

Single Nucleus Transcriptomics in Neurological Disorder Research

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DESCRIPTION

Single-nucleus transcriptomics has emerged as a transformative technology in neurological disorder research, enabling high-resolution analysis of gene expression patterns within individual nuclei extracted from complex brain tissues. The brain is composed of an extraordinary diversity of cell types, including neurons, astrocytes, oligodendrocytes, microglia, and various vascular and immune-associated cells. Traditional bulk Ribonucleic Acid (RNA) sequencing averages gene expression across heterogeneous populations, masking cell-type-specific signals that are essential for understanding neurological diseases. One of the most important advantages of single-nucleus transcriptomics is its applicability to archived brain samples, including postmortem human tissues. Many neurological disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis are studied using postmortem samples where intact cells are difficult to obtain. Nuclear RNA remains stable after tissue processing, making it an ideal source for transcriptomic analysis. This has significantly expanded the availability of human brain data and enabled large-scale studies of disease-associated transcriptional changes.

In neurological disorder research, single-nucleus transcriptomics provides critical insights into cellular heterogeneity and disease-specific cell states. Neurodegenerative diseases are progressive loss of neuronal function and complex interactions between multiple brain cell types. Single-nucleus sequencing has revealed that neuronal populations are not uniform but consist of diverse subtypes with distinct gene expression profiles. Some neuronal subpopulations are more vulnerable to degeneration, while others exhibit resistance, suggesting intrinsic molecular differences that influence disease progression.

In Alzheimer's disease, single-nucleus transcriptomics has identified distinct transcriptional changes in excitatory neurons, inhibitory neurons, astrocytes, and microglia. Microglial cells, which are the brain's resident immune cells, show strong activation signatures upregulation of inflammatory genes. Astrocytes also exhibit altered gene expression related to metabolic support and synaptic regulation, highlighting their involvement in neuronal dysfunction. Single-nucleus

transcriptomics has also been instrumental in studying amyotrophic lateral sclerosis, where motor neurons degenerate progressively. Analysis of motor cortex and spinal cord nuclei has revealed early changes in stress response pathways, RNA processing, and cytoskeletal organization. Beyond neurodegeneration, single-nucleus transcriptomics is increasingly used in psychiatric disorder research. Conditions such as schizophrenia, autism spectrum disorder, and major depressive disorder are associated with subtle but widespread changes in gene expression across brain cell types. Single-nucleus analysis has revealed altered transcriptional programs in synaptic signaling pathways, neurotransmitter systems, and neuronal connectivity. These findings support the hypothesis that psychiatric disorders arise from disruptions in neural circuit function rather than single-gene defects.

Another major contribution of single-nucleus transcriptomics is the identification of disease-associated cell states. In neurological disorders, cells often transition into abnormal transcriptional states that reflect stress, inflammation, or degeneration. These states are not restricted to a single cell type but can appear across multiple populations. Disease-associated microglia and reactive astrocytes have been identified based on distinct transcriptional signatures. These states are thought to play both protective and harmful roles depending on disease context. Spatial context is another important dimension in neurological research. Although single-nucleus transcriptomics does not inherently preserve spatial information, integration with spatial transcriptomics has enabled mapping of gene expression patterns within brain architecture. This combined approach has revealed region-specific vulnerability and spatial organization of disease-associated cell types. Single-nucleus transcriptomics also enables the study of epigenetically regulated gene expression in neurological disorders. Changes in chromatin accessibility and Deoxyribonucleic Acid (DNA) methylation often accompany transcriptional alterations in disease. Integration with single-nucleus Airborne Tactical Advantage Company (ATAC) sequencing provides insights into regulatory mechanisms driving gene expression changes. This multi-omics approach helps identify transcription factors and regulatory elements involved in disease pathogenesis. Additionally, nuclear RNA represents a subset of total cellular RNA, which may not fully reflect

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functional protein levels. Technical variability in nucleus isolation and sequencing depth can also affect data quality. Another challenge lies in interpreting the vast complexity of brain transcriptomic data. The brain contains an extremely diverse array of cell types and states, making it difficult to assign

functional roles to all observed transcriptional changes. Integrating transcriptomic data with proteomics, imaging, and electrophysiological data is essential for building a complete understanding of neurological function and disease.