Aging, disease and transcriptomic liberality derived from human RNA-seq data

Norichika OGATA[1,2]

[1]Nihon BioData Corp., Kawasaki, Kanagawa, Japan
[2]Graduate School of Engineering, Osaka University, Yamadaoka, Osaka, Japan

20-26-7, ShimoSakunobe, Kawasaki, Kanagawa, 213-0012, Japan
Email address: norichik@nbiodata.com

Abstract

Human tissues progressively lose their function during aging. In the context of cellular differentiation and dedifferentiation, this process can be quantified as decrease and increase in liberality, defined as transcriptome diversity. In this study, we collected over 5,000 human transcriptome datasets and measured their liberality. We found a positive correlation between aging and liberality, as well as between disease status and liberality.

Introduction

The human aging process has been investigated from multiple perspectives. At the cellular level, telomere shortening (Goldstein, 1990) and increasing spatial transcriptomic diversity at the individual level have been reported (Ma et al., 2024). Phenotypic observations indicate that human tissues lose their function with age, leading to the prediction that human cells undergo dedifferentiation during aging. To examine this hypothesis, we analyzed more than 5,000 RNA-seq datasets derived from human tissues across various ages (Shokhirev & Johnson, 2021). The metadata included age, sex, health condition, and batch information (Batch effects reflect technical conditions of the samples, such as tissue source and sampling time. Generally, RNA-seq data may be affected by surgical procedures, cell lysis, RNA extraction, library preparation, sequencing pool construction, and variation across sequencing instruments). We have no interest in sex. We measured liberality in these RNA-seq datasets and analyzed the effects of age and health condition on liberality.

Maternals and Methods

Raw count data derived from RNA-seq experiments were obtained as supplemental data from a previous study (Shokhirev & Johnson, 2021). Liberality was measured as previously described (Ogata et al., 2012, 2015). The contributions of metadata factors to liberality were analyzed using linear regression with the lm package in R (R Core Team, 2024). The model evaluated the effects of age and health condition (healthy vs. diseased) on liberality.

Results and Discussion

We measured liberality, defined here as the α-diversity of intracellular transcriptomes, in RNA-seq data collected from human tissues and compared it with sample metadata. Both

age and health status showed positive correlations with liberality. The age-dependent increase in liberality was greater in samples classified as healthy than in those classified as diseased. Nevertheless, the liberality of diseased samples was consistently higher than that of healthy samples. This suggests that the apparently weaker effect of age in diseased samples is not due to a suppression of age-related increases, but rather because poor health itself elevates liberality, thereby diminishing the apparent contribution of age. It is possible that samples considered healthy under current medical standards may in fact include undetected disease cases, and that the frequency of such hidden diseases increases with age.

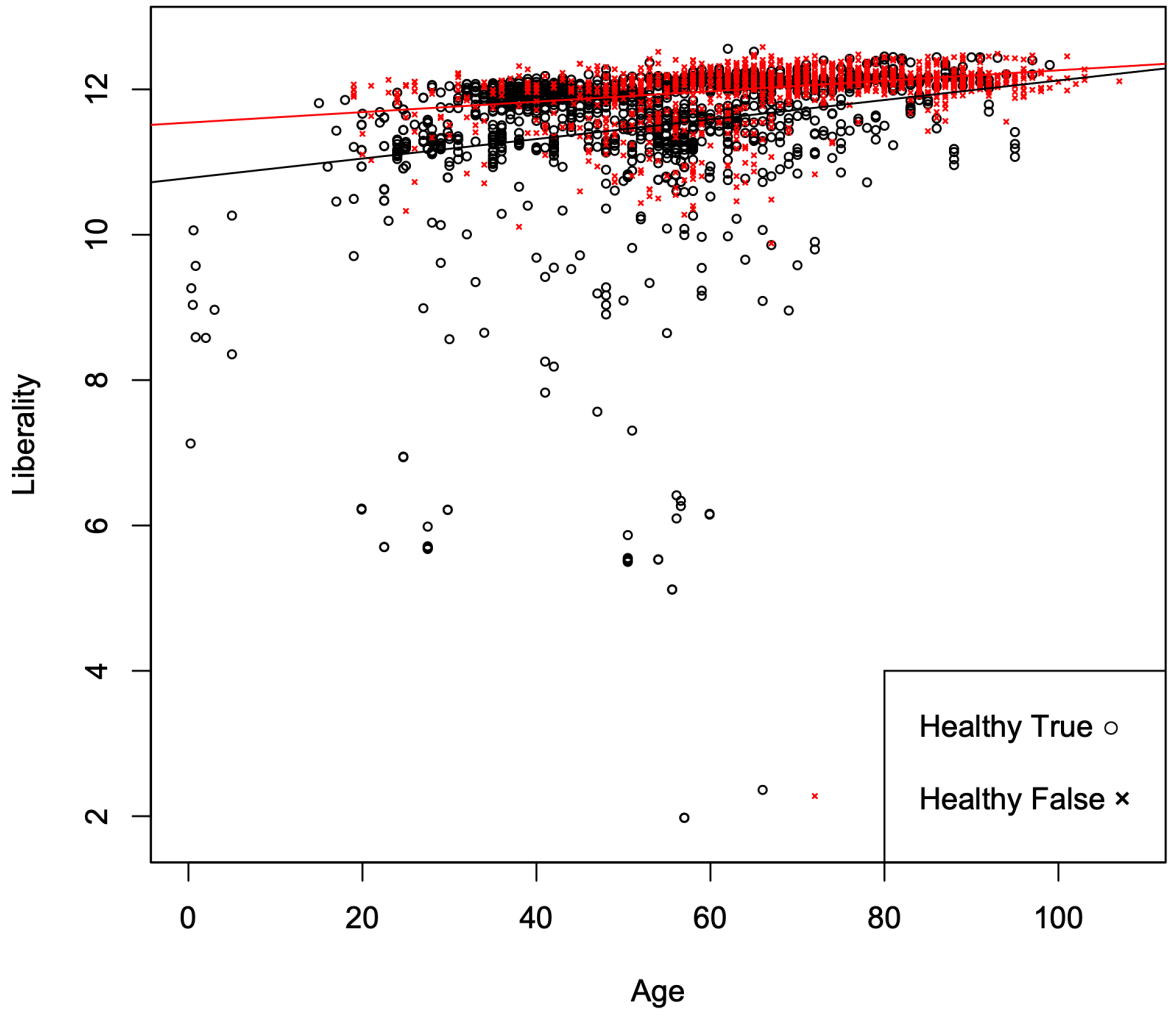

Figure 1. Correlation between Age and Liberality

References

Goldstein, S. (1990). Replicative senescence: the human fibroblast comes of age. *Science (New York, N.Y.)*, *249*(4973), 1129–1133. https://doi.org/10.1126/science.2204114

Ma, S., Ji, Z., Zhang, B., Geng, L., Cai, Y., Nie, C., Li, J., Zuo, Y., Sun, Y., Xu, G., Liu, B., Ai, J., Liu, F., Zhao, L., Zhang, J., Zhang, H., Sun, S., Huang, H., Zhang, Y., … Liu, G.-H. (2024). Spatial transcriptomic landscape unveils immunoglobin-associated senescence as a hallmark of aging. *Cell*, *187*(24), 7025–7044.e34. https://doi.org/10.1016/j.cell.2024.10.019

Ogata, N., Kozaki, T., Yokoyama, T., Hata, T., & Iwabuchi, K. (2015). Comparison between the amount of environmental change and the amount of transcriptome change. *PloS One*, *10*(12), e0144822. https://doi.org/10.1371/journal.pone.0144822

Ogata, N., Yokoyama, T., & Iwabuchi, K. (2012). Transcriptome responses of insect fat body cells to tissue culture environment. *PloS One*, *7*(4), e34940. https://doi.org/10.1371/journal.pone.0034940

R Core Team. (2024). *R: A Language and Environment for Statistical Computing*. https://www.R-project.org/

Shokhirev, M. N., & Johnson, A. A. (2021). Modeling the human aging transcriptome across tissues, health status, and sex. *Aging Cell*, *20*(1), e13280. https://doi.org/10.1111/acel.13280