

Towards Spatial Hallmarks of Cancer Detection and Treatment

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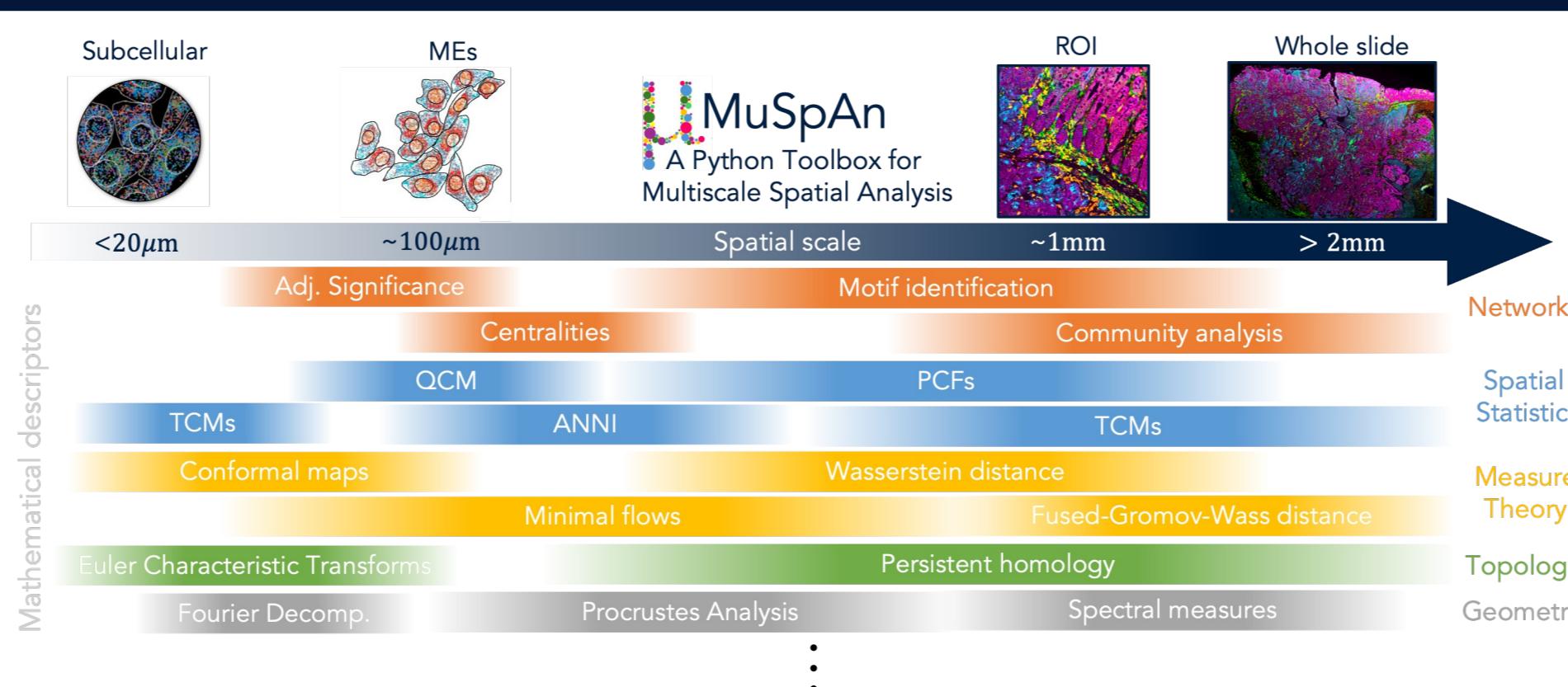
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Interpretable multiscale spatial analysis for cancer research

Introduction

Recent advances in multiplex imaging technologies, such as *in situ* transcriptomics and proteomics, have revolutionised our ability to capture intricate details across multiple biological scales, from molecular to tissue levels.

Despite these innovations, there remains a **critical shortage of analytical tools that can fully interpret and integrate the multiscale properties of the generated data**. This gap limits our ability to extract meaningful insights, underscoring the need for new computational approaches that fully exploit the complex information contained in these datasets.



MuSpAn is a Python toolbox for Multiscale Spatial Analysis, which provides a single platform for comprehensive multiscale analysis. It enables the **seamless construction of spatial analysis pipelines** using **well-established and cutting-edge mathematical tools** for quantitative spatial analysis [1].

Overview

Here we present two independent case studies from colorectal cancer which showcase the ability of MuSpAn to perform multiscale spatial analysis using alternative approaches:

Case Study 1: A discovery study seeking to identify spatial cell-cell interactions that are discriminatory between adenoma and carcinoma in colorectal neoplasia [2].

Case Study 2: A hypothesis-driven study on quantifying the effect of drug-induced spatial re-organisation of fibroblast and immune populations in tumours [3].

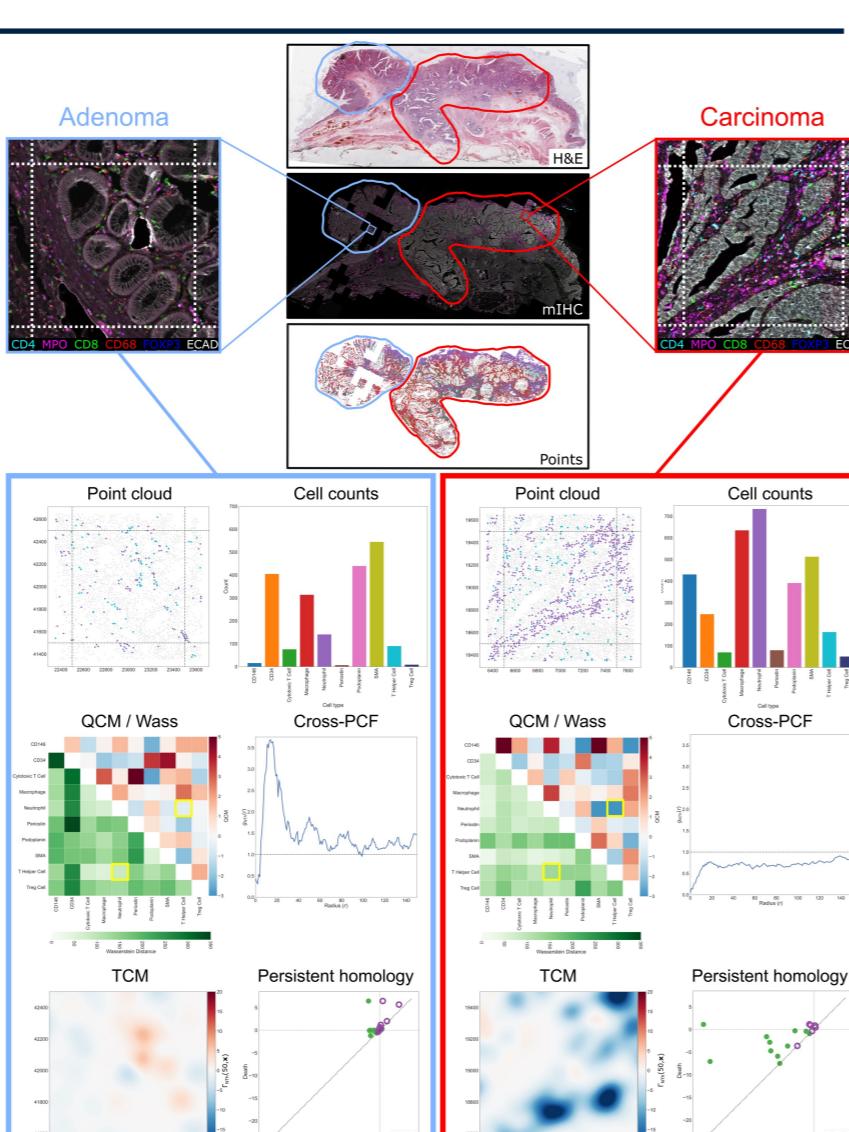
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Case study 1: Ensemble spatial methods delineate disease stage

The complexity of mammalian tissues, that occur across a spectrum of length scales, presents significant challenges for spatial analysis, increasing the gap between our capacity to generate and biologically interpret these datasets. Here, we have adapted a range of mathematical tools to develop a suite of spatial descriptors to determine how cell interactions change as colorectal cancer progresses from adenoma to carcinomas.

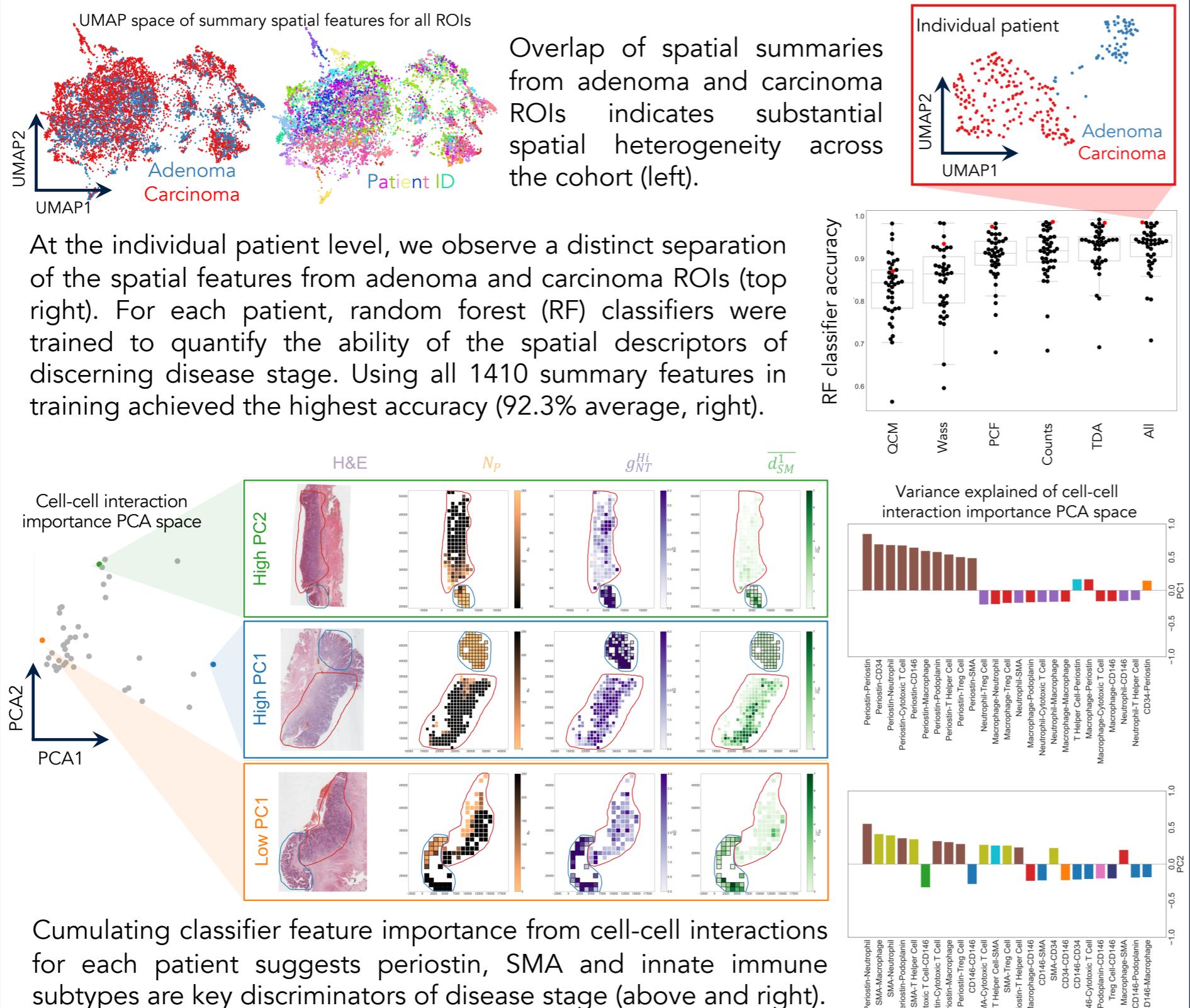
Methods

A curated ensemble of spatial metrics was used to describe cell-cell interactions within 10027 ROIs ($516 \times 516\mu\text{m}$) of multiplex IHC data contained within regions annotated adenoma or carcinoma across 43 patients (right).



Computing and distilling each metric for all pairwise combinations of the 10 stained stromal and immune subtypes generated a spatial feature vector with 1410 elements for each ROI.

Results



Cumulating classifier feature importance from cell-cell interactions for each patient suggests periostin, SMA and innate immune subtypes are key discriminators of disease stage (above and right).

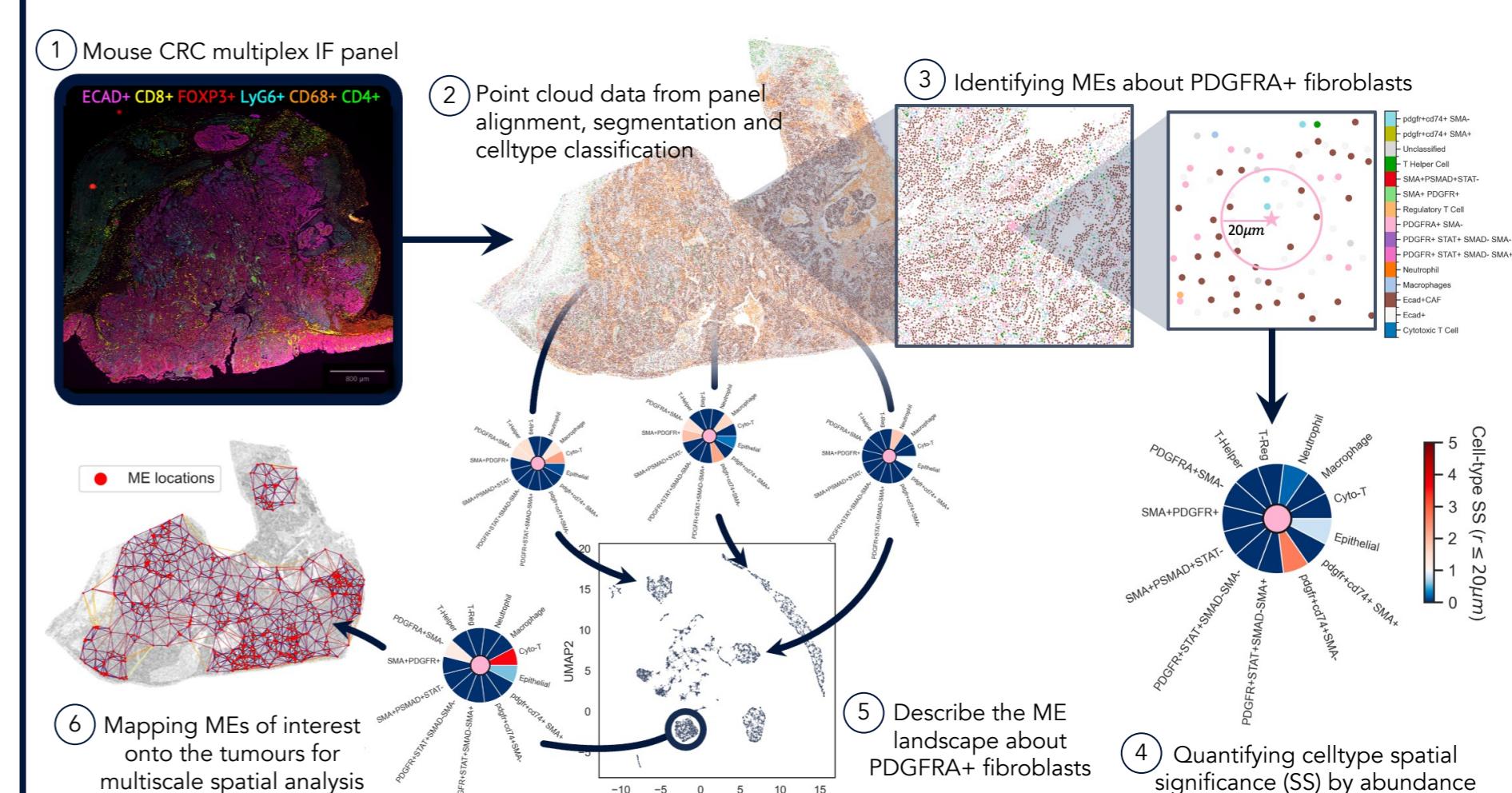
Conclusion

Using an unsupervised approach, we show that inter-patient spatial variability is greater than intra-patient differences between disease-stage. However, patient-specific analysis highlights similarities of core interacting cell types that drive the transition from adenoma to carcinoma.

Case study 2: TGFβ remodels the stromal-immune spatial landscape

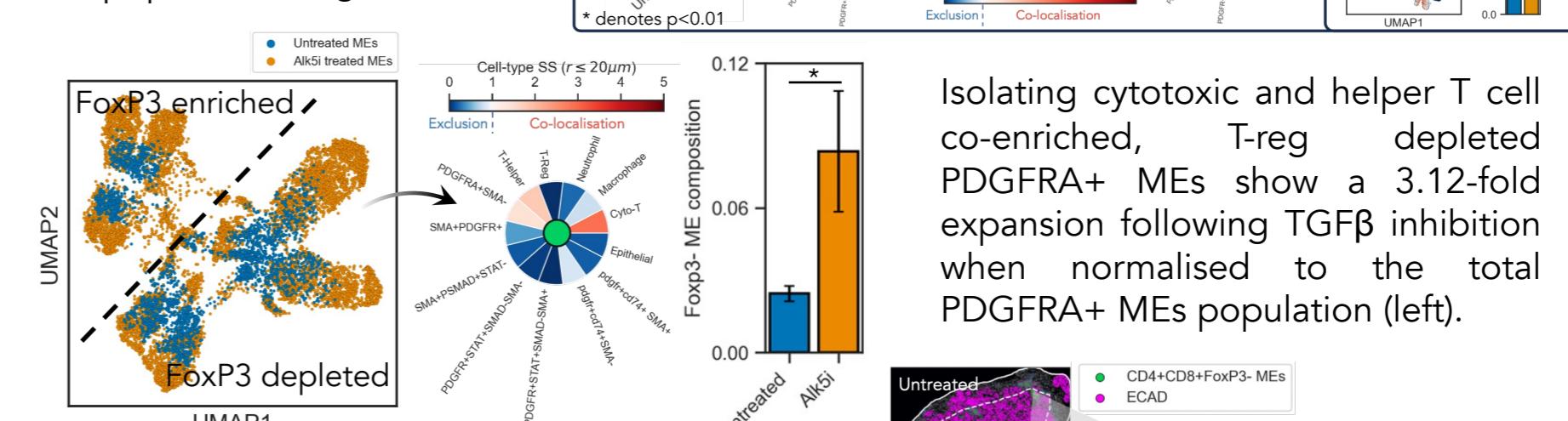
Transforming growth factor-β (TGFβ) is a key oncogenic pathway in colorectal cancer. In fibroblasts, overexposure to TGFβ yields a phenotypic shift to a pro-tumour state [4]. To isolate the behaviour of fibroblasts in tumour progression, we used epithelial deleted Alk5 (TGFβ blind) mouse models to quantify the impact of TGFβ exposure on the microenvironments (MEs) of normal fibroblasts from a multiscale perspective.

Methods



Results

Local spatial analysis reveals a significant increase of T-cell enriched MEs surrounding PDGFRA+ fibroblasts following Alk5-induced TGFβ inhibition. This ME expansion is amplified within the CD8+ and FoxP3+ subpopulations (right).



Examining the spatial distribution of these PDGFRA+ MEs, reveals significantly elevated infiltration within the inner 60% of the tumour mass. In addition, Topographical Correlation Maps (TCMs) [5] highlight increased localised spatial clustering of these MEs in the stromal compartments of the tumour (right).

Conclusion

Inhibition of TGFβ induces an influx of anti-tumour immune enriched MEs about PDGFRA+ fibroblasts within the tumour. These results suggest a dynamic interplay between immune infiltration and fibroblast spatial distribution mediated via local levels of active TGFβ.

