Open Access Journal of
Gerontology & Geriatric Medicine
ISSN: 2575-8543

Research Article
Volume 7 Issue 2 - March 2023
DOI: 10.19080/OAJGGM.2023.07.555706

OAJ Gerontol & Geriatric Med

Relation of Known Hallmarks of Aging to the Ontogenesis Program

Lev Salnikov*

University of Anti CA Biomed, USA

Submission: March 22, 2023; **Published:** March 31, 2023

***Corresponding author**: Lev Salnikov, Anti CA Biomed, USA

Abstract

A brief assessment of the current state of the use of Hallmarks of aging is given in the article. It is noted that the biological clock based on registration of DNA methylation process is only a statistical indicator and has no direct connection to the known mechanisms of aging, reflecting only the fact of genome regulation during ontogenesis. In other words, the process of genome methylation is not the leading program, but rather it fixes the result of the main program of ontogenesis. The same problems are inherent to aging markers based on registration of changes in RNA synthesis levels in different genes. In our opinion, the Hallmarks of aging should primarily be connected with or directly reflect the most fundamental bases and processes which are universal for any organisms. When analyzing the data on Hallmarks of aging, the greatest attention is paid to the late stages of ontogenesis. We believe that the main period of development is the stage of ontogenesis intended for physical growth and reaching sexual maturity. This is the period when the ontogenetic regulatory network of the organism stops its growth by the time it reaches reproductive period, triggering the cascade of processes leading to aging. The article briefly describes and shows the perspectives for using the "infrastructural hypothesis" for understanding the role of ontogenesis program in aging processes. From our point of view, the indicators we use in our "infrastructural" hypothesis are not only biologically justified but also prospective as Hallmarks of aging.

Keywords: Aging; Hallmarks of Aging; Ontogenesis Program; Functional Genome Groups; Methylation

Introduction

This paper presents a brief review of the main Hallmarks of aging we have today and the results obtained using them. To this day, the methods of measuring biological age have been well developed. A number of "biological clocks" indicating individual biological age have been created. Although we can see the arrows indicating age on such clocks, the mechanism that drives them is still hidden from us. The main question is still the connection of Hallmarks of aging with the mechanisms of aging and ontogenesis. The main question for gerontology - what is the cause of aging - is still a mystery, making it difficult to assess the Hallmarks of aging used in this phenomenon.

Currently, two main types of biomarkers are used to study aging and assess age. These are epigenetic markers, represented by the expression of gene methylation and various coordinated gene production clusters. Their parameters correlate well with age both in experimental animals and humans [1]. Consideration of the main Hallmarks of aging is useful as a unifying perspective, but how useful it is as an explanatory paradigm remains a question. The importance of Hallmarks of aging for understanding the underlying causes of aging in the way that a scientific paradigm or unifying theory should do remains a question [2].

DNA methylation, which affects chromatin state and gene expression, is one of the most studied genomic regulatory processes today [3,4]. The peculiarities of the regulatory function of methylation continue to be studied, but there is no doubt about the connection of this process with ontogenetic development and aging [5,6]. The works linking methylation to biological age in Mammalia are the most widespread in this direction [7-10]. The undoubted connection between methylation and aging processes provides an opportunity for experimental verification of various approaches to this problem. Data on the correlation between the methylation profile and biological age are also widely used as an efficiency criterion in works aimed at rejuvenation of organismal cells [11]. When assessing the large number of works devoted to genome methylation, the main conclusion is that this process is multidirectional.

Epigenetic regulation relates both to the genes themselves and the histone proteins that regulate their accessibility; its level behaves differently in different genes - it increases in some genes and decreases in others. Data on genome methylation can show biological age accurately enough, but as a statistical indicator it has no direct connection to the known mechanisms of aging, reflecting only the fact of genome regulation during ontogenesis. Here we

should note the work in which the authors make an attempt to link the methylation level with thermodynamic processes reflecting the fundamental basis of the organism's functioning [12].

In one of our works [13] we analyzed the appearance of coordinated variance changes with age, indirectly indicating an external influence on methylation indices, possibly related to the action of the ontogenesis program. We can conclude that many modern studies devoted to the analysis of genome methylation have never provided a clear answer to the question of the functional role of the methylation process itself [14-17]. It is possible that the process of genome methylation does not programs, but rather fixes the result of the ontogenesis program. The works on age-related changes in the transcriptome analyzed the changes that occur with RNA production during life. A gradual decrease in production during life was found, accompanied by multidirectional changes in RNA production levels in individual gene groups [18-20].

Summarizing the currently available data on age-associated reduction in gene expression, it can be argued that it contributes to a progressive decline in cellular functions. Understanding the mechanisms governing transcriptome aging is essential for determining the underlying aging mechanisms [21-30]. Simultaneous changes in methylation and RNA production reflect the work of the ontogenesis program, associated with differentiation and development of cell functions in the organism. Here again we see more multidirectional changes, but not aging per se. As already mentioned, the connection between the processes of aging and ontogenesis is obvious, but two approaches should be distinguished here. Many authors proceed from the assumption that aging, as well as organism development, is controlled by the ontogenesis program. In our opinion, the presence of a separate program aimed at the development of organism aging is not evolutionarily reasonable and has not been experimentally confirmed. We take a different approach, from the point of view of which ontogenesis is the program for successful reaching maturity, and aging is a reasonable, from the species' point of view, side effect [31,32].

There are two stages in the ontogenetic program. The first stage during embryogenesis involves the sequential inclusion of genes necessary for cell differentiation and organism formation. The second stage beginning in the postnatal period is for physical growth and reaching sexual maturity. It is during this period that the ontogenetic regulatory network of the organism stops its growth by the time it reaches reproductive period, triggering the cascade of processes leading to aging. It is necessary to distinguish the main cause of aging and the mechanisms that trigger it. For this purpose, we use the "infrastructural hypothesis" that we have outlined in previous works [33,34]. We explain aging by the gradual redistribution of a limited amount of resources between two main tasks of the organism: its self-sustenance based on the function of the housekeeping gene (HG) group, the atlas of which is presented in the work of the authors group [35] and the functional differentiation provided by the integrative gene group (IntG) that constitutes most of the remaining genes.

We argue that an insufficient level of repair is the main cause of aging. Understanding exactly how this deficiency arises is our main goal. Our confirmation of the differences in RNA production in the studied functional groups of the genome suggests that there is a global mechanism of ontogenesis that affects the activity of these groups and, most importantly, their correlation. As was shown in our recent work [36], the implementation of the ontogenesis program naturally leads to an imbalance of activity between HG and IntG groups. In turn, such imbalance leads to insufficient provision of cellular functions with their infrastructure represented in the genome by the HG functional group and, as a result, to aging of the organism. This indicates that the positive ontogenetic regulation in the beginning is aimed at ensuring development and reproduction, and provided by the increased level of HG production subsequently disappears, inevitably leading to aging. Thus, the main conclusion of this work is the fact of asymmetric effect of ontogenetic regulators on the cellular infrastructure represented by the HG functional group in the genome. Determining the specific regulatory factors of this event is the main goal of our future work.

When studying aging, most researchers focus on age-related changes occurring in the organism at a later age. During this period various studied parameters reach their maximum differences from their normal values. Research focusing on changes occurring in the second half of ontogenesis are limited to the consequences of aging processes, ignoring their causes. Besides this, the data on aging trait dynamics in experimental animals at a later age have one more disadvantage. The animals participating in these experiments are sort of long-livers, with certain genetic features allowing them to reach the age limit for the species. Thus, the experimental groups have their own natural selection, which significantly changes the overall picture of the obtained results. In our opinion, this fact should not only be taken into account in the experimental work, but it should be studied separately.

Conclusion

To conclude, it should be noted once again that Hallmarks of aging indicators should primarily be connected with or directly reflect the most fundamental bases and processes, universal for any organisms. From our point of view the indicators we use in our "infrastructural" hypothesis are not only biologically grounded but also prospective signs of aging from the point of view of their understanding.

References

1. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G (2023) Hallmarks of aging: An expanding universe. Cell 186(2): 243-278.

2. Gems D, De Magalhaes JP (2021) The hoverfly and the wasp: A critique of the hallmarks of aging as a paradigm. Ageing Res Rev 70: 101407.

How to cite this article: Lev Salnikov. Relation of Known Hallmarks of Aging to the Ontogenesis Program. OAJ Gerontol & Geriatric Med. 2023; 7(2): 555706. DOI: 10.19080/OAJGGM.2023.07.555706

3. Dhar GA, Saha S, Mitra P, Nag Chaudhuri R (2021) DNA methylation and regulation of gene expression: Guardian of our health. Nucleus (Calcutta) 64(3): 259-270.

4. Lee HT, Oh S, Ro DH, Yoo H, Kwon YW (2020) The Key Role of DNA Methylation and Histone Acetylation in Epigenetics of Atherosclerosis. J Lipid Atheroscler 9(3): 419-434.

5. Ake T Lu, Zhe Fei, Amin Haghani, et al. (2021) Universal DNA methylation age across mammalian issues. Rxiv.

6. Ciccarone F, Tagliatesta S, Caiafa P, Zampieri M (2018) DNA methylation dynamics in aging: how far are we from understanding the mechanisms? Mech Ageing Dev. 174:3-17.

7. Horvath S, Raj K (2018) DNA methylation-based biomarkers and the epigenetic clock theory of aging. Nature Reviews Genetics. Nature Publishing Group.

8. Galkin F, Mamoshina P, Aliper A, De Magalhaes JP, Gladyshev V N, et al. (2020) Biohorology and biomarkers of aging: Current state-of-the-art, challenges and opportunities. Ageing Research Reviews. Elsevier Ireland Ltd.

9. Trapp A, Kerepesi C, Gladyshev VN (2021) Profiling epigenetic age in single cells. Nat Aging.

10. Porter HL, Brown CA, Roopnarinesingh X, Giles CB, Georgescu C, et al. (2021) Many chronological aging clocks can be found throughout the epigenome: Implications for quantifying biological aging. Aging Cell 20(11): e13492.

11. Chen Y, Luttmann FF, Schoger E, Scholer HR, Zelarayán LC, et al. (2021) Reversible reprogramming of cardiomyocytes to a fetal state drives heart regeneration in mice. Science 373(6562): 1537-1540.

12. Tarkhov AE, Denisov KA, Fedichev HO (2022) Aging clocks, entropy, and the limits of age-reversal. bioRxiv preprint.

13. Salnikov L, Goldberg S, Sukumaran P, Pinsky E (2022) DNA methylation meta-analysis confirms the division of the genome into two functional groups, J. Cell Sci. Ther.

14. Zhang L, Silva TC, Young JI, Gomez L, Schmidt MA, et al. (2020) Epigenome-wide meta-analysis of DNA methylation differences in prefrontal cortex implicates the immune processes in Alzheimer's disease.Nature communications 11(1): 6114.

15. Gruzieva O, Xu CJ, Yousefi P, Relton C, Merid SK, et al. (2019) Prenatal particulate air pollution and DNA methylation in newborns: an epigenome-wide meta-analysis. Environmental health perspectives 127(5): 057012.

16. Policicchio S, Washer S, Viana J, Iatrou A, Burrage J, et al. (2020) Genome-wide DNA methylation meta-analysis in the brains of suicide completers. Translational psychiatry (1): 69.

17. Lee M, Huan T, McCartney DL, Chittoor G, de Vries M, et al. (2022) Pulmonary function and blood DNA methylation: a multiancestry epigenome-wide association meta-analysis. American Journal of Respiratory and Critical Care Medicine 206(3): 321-336.

18. Santra M, Dill KA, De Graff AMR (2019) Proteostasis collapse is a driver of cell aging and death. Proc Natl Acad Sci USA 116(44): 22173-22178.

19. Meyer DH, Schumacher B (2021) BiT age: A transcriptome-based aging clock near the theoretical limit of accuracy. Aging Cell 20(3).

20. Stoeger T, Grant RA, McQuattie-Pimentel AC, et al. (2022) Aging is associated with a systemic length-associated transcriptome imbalance. Nat Aging.

21. Stegeman R, Weake VM (2017) Transcriptional Signatures of Aging. J Mol Biol 429(16): 2427-2437.

22. Lu JY, Simon M, Zhao Y, Ablaeva J, Corson N, et al. (2022) Comparative transcriptomics reveals circadian and pluripotency networks as two pillars of longevity regulation. Cell Metab 34(6): 836-856.e5.

23. Stoeger T, Grant RA, McQuattie-Pimentel AC, et al. (2022) Aging is associated with a systemic length-associated transcriptome imbalance. Nat Aging.

24. Ferreira M, Francisco S, Soares AR, Nobre A, Pinheiro M, et al. (2021) Integration of segmented regression analysis with weighted gene correlation network analysis identifies genes whose expression is remodeled throughout physiological aging in mouse tissues. Aging (Albany NY) 13(14): 18150-18190.

25. Anastasiadi D, Esteve-Codina A, Piferrer F (2018) Consistent inverse correlation between DNA methylation of the first intron and gene expression across tissues and species. Epigenetics & Chromatin.

26. Pearce K, Cai D, Roberts AC, Glanzman DL (2017) Role of protein synthesis and DNA methylation in the consolidation and maintenance of long-term memory in Aplysia. Elife 6: e18299.

27. Spainhour JC, Lim HS, Yi SV, Qiu P (2019) Correlation Patterns Between DNA Methylation and Gene Expression in The Cancer Genome Atlas. Cancer Inform 18:1176935119828776.

28. Zhang Y, Liu C, Cheng H, Tian S, Liu Y, et al. (2020) DNA methylation and its effects on gene expression during primary to secondary growth in poplar stems. BMC Genomics 21(1):498.

29. Sales AJ, Maciel IS, Suavinha ACDR, Joca SRL (2021) Modulation of DNA Methylation and Gene Expression in Rodent Cortical Neuroplasticity Pathways Exerts Rapid Antidepressant-Like Effects. Mol Neurobiol 58(2): 777-794.

30. Zhang D, Deng Y, Kukanja P, et al. (2023) Spatial epigenome–transcriptome co-profiling of mammalian tissues. Nature.

31. Salnikov L (2022) Aging is a Side Effect of the Ontogenesis Program of Multicellular Organisms. Biochemistry (Mosc) 87(12): 1498-1503.

32. De Magalhaes JP, Church GM (2005) Genomes optimize reproduction: aging as a consequence of the developmental program. Physiology (Bethesda) 20: 252-9.

33. Salnikov L, Baramiya MG (2020) The Ratio of the Genome Two Functional Parts Activity as the Prime Cause of Aging. Frontiers in Aging 1.

34. Salnikov L, Baramiya MG (2021) From Autonomy to Integration, From Integration to Dynamically Balanced Integrated Co-existence: Non-aging as the Third Stage of Development. Frontiers in Aging 2.

35. Hounkpe BW, Chenou F, de Lima F, De Paula EV (2021) HRT Atlas v1.0 database: redefining human and mouse housekeeping genes and candidate reference transcripts by mining massive RNA-seq datasets. Nucleic Acids Res 49(D1): D947-D955.

36. Salnikov L, Goldberg S, Rijhwani H, Shi Y, Pinsky E (2023) The RNA-Seq data analysis shows how the ontogenesis defines aging. Frontiers in Aging 4: 1-17.

How to cite this article: Lev Salnikov. Relation of Known Hallmarks of Aging to the Ontogenesis Program. OAJ Gerontol & Geriatric Med. 2023; 7(2): 555706. DOI: 10.19080/OAJGGM.2023.07.555706

DOI: 10.19080/OAJGGM.2023.07.555706

How to cite this article: Lev Salnikov. Relation of Known Hallmarks of Aging to the Ontogenesis Program. OAJ Gerontol & Geriatric Med. 2023; 7(2): 555706. DOI: 10.19080/OAJGGM.2023.07.555706