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A Single Cell Omics Experiments as Tool for Benchmarking Bioinformatics Oncology Data Analysis Tools

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Abstract : The presence of tumor heterogeneity, where distinct cancer cells exhibit diverse morphological and phenotypic profiles, including gene expression, metabolism, and proliferation, poses challenges for molecular prognostic markers and patient classification for targeted therapies. Understanding the causes and progression of cancer requires research efforts aimed at characterizing heterogeneity, which can be facilitated by evolving single-cell sequencing technologies. However, analyzing single-cell data necessitates computational methods that often lack objective validation. Therefore, the establishment of benchmarking datasets is necessary to provide a controlled environment for validating bioinformatics tools in the field of single-cell oncology. Benchmarking bioinformatics tools for single-cell experiments can be costly due to the high expense involved. Therefore, datasets used for benchmarking are typically sourced from publicly available experiments, which often lack a comprehensive cell annotation. This limitation can affect the accuracy and effectiveness of such experiments as benchmarking tools. To address this issue, we introduce omics benchmark experiments designed to evaluate bioinformatics tools to depict the heterogeneity in single-cell tumor experiments. We conducted single-cell RNA sequencing on six lung cancer tumor cell lines that display resistant clones upon treatment of EGFR mutated tumors and are characterized by driver genes, namely ROS1, ALK, HER2, MET, KRAS, and BRAF. These driver genes are associated with downstream networks controlled by EGFR mutations, such as JAK-STAT, PI3K-AKT-mTOR, and MEK-ERK. The experiment also featured an EGFR-mutated cell line. Using 10XGenomics platform with cellplex technology, we analyzed the seven cell lines together with a pseudo-immunological microenvironment consisting of PBMC cells labeled with the Biolegend TotalSeq™-B Human Universal Cocktail (CITEseq). This technology allowed for independent labeling of each cell line and single-cell analysis of the pooled seven cell lines and the pseudo-microenvironment. The data generated from the aforementioned experiments are available as part of an online tool, which allows users to define cell heterogeneity and generates count tables as an output. The tool provides the cell line derivation for each cell and cell annotations for the pseudo-microenvironment based on CITEseq data by an experienced immunologist. Additionally, we created a range of pseudo-tumor tissues using different ratios of the aforementioned cells embedded in matrigel. These tissues were analyzed using 10XGenomics (FFPE samples) and Curio Bioscience (fresh frozen samples) platforms for spatial transcriptomics, further expanding the scope of our benchmark experiments. The benchmark experiments we conducted provide a unique opportunity to evaluate the performance of bioinformatics tools for detecting and characterizing tumor heterogeneity at the single-cell level. Overall, our experiments provide a controlled and standardized environment for assessing the accuracy and robustness of bioinformatics tools for studying tumor heterogeneity at the single-cell level, which can ultimately lead to more precise and effective cancer diagnosis and treatment.

Keywords : single cell omics, benchmark, spatial transcriptomics, CITEseq
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