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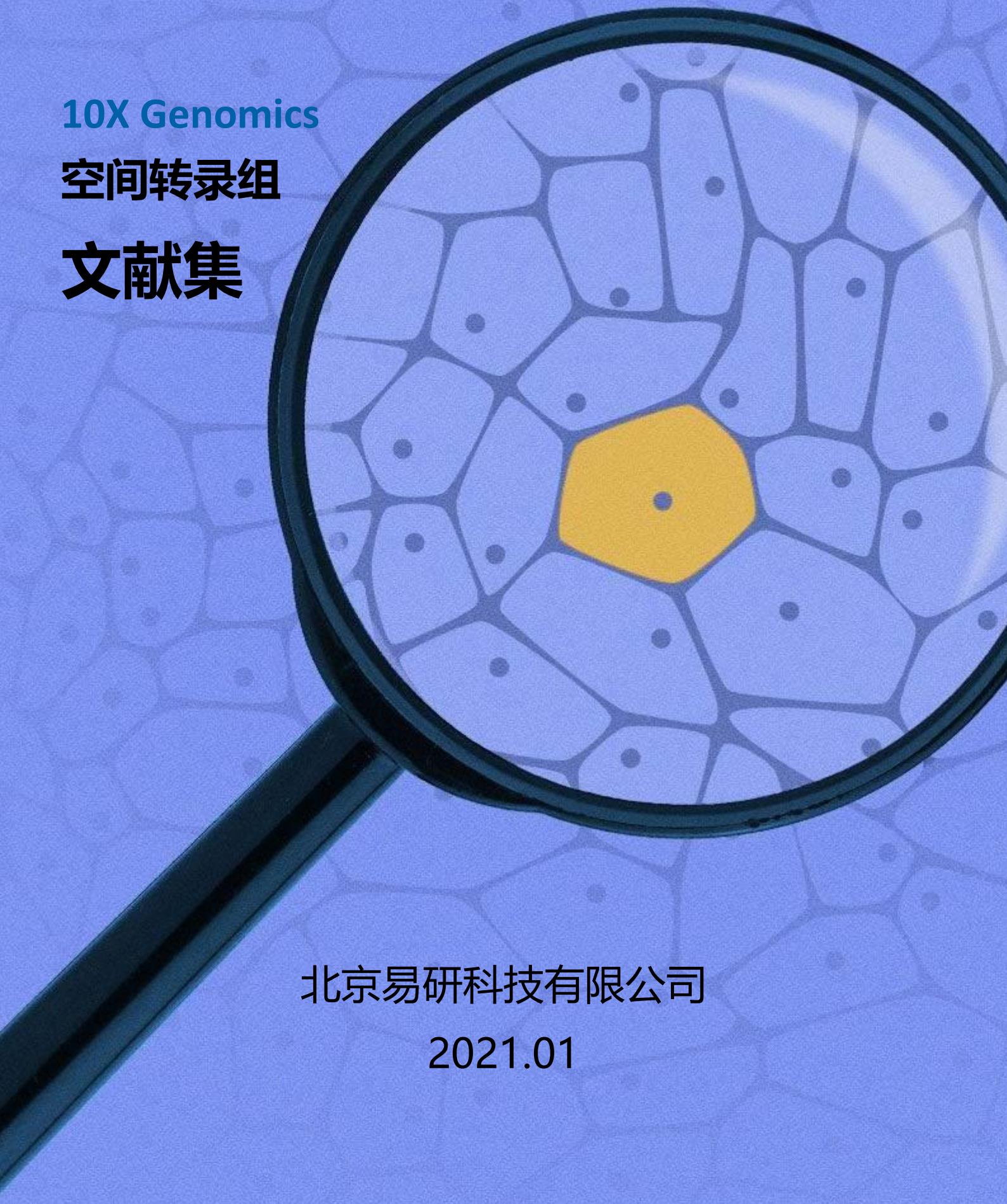

北京易研科技有限公司

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10×Genomics 空间转录组

已发表文献集

Spatial Transcriptomics and In Situ Sequencing to Study Alzheimer's Disease

Cell (IF: 38.62), 2020-8, Mark Fiers et al. DOI: 10.1016/j.cell.2020.06.038 PubMed: 32702314
Spatial Gene Expression, Mouse, Tissue section from Brain, Neuroscience.

Abstract

Although complex inflammatory-like alterations are observed around the amyloid plaques of Alzheimer\'s disease (AD), little is known about the molecular changes and cellular interactions that characterize this response. We investigate here, in an AD mouse model, the transcriptional changes occurring in tissue domains in a 100-μm diameter around amyloid plaques using spatial transcriptomics. We demonstrate early alterations in a gene co-expression network enriched for myelin and oligodendrocyte genes (OLIGs), whereas a multicellular gene co-expression network of plaque-induced genes (PIGs) involving the complement system, oxidative stress, lysosomes, and inflammation is prominent in the later phase of the disease. We confirm the majority of the observed alterations at the cellular level using in situ sequencing on mouse and human brain sections. Genome-wide spatial transcriptomics analysis provides an unprecedented approach to untangle the dysregulated cellular network in the vicinity of pathogenic hallmarks of AD and other brain diseases.

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Molecular atlas of the adult mouse brain

Science Advances (IF: 14.09), 2020-6, Joakim Lundeberg et al. DOI: 10.1126/sciadv.abb3446 PubMed: 32637622
Spatial Gene Expression, Mouse, Tissue section from Brain, Cell Atlas, Neuroscience.

Abstract

Brain maps are essential for integrating information and interpreting the structure-function relationship of circuits and behavior. We aimed to generate a systematic classification of the adult mouse brain based purely on the unbiased identification of spatially defining features by employing whole-brain spatial transcriptomics. We found that the molecular information was sufficient to deduce the complex and detailed neuroanatomical organization of the brain. The unsupervised (non-expert, data-driven) classification revealed new area- and layer-specific subregions, for example in isocortex and hippocampus, and new subdivisions of striatum. The molecular atlas further supports the characterization of the spatial identity of neurons from their single-cell RNA profile, and provides a resource for annotating the brain using a minimal gene set-a brain palette. In summary, we have established a molecular atlas to formally define the spatial organization of brain regions, including the molecular code for mapping and targeting of discrete neuroanatomical domains.

A clustering-independent method for finding differentially expressed genes in single-cell transcriptome data

Nature Communications（IF：13.61），2020-8，Alexis Vandenbon et al. DOI: 10.1038/s41467-020-17900-3 PubMed: 32859930.
Single Cell Gene Expression & Spatial Gene Expression，Mouse, Tissue section from Brain, Computational Method.

Abstract

A common analysis of single-cell sequencing data includes clustering of cells and identifying differentially expressed genes (DEGs). How cell clusters are defined has important consequences for downstream analyses and the interpretation of results, but is often not straightforward. To address this difficulty, we present singleCellHaystack, a method that enables the prediction of DEGs without relying on explicit clustering of cells. Our method uses Kullback-Leibler divergence to find genes that are expressed in subsets of cells that are non-randomly positioned in a multidimensional space. Comparisons with existing DEG prediction approaches on artificial datasets show that singleCellHaystack has higher accuracy. We illustrate the usage of singleCellHaystack through applications on 136 real transcriptome datasets and a spatial transcriptomics dataset. We demonstrate that our method is a fast and accurate approach for DEG prediction in single-cell data. singleCellHaystack is implemented as an R package and is available from CRAN and GitHub.

Single-cell and spatial transcriptomics enables probabilistic inference of cell type topography

Communications Biology(IF：11.20), 2020-10, Alma Andersson et al. DOI: 10.1038/s42003-020-01247-y PubMed: 33037292

Single Cell Gene Expression & Spatial Gene Expression, Mouse, Tissue section from Brain, Computational Method.

Abstract

The field of spatial transcriptomics is rapidly expanding, and with it the repertoire of available technologies. However, several of the transcriptome-wide spatial assays do not operate on a single cell level, but rather produce data comprised of contributions from a - potentially heterogeneous - mixture of cells. Still, these techniques are attractive to use when examining complex tissue specimens with diverse cell populations, where complete expression profiles are required to properly capture their richness. Motivated by an interest to put gene expression into context and delineate the spatial arrangement of cell types within a tissue, we here present a model-based probabilistic method that uses single cell data to deconvolve the cell mixtures in spatial data. To illustrate the capacity of our method, we use data from different experimental platforms and spatially map cell types from the mouse brain and developmental heart, which arrange as expected.

Seamless integration of image and molecular analysis for spatial transcriptomics workflows

BMC Genomics(IF：4.09)，2020-7, Ludvig Larsson et al. DOI: 10.1186/s12864-020-06832-3 PubMed: 32664861

Spatial Gene Expression, Mouse, Tissue section from Brain, Computational Method.

Abstract

Recent advancements in in situ gene expression technologies constitute a new and rapidly evolving field of transcriptomics. With the recent launch of the 10x Genomics Visium platform, such methods have started to become widely adopted. The experimental protocol is conducted on individual tissue sections collected from a larger tissue sample. The two-dimensional nature of this data requires multiple consecutive sections to be collected from the sample in order to construct a comprehensive three-dimensional map of the tissue. However, there is currently no software available that lets the user process the images, align stacked experiments, and finally visualize them together in 3D to create a holistic view of the tissue. We have developed an R package named STUtility that takes 10x Genomics Visium data as input and provides features to perform standardized data transformations, alignment of multiple tissue sections, regional annotation, and visualizations of the combined data in a 3D model framework. STUtility lets the user process, analyze and visualize multiple samples of spatially resolved RNA sequencing and image data from the 10x Genomics Visium platform. The package builds on the Seurat framework and uses familiar APIs and well-proven analysis methods. An introduction to the software package is available at https://ludvigla.github.io/STUtility_web_site/ .

Spatial Transcriptomics Reveals Genes Associated with Dysregulated Mitochondrial Functions and Stress Signaling in Alzheimer Disease

iScience (IF: 4.45), 2020-10, Joakim Lundeberg et al. DOI: 10.1016/j.isci.2020.101556 PubMed: 33083725
Spatial Gene Expression, Mouse, Tissue section from Brain, Neuroscience.

Abstract

Alzheimer disease (AD) is a devastating neurological disease associated with progressive loss of mental skills and cognitive and physical functions whose etiology is not completely understood. Here, our goal was to simultaneously uncover novel and known molecular targets in the structured layers of the hippocampus and olfactory bulbs that may contribute to early hippocampal synaptic deficits and olfactory dysfunction in AD mice. Spatially resolved transcriptomics was used to identify high-confidence genes that were differentially regulated in AD mice relative to controls. A diverse set of genes that modulate stress responses and transcription were predominant in both hippocampi and olfactory bulbs. Notably, we identify Bok, implicated in mitochondrial physiology and cell death, as a spatially downregulated gene in the hippocampus of mouse and human AD brains. In summary, we provide a rich resource of spatially differentially expressed genes, which may contribute to understanding AD pathology.

Visualization and analysis of gene expression in tissue sections by spatial transcriptomics

Science (IF: 44.37), 2016-7, Joakim Lundeberg et al. DOI: 10.1126/science.aaf2403 PubMed: 27365449
Spatial Gene Expression, Mouse, Tissue section from Brain, Assay Method.

Abstract

Analysis of the pattern of proteins or messengerRNAs (mRNAs) in histological tissue sections is a cornerstone in biomedical research and diagnostics. This typically involves the visualization of a few proteins or expressed genes at a time. We have devised a strategy, which we call spatial transcriptomics; that allows visualization and quantitative analysis of the transcriptome with spatial resolution in individual tissue sections. By positioning histological sections on arrayed reverse transcription primers with unique positional barcodes, we demonstrate high-quality RNA-sequencing data with maintained two-dimensional positional information from the mouse brain and human breast cancer. Spatial transcriptomics provides quantitative gene expression data and visualization of the distribution of mRNAs within tissue sections and enables novel types of bioinformatics analyses, valuable in research and diagnostics.

Exuberant fibroblast activity compromises lung function via ADAMTS4

Nature(IF：46.49)，2020-10，David F Boyd et al. DOI: 10.1038/s41586-020-2877-5 PubMed: 33116313
Spatial Gene Expression & Single Cell Immune Profiling, Human & Mouse, Tissue section from Lung, Infectious Disease.

Abstract

Severe respiratory infections can result in acute respiratory distress syndrome (ARDS). There are no effective pharmacological therapies that have been shown to improve outcomes for patients with ARDS. Although the host inflammatory response limits spread of and eventually clears the pathogen, immunopathology is a major contributor to tissue damage and ARDS. Here we demonstrate that respiratory viral infection induces distinct fibroblast activation states, which we term extracellular matrix (ECM)-synthesizing, damage-responsive and interferon-responsive states. We provide evidence that excess activity of damage-responsive lung fibroblasts drives lethal immunopathology during severe influenza virus infection. By producing ECM-remodelling enzymes-in particular the ECM protease ADAMTS4-and inflammatory cytokines, damage-responsive fibroblasts modify the lung microenvironment to promote robust immune cell infiltration at the expense of lung function. In three cohorts of human participants, the levels of ADAMTS4 in the lower respiratory tract were associated with the severity of infection with seasonal or avian influenza virus. A therapeutic agent that targets the ECM protease activity of damage-responsive lung fibroblasts could provide a promising approach to preserving lung function and improving clinical outcomes following severe respiratory infections.

Multimodal Analysis of Composition and Spatial Architecture in Human Squamous Cell Carcinoma

Cell (IF: 38.62), 2020-7, Joakim Lundeberg et al. DOI: 10.1016/j.cell.2020.05.039 PubMed: 32579974
Single Cell Gene Expression & Spatial Gene Expression, Human, Tissue section from Skin, Cancer Research.

Abstract

To define the cellular composition and architecture of cutaneous squamous cell carcinoma (cSCC), we combined single-cell RNA sequencing with spatial transcriptomics and multiplexed ion beam imaging from a series of human cSCCs and matched normal skin. cSCC exhibited four tumor subpopulations, three recapitulating normal epidermal states, and a tumor-specific keratinocyte (TSK) population unique to cancer, which localized to a fibrovascular niche. Integration of single-cell and spatial data mapped ligand-receptor networks to specific cell types, revealing TSK cells as a hub for intercellular communication. Multiple features of potential immunosuppression were observed, including T regulatory cell (Treg) co-localization with CD8 T cells in compartmentalized tumor stroma. Finally, single-cell characterization of human tumor xenografts and in vivo CRISPR screens identified essential roles for specific tumor subpopulation-enriched gene networks in tumorigenesis. These data define cSCC tumor and stromal cell subpopulations, the spatial niches where they interact, and the communicating gene networks that they engage in cancer.

Integrating microarray-based spatial transcriptomics and single-cell RNA-seq reveals tissue architecture in pancreatic ductal adenocarcinomas

Nature Biotechnology (IF: 42.3), 2020-1, Diane M Simeone et al. DOI: 10.1038/s41587-019-0392-8
PubMed: 31932730
Spatial Gene Expression, Human, Tissue section from Pancreas, Cancer Research, Cell Atlas.

Abstract

Single-cell RNA sequencing (scRNA-seq) enables the systematic identification of cell populations in a tissue, but characterizing their spatial organization remains challenging. We combine a microarray-based spatial transcriptomics method that reveals spatial patterns of gene expression using an array of spots, each capturing the transcriptomes of multiple adjacent cells, with scRNA-Seq generated from the same sample. To annotate the precise cellular composition of distinct tissue regions, we introduce a method for multimodal intersection analysis. Applying multimodal intersection analysis to primary pancreatic tumors, we find that subpopulations of ductal cells, macrophages, dendritic cells and cancer cells have spatially restricted enrichments, as well as distinct coenrichments with other cell types. Furthermore, we identify colocalization of inflammatory fibroblasts and cancer cells expressing a stress-response gene module. Our approach for mapping the architecture of scRNA-seq-defined subpopulations can be applied to reveal the interactions inherent to complex tissues.

Spatiotemporal dynamics of molecular pathology in amyotrophic lateral sclerosis

Science(IF：44.37), Apr 2019, Silas Maniatis et al. DOI: 10.1126/science.aav9776 PubMed: 30948552
Spatial Gene Expression, Mouse, Tissue section from Spinal Cord, Neuroscience.

Abstract

Paralysis occurring in amyotrophic lateral sclerosis (ALS) results from denervation of skeletal muscle as a consequence of motor neuron degeneration. Interactions between motor neurons and glia contribute to motor neuron loss, but the spatiotemporal ordering of molecular events that drive these processes in intact spinal tissue remains poorly understood. Here, we use spatial transcriptomics to obtain gene expression measurements of mouse spinal cords over the course of disease, as well as of postmortem tissue from ALS patients, to characterize the underlying molecular mechanisms in ALS. We identify pathway dynamics, distinguish regional differences between microglia and astrocyte populations at early time points, and discern perturbations in several transcriptional pathways shared between murine models of ALS and human postmortem spinal cords.

A Spatiotemporal Organ-Wide Gene Expression and Cell Atlas of the Developing Human Heart

Cell (IF: 38.62), 2019-12, Christer Sylvén et al. DOI: 10.1016/j.cell.2019.11.025 PubMed: 31835037
Single Cell Gene Expression & Spatial Gene Expression, Human, Tissue section from Heart, Developmental Biology.

Abstract

The process of cardiac morphogenesis in humans is incompletely understood. Its full characterization requires a deep exploration of the organ-wide orchestration of gene expression with a single-cell spatial resolution. Here, we present a molecular approach that reveals the comprehensive transcriptional landscape of cell types populating the embryonic heart at three developmental stages and that maps cell-type-specific gene expression to specific anatomical domains. Spatial transcriptomics identified unique gene profiles that correspond to distinct anatomical regions in each developmental stage. Human embryonic cardiac cell types identified by single-cell RNA sequencing confirmed and enriched the spatial annotation of embryonic cardiac gene expression. In situ sequencing was then used to refine these results and create a spatial subcellular map for the three developmental phases. Finally, we generated a publicly available web resource of the human developing heart to facilitate future studies on human cardiogenesis.

Spatial detection of fetal marker genes expressed at low level in adult human heart tissue

Scientific Reports(IF：4.58), 2017-10, Michaela Asp et al. DOI: 10.1038/s41598-017-13462-5 PubMed: 29021611
Spatial Gene Expression, Human, Tissue section from Heart, Genetic Health.

Abstract

Heart failure is a major health problem linked to poor quality of life and high mortality rates. Hence, novel biomarkers, such as fetal marker genes with low expression levels, could potentially differentiate disease states in order to improve therapy. In many studies on heart failure, cardiac biopsies have been analyzed as uniform pieces of tissue with bulk techniques, but this homogenization approach can mask medically relevant phenotypes occurring only in isolated parts of the tissue. This study examines such spatial variations within and between regions of cardiac biopsies. In contrast to standard RNA sequencing, this approach provides a spatially resolved transcriptome- and tissue-wide perspective of the adult human heart, and enables detection of fetal marker genes expressed by minor subpopulations of cells within the tissue. Analysis of patients with heart failure, with preserved ejection fraction, demonstrated spatially divergent expression of fetal genes in cardiac biopsies.

Integrating spatial gene expression and breast tumour morphology via deep learning

Nature Biomedical Engineering (IF: 18.95), 2020-8, Joakim Lundeberg et al. DOI: 10.1038/s41551-020-0578 PubMed: 32572199

Spatial Gene Expression, Human, Tissue section from Breast, Computational Method.

Abstract

Spatial transcriptomics allows for the measurement of RNA abundance at a high spatial resolution, making it possible to systematically link the morphology of cellular neighbourhoods and spatially localized gene expression. Here, we report the development of a deep learning algorithm for the prediction of local gene expression from haematoxylin-and-eosin-stained histopathology images using a new dataset of 30,612 spatially resolved gene expression data matched to histopathology images from 23 patients with breast cancer. We identified over 100 genes, including known breast cancer biomarkers of intratumoral heterogeneity and the co-localization of tumour growth and immune activation, the expression of which can be predicted from the histopathology images at a resolution of 100 μm. We also show that the algorithm generalizes well to The Cancer Genome Atlas and to other breast cancer gene expression datasets without the need for re-training. Predicting the spatially resolved transcriptome of a tissue directly from tissue images may enable image-based screening for molecular biomarkers with spatial variation.

Massive and parallel expression profiling using microarrayed single-cell sequencing

Nature Communications(IF：13.61), 2016-10, Sanja Vickovic et al. DOI: 10.1038/ncomms13182 PubMed: 27739429

Spatial Gene Expression, Human, Breast adenocarcinoma cell line, Agri genomics.

Abstract

Single-cell transcriptome analysis overcomes problems inherently associated with averaging gene expression measurements in bulk analysis. However, single-cell analysis is currently challenging in terms of cost, throughput and robustness. Here, we present a method enabling massive microarray-based barcoding of expression patterns in single cells, termed MASC-seq. This technology enables both imaging and high-throughput single-cell analysis, characterizing thousands of single-cell transcriptomes per day at a low cost (0.13 USD/cell), which is two orders of magnitude less than commercially available systems. Our novel approach provides data in a rapid and simple way. Therefore, MASC-seq has the potential to accelerate the study of subtle clonal dynamics and help provide critical insights into disease development and other biological processes.

Investigating higher-order interactions in single-cell data with scHOT

Nature Methods(IF：36.15), 2020-8, Shila Ghazanfar et al. DOI: 10.1038/s41592-020-0885-x PubMed: 32661426
Spatial Gene Expression, Mouse, Tissue section from Olfactory Bulb, Computational Method.

Abstract

Single-cell genomics has transformed our ability to examine cell fate choice. Examining cells along a computationally ordered 'pseudotime' offers the potential to unpick subtle changes in variability and covariation among key genes. We describe an approach, scHOT-single-cell higher-order testing-which provides a flexible and statistically robust framework for identifying changes in higher-order interactions among genes. scHOT can be applied for cells along a continuous trajectory or across space and accommodates various higher-order measurements including variability or correlation. We demonstrate the use of scHOT by studying coordinated changes in higher-order interactions during embryonic development of the mouse liver. Additionally, scHOT identifies subtle changes in gene-gene correlations across space using spatially resolved transcriptomics data from the mouse olfactory bulb. scHOT meaningfully adds to first-order differential expression testing and provides a framework for interrogating higher-order interactions using single-cell data.

Automation of Spatial Transcriptomics library preparation to enable rapid and robust insights into spatial organization of tissues

BMC Genomics(IF：4.09), 2020-12, Emelie Berglund et al. DOI: 10.1186/s12864-020-6631-z PubMed: 32293264
Spatial Gene Expression, Mouse, Tissue section from Olfactory Bulb, Assay Method.

Abstract

Interest in studying the spatial distribution of gene expression in tissues is rapidly increasing. Spatial Transcriptomics is a novel sequencing-based technology that generates high-throughput information on the distribution, heterogeneity and co-expression of cells in tissues. Unfortunately, manual preparation of high-quality sequencing libraries is time-consuming and subject to technical variability due to human error during manual pipetting, which results in sample swapping and the accidental introduction of batch effects. All these factors complicate the production and interpretation of biological datasets. We have integrated an Agilent Bravo Automated Liquid Handling Platform into the Spatial Transcriptomics workflow. Compared to the previously reported Magnatrix 8000+ automated protocol, this approach increases the number of samples processed per run, reduces sample preparation time by 35%, and minimizes batch effects between samples. The new approach is also shown to be highly accurate and almost completely free from technical variability between prepared samples. The new automated Spatial Transcriptomics protocol using the Agilent Bravo Automated Liquid Handling Platform rapidly generates high-quality Spatial Transcriptomics libraries. Given the wide use of the Agilent Bravo Automated Liquid Handling Platform in research laboratories and facilities, this will allow many researchers to quickly create robust Spatial Transcriptomics libraries.

Barcoded solid-phase RNA capture for Spatial Transcriptomics profiling in mammalian tissue sections

Nature protocols(IF：10.42), Oct 2018, Fredrik Salmén et al. DOI: 10.1038/s41596-018-0045-2 PubMed: 30353172
Spatial Gene Expression, Mouse, Tissue section from Olfactory Bulb, Assay Method.

Abstract

Spatial resolution of gene expression enables gene expression events to be pinpointed to a specific location in biological tissue. Spatially resolved gene expression in tissue sections is traditionally analyzed using immunohistochemistry (IHC) or in situ hybridization (ISH). These technologies are invaluable tools for pathologists and molecular biologists; however, their throughput is limited to the analysis of only a few genes at a time. Recent advances in RNA sequencing (RNA-seq) have made it possible to obtain unbiased high-throughput gene expression data in bulk. Spatial Transcriptomics combines the benefits of traditional spatially resolved technologies with the massive throughput of RNA-seq. Here, we present a protocol describing how to apply the Spatial Transcriptomics technology to mammalian tissue. This protocol combines histological staining and spatially resolved RNA-seq data from intact tissue sections. Once suitable tissue-specific conditions have been established, library construction and sequencing can be completed in ~5-6 d. Data processing takes a few hours, with the exact timing dependent on the sequencing depth. Our method requires no special instruments and can be performed in any laboratory with access to a cryostat, microscope and next-generation sequencing.

Exploring inflammatory signatures in arthritic joint biopsies with Spatial Transcriptomics

Scientific Reports(IF：4.58), 2019-12, Konstantin Carlberg et al. DOI: 10.1038/s41598-019-55441-y PubMed: 31831833
Spatial Gene Expression, Human, Tissue section from synovial, Immunology.

Abstract

Lately it has become possible to analyze transcriptomic profiles in tissue sections with retained cellular context. We aimed to explore synovial biopsies from rheumatoid arthritis (RA) and spondyloarthritis (SpA) patients, using Spatial Transcriptomics (ST) as a proof of principle approach for unbiased mRNA studies at the site of inflammation in these chronic inflammatory diseases. Synovial tissue biopsies from affected joints were studied with ST. The transcriptome data was subjected to differential gene expression analysis (DEA), pathway analysis, immune cell type identification using Xcell analysis and validation with immunohistochemistry (IHC). The ST technology allows selective analyses on areas of interest, thus we analyzed morphologically distinct areas of mononuclear cell infiltrates. The top differentially expressed genes revealed an adaptive immune response profile and T-B cell interactions in RA, while in SpA, the profiles implicate functions associated with tissue repair. With spatially resolved gene expression data, overlaid on high-resolution histological images, we digitally portrayed pre-selected cell types in silico. The RA displayed an overrepresentation of central memory T cells, while in SpA effector memory T cells were most prominent. Consequently, ST allows for deeper understanding of cellular mechanisms and diversity in tissues from chronic inflammatory diseases.

Spatial modeling of prostate cancer metabolic gene expression reveals extensive heterogeneity and selective vulnerabilities

Scientific Reports(IF：4.58), Feb 2020, Yuliang Wang et al. DOI: 10.1038/s41598-020-60384-w PubMed: 32103057
Spatial Gene Expression, Human, Tissue section from Prostate, Computational Method.

Abstract

Spatial heterogeneity is a fundamental feature of the tumor microenvironment (TME), and tackling spatial heterogeneity in neoplastic metabolic aberrations is critical for tumor treatment. Genome-scale metabolic network models have been used successfully to simulate cancer metabolic networks. However, most models use bulk gene expression data of entire tumor biopsies, ignoring spatial heterogeneity in the TME. To account for spatial heterogeneity, we performed spatially-resolved metabolic network modeling of the prostate cancer microenvironment. We discovered novel malignant-cell-specific metabolic vulnerabilities targetable by small molecule compounds. We predicted that inhibiting the fatty acid desaturase SCD1 may selectively kill cancer cells based on our discovery of spatial separation of fatty acid synthesis and desaturation. We also uncovered higher prostaglandin metabolic gene expression in the tumor, relative to the surrounding tissue. Therefore, we predicted that inhibiting the prostaglandin transporter SLCO2A1 may selectively kill cancer cells. Importantly, SCD1 and SLCO2A1 have been previously shown to be potently and selectively inhibited by compounds such as CAY10566 and suramin, respectively. We also uncovered cancer-selective metabolic liabilities in central carbon, amino acid, and lipid metabolism. Our novel cancer-specific predictions provide new opportunities to develop selective drug targets for prostate cancer and other cancers where spatial transcriptomics datasets are available.

Spatial maps of prostate cancer transcriptomes reveal an unexplored landscape of heterogeneity

Nature Communications(IF：13.61), Jun 2018, Emelie Berglund et al. DOI: 10.1038/s41467-018-04724-5 PubMed: 29925878
Spatial Gene Expression, Human, Tissue section from Prostate, Cancer Research.

Abstract

Intra-tumor heterogeneity is one of the biggest challenges in cancer treatment today. Here we investigate tissue-wide gene expression heterogeneity throughout a multifocal prostate cancer using the spatial transcriptomics (ST) technology. Utilizing a novel approach for deconvolution, we analyze the transcriptomes of nearly 6750 tissue regions and extract distinct expression profiles for the different tissue components, such as stroma, normal and PIN glands, immune cells and cancer. We distinguish healthy and diseased areas and thereby provide insight into gene expression changes during the progression of prostate cancer. Compared to pathologist annotations, we delineate the extent of cancer foci more accurately, interestingly without link to histological changes. We identify gene expression gradients in stroma adjacent to tumor regions that allow for re-stratification of the tumor microenvironment. The establishment of these profiles is the first step towards an unbiased view of prostate cancer and can serve as a dictionary for future studies.

Gene expression profiling of periodontitis-affected gingival tissue by spatial transcriptomics

Scientific Reports(IF：4.58), 2018-6, Anna Lundmark et al. DOI: 10.1038/s41598-018-27627-3
PubMed: 29921943
Spatial Gene Expression, Human, Tissue section from Gingival, Immunology.

Abstract

Periodontitis is a highly prevalent chronic inflammatory disease of the periodontium, leading ultimately to tooth loss. In order to characterize the gene expression of periodontitis-affected gingival tissue, we have here simultaneously quantified and localized gene expression in periodontal tissue using spatial transcriptomics, combining RNA sequencing with histological analysis. Our analyses revealed distinct clusters of gene expression, which were identified to correspond to epithelium, inflamed areas of connective tissue, and non-inflamed areas of connective tissue. Moreover, 92 genes were identified as significantly up-regulated in inflamed areas of the gingival connective tissue compared to non-inflamed tissue. Among these, immunoglobulin lambda-like polypeptide 5 (IGLL5), signal sequence receptor subunit 4 (SSR4), marginal zone B and B1 cell specific protein (MZB1), and X-box binding protein 1 (XBP1) were the four most highly up-regulated genes. These genes were also verified as significantly higher expressed in gingival tissue of patients with periodontitis compared to healthy controls, using reverse transcription quantitative polymerase chain reaction. Moreover, the protein expressions of up-regulated genes were verified in gingival biopsies by immunohistochemistry. In summary, in this study, we report distinct gene expression signatures within periodontitis-affected gingival tissue, as well as specific genes that are up-regulated in inflamed areas compared to non-inflamed areas of gingival tissue. The results obtained from this study may add novel information on the genes and cell types contributing to pathogenesis of the chronic inflammatory disease periodontitis.

An automated approach to prepare tissue-derived spatially barcoded RNA-sequencing libraries

Scientific Reports(IF：4.58), 2016-11, Anders Jemt et al. DOI: 10.1038/srep37137 PubMed: 27849009
Spatial Gene Expression, Human, Tissue section from Gingival, Assay Method.

Abstract

Sequencing the nucleic acid content of individual cells or specific biological samples is becoming increasingly common. This drives the need for robust, scalable and automated library preparation protocols. Furthermore, an increased understanding of tissue heterogeneity has lead to the development of several unique sequencing protocols that aim to retain or infer spatial context. In this study, a protocol for retaining spatial information of transcripts has been adapted to run on a robotic workstation. The method spatial transcriptomics is evaluated in terms of robustness and variability through the preparation of reference RNA, as well as through preparation and sequencing of six replicate sections of a gingival tissue biopsy from a patient with periodontitis. The results are reduced technical variability between replicates and a higher throughput, processing four times more samples with less than a third of the hands on time, compared to the standard protocol.

Spatially Resolved Transcriptomics Enables Dissection of Genetic Heterogeneity in Stage III Cutaneous Malignant Melanoma

Cancer research(IF：10.12), Oct 2018, Kim Thrane, DOI: 10.1158/0008-5472.CAN-18-0747 PubMed: 30154148
Spatial Gene Expression, Human, Tissue section from Lymph Node, Cancer Research.

Abstract

Cutaneous malignant melanoma (melanoma) is characterized by a high mutational load, extensive intertumoral and intratumoral genetic heterogeneity, and complex tumor microenvironment (TME) interactions. Further insights into the mechanisms underlying melanoma are crucial for understanding tumor progression and responses to treatment. Here we adapted the technology of spatial transcriptomics (ST) to melanoma lymph node biopsies and successfully sequenced the transcriptomes of over 2,200 tissue domains. Deconvolution combined with traditional approaches for dimensional reduction of transcriptome-wide data enabled us to both visualize the transcriptional landscape within the tissue and identify gene expression profiles linked to specific histologic entities. Our unsupervised analysis revealed a complex spatial intratumoral composition of melanoma metastases that was not evident through morphologic annotation. Each biopsy showed distinct gene expression profiles and included examples of the coexistence of multiple melanoma signatures within a single tumor region as well as shared profiles for lymphoid tissue characterized according to their spatial location and gene expression profiles. The lymphoid area in close proximity to the tumor region displayed a specific expression pattern, which may reflect the TME, a key component to fully understanding tumor progression. In conclusion, using the ST technology to generate gene expression profiles reveals a detailed landscape of melanoma metastases. This should inspire researchers to integrate spatial information into analyses aiming to identify the factors underlying tumor progression and therapy outcome. Applying ST technology to gene expression profiling in melanoma lymph node metastases reveals a complex transcriptional landscape in a spatial context, which is essential for understanding the multiple components of tumor progression and therapy outcome.

Spatially resolved transcriptome profiling in model plant species

Nature Plants(IF：13.25), 2017-5, Stefania Giacomello et al. DOI: 10.1038/nplants.2017.61 PubMed: 28481330
Spatial Gene Expression, Tissue section from Arabidopsis thaliana, Assay Method.

Abstract

Understanding complex biological systems requires functional characterization of specialized tissue domains. However, existing strategies for generating and analysing high-throughput spatial expression profiles were developed for a limited range of organisms, primarily mammals. Here we present the first available approach to generate and study high-resolution, spatially resolved functional profiles in a broad range of model plant systems. Our process includes high-throughput spatial transcriptome profiling followed by spatial gene and pathway analyses. We first demonstrate the feasibility of the technique by generating spatial transcriptome profiles from model angiosperms and gymnosperms microsections. In Arabidopsis thaliana we use the spatial data to identify differences in expression levels of 141 genes and 189 pathways in eight inflorescence tissue domains. Our combined approach of spatial transcriptomics and functional profiling offers a powerful new strategy that can be applied to a broad range of plant species, and is an approach that will be pivotal to answering fundamental questions in developmental and evolutionary biology.

TGFβ-blockade uncovers stromal plasticity in tumors by revealing the existence of a subset of interferon-licensed fibroblasts

Nature Communications(IF：13.61), 2020-12, Angelo L Grauel et al. DOI: 10.1038/s41467-020-19920-5
PubMed: 33298926
Single Cell Gene Expression & Spatial Gene Expression, Mouse, Tissue section from Tumor solid, Cancer Research, Immuno-oncology.

Abstract

Despite the increasing interest in targeting stromal elements of the tumor microenvironment, we still face tremendous challenges in developing adequate therapeutics to modify the tumor stromal landscape. A major obstacle to this is our poor understanding of the phenotypic and functional heterogeneity of stromal cells in tumors. Herein, we perform an unbiased interrogation of tumor mesenchymal cells, delineating the co-existence of distinct subsets of cancer-associated fibroblasts (CAFs) in the microenvironment of murine carcinomas, each endowed with unique phenotypic features and functions. Furthermore, our study shows that neutralization of TGFβ in vivo leads to remodeling of CAF dynamics, greatly reducing the frequency and activity of the myofibroblast subset, while promoting the formation of a fibroblast population characterized by strong response to interferon and heightened immunomodulatory properties. These changes correlate with the development of productive anti-tumor immunity and greater efficacy of PD1 immunotherapy. Along with providing the scientific rationale for the evaluation of TGFβ and PD1 co-blockade in the clinical setting, this study also supports the concept of plasticity of the stromal cell landscape in tumors, laying the foundation for future investigations aimed at defining pathways and molecules to program CAF composition for cancer therapy.

SpatialCPie: an R/Bioconductor package for spatial transcriptomics cluster evaluation

BMC Bioinformatics(IF：3.02), Dec 2020, Joseph Bergenstråhle et al. DOI: 10.1186/s12859-020-3489-7
PubMed: 32349652
Spatial Gene Expression, Computational Method.

Abstract

Technological developments in the emerging field of spatial transcriptomics have opened up an unexplored landscape where transcript information is put in a spatial context. Clustering commonly constitutes a central component in analyzing this type of data. However, deciding on the number of clusters to use and interpreting their relationships can be difficult. We introduce SpatialCPie, an R package designed to facilitate cluster evaluation for spatial transcriptomics data. SpatialCPie clusters the data at multiple resolutions. The results are visualized with pie charts that indicate the similarity between spatial regions and clusters and a cluster graph that shows the relationships between clusters at different resolutions. We demonstrate SpatialCPie on several publicly available datasets. SpatialCPie provides intuitive visualizations of cluster relationships when dealing with Spatial Transcriptomics data.

ST viewer: a tool for analysis and visualization of spatial transcriptomics datasets

Bioinformatics(IF：9.85), Mar 2019, José Fernández Navarro, DOI: 10.1093/bioinformatics/bty714
PubMed: 30875427
Spatial Gene Expression, Computational Method.

Abstract

Spatial Transcriptomics (ST) is a technique that combines high-resolution imaging with spatially resolved transcriptome-wide sequencing. This novel type of data opens up many possibilities for analysis and visualization, most of which are either not available with standard tools or too complex for normal users. Here, we present a tool, ST Viewer, which allows real-time interaction, analysis and visualization of Spatial Transcriptomics datasets through a seamless and smooth user interface. The ST Viewer is open source under a MIT license and it is available at https://github.com/SpatialTranscriptomicsResearch/st_viewer. Supplementary data are available at Bioinformatics online.

ST Spot Detector: a web-based application for automatic spot and tissue detection for spatial Transcriptomics image datasets

Bioinformatics(IF：9.85), 2018-6, Kim Wong et al. DOI: 10.1093/bioinformatics/bty030 PubMed: 29360929
Spatial Gene Expression, Computational Method.

Abstract

Spatial Transcriptomics (ST) is a method which combines high resolution tissue imaging with high troughput transcriptome sequencing data. This data must be aligned with the images for correct visualization, a process that involves several manual steps. Here we present ST Spot Detector, a web tool that automates and facilitates this alignment through a user friendly interface. jose.fernandez.navarro@scilifelab.se. Supplementary data are available at Bioinformatics online.

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