Internship Proposal

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Project Title:
How cell cycle dynamics changes with aging: a scRNAseq data analysis of the aged cell cycle

Level:

Master Student

Project Summary:

Today, 8.5% of people worldwide are aged over 65 and 1 in 5 people will be old in 2050 [1]. The unprecedented rate at which the world's elderly population is growing, is leading to significant burden on the healthcare systems of every country due to higher incidence of old-age co-morbidities such as cardiovascular, neurodegenerative and cancer diseases. Understanding the process of aging at molecular, cellular, and physiological levels is crucial for comprehensive strategies for healthspan extension. One key factor in aging is cellular senescence, which involves permanent cell-cycle arrest and the secretion of pro-inflammatory molecules (known as SASP), and has been shown to contribute to age-related diseases [2]. However, the mechanisms behind cell cycle slowdown in aged proliferating cells, the deregulation and/or changes in the cell cycle core machinery network [3], error propensity, and ultimately senescence onset, remain poorly understood. To fill this lack of knowledge in the aging field, our lab generated a single cell RNAseq dataset of human dermal fibroblasts from skin biopsies of healthy donors with ages ranging from neonatal to octogenarian [4,5]. With the comprehensive analysis of this dataset we will tackle how cell cycle dynamics changes with aging, shedding light on the underlying mechanisms responsible for the loss of proliferative capacity and to potentially disclose novel targets for rejuvenating strategies.

Work to be developed by the student:

We aim to perform robust cell cycle sub-phase detection per age and across ages, cell cycle pseudo-time quantification across ages, find the variable genes with cell cycle in aging and, if possible, distinguish proliferating and resting cells and their ratios across ages, contributing

to the characterization of the cell cycle dynamics with aging based on scRNAseq data. We plan to use available scRNAseq data analysis tools such as DeepCycle [6], scVelo [7], scran [8], slingshot [9], ElPiGraph [10], following useful tips such as in [11] and similar literature. We anticipate that our work may uncover new druggable cell cycle targets that could be leveraged to counteract the loss of proliferative capacity and cell fitness associated with aging with the potential to extend organismal healthspan. By promoting healthy lives and well-being at all ages, we hope to contribute to the broader societal goal of ensuring optimal health and quality of life for everyone.

The person involved is expected to contribute with streamlined pipelines (e.g. GitHub, snakemake or similar) for scRNAseq data analyses of the cell cycle along advancing age, performing the tasks mentioned above as well as additional ones relevant in the context of the data. Preference is given to someone with prior experience in Unix and the command line, as well as familiarity with data analysis and bioinformatics.
We expect the internship to last at least 6-12 months and it could be suitable for a master thesis project.

References:

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[5] Ferreira JF, Galhardo M, Teixeira J, et al. FOXM1 expression reverts aging chromatin profiles through repression of the senescence-associated pioneer factor AP-1. BioRxiv (2023)

[6] Riba A, Oravecz A, Durik M. et al. Cell cycle gene regulation dynamics revealed by RNA velocity and deep-learning. Nat Commun 13, 2865 (2022)

[7] Bergen V, Lange M, Peidli S. et al. Generalizing RNA velocity to transient cell states through dynamical modeling. Nat Biotechnol 38, 1408–1414 (2020)

[8] Lun ATL, McCarthy DJ, Marioni JC (2016). “A step-by-step workflow for low-level analysis of single-cell RNA-seq data with Bioconductor.” F1000Res., 5, 2122

[9] Street K, Risso D, Fletcher R, et al. (2018). “Slingshot: cell lineage and pseudotime inference for single-cell transcriptomics.” BMC Genomics, 477

[10] Albergante L, Mirkes EM, Chen H, et al (2018). Robust and scalable learning of data manifolds with complex topologies via ElPiGraph. ArXiv, abs/1804.07580.

[11] Chervov AV & Zinovyev AY. (2022). Computational challenges of cell cycle analysis using single cell transcriptomics

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