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Editorial

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Complex molecular networks promote longevity

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Abbreviations: DNA, deoxyribonucleic acid; ROS, reactive oxygen species

Editorial

People have always tried to halt ageing and to get closer to immortality. Basic healthcare and medical advances in wealthier countries have advanced lifespan and for the first time in human history a flourishing increase in the number of elderly people is much more expected than a boom in the number of children under the age of five. Behind this perspective the serious problem of people living longer but not healthier lies and raises major concerns in the field of Biomedicine. The long-standing struggle with age-associated chronic conditions, often many at once, will definitely continue. Ageing unavoidably leads to a drop in physical performance, disturbances in the overall physiology, steady senescence and finally to death. And though it is deeply rooted in our conscience that this is an unavoidable process we should not forget that there are organisms that exhibit negligible senescence and have a very prolonged lifespan. Species like the red sea urchin, some turtles, the naked mole rat and several others are examples for long living organisms and commonly are under extensive studies in order to reveal the most intimate molecular and cellular mechanisms which permit them to live longer. To understand the ability to delay the onset of ageing and moreover to find the mechanisms for combating age-associated diseases like cancer, dementia, respiratory disease, heart disease, etc. has been and always will be a good motivation for many scientific endeavours in the field.

Ageing is complicated and very individual. It is believed that almost all cellular processes take part in it. Some of the common characteristics of ageing are genome instability, telomere shortening, mitochondrial dysfunction and loss of proteostasis.[1] Among these mechanisms several emerge as key regulators of cellular senescence and organismal ageing and therefore have attracted more scientific attention. For example huge amount of data have been collected on the connection between ageing and genome instability, ROS production, DNA damage, disordering of mitochondria and telomere attrition. By using the power of data mining Kogan et al.[2] have recently developed a mathematical model which was able to shed light on the phenomenon of negligible senescence. The model shows that lack of ageing in some organisms is due mostly to changes in the stability of their genome networks and also due to alterations in the potential of DNA repair mechanisms. Moreover, the high quality and constancy in the functions of these mechanisms unambiguously lead to a relative insusceptibility to stress. This is surprising in the sense that stress has always been thought to be one of the major culprits for ageing.[3,4] In the discussed mathematical model the authors point out that long-lived organisms possess exceptionally stable gene expression networks which could be due to a steadier DNA repair system.[2] The proposed mathematical model is tested by previously published experimental data on *Drosophila* fruit flies put on normal and on calorie-restricted diet (calorie-restricted diet is associated with prolonged lifespan in *Drosophila*).[5] Authors have observed increased deviation in the flies' transcriptome with age. Notably, according to the mathematical model calorie-restricted and normally fed flies aged in similar way but at different rates. What the authors argue[2,6] is that probably there are two distinct classes of ageing in regard to the dynamics of the process of growing old. The first type is characterized with high DNA repair rates and low gene network connectivity which leads to age-independent mortality. The authors stress on the fact that this is exactly what is generally seen in long-lived organisms. If, however, the repair mechanisms are weak and there is instability in the gene regulation connectivity it appears that this leads to accumulation of errors in the genome and therefore to an increased rate of ageing.

Understandably, a curious question arises here. It is very important to know where, i.e. in which cellular compartments, or to which particular cellular functions to look for the roots of ageing and correspondingly for the mechanisms for prolonging life. We believe that mathematical models that discus and moreover predict important cellular processes bring novel ways of looking at the mechanisms of cellular processes like ageing and longevity and unequivocally can provoke different experimental approaches in the field. Two very important phenomena sit in the centre of long life and ageing and these are the genome stability and the quality of DNA repair mechanisms. Apparently, the dynamics of DNA repair mechanisms depends on the stable networks of gene expression because all necessary factors for efficient DNA repair have to be extensively expressed and moreover have to be in stoichiometric ratios for the powerful execution of the repair process.

On the other hand, gene expression is attributed to the genome organization in chromatin in the nucleus. Chromatin structure is a major epigenetic mechanism and thus is considered to be a central player in the processes of maintaining genome stability, regulating gene expression and potentiating DNA repair. Therefore, when processes like ageing are considered it is advisable to look at the changes in chromatin organization and moreover in its dynamics. Strangely enough, the transformations of chromatin structure during ageing are not well studied. This lack of information is especially true if we refer to the higher-order chromatin organization which apparently is the main guardian of genome stability. Nevertheless, it is well known that when the cells age a good part of the histones disappears which inevitably causes disruption of the higher-order

chromatin organization.[7,8] Indeed, disappearance of the 30 nm fibre and disturbance in the loop organization (which represents the higher-order structuring of chromatin) has been recently shown for old yeast cells.[9] It has been proven that cells which have completely disordered chromatin organization due to a mutation in the gene for the linker histone exhibit premature ageing phenotypes and genome instability which result in premature death of the cells in comparison to the control ones. It is not surprisingly, therefore, to understand why old cells and their genomes are more susceptible to stress conditions as the mathematical model of Kogan et al.[2] suggests.

We agree that mathematical models like this one are simplistic and are built "on the basis of very generic assumptions" as the authors state. Therefore, more experimental data are needed to describe the full spectrum of connections and networks in the process of ageing. It is more than obvious that gene expression, DNA repair and chromatin as a guardian of genome stability are in the basis of ageing and organismal lifespan. And knowing the complex genetic interactions in detail during the timeline of ageing could bring invaluable insights of the most intricate mechanisms of growing old. This could possibly allow us to manipulate them so to prolong life and simultaneously to minimize the physical disabilities associated with the age.

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Conflict of interest

Author declares that there is no conflict of interest.

References

1. Lopez-Otin C, Blasco MA, Partridge L, et al. The Hallmarks of Aging. *Cell*. 2013;153(6):1194–1217.
2. Kogan V, Molodtsov I, Menshikov LI, et al. Stability analysis of a model gene network links aging, stress resistance, and negligible senescence. *Scientific reports*. 2015;5:13589.
3. Cooke MS, Evans MD, Dizdaroglu M, et al. Oxidative DNA damage: mechanisms, mutation, and disease. *FASEB Journal: official publication of the Federation of American Societies for Experimental Biology*. 2003;17(10):1195–1214.
4. Laun P, Pichova A, Madeo F, et al. Aged mother cells of *Saccharomyces cerevisiae* show markers of oxidative stress and apoptosis. *Molecular microbiology*. 2001;39(5):1166–1173.
5. Pletcher SD, Macdonald SJ, Marguerie R, et al. Genome-Wide Transcript Profiles in Aging and Calorically Restricted *Drosophila melanogaster*. *Current biology*. 2002;12(9):712–723.
6. Kogan N, Tucker J, Porter M. Extending the Human Life Span: An Exploratory Study of Pro- and Anti-Longevity Attitudes. *International journal of aging & human development.* 2011;73(1):1–25.
7. Dang W, Steffen KK, Perry R, et al. Histone H4 lysine 16 acetylation regulates cellular lifespan. *Nature*. 2009;459:802–807.
8. Garinis GA, van der Horst GT, Vijg J, et al. DNA damage and ageing: new-age ideas for an age-old problem. *Nature cell biology*. 2008;10:1241–1247.
9. Uzunova K, Georgieva M, Miloshev G. Saccharomyces cerevisiae Linker Histone—Hho1p Maintains Chromatin Loop Organization during Ageing. *Oxidative medicine and cellular longevity*. 2013;437146.

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