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EC PSYCHOLOGY AND PSYCHIATRY
Research Article

Spatial Multiomics Analysis in Psychiatric Disorders

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Received: May 17, 2023; **Published:** June 19, 2023

Abstract

The aim of this study is to provide a comprehensive overview of spatial multiomics analysis, including its definition, processes, applications, significance and relevant research in psychiatric disorders. To achieve this, a literature search was conducted, focusing on three major spatial omics techniques and their application to three common psychiatric disorders: Alzheimer's disease (AD), schizophrenia, and autism spectrum disorders. Spatial genomics analysis has revealed specific genes associated with neuropsychiatric disorders in certain brain regions. Spatial transcriptomics analysis has identified genes related to AD in areas such as the hippocampus, olfactory bulb, and middle temporal gyrus. It has also provided insight into the response to AD in mouse models. Spatial proteogenomics has identified autism spectrum disorder (ASD)-risk genes in specific cell types, while schizophrenia risk loci have been linked to transcriptional signatures in the human hippocampus. In summary, spatial multiomics analysis offers a powerful approach to understand AD pathology and other psychiatric diseases, integrating multiple data modalities to identify risk genes for these disorders. It is valuable for studying psychiatric disorders with high or low cellular heterogeneity and provides new insights into the brain nucleome to predict disease progression and aid diagnosis and treatment.

Keywords: *Spatial Genomics; Spatial Transcriptomics; Spatial Proteogenomics; Alzheimer's Disease; Schizophrenia; Autism Spectrum Disorder*

Introduction

The central dogma of molecular biology describes the flow of genetic information: DNA is transcribed into RNA, which is then translated into protein. Each set of molecules - DNA, RNA, and protein - constitutes the genome, transcriptome, and proteome, respectively.

However, the organization of these molecules in the human body is not linear but rather three-dimensional and complex, composing up to trillions of cells, and distinct organs and tissues. RNAs and proteins are distributed in an organ-, tissue-, and cell-specific manner, with cellular or subcellular heterogeneity and complicated interactions between cells and the microenvironment [1]. Moreover, within the eukaryotic nucleus, DNA molecules wrap around histone proteins to form nucleosomes, which then condense into chromatin. Chromatin is then organized into higher-order structures including chromosome territories, chromatin loops, topologically associating domains, and A/B compartments [2].

These hierarchically organized structures regulate gene transcription, which is responsible for numerous biological processes during brain development and adult plasticity. By analyzing these structures simultaneously using multiple techniques, we can obtain a comprehensive understanding of disease mechanisms at the single-cell level in the context of tissues. This requires spatial biology analysis, including spatial genomics, spatial transcriptomics, and spatial proteomics in the present review.

Definitions of spatial biology: Spatial biology is an interdisciplinary field that includes spatial genomics, spatial transcriptomics, and spatial proteomics. Spatial genomics involves studying the three-dimensional arrangement of genetic material within cells and tissues. In contrast, spatial transcriptomics (or: spatially resolved transcriptomics (SRT)) is an innovative technology that combines quantitative transcriptomics with high-resolution tissue imaging and bioinformatic analyses. This technology anchors the expression data to the physical map of the organ or tissue(s) of interest, enabling researchers to determine the spatial organization of gene expression within tissues and cells [3]. Spatial proteomics, on the other hand, aims to identify and quantify the location of proteins within cells and tissues. Furthermore, spatial proteogenomics is an emerging field that combines spatial proteomics and genomics, providing a comprehensive understanding of the relationship between the spatial organization of proteins and their corresponding genetic information.

Processes of spatial biology analysis: Spatial biology studies the spatial organization of cells, their interactions, and their influence on the tissue microenvironment. Specifically, spatial genomics and transcriptomics investigate how spatial arrangement affects gene expression and cell behavior using specialized imaging techniques and high-throughput RNA sequencing. Spatial transcriptomics explores cell heterogeneity, microenvironment, function, and cellular interactions to deeply understand cell-specific responses and spatial localization in diseases [1]. There are various methods for SRT, including *in situ* sequencing-based SRT, *in situ* hybridization-based SRT, *in situ* capture-based SRT, microdissection-based SRT, living cell markers-based SRT, SRT by sequencing (SRT-seq), and SRT by imaging (SRTI) [1]. Spatial proteomics maps protein distribution in a spatial context using microscopy-based methods, mass spectrometry-based imaging, and bioinformatics. Spatial proteogenomics integrates techniques from spatial proteomics and genomics to generate comprehensive coverage of RNA and protein within a single tissue sample. In summary, spatial multi-omics integrates various molecules (DNA, RNA, proteins) and information with four-dimensional resolution (spatial and temporal) to provide a detailed cellular atlas from single cells to entire organisms [1].

Application of spatial biology analysis: Researchers can utilize SRT analysis, a powerful technique, to investigate gene expression patterns and cellular organization in complex tissues. SRT analysis enables visual representation and identification of gene expression and cell location within a tissue sample, facilitating unbiased molecular characterization of tissue sections and identification of differentially expressed genes with spatial patterns [3]. It also helps decode dysregulated cellular networks near Alzheimer's and other brain diseases' pathogenic markers and provides valuable information on the spatial relationships between different cell types, gene expression patterns, and biological pathways within tissues [4]. Combining SRT analysis with calcium imaging and/or optogenetic probing allows for multimodal analysis that produces interpretations of circuit activity specific to particular cell types, fully utilizing the potential of SRT analysis to unveil complex intercellular interactions, gene regulatory networks, and subcellular structures under physiological and pathological conditions. The application of SRT analysis enables the mapping of cellular heterogeneity, complex tissue structures, and dynamic changes during development and diseases [1]. Overall, SRT analysis holds great potential for a wide range of applications in the study of developmental biology, disease pathology, and drug discovery.

Significance of spatial biology analysis: Spatial genomics, transcriptomics, and proteomics can revolutionize our understanding of complex biological systems by creating detailed maps of gene expression patterns, providing a spatially resolved view of gene expression within tissues, and identifying potential therapeutic targets for disease. Spatial proteomics can also help to elucidate the roles of different proteins in biological processes and potential drug targets for diseases at protein level. Furthermore, spatial proteogenomics has the potential to provide new insights into the fundamental principles of biology and advance personalized medicine. These multi-omics analyses can offer reliable information for investigating disease causation, therapeutic targets, and biomarker discovery.

The organization of the spatial genome, transcriptome, and proteome is closely linked to their respective functions. Disruption of this organization in the brain can lead to dysregulated gene expression in the nervous system, which may contribute to the development of brain disorders [2]. The neocortex, which comprises six distinct layers, is composed of different cell types with varying densities and gene expression patterns [5]. Accurately localizing spatial gene expression within these layers at a cellular resolution can deepen our understanding of the pathology of neuropsychiatric disorders or specific aspects of these disorders that are layer-specific [6]. In this study, we aim to review the findings of spatial multiomics analyses in psychiatric disorders.

Methodology

A systematic literature search was conducted using the PubMed database to identify papers published up to May 2023, with the search terms "Spatial* AND (genom* OR transcriptom* OR proteogenom* OR proteom*)". From over 1000 papers, we extracted eight that studied on any psychiatric disorder. The present study reviewed, summarized, and discussed the positive findings regarding spatial multi-omics in psychiatric disorders.

Results

The organization of gene expression in the brain is often specific to certain layers or regions and may contribute to the development of various neuropsychiatric disorders, which rationalizes the spatial biology analysis in the field. For example, in the dorsolateral prefrontal cortex, which is implicated in multiple neuropsychiatric conditions [7], spatial transcriptomics analysis has identified several laminar flow marker genes, such as AQP4 (Layer 1; L1), HPCAL1 (L2), FREM3 (L3), TRABD2A (L5), and KRT17 (L6) [1], that may underlie layer-specific brain disorders. Similarly, spatial proteomics analysis has revealed several region-specific genes enriched in neuronal cells within the cerebral cortex at the protein level [8] and transcriptional biomarkers of inhibitory and excitatory neurons within the frontal cortex that may contribute to region-specific brain disorders [8]. To date, spatial multiomics research has predominantly concentrated on AD, with only a limited number of studies investigating schizophrenia, ASD and other psychiatric diseases.

Genome-scale chromosome conformation mappings ('Hi-C') have linked locus-specific abnormal expansion of repeat sequences at the boundaries of self-associating topological chromatin domains to neurodevelopmental and neurodegenerative diseases such as AD [9]. Spatial transcriptomics analysis identified differentially expressed genes in the hippocampus and olfactory bulb of early AD, revealing a diverse set of stress response and transcription modulating genes in both regions [4]. The analysis found the *Bok* gene, implicated in mitochondrial physiology and cell death, to be spatially downregulated in the hippocampal CA3 region of both mouse and human AD brains, highlighting its importance in AD pathogenesis [3]. SRT identified layer-specific differentially expressed genes (DEGs), including AD-related signals, in the middle temporal gyrus 2/3 cortical layer [10]. In an AD mouse model, SRT identified conserved plaque-induced and oligodendrocyte gene (*OLIG*) responses, suggesting complement as an essential component of cellular interactions in the amyloid plaque microenvironment, and *OLIG* upregulation may protect against AD [4,10]. Moreover, SRT in human AD brain cortical laminae and the white matter identified unique gene signatures and biological pathways contributing to AD pathology vulnerability [10]. Single-molecule fluorescent *in situ* hybridization validated cell-type-specific expression of novel and previously reported DEGs associated with AD pathology at the single-cell level, while gene co-expression analyses revealed eight gene modules, four of which had significantly altered co-expression patterns in the presence of AD pathology [10].

Using Laser capture microdissection coupled with RNA sequencing (LCM-seq) technology, a study identified 15 transcriptional signatures associated with schizophrenia risk loci, including *GRM3* and *CACNA1C*, which encode G protein-coupled receptors and ion channels, in the human hippocampal dentate gyrus granular cell layer (DG-GCL) [11]. The DG-GCL also had 9 million expressed quantitative trait loci (eQTLs) [1,11]. Integrative cell-type-specific Hi-C and transcriptomic analysis identified an expanded genomic risk space for sequences conferring liability for schizophrenia and other cognitive diseases, particularly in the hippocampus, which is closely associated with schizophrenia pathogenesis [9]. Finally, spatial proteogenomics identified 20 ASD-risk genes disrupted in distinct cell-types, including *GRIK1, EMX2, STXBP6*, and *KCNJ3*, which are predominantly distributed in certain human interactome modules and may regulate some of the known ASD loci [8].

Discussion and Conclusion

Spatial multiomics analysis offers a rich resource of spatially differentially expressed genes and an unparalleled approach to unraveling the dysregulated cellular network surrounding pathogenic hallmarks of AD and other brain diseases for understanding AD pathology [3]. The analysis's findings can aid in understanding the complex architecture and neuronal/glial response to AD pathology in vulnerable brain regions [10]. Additionally, the analysis integrates multiple data modalities, providing insight into disease progression and biomarker discovery [8]. Tissue-wide cell-specific spatial multiomics modeling can identify risk genes for psychiatric disorders [8]. Spatial multiomics analysis can also be leveraged to comprehend disease mechanisms, select therapeutic targets, and establish biomarkers. The discovery of cell type-specific associations by spatial multiomics analysis can considerably benefit the development of experimental models for psychiatric disorder treatment, offering powerful tools to unveil the molecular mechanisms of these disorders at the single-cell or subcellular level [1].

Spatial multiomics techniques provide a spatial context to evaluate cell diversity, states, and interactions, with location being crucial to comprehending cell function and biology. This spatially resolved cellular information is valuable in understanding diseases that affect organs with high homogeneity and structural organization, as well as those with cellular heterogeneity, such as those related to neuroscience [1]. Investigating spatial multiomics can improve our understanding of the nervous system and its associated psychiatric disorders by revealing new insights into the brain nucleome and identifying potential biomarkers to predict disease progression, significantly aiding in diagnosis and treatment [1,9].

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Volume 12 Issue 6 June 2023