Unveiling the Transcriptional and Cellular Landscape of Age across Human Tissues

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***Keywords*—Aging, Cell type deconvolution, Single-cell transcriptomics**

EXTENDED ABSTRACT

As the aging population grows progressively around the globe, the need to research and develop strategies to healthy aging is ever more critical and takes on new urgency[1]. Primary hallmarks of aging include cell autonomous changes linked to epigenetic alterations, genomic instability, telomere attrition and loss of proteostasis (protein homeostasis), which are followed by antagonistic responses such as deregulated nutrient sensing, altered mitochondrial function and cellular senescence. In addition, many functions of the immune system show a progressive decline with age, referred as immunosenescence, leading to a higher risk of infection, cancer, and autoimmune diseases[2]. Although chronological age is the most powerful risk factor for most chronic diseases, the underlying molecular mechanisms that lead to generalized disease susceptibility are largely unknown[3].

In recent years, rapidly developing high-throughput omics have provided a broader insight, with the identification of a number of longevity-relevant loci based on genome-wide association studies (GWAS) and epigenome analyses. Despite this success, *APOE*, *FOXO3* and *5q33.3* are the only identified loci consistently associated with longevity[3]. Hence, the complexity of the aging phenomenon, influenced by genetic and epigenetic regulation, post-translational regulation, metabolic regulation, host–microbiome interactions, lifestyle, and many other elements, primarily explains the poor understanding of many of the molecular and cellular processes that underlie the progressive loss of healthy physiology[4].

Whether these hallmarks of aging occur across different tissues, and what are the aging changes driven by expression, splicing or cell type composition remains poorly understood. Since studies in model organisms have shown that aging is characterized by distinct alterations at the molecular, cellular and tissue level[5], a transcriptome analysis might lend greater insight than a static genetic investigation. However, since bulk samples of heterogeneous mixtures (i.e., tissues) only represent averaged expression levels, many relevant analyses are typically confounded by differences in cell type proportions[3]. Therefore, one of the major goals of this study is to disentangle the age-related gene expression changes to the cellular composition variation across tissues and individuals, as shown in Fig.1. Ultimately, this information can promote the development of personalized medicine, as well as understanding the biological mechanism of the aging process.

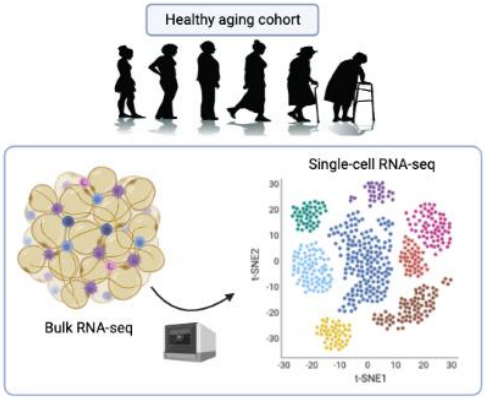

Fig. 1 Cartoon illustration showing an overview of the study workflow.

A. Age-related Gene Expression and Splicing Patterns Vary Among Human Tissues

To understand how individual variation in gene expression and splicing can explain phenotypic differences (such as age, sex, ancestry or BMI) between individuals, we conducted a human transcriptome-wide analysis taking advantage of the publicly available 17,382 high-quality RNA-sequencing (RNA-seq) human samples from 838 postmortem donors across 49 tissue types of version 8 of the Genotype-Tissue Expression (GTEx) dataset[6], being the largest catalog to date of genetic regulatory variants affecting gene expression and splicing in *cis* and *trans* across tissues. Using gene-centric analysis, such as differential gene expression and splicing analysis (DEA and DSA, respectively) together with hierarchical partitioning, we discovered that age-related gene expression and splicing patterns notably vary in a tissue-wise fashion manner. Specifically, the largest gene expression changes with age were observed in arteries, while the major changes in splicing appeared in some brain regions.

B. Cell Type Abundance Across Tissues is Largely Associated with Age

To assess how cell type composition could be confounding the observed gene expression variation with age across tissues, we performed a cell type enrichment analysis from GTEx gene expression data using *xCell*[7] to study the association between *xCell* enrichment scores and the different individual traits across tissues. Interestingly, we noticed a larger association between cell type abundance and age in different tissues compared to the other individual traits, which point toward relevant cellular composition changes during aging.

C. Single-Cell Transcriptomic Analysis Across Individuals

To further elucidate cell-specific changes occurring across multiple cell types and organs, as well as age-related changes in the cellular composition of different organs, we will benefit from emerging single-cell RNA-sequencing (scRNA-seq) technologies. To this end, we will analyze the large number of single cell transcriptomic profiles from PBMCs (Peripherial Blood Mononuclear Cells) of many individuals provided by the single-cell eQTLGen (sc-eQTLGen) Consortium[8]. The accessibility and clinical relevance of PBMCs have made them the most studied cell types in current population-based scRNA-seq datasets. In the context of our analysis, it will help to shed light on the interplay between the age-related changes that affect different components of the immune system.

D. ACKNOWLEDGEMENTS

We acknowledge the donors for their tissue donations for the GTEx research study. We thank the involvement of the large number of research groups participating in the current development of the sc-eQTLGen Consortium.

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Author biography

Aida Ripoll Cladellas was born in Barcelona, Spain, in 1994. She received the BSc degree in Human Biology from the University of Pompeu Fabra, Barcelona, Spain, in 2017, and the MSc degree in Bioinformatics for Health Sciences from the University of Pompeu Fabra, Barcelona, Spain, in 2019.

Since September 2019, she has been with the Transcriptional and Functional Genomics Lab (TFGL) lead by Marta Melé at the Department of Life Sciences in the Barcelona Supercomputing Center (BSC), where she joined as a research engineer (RE1), and last September 2020 she started her PhD project on studying the human transcriptome changes with aging.