

Abstract

Title: Best practices of multiome data analysis and application to anti-tumor immunity in obesity

Technological advances in single-cell sequencing have expanded the detection of cell phenotype beyond the transcriptome, allowing for more refined characterization of cell types and discovery of novel therapeutic targets. Notably, paired scRNA-seq and scATAC-seq, called multiome data, facilitates inference of how variation in chromatin accessibility regulates gene expression and cell identity. However, unlike scRNA analysis, procedures of scATAC analysis lack consensus, mainly due to the high sparsity and the unfixed feature set of the original data. In this talk, we first present evaluating differential representations of scATAC by integrating with scRNA and validating against the pairing information of multiome data. We show that several decisions in current scATAC processing tools result in loss of information and recommend best practices of featurization and downstream analysis. Next, we demonstrate the power of multiome through an analysis of new multiome data from tumor-infiltrating CD8⁺ T cells in obesity. We find an enrichment of progenitor exhausted CD8⁺ T cells in obese tumors, and generate a new hypothesis for "the obesity paradox", namely why certain obese patients have improved response to immune checkpoint inhibitors despite displaying impaired anti-tumor immunity.

Textbook

Bioinformatics Algorithms: An Active Learning Approach, 3rd Edition, by Philip Compeau & Pavel Pevzner, Chapters 1-10

Reading list

Integration of single-cell data

1. Luecken MD, Büttner M, Chaichoompu K, *et al.* Benchmarking atlas-level data integration in single-cell genomics. *Nat Methods*. 2022;19(1):41–50. <https://doi.org/10.1038/s41592-021-01336-8>
2. Stuart T, Butler A, Hoffman P, *et al.* Comprehensive Integration of Single-Cell Data. *Cell*. 2019;177(7):1888–902.e21. <https://doi.org/10.1016/j.cell.2019.05.031>
3. Korsunsky I, Millard N, Fan J, *et al.* Fast, sensitive and accurate integration of single-cell data with Harmony. *Nat Methods*. 2019;16(12):1289–96. <https://doi.org/10.1038/s41592-019-0619-0>

Single-cell multi-omic technology and analysis

4. Baysoy A, Bai Z, Satija R, *et al.* The technological landscape and applications of single-cell multi-omics. *Nat Rev Mol Cell Biol.* 2023;24:695–713.
<https://doi.org/10.1038/s41580-023-00615-w>
5. Mereu E, Lafzi A, Moutinho C, *et al.* Best practices for single-cell analysis across modalities. *Nat Rev Genet.* 2023;24(9):550–72.
<https://doi.org/10.1038/s41576-023-00586-w>
6. Chen H, Lareau C, Andreani T, *et al.* Modeling fragment counts improves single-cell ATAC-seq analysis. *Nat Methods.* 2020;17(11):1296–304.
<https://www.nature.com/articles/s41592-023-02112-6>
7. Luo S, Germain PL, Robinson M, *et al.* Benchmarking computational methods for single-cell chromatin data analysis. *Genome Biol.* 2024;25:225.
<https://doi.org/10.1186/s13059-024-03356-x>
8. Lause J, Berens P, Kobak D. Analytic Pearson residuals for normalization of single-cell RNA-seq UMI data. *Genome Biol.* 2021;22:258.
<https://doi.org/10.1186/s13059-021-02451-7>

CD8+ T cell anti-tumor response in obesity

9. Ringel AE, Drijvers JM, Baker GJ, *et al.* Obesity Shapes Metabolism in the Tumor Microenvironment to Suppress Anti-Tumor Immunity. *Cell.* 2020;183(7):1848–66.e26.
<https://doi.org/10.1016/j.cell.2020.11.009>
10. Dolina JS, Van Braeckel-Budimir N, Thomas GD, *et al.* CD8+ T Cell Exhaustion in Cancer. *Front Immunol.* 2021;12:715234. <https://doi.org/10.3389/fimmu.2021.715234>