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REVIEW

Age-Related Dysfunctions: Evidence and Relationship with Some Risk Factors and Protective Drugs

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Abstract—The theories interpreting senescence as a phenomenon favored by natural selection require the existence of specific, genetically determined and regulated mechanisms that cause a progressive age-related increase in mortality. The mechanisms defined in the subtelomere–telomere theory suggest that progressive slackening of cell turnover and decline in cellular functions are determined by the subtelomere–telomere–telomerase system, which causes a progressive "atrophic syndrome" in all organs and tissues. If the mechanisms underlying aging-related dysfunctions are similar and having the same origin, it could be hypothesized that equal interventions could produce similar effects. This article reviews the consequences of some factors (diabetes, obesity/dyslipidemia, hypertension, smoking, moderate use and abuse of alcohol) and classes of drugs [statins, angiotensin-converting enzyme (ACE) inhibitors, sartans] in accelerating and anticipating or in counteracting the process of aging. The evidence is compatible with the programmed aging paradigm and the mechanisms defined by the subtelomere–telomere theory but it has no obvious discriminating value against the theories of non-programmed aging paradigm. However, the existence of mechanisms, determined by the subtelomere–telomere–telomerase system and causing a progressive age-related decline in fitness through gradual cell senescence and cell senescence, is not justifiable without an evolutionary motivation. Their existence is expected by the programmed aging paradigm, while is incompatible with the opposite paradigm.

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Aging, or senescence, defined as "increasing mortality with increasing chronological age in populations in the wild" [1] is a phenomenon observed for many species, humans included [2-5], and has its possible explanation in many theories [6, 7].

These hypotheses, although very diversified, exemplify two opposite interpretations [8, 9] that should be considered as paradigms, in Kuhn's meaning, for their important and very different premises and implications [10].

The non-programmed aging paradigm explains aging as the effect of harmful factors that natural selection cannot sufficiently counteract [11], while the programmed aging paradigm justifies senescence as a specific physiological function determined by supra-individual natural selection [1, 9, 12-17]. For the second paradigm, aging is not an isolated phenomenon but belongs to common physiological events, that have been known for a long time [2], but only recently were identified as an

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; AD, Alzheimer's disease; AMD, age-related macular degeneration; ARB, angiotensin receptor blocker, or AT_1 (angiotensin II receptor type 1) antagonist, or sartan; EPC, endothelial progenitor cell; PCD, programmed cell death; PD, Parkinson's disease.

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important group of phenomena deserving their specific name of *phenoptosis* (programmed death of an organism) [18, 19].

Although non-programmed aging is still the most accepted and widespread concept [20-25], multiple theoretical and empirical findings support the programmed aging paradigm and refute the opposite interpretation of aging [8, 9, 26]. Moreover, following the programmed aging concept, it is possible to describe, at least in general terms, the physiology [27-30], pathology [29, 31], and phylogeny [12] of aging.

This review is intended to highlight some correspondences between age-related dysfunctions and effects of various factors (diabetes, obesity/dyslipidemia, hypertension, smoking, moderate use and abuse of alcohol) and certain types of drugs [statins, angiotensin-converting enzyme (ACE) inhibitors, sartans] observed in the studies on humans and animal models.

These findings will be illustrated in the context of aging mechanisms suggested within the programmed aging paradigm. This description could be defined as the telomere theory [27], or more precisely subtelomere–telomere theory. Alternative interpretations of aging mechanisms in the context of the programmed aging paradigm are also possible [32-34], but in this paper, only the subtelomere–telomere theory will be considered as a working hypothesis, as more consistent with the evidence.

THE SUBTELOMERE–TELOMERE THEORY

A short explanation of the subtelomere–telomere theory of aging [27-30] is necessary. Each end of a eukaryotic DNA molecule has a sequence, telomere, composed of the same repeated motif (TTAGGG in humans [35] and many other species [36]). The enzyme that replicates DNA (DNA polymerase) cannot fully duplicate the DNA molecule and so a small part of the telomere remains unreplicated [37]. This inadequate replication can be easily compensated by another enzyme, telomerase (predicted in 1973 [38] and found in 1985 [39]), which restores the original DNA length. The activity of telomerase is under genetic regulation [40]. Inactive telomerase limits the maximum number of possible DNA duplications, i.e., it is the cause of Hayflick's limit [41, 42]. Partially active telomerase allows a greater but finite number of duplications, while fully active telomerase, as in the germ line, allows an unlimited number of duplications [27]. Each telomere is protected by a heterochromatin hood [27]. In the first cell of a new organism, at a phase that could be defined as a "reset" phase, the heterochromatin hood is shaped proportionally to the telomere length. In all the replications in the germ and progeny cells, it is essential that the hood is duplicated without its length being altered [30]. As the telomere shortens, the hood covers and represses an increasing portion of the DNA molecule adjacent to the telomere [27], the subtelomere. As the subtelomere portion covered and repressed by the hood increases, there are two effects:

1) Cellular functions deteriorate and, consequently, cell-specific secretions are progressively altered with the deterioration of the surrounding milieu and other cells dependent on the altered cell [27]. This phenomenon has been named telomere position effect [43] and, perhaps more precisely, gradual cell senescence [12].

2) The telomere oscillates between the state in which it is "capped" by the hood and the one in which it is "uncapped" and therefore, vulnerable to the inhibition of duplication [44]. Progressive subtelomere repression increases the proportion of time during which the telomere is uncapped [44] and susceptible to the activation of a specific cellular program, the cell senescence program [45], which blocks cellular duplication and creates the condition in which gradual cell senescence is at its highest level [27]. These concepts are summarized in Fig. 1.

Vertebrate cells are subjected to various types of programmed cell death (PCD), such as (i) detachment of cells from internal walls of body cavities, (ii) keratinization and detachment of epidermis and hair cells, and (iii) apoptosis. PCD is compensated by the duplication of stem cells (cell turnover). In a young organism, this compensation is optimal, but becomes increasingly incomplete and slow at older ages. This defective turnover, along with the increase in the number (to a different degree) of less functional cells due to gradual cell senescence and cell senescence, causes what has been defined as the "atrophic syndrome" [28]: "(i) reduced mean cell duplication capacity and slackened cell turnover; (ii) reduced number of cells (atrophy); (iii) substitution of missing specific cells with nonspecific cells; (iv) hypertrophy of the remaining specific cells; (v) altered functions of cells with shortened telomeres or definitively in noncycling state; (vi) alterations of the surrounding milieu and of the cells depending from the functionality of the senescent or missing cells; (vii) vulnerability to cancer because of dysfunctional telomere-induced instability" [29].

The atrophic syndrome progressively affects the fitness and underlies the age-related increase in mortality, i.e., aging. It should be emphasized that:

– the telomerase activity is under genetic control and does not pose a limit to cell functionality and duplication capabilities imposed by hypothetical physical or chemical insuperable constraints. This is evidenced by the existence of species with no age-related mortality increase and telomerase decline [46]. Moreover, gradual cell senescence is completely reversible by the simple reactivation of telomerase [47]; cell senescence at its first phase [48] and under specific artificial conditions [49] is reversible too;

– limitations of telomerase activity, and, as a consequence, gradual cell senescence and activation of cell

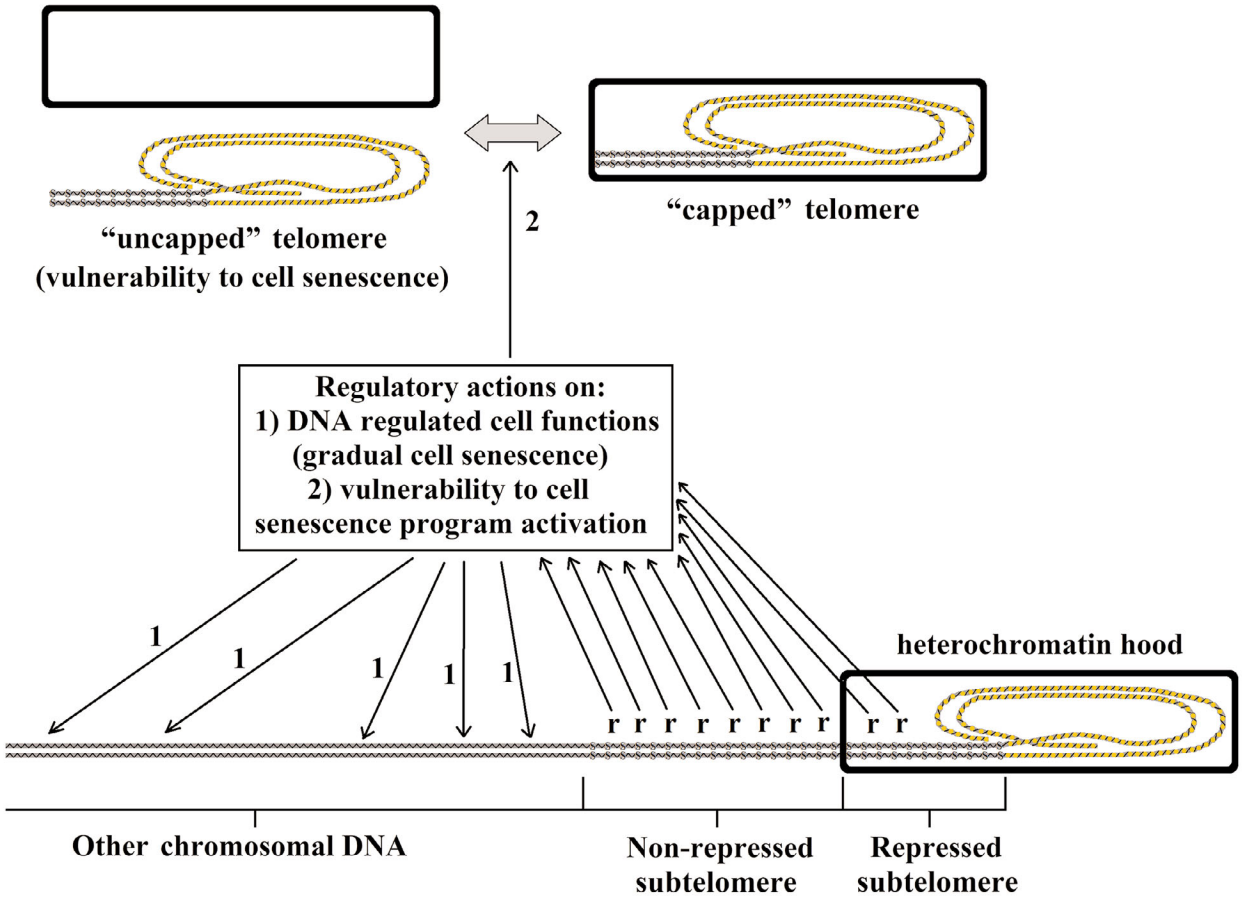

Fig. 1. Effects of telomere shortening on the telomeric hood and subtelomere. Telomere shortening causes the sliding of the telomeric hood on the subtelomere that is progressively repressed (taken with modifications from [53]).

senescence program, are by no means a preventive defense against cell proliferation in the event of neoplasm formation. Arguments and evidence against this explanation, which would justify such limitations in a way compatible with the non-programmed aging paradigm, have already been discussed elsewhere [26, 30, 31, 50] and will not be repeated here;

– for the aforesaid mechanisms, the existence of stem cells that allow cell turnover and show an age-related decline in the number and functional capacity is necessary. Various studies have documented the existence of such stem cells and highlighted the relationship between aging and their decline, as well as the possibility to use stem cells in counteracting the aging process [51, 52];

– the functional decline of tissues or organs constituted by perennial cells, i.e., cells not undergoing turnover, is well explained by the functional decline and turnover failure of their satellite cells [53] ("indirect" aging, while the decline of organs/tissues with no perennial cells could be defined as "direct" aging [7]).

Figure 2 illustrates some of the dysfunctions caused by the progressive atrophic syndrome in various organs/tissues with the distinction between dysfunctions caused by "direct" or "indirect" aging. A detailed description of how these dysfunctions develop is outside the scope of this review.

DISCUSSION

Relationship between age-related dysfunctions and risk factors or protective drugs. In 2003, Hill et al. [54] pointed out that the number of endothelial progenitor cells (EPCs), which are essential for the endothelial cell turnover, decreases with age and this decline is associated with various known risk factors for cardiovascular disease (smoking, diabetes, hypertension, body mass index, i.e., overweight and obesity). Moreover, the reduction in EPCs and Framingham risk score [55] were of equal value as predictors of the cardiovascular disease risk [54]. The authors suggested that EPC decline was caused by the accelerated turnover of endothelial cells that, in turn, resulted from chronic damage factors: "continuous endothelial damage or dysfunction leads to an eventual

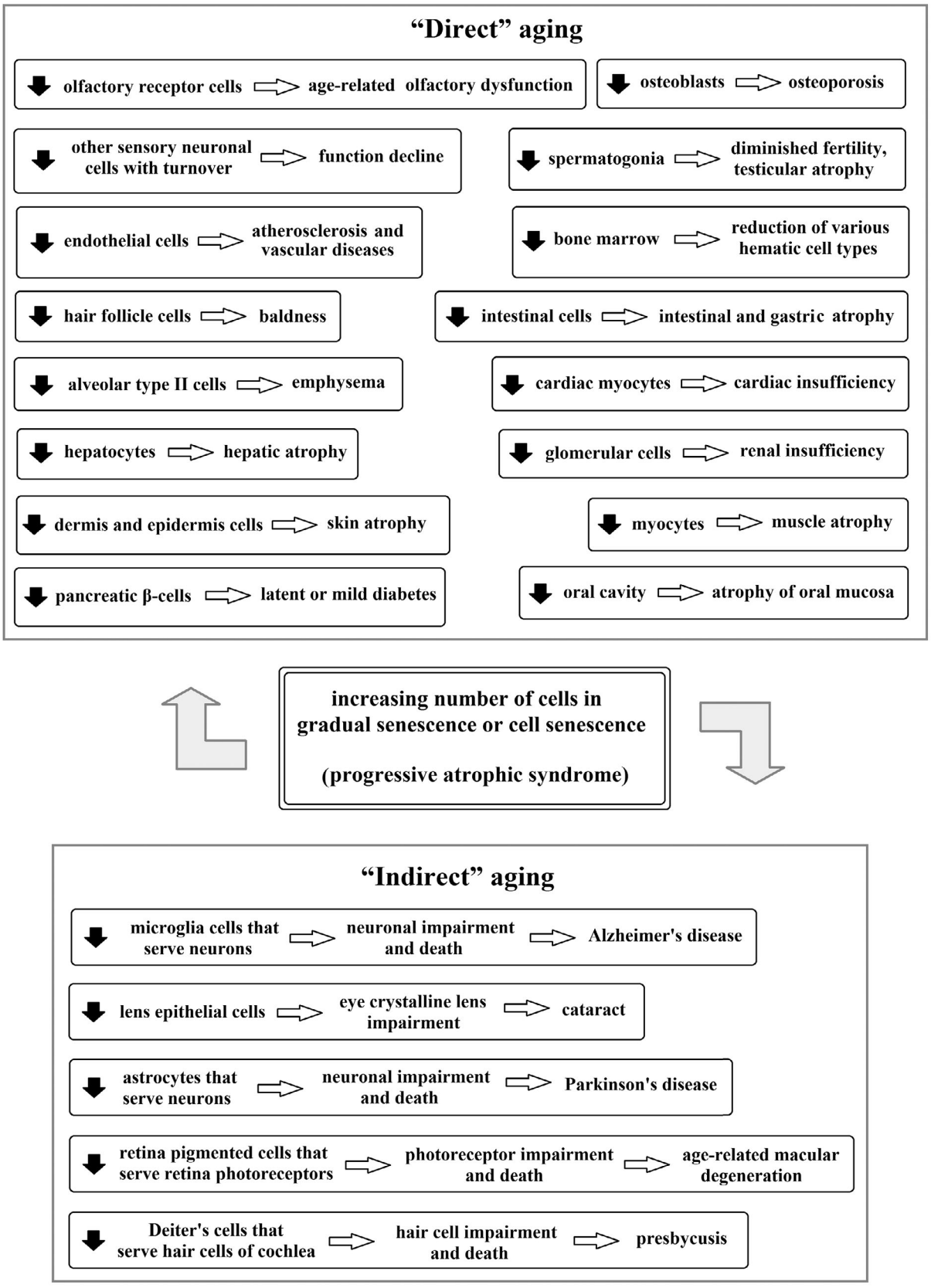

Fig. 2. Some dysfunctions caused by progressive atrophic syndrome in various organs/tissues. When the functional cells of a tissue/organ are subjects of turnover, their failure results in "direct" aging. For tissue/organs with perennial cells, the decline is caused by the failure of their trophic cells ("indirect" aging).

depletion or exhaustion of a presumed finite supply of endothelial progenitor cell . . . continuous risk-factor-induced injury may lead to eventual depletion of circulating endothelial cells" [54].

This mechanism seemed similar to the pathogenesis of muscular dystrophy, in which a genetic defect causes muscle cell death and progressively exhausts the ability of muscle stem cells to replace the myocytes [56, 57]. Other age-related dysfunctions could be explained analogously [58, 59].

Furthermore, statins, ACE inhibitors, and AT1 blockers (sartans), generally considered as protective drugs in cardiovascular disorders, are known to improve the endothelial function [60]. Statins accelerate re-endothelialization through EPCs [61], and this could explain their effects in the prevention and treatment of cardiovascular diseases. Similar action could be hypothesized for the other "protective drugs".

In a recent work [30] aimed to explain the aging of perennial cells by the decline of their satellite cells, interesting analogies were highlighted between the age-related dysfunctions of these perennial cells and the above-mentioned risk factors and protective drugs. In another work [7], such similarities were further documented. The present work seeks to significantly extend this investigation to other age-related dysfunctions.

The dysfunctions investigated in the cited works are: (A) endothelial disfunction; (B) olfactory dysfunction; (C) age-related macular degeneration (AMD); (D) Alzheimer's disease (AD); (E) Parkinson's disease (PD); (F) hearing impairment; (G) emphysema and related diseases; (H) skin atrophy; (I) osteoporosis; (J) atrophy of other sensory neuronal cells undergoing turnover (excluding olfactory dysfunction); (K) cataract; (L) testicular atrophy; (M) muscle atrophy; (N) cardiac insufficiency and related diseases; (O) reduction of various blood cell types; (P) diabetes and impairment of glucose tolerance; (Q) hepatic atrophy and related diseases; (R) renal insufficiency; (S) atrophy of oral mucosa and salivary glands; (T) intestinal and gastric atrophy; (U) alopecia (table).

Exceptions from the evidence. The results are summarized in the table. Using endothelial dysfunction as a term of comparison, other age-related conditions were similar to this disorder with regards to the effects of diabetes, obesity/dyslipidemia, hypertension, smoking, moderate alcohol use, alcohol abuse, statins, and ACE inhibitors/sartans (ACE-Is/ARBs).

Disregarding possible relationships for which no specific studies are unavailable or for which the studies produced contradictory results, there are some important exceptions (grey calls in the table) that must be mentioned:

– (E5) *Beneficial effect of smoking on PD*. It is the only case when smoking counteracts an age-related dysfunction. This could be explained by the effect of nicotine stimulation on nicotinic acetylcholine receptors [62], similar to the effect of dopaminergic stimulants used to treat PD. The pharmacological effects of nicotine on PD would largely overcome a possible harmful effect caused by smoking;

– (G3) *Emphysema inversely related to obesity/dyslipidemia*. This could be a false relationship caused by a greater mass of fat squeezing the lungs in obese subjects;

– (M8 and Q8) *Statin-induced damage to muscle and liver cells*. An easy explanation is selective harmful action of statins on myocytes and, to a lesser extent, on hepatocytes [63];

– (P8) *Slight exacerbation of diabetes by statins*. This harmful effect, which appears to be limited to high statin doses [64] and is largely overcome by the positive effects of statins on diabetes, has not yet been explained [63];

– (O2-O5, O8) *Diabetes*, *obesity/dyslipidemia*, *hypertension, and smoking increase WBC* (*white blood cell*) *count*. These phenomena are easily explained by the pro-inflammatory action of the aforesaid dysfunctions on the WBC count. In turn, WBC reduction by statins would be a consequence of the anti-inflammatory effects of these drugs [65].

Possible opposite interpretations of the evidence. Indeed, all the shown relationships may be interpreted in very different ways in the contexts of the two opposite paradigms. Consistently with the programmed aging paradigm, a minority of studies attribute the aforesaid dysfunctions (e.g., endothelial dysfunction [66], AD [67], hearing impairment [68], emphysema [69], and intestinal and gastric atrophy [70]) to the consequences of telomere shortening.

Conversely, the majority of studies view the same dysfunctions in terms of the non-programmed aging paradigm. These studies invoke various mechanisms, mostly involving accumulation of oxidized substances (endothelial dysfunction [60, 61], olfactory dysfunction [71], AMD [72], AD [73], PD [74], hearing impairment [75], emphysema [76], osteoporosis [77], muscle atrophy [78], cardiac insufficiency and disease [79], diabetes and impairment of glucose tolerance [80], hepatic atrophy and disease [81]).

CONCLUSION

In plain contrast with the tenets of the opposite paradigm, the programmed aging paradigm requires the existence of specific, genetically determined and regulated mechanisms that cause an age-related progressive reduction in fitness (i.e., aging). The mechanisms expounded within the subtelomere–telomere theory framework fully satisfy this requirement but contradict what is predicted by the non-programmed aging paradigm. Specific mechanisms that are common to the entire aging process are perfectly compatible with the possibility and evidence

Relation between some dysfunctions and some risk factors or protective drugs

Dysfunction in the elderly	Cell turnover of specific cells		Effect on the risk by:							Protective effect by:	
			age	dia-betes	obesity/ dyslipid-emia	hyper-ten-sion	smok-ing	moderate alcohol use	alcohol abuse	sta-tins	ACE-I/ ARB
			1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Endothelial dysfunction	yes	**A**	+	+	+	+	+	–	+	+	+
Olfactory dysfunction	yes	**B**	+	+	+	+	+	·	+	+	·
AMD	no	**C**	+	+	+	+	+	–/	+	**?**	**–?**
AD	no	**D**	+	+	+	+	+	–	+	+	+
PD	no	**E**	+	+	+	+/	–	–	+	+	+
Hearing impairment	no	**F**	+	+	+	+	+	–	+	+	+
Emphysema and related diseases	yes	**G**	+	+	–	+	+	–	+	+	+
Skin atrophy	yes	**H**	+	+	·	·	·	·	·	+	+
Osteoporosis	yes	**I**	+	+	+	+	+	–	+	+	+
Atrophy of other sensory neuronal cells with turnover	yes	**J**	+	+	·	·	+	·	+	·	·
Cataract	yes	**K**	+	+	+	+	+	–	+	+**?**	+
Testicular atrophy	yes	**L**	+	+	+	·	+	/	+	·	/
Muscle atrophy	yes	**M**	+	+	+	·	+	·	+	–	+
Cardiac insufficiency and related diseases	yes	**N**	+	+	+	+	+	–	+	+	+
Reduction of various hematic cell types	yes	**O**	+	–	–	–	–	**?**	+	–	·
Diabetes and impairment of glucose tolerance	yes	**P**	+		+	+	+	–	+	–/	+
Hepatic atrophy and related diseases	yes	**Q**	+	+	+	·	+	·	+	–/	+
Renal insufficiency	yes	**R**	+	+	+	+	+	–	+	+	+
Atrophy of oral mucosa and salivary glands	yes	**S**	+	+	·	+**?**	+	·	+	·	·
Intestinal and gastric atrophy	yes	**T**	+	·	·	·	+	·	·	·	·
Alopecia	yes	**U**	+	+	+	+	+	+**?**	+	·	·

Notes: (+) risk or protective effect increased; (–) risk or protective effect decreased; (/) risk or protective effect unaltered; (?) ambiguous results; (.) no specific study.

that there are alterations of such mechanisms with multiple effects on all or most aging conditions. Consequently, the relationships reported in this article are perfectly compatible with the programmed aging paradigm.

However, a supporter of the opposite paradigm might argue that the general actions of unprogrammed causes proposed as the aging mechanisms are also perfectly compatible with the possibility of similar general effects caused by specific drugs or harmful factors. Therefore, the correct assumption is that the evidence briefly presented in the preceding section cannot be regarded as a test to discriminate between the validity of the two opposing paradigms.

This article only seeks to verify whether the aforesaid empirical evidence is compatible with the subtelomere–telomere theory formulated within the tenets of the programmed aging paradigm. Theoretical arguments and empirical evidence in support of or against each of the two paradigms have already been discussed in other works [8, 9, 26]. In any case, the existence of mechanisms determined by the subtelomere–telomere–telomerase system and causing a progressive age-related decline in fitness through gradual cell senescence and cell senescence is not justifiable without the evolutionary motivation. This is required by the programmed aging paradigm but is incompatible with the opposite paradigm.

In conclusion, there are some more practical considerations.

1) Exposure to toxic substances and unhealthy lifestyles or eating habits (damaging factors) are known causes (or aggravating factors) in hypertension, diabetes, obesity, dyslipidemia, cardiovascular diseases, neurological dysfunctions, and other age-related disorders. This exposure is harmful to cells; it accelerates cell turnover and leads to the anticipation of physiological aging. However, damaging factors are not the cause of aging but rather acceleration and worsening of aging.

2) Protective drugs, e.g., statins, ACE inhibitors, and sartans appear to counteract cellular damage and slow down cell turnover.

3) Avoidance of damaging factors or the use of protective drugs do not block aging but are only able to restrain the effects of aging acceleration. In fact, no studies are showing that protective drugs can block the aging process.

4) An individual unexposed to damaging factors does not remain in a stable fitness condition but ages physiologically, as evidenced by studies on primitive populations. In such populations, starting from a certain age, a progressive reduction in fitness, or aging, is observed. Individuals of such populations are not significantly affected by diabetes, hypertension, obesity, cardiovascular disease; their death is due to accidents and events, which they cannot prevent because of declining fitness [50].

5) Actions directed to modify the aging process are conceivable if aging is a genetically determined and regulated phenomenon, i.e., if the thesis of the programmed aging paradigm is true, but this requires actions on the subtelomere–telomere system and/or genetic modifications [30]. This is quite different from the actions that accelerate or slow down the physiological process of aging discussed in this article.

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