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Review Article

Perspectives for Using RNA Sequencing Analysis of the Genome to Understand the Mechanisms of Aging

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Abstract

This article provides a brief overview of recent results obtained using whole genome RNA-Seq of *Mus musculus* during their lifespan. In the works devoted to age-related changes of the transcriptome, a smooth decrease of its production with age was found. At the same time, multidirectional changes in the level of RNA production were found for separate groups of genes. The obtained data were characterized by a high level of the dispersion, which does not allow obtaining statistically significant results in most cases. As a promising research direction in this area, a brief review of our recently published article is presented. Using our approach of considering functional groups of the genome, results were obtained that allow us to advance our understanding of the mechanisms of aging. Changes in the age-related dynamics of RNA production occur during the reproductive period of life, which has the lowest actual mortality risk for *Mus musculus*. A trend toward a significant shift in between infrastructural and functional genes ratio occurred after the end of the reproductive period, coinciding with the onset of increased *Mus musculus* mortality. One of the tasks aimed at further study of proteome changes during aging is comparative analysis of proteome changes occurring simultaneously in different tissues of the organism. For each type of tissue there is a different ontogenetic program with its own maturation pathway. Thus the ontogenesis program of an organism is a sum of programs. Infrastructural deficiency arising during ontogenesis in one tissue accelerates this process in other tissues.

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Introduction

The relatively recent introduction of whole genome RNA sequencing in experimental animals has enabled gerontologists to conduct studies of proteome changes during life and has become one of the main pathways for investigating the fundamental mechanisms of aging. In the works devoted to age-related changes in the transcriptome, a smooth decrease in its production during life was found. Simultaneously, multidirectional changes in the level of RNA production were found for individual groups of genes [1-3]. Summarizing the currently available data on age-associated decrease in gene expression, it can be stated that it corresponds to a progressive decrease in cellular functions both in individual tissues and in the whole organism. Obviously, studying the causes and mechanisms that determine the aging transcriptome is necessary to understand the underlying mechanisms of aging [3-5]. Thus, although the available data have not yet shown striking results, it is clear that this line of research should be developed.

For us, the fundamental approach is that we consider not individual genes, but their ontogenetically determined and different in their role in the organism functional groups necessary both for the implementation of the ontogenesis program and for the normal functioning of the organism. We proceed from the assertion that insufficient level of repair is the main cause of aging. Understanding exactly how this deficiency arises is our main objective. The connection between ontogenesis and aging is obvious to us, in which aging itself is a by-product of the ontogenesis program. Based on our theoretical model based on the division of the genome into two functional groups [6], one of the main criteria for its verification is the question of whether the level of RNA synthesis and related resources are redistributed between the functional groups of genes we have identified - HG (a group of housekeeping genes responsible for the maintenance of cellular infrastructure) and IntG (a group of genes responsible for the functions of the organism) during ontogenesis. Our last article [7] is devoted to analyzing the ratio of their activity based on the results of RNA sequencing during ontogenesis. We were mainly interested in the reproductive age period, when the organism demonstrates the greatest resistance to external influences. At this time, changes occur, the consequence of which is aging, and in our work we will consider this period. In this work we set the following goal: using mathematical statistics to obtain results capable of verifying our assumptions about the relationship between ontogenesis and aging based on the analysis of the RNA synthesis database. In our work, we faced characteristics and limitations related to the database we used. The largely high "noise" of the data did not always allow us to obtain statistically significant answers, but we were able to see a number of trends in the data that indirectly support our hypothesis.

Let us highlight the established facts of our proposed theoretical justification of our hypothesis. Data analysis showed that the level of RNA production in HG and IntG genes had statistically significant differences (P-value <0.0001) during the whole observation period. During the observation period, statistically significant dynamics of RNA production decrease in the HG group in contrast to IntG was

determined (p-value = 0.0045). The obtained decrease in the level of RNA production in the HG group for all tissues coincides exactly with the reproductive age in *Mus musculus* and falls within the period from 1 to 9 months and basically ends by the age of 15 months [8]. Comparing the data on the mortality rate of *Mus musculus* with the obtained results we note that their mortality rate starts to increase significantly from 18 months of age, exactly when the production of HG group genes reaches its minimum value. Starting from this age, the actual risk of mortality begins to increase, increasing more than two-fold by the age of 24 months [9,10]. Given that the database contains only 10 time points, it was possible to obtain statistically significant results on the slope of the curves (correlation with age) only for the combination. Less extended time segments showed only trends. Thus, the detected significant change in the HG/IntG ratio in the post-reproductive stage of ontogenesis indirectly confirms our hypothesis. This imbalance, in turn, leads to insufficient provision of cellular functions with their infrastructure represented in the genome by the functional group HG, which may trigger the whole cascade of changes leading to aging of the organism.

As we have indicated earlier [11-14], most researchers focus on age-related changes occurring in the body in late life. During this period, the various indices under study reach their maximum differences from their normal values. Studies focusing on changes occurring in the second half of ontogenesis are doomed to deal only with the consequences of aging processes, missing their causes. In addition, data on the dynamics of aging signs in experimental animals at late ages suffer from another drawback. The animals involved in these experiments are a kind of long-livers, with certain genetic features that allow them to reach the ultimate ages for the species. We observed a similar picture in our work, where we recorded a tendency for the HG level to rise in *Mus musculus* during the last period of their life. This result can be explained by the fact that the experimental groups undergo their own natural selection, which significantly changes the general picture of the obtained results. In our opinion, this fact should not only be taken into account in experimental work, but should be studied separately.

In conclusion, we note that the results of any analysis of the available data, and in our case it is the results of analyzing the level of RNA production, depend on a correctly posed question at the beginning of the study. We have demonstrated that the analysis of data obtained by RNA sequencing in terms of large functional groups of genes is one of the most promising, allowing further work in this direction. One of the tasks aimed at further study of proteome changes during aging is comparative analysis of proteome changes occurring simultaneously in different tissues of the organism [15,16]. Each type of tissue has its own ontogenetic program with its own pathway of maturation. Thus the ontogenesis program of an organism is a sum of programs. Infrastructural deficiency arising during ontogenesis in one tissue accelerates this process in other tissues. Thus, the study of RNA sequencing data obtained during the life of laboratory animals has great prospects for understanding the aging processes.

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Ethics Declarations

The author declares that he has no conflicts of interest. This article does not contain any studies involving human participants or animals performed by any of the authors.

References

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

2. Meyer DH, Schumacher B (2021) BiT age: A transcriptome-based aging clock near the theoretical limit of accuracy. Aging Cell 20: 13320.

3. Stoeger T, Grant RA, McQuattie-Pimentel AC, Anekalla KR, Liu SS, et al. (2022) Aging is associated with a systemic length-associated transcriptome imbalance. Nat Aging 2: 1191-1206.

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

5. 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: 836-856.

6. 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: 18150-18190.

7. Salnikov L (2023) Relation of Known Hallmarks of Aging to the Ontogenesis Program. OAJ Gerontol & Geriatric Med 7: 555706.

8. Brust V, Schindler PM, Lewejohann L (2015) Lifetime development of behavioural phenotype in the house mouse (*Mus musculus*). Front Zool 12: 17.

9. Gavrilova NS, Gavrilov LA (2015) Biodemography of old-age mortality in humans and rodents. J Gerontol A Biol Sci Med Sci 70: 1-9.

10. Kinzina ED, Podolskiy DI, Dmitriev SE, Gladyshev VN (2019) Patterns of Aging Biomarkers, Mortality, and Damaging Mutations Illuminate the Beginning of Aging and Causes of Early-Life Mortality. Cell Rep 29: 4276-4284.

11. Salnikov L, Goldberg S, Rijhwani H, Shi Y, Pinsky E (2023) The RNA-Seq data analysis shows how the ontogenesis defines aging. Front Aging 4: 1143334.

12. Salnikov L, Baramiya MG (2020) The Ratio of the Genome Two Functional Parts Activity as the Prime Cause of Aging. Front Aging 1: 608076.

13. 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. Front Aging 2: 655315.

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

15. Srivastava A, Barth E, Ermolaeva MA, Guenther M, Frahm C, et al. (2020) Tissue-specific Gene Expression Changes Are Associated with Aging in Mice. Genomics Proteomics Bioinformatics 18: 430-442.

16. Yamamoto R, Chung R, Vazquez JM, Sheng H, Steinberg PL, et al. (2022) Tissue-specific impacts of aging and genetics on gene expression patterns in humans. Nat Commun 13: 5803.

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