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A harmonized single-cell transcriptomic atlas of human neuroblastoma

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Background: Single-cell and single-nucleus RNA sequencing (scRNA-seq or snRNA-seq) are powerful technologies to study the transcriptomic heterogeneity of tumors, including neuroblastoma. Previous studies using scRNA-seq and snRNA-seq were focused on tumoral heterogeneity and aggressiveness in relation to normal developmental and cell-of-origin. While useful, these studies have also raised novel questions.

Aims: At present, a comprehensive overview of these studies and data is lacking. In this study, we present a meta-analysis of published scRNA-seq and snRNA-seq datasets for neuroblastoma patient tumors. We compared wet lab and bioinformatics processing procedures across these studies and combined data to form an integrated transcriptomic atlas of human neuroblastoma tumors.

Methods: We reviewed all published scRNA-seq and snRNA-seq (n=9) studies and collected metadata, including patient information, sample processing details, wet lab protocol, and bioinformatics approaches (quality control, canonical gene marker selection, and cell type annotation). Thereafter, selected studies were combined to generate a cellular atlas, using benchmarked integration tools to correct for technical bias while preserving biological heterogeneity.

Results: Different wet lab protocols and bioinformatics pipelines were applied across the different studies. Most notably, this resulted in a discrepancy in the tumoral composition obtained with scRNA-seq compared to snRNA-seq, with a lack of neuroendocrine cells in scRNA-seq data. Data from more than 50 tumors across various studies (performed on the 10X Genomics platform) were normalized to largely overcome differences in the applied wet lab and bioinformatics approaches. As a result, a harmonized atlas of the transcriptomic landscape of human neuroblastoma tumors was generated. This atlas allows for gaining a more comprehensive view of the heterogeneity of malignant cells and the tumor microenvironment. To illustrate the power of the generated cell atlas as a framework for future single-cell studies, we mapped newly generated scRNA-seq and snRNA-seq data to this reference atlas for cell annotation and observed agreement with manual cell annotation.

Conclusion: Our study provides a comprehensive and harmonized view of the single-cell transcriptomic landscape of neuroblastoma and serves as a valuable reference resource for newly generated scRNA-seq and snRNA-seq data.