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Aging of perennial cells and organ parts according to the programmed aging paradigm

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Abstract If aging is a physiological phenomenon—as maintained by the programmed aging paradigm—it must be caused by specific genetically determined and regulated mechanisms, which must be confirmed by evidence. Within the programmed aging paradigm, a complete proposal starts from the observation that cells, tissues, and organs show continuous turnover: As telomere shortening determines both limits to cell replication and a progressive impairment of cellular functions, a progressive decline in age-related fitness decline (i.e., aging) is a clear consequence. Against this hypothesis, a critic might argue that there are cells (most types of neurons) and organ parts (crystalline core and tooth enamel) that have no turnover and are subject to wear or manifest alterations similar to those of cells with turnover. In this review, it is shown how cell types without turnover appear to be strictly dependent on cells subjected to turnover. The loss or weakening of the functions fulfilled by these cells with turnover, due to telomere shortening and turnover slowing, compromises the vitality of the served cells without turnover. This determines well-known clinical manifestations, which in their early forms are described as distinct diseases (e.g., Alzheimer's disease, Parkinson's disease, age-related macular degeneration, etc.). Moreover, for the two organ parts (crystalline core and tooth enamel) without viable cells or any cell turnover, it is discussed how this is entirely compatible with the programmed aging paradigm.

Keywords Aging · Cell turnover · Cell senescence · Parkinson disease · Alzheimer disease · Age-related macular degeneration

Introduction

Aging, which is here precisely described and defined as "increasing mortality [i.e., decreasing fitness] with increasing chronological age in populations in the wild," (Libertini 1988) alias "actuarial senescence in the wild" (Holmes and Austad 1995), is widely documented (Nussey et al. 2013).

There are two mutually incompatible interpretations of aging (Libertini 2015a), which for their opposite and important implications are certainly paradigms in the meaning proposed by Kuhn (1962)).

The "old paradigm" describes aging as the random age-related overlapping of many degenerative processes, which, in principle, might be partially retarded and contrasted but never entirely tamed (Libertini 2015a). In contrast, the "new paradigm," or programmed aging paradigm, explains aging as a physiological phenomenon, favored by evolution in terms of supra-individual natural selection (Libertini 2015a), i.e., a particular type of phenoptosis (Skulachev 1997) alias "the programmed death of an individual" (Skulachev 1999). This implies

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that aging is the outcome of specific genetically determined and regulated mechanisms, and therefore, in principle, it might be entirely tamed (Libertini 2009a).

The discussion about the evidence and the arguments that are in support or against each of the two paradigms is debated in another paper (Libertini 2015a) and is not the topic of the present review.

For our goals, it will suffice to say that evidence and arguments appear to be clearly in support of the new paradigm and in contrast with the old paradigm (Libertini 2015a), though the opposite paradigm remains the prevalent idea (Kirkwood and Melov 2011).

The aforementioned mechanisms that determine a progressive age-related fitness impairment have been described in brief in another paper (Libertini 2014), and, here, only a brief mention of them will be given.

The various cell types that constitute a vertebrate organism are subject to various kinds of programmed cell death (PCD), which are balanced by an equivalent proliferation of stem cells. The replication of these cells is subject to genetically determined and regulated limitations, due to telomerase inhibition and therefore to restrictions in telomere length restoration (Libertini 2009a). Telomere shortening leads to an increasing probability of the complete blocking of cell duplication capacity plus a wide impairment of cell functions (Fossel 2004), i.e., cell senescence (Ben-Porath and Weinberg 2005), and also to a progressive impairment of cell functions, i.e., gradual cell senescence (Fossel 2004; Libertini 2014, 2015b). The progressive limitation for stem cells in replacing cells eliminated by PCD leads to a gradual slowing of cell turnover. This, together with the effects of on/off and gradual senescence, progressively determines an atrophic syndrome for all organs and tissues that is characterized by the following:

a) "Reduced mean cell duplication capacity and slackened cell turnover
b) Reduced number of cells (atrophy)
c) Substitution of missing specific cells with non-specific cells
d) Hypertrophy of the remaining specific cells
e) Altered functions of cells with shortened telomeres or definitively in noncycling state
f) Alterations of the surrounding milieu and of the cells depending from the functionality of the senescent or missing cells
g) Vulnerability to cancer because of dysfunctional telomere-induced instability ..." (Libertini 2014)

A fair objection against this mechanism, in particular regarding its ability to explain all aging features, is that this would be contradicted by the existence of cell types and organ parts that are not subject to renewal but show aging alterations as cell types and organs that are subject to cell turnover.

In this regard, in an aforementioned paper (Libertini 2014), a partial and short answer has already been given, but given the importance of the subject, it is necessary that this answer is deepened and enriched here with further elements.

Discussion

Neurons

A neuron, in general, is connected to many other neurons. According to one estimate, the human brain has about 10^{11} neurons interconnected by 10^{14} synapses (Williams and Herrup 1988). This means that, on average, a neuron has 1000 connections with other neurons. For a hypothetical neuron turnover, analogous to that of other cell types, the imaginary unlikely mechanism should also precisely restore, for each neuron, all the pre-existent links with the other neurons, to avoid the loss of neuron function deriving from wrong connections.

This explains why—with few exceptions (Horner and Gage 2000; Zhao et al. 2008)—there is no neuron turnover unlike the continuous renewal of other cell types. But this contrasts with the need to maintain the full functionality of the neurons, and of the nervous tissue in general, despite the passage of time.

These two seemingly incompatible requirements are satisfied by a mechanism that may be understood in its principles starting from the study of the most accessible and well-studied type of cells in the central nervous system, namely, retina photoreceptor cells.

Photoreceptor nervous cells

The retina is an extroversion of the brain, and the first processing of data detected by photoreceptor cells (cones and rods) is carried out in it. These cells are highly differentiated nervous cells, without turnover like almost all neurons, and are metabolically dependent on other cells with turnover, specifically the cells of the

retinal pigment epithelium (RPE cells), which are highly differentiated gliocytes with turnover. The tops of photoreceptor cells lean on RPE. Each day, 10 % of photoreceptor cell membranes, on which photopsin molecules lie, are phagocytized by an RPE cell and substituted, by the photoreceptor cell, with an equal amount of new membrane. Each RPE cell serves 50 cones or rods, and, therefore, each day an RPE cell metabolizes photopsin membranes of about five cones or rods, demonstrating a very high metabolic activity. Photoreceptor cells cannot survive without the macrophagic activity of RPE (Fine et al. 2000; Jager et al. 2008).

With the age-related decline of RPE turnover, in RPE cells there is an accumulation of damaging substances, such as A2E, a vitamin A-derived breakdown product (Sparrow 2003). The death of RPE cells, also through the action of these substances, causes holes in the RPE layer, when the cell is not substituted by a new cell, and the deficiency of their function kills the photoreceptors not served (Berger et al. 1999).

Above all, this is manifested in the functionality of the most sensitive part of the retina, the macula—where the accumulation of A2E is most abundant (Sparrow 2003; Ablonczy et al. 2012)—from which the name "age-related macular degeneration" (AMD) comes (Fine et al. 2000).

With particularly abnormal deficiencies of RPE cells, AMD arises at lower ages and is considered a distinct disease, while at later ages its frequency increases exponentially and must be considered a feature of the senile state. In fact, AMD affects 5, 10, and 20 % of subjects 60, 70, and 80 years of age, respectively (Berger et al. 1999), and it is likely that a large proportion of older individuals suffer from AMD.

There is an association between AMD and unhealthy lifestyles (Mares et al. 2011) that reduce the number of endothelial progenitor cells, a likely consequence of a quicker cell turnover of endothelial cells (Hill et al. 2003), and that could have an analogous harmful effect on RPE: Risk factors for endothelial cells, and so for cardiovascular diseases, such as smoking, diabetes, and obesity, are also risk factors for AMD (Klein et al. 2007).

Moreover, while "The retina, with its high oxygen content and constant exposure to light, is particularly susceptible to oxidative damage" (Chong et al. 2007), the meta-analysis of 12 studies did not show that antioxidant supplements prevented early AMD (Chong et al. 2007).

Brain neurons and Alzheimer's disease

As photoreceptor cells (specialized types of neurons without turnover) depend on other cells (RPE cells, specialized gliocytes with turnover), other types of neurons—such as those of the cerebral cortex, basal nuclei, and other parts of the central nervous system—appear to depend on other types of gliocytes. If this is true, cell senescence and gradual cell senescence of these gliocytes should cause pathologies analogous to AMD.

Indeed, neurons of the central nervous system are perennial cells, but their vitality depends on other cells (e.g., microglia, a type of gliocyte) that exhibit turnover. Microglia cells degrade β-amyloid protein (Qiu et al. 1998; Vekrellis et al. 2000; Miners et al. 2008), and this function is known to be altered in Alzheimer's disease (AD) (Bertram et al. 2000) with the consequent noxious accumulation of the protein.

Therefore, replicative senescence and gradual cell senescence of these gliocytes should cause pathologies similar to AMD. Without the key example of AMD, it was previously hypothesized that AD was dependent upon the decline in function of these particular gliocytes determined by telomere shortening (Fossel 1996; Fossel 2004): "One function of the microglia (Vekrellis et al. 2000) is degradation of β-amyloid through insulin-degrading enzyme (IDE), a function known to falter in Alzheimer disease (Bertram et al. 2000)" (p. 233), and "telomere lengths of circulating monocytes can serve as an independent predictor in at least vascular dementia (von Zglinicki et al. 2000)" (p. 235) (Fossel 2004).

The hypothesis that AD is caused by cell senescence of microglia cells has been reproposed by others (Libertini 2009a, 2009b; Flanary 2009).

As for AMD, there are precocious familial cases of AD that are considered distinct diseases with genetic causes (Fossel 2004). Disregarding these cases, AD frequency increases exponentially with age: 1.5 % at the age of 65 and 30 % at 80 (Gorelick 2004), with a very high probability that centenarians are affected by it.

AD could have, at least partially, a vascular etiology due to age-related endothelial dysfunction (Fossel 2004), but "A cell senescence model might explain Alzheimer dementia without primary vascular involvement" (Fossel 2004).

Discarding the simplistic deduction that AD is only a consequence of vascular dysfunction, it is likely that there is a common pathogenetic mechanism: endothelial dysfunction caused by insufficient endothelial

progenitor cells in the first case (Hill et al. 2003), and microglia dysfunction caused by insufficient microglia progenitor cells in the second. In both cases, the telomere-telomerase system is the primary causal factor and cardiovascular/AD risk factors accelerate telomere failure, whereas "protective" drugs counter these effects.

In fact, telomeres have been shown to be significantly shorter in patients with probable AD than in apparently healthy control subjects (von Zglinicki et al. 2000). Moreover, there is an association between AD and cardiovascular risk factors (Vogel et al. 2006; Rosendorff et al. 2007). Drugs, such as statins, ACE inhibitors, and sartans, which are all considered "protective drugs" for cardiovascular diseases, are effective against AD (Vogel et al. 2006; Ellul et al. 2007).

As for AMD, in contrast to the hypothesis that the primary cause of AD is the accumulation of β-amyloid and tau protein, attempts by pharmaceutical societies to counter or eliminate the effects of these substances have been a large therapeutic failure for AD (Abbott 2008). In particular, drugs or even vaccines that attempted to counter the formation of β-amyloid have provided disappointing results (Gorelick 2004): "Post-mortem analyses showed that almost all the patients had stripped-down amyloid plaques, despite most of them having progressed to severe dementia before they died" (Gorelick 2004).

Attempts to treat the cognitive alterations of AD, in the hope that this could stop the disease, have been another huge failure (Hill et al. 2003; Ballard et al. 2009). Antipsychotic drugs appear to increase the long-term risk of mortality (Ballard et al. 2009), while cholinesterase inhibitors (e.g., donezepil, galantamine, and rivastigmine) and *N*-Methyl-D-aspartate receptor antagonist (e.g., memantine) "are marginally effective at best" (Abbott 2008).

Brain neurons and Parkinson's disease

Parkinson's disease (PD) is a degenerative disorder of the central nervous system characterized by the accumulation inside neurons of alpha-synuclein (AS), a protein that forms inclusions known as Lewy bodies (Davie 2008; Schulz-Schaeffer 2010). Dementia with Lewy bodies (DLB), which is classified as a Parkinson-plus syndrome (Nuytemans et al. 2010), is a primary parkinsonism with additional features (Samii et al. 2004). In multiple system atrophy, a rare genetic disease, AS accumulates in oligodendrocytes (Sturm and Stefanova 2014).

PD, DLB, and multiple system atrophy are defined as synucleinopathies for the accumulation of the aforementioned protein, while AD is defined as a tauopathy for the accumulation of tau protein in the form of neurofibrillary tangles (Galpern and Lang 2006), but clinical and pathological manifestations overlap between these types of neuropathies (Aarsland et al. 2009).

PD is considered mainly a disease affecting the motor system, as it shows typical movement disorders, but it also has various nonmotor symptoms, such as sensory deficits (Barnett-Cowan et al. 2010). Dementia, the most typical manifestation of AD, is present at advanced stages of PD, while neurofibrillary tangles are present in brains suffering from PD (Galpern and Lang 2006). However, senile plaques and neurofibrillary tangles, which are characteristic of AD, are uncommon in PD without dementia (Dickson 2007).

The risk of dementia in PD patients is two to six times that of the whole population (Jankovic 2008; Caballol et al. 2007) and increases with the duration of the disease (Caballol et al. 2007).

Behavior and mood alterations (e.g., apathy, depression, anxiety, etc.) are common symptoms in PD patients with dementia and, in PD cases without cognitive impairment, are more common than in the general population (Jankovic 2008).

Only AD is more frequent than PD among the neurodegenerative disorders (Yao et al. 2013; de Lau and Breteler 2006). PD frequency is about 0.3 % in industrialized countries and increases from 1 % in individuals older than 60 to 4 % in the population older than 80 (de Lau and Breteler 2006), with a mean age of onset of around 60; however, in 5–10 % of cases, it begins before 50 years of age (Samii et al. 2004).

"PD and DLB are common neurodegenerative diseases in the population over the age of 65. About 3% of the general population develops PD after the age of 65, whereas about 20% of all diagnosed dementia patients have DLB (McKeith, 2004; Dorsey et al., 2007). In both disorders movement and cognition, as well as mood and autonomic function are severely affected. Diagnosis to distinguish PD and DLB is very difficult, because of the overlap of symptoms and signs (Henchcliffe et al., 2011)" (Brück et al. 2015).

PD symptoms are a clear consequence of cell death in the pars compacta region of the substantia nigra, which causes a greatly reduced activity of dopamine secretion, although the mechanism by which the neurons are lost is debated (Obeso et al. 2008).

In PD evolution, in a first pre-clinical phase, Lewy bodies are shown in the olfactory bulb, pontine tegmentum, and medulla oblongata. Later, they appear in the substantia nigra, in some areas of the midbrain and basal forebrain, and finally in the neocortex (Davie 2008). In these places, there is neuronal degeneration, but it has been proposed that Lewy bodies could be a protection against harmful factors and not the cause of cell death (Obeso et al. 2010; Schulz-Schaeffer 2010). However, in demented AD individuals, Lewy bodies are largely present in cortical areas and "reduced AS clearance is involved in the generation of AS inclusions in DLB and PD" (Brück et al. 2015).

"Glial cells are important in supporting neuronal survival, synaptic functions and local immunity. However, glial cells might be crucial for the initiation and progression of different neurodegenerative diseases, including ASP" (Brück et al. 2015).

"... microglial cells contribute to the clearance of debris, dead cells and AS thereby supporting neuronal survival. But on the other hand, microglial cells can get over activated in the course of the disease and might contribute to disease initiation and progression by enhancing neurodegeneration through elevated oxidative stress and inflammatory processes" (Brück et al. 2015).

These elements suggest that the activation of microglial and astroglial cells could be a reaction to AS accumulation, which, in turn, would be caused by the loss of trophic functions of specific gliocytes, in particular those dedicated to axon trophism. These gliocytes could be astrocytes (Morales et al. 2015), and the decline of their function would be a consequence of their decline in turnover, as is the case for the decline of RPE cells and the subsequent AMD.

The metabolic syndrome is an important risk factor for PD (Zhang and Tian 2014). A study has demonstrated that high skinfold thickness in midlife is associated with PD (Abbott et al. 2002). Another study found that obesity in middle age increases the risk of future dementia independently of other conditions, and perhaps adiposity works together with other risk factors to increase neurodegenerative disease (Whitmer et al. 2005). In addition, some evidence shows that body mass index is associated with a risk of PD and that the effect is graded and independent of other risk factors (Hu et al. 2006).

In aging, hyperglycemia is also associated with PD through damage to the central nervous system, a consequence of long-term exposure to glucose (Tomlinson and Gardiner 2008; Hu et al. 2007). Epidemiologic studies suggest that previous type 2 diabetes is also a risk factor for developing PD (Mercer et al. 2005).

Hyperhomocysteinemia, a risk factor for endothelial dysfunction (Woo et al. 1997), has been shown to be involved in neurodegenerative disorders, such as AD and PD (Kruman et al. 2000).

Statin use appears to lower the risk of PD (Gao et al. 2012; Friedman et al. 2013; Undela et al. 2013). Captopril, an angiotensin-converting enzyme inhibitor, protects nigrostriatal dopamine neurons in PD animal models (Lopez-Real et al. 2005; Sonsalla et al. 2013).

Strangely, smoking, a risk factor for AMD (Klein et al. 2007), appears to lower PD risk (de Lau and Breteler 2006).

Olfactory receptor cells

Olfactory receptor cells (ORCs) are an example of neurons with turnover (see below).

In the upper part of the nasal cavity, the odor perception takes place through ORCs, which are specialized neurons that "have a single dendrite that extends to the apical surface of the epithelium and ends in a terminal knob, which has many small cilia extending into the mucosa. A single axon projects through the basal side of the epithelium through the lamina cribrosa to terminate in the olfactory bulb. Each of the receptor neurons expresses one of a family of over 1000 olfactory receptor proteins. The neurons are surrounded by glial-like cells, called sustentacular cells. Other cells in the epithelium contribute to the continual production of the new receptor neurons" (Bermingham-McDonogh and Reh 2011).

The continuous renewal of the ORCs in healthy adult individuals is well documented (Maier et al. 2014).

"The ongoing genesis of olfactory receptor cells is common to all vertebrates (see Graziadei and Monti Graziadei, 1978, for review) and the rate of production is quite high. The production of new olfactory receptor cells is critical to the maintenance of this system, as the olfactory receptor cells only last a few months. The rate of production of new olfactory receptor cells is balanced by their loss so that a relatively stable population of these receptors is maintained" (Bermingham-McDonogh and Reh 2011).

In a healthy, undamaged olfactory epithelium, the continuous renewal of ORCs is ensured by slowly cycling stem cells (globose basal cells) and by transit-

amplifying progenitor cells (horizontal basal cells) (Caggiano et al. 1994; Chen et al. 2004; Huard et al. 1998; Iwai et al. 2008; Leung et al. 2007). This model of cell turnover is analogous to that of other cell types (e.g., epidermis) (Watt et al. 2006).

ORC turnover is (i) necessary, as these cells are very exposed to external insults, and (ii) simple, as each neuron has a single dendrite and a single axon. Therefore, unlike most neurons, ORCs undergo cell turnover and an age-related slowing of such turnover should impair the olfactory function. This does not exclude the possibility that the age-related slowing of the turnover for (i) glial cell satellites of ORCs, (ii) neurons of the olfactory bulb, or (iii) other olfactory areas in the central nervous system may contribute to a decline in olfactory function.

About half of the individuals between 65 and 80 years of age suffer from evident olfactory dysfunction (Doty et al. 1984; Duffy et al. 1995; Murphy et al. 2002), and olfactory impairment increases with age (Schubert et al. 2012).

Hyposmia is often a precocious sign of PD and an early and constant characteristic both of AD and of DLB (Factor and Weiner 2008). Olfactory dysfunction is a symptom present in AD, in PD dementia, and in other forms of dementias (Barresi et al. 2012). Estimated numbers of olfactory dysfunction may be as high as 100 % in AD (Duff et al. 2002) and 90 % in PD (Doty 2012).

Hearing neurons

The organ of Corti, in the cochlea (inner ear), for its hearing function is equipped with auditory cells, which are differentiated neurons, divided into an internal row (inner hair cells) and some external rows (outer hair cells), which are connected to specialized neurons (spiral ganglion neurons). There are 15,500 hair cells and 35,000 neurons in each cochlea of a newborn (Wong and Ryan 2015). Both of these types of cells, like most neurons, are perennial cells (Wong and Ryan 2015): "... no epithelial maintenance has been described for the hair cells of the cochlea of mammals, though hair cell addition and repair occur in lower vertebrates... " (Maier et al. 2014).

Age-related hearing loss, or presbycusis, is well known—>50 % in individuals older than 60 (Zhan et al. 2010)—and may be aggravated by other factors, such as noise exposure, diabetes, or hypertension (Wong and Ryan 2015). However, even in healthy animals reared in silence, presbycusis is still observed (Sergeyenko et al. 2013; Yan et al. 2013).

There is an association between hypacusia and incident dementia (Lin et al. 2011). The incidence of PD was shown to be 1.77 times more likely in patients with hearing loss than in those without hearing loss (Lai et al. 2014), and hearing impairment is a common feature in idiopathic PD (Vitale et al. 2012).

Neuropathies: a synthesis

Neurons, in their multiple differentiated forms, appear to be perennial cells that, in turn, require auxiliary cells, namely, differentiated forms of gliocytes, with some exceptions for their perennial status (e.g., ORCs). These gliocytes are not perennial cells but are subject to turnover.

The slowdown in the turnover of the above-mentioned gliocytes gradually impairs the function of the served neurons to the point of their death.

Furthermore, the factors for other cell types that, in general, appear to accelerate the turnover or otherwise accelerate the achievement of the limits in duplication capacity (e.g., diabetes, overeating, unhealthy lifestyles, etc., or in brief "risk factors") should generally also accelerate this impairment. In contrast, the factors for other cell types that, in general, appear to have the opposite effects (e.g., "protective drugs," healthy lifestyles, etc., or in brief "protective factors") similarly should slow this decline.

These concepts place in the same category a number of troubles (AD, PD, DLB, AMD, presbycusis, age-related hyposmia) that are generally considered distinct diseases while they appear to be all caused by physiological cell turnover decline (i) of ORCs for age-related hyposmia or (ii) of satellite gliocyte cells for the other troubles) (Fig. 1). The term "trouble" instead of "disease" has been used to highlight the fact that they are features of a physiologic phenomenon—aging—and not specific pathologies.

The data reported above separately for each trouble may be summarized as follows:

- For all the aforementioned troubles (excluding a small percentage of cases with early onset and clear genetic origin), the relationship between age of onset, rate of aggravation, and other characteristics of aging in tissues/organs that undergo turnover

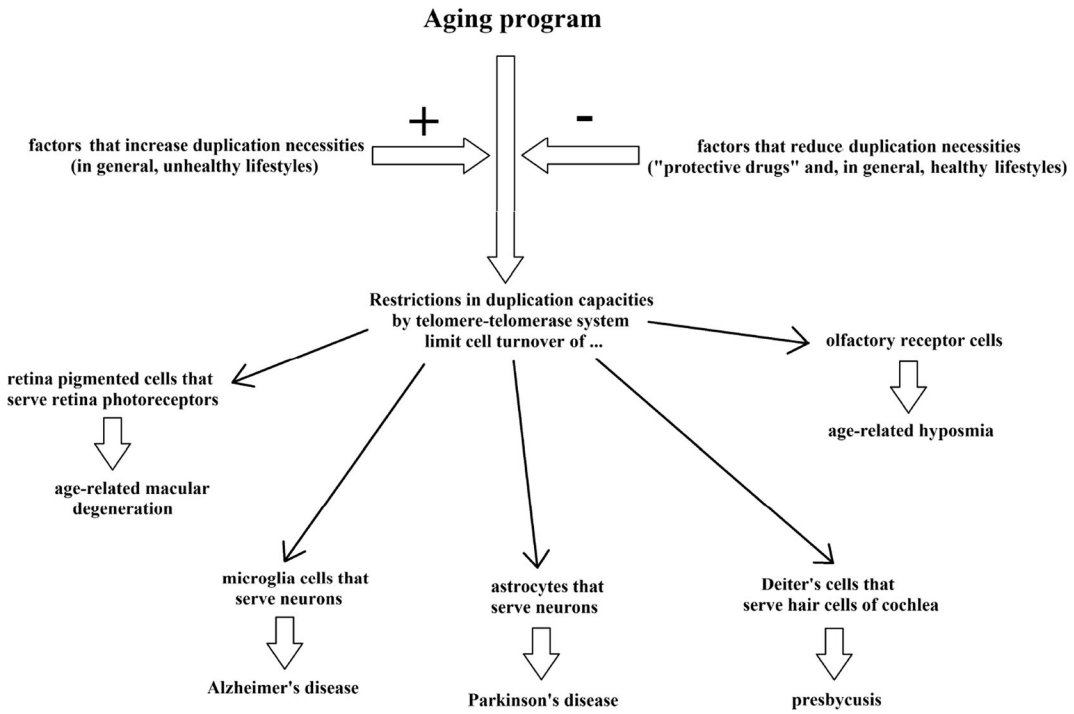

Fig. 1 Scheme for aging of neuron types that are perennial cells as a consequence of turnover decline of satellite gliocytes. The turnover decline of olfactory receptor cells is the main direct cause of olfactory function decline

- The relationship between aggravation and/or increased incidence of each of these troubles and risk factors for other types of tissues/organs subject to turnover
- Conversely, the relationship between slowdown/lower incidence of each trouble and protective factors for other types of tissues/organs that undergo turnover

Eye crystalline lens

The lens has three main parts: the lens capsule, the lens epithelium, and the lens fibers. The lens capsule forms the outermost layer of the lens, and the lens fibers form the bulk of the interior of the lens. The lens capsule, a smooth, elastic, and transparent basement membrane, completely surrounds the lens; it is composed of collagen and is synthesized by the lens epithelium (Forrester et al. 1996). The lens epithelium is only on the anterior side of the lens between the lens capsule and the outermost layer of lens fibers. The cells of the lens epithelium regulate most of the homeostatic functions of the lens (Candia 2004).

Lens epithelium cells are also progenitors for new lens fiber cells that are constantly produced in the embryo, fetus, infant, and adult. After birth, the lens continues to grow, and the new lens fiber cells are added as outer layers in the germinative zone, which is in the equatorial area of the lens epithelium. After the transformation in lens fiber cells, the lens epithelial cells elongate, detach from the capsule and epithelium cells, begin to synthesize crystallin protein, and, finally, lose their nucleus, becoming mature lens fiber cells (Forrester et al. 1996).

The change of lens shape, which determines a greater or lesser dioptric power and therefore allows the correct image focusing on the retina, is a function of the differential contraction of the ciliary muscle (Forrester et al. 1996).

The lens, and its capacity for accommodation, is subject to three types of age-related alterations, of which only the first depends on cell turnover:

1. Cell turnover decline of the lens epithelial cells

The crystalline lens has no nucleated cell in its core, and its functionality, in particular the transparency, depends on lens epithelial cells that undergo turnover (Tassin et al. 1979).

"Many investigators have emphasized post-translational alterations of long-lived crystalline proteins

as the basis for senescent ocular cataracts. It is apparent in Werner syndrome that the cataracts result from alterations in the lens epithelial cells," (Martin and Oshima 2000) which is consistent with the age-related reduction in growth rate of lens epithelial cells described in healthy human subjects (Tassin et al. 1979).

Smoking and diabetes, which are risk factors for cardiovascular diseases (Hill et al. 2003), are risk factors for cataracts, as well (Delcourt et al. 2000).

Statins lower the risk of nuclear cataract, which is the most common type of age-related cataract (Klein et al. 2006). This could be explained by their "putative antioxidant properties" (Klein et al. 2006), but it is more rational to suppose that their effects on lens epithelial cells are analogous to those on endothelial cells (Hill et al. 2003).

2. Lens enlargement with progressive loss of accommodation ability

The progressive age-related lens enlargement, due to the slow proliferation of lens epithelial cells in the equatorial area, progressively reduces the accommodation capacity of the lens for near vision. This sight reduction (presbyopia), with the consequent fitness alteration, happens to humans at ages existing in the wild. In fact, at the age of 50, when presbyopia is the normal condition, surviving individuals represent about 40 % in a population in wild conditions (Hill and Hurtado 1996). Since a higher or lower growth rate of crystalline lens is genetically regulated, the fitness reduction determined by presbyopia is an element of the aging process that is not dependent on the slowing of cell turnover but, at the same time, not resulting from uncontrollable "wear and tear" phenomena.

3. Chemical alterations of lens proteins

"In the lens proteins (crystallins) of big whales, spontaneous isomerization of L-amino acids to D-amino acids occurs at any age. Crystallins are synthesized during formation of lens and originally contain, as any othe r proteins, only L-amino acids. Crystallins are practically not replaced during entire life of the whale. L-D isomerization is not encoded by genomes and it is a chemical property of amino acids. Fortunately, this process is very slow (2% per 10 years). However, after 200 years, 40% of L-amino acids are already isomerized to D-amino acids in crystallins, an event strongly affecting the spatial structure of these proteins and apparently their unique ability to be absolutely transparent for the visible light. If such a process results in formation of cataract, it may lead to blindness which should make impossible the life of old whale in the ocean. He should die, such a death being age-dependent. And nevertheless it cannot be regarded as slow phenoptosis" [Vladimir Skulachev, observation as editor-in-chief for (Libertini 2012)]. Clearly, this age-related biochemical alteration must be classified within the wear and tear category, but the possible formation of cataracts, a deadly fitness alteration, could happen at ages rarely or never existing in natural conditions and therefore cannot be contrasted or shaped by natural selection.

Teeth

A species is defined as monophyodont, diphyodont, or polyphyodont when in its life cycle it has one, two, or many successive sets of teeth, respectively (Buchtova et al. 2012). In our species, which is diphyodont, a set of deciduous teeth (milk teeth) is replaced by a new set of permanent (adult) teeth, which has no subsequent turnover.

Many reptiles, such as geckos and crocodiles, most toothed fishes and other vertebrates are polyphyodont (Fuenzalida et al. 2000; Gaete and Tucker 2013). Most mammals are diphyodont, such as our species, but others (e.g., elephants, kangaroos and manatees) are polyphyodont. However, mammalian ancestors (Therapsida) were polyphyodont (D'Emic et al. 2013), and this suggests that the limit of two sets of teeth is an adaptation.

In our species, as regards the teeth and the adjacent anatomical areas, the various components of the pulp, the gums, and the bone that supports the teeth are subject to turnover like identical cells in other parts of the body. The enamel, however, is not subject to turnover and is therefore subject to wear, which clearly increases with age.

This is different from the turnover of the other parts of the body and might seem to be evidence in support of the ancient belief that aging is simply the result of the accumulation of excessive wear and damage of various kinds.

In contrast to this interpretation, we should first consider what happens in natural conditions and not limit ourselves to inferences based on what happens in modern artificial conditions.

In natural conditions, phenomena such as dysodontiasis, caries, and periodontal disease, and their complications, which affect, to varying degrees, the vast majority of "civilized" individuals and lead to the loss of

the teeth or, in general, to their impaired function, are uncommon phenomena (Price 1939).

The monumental book of Price, with its exceptional photographic documentation, demonstrates unequivocally that people living in primitive conditions do not have the dental disease of a civilized man (Price 1939). The following are excerpts from this book (Price 1939):

"Another important source of information regarding the Aborigines of Australia was provided by a study of the skeletal material and skulls in the museums at Sydney and Canberra, particularly the former. I do not know the number of skulls that are available there for study, but it is very large. I examined many and found them remarkably uniform in design and quality. The dental arches were splendidly formed. The teeth were in excellent condition with exceedingly little dental caries" (Ch. 10).

"... there are some excellent collections of skulls in museums in Peru, with the skulls in position where they can be readily studied for the shape of the dental arches. When we have in mind that from 25 to 75 per cent of individuals in various communities in the United States have a distinct irregularity in the development of the dental arches and facial form, the cause and significance of which constitutes one of the important problems of this study, the striking contrast found in these Peruvian skulls will be seen to constitute a challenge for our modern civilizations. In a study of 1,276 skulls of these ancient Peruvians, I did not find a single skull with significant deformity of the dental arches" (Ch. 13).

"Several studies have been made dealing with the incidence of dental caries or tooth decay among these ancient cultures. The author of 'Bird Islands of Peru' (MURPHY, R. C. Bird Islands of Peru. New York, Putnam, 1925) states that in his examination of fifty mummies in succession he found only four with a tooth with dental caries. This again is in striking contrast to our modernized communities in which from 95 to 100 % of all the members of a community group suffer from dental caries. I have shown in connection with the Indians of the western coast of Canada that in six highly modernized communities where the Indians were using white man's foods, 40 % of all the teeth had been attacked by dental caries. A similar high percentage was found in the Indians now living in Florida. The ancient burials in southern Florida revealed apparent, complete immunity. These were pre-Columbian burials" (Ch. 13).

Therefore, under natural conditions, the only permanent dentition is quite sufficient for the whole of life and is not a limiting factor for the duration of life.

Certainly, in natural conditions, for a person who lived, say, 200 years, this unique permanent dentition would be a limiting factor for his lifespan. But the only permanent dentition is adaptive for the duration of life found in natural conditions, so there are no selective pressures in favor of solutions that provide for the substitution (turnover) of the permanent dentition. In cases where the duration had been greater, the solution would have been as easy as is clearly indicated in many species, in which increased tooth wear requires a more or less rapid renewal of teeth. The elephant has six dentitions (Shoshani 2000), and alligators can replace up to 50 times their teeth (Wu et al. 2013): The number of replacements is specific enough for the duration of their lives. Other species with strong wear have multiple substitutions, unlimited in their number (Fuenzalida et al. 2000; Gaete and Tucker 2013), or they exhibit a continuous growth of the teeth as they wear out [e.g., rodents (Single et al. 2001)].

Conclusion

The criticisms against the programmed aging paradigm based on the existence of perennial cells or organ parts not subjected to turnover are clearly overcome by the evidence discussed above. Moreover, this evidence supports and documents further the existence, predicted by the programmed aging paradigm as indispensable, of genetically determined and regulated mechanisms that gradually reduce organism fitness.

Additional elements and insights emerge from the evidence expounded earlier:

1. The factors (e.g., harmful foods and inhalations, unhealthy lifestyles, exposure to harmful factors, etc.) that damage cells and thus accelerate cell turnover appear to accelerate and anticipate the physiological process of aging.

2. In contrast, the reduction or avoidance of these "risk" factors and the use of "protective drugs" (e.g., statins, ACE inhibitors, sartans) reduce the risk both of the troubles caused by the slackened turnover of cell types subject to turnover (e.g., arteriosclerosis due to endothelial turnover failure, senile emphysema due to alveolocyte turnover failure, etc.) and of disorders related to cells or structures not subject to turnover but that suffer from slackened turnover of cells that are trophic to them (e.g., AD, PD, AMD, etc., caused by the failure of their specific trophic differentiated gliocytes).

3. The complete avoidance of the risk factors does not slow down or eliminate aging with its physiological rhythms in optimal conditions.

4. In general, disregarding the particular cases where a genetic alteration is the cause of a precocious form, the difference between the physiological form of a trouble due to aging and the precocious forms of the same trouble (in this case definable as diseases), apart from the anticipating causes, is mainly (or only) in the onset time and the speed of worsening of its manifestations. Therefore, it is difficult practically to distinguish between the precocious forms (due to specific and modifiable risk factors) and physiological forms (which are part of the aging phenomenon and cannot be modified by the avoidance of risk factors or by the use of protective drugs).

5. The above-mentioned physiological forms of these diseases and aging in general are directly or indirectly dependent on telomere shortening. It has been well known from 1998 that telomerase activation elongates telomeres, restores cell duplication capacities, and erases all the manifestations of cell senescence (Bodnar et al. 1998; Counter et al. 1998; Vaziri 1998; Vaziri and Benchimol 1998), i.e., all the manifestations of cell senescence and gradual cell senescence. In the search for methods to slow or reverse aging, a preliminary step should be to find a cure for troubles, such as AD, PD, and AMD, which are highly debilitating or deadly. This could be the best way to show the validity and the usefulness of the approach and the methodology proposed. For several years, countering AD by telomerase reactivation has been suggested (Fossel 1996; Fossel 2004). The same proposal was formulated for AMD (Libertini 2009b). In this article, it is useful to point out that it would be useful for PD, presbycusis, and age-related hyposmia, as well. As regards AMD, it is interesting to note that in the first experiment that showed how the manifestations of cell aging are fully reversible, this was demonstrated for retina RPE cells (and for another cell type): "two telomerase-negative normal human cell types, retinal pigment epithelial cells and foreskin fibroblasts, were transfected with vectors encoding the human telomerase catalytic subunit. In contrast to telomerase-negative control clones, which exhibited telomere shortening and senescence, telomerase-expressing clones had elongated telomeres, divided vigorously, and showed reduced staining for beta-galactosidase, a biomarker for senescence. The ability to maintain normal human cells in a phenotypically youthful state could have important applications in research and medicine" (Bodnar et al. 1998).

A final general consideration may be useful. The criticisms against a theory may serve to falsify the hypothesis and determine its rejection if it is wrong. However, if the theory is correct, the criticisms lead to insights that confirm it and open the way for further developments. The intelligent criticism that the programmed aging paradigm could be invalidated by the existence of perennial cells or organ parts appears to be overcome by the evidence, and this, moreover, leads to proposals that could be of extreme importance, both for remedies for widespread and debilitating disorders and for a valid, not unrealistic or utopian, approach to controlling aging.

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