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Spatiotemporal Omics: Integrating Multi-Omics Data for Translational Research and Drug Development

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ABSTRACT
Spatiotemporal omics is an innovative approach that integrates various multi-omics data—such as genomics, transcriptomics, proteomics, epigenomics, and metabolomics—within spatial and temporal contexts to provide a comprehensive understanding of biological systems. This approach aims to uncover cellular dynamics, molecular interactions, and disease mechanisms across diverse fields, including neuroscience, developmental biology, cancer research, and precision medicine. Cutting-edge technologies such as Stereo-seq, Slide-seq, DBiT-seq, and MISAR-seq enable high-resolution mapping of gene and protein expression within intact tissues, revealing complex spatial heterogeneity and cellular organization. Through integration with artificial intelligence and machine learning algorithms, complex multi-omics data can be analyzed holistically to generate accurate predictive models. Research findings show that spatiotemporal omics effectively identifies tumor microenvironments, drug resistance mechanisms, neural connectivity, and organ development pathways. In precision medicine, this approach offers significant opportunities for discovering novel biomarkers and developing personalized therapies based on patients' molecular profiles. Despite ongoing challenges such as technical complexity and high costs, spatiotemporal omics holds great potential to revolutionize biomedical research and clinical practice in the future.

Keywords: Developmental biology, Drug resistance, Neuroscience, Precision medicine, Spatial transcriptomics, Tumor microenvironment.

INTRODUCTION

Regulation of biological processes occurs at multiple scales, ranging from organelles, cells, tissues, organs, to organisms, all of which are critical to understanding the basic mechanisms that sustain life. The rapid progress in modern biology is inseparable from the advent of omics and high-throughput technologies that enable comprehensive analysis and provide deep insights into genomics, transcriptomics, proteomics, epigenomics and metabolomics. Although these omics approaches provide a wealth of molecular information, a major challenge in biological research is the limited spatial resolution and integration of temporal dynamics, which spatiotemporal omics attempts to address. In contrast to traditional omics, spatiotemporal omics does not only

focus on measuring molecular profiles, but also considers the exact localization in tissues and changes that occur over time (X. Wang & Fan, 2021). This transformative technology integrates spatial and temporal data to provide a multidimensional perspective on cellular dynamics, molecular interactions, and disease mechanisms (X. Wang & Fan, 2021).

Spatiotemporal omics technologies, such as Stereo-seq, allow researchers to capture cellular gene expression patterns while maintaining spatial context within tissues, resulting in revolutionary discoveries in the fields of neuroscience, oncology, and developmental biology (Du et al., 2023). Technologies such as Slide-seq V2 allow researchers to map RNA expression directly from intact tissue, which reveals disease-specific cell environments (Marshall et al., 2022). DbiT-seq is another important advancement that uses deterministic coding in tissues to map mRNAs and proteins with high spatial resolution, allowing for more detailed visualization. The Spatiotemporal Omics Consortium (STOC), which brings together global scientific efforts, highlights the urgency of creating a comprehensive atlas of spatiotemporal cells to deepen our understanding of biological processes and their impact on health and disease (STOC, n.d.).

Previous research has shown that an understanding of spatial and temporal regulation in tissues is critical in unraveling the pathogenesis of various diseases, including cancer, neurological diseases and developmental disorders. For example, a research by (L. Liu et al., 2024) showed how spatiotemporal omics technology can help identify gene expression patterns in cancer, which can accelerate the discovery of more targeted therapies. Meanwhile, (Marshall et al., 2022) in their research revealed how Slide-seq V2 provides new insights into the spatial relationships between cells in tumors, which opens up new opportunities for the development of location-based therapies. Another research by (Y. Liu et al., 2020) showed the potential use of DbiT-seq in visualizing proteins in a highly detailed spatial context, which provides a deeper understanding of molecular interactions in neurodegenerative diseases.

The urgency of this research lies in the pressing need to overcome the limitations that exist in molecular biology research that relies solely on traditional omics techniques. Although omics provides information on molecular expression, without the spatial and temporal context, much important information is lost. Therefore, this research will fill the gap in our understanding of biological dynamics by utilizing spatiotemporal omics technology to explore molecular interactions in the context of space and time. The novelty of this research lies in the integration of multi-omics data with spatial and temporal perspectives that have not been widely explored in disease research, especially in the development of precision medicine-based therapies.

Based on the above background, the purpose of this research is to explore the application of spatiotemporal omics technology in translational research, especially in the development of more targeted therapies in the treatment of cancer, neurological disorders, and developmental diseases. The benefit of this research is to make a significant contribution to the advancement of biomedical science, which in turn can accelerate the discovery of new therapies and more effective treatments for patients with difficult-to-treat diseases.

RESEARCH METHOD

The methodology employed in this paper adopted a systematic and scientific approach to ensure comprehensive and credible analysis. An extensive literature review was conducted using databases such as PubMed, Scopus, and Web of Science, focusing on the keywords “spatiotemporal omics,” “spatial transcriptomics,” and “precision medicine.” Priority was given to articles published within the last five years, particularly those introducing transformative technologies like Stereo-seq, Slide-seqV2, and DBiT-seq. Both experimental and review studies were examined to provide a balanced understanding of the topic. A structured outline guided the flow of discussion, beginning with the historical background of spatiotemporal omics, followed by its application in key fields such as neuroscience, cancer research, developmental biology, and precision medicine. Complex methods, including spatial transcriptomics and proteomics, were described in detail to enhance clarity, supported by computational tools and artificial intelligence for the analysis of high-dimensional omics data.

The manuscript incorporated visual elements such as figures and tables to effectively present intricate findings. All references were thoroughly verified and formatted in accordance with Scopus journal standards. Ethical considerations were acknowledged, especially for studies involving human or animal tissues. Additionally, the paper addressed ongoing challenges such as high costs and technical complexity, while highlighting the transformative potential of spatiotemporal omics in biomedical research. The manuscript underwent multiple revisions to improve clarity, coherence, and scientific validity. Expert feedback was integrated throughout the writing process to ensure accuracy and relevance. Overall, this paper aims to contribute to the growing body of knowledge by synthesizing current research and offering insights into the future directions of spatiotemporal omics.

RESULT AND DISCUSSION

Spatiotemporal Omics: A New Dimension in Biology

Biology has evolved through key milestones that transformed our understanding of life. The cell theory by (Müller-Wille, 2010) and the DNA double-helix model by (Klug, 2004) laid foundational knowledge. The Human Genome Project further advanced biology by decoding the complete human genome. It produced three main tools: a genetic map to locate inherited genes, a physical map with overlapping DNA fragments for future analysis, and a DNA sequence map covering all 3 billion base pairs. This database enabled disease-related gene discovery and drug target development. Applications include genetic testing for diseases like cystic fibrosis and type 1 diabetes as well as gene therapy (Murray et al., 1994).

Biological advancements have led to spatiotemporal omics, integrating spatial and temporal data for deeper insights (X. Liu et al., 2024). Spatial multi-omics allows simultaneous analysis of transcriptomics, proteomics, genomics, epigenomics, and metabolomics within the

same tissue, enhancing understanding in areas like developmental biology, neuroscience, and cancer studies (X. Liu et al., 2024).

Though cells share the same DNA, epigenetic mutations regulate gene expression. Spatial genomics is used to profile genome-wide changes in development and disease (Jena et al., 2024), including in-situ sequencing (Payne et al., 2021) and Slide-DNA-seq(Rodriques, Stickels, Goeva, Martin, Murray, Vanderburg, et al., 2019). Spatial transcriptomics detects and quantifies RNA within tissues using methods like smFISH (Lee et al., 2016), MERFISH (K. H. Chen et al., 2015), seqFISH (Shah et al., 2017), FISSEQ (Liao et al., 2021), Stereo-seq (Xia et al., 2022).

Spatial proteomics studies protein localization in cells and tissues, aiding in biomarker discovery and spatial atlas construction (Lammi & Qu, 2024). Protein function is tied to localization due to different interaction environments (Lundberg & Borner, 2019). Techniques include mass spectrometry-based and imaging-based methods (Christopher et al., 2021).

The epigenome, containing histone and DNA modifications, controls cell states within tissues. Spatial epigenomics offers insights into disease-related epigenetic regulation, with techniques such as CUT&Tag (Schueder & Bewersdorf, 2022) and MERFISH (Lu et al., 2022).

Metabolites are essential as substrates, intermediates, or final products in biological processes. Understanding spatial metabolomics is key to identifying tissue-specific phenotypes (Santos et al., 2024). Techniques of spatial metabolomics such as FT-MS (Ghaste et al., 2016), NMR (Dona et al., 2016), and LC/MS (Thomas et al., 2022).

Applications in Neuroscience and Developmental Biology

Spatial omics provides deep insights into cellular and molecular landscapes, enabling the research of gene expression and protein localization. In neuroscience, it reveals neural circuitry patterns, regional heterogeneity, and brain atlas composition. In developmental biology, it uncovers processes like embryogenesis, morphogenesis, and organogenesis (Jung & Kim, 2023).

Spatial transcriptomics maps gene expression in intact brain tissues, preserving spatial context lost in scRNA-seq. It enables cell atlas generation, such as the Human Cell Atlases and BRAIN Initiative Cell Census Network (BICCN), which catalogs brain cell types across species and developmental stages, particularly in the hippocampus and dorsolateral prefrontal cortex (Cao et al., 2024); (Center, 2025).

Using seqFISH, researchers identified 13 distinct cell clusters targeting 250 genes in the mouse hippocampus, showing increased heterogeneity in ventral CA1. MERFISH combined with scRNA-seq revealed ~70 neuronal cell types in the hypothalamus (Moffitt et al., 2018). In the human thalamus, MERFISH and scRNA-seq highlighted first-trimester GABAergic and glutamatergic neuron organization (Kim et al., 2023).

Spatial omics also supports brain disease research. The Ivy Glioblastoma Atlas Project (Ivy GAP) maps glioblastoma microenvironments and identifies drug target cells using RNA-seq and laser microdissection (Yu et al., 2017). It revealed CD8+ T cell hypofunctionality due to poor CD4+ interaction. Dendritic cell vaccines may improve CD8+ activation (Naulaerts et al., 2023).

At the protein level, SUM-PAINT imaging visualizes over 30 proteins in the hippocampus with single-protein resolution, identifying synapse types and neuronal architectures (Unterauer et al., 2024). In developmental biology, spatial transcriptomics supports atlas creation for embryogenesis, showing sequential gene expression during tissue differentiatio (Du et al., 2023). For instance, gastrulation produces the endoderm, mesoderm, and ectoderm, which develop into organ systems (Muhr et al., 2023). COSMOS integrates spatial transcriptomics and proteomics using graph networks, identifying 22 proteins and 254 genes in mouse embryo brain with accurate domain segmentation (Zhou et al., 2025). MISAR-seq enables spatial profiling of chromatin accessibility and gene expression (Jiang, Zhou, Qian, Zhu, Wang, Li, Shen, Wang, et al., 2023). SPARC-seq further maps chromatin accessibility and transcriptomes in E15.5 mouse brain, identifying ATAC and RNA clusters matching known cell types(Jiang, Zhou, Qian, Zhu, Wang, Li, Shen, Qu, et al., 2023).

Cancer Research and Tumor Microenvironment Analysis

Cancer is a complex disease characterized by uncontrolled cell growth, genetic mutations, and interactions within the tumor microenvironment (TME). The TME is composed of immune cells, fibroblasts, endothelial cells, and tissue-resident cells. Advances in spatial profiling and computational methods enable understanding of spatial and molecular diversity in tumors (de Visser & Joyce, 2023).

Cancer is influenced by genetic alteration, metabolic reprogramming, immune surveillance, and therapeutic stress. High-dimensional spatial mapping at different times recaps cancer evolution (Y. Wu et al., 2022). A major problem in cancer is TME heterogeneity, causing spatial and temporal variations (Dagogo-Jack & Shaw, 2018). Spatial transcriptomics reveals prostate cancer TME diversity and dynamic gene expression, showing different gene activity in center and periphery (Berglund et al., 2018).

Melanoma also shows genetic heterogeneity with diverse subclones. Spatial transcriptomics examined heterogeneity in melanoma and lymph node metastases. HLA and CD74 expression correlates with survival and appears in transition zones, giving insight into heterogeneity and resistance (Thrane et al., 2018). Understanding the TME spatial organization is essential for discovering tumourigenesis mechanisms and designing novel therapeutic strategies.

Cellular plasticity, driven by microenvironment and genetic changes, alters cell phenotype, promoting tumor progression and drug resistance. Metaplasia involves chromatin changes and gene expression shifts. EMT is critical in cancer development, with epithelial cells becoming motile and invasive (Derynck & Weinberg, 2019).

Although it is controversial, most researchers agree that cancer cells require plasticity that is in equilibrium between epithelial and mesenchymal phenotypes to adapt themselves to different conditions. In invasive carcinomas, this shifts to mesenchymal. Spatial transcriptomics identifies markers like TNC, TGFB, WEE1, FOS, RHOB, and VIM in lung tumors (Takano et al.,

2024). Another research using Visium and CellCharter found spatial heterogeneity in lung cancer, with NDRG1 upregulated in some clusters. A niche with hypoxia-responsive and EMT profiles, surrounded by tumor-associated neutrophils (TANs), was found. TANs amplify chemokine signals, promoting migration and EMT (Varrone et al., 2024).

Integrating Multi-Omics Data: A Systems Biology Approach

The rapid advancements in high-throughput technologies have enabled the production of diverse omics data—genomics, transcriptomics, proteomics, metabolomics, and epigenomics. While each dataset offers unique insights, integrating spatial multi-omics data through systems biology enables a holistic view of cellular and organismal function. Computational tools and data-driven models support the simultaneous analysis of multiple modalities in the same area.

Spatial epigenomics and transcriptomics can be integrated using spatial ATAC-seq or CUT&Tag with transcriptomics via deterministic cobarcoding. Applied to embryonic and juvenile mouse and human brain, this approach produced a more comprehensive atlas of gene regulation. Spatial ATAC-RNA-seq showed that chromatin accessibility alone may not fully distinguish all cell types, while integrated analysis identified novel clusters not seen with single modalities (Zhang et al., 2023).

Combining spatial transcriptomics and metabolomics has revealed complex molecular interactions. In Parkinson's disease studies, integration of barcoded transcriptomics with MALDI-MSI and histological staining showed dopamine presence in specific brain regions and identified gene expressions associated with it in both mouse and human brains (Vicari et al., 2024).

MiP-seq is a high-throughput in situ sequencing method that profiles DNA, RNA, proteins, and biomolecules at subcellular resolution. It uses padlock probes for multiplex detection, enabling the mapping of hundreds of genes within two sequencing cycles. MiP-seq has been applied to spatially map the nucleus of brain regions and to detect viral mRNA and proteins in infected PK-15 cells (X. Wu et al., 2024).

Spatiotemporal omics allows the construction of high-resolution spatial atlases, enabling the research of cell composition, interactions, and tumor heterogeneity. Integrating spatial omics deepens understanding of cell development, function, and disease progression, and provides promising insights into tumor metabolism, therapeutic targets, and biomarkers (X. Liu et al., 2024).

Discussion

Advances in Spatial Transcriptomics

Spatial transcriptomics is a breakthrough in molecular biology, enabling gene expression profiling in intact tissues and offering insights into cellular behavior and interactions. Initially, transcriptomics used hybridization-based microarrays and later RNA-seq with next-generation sequencing (Tzec-Interián et al., 2024). Single-cell RNA sequencing (scRNA-seq) allowed transcriptome analysis at cellular level, but faced challenges like cell isolation stress, especially in delicate tissues like the brain (Haque et al., 2017); (Maynard et al., 2021).

Spatial transcriptomics addresses these limitations by preserving spatial context, allowing analysis of gene expression patterns and cell interactions within tissue structures (Haque et al., 2017). Recognized as Nature Methods "Method of the Year 2020" (Marx, 2021), spatial transcriptomics relies on imaging-based and sequencing-based techniques.. Imaging-based methods, such as in situ hybridization (ISH) and in situ sequencing (ISS), use labeled probes to detect RNA in tissues. smFISH (Femino et al., 1998), evolved into seqFISH and seqFISH+ for multiplexing, and MERFISH for high-resolution RNA imaging (Eng et al., 2019); (K. H. Chen et al., 2015). ISS technologies like FISSEQ, ExSeq, and STARmap improved detection and reduced errors (Yue et al., 2023) though they remain time- and data-intensive.

Sequencing-based approaches avoid image processing limitations. Techniques include laser capture microdissection, Tomo-seq (Kruse et al., 2016), Geo-seq (J. Chen et al., 2017) and Slide-seq, which uses DNA-barcoded beads for RNA localization (Rodriques, Stickels, Goeva, Martin, Murray, V, et al., 2019). Slide-seqV2 improved recovery rates (Stickels et al., 2021). HDST offers denser spatial resolution (Vickovic et al., 2019), while DBiT-seq combines mRNA and protein profiling via microfluidic barcoding. Stereo-seq currently provides the highest resolution (Xia et al., 2022).

Neuroscience and Neural Connectivity

Neural functions are defined by the connections between neurons. Spatial transcriptomics provides insights into gene expression with spatial resolution, allowing accurate identification of individual cells and their interactions (Chan et al., 2022). Excessive folic acid intake during early pregnancy has been shown to disrupt neurogenesis and axon myelination pathways, particularly in the thalamus and dentate gyrus, thereby affecting the expression of genes related to learning and memory (Xu et al., 2024).

Visium spatial transcriptomics has been used to investigate chronic social defeat stress (CSDS) in mice, revealing region-specific transcriptional changes associated with stress susceptibility. It revealed transcriptional changes in the hippocampus, isocortex, and amygdala, emphasizing inter-regional signaling networks involved in stress susceptibility (T. Wang et al., 2023). Spatial transcriptomics, complementing scRNA-seq, helped identify region-specific gene expression linked to mental health disorders and intercellular communication (Heydari & Sindi, 2023); (Junaid et al., 2025).

The integration of spatial transcriptomics and metabolomics has been applied to examine traumatic brain injury (TBI), uncovering molecular and functional alterations across injury severity levels. They found metabolic heterogeneity, increased lipid peroxidation, and altered myo-inositol levels. Genes like S1PR5 and SLC5A11 were linked to lipid metabolism and apoptosis, validated in animal models (Zheng et al., 2023).

Aging-related brain changes were explored by Hahn et al. (2023) using spatial transcriptomics in young and aged mice. Senescent cells accumulated in white matter and

hippocampus, with neuroinflammatory gene signatures linked to cognitive decline (Hahn et al., 2023).

In Alzheimer's disease (AD), spatial transcriptomics revealed disrupted neural connectivity and amyloid plaque-associated gene networks (W. T. Chen et al., 2020). Single nucleus RNA-seq and spatial analysis showed increased oligodendrocyte presence in white matter, indicating reparative responses. (Fan & Li, 2024) identified disease-associated oligodendrocyte subtypes and 12 upregulated genes, with PLXDC2 emerging as a potential early biomarker..

Cancer Microenvironments and Drug Resistance

Tumors are complex ecosystems composed of host cells, secreted factors, and extracellular matrix (ECM). The tumor microenvironment (TME) plays a key role in cancer development, progression, and therapeutic resistance by facilitating communication between tumor and surrounding cells (Arneth, 2020); (de Visser & Joyce, 2023).

In breast cancer, spatial transcriptomics enables localization of functional gene expression, enhancing understanding of tumor heterogeneity and immune escape. Combining scRNA-seq and spatial data has identified LSM1 as a biomarker linked to macrophage activity and cancer progression (Tzeng et al., 2023). A lipid-rich TME subtype, tumor-adipose microenvironment, is especially relevant in breast cancer due to adipocyte abundance. Lipid-associated macrophages exhibit immunosuppressive traits and heightened phagocytosis (Z. Liu et al., 2022).

Pancreatic cancer exhibits heterogeneity in gene expression and tissue damage. Spatial transcriptomics revealed a KRT13+FAB5+ malignant subpopulation and damage to exocrine more than endocrine tissue, while fibroblasts in adjacent tissue showed tumor-suppressive potential (Ren et al., 2023). Pancreatic cancer exhibits heterogeneity in gene expression and tissue damage. Spatial transcriptomics revealed a KRT13+FAB5+ malignant subpopulation and damage to exocrine more than endocrine tissue, while fibroblasts in adjacent tissue showed tumor-suppressive potential (B. Yang et al., 2022). TME components—such as TAMs, CAFs, and TA-MSCs—promote drug resistance via cytokine secretion. The ECM also contributes by forming physical barriers, remodeling environments, and activating survival pathways (T. Xu et al., 2021); (Bai et al., 2018); (Marozzi et al., 2021)

Spatial transcriptomics (ST) has revolutionized understanding of TME, aiding in tumor subtype classification, biomarker discovery, prognosis, and therapy prediction. Despite its high potential, ST faces limitations like cost and data complexity (Q. Li et al., 2022)

Drug resistance, once known in antibiotics, now widely affects cancer therapy. Mechanisms include drug efflux, DNA repair, EMT, target alteration, and drug inactivation (Housman et al., 2014). In hepatocellular carcinoma, overexpression of oncogenic protein SPINK1 promotes chemoresistance to sorafenib and oxaliplatin by upregulating CES2 and CYP3A5. Spatial transcriptomics identified SPINK1 as a key therapeutic target (C. Yang et al., 2024). Overall, spatial omics enhances our understanding of molecular heterogeneity and spatial dynamics in tumors, providing new avenues for diagnosis and treatment in oncology..

Organogenesis and Developmental Biology

Developmental biology studies how a multicellular organism grows from a single cell. Understanding when, where, and how genes are expressed during this process is essential (Ko, 2001). Early studies relied on bulk RNA-seq and scRNA-seq to capture molecular activity, with scRNA-seq offering higher resolution of cellular differences (Hrdlickova et al., 2017). However, these methods lacked spatial context, which spatial transcriptomics now provides by mapping gene expression within tissue structures (Choe et al., 2023).

Traditional dissociation-based techniques couldn't preserve tissue architecture, limiting spatial gene analysis. Recent advances now allow exploration of cell organization in both adult tissues and developing embryos. While most embryogenesis studies use animal models, research in human embryos remains limited due to ethical constraints (Y. Xu & Shi, 2023).

scRNA-seq was first used in 2009 on a mouse embryo, revealing over 5,000 genes—surpassing earlier microarray capabilities (Tang et al., 2009). Kumar et al. (2023) used Slide-seq to create a 3D transcriptomic map of mouse embryos (E8.5 to E9.5), identifying early organ development patterns and building sc3D to research local gene regulatory networks (Sampath Kumar et al., 2023). In humans, gastrulation—key to early development—remains poorly understood due to access limitations. Tomo-seq applied to human gastruloids treated with WNT agonist revealed gene expression patterns comparable to Carnegie-stage-9 embryos (Moris et al., 2020).

Spatial transcriptomics combined with scRNA-seq has been performed on seven human embryos (4–6 weeks), identifying spatially organized cell types, including previously uncharacterized head mesoderm cells (Y. Xu & Shi, 2023). Transcriptomic profiling of 88 pre-implantation embryos revealed early lineage differentiation into trophectoderm, epiblast, and primitive endoderm. Furthermore, the integration of spatial transcriptomics and scRNA-seq enabled the construction of cardiac transcriptional maps across three embryonic heart stages, which were validated using in situ sequencing (Petropoulos et al., 2016). A similar approach without in situ sequencing was used to profile the liver at 8 and 17 post-conception weeks, identifying over 20 cell types and their differentiation in fetal development (Hou et al., 2021).

Applications in Precision Medicine

Traditional treatments followed a "one-size-fits-all" model, often ineffective for 20% of patients due to genetic differences. Evidence-based medicine improved care but relied on population-level data. Precision medicine addresses this by tailoring treatment based on individual genetic, environmental, and lifestyle factors (Vogenberg et al., 2010); (Visvikis-Siest et al., 2020). Though the human genome is 99.1% identical, the 0.9% variation significantly affects disease risk and drug response (Ahmed et al., 2020).

Advances in spatial omics technologies have accelerated the identification of biomarkers linked to specific diseases, paving the way for targeted therapies. Biomarkers play a strategic role in precision medicine to improve human health to each individual or subgroups by adjusting the

treatment or doses based on the use of disease-specific biomarkers (Slikker, 2018). In endometrial cancer, spatial proteomics were used for examining the proteomics of sentinel lymph nodes in patients with endometrial cancer. Aboulouard et al. (2021) identified biomarkers that are associated with clinical prognosis. PRSS3, PTX3, and ASS1 are the biomarkers associated with a poor prognosis, while ALDH2 and ANX1 are correlated with a positive outcome (R. Li & Zhou, 2021). In cutaneous T cell lymphoma, CODEX multiplexed tissue imaging and RNA-seq were performed on tumor patients skin. This research focused on spatial distribution of different types of immune cells (PD-1+ CD4+ T cells, tumor cells, and immunosuppressive Tregs) within tumors. Based on their spatial distribution, researchers developed a biomarker, which predicts how well patients with cutaneous T-cell lymphoma will respond to pembrolizumab. An increased in biomarker associated with an elevation of T cell suppressive activity and is correlated with non-response, and vice versa (Phillips et al., 2021). In non small cell lung cancer, researchers investigated biomarkers candidate that are correlated to immune checkpoint inhibitor resistance. The method used were digital spatial profiling to detect proteins in four molecular compartments (tumor, leukocytes, macrophages, and immune stroma). It was revealed that CD66b in the immune stroma molecular compartment significantly associated with shorter overall survival (Moutafi et al., 2022).

In cutaneous squamous cell carcinoma, transcriptomic mapping showed tumor-specific keratinocyte gene clusters at invasive fronts, highlighting their role in metastasis (Ji et al., 2020). In intrahepatic cholangiocarcinoma, Stereo-seq revealed fibroblast and immune cell dominance at invasive regions, with markers of cell proliferation (L. Wu et al., 2021). Similarly, Visium-based spatial transcriptomics in primary liver cancer demonstrated how tumor capsules affect spatial clustering and immune cell infiltration (R. Wu et al., 2021).

Spatial omics approaches have been widely used in cancer research, but its potential extends far beyond it. This technology has also been applied to uncover the mechanisms and spatial organization in non-cancerous diseases. The patients suffered from respiratory disease COVID-19 were observed for their tissues samples, particularly alveolar, airway, and vascular compartments. Spatial transcriptomics revealed that pathways of inflammatory response were increased in the lungs of patients with COVID-19 as compared with normal patients mainly in the alveolar and airway in early stage. The comparison also showed an increased in interactions between fibroblasts and macrophages suggesting a contribution to fibrosis and the thickening of the alveolar wall in late stage (Rendeiro et al., 2021). In the research of myocardial infarction, which is the largest contributor for cardiovascular related deaths, researchers used an integration of snRNA-seq and snATAC-seq together with Visium spatial transcriptomics to spatially map human cardiac tissue in healthy condition and post-myocardial infarction. The mechanism of which fibroblasts differentiate to myofibroblasts that induced progression to cardiac fibrosis was observed from the increasing and reducing of specific markers. Novel insights into gene

regulation across different zones, such as the ischemic core, border zone, and fibrotic zones (Kuppe et al., 2022).

Utilizing scRNA-seq and spatial transcriptomics, a research on chronic human tendon disease built an atlas of cellular environment from healthy and diseased tissues. It was discovered that there is a unique population of cycling macrophage residing in diseased tendon tissue, while in the healthy tissue, the profile of macrophage mostly resembled tissue repair activity. The identification of specific factors in tenocytes and macrophages and the role of stromal cells in immune activation highlight the importance of these markers in targeted tendon disease treatment (Akbar et al., 2021). Taken together, the above researches demonstrate the application of spatiotemporal omics in identifying patient-specific molecular profiles. This approach enhances therapeutic outcomes by aligning treatment with individual omics landscapes.

Emerging Techniques and Future Directions

Spatiotemporal omics has emerged as a powerful tool for understanding biological systems by providing insights into gene regulation, tissue structure, and cellular interactions. Spatial multi-omics enables simultaneous analysis of various data types. For example, DBiT-seq captures both protein and mRNA expression in the same tissue, and MISAR-seq profiles chromatin accessibility alongside gene expression. Technologies like Stereo-seq offer near single-cell resolution for detailed spatial visualization.

The future of this field involves integrating AI and machine learning to process complex, high-volume data. Deep learning can uncover hidden patterns and aid in constructing predictive models, including comprehensive cell atlases. In drug development, spatiotemporal omics helps identify disease-associated genes, drug response pathways, and treatment efficacy across different cell types—supporting the development of precision therapies. Despite its promise, the technology faces challenges such as high costs and technical complexity. However, with continued advancement, spatiotemporal omics is expected to transform clinical research and precision medicine..

CONCLUSION

In conclusion, the the concept of spatiotemporal omics is a groundbreaking approach of modern biology that allows for comprehensive analysis of genomics, transcriptomics, proteomics, epigenomics, and metabolomics with the integration of spatial and temporal context. This transformative technology has provide abundant insights into cellular and molecular landscapes, precise localization of cells and gene expression within tissue, hence understanding the complex biological systems in a variety of fields, such as developmental biology, neuroscience, cancer research, and precision medicine. As the technology conitnues to improve, spatiotemporal omics is going to is expected to revolutionize researchers' approaches

to deciphering molecular complexity, discovering novel therapies, and advancing translational research in the future.

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