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Research Progress in Single-Cell RNA Sequencing and Spatial Transcriptomics for Precision Oncology

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Abstract. Tumor heterogeneity is one of the key factors leading to diagnostic errors, difficulty in identifying subtle cellular differences, and the occurrence of immune escape. Although single-cell RNA sequencing (scRNA-seq) has elucidated the molecular characteristics and heterogeneity at the single-cell level, it fails to retain spatial location information. In contrast, spatial transcriptomics (ST) technology can simultaneously acquire gene expression information and cellular localization, providing a unique perspective for studying the tumor microenvironment, cell-cell interactions, and other aspects. The integrated application of scRNA-seq and ST technologies enables the analysis of tumor heterogeneity from both molecular and spatial dimensions, offering comprehensive information support for precision medicine. The complementary advantages of these two technologies not only overcome the limitations of traditional methods but also promote the research on complex mechanisms such as tumor heterogeneity and the tumor microenvironment, accelerating the translational process of clinical applications.

Keywords: Spatial Transcriptomics, Single-Cell RNA Sequencing, Tumor, Precision Medicine

1. Principles of single-cell RNA sequencing technology and spatial transcriptomics technology

1.1. Single-cell RNA sequencing technology

Single-cell RNA sequencing (scRNA-seq) technology reveals the heterogeneity and dynamic changes within cell populations through high-resolution analysis of the transcriptome of individual cells. Current mainstream high-throughput technical approaches include Drop-seq and InDrop, with the core workflow as follows: first, microfluidic technology is used to isolate and encapsulate single cells; cell lysis and mRNA capture are completed inside the droplets, followed by the introduction of cell barcodes and unique molecular identifiers (UMIs); then reverse transcription, library construction, and sequencing are performed; finally, bioinformatics analyses including quality control, sequence alignment, and gene expression quantification are carried out based on the obtained data [1,2]. With scRNA-seq technology, researchers can identify cell types, analyze cell heterogeneity, track cell state transitions, and reconstruct cell developmental trajectories. Compared with traditional bulk sequencing, scRNA-seq can detect more subtle intercellular differences and

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provide a new perspective for analyzing the cellular composition and dynamic changes of diseased tissues, greatly advancing medical research.

1.2. Spatial transcriptomics technology

Spatial transcriptomics (ST) technology enables high-throughput analysis of the transcriptome while retaining the spatial location information of tissues. Its core principle is to place tissue sections on oligonucleotide arrays with spatial barcodes and obtain spatial information of gene expression through position-specific capture and sequencing. The general workflow of this technology [3] is: a. First, frozen or paraffin-embedded tissue sections are placed on glass slides modified with oligonucleotide probes, which contain unique spatial barcode sequences, poly(dT) capture regions, and UMIs; b. After tissue permeabilization, mRNA is released and binds to position-specific probes, and spatially barcoded cDNA is generated via reverse transcription; c. Subsequently, in situ amplification, library construction, and sequencing are performed, and the sequencing data are mapped back to the original tissue positions by combining barcode information to construct spatially resolved gene expression profiles.

ST technology is innovative as it addresses the problem that traditional transcriptome analysis technologies cannot obtain spatial information, effectively minimizes mRNA diffusion, and maintains high detection sensitivity [4]. Compared with methods such as laser capture microdissection and single-molecule fluorescence in situ hybridization, ST technology features both whole-transcriptome coverage and high-throughput advantages, strongly promoting the research on tissue function analysis and disease mechanisms [5].

2. Advantages and limitations of the technologies

Compared with traditional bulk sequencing methods, scRNA-seq technology shows advantages in resolution and the study of tissue heterogeneity. The high resolution of scRNA-seq allows researchers to identify cell subsets that are difficult to detect in cell clusters and conduct cell dynamic analysis [6]. For example, scRNA-seq can not only track the differentiation trajectories of cell lineages, identify new cell subsets, but also capture the dynamic responses of cells to environmental stimuli as well as changes in the cell cycle and cell states [7-9]. These applications have promoted the research on cell functions and disease development [10]. With the continuous development of technical platforms, scRNA-seq has gained more advantages. Initially, the amplification technologies of scRNA-seq borrowed traditional in vitro transcription and polymerase chain reaction methods, relying on linear or exponential amplification to generate sufficient cDNA for sequencing [11,12]. Later emerging droplet-based single-cell sequencing and the Chromium system of 10×Genomics have achieved high-throughput and low-cost single-cell transcriptome analysis using UMIs and microfluidic technology, overcoming the bias and low efficiency that may be caused by PCR amplification and in vitro transcription methods [13].

Despite numerous breakthroughs, scRNA-seq still has certain limitations. For instance, the high-throughput nature of scRNA-seq poses challenges to data processing and storage [14]; in addition, the sparsity and uncertainty of transcriptomic data increase the complexity of data analysis [15].

Traditional transcriptomics technologies such as RNA sequencing can provide high-throughput gene expression information, but tissues need to be homogenized before analysis, resulting in the complete loss of spatial information [16]. To obtain the spatial location of gene expression, researchers usually adopt in situ hybridization (ISH) technology. ISH binds labeled probes to target RNA to visualize the expression location of specific genes in tissues, but it has limited resolution

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and throughput [17]. To simultaneously obtain high-throughput gene expression information and spatial locations, ST technology has emerged. One mainstream strategy is to place tissue sections on glass slides with unique spatial barcodes, generate transcriptome profiles for each position using high-throughput sequencing, and integrate gene expression information with spatial locations [3]. As an emerging multi-omics technology, ST integrates molecular biology, sequencing technology, and bioinformatics to systematically reveal the spatial distribution rules of gene expression in tissue in situ, promoting the progress of medical research. This technology deepens the understanding of the complexity of biological systems and plays a key role in analyzing cell heterogeneity, tissue structure, and functional dynamics.

In recent years, the resolution of ST technology has made breakthrough progress. Among them, in situ sequencing (ISS) based on in situ imaging and multiplexed error-robust fluorescence in situ hybridization (MERFISH) [18] can achieve single-cell even subcellular resolution; high-throughput technologies based on spatial barcodes such as 10× Visium and Slide-seq [19] have also improved the resolution to multicellular or near single-cell levels. Compared with traditional scRNA-seq technology, these spatial technologies make up for the fundamental defect of scRNA-seq that spatial information is lost due to tissue dissociation, play an important role in research fields such as the tumor microenvironment, and can be used to reveal cell-cell interactions, cell heterogeneity, and therapeutic targets [20]. In addition, the integration of spatial omics with proteomics and epigenetics can advance the research on multi-level regulatory mechanisms.

Although ST has broad application prospects, its development still faces many challenges. First, the data generated by this technology are extremely massive, placing high demands on data processing, storage, and analysis algorithms. Second, due to technical barriers, the experimental cost is high and popularization is difficult. Third, the technology still has the problem of insufficient resolution. At the technical principle level, mainstream high-throughput technologies often include multiple cells in a single detection unit, affecting the resolution [17]. For example, the capture spot diameter of the Visium platform is 55 μm, and that of the ST platform is 100 μm; each capture spot may contain multiple cells, limiting the spatial resolution at the single-cell level [21]. In terms of data analysis, the high noise, multimodality of ST data, and batch effects caused by differences in experimental procedures together lead to a decrease in the accuracy of cluster analysis [22]. Therefore, more advanced methods need to be developed and applied to fully tap the potential of the data [22]. In addition, the mixing of cell types and the complexity of spatial structures make it difficult to distinguish the gene expression patterns of different cell types at the original resolution [23]. Algorithms based on Bayesian statistics such as BayesSpace can enhance spatial resolution computationally, but they still cannot completely break through the physical resolution limit of the technical platform itself [21]. Complex experimental procedures and sample preparation steps may also introduce bias, affecting the final data quality and effective resolution.

3. Application progress

3.1. Research on tumor cell heterogeneity

Tumor cell heterogeneity is one of the key factors leading to therapy resistance and tumor recurrence. scRNA-seq and ST technologies have made certain progress in this research field, providing powerful technical tools for in-depth analysis of tumor heterogeneity.

scRNA-seq reveals the gene expression characteristics of different cell subsets within tumors at single-cell resolution through high-throughput sequencing, and identifies cell populations with specific functions or genetic characteristics [24]. This technology has promoted research on tumor

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progression, drug resistance, and immune microenvironment regulation. For example, Tirosh et al. [25] performed single-cell sequencing on human oligodendroglioma with IDH1 or IDH2 mutations and found that cells within the tumor presented a differentiation hierarchical structure; most cancer cells had specialized glial cell differentiation programs, while a small number of undifferentiated cells had expression programs associated with neural stem cells, leading to the inference that these cells are the main drivers of tumor growth. Li et al. [26] used cervical cancer (CC) tumor tissues and paired normal adjacent non-tumor (NAT) tissues as samples to reveal extensive heterogeneity of human CC malignant cells, identify different CC subtypes, and discover cancer-associated fibroblasts (CAFs) that may accelerate CC tumor progression, providing potential targets for the precision diagnosis and treatment of CC.

The application of ST in heterogeneity research is mainly reflected in the following aspects:

This technology can analyze the differences in gene expression in different regions of tumors and identify intratumoral subclonal architectures. Lomakin et al. [27] developed a genetic clone localization workflow centered on base-specific in situ sequencing (BaSISS) technology, generated tissue atlases of multifocal breast cancers at the early stages of ductal carcinoma in situ (DCIS), invasive cancer, and lymph node metastasis progression, and found prominent differences in gene expression profiles between different regions within the tumors, which may be associated with malignant phenotypes such as tumor invasion, metastasis, and drug resistance.

ST can also be used to analyze cell-cell interactions in the tumor microenvironment. Ravi et al. [28] used spatially resolved multi-omics approaches to identify five transcriptional programs of glioblastomas (GBM), among which the reactive-immune program was associated with high expression of inflammation-related genes (e.g., HLA-DRA, C3, CCL3), suggesting that there is an interaction between tumor cells and immune cells, which affects the formation of tumor immune escape and immunosuppressive microenvironment.

ST technology helps researchers deeply understand the evolutionary process of tumor cells. Through high-resolution spatial transcriptomic analysis of tumor tissues, researchers can track the evolutionary trajectories of tumor cells. Mo [29] et al. selected 131 tumor sections from six different cancer types as samples for comprehensive characterization, and combined ST, CODEX analysis platforms, and bulk sequencing data to depict distinct tumor regions separated by stromal components, revealing the complexity of tumor evolution.

3.2. Analysis of the tumor microenvironment

Tumor behaviors such as growth, metastasis, and immune escape are closely related to the microenvironment in which they reside. Researchers have systematically analyzed the composition and functional characteristics of the tumor microenvironment (TME) by integrating scRNA-seq and ST technologies. scRNA-seq can reveal cell heterogeneity in the TME, thereby accurately identifying different cell types and their functional states. In the field of glioma research, Rajendran et al. [30] constructed a murine glioma model and found differences in the immune cell atlases of low-grade glioma (LGG) and high-grade glioma (HGG): the infiltration of CD4+ T cells, CD8+ T cells, and natural killer (NK) cells was increased in LGG, while such infiltrating cells were suppressed in HGG. In the research on head and neck squamous cell carcinoma (HNSCC), PURAM et al. [31] performed single-cell analysis on tumor samples from 18 patients and found that malignant cells had heterogeneity in the expression of programs such as cell cycle, hypoxic response, and epithelial differentiation, and the expression of partial epithelial-to-mesenchymal transition (p-EMT) programs was associated with the invasive and metastatic abilities of tumors.

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ST technology can analyze the TME from the spatial dimension. The spatially resolved T cell receptor sequencing (SPTCR-seq) technology developed by Benotmane et al. [32] can be used to analyze the highly sensitive spatial distribution of T cell receptors in glioblastomas, exploring the distribution and clonal expansion patterns of T cells in the TME; this study not only demonstrated the application of ST technology in analyzing T cell functional states but also discovered the potential key roles of natural killer (NK) cells and B cells in T cell exhaustion; integrating spatial transcriptomic and metabolomic data, the research further identified the association between T cell metabolic states and functional states, providing a new perspective for understanding tumor immunosuppressive mechanisms. Ren et al. [33] focused on the microenvironmental specificity and regulatory mechanisms of glioma stem-like cells, found that radial glial stem-like (RG-like) cells were enriched in the neuron-rich invasive front niche, identified specific regulatory programs of RG-like cells in this microenvironment using long-read spatial transcriptomics technology, and functionally verified the key role of the FAM20C gene in promoting the invasive growth of such cells.

3.3. Clinical applications

scRNA-seq and ST technologies have extensive roles in the clinical applications of tumors, including precision diagnosis and immunotherapy prediction.

Early-growing tumors may be difficult to detect due to their relatively small size and hidden growth locations; scRNA-seq and ST technologies have found new possibilities for the detection of early-stage tumors. For example, Ni et al. [34] combined single-cell Raman spectroscopy (SCRS) with scRNA-seq to accurately identify molecular changes in normal, early-stage, and metastatic pancreatic cancer cells, revealing gene expression patterns related to cell adhesion, migration, and the extracellular matrix. Hu et al. [35] combined scRNA-seq and ST technologies and found that ETS-negative prostate cancers all highly expressed Type 2 and SFTPA2+ gene signatures, suggesting that Type 2 and SFTPA2+ luminal cells may be the origin of ETS-negative prostate cancer.

In addition to playing a role in early diagnosis, scRNA-seq and ST technologies can also help researchers analyze tumor immune escape mechanisms and address the problem of poor prognosis. Han et al. [36] constructed a single-cell atlas named TabulaTIME covering 36 cancer types, and through spatial localization analysis, they found that CTHRC1+ CAFs and SLPI+ macrophages form a unique ecotype at the tumor boundary, which limits immune cell infiltration and is significantly associated with poor prognosis in patients. Tirosh et al. [37] analyzed melanoma using scRNA-seq technology and found that malignant cells within the same tumor had two transcriptional states simultaneously, and identified the AXL-high cell subset, which exhibited T cell exclusion and reduced immune cell infiltration. These findings are helpful for the development of combination therapies to overcome tumor drug resistance.

4. Combined application of single-cell RNA sequencing technology and spatial transcriptomics technology

scRNA-seq effectively reveals cell heterogeneity and dynamic changes but has the disadvantage of being unable to provide spatial location information; although ST can obtain the spatial distribution of gene expression, it has certain limitations in resolution and cell type identification. Complementing the advantages of the two technologies and integrating molecular and spatial information can more comprehensively analyze tumor heterogeneity and provide a more complete

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research paradigm for precision medicine. The breakthrough progress brought by the integration of the two technologies is mainly reflected in the following three aspects:

In terms of tumorigenesis mechanism elucidation, Sun et al. [38] systematically revealed the spatial distribution patterns of key cell subsets in precancerous lesions of oral squamous cell carcinoma (OSCC) by combining scRNA-seq and ST technologies; the researchers not only identified characteristic cell subsets during the epithelial-mesenchymal transition process but also discovered that immune heterogeneous monocytes regulate the molecular mechanisms of tumor initiation through the spatial gradient distribution of the VEGF signaling pathway. This spatially resolved analysis of cell-cell interaction networks has identified precise molecular coordinates for predicting early intervention targets.

In terms of tumor targeted therapy, Xiao et al. [39] constructed a cellular ecosystem atlas of colorectal cancer (CRC) by integrating data from 41,700 cells with high-precision spatial transcriptomic data. This study not only identified 7 clinically relevant malignant cell subtypes but also revealed specific interaction patterns at the tumor-stroma interface through spatial regional annotation, and found the hub role of the C5AR1-RPS19 ligand-receptor pair in inter-compartment communication. The above findings indicate that intervening in key communication hubs of the tumor ecosystem may become a new targeted therapy strategy.

In terms of clinical translational application, Wang et al. [40] established a multi-omics analysis pipeline suitable for frozen samples, successfully realized the integrated analysis of single-nucleus RNA/TCR sequencing with spatial transcriptomics and whole-genome sequencing, achieved 3D reconstruction of tumor clonal dynamic evolution during anti-PD-1 therapy, and compared the cross-organ molecular atlases of metastatic melanoma. This study not only solved the technical bottleneck of clinical sample preservation but also provided new ideas for personalized treatment response prediction through multimodal data.

The above studies collectively indicate that the integrated application of scRNA-seq and ST technologies is promoting the transformation of tumor research from cellular composition analysis to spatial interaction network analysis. By revealing the three-dimensional correlation of cell type-spatial location-molecular function in the tumor microenvironment, this technical system creates more efficient research tools for discovering precision diagnosis and treatment targets, predicting responses, and overcoming drug resistance.

5. Conclusions and prospects

The rapid development of scRNA-seq and ST technologies is profoundly transforming the research paradigm of precision oncology, providing multidimensional perspectives for analyzing tumor heterogeneity, microenvironmental interactions, and therapy resistance mechanisms. scRNA-seq reveals cell subset differences and dynamic changes that cannot be captured by traditional bulk sequencing with single-molecule resolution, while ST clarifies the spatial interaction rules between tumor cells and microenvironmental components by retaining tissue in situ information. The synergistic application of the two has achieved breakthrough progress in various tumors, not only successfully identifying key cell subsets driving tumor progression but also revealing the spatial characteristics of tumor-microenvironment interactions (such as immunosuppressive niches and premetastatic microenvironment remodeling), providing a theoretical basis for the development of targeted intervention strategies.

Currently, ST technology still needs to be improved in terms of throughput and resolution. The optimization of imaging technologies and sequencing methods makes it possible to construct subcellular-level whole-transcriptome spatial expression profiles. Precision oncology can achieve

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breakthroughs in three core directions: iterative optimization and integration of technical platforms, systematic advancement of clinical translation, and comprehensive improvement of data analysis capabilities. Combining multi-dimensional omics data such as epigenome, proteome, and spatial transcriptome will promote the construction of more comprehensive tumor regulatory networks. At the clinical translation level, it is necessary to establish standardized experimental procedures and data analysis specifications. In addition, the development of tumor typing models using high-throughput spatial data can optimize personalized treatment strategies and realize dynamic monitoring of therapeutic efficacy, providing key support for precision tumor intervention and long-term management. In the field of data interpretation, with the exponential growth of multimodal data, the development of next-generation artificial intelligence algorithms has become the main driving force, which can in-depth mine spatiotemporal patterns, infer cell-cell communication, and predict treatment responses.

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