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Does telomere elongation lead to a longer lifespan if cancer is considered?

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Abstract

As cell proliferation is limited due to the loss of telomere repeats in DNA of normal somatic cells during division, telomere attrition can possibly play an important role in determining the maximum life span of organisms as well as contribute to the process of biological ageing. With computer simulations of cell culture development in organisms, which consist of tissues of normal somatic cells with finite growth, we obtain an increase of life span and life expectancy for longer telomeric DNA in the zygote. By additionally considering a two-mutation model for carcinogenesis and indefinite proliferation by the activation of telomerase, we demonstrate that the risk of dying due to cancer can outweigh the positive effect of longer telomeres on the longevity.
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1. Introduction

Telomeres are tandem repeated noncoding sequences of nucleotides at both ends of the DNA in eukaryotic chromosomes stabilizing the chromosome ends and preventing them from end-to-end fusion or degradation [1]. Polymerase cannot completely replicate the $3'$ end of linear DNA, so telomeres are shortened at each DNA replication [2]. This end replication problem leads to a finite replicative capacity for normal somatic cells [3]. They can only divide up to a certain threshold, the Hayflick limit [4,5]. The enzyme telomerase, repressed in most normal somatic cells, synthesizes and elongates telomere repeat sequences at the end of DNA strands so that certain cells like germline cells are immortal and indefinite in growth [6,7].

Most forms of cancer follow from the accumulation of somatic mutations [8,9]. Cancer-derived cell lines and 85–90% of primary human cancers are able to synthesize high levels of telomerase and thus are able to prevent further shortening of their telomeres and proliferate indefinitely [10]. But if cells are premalignant or already cancerous and telomerase is not yet activated, the proliferative capacity of these cells and therefore the

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accumulation of mutations is determined by the remaining telomere length [11]. So the frequency of malignant cancer should be higher for longer telomeres in normal somatic cells.

Recently published data show that longer telomeric DNA increased the life span of nematode worms [12]. Experiments are running [13] whether there is a positive effect on the longevity also for organisms with renewing tissues if the telomere length in fetal cells is increased [13]. As the probability for the incidence of cancer is correlated to the replicative potential of the mutated cells [14], one can ask the following question: is an extension of life span possible if telomeres in embryonic cells are elongated and cancer is considered? An answer to this question could be given by computer simulations as the presented model focuses on organismal ageing due to the loss of telomeres in DNA and neglects other effects which lead to a decreasing survival probability with age.

As shortening of telomeres is one of the supposed mechanisms of ageing on cellular level, most stochastical and analytical studies investigate this relationship [15–19]. A theoretical model which directly relates telomere attrition to human ageing was first suggested by Aviv et al. [20]. Here we present a different telomere dynamics model providing requirements to study the effects of (a) different mean telomere lengths in constituting cells, as well as of (b) somatic mutations leading to cancer progression and indefinite proliferation due to telomerase activity on the ageing of organisms.

2. Basic model of biological ageing due to telomere attrition

Every organism is developed from a single progenitor cell, the zygote (Fig. 1). The initial telomere length of zygote cells is assumed to be normally distributed with mean μ_z and standard deviation σ_z [21]. Telomere repeats lost per division (TRLPD) are randomly chosen at each division of every cell from a normal distribution with mean μ_{TRLPD} and standard deviation σ_{TRLPD}. A dividing cell produces a clone who inherits the replicative capacity of the progenitor cell at this age. Cells can divide until nearly all their original telomeres are lost.

For every organism the dynamics of the model is as follows: divisions of the zygote and the stem cells derived from it occur six times in the early embryo. Each of these cells is the progenitor of one tissue. This is followed by a period of population doublings where all cells divide once in every timestep until 2^7 cells are present in each tissue. In the following maturation stage, cells are chosen randomly for division until each tissue reaches the adult size of 10^4 cells. It takes about 26 timesteps until an organism is mature.

Ageing starts now. In every timestep first cells die with 10% probability due to events like necrosis or apoptosis. 10 percent of the cells of the corresponding tissue are then randomly chosen for division to fill this gap. The replacement does not have to be complete as the chosen cell could probably not divide anymore due to telomere attrition. After some time the tissue will start shrinking. The random choice of dying and dividing cells in differentiated tissues is in accordance with nature as for example in epithelium the choice of cells to be exported from the basal layer is random [24,25]. The organism dies, if its total cell population size shrinks to 50% of the mature size. The results presented in the following do not depend qualitatively on the choice of this threshold.

3. Results without cancer

In the implementation of this model, linear congruential generators are used to produce the required random numbers and normally distributed variables are generated with the Box–Muller algorithm [22,23]. Resulting age distributions for different mean telomere lengths in the zygote cells are shown in Fig. 2. The shape of these distributions is analogous to empirical data of many human and animal populations. We obtain a positive effect on the longevity of the organisms if the mean telomere length in the precursor cell is increased. The chosen mean doubling potentials of the zygote cells are 30, 40 and 50 with the choice of $\mu_z =$ 1500, 2000, 2500 and $\mu_{TRLPD} = 50$. The number of mitotic divisions observed in human fibroblasts is higher [26], but the choice of this parameter is reasonable as the number of considered cells per mature organism (640 000) in this model is also much lower than in human organisms where the total number of cells is of the order of 10^{13} [24]. Non-dividing cells are not included in the model as we focus on ageing due to the progressive shrinking of tissues driven by telomere shortening. Our results will be given below as part of Fig. 5.
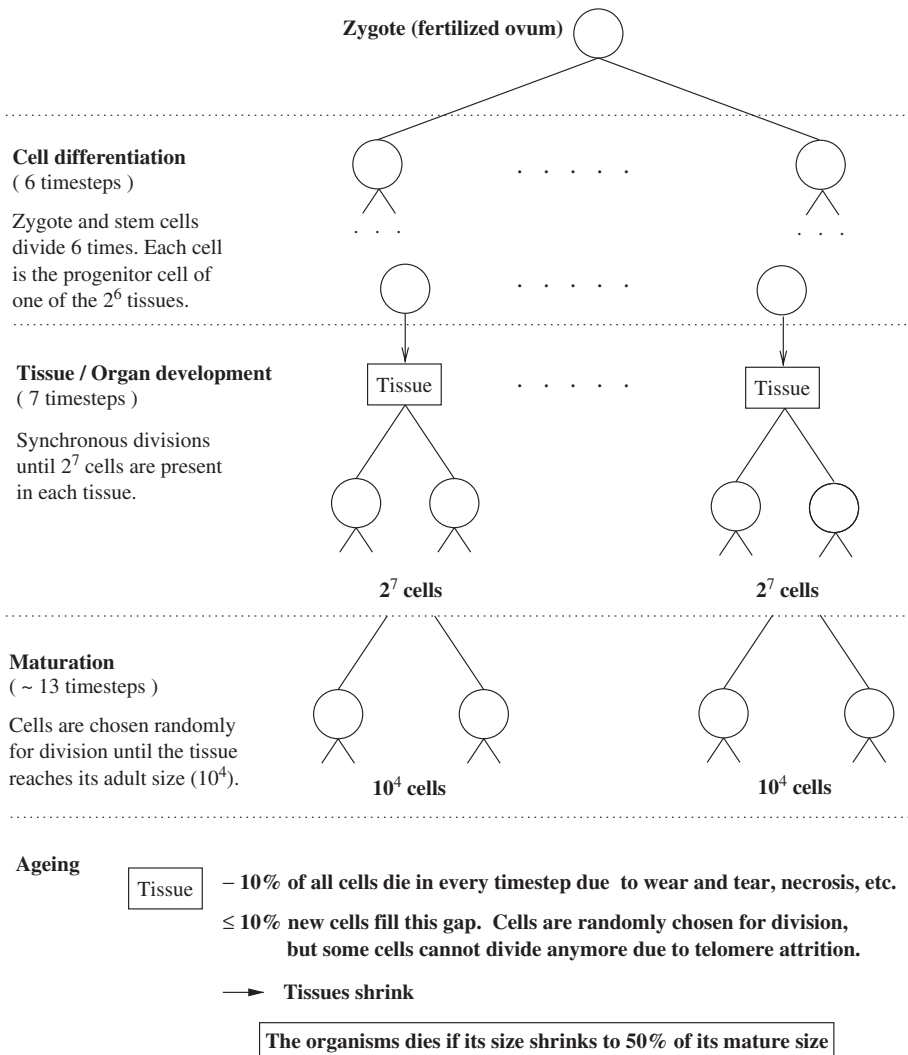
Fig. 1. Dynamics of cell proliferation in one organism in the basic model.

4. Introducing carcinogenesis and telomerase

Clonal cancer is now introduced in the model. In accordance to the model of Moolgavkar et al., one of our assumptions is that malignant tumors arise from independently mutated progenitor cells [27]. For most forms of carcinoma, transformation of a susceptible stem cell into a cancer cell is suggested to be a multistage process of successive mutations with a relatively low probability for the sequential stages [8,28]. Two independent and irreversible hereditary mutation stages are considered here, which can occur at every level of development of the organism during cell division.

The first premalignant stage to be considered is a promotion stage: a dividing cell can mutate with small probability p_{mut} [24]. All descendant cells inherit this mutation. This mutation leads to a partial escape from homeostatic control of growth by the local cellular environment [11,29]. Cells on the promotion stage have a selective advantage over unaffected cells [30]. In our model they are chosen first for division during maturation and for filling up the gap in the ageing period.

The subsequent transition can occur again with probability p_{mut} during division. If a cell reaches this second stage of mutation it is a progenitor of a carcinoma. An explosive clonal expansion to a fully malignant
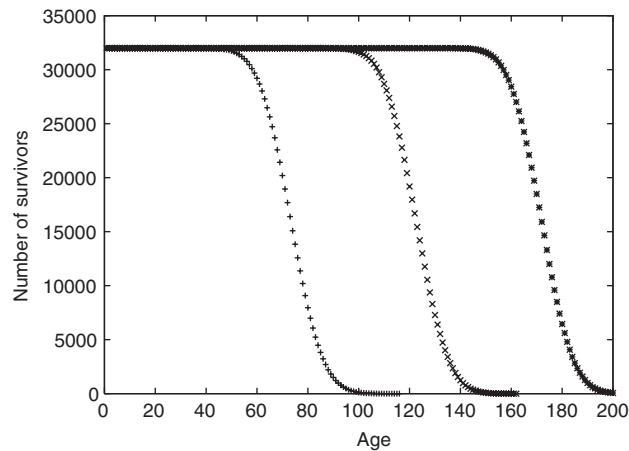
Fig. 2. Age distribution of 32 000 organisms with telomere lengths of $\mu_z = 1500 (+)$, $\mu_z = 2000 (\times)$ and $\mu_z = 2500 (*)$; $\sigma_z = 100$, $\mu_{TRLPD} = 50$, $\sigma_{TRLPD} = 10$.

compartment happens [29]. This cell and the clonal progeny doubles in the current timestep until it is no more possible due to telomere attrition. This expansion leads only to an increase of the malignant cell population size. As a certain fraction of cells is killed per unit time and clonal expansions only occur with a very small probability, the tumor environments may not continue growing, eventually shrink, or even die [31]. We assume that it is necessary for advanced cancer progression and therefore for the development of a deadly tumor that fully mutated cells are able to activate telomerase [32].

In our model, telomerase activation is possible at every age of the organism in normal and mutated cells during division with a very low probability p_{telo}. The irreversible loss of replicative potential is stopped in these cells. As the contribution of telomerase to tumorigenicity is not yet completely understood [33–35], we assume that death of an organism due to cancer occurs if telomerase is reactivated in at least one fully mutated cell [36]. We treat the time interval between the occurrence of the deadly tumor and death as constant, so we set this interval to zero.

5. Effects of different telomere lengths considering cancer

Fig. 3 shows simulation results for $\mu_z = 1500$ and 2500. As we consider a lower complexity by choosing a lower number of tissues and cells per organism, we assume higher mutation rates for the incidence of cancer than observed in nature [37,38]. The age distribution for shorter initial telomere lengths considering cancer is shifted to the left but still very old organisms exist. For longer telomeres the age distribution is again shifted to the left but even behind the distributions for shorter telomeres with and without considering carcinogenesis.

Thus without considering cancer, organisms with longer zygote telomeres live longer, as the life expectancy of the organisms increases linear for longer telomeres. But if cancer is considered this effect is reversed for longer initial mean telomere lengths (Fig. 4).

The force of mortality [39] resulting from this model is shown for $\mu_z = 1500$ with and without considering cancer in comparison to empirical human mortality data (Fig. 5). It agrees to some extent with human mortality functions provided cancer is incorporated into the model and decelerates at advanced ages, as claimed for human and animal populations [40,41]. The hump in the curve at younger ages, occurring also for other parameter sets, fits to data of many human mortality tables.

6. Conclusion

The expected simulation result of the basic model without cancer is an increase of life span of most organisms with longer initial telomeres. After introducing somatic mutations promoting cancer and
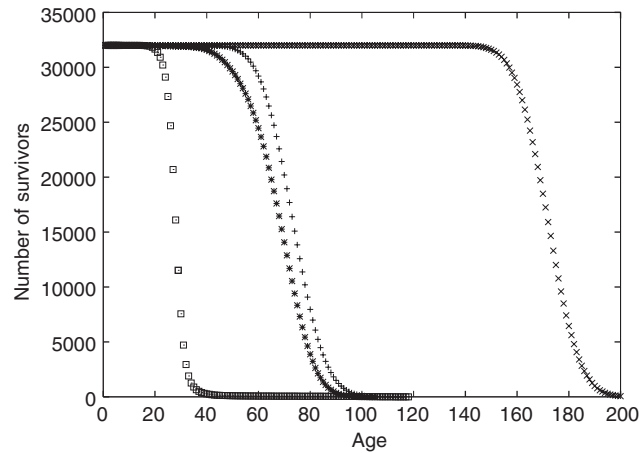
Fig. 3. Age distribution of 32 000 organisms with telomere lengths of $\mu_z = 1500$ with ($*$) and without cancer ($+$) and $\mu_z = 2500$ with ($\square$) and without cancer ($\times$); $\sigma_z = 100$, $\mu_{TRLPD} = 50$, $\sigma_{TRLPD} = 10$. Cancer mutations are possible with $p_{mut} = 5 * 10^{-5}$. Telomerase can be activated with $p_{telo} = 10^{-5}$.
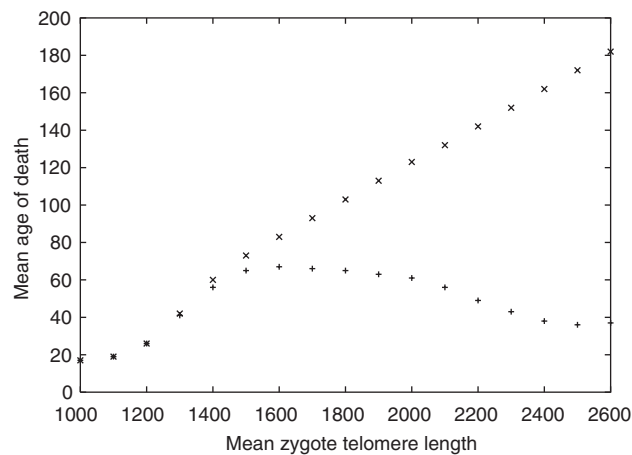

Fig. 4. Mean age of death for different initial zygote telomere lengths μ_z (32 000 organisms) without cancer ($\times$) and introducing carcinogenesis ($+$).

telomerase activation in this model, the survival probability is lower for each considered initial telomere length in certain time intervals in adult ages.

But even low probabilities for the two mutation stages and for the activation of telomerase lead to a strong reduction of life span for longer telomeres. So the implication of two-stage carcinogenesis for the incidence of cancer in this simple model of cell proliferation in organisms is that life expectancy and life span of complex organisms cannot be increased by artificially elongating telomeres in primary cells, for example during a cloning procedure.

Further improvements, extensions and applications of this model are possible. With respect to the role of telomeres and telomerase in carcinogenesis, may be this computational approach can contribute to the development of a comprehensive theoretical model in oncology uniting mutagenesis and cell proliferation [42].
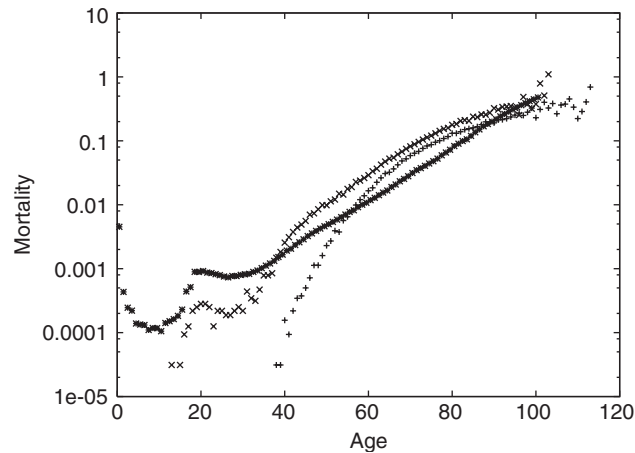
Fig. 5. Mortality function for $\mu_z = 1500$ with ($\times$) and without cancer ($+$), 32 000 organisms considered, $\sigma_z = 100$, $\mu_{TRLPD} = 50$, $\sigma_{TRLPD} = 10$; German men ($*$) from www.destatis.de (June 2004) (Sterbetafel, 2000/2002).

Acknowledgements

References

[1] E.H. Blackburn, Nature 350 (1991) 569.
[2] C.B. Harley, A.B. Futcher, C.W. Greider, Nature 345 (1990) 458.
[3] A.M. Olovnikov, J. Theor. Biol. 41 (1973) 181.
[4] L. Hayflick, P.S. Moorhead, Exp. Cell Res. 25 (1961) 585.
[5] L. Hayflick, Exp. Gerontol. 38 (2003) 1231.
[6] C.W. Greider, E.H. Blackburn, Cell 43 (1985) 405.
[7] J.W. Shay, W.E. Wright, Nature Rev. 1 (2000) 72.
[8] C.O. Nordling, Br. J. Cancer 7 (1953) 68.
[9] E.R. Fearon, B. Vogelstein, Cell 61 (1990) 759.
[10] N.W. Kim, M.A. Piatyszek, K.R. Prowse, C.B. Harley, M.D. West, P.L. Ho, G.M. Coviello, W.E. Wright, S.L. Weinrich, J.W. Shay, Science 266 (1994) 2011.
[11] S.H. Moolgavkar, E.G. Luebeck, Cancer 38 (2003) 302.
[12] K.S. Joeng, E.J. Song, K.J. Lee, J. Lee, Genetics 36 (2004) 6071.
[13] R.P. Lanza, J.B. Cibelli, C. Blackwell, V.J. Cristofalo, M.K. Francis, G.M. Baerlocher, J. Mak, M. Schertzer, E.A. Chavez, N. Sawyer, P.M. Lansdorp, M.D. West, Science 288 (2000) 665.
[14] J.W. Shay, W.E. Wright, Radiat. Res. 155 (2001) 188.
[15] M.Z. Levy, R.C. Allsopp, A.B. Futcher, C.W. Greider, C.B. Harley, J. Mol. Biol. 225 (1992) 951.
[16] O. Arino, M. Kimmel, G.F. Webb, J. Theor. Biol. 177 (1995) 45.
[17] P. Olofsson, M. Kimmel, Math. Biosci. 158 (1999) 75.
[18] I. Rubelj, Z. Vondracek, J. Theor. Biol. 197 (1999) 425.
[19] P.D. Sozou, T.B. Kirkwood, J. Theor. Biol. 213 (2001) 573.
[20] A. Aviv, D. Levy, M. Mangel, Mech. Ageing Dev. 124 (2003) 829.
[21] J. op den Buijs, P.P. van den Bosch, M.W. Musters, N.A. van Riel, Mech. Ageing Dev. 125 (2004) 437.
[22] S.J. Tu, E. Fischbach, Int. J. Mod. Phys. C 16 (2005) 281.
[23] G.E.P. Box, M.E. Muller, Ann. Math. Stat. 29 (1958) 610.
[24] L. Cairns, Nature 255 (1975) 197.
[25] S.A. Frank, Y. Iwasa, M.A. Nowak, Genetics 163 (2003) 1527.
[26] R.C. Allsopp, H. Vaziri, C. Patterson, S. Goldstein, E.V. Younglai, A.B. Futcher, C.W. Greider, C.B. Harley, Proc. Natl. Acad. Sci. USA 89 (1992) 10114.

[27] S.H. Moolgavkar, A. Dewanji, D.J. Venzon, Risk Anal. 8 (1998) 383.
[28] P. Armitage, R. Doll, Br. J. Cancer 8 (1954) 1.
[29] A. Sarasin, Mutat. Res. 544 (2003) 99.
[30] P. Armitage, R. Doll, Br. J. Cancer 11 (1957) 161.
[31] E. Hiyama, K. Hiyama, T. Yokoyama, Y. Matsuura, M.A. Piatyszek, J.W. Shay Nat. Med. 1 (1995) 249.
[32] J.W. Shay, J. Natl. Cancer Inst. 91 (1999) 4.
[33] T. Hiyama, H. Yokozaki, Y. Kitadai, K. Haruma, W. Yasui, G. Kajiyama, E. Tahara, Virchows Arch. 434 (1999) 483.
[34] V. Kanjuh, M. Knežević, E. Živka, M. Ostojić, B. Beleslin, Arch. Oncol. 9 (2001) 3.
[35] M.A. Blasco, W.C. Hahn, Trends Cell Biol. 13 (2003) 289.
[36] S.H. Moolgavkar, A.G. Knudson Jr., J. Natl. Cancer Inst. 66 (1998) 1037.
[37] E.G. Luebeck, S.H. Moolgavkar, Proc. Natl. Acad. Sci. USA 99 (2002) 15095.
[38] J.W. Drake, B. Charlesworth, D. Charlesworth, J.F. Crow, Genetics 148 (1998) 1667.
[39] A.R. Thatcher, V. Kannisto, J.W. Vaupel, The Force of Mortality at Ages 80 to 120, Monographs on Population Aging, vol. 5, Odense University Press, Denmark, 1998.
[40] J.M. Robine, J.W. Vaupel, Exp. Gerontol. 36 (2001) 915.
[41] J.W. Vaupel, J.R. Carey, K. Christensen, T.E. Johnson, A.I. Yashin, N.V. Holm, I.A. Iachine, A.A. Khazaeli, P. Liedo, V.D. Longo, Yi Zeng, K.G. Manton, J.W. Curtsinger, Science 280 (1998) 855.
[42] R.A. Gatenby, P.K. Maini, Nature 421 (2003) 321.