Neuro-Oncology Advances
8(S1), vdaf133, 2026 | https://doi.org/10.1093/noajnl/vdaf133

Current landscape of single-cell genomics in meningioma

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Abstract

Meningiomas are the most common primary intracranial tumor in adults. Traditional bulk genomic and histopathological analyses have provided valuable insights into meningioma biology. Recent advances in single-cell sequencing technologies have enabled the comprehensive study of a tumor's transcriptome and epigenome at a single-cell resolution, along with spatially resolved data and functional genomics approaches. These strategies allow for the profiling of complex intratumoral and intertumoral heterogeneity, the identification of gene regulatory networks, and the characterization of distinct cell populations within the tumor microenvironment that drive tumor behavior. In this review, we examine the current landscape of single-cell omics in meningioma research and highlight opportunities for future discovery.

Key Points

- Single-cell transcriptomics provide key insights into meningioma heterogeneity.
- Integration of single-cell transcriptomics and epigenomics as well as functional genomics are underexplored in meningioma.

Meningiomas represent the most common primary intracranial tumor in adults. They account for over 40% of all brain tumors and over 56% of nonmalignant brain tumors.[1] Additionally, there has been an increase in the incidence of meningioma diagnosis over the past decade, which has thought to be related to an increase in brain imaging diagnostics.[2] Most meningiomas are benign, grow slowly, and can be cured through surgical resection. However, their clinical behavior is heterogeneous, with grading from WHO grade 1 to 3 based on histopathological features. The latest WHO classification also includes molecular markers, such as CDKN2A/B homozygous deletion or TERT promoter mutation as criteria that result in WHO grade designation[3]. Given the significant heterogeneity in the tumor behavior with respect to tumor recurrence and response to radiation, there have been substantial efforts to molecularly profile these tumors.[4–8] These efforts have yielded molecular subgroupings that have divergent clinical outcomes. While a more biological approach has provided additional granularity beyond standard histopathological grading, effective adjuvant therapies remain significantly limited which poses a significant challenge in the management of those that recur after surgery.[9,10]

Tumors are comprised of both neoplastic and non-neoplastic cell populations with complex spatial organization. Our ability to understand the biology at a single-cell resolution is critical for such a disease with complex tissue organization and cell populations.[11] High-resolution single-cell analyses have resulted in the unparalleled ability to profile heterogeneity within neoplastic cells and to understand the complex interactions between neoplastic and non-neoplastic cells within the tumor microenvironment (TME). In the context of meningioma, single-cell transcriptomics has provided insights into the cellular heterogeneity and diverse cell populations and their interactions within the tumor microenvironment.[4,6] Additionally, complementary technologies like spatial transcriptomics have provided additional insights into the spatial organization and cell interaction.[12]

Single-cell transcriptomics, including single-cell RNA sequencing (scRNA-seq) from fresh tissue and single-nucleus RNA sequencing (snRNA-seq) from frozen or formalin-fixed samples, provide information into tumor cell type and transcriptional heterogeneity. While scRNA-seq captures whole-cell transcriptomes, including cytoplasmic mRNAs, snRNA-seq captures nuclear RNA, and is often enriching for longer or unspliced transcripts. These differences can affect the detection of certain cell types and gene expression profiles, with scRNA-seq favoring readily dissociable cells like immune populations, while snRNA-seq better captures large, fragile, or adherent cells embedded in the tissue matrix. In this review, we highlight the key discoveries enabled by sn/sc-RNA seq and other single-cell omics technologies in meningioma research. We explore their contributions to understanding tumor heterogeneity and discuss opportunities for applying and integrating additional single-cell omics in the study of meningiomas (Figure 1).

Tumor Microenvironment

Tumor cells are known to recruit ostensibly "normal" cells into a complex microenvironment that enables the neoplastic cells to grow, evading host defense mechanisms, and this plays a key role in resistance to therapy.[11,13] Bulk molecular profiling, including RNA sequencing, DNA methylation, and ATAC sequencing has yielded substantial insights into the cells within the TME and their epigenetic regulation. Though these approaches can be used to comprehensively study intertumoral heterogeneity, they are inherently limited in their ability to deconstruct the intratumoral heterogeneity of the TME. Other methods to overcome this include tumor dissociation and flow cytometry; however, this is a targeted approach via antibody staining and therefore is limited in the ability to comprehensively explore the complexities of the tissue microenvironment.[14,15]

One of the critical contributions of scRNA-seq in cancer research has been the ability to dissect the cellular composition of the TME at single-cell resolution. By profiling the transcriptomic signatures of individual cells, scRNA-seq enables the identification of distinct cell types and cell states, providing insights into their roles in tumor progression. To this end, scRNA-seq profiling of human meningiomas has found that the overall TME seems to comprise approximately 70% neoplastic cells with the second largest proportion being immune cells (macrophage and T cells) followed by fibroblasts and endothelial cells.[4] Additionally, the immune component of the microenvironment has been shown to be a critical component of the tumor microenvironment within meningioma.[4] Single-cell immune profiling with V(D)J sequencing has added additional granularity for the diversity of T cells and B cell clonotypes within the tumor microenvironment.[16,17] In a study consisting of 6 meningioma samples and 7 non-tumor associated dura samples, single-cell TCR sequencing demonstrated that tumor-adjacent dura harbored shared T cell clonotypes with adjacent meningioma tissue.[18] TCR sequencing enables a deeper understanding of the adaptive immune response, shedding light on the clonality and specificity of T-cell populations in the TME.

Spatial transcriptomics is a complementary technology to sc/snRNA-seq that integrates spatial information with gene expression data. This offers an additional layer of insight into the TME by maintaining the positional context of cells within the tumor in 2-dimensional space. In the context of meningioma, spatial transcriptomics has identified divergent gene expression programs across histologically distinct regions in a cohort of WHO grade 2 and 3 meningiomas.[12] However, early generations of spot-based spatial transcriptomics were limited by resolution constraints, as each spatial "spot" contained multiple cells, making it difficult to resolve single-cell gene expression. Additionally, other techniques with higher resolutions only captured partial transcriptomes through targeted panels, limiting the ability to perform full-scale

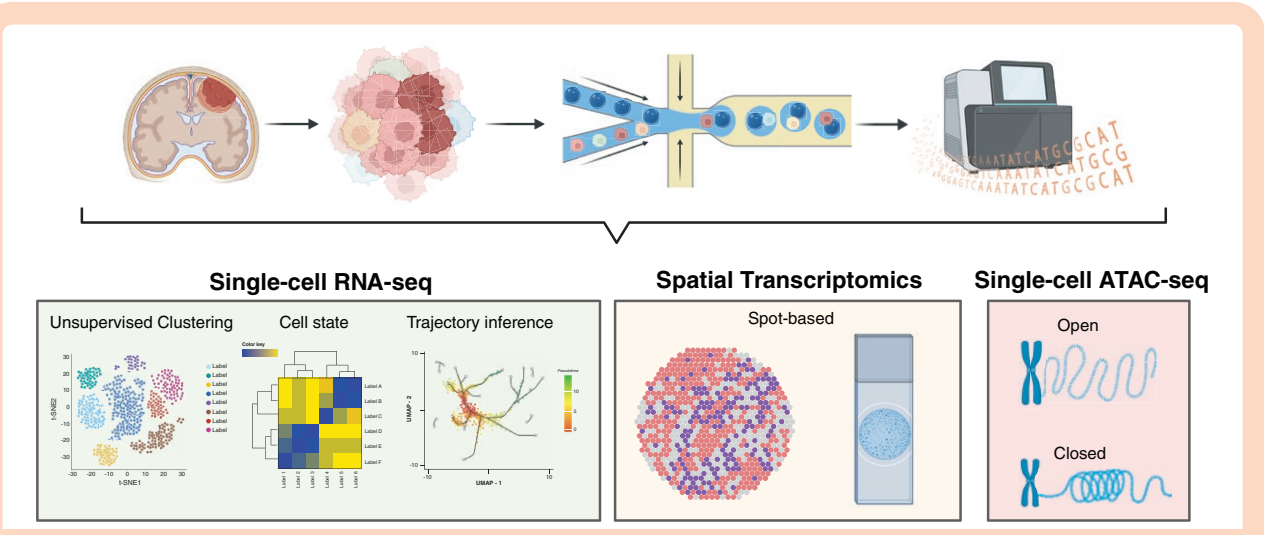

Figure 1. Graphical depiction of single-cell genomic techniques in meningioma.

gene expression analyses. Newer advancements, including higher-resolution techniques such as VisiumHD, Slide-seq, and EEL-FISH, have circumvented these limitations by enabling transcriptome-wide profiling at cellular and even subcellular resolution.[19–21] These next-generation methods improve spatial resolution while preserving full transcriptomic data, making them powerful tools for exploring the TME.

Intratumoral and Intertumoral Heterogeneity

The application of scRNA-seq to meningioma has allowed for the characterization of tumor heterogeneity beyond traditional histopathological assessments. By enabling the analysis of individual cells within a tumor, scRNA-seq has revealed distinct cellular subpopulations and molecular subtypes that were previously unrecognized by bulk models. A compendium of the publicly available single-cell and spatial transcriptomic datasets in meningioma are summarized in Table 1.[4,6,12,18,22,23]

scRNA-seq has been instrumental in refining the molecular subtyping of meningiomas, and providing infomration about its intertumoral and intratumoral heterogeneity. This heterogeneity has been demonstrated through unsupervised clustering patterns observed within both neoplastic and non-neoplastic cell populations.[4] As seen in other cancers, non-neoplastic cells, such as immune and stromal cells, consistently cluster by cell type across different patients. In contrast, neoplastic cells exhibit patient-specific clustering, underscoring the significant intertumoral heterogeneity and transcriptomic variability.

A significant advancement in bulk molecular tumor profiling has been the classification of meningiomas into molecular groupings.[4–8,24] Several studies have described independent molecular classifications based on bulk RNA-sequencing, DNA methylation, copy number variation, or integration of these techniques. Our group previously identified 4 consensus molecular groups with distinct clinical outcomes: immunogenic (MG1), NF2-wildtype, hypermetabolic (MG2), and proliferative (MG4). Other groups have independently identified similar groupings with a variable number of independent groups, and the differences among these systems have been described previously.[8] While these classifications have provided valuable insights, scRNA-seq has further refined our understanding by revealing distinct cellular subpopulations and molecular subtypes within these tumors.

For instance, scRNA-seq-based clustering revealed that each cluster corresponded to a distinct cell population (immune, stromal, or neoplastic), rather than exclusively to variations in neoplastic gene expression. The immunogenic, NF2-wildtype, and hypermetabolic tumors contain abundant stromal and immune cells, and display multiple clusters representing these different populations.[4] In contrast, the proliferative (MG4) tumors which are composed almost entirely of neoplastic cells resolve into fewer clusters, as nearly all cells belong to one dominant population. Unlike other tumors such as glioblastoma, the presence of neoplastic subpopulations was rare, but when present they were more commonly found in hypermetabolic and proliferative tumors. The absence of clear subclusters within neoplastic cells suggests either a homogeneous population of neoplastic cells or a shared proliferative state. The presence of one dominant cluster with minor subpopulations showing consistent copy-number profiles indicates limited subclonal expansion. These findings highlight the utility of scRNA-seq in studying the heterogeneity within tumors that might otherwise appear uniform based on bulk analysis. In another study, scRNA-seq was performed on 57,114 cells from 8 meningioma samples and classified into three groups based on DNA methylation.[6] In this cohort, scRNA-seq demonstrated increased expression of HLA markers within immune-enriched meningiomas compared to hypermitotic and merlin-intact groupings.

Tumor Transcriptional Programs

The identification of marker genes through scRNA-seq has reinforced the classification of meningiomas into broader molecular meta-programs. Interestingly, these meta-programs have largely aligned with the previously defined integrative molecular groups and include pathways related to the cell cycle, cellular metabolism, and immune

Table 1. Summary of Single-cell Sequencing Identified in Meningioma Studies

First Author	Year	Omics	Sample	Accession number
Nassiri[4]	2021	sn-RNA	8 meningioma samples and 2 healthy dura samples	EGAC00001001136
Harmanci[20]	2022	scRNA	2 samples from 1 patient	GSE213544
Wang[18]	2022	scRNA with V(D)J enrichment	6 meningioma samples and 7 dura samples	PRJNA826269, zenodo.6473604
Choudhury[6]	2022	scRNA	10 human samples from 6 patients consisting of 8 tumors and 2 dura samples	GSE183655
Lucas[12]	2024	Spatial transcriptomic (10x Visium)	16 human samples from 9 patients consisting of 10 tumors	PRJNA950017
Eaton[19]	2024	scRNA	12 CH-157MN patient-derived xenografts	*GSE224347*

signaling.[4] Notably, immune-enriched meningiomas have been characterized by high levels of immune cell infiltration and specific gene expressions, particularly involving human leukocyte antigen (HLA) genes.[6] These immune signatures are often accompanied by significant genetic alterations, such as copy number variations, that influence the immune landscape of the tumor. Other prominent profiles related to cell cycle, cellular metabolism, inflammatory TNF signaling, and a general mesenchymal program.

Non-negative matrix factorization (NMF) is a powerful tool in scRNA-seq datasets in cancer to dissect tumor heterogeneity.[25,26] NMF is particularly effective for identifying gene metaprograms, which are sets of genes that reflect shared biological processes or functional states across heterogeneous cell populations. By deconstructing high-dimensional and sparse gene expression matrices, NMF can reveal underlying molecular programs without requiring prior knowledge of specific cell types. In oncology, NMF has been applied to uncover functional subpopulations within tumors, revealing distinct molecular programs in both neoplastic and non-neoplastic cells within the TME.[27] While distinct clusters of neoplastic cells were rare in this study, in cases where they were observed, they often formed minor subclusters within a dominant tumor cell population. Beyond clustering, NMF enables a deeper exploration of tumor heterogeneity by identifying shared biological processes that are recurrent across samples, even when individual tumor subpopulations vary.

These gene metaprograms can help delineate the functional diversity of neoplastic cells, capturing both dominant and rare cell states that drive tumor behavior. For example, in gliomas, NMF has been used to differentiate different cell states that harbor unique gene expression, and behavior.[25,28] Similarly, in meningiomas, NMF has been applied and demonstrated increased granularity, though overall concordance with the molecularly defined consensus subgroups.[4] This was also seen when applying gene signatures obtained from scRNA-seq and applying to bulk mRNA sequencing.[4]

Moreover, combining NMF with other computational approaches, such as gene set enrichment analysis or pathway-specific annotations, can enhance the biological interpretation of gene metaprograms, helping to connect transcriptional signatures with actionable therapeutic targets. As single-cell technologies continue to evolve, NMF remains a key computational strategy for resolving complex tumor ecosystems and understanding mechanisms of resistance, invasion, and metastasis.

Tumor Evolution

Whole-genome single-cell sequencing was among the earliest applications of single-cell sequencing techniques.[29] This initial approach required flow sorting and massively parallel sequencing with relatively low coverage (~6% of the genome). However, the read depth allowed for the inference of copy number variations, enabling tumor mutational and evolutionary analysis. These efforts demonstrated that most meningiomas exhibit NF2 mutations, however, the subset that is non-NF2 mutated typically harbor other mutations including TRAF7, KLF4, and AKT1, often with multiple mutations in a single tumor.[30] To study the temporal occurrence of these mutations, Dogan et al. performed single-cell amplicon-based DNA sequencing on seven meningiomas that were known to have TRAF7, KLF4, and AKT1 mutations.[31] Analysis of 875,000 cells revealed three subclones in each sample: (1) wildtype, presumed to represent non-neoplastic cells; (2) a subclone with a TRAF7 mutation; and (3) a subclone with co-occurring TRAF7 and either KLF4 or AKT1 mutations. Interestingly, none of the subclones harbored isolated KLF4 or AKT1 alterations. Taken together, these findings suggest that TRAF7 mutations typically occur first in meningiomas with co-occurring mutations in KLF4 or AKT1.

With advancements in sn/sc-RNA-seq enabling high-throughput tumor profiling, computational methods such as trajectory inference and pseudotime have been developed to map the developmental pathways of cells.[32–34] While not initially designed for application in oncology, these tools have been used to help improve our understanding of meningioma biology.[35] Trajectory inference has enabled the reconstruction of differentiation pathways within neoplastic cells which can identify subpopulations with distinct proliferative or quiescent states, providing insights into tumor evolution and therapeutic resistance. In addition to tracing neoplastic cell development, trajectory inference has also been applied to study the immune landscape of meningiomas. For instance, in meningiomas, trajectory inference has revealed distinct developmental paths for macrophages, which are the most abundant immune cells within these tumors.[36] One trajectory was determined to be pro-tumorigenic and defined by a MIF-CD74 interaction which presents a potential therapeutic avenue to be explored.[36] With regard to neoplastic cells, a small, highly proliferative cluster of neoplastic cells, marked by the expression of genes such as MKI67 and TOP2A, has been identified in atypical and transitional meningiomas.[36] These cells are located at the beginning of the pseudotime differentiation trajectory, indicating their potential role in driving tumor progression. The identification of such proliferative clusters underscores the utility of scRNA-seq in highlighting cellular populations as potential targets for therapeutic intervention.

Future Direction with Single-cell Genomics in Meningioma

While sc/sn-RNA-seq has yielded new insights into the biology and heterogeneity of meningioma, other single-cell omics technologies have not yet been explored to the same extent, making them an exciting avenue for future discovery.[37,38] Understanding cell-level regulatory machinery at all levels, from the epigenetic to the protein level, could generate novel insights into mechanisms of meningioma tumorigenesis, drivers of heterogeneity, and therapeutic resistance/vulnerabilities.

Single-cell epigenetic and genomic profiling, often performed in tandem with scRNA-seq, have generated important insights into the heterogeneity of various cancers. For example, single-cell assays for transposase-accessible

chromatin (ATAC) sequencing, which measures chromatin accessibility, have been used to identify cell states associated with treatment resistance in prostate cancer and to resolve some of the intratumoral heterogeneity of glioma.[39,40] sc-DNA methylation has also offered insights into cellular hierarchy and epigenetically mediated cell state transitions of glioma and helped map the clonal evolution of colorectal cancer, both of which have important correlates to therapeutic vulnerabilities.[41,42]

At the genomic level, single-cell sequencing has recently been used to identify and rigorously trace treatment-resistant subclones in leukemia and breast cancer, offering an understanding of gene-level drivers of treatment resistance at unprecedented resolution and, by consequence, insights into critical treatment targets.[43,44] Single-cell proteomics, while less commonly used, is becoming increasingly accessible as a means to understand cell function and cell–cell interactions within a tumor microenvironment.[45] This approach has been used to identify sources of cellular heterogeneity in prostate cancer demonstrating its potential utility more broadly.[46] While scRNA-seq has provided valuable insights into meningioma heterogeneity, its widespread application has been limited by the high cost compared to bulk sequencing strategies, making large-scale profiling less feasible. Future studies could overcome this limitation by leveraging smaller scRNA-seq datasets to deconvolute bulk RNA-seq data, allowing for tumor heterogeneity analysis at scale. This strategy has already been successfully applied in various cancers, enabling the analysis of large populations with diverse biological features. Applying similar strategies to meningiomas could enhance our ability to define molecular subpopulations, improve classification, and identify novel therapeutic vulnerabilities.[4,47]

With regards to refining the TME, spatial transcriptomics has the potential to map tumor-immune interactions, identifying spatially restricted treatment-resistant subpopulations, and characterizing the role of the extracellular matrix in tumor invasion. Integrating spatial transcriptomics with other multimodal approaches, such as spatial proteomics and metabolomics, could further enhance our understanding of meningioma biology by linking gene expression changes to protein function and metabolic activity in a spatially resolved manner. As these technologies continue to evolve, they hold significant promise for uncovering spatially driven transcriptional programs, refining precision medicine strategies, and identifying novel therapeutic targets tailored to distinct TME.

Additionally, functional genomics approaches have the potential to uncover gene dependencies and regulatory mechanisms driving tumor biology. For instance, single-cell CRISPR screens enable high-throughput interrogation of gene function by coupling pooled gene knockouts with scRNA-seq readouts to measure transcriptomic consequences at single-cell resolution.[48] By combining CRISPR-mediated gene perturbations with scRNA-seq, genetic alterations can be directly linked to transcriptional changes within heterogeneous cell populations. This approach allows for the systematic identification of genes involved in key biological processes, such as cell proliferation, differentiation, drug resistance, and immune evasion. By targeting oncogenes, tumor suppressors, or key signaling pathways, these screens can reveal differential effects on subpopulations of tumor cells, highlighting the complexity of intratumoral heterogeneity. For example, in squamous cell carcinoma, in vivo CRISPR screens have identified TNF signaling program to be associated with epithelial-to-mesenchymal transition which enables tissue invasion and is associated with shorter survival.[49] Additionally, single-cell CRISPR screens have been used to validate oncogenic drivers in GBM malignant cells both in cell culture and orthotopic allografts.[50] However, this approach remains largely unexplored in meningioma to date.

While the application of single-cell omics technologies to meningiomas has provided valuable insights, the use of different platforms, protocols, and analytical pipelines presents a significant challenge for direct cross-study comparisons. Variations in sequencing depth, resolution, and cell dissociation methods can influence data interpretation, making it difficult to draw precise conclusions across studies. Additionally, while some approaches focus on transcriptomics, others emphasize chromatin accessibility, proteomics, or spatial context, each offering distinct but sometimes non-overlapping insights. As technology advances and standardized frameworks for multi-omics integration emerge, future studies may allow for more direct comparisons, enabling a more comprehensive and unified understanding of meningioma biology.

Overall, the integration of multiple single-cell omics technologies including functional approaches, which are now able to provide data at the epigenetic, genetic, transcriptomic, and protein levels, has made a considerable impact on our understanding of cancer heterogeneity and treatment response. Driven by these previous successes, it will be important to apply these same approaches to meningioma. This is likely to yield new insights into their biology and, more importantly, targets for novel therapeutic options.

Keywords

meningioma | single-cell RNA sequencing | tumor microenvironment | tumor heterogeneity | multiomics | functional genomics

Funding

This work was supported by a generous dontation from the University Health Network Division of Neurosurgery

Supplement sponsorship

This article appears as part of the supplement "Single-Cell Technologies," sponsored by the Princess Margaret Cancer Research Centre and the Toronto Western Hospital Division of Neurosurgery.

Conflict of interest statement

The authors of this manuscript have no conflicts of interest to disclose.

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