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Review

Evidence from Meta-Analysis Demonstrating Functional Asymmetry of Genome Methylation

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ABSTRACT

Aging is increasingly understood as a continuation of ontogenesis rather than a consequence of damage accumulation. In this study, we reanalyze and reinterpret data obtained in our previous meta-analysis (Salnikov et al., 2022 preprint), which examined DNA methylation across human genes grouped by function. By dividing the genome into two functional categories-housekeeping genes (HG), responsible for cellular maintenance and integrative genes (IntG), responsible for specialized cellular functions-we demonstrate fundamental asymmetry in methylation dynamics. The results reveal significant differences in absolute methylation levels and age-related trajectories between these groups. Methylation in HG remains stable with age, while IntG shows a pronounced decline, particularly in promoter regions ($p < 0.0026$). Additionally, the variance of methylation in IntG decreases with age, indicating coordinated regulation rather than stochastic drift. This pattern suggests that the ontogenetic epigenetic program continues to act selectively on IntG genes throughout life, driving an imbalance in genomic regulation. We propose that this functional asymmetry underlies aging through persistent activation of developmental regulatory mechanisms. The reinterpretation of previously obtained data supports a model in which aging results from the continued implementation of the epigenetic program of ontogenesis, offering new directions for rejuvenation strategies aimed at resetting this program, including non-dividing cell auto cloning.

Keywords: Aging, Ontogenesis, Epigenetic program, DNA methylation

1. Introduction

Currently, most researchers studying aging attribute a leading role in this process to the epigenetic program of ontogenesis[1-4]. In this work, we focus our attention on the ontogenesis program itself, analyzing the main processes of its implementation. The epigenetic mechanisms by which the ontogenesis program is implemented are largely based on the process of DNA methylation, linking developmental biology and the biology of aging. However, despite the large number of studies devoted to this topic, it remains unclear why the implementation of the ontogenesis program ultimately leads to the aging of the organism. Epigenetic programs that determine which genes are active and which are silenced in each cell type regulate ontogenesis or the process of organism development from zygote to adult. During embryonic and early postnatal development, waves of methylation and demethylation shape cell identity by turning specific lineage-specific genes on and off. In other words, ontogenesis is the gradual implementation of an epigenetic program with DNA methylation as the central regulatory tool. In addition to chromatin modification, DNA methylation, primarily in CpG dinucleotides, is a key mechanism

for stable gene suppression[5]. After completing its development, the organism enters a relatively stable "maintenance" phase. However, methylation patterns are not static, as some methylation marks associated with development are not completely removed, remaining in the form of "epigenetic memory." In other words, the initiated epigenetic program of ontogenesis continues its work and age-related methylation shifts gradually change the established pattern of organism development. It is precisely at the end of the fertile period that significant changes occur in the level of DNA methylation, accompanied by significant shifts in gene production and cell metabolism[6,7]. Starting with the work of Horvath[8,9], who proposed a method for measuring the age of an organism based on data on predictable changes in DNA methylation in certain CpG sites, this method has gained great popularity[10-13]. Interestingly, many of these CpGs are located near developmental genes and homeobox (HOX) genes, which are key regulators of ontogenesis[14]. This suggests that aging is not a random erosion of methylation, but a regulated, predictable continuation of the ontogenetic trajectory of methylation. In other words, "epigenetic age" is largely determined by how far the ontogenetic methylation program has progressed or deviated. However, while in the early stages of ontogenesis, its epigenetic program directly reflects the course of the organism's development, in the "maintenance" phase that follows sexual maturity, changes in methylation patterns are largely random and not directly related to the age of the organism. A wealth of evidence suggests that aging reflects the late-life manifestations of developmental programs interacting with stochastic drift and damage[15]. Methylation and transcriptomics clocks may be accurate, but age prediction alone cannot distinguish programmed ontogenesis from accumulated variability. Modeling shows that clocks can arise solely from stochastic variations, even in response to interventions such as CR and reprogramming, which cautions against over interpreting clocks as direct indications of a developmental "program"[16]. The main question about the cause of the destructive action of the continuing epigenetic program of ontogenesis remains unclear. In this work, we will attempt to answer it by analyzing methylation activity during ontogenesis and its relationship to the activity of the cellular genome and metabolic processes. The specific features of the epigenetic program of ontogenesis in the post-reproductive period and related to aging processes are demonstrated by the data we presented earlier, the analysis of which we will show below[17]. The main difference between the data presented here and other studies of age-related changes in methylation levels is that this study compared age-dependent methylation levels in two functional groups of the genome that we identified. These groups were genes representing "home genes" (HG)[18] or in other words, the cellular infrastructure and a group of genes that determine specialized cellular function (IntG). A more detailed justification for this functional division of the cellular genome is presented in our previous works[19-20].

1.1. Meta-analysis data on methylation levels depending on age in HG IntG gene groups

We conducted a meta-analysis of human genome methylation data, focusing on 100 genes divided into functional groups: HG, responsible for maintaining vital functions and integrative genes IntG. Significant differences in absolute methylation levels were found between the HG and IntG groups ($p<0.0001$, t-test). In addition, genes belonging to the IntG group showed a reliable decrease in methylation with age, while HG levels remained constant. In our study, we separately assessed the methylation levels of both gene bodies and promoters. Thus, in the HG group, the average methylation of gene bodies was 0.3560 and that of promoters was 0.2402 ($p<0.0001$), while in the IntG group, the average methylation of gene bodies was 0.6179 and that of promoters was 0.5553 ($p<0.0001$). Promoter methylation showed a more pronounced decrease in IntG compared to HG ($p=0.0026$), as clearly **(Figure 1)**.

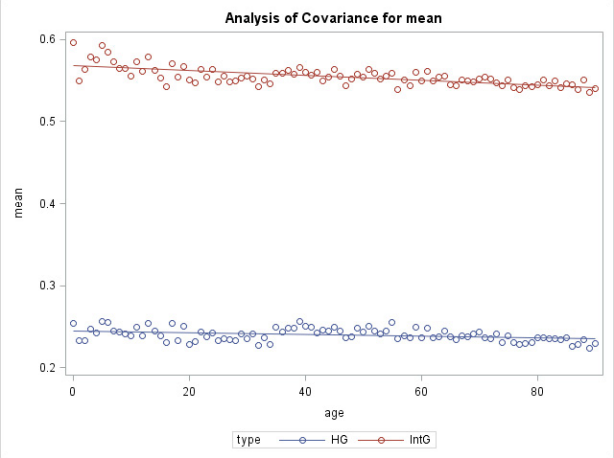

Figure 1: Age-related changes in the methylation level of gene promoters in the HG and IntG groups. The X-axis represents age in years. The Y-axis represents the level of methylation.

The study also examined the variation in methylation data within identified gene groups. The mean standard deviation (STD) for IntG was 0.3363 and for HG was 0.2932 ($p<0.0001$), with the STD for IntG decreasing with age, indicating a coordinated reduction in methylation variation ($p=0.0454$). In contrast, variation in HG remained stable, confirming its ontogenetic stability.

2. Discussion

Analysis of the data presented above gives a significantly different picture of age-related changes in DNA methylation than data showing the total indicators of this process[21-23]. It was precisely our earlier division of the cellular genome into two functional groups-HG and IntG that allowed us to see new data on genome methylation. As the results show, the level of methylation in the HG functional group remains virtually stable during the observation period and the dispersion of data remains at the same level. In turn, the methylation level of the IntG gene group steadily decreases with age, especially in promoter genes, which corresponds to data on a global decrease in methylation levels obtained by other authors[24-27]. The currently available data on the relationship between methylation levels and gene biosynthesis are contradictory, which does not allow us to draw a clear conclusion about the increase in IntG gene expression due to a decrease in their methylation levels with age[28-32]. By investigating the amount of dispersion of methylation level data in the functional groups we identified, we wanted to find out how this indicator, which reflects fluctuations in gene regulation, changes. It was found that the dispersion of gene promoter methylation data in the IntG group differs significantly from that in the HG group and decreases with age, repeating the downward trajectory of the methylation process itself. The identified coordinated decrease in the dispersion of promoter methylation values with age indirectly indicates the presence of specific properties inherent only to the IntG group. According

to the Information Theory of Aging[33,34], which assumes uniform "wear" of epigenetic marks over time, associated with both stochastic causes and DNA repair processes that disrupt the existing distribution of gene methylation. According to these ideas, these processes should be similar in all genes in the genome. Our data clearly contradict this assumption. Not only did we obtain direct confirmation of the validity of the functional division of the cellular genome into two functional groups, but we also obtained grounds for asserting that the epigenetic program of ontogenesis has a targeted effect on only one of them, namely IntG. Analyzing the level of mRNA production in the functional groups of the genome we isolated, we obtained confirmation that with age, their production increases in the IntG group with a simultaneous decrease in the HG group[35,36]. Such "one-sided" regulation by the epigenetic program of ontogenesis undeniably creates the conditions for positive feedback, allowing for increased consumption of cellular resources for the production of IntG genes. This shift in the balance of resource consumption is facilitated by the fact that IntG genes receive a fairly constant stimulating effect from the body's neuroendocrine system, aimed at maintaining their functions[37]. In addition, the constant synthesis of specialized proteins increases the stability of the mRNA encoding them, directing and amplifying the shift in the consumption of cellular resources in their favor, using positive feedback in the biosynthesis process[38,39]. The presented picture of age-related changes in epigenetic regulation confirms our assumption about the main causes of aging[40] and explains the emergence of shifts in the epigenetic program of ontogenesis regulation. The data presented also show the promise of rejuvenation work based on "restarting" the epigenetic regulation program of ontogenesis[41-43]. In particular, the direction of rejuvenation based on autocloning[44], which we proposed earlier. Here we mean the artificial initiation of cell division, during which one of the daughter nuclei is not formed, leaving the cell in its original state without physical division and receiving a renewed nucleus. If successful, this approach opens up the possibility of "restarting" the epigenetic program of ontogenesis, allowing not only to eliminate regulatory asymmetry, but also to renew postmitotic cells without disrupting their structure.

3. Author Contributions

LS: Writing–original draft, Writing–review and editing.

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5. Conflict of Interest

Author LS, employed by AntiCa Biomed, declares no conflict of interest.

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