ISSN 0006-2979, Biochemistry (Moscow), 2013, Vol. 78, No. 9, pp. 1054-1060. © Pleiades Publishing, Ltd., 2013.
Published in Russian in Biokhimiya, 2013, Vol. 78, No. 9, pp. 1345-1353.

Telomere Biology: Cancer Firewall or Aging Clock?

J. J. Mitteldorf

Department of EAPS, Massachusetts Institute of Technology, Cambridge MA 02138, USA; E-mail: josh@mathforum.org

Received February 15, 2013

Abstract—It has been a decade since the first surprising discovery that longer telomeres in humans are statistically associated with longer life expectancies. Since then, it has been firmly established that telomere shortening imposes an individual fitness cost in a number of mammalian species, including humans. But telomere shortening is easily avoided by application of telomerase, an enzyme which is coded into nearly every eukaryotic genome, but whose expression is suppressed most of the time. This raises the question how the sequestration of telomerase might have evolved. The predominant assumption is that in higher organisms, shortening telomeres provide a firewall against tumor growth. A more straightforward interpretation is that telomere attrition provides an aging clock, reliably programming lifespans. The latter hypothesis is routinely rejected by most biologists because the benefit of programmed lifespan applies only to the community, and in fact the individual pays a substantial fitness cost. There is a long-standing skepticism that the concept of fitness can be applied on a communal level, and of group selection in general. But the cancer hypothesis is problematic as well. Animal studies indicate that there is a net fitness cost in sequestration of telomerase, even when cancer risk is lowered. The hypothesis of protection against cancer has never been tested in animals that actually limit telomerase expression, but only in mice, whose lifespans are not telomerase-limited. And human medical evidence suggests a net aggravation of cancer risk from the sequestration of telomerase, because cells with short telomeres are at high risk of neoplastic transformation, and they also secrete cytokines that exacerbate inflammation globally. The aging clock hypothesis fits well with what is known about ancestral origins of telomerase sequestration, and the prejudices concerning group selection are without merit. If telomeres are an aging clock, then telomerase makes an attractive target for medical technologies that seek to expand the human life- and health-spans.

DOI: 10.1134/S0006297913090125

Key words: telomere, telomerase, cancer, programmed aging, adaptive aging, evolution

Elsewhere in this issue [1], I discuss the concept of a biological clock for aging. Telomeres may be the closest thing yet discovered to a master clock that determines the expression of senescent phenotypes not only in cells but in whole organisms as well. In all eukaryotes, telomeres shorten with each cell division, creating the machinery for a replication counter. Chromosomes with short telomeres cannot express their genes or copy themselves effectively. Short telomeres can induce a cell into a state of dormancy, or worse the cell can become actively toxic to surrounding tissues.

Telomerase is an enzyme that recharges telomeres, restoring their length via replication from an RNA template. The gene for telomerase is present in nearly every eukaryotic cell – as it must be, to permit long-term survival of the lineage. (Rare exceptions include *Drosophila*, which has evolved different means of telomere maintenance [2].) But curiously, expression of telomerase is tightly controlled in many metazoan species as well as protists. This creates a condition in which cells and entire organisms can senesce and die for lack of telomerase.

The specter of an organism dying for want of a cheap and readily-available enzyme points to a fundamental question of adaptive purpose. Many readers of this journal see in this situation a manifest indication of an adaptive program for aging; but most biologists deny on grounds of fundamental theory the possibility that such a genetic program could have evolved, and thus they look for an offsetting individual benefit from the withholding of telomerase, a benefit sufficiently potent to overcome the full cost of senescence.

In many birds [3] and mammals, including humans, telomere length is inversely correlated with age, and short telomeres are a mortality risk independent of age. This suggests a causal relationship between telomere attrition and lifespan. Telomeres shorten with age in primates [4], horses [5], dogs [6], cats [7], sheep [8], cows [9], and some rodents [10] (though not in bats [11], pigs [12], or most mice [10]). In telomerase-limited animals, telom-

erase is expressed copiously in early stages of the embryo, but then very sparingly during development and adult life, so that telomeres are permitted to shorten progressively through the lifespan. Short telomeres contribute substantially to senescence and the diseases of old age:

- by reducing the pool of stem cells available for healing and replenishment of tissues and organs;
- by crippling reproduction of leukocytes that provide immune surveillance;
- cells with short telomeres also secrete proinflammatory signals that contribute to the prevalence of atherosclerosis, cancer, and Alzheimer's disease at advanced ages.

In some protists, telomere attrition already served as an ancestral aging clock. In paramecia, for example, telomerase is not expressed during mitosis, but only during conjugation. Hence paramecia may reproduce clonally through a few hundred generations, before their telomeres become shortened and they enter a senescent state, losing viability. They are compelled to conjugate, blending their genomes sexually with a partner cell. Hence the rationing of telomerase serves to enforce an imperative to share genes. It is a constraint on individual selection, and an imperative to share genes communally, enhancing diversity and insuring against evolutionary dead ends [13].

This exclusive association of telomerase with sexual activity finds an echo in higher organisms that express telomerase only once, at the beginning of a lifetime. This is suggestive of a conserved evolutionary purpose that has survived a billion years since the dawn of eukaryotic life. My hypothesis is that in animals as in protists, telomeres are permitted to shorten in order to limit lifespan, to promote demographic homeostasis [14], and ultimately to put a check on runaway individual selection and support a diverse community that is more robust in an unpredictable world [15, 16].

But these are benefits that accrue only to the group. Aging imposes a fitness cost on the individual. Hence the concept of an aging clock is anathema to biologists who believe in the most standard version of evolutionary theory. Programmed death reduces individual fitness, the only kind of fitness that is recognized by a majority of the evolutionary community. How, then, might strict rationing of telomerase have evolved within the majority version of natural selection? The hypothesis has been that withholding telomerase provides a firewall against cancer. When cells become malignant and threaten to replicate out of control, their growth can be halted by replicative senescence.

This hypothesis fails on many grounds, as I will argue in the remainder of this article. We are left with the forbidden hypothesis that telomere attrition has evolved as an aging clock [17]. This is bad news for conventional evolutionary theory, but good news for anti-aging medicine, which has found a target in promoting the gene for telomerase [18].

EVIDENCE THAT TELOMERASE CAN EXTEND LIFESPAN IN ANIMALS

In 2003, Cawthon et al. [19] demonstrated a powerful statistical link between telomere length and lifespan. Drawing on historic blood samples from the 1980s, they traced the medical histories and mortality data from a sample of 143 sixty-year-old subjects, and correlated the results with leukocyte telomere length. Subjects in the lowest quartile of telomere length had twice the overall mortality risk of subjects in the highest quartile.

Before this study, there was a general expectation on evolutionary grounds that telomere length should *not* be related to human aging. If extending lifespan were as simple as expressing telomerase, then natural selection should have found this expedient long ago, and increased telomerase expression until telomere length was no longer a limit on lifespan. The Cawthon results forced many researchers to consider for the first time the possibility that people could be dying for lack of telomerase.

Association between telomere length and life expectancy was confirmed in three studies of animals in the wild [3, 20, 21]. The question remained open whether longer telomeres were a marker or a cause of life expectancy. This question has been addressed with animal studies. Telomeres have been extended by adding ectopic copies of the telomerase gene, by genetically programming the expression of telomerase via a tamoxifen switch, and by oral administration of a plant-derived compound that promotes telomerase expression. Lifespan extension has been detected in worms, mice, and rats.

Joeng et al. [22] created a strain of *C. elegans* worms with longer telomeres using not telomerase, but a telomere-binding protein called HRP-1. Lifespan was extended 19% by this intervention. The result was unexpected because telomeres do not erode over the lifespan of *C. elegans*. In fact, the adult worms are post-mitotic: there are no stem cells, no replenishment of tissues during a single worm's lifetime. It should not be possible for telomeres to function as an aging clock. Life extension of the HRP-1 worms was dependent on the presence of DAF-16, an upstream modifier of aging that is thought to be a master regulator of dauer formation in response to environmental hardships.

Tomas-Loba [23] first demonstrated life extension in mice using a strain that was engineered with extra copies of the telomerase (TERT) gene. Because it was widely believed that telomerase expression could cause cancer, they used mice that were cancer-resistant via modified p53. These mice lived 40% longer than controls, and markers of senescence such as inflammation, glucose tolerance, and neurological measures appeared on a delayed schedule. This result was unexpected because wild-type mice express telomerase copiously, and their telomeres are long enough to last through several lifetimes without obvious effects on health and longevity [24-26].

ASSOCIATION OF TELOMERASE WITH CANCER

Most human cancer cells express telomerase; this constitutes evidence that cancer causes telomerase activity, but not that telomerase activity causes cancer. On the contrary, a number of studies have found an association between short telomeres and cancer risk in humans [27-29].

Some studies in mice have found an increase in cancer incidence when telomerase was overexpressed. Female mice with extra (transgenic) copies of the telomerase gene developed breast tumors, while control mice had cancers in other organs, but not breast [30]. Transgenic telomerase targeted to thymocytes (stem cells of the thymus) resulted in an increased incidence of T-cell lymphoma [31]. Similarly, telomerase overexpression in skin stem cells increased the rate of skin cancer [32].

All these authors note that a puzzling aspect of the result – telomerase is already abundantly expressed in mice, and telomeres are never critically short. According to the standard hypothesis, telomerase rationing should serve the body by halting tumors when they reach a size determined by beginning telomere length. Any association of telomerase with *initiation* of cancer must be by a different mechanism, not yet understood.

Laboratory mice are not among the species whose lifespans are limited by telomere attrition, so the evolutionary theory about telomerase rationing ought not to apply to them at all. These results are interesting, and suggestive that telomerase plays other roles in metabolism, perhaps as a growth promoter [33]; but results in mice cannot be cited as evidence for the standard hypothesis that applies to humans, dogs, horses, etc. (but not to mice).

THE CLASSICAL HYPOTHESIS

The original theory as articulated by Carol Greider in 1990 [34] continues to predominate, even though key pieces of it have been falsified. The original theory was this.

1. Chromosomes lose a bit of telomere with each cell replication, and they become dormant and inactive if their telomeres shorten past a critical point.

2. The function of telomerase is to replenish telomeres and prevent them from becoming critically short.

3. Cancer cells require telomerase in order to replicate indefinitely and out of control.

4. Stem cells and other somatic cells have no need for telomerase, so long as their telomeres are long enough for the replications required of them in a lifetime.

5. Maximal lifespan has been a target of natural selection, taking into account the body's conflicting needs for renewal and protection from the risk of cancer.

6. The optimal solution that nature has found is to set telomeres in the embryo at a length sufficient for a lifetime of replication, and to keep telomerase under lock and key thereafter. Thus the need to liberate telomerase provides one more step in the transformation a cell must undergo in order to become cancerous.

We know now that the story is more complicated at every step. Does the central thrust of the narrative still hold? The bottom line question is whether telomere length and telomerase activity in the soma are set at levels that maximize lifespan overall. Answer: There is substantial evidence that freer expression of telomerase has a net effect of lengthening lifespan, both in humans and animal models. Natural selection has set telomerase expression at a level that is so low that it limits lifespan. Indeed, some organisms that are not subject to cancer (e.g. worms [22], protists [13]) have lifespans that are limited for lack of telomerase. In humans, senescent cells constitute not merely loss of a resource for renewal and growth, but active agents of destruction [35]; and in humans, short telomeres appear to be responsible not just for shorter lifespans [19] but even for *increased* cancer risk [28].

Step (1) has been modified: cells with short telomeres normally become bad actors, not just passive bystanders. They secrete inflammatory cytokines, and a few senescent cells can signal the body to enter a state of elevated inflammation that heralds cancer, heart disease, and arthritis [36, 37]. Alternatively, if p53 is deactivated, the cell can become cancerous, or it can continue to replicate until DNA damage is detected and triggers apoptotic death [33].

The life-shortening effect of senescent cells was demonstrated [38] in a 2011 study of transgenic mice. Baker et al. demonstrated that they could delay the onset of senescent phenotypes and prolong healthspan simply by imposing on these mice an artificial scheme for selectively poisoning senescent cells.

Less prominently, step (2) has been modified: there is evidence that extension of telomeres is not the only action of telomerase. Cong [33] reviews evidence that telomerase is imported by mitochondria, where it modifies signals that control apoptosis (in both directions, promoting or inhibiting apoptosis depending on context) [39]. Telomerase also facilitates repair in response to DNA damage [40] and modifies gene expression (reviewed in [33]).

Step (3). Telomerase is turned on in most human cancers, but there remain 10-15% of cancers that manage to proliferate and metastasize without telomerase [41]. This is still not well understood. Blasco [42] found that telomerase expression in mouse tumors was uncorrelated to detection of the RNA part of the telomerase, which presumably is necessary to extend telomeres.

Step (4). Telomerase seems to "moonlight" as a growth hormone, in addition to its primary function in restoring lost telomere length [33, 43].

Step (5). There are abundant examples of mechanisms by which natural selection seems to have shortened lifespan "gratuitously", without pleiotropic benefit. (In worms, many genes are known that shorten lifespan, and for which no benefit has yet been identified. Already in 1992, Stearns provided a list of such cases at the back of his book on *Evolution of Life Histories* [44].) The proposition that maximal lifespan is a target of natural selection has a lot of explaining to do.

Step (6). This is the bottom line question on which the plausibility of the classical hypothesis hinges: Is telomerase expression titrated in such a way as to maximize lifespan? There is no experimental evidence in support of this proposition, and some direct reasons to believe it is false.

WHY THE CLASSICAL HYPOTHESIS IS UNTENABLE

If lifespan were indeed maximized, then we would expect that there is a small decrease in lifespan when expression of telomerase is artificially modulated in either direction. Lifespan would be expected to decrease when telomerase is added, because the cancer burden is increased; and life expectancy would be expected to decrease when telomerase was subtracted (even though cancer rates should be depressed), perhaps because growth and healing are compromised. Both decreases ought to be small, because they are second order deviations from a broad, rounded peak. Instead, we find that increased telomere length *always* increases net lifespan. This is true in humans [19, 45], in laboratory mice [46], and in wild animals [3, 20, 21].

Note that the original finding that telomerase expression could extend the lives of laboratory mice [23] was limited to a strain that was cancer resistant. The more recent result of de Jesus [46] confirms that even in normal mice, increased telomerase expression leads to increased life expectancy. In contrast, the findings associating excess telomerase with higher cancer mortality [32] require an unnatural carcinogenic load. There is no evidence that the cancer protection afforded by limited telomerase in mice actually leads to a net lengthening of lifespan, either in the laboratory or in the wild.

There is diverse evidence linking longer telomeres with longer lifespan in worms [22], lab mice [46], wild mammals [21], birds [3, 20], and humans [19]. It has been argued that correlation is no proof of causality, and it is conceivable that environmental stressors cause higher mortality rates and also necessitate cell proliferation, which tends to shorten telomeres. Frequent infections might cause the immune system to be more active in some people than others, and we might expect telomeres in blood cells to be shortened in such people; but we would not expect that those who successfully fight off an infection or other stressors would have a shortened life expectancy. It is counter-intuitive but true that lifespan can be extended hormetically in people who are exposed to pathogens. And the idea of demographic correlation fails completely in the laboratory animal studies. The worms with extended lifespans had telomeres that were lengthened biochemically, and the mice were transfected to add telomerase late in life.

It has sometimes been argued that withholding telomerase has a benefit early in life, but imposes a cost later in life, when senescent cells begin to accumulate and cause problems. This would seem to be the classic definition of pleiotropy, as conceived by Williams [47]. This, however, is an outmoded idea of pleiotropy. In the 1950s when the idea was first proposed, it might have been reasonable to suppose that evolution was forced to make a binary choice between presence and absence of a given protein. But we now know that gene expression is the subject of an evolutionary program at least as intricate as the genes themselves, and that the time and place of expression for each individual gene is tightly regulated. It is inconceivable that the body would be unable to express telomerase late in life (when it is most needed) just because telomerase expression was inhibited early in life (when it might theoretically do more harm than good).

The best evidence for the classical hypothesis is: (a) that most cancer cells turn on telomerase; (b) that transgenic mice with increased telomerase have higher cancer susceptibility, and (c) cross-species analysis of telomerase activity and cancer risk. I respond to each of these.

a) It is true that as normal cells turn cancerous, 85-90% find ways to activate telomerase expression [41]. This would be expected to make these cancers more virulent and dangerous. This fact must be a component of the evolutionary pressure that has evolved telomerase expression in different species. I do not believe that it is the central driving force that has caused telomerase expression to be restricted, but rather a modifier in some species where cancer is a significant factor restricting reproductive fitness.

b) Blasco's group in Madrid [32] created a strain of mice with an extra, transplanted gene for telomerase. These animals were able to heal more rapidly in response to tissue injuries, but they were also more susceptible to carcinogens. In another strain of transgenic mice, the same research group [48] report that mean and maximum lifespan *increased* with artificially high telomerase expression, despite a higher incidence of early cancers. This indicates that cancer susceptibility has affected the evolved expression of telomerase, but that cancer prevention is unlikely to be the primary evolutionary purpose.

c) Gorbunova et al. [10] looked in a sample of 15 rodent species for patterns in telomere length and telomerase expression that might support the evolutionary hypothesis concerning cancer. Unexpectedly, they found no correlation between lifespan and telomere length or lifespan and telomerase activity. What they did find was a

weak (logarithmic) but highly significant tendency for larger animals to have reduced telomerase activity. They interpreted this to mean that the need for cancer protection grows with body mass (number of potentially cancerous cells), but not with lifespan. If more cells mean more cancer risk, why should the relationship be logarithmic? And why did the correlation with lifespan, the original target of their research, fail to appear? My interpretation is that such weak and inconsistent correlations suggest a *modifier* of evolutionary function, rather than an independent adaptation. Gomez et al. [49] worked with a broader database of mammals, to demonstrate that ancestral mammals had short telomeres, and that species like mice that have evolved from them in the direction of more liberal expression of telomerase.

The hypothesis that telomerase is restricted to achieve a net increase in lifespan via cancer prevention is certainly false. Were it not for the unthinkability of the alternative – programmed death – the theory would be dead in the water. If it is to be rescued, the theory must be patched to say that rationing telomerase prevents so many early deaths that there is a net benefit in fitness, even though lifespan is shortened [48]. Rodier and Campisi [50] recognize the evolutionary paradox, and outline a theory of this sort. They recognize and catalog the many pro-aging actions from the inapt secretions of senescent cells: inflammation, dysregulation of growth and differentiation, disruption of tissue integrity and angiogenesis. These add to the stark fact that diminished stem cell numbers impair healing and repair. But (presumably for theoretical reasons) they do not consider the possibility that these may be evolved, proactive mechanisms of senescence.

They state explicitly the pleiotropic premise that the early benefits of avoiding cancer outweigh the late cost of foreshortened lifespan, and they make a qualitative case for the plausibility of this idea without attempting a quantitative accounting. For their theory to be viable, it should be demonstrated (1) that the benefit from early cancer prevention is sufficient to offset the increase in cancer and all-cause mortality later on, and (2) that age-specific telomerase expression, the obvious resolution of this tradeoff, is unavailable as an evolutionary pathway.

Until these theoretical lacunae are patched, it remains a striking paradox that telomerase is hidden for the evolutionary purpose of preserving life by avoiding cancer, and yet the paucity of telomerase has a net effect of both increasing the cancer burden and shortening lifespan.

WHY THE AGING CLOCK HYPOTHESIS IS PREFERRED

The aging clock hypothesis applies to all species that suffer life shortening through cellular senescence, but the cancer theory only applies to those species that are subject to cancer. Cellular senescence evolved first in lower organisms, where cancer is unknown, and was presumably passed down to higher animals that *are* subject to cancer. This argues strongly against the idea that protection against cancer was the primary and original purpose of permitting telomeres to shorten.

The cancer theory posits a tradeoff, which must result in greater fitness in the wild with short telomeres than with long. Before 2003, it was generally assumed that short telomeres *could not* be life limiting, as it would violate this condition. Now we know that, for lack of telomerase, lifespan is curtailed. We have data demonstrating this for humans, for several wild species of mammals and birds, and for laboratory mice. The protection against cancer, which is afforded by short telomeres, is more than offset by the life-shortening effects of short telomeres. *Le jeu ne vaut pas la chandelle.* How could nature be clearer in showing us the face of programmed death?

If cellular senescence is designed to cut off cancerous cell lines, why would senescent cells remain alive and toxic? They could, instead, be programmed to be good citizens and dismantle themselves via apoptosis to facilitate recycling of proteins and nutrients. The fact that senescent cells emit poisons is completely consonant with the theory that cellular senescence is a form of programmed organismal death. But from the perspective of the cancer theory, the poisoning of the body must be regarded as an unexplained evolutionary error.

I would not deny that short telomeres may serve as an anti-cancer shield in some circumstances; but this benefit alone is insufficient to explain the adaptation because, after all, the net result of holding back telomerase is to *shorten* lifespan and to *increase* cancer risk.

The hypothesis that telomere attrition is an aging clock evolved by natural selection for the purpose of limiting lifespan applies in all relevant taxa. The worst thing that can be said about it is that its evolution must have required group selection. Since 1970s, the conservative opinion [51, 52] has been that no form of group selection can compete for speed and efficiency with individual selection, where the two conflict. But this has been abundantly refuted in the general case [53] and with respect to programmed aging, specific mechanisms have been advanced and modeled, demonstrating plausible dynamics by which the long-term advantage of shorter lifespan might prevail over the short-term advantage of longer lifespan [14, 16, 54]. Thus it is fundamentally plausible that telomere attrition evolved as an aging clock.

The popular alternative hypothesis that telomere attrition evolved as a firewall against neoplastic transformation has no integrity, because there are categories of organism to which it does not apply. Statistical genetics demonstrates that this form of senescence has an ancient

evolutionary origin [49] probably going back to the first eukaryotes [13]. Thus there are taxa to which this mechanism does not apply because they are not subject to cancer, including the first organisms in which telomere attrition evolved. And quantitatively the hypothesis fails because the presumed avoidance of cancer comes at a net cost in average life expectancy and, presumably, in individual fitness as well.

I am grateful for personal discussions with Bill Andrews of Sierra Sciences, who helped to generate some of the ideas in this essay, and who corrected several technical points in a later draft. Aubrey de Grey offered a helpful critique of these ideas.

REFERENCES

1. Mitteldorf, J. (2013) *Biochemistry* (Moscow), **78**, 1048-1053.
2. Melnikova, L., and Georgiev, P. (2005) *Chromosome Res.*, **13**, 431-441.
3. Pauliny, A., Wagner, R. H., Augustin, J., Szep, T., and Blomqvist, D. (2006) *Mol. Ecol.*, **15**, 1681-1687.
4. Herbig, U., Ferreira, M., Condel, L., Carey, D., and Sedivy, J. M. (2006) *Science*, **311**, 1257.
5. Argyle, D., Ellsmore, V., Gault, E. A., Munro, A. F., and Nasir, L. (2003) *Mech. Ageing Devel.*, **124**, 759-764.
6. McKevitt, T. P., Nasir, L., Devlin, P., and Argyle, D. J. (2002) *J. Nutr.*, **132**, 1604S-1606S.
7. Brummendorf, T. H., Mak, J., Sabo, K. M., Baerlocher, G. M., Dietz, K., Abkowitz, J. L., and Lansdorp, P. M. (2002) *Exp. Hematol.*, **30**, 1147-1152.
8. Cui, W., Wylie, D., Aslam, S., Dinnyes, A., King, T., Wilmut, I., and Clark, A. J. (2003) *Biol. Reprod.*, **69**, 15-21.
9. Choi, D., Cho, C., and Sohn, S. (2008) *J. Animal Sci. Technol.*, **50**, 445-456.
10. Seluanov, A., Chen, Z., Hine, C., Sasahara, T. H., Ribeiro, A. A., Catania, K. C., Presgraves, D. C., and Gorbunova, V. (2007) *Aging Cell*, **6**, 45-52.
11. Wang, L., McAllan, B. M., and He, G. (2011) *Biochemistry* (Moscow), **76**, 1017-1021.
12. Fradiani, P., Ascenzioni, F., Lavitrano, M., and Donini, P. (2004) *Biochimie*, **86**, 7-12.
13. Clark, W. R. (2004) *Adv. Gerontol.*, **14**, 7-20.
14. Mitteldorf, J. (2006) *Evol. Ecol. Res.*, **8**, 561-574.
15. Libertini, G. J. (1988) *Theor. Biol.*, **132**, 145-162.
16. Martins, A. C. (2011) *PLOS One*, **6**, e24328.
17. West, M. D. (2003) *The Immortal Cell*, Doubleday, New York.
18. Bernardes de Jesus, B., Schneeberger, K., Vera, E., Tejera, A., Harley, C. B., and Blasco, M. A. (2011) *Aging Cell*, **10**, 604-621.
19. Cawthon, R. M., Smith, K. R., O'Brien, E., Sivatchenko, A., and Kerber, R. A. (2003) *Lancet*, **361**, 393-395.
20. Haussmann, M. F., Winkler, D. W., and Vleck, C. M. (2005) *Biol. Lett.*, **1**, 212-214.
21. Bize, P., Criscuolo, F., Metcalfe, N. B., Nasir, L., and Monaghan, P. (2009) *Proc. Biol. Sci.*, **276**, 1679-1683.
22. Joeng, K. S., Song, E. J., Lee, K. J., and Lee, J. (2004) *Nat. Genet.*, **36**, 607-611.
23. Tomas-Loba, A., Flores, I., Fernandez-Marcos, P. J., Cayuela, M. L., Maraver, A., Tejera, A., Borras, C., Matheu, A., Klatt, P., Flores, J. M., Vina, J., Serrano, M., and Blasco, M. A. (2008) *Cell*, **135**, 609-622.
24. Wynford-Thomas, D., and Kipling, D. (1997) *Nature*, **389**, 551-552.
25. Chang, S. (2005) *Mutat. Res.*, **576**, 39-53.
26. Mendelsohn, A. R., and Larrick, J. W. (2012) *Rejuvenation Res.*, **15**, 435-438.
27. Wright, W. E., and Shay, J. W. (2005) *J. Am. Geriatr. Soc.*, **53**, S292-S294.
28. Wu, X., Amos, C. I., Zhu, Y., Zhao, H., Grossman, B. H., Shay, J. W., Luo, S., Hong, W. K., and Spitz, M. R. (2003) *J. Natl. Cancer Inst.*, **95**, 1211-1218.
29. Ma, H., Zhou, Z., Wei, S., Liu, Z., Pooley, K. A., Dunning, A. M., Svenson, U., Roos, G., Hosgood, H. D., 3rd., Shen, M., and Wei, Q. (2011) *PLoS ONE*, **6**, e20466.
30. Artandi, S. E., Alson, S., Tietze, M. K., Sharpless, N. E., Ye, S., Greenberg, R. A., Castrillon, D. H., Horner, J. W., Wieler, S. R., Carrasco, R. D., and DePinho, R. A. (2002) *Proc. Natl. Acad. Sci. USA*, **99**, 8191-8196.
31. Canela, A., Martin-Caballero, J., Flores, J. M., and Blasco, M. A. (2004) *Mol. Cell. Biol.*, **24**, 4275-4293.
32. Gonzalez-Suarez, E., Samper, E., Ramirez, A., Flores, J. M., Martin-Caballero, J., Jorcano, J. L., and Blasco, M. A. (2001) *EMBO J.*, **20**, 2619-2630.
33. Cong, Y., and Shay, J. W. (2008) *Cell Res.*, **18**, 725-732.
34. Greider, C. W. (1990) *Bioessays*, **12**, 363-369.
35. Schoeftner, S., Blanco, R., Lopez de Silanes, I., Munoz, P., Gomez-Lopez, G., Flores, J. M., and Blasco, M. A. (2009) *Proc. Natl. Acad. Sci. USA*, **106**, 19393-19398.
36. Campisi, J. (2005) *Cell*, **120**, 513-522.
37. Rodier, F., Coppe, J. P., Patil, C. K., Hoeijmakers, W. A., Munoz, D. P., Raza, S. R., Freund, A., Campeau, E., Davalos, A. R., and Campisi, J. (2009) *Nat. Cell Biol.*, **11**, 973-979.
38. Baker, D. J., Wijshake, T., Tchkonia, T., LeBrasseur, N. K., Childs, B. G., van de Slius, B., Kirkland, J. L., and van Deursen, J. M. (2011) *Nature*, **479**, 232-236.
39. Sahin, E., Colla, S., Liesa, M., Moslehi, J., Muller, F. L., Guo, M., Cooper, M., Kotton, D., Fabian, A. J., Walkey, C., Maser, R. S., Tonon, G., Foerster, F., Xiong, R., Wang, Y. A., Shukla, S. A., Jaskelioff, M., Martin, E. S., Heffernan, T. P., Protopopov, A., Ivanova, I., Mahoney, J. E., Kost-Alimova, M., Perry, S. R., Bronson, R., Liao, R., Mulligan, R., Shirihai, O. S., Chin, L., and DePinho, R. A. (2011) *Nature*, **470**, 359-365.
40. Masutomi, K., Yu, E. Y., Khurts, S., Ben-Porath, I., Currier, J. L., Metz, G. B., Brooks, M. W., Kaneko, S., Murakami, S., DeCaprio, J. A., Weinberg, R. A., Stewart, S. A., and Hahn, W. C. (2003) *Cell*, **114**, 241-253.
41. Shay, J. W., and Bacchetti, S. (1997) *Eur. J. Cancer*, **33**, 787-791.
42. Blasco, M. A., Lee, H. W., Hande, M. P., Samper, E., Lansdorp, P. M., DePinho, R. A., and Greider, C. W. (1997) *Cell*, **91**, 25-34.
43. Shay, J. W. (2005) *The Scientist*, **19**, 18-19.
44. Stearns, S. C. (1992) *The Evolution of Life Histories*, Oxford University Press, Oxford, New York.

45. Kimura, M., Hjelmborg, J. V., Gardner, J. P., Bathum, L., Brimacombe, M., Lu, X., Christiansen, L., Vaupel, J. W., Aviv, A., and Chistensen, K. (2008) *Am. J. Epidemiol.*, **167**, 799-806.
46. Bernardes de Jesus, B., Vera, E., Schneeberger, K., Tejera, A. M., Ayuso, E., Bosch, F., and Blasco, M. A. (2012) *EMBO Mol. Med.*, **4**, 691-704.
47. Williams, G. (1957) *Evolution*, **11**, 398-411.
48. Gonzalez-Suarez, E., Geserick, C., Flores, J. M., and Blasco, M. A. (2005) *Oncogene*, **24**, 2256-2270.
49. Gomes, N. M. V., Ryder, O. A., Houck, M. L., Charter, S. J., Walker, W., Forsyth, N. R., Austad, S. N., Venditti, C., Pagel, M., Shay, J. W., and Wright, W. E. (2011) *Aging Cell*, **10**, 761-768.
50. Rodier, F., and Campisi, J. (2011) *J. Cell Biol.*, **192**, 547-556.
51. Williams, G. (1966) *Adaptation and Natural Selection*, Princeton University Press, Princeton.
52. Maynard Smith, J. (1976) *Q. Rev. Biol.*, **51**, 277-283.
53. Sober, E., and Wilson, D. S. (1998) *Unto Others: The Evolution and Psychology of Unselfish Behavior*, Harvard University Press, Cambridge, MA.
54. Trubitsyn, A. (2006) *Adv. Gerontol.* (Russia), **19**, 13-24.