et al., 2006; Berninger et al., 2011; Gan et al., 2011], which is of a higher complexity level than the entire protein-coding genome. The only one yet proven function of piRNA is the silencing of mobile genetic elements [Malone and Hannon, 2009; Siomi et al., 2011]. Existing in a wide variety of different organisms and pending future discoveries, the piRNA system appears to be a candidate for one of the mechanisms of germline immortality.

ACCUMULATION OF LIPOFUSCIN: ALL THE REST?

Brown granules accumulate in the cytoplasm of a wide variety of human and animal tissues over time and consist of a heterogeneous material called lipofuscin, or age pigment. Lipofuscin was found to accumulate in the heart and skeletal muscles, brain, thyroid gland, retina, liver, kidney, adrenals, erythrocytes, skin, and gastrointestinal tract (see reviews of Porta [2002] and Jung et al. [2007]). The accumulation in the skin accounts for some of the senile pigment deposits along with those formed by melanocytes. Two major chemical components of lipofuscin are lipids and proteins [Hendley et al., 1963; Taubold, 1975], but some sugars and many metals, such as aluminum, iron, copper, zinc, and mercury, also accumulate in lipofuscin granules [Dalefield et al., 1994; Jolly et al., 1995]. Protein composition of lipofuscin vary among tissues with the prevalence of tissue-specific species. Lipofuscin is typically considered to be a product of mitochondria-stimulated lipid peroxidation and protein oxidative damage that fails to be resolved by lysosomes; however, there is evidence that significant portions of the pigments are not chemically related to the oxidative damage [Jolly et al., 2002]. Lipofuscin accumulates gradually during an individual's lifetime; a linear accumulation throughout life that starts in infancy was shown in human [Benavides et al., 2002] and rat brains [Sharma et al., 1993] and cardiac myocytes [Schmucker and Sachs, 2002], while in equine thyroid glands, faster rates were observed within the first few years after birth followed by a slowing of the process [Dalefield et al., 1994]. Slightly higher rates of formation of multiple metabolic products as compared to their clearance in combination with oxidative damage may cause their aggregation into lipofuscin granules. Furthermore, some lipofuscin components are considered to be non-degradable and therefore can only accumulate, such as the end product of the retinoic acid metabolic pathway, A2E [Sparrow et al., 2008]. Lipofuscin is especially enriched in tissue-specific molecules: for example, the retinol light cycle metabolites in retina cells [Eldred and Lasky, 1993; Sakai et al., 1996; Parish et al., 1998].

Several examples of adverse effects of lipofuscin on tissue functions have been described in the literature. Retinal lipofuscin accumulation is associated with age-related macular degeneration [Solbach et al., 1997; Holz et al., 2001; Hwang et al., 2006], while lipofuscin accumulation in the brain is associated with neurodegenerative disorders, such as Alzheimer's disease [Mountjoy et al., 2005].

There is no evidence to date of lipofuscin accumulation in bacteria, ES or iPS cells, suggesting that it is a product of tissue-specific components for which optimal catabolic pathways have not yet evolved.

HYPOTHESIS: OTHER DEVIATIONS IN GENERAL HOMEOSTASIS AND THEIR DEPENDENCE ON METABOLIC RATES

It is well accepted that many genes that are responsible for energy metabolism are linked to aging rates. These genes include members of the insulin and insulin-like growth factor pathways, IGFR and its regulator Clotho, downstream signal messengers and transcription factors (Daf2 and Daf16 in *Drosophila*, etc.). Insulin signaling is proportional to general metabolism and cell growth rates and to lifespan in a wide variety of model species (i.e., *C. elegans*, *Drosophila*, mouse, and human). To a lesser extent, this is also related to other processes of growth and metabolism and their related pathways and genes, such as growth hormone signaling, sirtuins, and Indy. At the same time, caloric restriction is well known to increase life expectancy.

Because energy metabolism sets up the overall speed of biological processes, it may also determine the speed of those that are subject to imperfect homeostasis that are either already discovered (some of them listed above) or yet unknown. Potentially, the number of unbalanced processes in somatic cells can be unlimited because any accumulations of phenotypically manifesting deviations beyond the reproductive age are not subject to natural selection; moreover, those which theoretically should appear beyond the current maximum lifespan could no be identified yet.

REVERSION TO THE PRIMARY STATE: TREATMENT PERSPECTIVES AND ALTERNATIVES

To address the question of whether aging therapy is realistic, one may ask first if the aging process is principally reversible. The possibility of somatic cell nucleus reversion to a primitive germline state was originally shown as early as the 1950s in the famous, cutting-edge experiments for cloning the frog by somatic cells nucleus transfer to oocyte [Gurdon et al., 1958]. Beginning with the cloning of the sheep Dolly in 1996 [Campbell et al., 1996], a complete series of cloning experiments using different species was conducted, including some animals that were dead [Lanza et al., 2000a] and extinct [Folch et al., 2009]. Dr. Robert Lanza was also the first to show a reversal of aging processes on the molecular level by somatic cell nuclear transfer [Lanza et al., 2000b]. Finally, the principles were proved by the reprogramming of human and mouse adult fibroblasts into ES-like (iPS) cells in the laboratory of Dr. Shinya Yamanaka [Takahashi and Yamanaka, 2006; Takahashi et al., 2007]. These experiments revealed the key mechanism

involved in the reversal of the states of somatic cells by select transcription factors through the rewriting of the overall epigenetic signature of the genome [Maherali et al., 2007; Wernig et al., 2007]. The strategy of producing autologous stem cells from a patient's own body may have tremendous therapeutic potential due to its ability to aviod all immunological problems, and therefore it has been widely popular in the stem cell field. However, the efficiency of such reprogramming significantly decreases with age of a donor organism [Li et al., 2009]. Recently, the laboratories of Drs. Konrad Hochedlinger and Manuel Serrano/Maria Blasco simultaneously found that senescence is a major obstacle to the reprogramming process, and deficiency in Cdkn2b (p16/p19) increases reprogramming efficiency significantly [Li et al., 2009; Utikal et al., 2009]. It was also found that the de novo epigenetic repression of the p16/p19 locus is required and rate-limiting for the entire reprogramming process [Li et al., 2009].

Therefore, in the process of reprogramming, somatic cells reactivate telomerase expression [Takahashi et al., 2007; Marion et al., 2009], rebuild telomeres [Suhr et al., 2009], repair aging mitochondria [Suhr et al., 2010], reactivate the second X-chromosome in females [Maherali et al., 2007], reload entire epigenetic programs [Mikkelsen et al., 2008], and under some poorly defined circumstances, even repress active p16/p19 [Li et al., 2009]. As a result, they regain their abilities of unlimited clonal growth and clonal selection. Not surprisingly, along with the acquisition of this ability, iPS cells, similar to ES and germ cells, acquire tumorigenicity and form teratomas when injected into the body [Takahashi and Yamanaka, 2006; Takahashi et al., 2007]. To eliminate this problem, similar to ES therapy, iPS cells must be thoroughly differentiated into the necessary cell type and meticulously characterized before transplantation. They can also be differentiated into adult stem cells (mesenchymal stem cells, neuronal stem cells, etc.), similar to ES cells. However, both ES- and iPS-derived adult stem cells retain the ability to form teratomas in vivo in the majority of cases, which results from the fairly small percentage of cells that remain undifferentiated in the stem cell population. Different approaches have recently emerged to solve this problem. One is to filter out remaining multipotent cells by some "stemness" marker expression (e.g., Sox1, Nanog, Tra-1), either by fluorescent cell sorting or laser-assisted photoablation [Chung et al., 2006; Terstegge et al., 2010]. These procedures require either the preliminary integration of fluorescent reporters or efficient immunorecognition. Alternatively, culturing under certain conditions may allow for the acquisition of cleaner adult stem cells similar to that which is shown for ES cell-derived neuronal stem cells [Bajpai et al., 2009; Koch et al., 2009]. Although challenging, such techniques are currently feasible to develop.

In the terms of aging therapy, however, the biggest challenge may be the engraftment of such "young" revertants to the tissues. The multiple studies have shown that adult stem cells have high affinities for their niche and easily repopulate damaged tissues to assist with the repairing. However, the homing of exogenously introduced adult stem cells to whole, intact and highly structured tissues remains elusive. Unless a safe and efficient way of replacing aging and senescent cells with exogenous re-programmed cells is found, aging therapy will not be possible.

The other direction of whole organs engineering with reprogrammed cells still remains in the realm of science fiction because of the strong limitation on angiogenesis in such structures [Mandoli et al., 2010], although some progress has been made to this end with the help of ES cells [Lanza et al., 2002]. Along with regenerative medicine, principally alternative and traditional methods of fighting aging aim to address every particular imperfect homeostatic issue separately. Particularly promising in this direction may be to discover the means of removal of senescent cells [Bennett and Kay, 1981; Rebo et al., 2010], clearing of accumulated proteins [Selkoe, 2011] and lipofuscin [Wu et al., 2011] and the activation of endogenous stem cell pools. In addition, somewhat risky human subject trials have been recently launched that aim to slow the aging process by means of a moderate activation of telomerase [Harley et al., 2011].

DISCUSSION

As with any hypothesis, the relevance of near-perfect homeostasis to aging mechanisms must be experimentally validated over time. If it holds true, a common trait should be observed for many of the aging mechanisms, such as occurrence of characteristic accumulation or loss steadily over the lifespan rather than beginning at a certain age. From the other hand, the phenotypic manifestation of these phenomena will rather occur at a certain age when the processes overcome their threshold beyond the norm of reaction. Although many aging processes (such as osteoporosis) begin to manifest at a post-reproductive age, some aging signs manifest long before menopause. For example, notable decreases in the regeneration abilities of many tissues and in skin elasticity, the accumulation of lipofuscin and cell senescence have been already observed in early childhood or even infancy.

Both the magnitudes of homeostatic deviations and thresholds of their manifestation may be completely different for different processes and species, depending on the balance of the entire system. This is the cause of the entire variety of aging processes, between species and even between individuals. For those that cannot yet be determined because of lifespan limitation, we formulated the aging first-come basis rule: the knowledge of aging processes for each particular species is limited to those that have the highest amplitude of homeostatic deviation and more prevalent adverse effects that manifest earlier and are more detrimental to the lifespan of a particular species.

Although far from complete coverage, some of the widely known mechanisms of aging from the point of view of imperfect homeostasis in somatic cells are described above. It is evident that many of these homeostatic problems are related to mechanisms involved in anti-cancer protection or in performing complex specialized functions in multicellular systems (as in the case of amyloid accumulation in brain neurons). Some crucial aging-related mechanisms, such as the involvement of hypothalamic and pituitary hormones, circadian rhythms, insulin and growth-related hormones, were not described in this review, although they drive the timing of biological processes on an organismal level and therefore the overall speed of aging.

The proposed mechanism above differs from the accumulation of errors because an ''error'' denotes faults in the existing ''perfect'' homeostasis mechanism, while such a mechanism has not yet been evolutionarily developed. Therefore, aging is basically an internal property of biological processes rather than the stochastic accumulation of exogenous damage and errors. A mathematical model for the aging process as a function of multiple homeostatic deviations may be developed in the future, and computational approaches to search for optimal solutions may be applied for modeling perfectly balanced systems with extremely high complexity levels.

CONCLUSION

Many biological processes in multicellular organisms possess a one-directional deviation from homeostasis that causes system components to accumulate or be depleted with time. This deviation results from the social complexity of the multicellular body and the requirements for protection against clonal growth. Phenotypic manifestation begins after a certain threshold of accumulation/depletion and may represent the most generalized mechanism of aging. In this regard, mechanisms of non-aging in complex, multicellular biological systems have not yet been evolutionarily developed.

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