Evaluation of Spatial Transcriptomics for Cancer Research

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Abstract

The development of new oncology drugs is greatly hampered by tumour heterogeneity. Finding novel targets and useful model systems requires an understanding of the spatial tumour landscape. Here, by profiling 40 tissue slices and 80,024 capture sites across a variety of tissue types, sample formats, and RNA capture chemistries, we investigate the usefulness of Spatial Transcriptomics (ST) for oncology discovery. By utilising matched pathology analysis, which gives a ground truth for tissue section composition, we validate the precision and integrity of ST. Then, using spatial data, we show how important tumour depth parameters such as hypoxia, necrosis, vasculature, and extracellular matrix change may be captured. In syngeneic cancer models, we also use spatial context to pinpoint relative cell-type locations that demonstrate the anti-correlation of tumour and immune cells. In clinical pancreatic adenocarcinoma samples, we demonstrate target identification methods and highlight tumour intrinsic indicators and paracrine signalling.

Keywords: Oncology • Spatial genomics • Cancer biology • Cancer genomics • Tumors • Pancreatic cancer • Digital pathology • Spatial transcriptomics • Biomarkers

Introduction

Malignant and non-malignant cells interact in different compartments within the complex microenvironment that exists in tumours. These compartments include the tumour parenchyma (i.e., tumour cells), stroma (e.g., fibroblasts and vasculature), and immune system (e.g., adaptive and innate immune cells). These compartments may interact with one another internally, as in the case of commensal dynamics between diverse tumour clones, or externally, as in the case of tumour cells' immune suppression. Cancer evolves as a result of the considerable cellular heterogeneity and signalling complexity, which also influences treatment response and resistance. Oncology medication discovery and development are significantly hampered by tumour heterogeneity, and reductionist model systems (such as cultured cells and mice models) might not accurately reflect the complexity of actual tumours. A precise geographical and molecular taxonomy of the tumour landscape is necessary for the identification of novel targets and suitable model systems. By retaining the localization of tissue transcriptomes inside their original architecture, recent developments in spatial genomics show promise for wide characterisation of tumour tissue structure, spatial contextualization of existing biomarkers, and de novo detection of spatial relationships. We conducted a thorough evaluation of the applicability of Spatial Transcriptomics (ST); hereafter referred to as spatial genomics) for cancer, with an emphasis on drug discovery. The use of ST in cancer comes with a number of unique issues that must be taken into account. First, unlike the well-structured tissues (such as the spinal cord) employed in early ST experiments, tumours are highly diverse and can generate disorderly malignant formations interspersed within normal tissue. This characteristic called for a particular evaluation of ST resolution and performance in tumour tissue. Second, Formalin-Fixed, Paraffin-Embedded (FFPE) tissues are the specimens that are most frequently employed for clinical pathology examination and are most easily accessible for molecular profiling.In contrast to the Fresh Frozen (FF) samples that have been sequenced in the majority of spatial genomics research to far, 21 FFPE tissues had worse transcriptome quality. To offer recommendations for the selection of the best tissue samples, a detailed comparison of the frozen and FFPE protocols' performance is necessary. Third, it is possible to supplement and validate transcriptomic measurements with additional standard and cutting-edge histologic imaging data by overlaying transcriptome maps created by a ST experiment with pathology analysis. However, validation and further integration are required to determine the validity of these multi-modal measurements (imaging and expression). Last but not least, the current spatial genomics technology analyses cell mixes instead of single cells, demanding a modification to the current genomics analytical frameworks to accommodate these low-bulk spatial outputs. . We conducted a rigorous evaluation of ST encompassing a variety of tissue types, sample formats, RNA capture chemistries, and computational frameworks in order to resolve these difficulties. We used a well-structured non-malignant tissue, two mouse syngeneic tumour models with different Tumour Microenvironments (TMEs), and clinical tumour specimens with a variety of typical heterogeneous tissue compositions to set up our assays and analysis process. We tested the effectiveness of several ST methods, including polyA-based ST using FF tissue (hereafter referred to as FF-polyA-ST), polyA- and probe-based transcriptome capture strategies using FFPE tissues (hereafter referred to as FFPE-polyA-ST and FFPE-probes-ST, respectively). We created what is known as the spatial validation framework to integrate gene expression and digital pathology. Histology, the de facto method for describing tissue architecture, can be used to validate the distribution of expression data and understand it. We also investigated the applicability of current single-cell genomics analytic methods for target identification to spatial genomics.