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MINI-REVIEW

Two Types of Survival Curves of Different Lines of Progeric Mice

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Abstract—For most of their lifespan, the probability of death for many animal species increases with age. Gompertz law states that this increase is exponential. In this work, we have compared previously published data on the survival kinetics of different lines of progeric mice. Visual analysis showed that in six lines of these rapidly aging mutants, the probability of death did not strictly depend on age. In contrast, ten lines of progeric mice have survival curves similar to those of the control animals, that is, in agreement with Gompertz law, similar to the shape of an exponential curve upside down. Interestingly, these ten mutations cause completely different cell malfunctions. We speculate that what these mutations have in common is a reduction in the lifespan of cells and/or an acceleration of the transition to the state of cell senescence. Thus, our analysis, similar to the conclusions of many previously published works, indicates that the aging of an organism is a consequence of the aging of individual cells.

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Since the mid-nineties, Vladimir Petrovich Skulachev has worked a lot on various aspects of the aging process. Certainly, there was some synergy between his work on the theory of phenoptosis and his medically important project on Skulachev ions. There were many articles on the topic of aging, a book, there were several conferences. There were seminars on Thursdays. Once he is gone, interest in the basic aspects of aging has somehow faded in our institute. I take this opportunity to address the readers of the journal Biochemistry (Moscow), the participants of those seminars: should we resume Thursday's seminars on gerontology? Are all our common intellectual efforts on the topic of aging already in the past?

Of course, he and I discussed the issues of aging not only at seminars, but also at home, well, or on a walk with the dog. I miss these conversations. I think he would be interested in one curious fact that came to light in the process of reading literature on rapidly aging mice.

Fedor

INTRODUCTION

Mice with mutations that cause accelerated aging are widely used in laboratory practice. In particular, this is done so that experiments on the lifespan of mice do not take too much time. It is important to distinguish progeric mutations from mutations that simply shorten the lifespan of an animal. Progeric animals are those, whose life expectancy is significantly lower than the control ones, and at the same time, with age, they exhibit typical signs of aging, such as kyphosis, atrophy of fat and muscle tissue, cardiomyopathy, and a number of others (see review [1]). Oddly enough, the set of these traits does not include the shape of the mouse survival curve. It is well known that the probability of death, for the most of the lifespan, increases with age according to an exponential relationship. This is Gompertz law, which governs the survival kinetics of mice, humans, and many other living beings (see review [2]). In this work, we tried to determine

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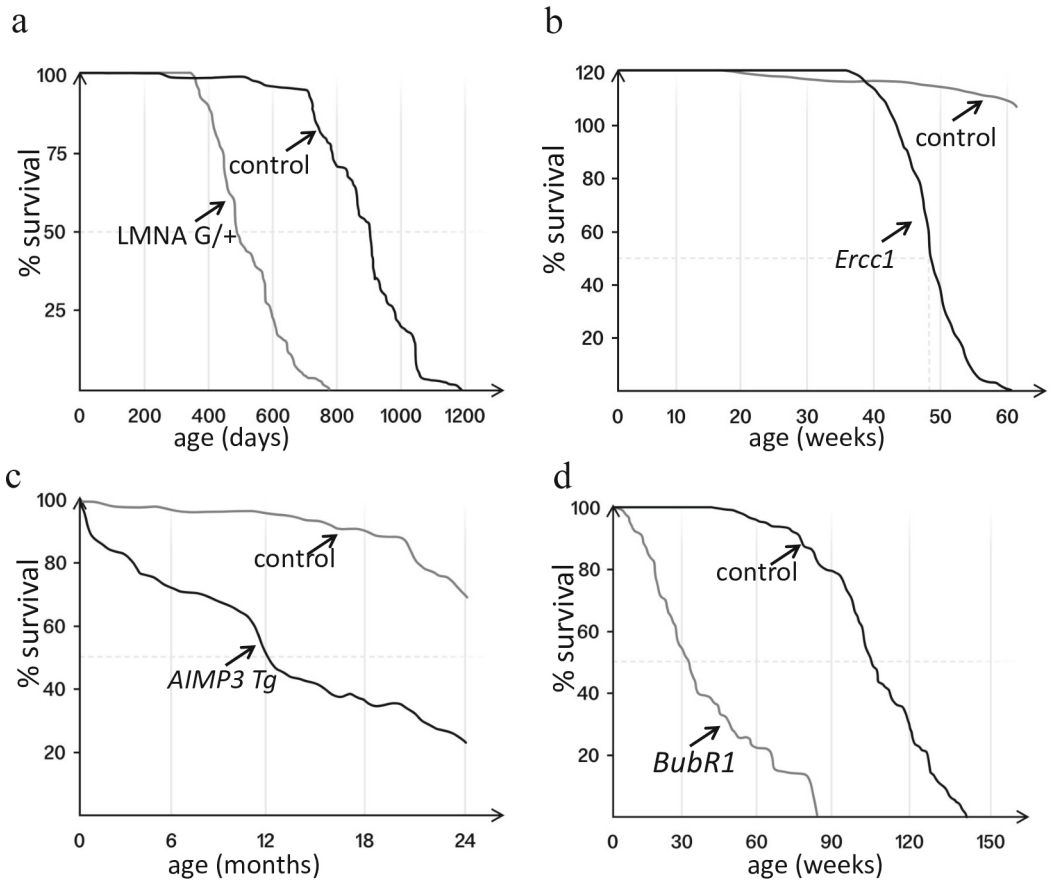

Two types of survival curves of progeric mice. Panels (a) and (b) show the curves similar to those of control animals. The curves in panels (c) and (d) are visually different from those presented in panels (a) and (b). The graphs are based on data from the works cited in the text.

which of the progeric mouse strains have (or are similar to) the inverted exponential shape of their survival curves, according to Gompertz law.

SURVIVAL CURVES OF PROGERIC MICE

Visual analysis of the shapes of the curves showed that they are of two types. One type of curve is similar to that of control mice, that is, apparently consistent with Gompertz's law. The second type of curves differs significantly from the first. It can be assumed that in these progeric mice the probability of death does not strictly depend on age. Figure (a and b) shows the examples of survival curves of the first type; figure (c and d) – the ones of the second type. Graphs represent: a) the survival curve of the LmnaG608G mutant; b) Ercc1$^{-/-}$ mutant; c) BubR1H/H mutant; d) AIMP3Tg mutant. The graphs were made based on the data presented in [3-6], respectively.

Table shows the majority of progeric mouse strains used in laboratory practice (see table 5.2 of the review [1]). According to the results of the visual analysis, these lines are divided into two groups: those whose survival curves are similar to the curves in figure (a and b) and those that are similar to those of figure (b and d). As can be seen from table, the survival curves of ten mutant lines are similar to those of control mice, as in figure (a and b, left column).

It is noteworthy that the mutations presented in the left column of table are of a completely different nature. They affect lamin A, nuclear DNA repair, mitochondrial DNA replication, protection from oxidative stress, histone deacetylation, tumor growth suppression. However, these very different interventions in cell physiology apparently have a very similar result at the organismal level: acceleration of aging kinetics in agreement with Gompertz law. How can this be explained? It is possible that all of these mutations, each in its own unique way, either reduce the lifespan of cells or accelerate the transition to a state of senescence. Indeed, it is well known that the tissue composition of organs changes with aging. For example, in skeletal muscles, myofibrils undergo atrophy and are then replaced by cells of adipose and connective tissue. In addition, in various tissues, the proportion of cells in the senescence state increases with age.

Mutations that cause accelerated aging in mice and the functions of the proteins encoded by the mutated genes

Progeric mice with the survival curves of similar shapes to the control animals	Progeric mice without visual dependency of death probability on the age
Lmna^{G608G}, lamin A, structural protein of nuclear envelope	*ku86*$^{-/-}$, recombination, double strand DNA break reparation
Xpd$^{-/-}$, DNA repair	*top3B*$^{-/-}$, topoisomerase
Ercc1$^{-/-}$, DNA repair	*BubR1*$^{h/h}$, mitotic checkpoint
PolgA$^{(mut)}$, mitochondrial DNA polymerase	*Terc1*$^{-/-}$*Atm*$^{-/-}$, telomere maintenance
Sod1$^{-/-}$, superoxide dismutase	*Sirt1*$^{-/-}$, deacetylation of histones
MsrA$^{-/-}$, methionine sulfoxidereductase	AIMP3Tg, tumor suppressor
p62$^{-/-}$, adaptor protein, autophagy, and oxidative stress	–
Mtr$^{-/-}$, telomerase	–
Sirt6$^{-/-}$, deacetylation of histones	–
p53$^{+/m}$, tumor suppressor	–

In other words, this observation provides further evidence that the primary cause of aging is the aging of individual cells, and not, for example, age-related changes in cell–cell interactions. The fact that progeric mutations shorten the lifespan of cultured cells is shown for at least two mutations presented in the left column of table. There is evidence that the aging of primary fibroblasts collected from patients with progeria caused by a mutation in lamin A occurs faster than in the control cells [7]. The same is observed in blood cell precursors (hematopoetic progenitors) from progeric mice with a knockout *Ercc1* (DNA repair) gene [8]. These two studies examined so-called replicative aging.

It should be noted that there are two types of experimental models of the aging of cultured cells: replicative and chronological. Most of the work in this area is devoted to replicative aging. Thus, it was shown that the number of divisions of primary fibroblasts is limited by the Hayflick limit. Chronological aging is due to the fact that after reaching the monolayer state, cell division stops, and after some time the cells begin to die. Both models have their limitations, but are successfully used to search for geroprotectors [9].

Finally, one can ask: can geroprotectors or genetic interventions change the type of survival curve of progeric mice? We were unable to find examples of the transformation of a curve of the first type (visually obeying the Gompertz law) into a curve of the second type. For example, the mitochondrially targeted antioxidant SkQ1 significantly increases the lifespan of PolgA(mut) mice, but the shape of the survival curve does not change ([10], Fig. 9). Curves of the second type can change. Thus, the deletion of p21 gene, whose expression is activated by DNA damage, prolongs the life of mice with the deletion of telomerase Terc1. In this case, the shape of the survival curve becomes visually similar to an inverted exponential ([11], Fig. 1).

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REFERENCES

1. Liao, C.-Y., and Kennedy, B. K. (2014) Mouse models and aging: longevity and progeria, *Curr. Top. Dev. Biol.*, **109**, 249-285, doi: 10.1016/B978-0-12-397920-9.00003-2.
2. Gavrilov, L. A., and Gavrilova, N. S. (2015) New developments in the biodemography of aging and longevity, *Gerontology*, **61**, 364-371, doi: 10.1159/000369011.
3. Cabral, W. A., Tavarez, U. L., Beeram, I., Yeritsyan, D., Boku, Y. D., Eckhaus, M. A., Nazarian, A., Erdos, M. R., and Collins, F. S. (2021) Genetic reduction of mTOR extends lifespan in a mouse model of Hutchinson-Gilford Progeria syndrome, *Aging Cell*, **20**, e13457, doi: 10.1111/acel.13457.

4. Vermeij, W. P., Dollé, M. E. T., Reiling, E., Jaarsma, D., Payan-Gomez, C., Bombardieri, C. R., Wu, H., Roks, A. J. M., Botter, S. M., van der Eerden, B. C., Youssef, S. A., Kuiper, R. V., Nagarajah, B., van Oostrom, C. T., Brandt, R. M. C., Barnhoorn, S., Imholz, S., Pennings, J. L. A., de Bruin, A., Gyenis, Á., Pothof, J., Vijg, J., van Steeg, H., and Hoeijmakers, J. H. J. (2016) Restricted diet delays accelerated ageing and genomic stress in DNA-repair-deficient mice, *Nature*, **537**, 427-431, doi: 10.1038/nature19329.
5. Wijshake, T., Malureanu, L. A., Baker, D. J., Jeganathan, K. B., van de Sluis, B., and van Deursen, J. M. (2012) Reduced life- and healthspan in mice carrying a mono-allelic BubR1 MVA mutation, *PLoS Genet.*, **8**, e1003138, doi: 10.1371/journal.pgen.1003138.
6. Oh, Y. S., Kim, D. G., Kim, G., Choi, E.-C., Kennedy, B. K., Suh, Y., Park, B. J., and Kim, S. (2010) Downregulation of lamin A by tumor suppressor AIMP3/p18 leads to a progeroid phenotype in mice, *Aging Cell*, **9**, 810-822, doi: 10.1111/j.1474-9726.2010.00614.x.
7. Goldman, R. D., Shumaker, D. K., Erdos, M. R., Eriksson, M., Goldman, A. E., Gordon, L. B., Gruenbaum, Y., Khuon, S., Mendez, M., Varga, R., and Collins, F. S. (2004) Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome, *Proc. Natl. Acad. Sci. USA*, **101**, 8963-8968, doi: 10.1073/pnas.0402943101.
8. Prasher, J. M., Lalai, A. S., Heijmans-Antonissen, C., Ploemacher, R. E., Hoeijmakers, J. H. J., Touw, I. P., and Niedernhofer, L. J. (2005) Reduced hematopoietic reserves in DNA interstrand crosslink repair-deficient *Ercc1* mice$^{-/-}$, *EMBO J.*, **24**, 861-871, doi: 10.1038/sj.emboj.7600542.
9. Khokhlov, A. N., and Morgunova, G. V. (2017) Testing of geroprotectors in experiments on cell cultures: pros and cons, in *Anti-Aging Drugs: From Basic Research to Clinical Practice* (Vaiserman, A. M., ed) Royal Society of Chemistry, p. 53-74, doi: 10.1039/9781782626602-00051.
10. Shabalina, I. G., Vyssokikh, M. Y., Gibanova, N., Csikasz, R. I., Edgar, D., Hallden-Waldemarson, A., Rozhdestvenskaya, Z., Bakeeva, L. E., Vays, V. B., Pustovidko, A. V., Skulachev, M. V., Cannon, B., Skulachev, V. P., and Nedergaard, J. (2017) Improved health-span and lifespan in mtDNA mutator mice treated with the mitochondrially targeted antioxidant SkQ1, *Aging (Albany NY)*, **9**, 315-339, doi: 10.18632/aging.101174.
11. Choudhury, A. R., Ju, Z., Djojosubroto, M. W., Schienke, A., Lechel, A., Schaetzlein, S., Jiang, H., Stepczynska, A., Wang, C., Buer, J., Lee, H.-W., von Zglinicki, T., Ganser, A., Schirmacher, P., Nakauchi, H., and Rudolph, K. L. (2007) Cdkn1a deletion improves stem cell function and lifespan of mice with dysfunctional telomeres without accelerating cancer formation, *Nat. Genet.*, **39**, 99-105, doi: 10.1038/ng1937.