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Review Article

Research Progress of Spatial Transcriptomics in the Field of Laryngeal Cancer and Other Tumors

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Abstract

Multicellular organisms with different tissues and organs are three-dimensional complex life forms with both temporal and spatial specificity of gene expression. While temporal specificity can be obtained through assays and analyses at different time points, spatial specificity has only just been investigated at the macroscopic organismal level. Recent developments in single-cell sequencing technologies have enabled high-throughput analysis of spatially specific gene expression studies at the cellular level, and thus high-precision spatial transcriptomics studies are just beginning to emerge as the next frontier in histology. In this paper, we review the recent progress of spatial transcriptomic techniques in the field of laryngeal cancer and other tumors, which has implications for the exploration of the pathogenesis of laryngeal cancer and other malignancies.

Keywords: Laryngeal cancer; Malignancy; Pathogenesis; Spatial transcriptomics.

Introduction

Following the selection of single-cell sequencing and single-cell multi-omics as Nature Methods' Method of the Year in 2013 and 2019 respectively, spatial transcriptional techniques were selected as Nature Methods' Method of the Year in 2020 [1-3]. Genomics, transcriptomics, proteomics and metabolomics have been derived from the study of DNA, RNA, proteins, and metabolites, respectively, according to the law of genetic centers [4]. The transcriptome is the total number of transcription products and their quantity in a cell under certain time and environmental conditions [5]. Comparing transcriptome differences at the level of different tissues, conditions, time points and even individual cells can explain gene regulation mechanisms and differential expression information, reveal details of systems biology and reflect disease

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development processes. The aim of transcriptomics research is to explain the function of certain key genes and to identify changes in gene expression [6]. The latest generation of sequencing technologies allows direct sequencing of RNA, facilitating the development of novel research methods such as single-cell transcriptome sequencing and spatial transcriptome [7].

The concept of spatial transcriptomics

Spatial Transcriptomics (Spatial Transcriptomics) is a technique used to parse RNA-seq data at a spatial level. It refers to the generation of full transcriptomic data from a complete tissue sample, thus enabling the localization and differentiation of active expression of functional genes within a specific tissue region, and the histological study that preserves the spatial information of the sample intact on tissue sections. The spatial transcriptome can demonstrate gene expression in different regions of a tissue section, map the locations on the tissue where specific transcripts are present, indicate methods for site-specific expression of specific genes, thus revealing signaling pathways activated in fine pathological regions and completing methods for resolving the mechanisms by which molecular features drive pathological features. This technique has led to new discoveries that will help scientists to better understand disease and biological processes [8].

Exploring the application of cutting-edge technologies in spatial transcriptomics

In the Nature Methods 2020 annual collection of technical review articles, Zhuang X provides an in-depth discussion of image-based spatial transcriptomic approaches that offer the highest spatial resolution and provide analysis of subcellular information [9]. FISH-based methods are described and how they can be driven to reach a larger number of targets or cover a larger number of cells. How spatial transcriptomics enables subcellular transcriptome mapping and the relationship to genomic organization is discussed, while Close JL et al describe methods that combine spatial localization and scRNA-Seq [10]. Cells were barcoded according to their position in tissue sections, providing unbiased capture of transcriptome profiles at relatively high throughput. The expectation is that multimodal spatial analysis will be achieved, enabling parallel measurements of the transcriptome, genome and proteome, while Larsson L et al explored why these techniques are so important for understanding complex tissues and the progress researchers have made in mapping the tissue of brain cells [11]. The spatial transcriptome can reveal heterogeneity between cells in different spatial locations and has an important role in developmental biology, tumors heterogeneity and immune-related research [12]. One of the first spatial transcriptome studies in a single section of tissue was carried out by Lundeberg of the Karolinska Institute, Royal Institute of Technology, Sweden, who published a paper in Science in 2016, depicting transcriptome data with two-dimensional positional information from mouse brain and human breast cancer through unique positional barcode information [13]. Lundeberg et al[13] described a new technique for transcriptomics research and introduced the

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concept of "spatial transcriptomics". The company 10×Genomics Visium acquired Spatial Tranomics, a company specializing in spatial transcriptomics. Its existing products use patented coated slides that can hold six individual tissue sections per slide to obtain RNA sequencing data at spatial resolution.

Existing issues and responses in transcriptomic studies of laryngeal cancer

Currently, transcriptomic studies on laryngeal cancer are mostly sequenced and annotated with major databases, and basic analysis of the coding genes of interest is performed by means of GO enrichment and KEGG enrichment [14-20]. However, the interactions between the local microenvironment and tumor cells in laryngeal cancer tumors, the relationship between tumor heterogeneity and related gene expression, the spatial structure, biological functions and interactions of different cells and even sub-cells, the spatial variation of related gene expression and their biological characterization need to be further explored in depth. In most transcriptome studies, the correspondence between the transcriptome and its biomarkers or prognostic features has mostly been obtained in an indirect manner [14]. Only one applied single-cell RNA sequencing to analyze the cellular composition and molecular characteristics of laryngeal squamous cell carcinoma (LSCC) tissues. song L et al performed immunehisto-chemical staining of LSCC tissues to determine the spatial location of tumor cells [15]. Survival analysis of marker genes was performed in The Cancer Genome Atlas to verify the correlation between each cell cluster and patient prognosis. LSCC tissue cells were finely divided into different clusters, including tumor cells, immune cells, epithelial cells, fibroblasts and endothelial cells.

Current status of laryngeal cancer tumor microenvironment research

The tumor microenvironment (TME) is a dynamic system formed by the interaction of tumor cells, surrounding mesenchymal cells (e.g., immune cells, fibroblasts, endothelial cells, adipocytes and neo capillary system), extracellular matrix cellular matrix (ECM) and signaling molecules (e.g., cytokines and chemokines) [16]. The dynamics of TME heterogeneity is dependent on immune cells, immune mediators and their gene and protein profiles [17]. All anti-tumor/pro-tumor factors make up the immune network in the tumor microenvironment that determines tumor initiation, progression and outcome. Understanding the intrinsic components of the microenvironment allows us to describe the complete immune microenvironment, including heterogeneity, intercellular communication and interaction. Tumor heterogeneity plays an important role in treatment resistance [18]. Laryngeal cancer is a highly heterogeneous disease, as reflected not only by the great variation between individuals, but also within the same tumor [19]. The heterogeneity of laryngeal cancer is mainly reflected in differences in molecular typing, drug resistance, disease evolution and survival [20]. Effective detection of heterogeneity in laryngeal cancer is important in treatment, and previous approaches to describe heterogeneity have mainly included genetic, pathological and imaging analyses, but in-

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depth studies based on spatial transcriptome level are lacking [21].

Summary

Transcriptomic analysis can identify novel transcriptional networks in complex biological systems of tumors, identify tumor-associated signaling pathways and reveal details of tumor systems biology, leading to a wide range of applications in the diagnosis, classification, detection and treatment of tumors [22]. Integrative studies to resolve the spatial composition of cell types in tissues have been used to map rare subpopulations and cell types using a small subset of genes [23]. Recently developed spatial transcriptomics methods [24] enable the analysis of whole tissue sections using spatially barcoded Oligo deoxythymidine microarrays. st (the predecessor to 10× Genomics Visium sequencing technology) has been used to study mouse olfactory bulbs [25], melanoma [26], prostate cancer [27], gum tissue [28], heart tissue [29], and spinal cord tissue [30], and plant species [31]. the main limitation of ST is its lack of cellular resolution. Each spot will capture the transcriptome of 10-200 cells, depending on the tissue context [32]. In contrast, in the field of various disease studies, oncology research is the earliest direction in which spatial transcriptome sequencing technology (10×Genomics Visium, 10-fold Genomics Visual Spatial Gene Expression) has been used, and a small number of studies have begun to be reported in prostate cancer [33], melanoma [34], breast cancer [35], pancreatic ductal carcinoma [36], and squamous skin cancer [37].

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