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論文題目	Data-driven detection of age-related arbitrary monotonic changes in single-cell gene expression distributions		

（論文内容の要旨）

Background: Aging is typically associated with a progressive decline in functional integrity and homeostasis. Understanding the genetic mechanisms that underlie aging is critical for countering aging. In the field of genetics, considerable effort has been directed toward searching for aging-related genes, and recent omics studies have been conducted to comprehensively identify genes associated with aging in different tissues. While several methods have been developed for detecting the genes whose expression values monotonically change during aging using bulk data, such computational method for aging single cell genomics has been limited. Novel methodological considerations are needed to extend data-driven detection of aging changes in transcriptome data to the entire single-cell expression profile. Here, it proposed a new workflow for detecting the potential age-related gene screening methods based on information theory

Methods: In this study, it introduces a novel workflow that can detect arbitrary monotonic changes in single-cell expression. The input data are single-cell RNA-seq datasets from different donors. The single-cell expression data of a gene can be expressed as a probability distribution. The dissimilarity of a single-cell expression profile between samples can be calculated using Hellinger distance metric. And a dissimilarity matrix based on the absolute value of the differences between the donor ages of the sample is also calculated. Spearman correlation coefficient between the elements of the upper triangular matrices of the two distance matrices serves as an indicator of the association between single cell expression profile and age for each gene. it uses both simulation and real single cell-RNA data to demonstrate that.

Result: Simulation analysis showed that this workflow can detect monotonic distribution changes which could not be detected by conventional bulk data analysis. Next, it applies the method to the large-scale single-cell RNA-seq dataset. It uses public single cell RNA dataset contains 20,138 genes in 245,389 cells derived from various organs of multiple mouse donors of different ages. It focuses the analysis on four organs (kidney, limb muscle, lung, and marrow) which more than 10 mice were measured in this dataset. It applies the proposed workflow to this preprocessed dataset and detects the genes with the age-related change of the single-cell expression profile. The visualization of the single cell expression distribution change during aging for the detected genes has shown that the specific patterns of change are diverse even among those genes that are strongly associated with age and single-cell expression profile.

Conclusion: In this study, it develops a novel workflow to detect changes in the distribution of arbitrary monotonic age-related changes in single-cell expression profiles. Since single-cell expression profiles can be analyzed as probability distributions of gene expression, it proposes a method that combines the quantification of differences between distributions using information theory, and association analysis based on distance matrices. This technique is potentially useful as a simple screening method for identifying aging-related cellular features.

（論文審査の結果の要旨）

加齢に伴う遺伝子発現の変化は、老化の背後にある分子的なメカニズムを理解する上で重要である。遺伝子の発現量は、細胞種の違いで大きく異なる上、加齢によってその割合も変化するため、詳細な発現解析には、1 細胞遺伝子発現解析が有効である。しかしながら、複雑な細胞の多様性によって、細胞全体の発現変化を高精度に比較することは困難であった。そこで本研究では、細胞レベルで測定された遺伝子発現量を確率的に捉え、細胞集団間の確率分布を比較することで、加齢に伴い発現が変化する遺伝子群を検出する解析手法を開発した。提案手法では、確率分布間の距離指標によって、異なる年齢間における細胞全体の発現の違いを表現する。この距離指標および年齢差に基づく二つの距離行列に対し、マンテル検定を用いて加齢と発現変化の関連性を評価する。この手法を、公開されているマウスの 1 細胞トランスクリプトームデータセットに適用した結果、四肢筋において、加齢と関連する 13 個の遺伝子(*Jhdm1d*, *Grb10*, *Jmjd6*, *Acot9*, *Aldh2*, *AI607873*, *Plac9*, *Gt(ROSA)26Sor*, *Six1*, *Wisp1*, *Nr1d2*, *Tnfsf9*, *Plscr1*)を検出した。このように開発手法は、細胞種の多様性の違いを考慮せずに、1 細胞トランスクリプトームデータから加齢と関連する遺伝子をスクリーニングできる。

したがって、本論文は博士（医学）の学位論文として価値あるものと認める。なお、本学位授与申請者は、令和 6 年 5 月 28 日実施の論文内容とそれに関連した試問を受け、合格と認められたものである。

要旨公開可能日：　　年　　月　　日　以降