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A Bayesian framework for cell-based microdomain discovery from spatially resolved single-cell omics datasets

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Background

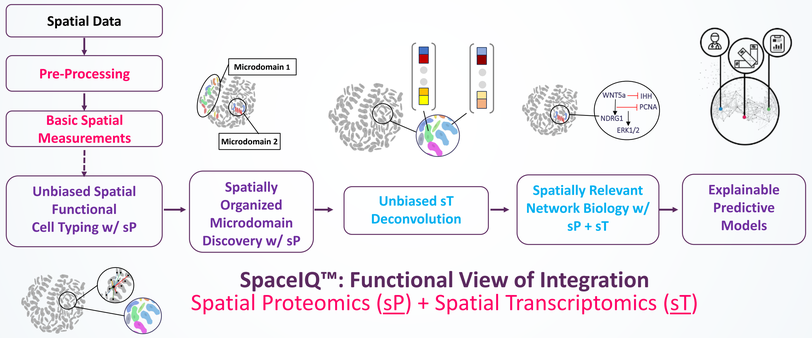
- The emergence of single-cell spatial omics platforms generating high-plex proteomic and transcriptomic measurements sets the foundation for accurate downstream biologically interpretable analyses.
- This includes biased and unbiased approaches for cell typing, cell-cell interactions and the discovery of microdomains, complex multicellular microenvironments, underlying disease progression.

Problem

- There is a lack of a computational framework for optimizing unbiased approaches with biological priors for unraveling a deeper understanding of disease mechanisms.
- This requires innovative integrational methods that assign confidence and robustness to data-driven biological hypotheses, e.g., presence of transition cells and other rare cell types, emergent microdomains and spatially modulated network biology.

Solution

- We present a Bayesian computational approach, **SpaceIQ™** [1,2], that not only elucidates potential novel hypotheses driving disease mechanisms, but also cross-references existing working hypotheses from alternative methods.
- SpaceIQ is agnostic to imaging platforms with the ability to ingest any combinatorial forms of spatial data (e.g., transmitted light, proteomics and transcriptomics).



SpaceIQ™: Functional View of Integration
Spatial Proteomics (sP) + Spatial Transcriptomics (sT)

Results

- To illustrate our approach, we compare the results from **SpaceIQ** to the interpretative analyses presented in He et al. Nat Biotech 2022, a publicly available 960-plex RNA data from CosMx platform on NSCLC samples.
- We aim to provide additional mechanistic insights underlying Stage II/III progression that can augment the biological annotations reported.
- We have identified 16 unbiased cell types with probabilistic representation of a priori phenotypes annotated as myeloid, lymphocytes, endothelial, epithelial/tumor, and fibroblast.
- IFI27, SOX4, MALAT1, TYK2, CD74, HLADRB1, and COL3A1 were among the highly-expressed discriminatory genes among cell types. 28 significant spatial interactions (p<0.1) were found resulting in 7 microdomains.
- Comparison of microdomains to niche neighborhoods defined in He et al. shows that macrophages in the stroma and TLS play a role in tumor progression.
- Ligand-Receptor analysis on microdomains identified IL-2 signaling, GPCR ligand binding, TNF activity, and TGF regulation to be significant cell-cell communication channels in NSCLC progression (p<1e-04).

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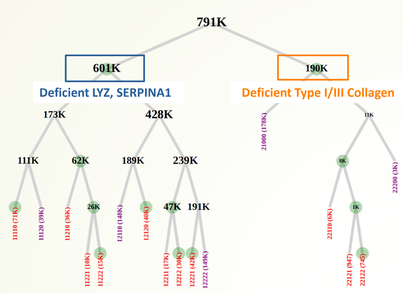
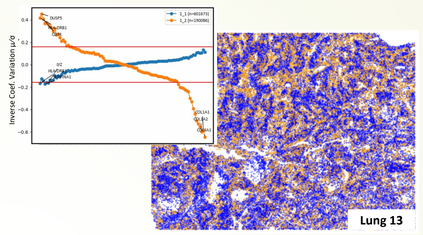
PUBLICATIONS

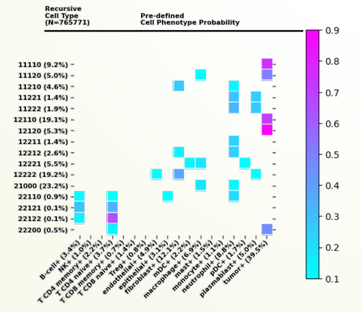
Unbiased Cell Typing Extracts Numerically Stable, Spatially Distinct and Biologically Interpretable Recursive Cell Types



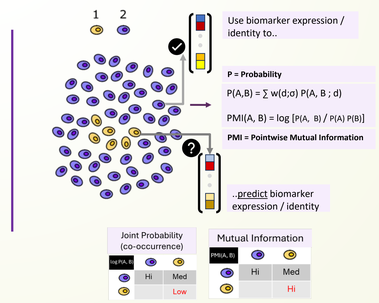


1. Green circles denote distinct sub-populations based on goodness-of-cluster
2. Red cell types denote a sub- population with a distinct parent not from level 1
3. Purple cell types denote cell population that derive level 1 distinctiveness

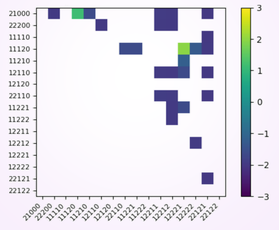
Bayesian Interpretation of Recursive Cell Types Using Pre-Defined Tumor/Immune Phenotype Likelihoods



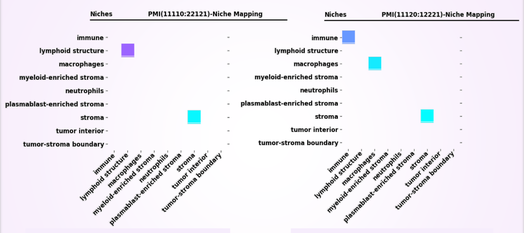
Pointwise Mutual Information (PMI) [3] Maps Quantify Spatial Heterogeneity



Ratio of PMI Maps Between Stage-II vs Stage-III patients for Recursive Cell Types ($p < 0.1$)



Niches Associated with PMI Interactions



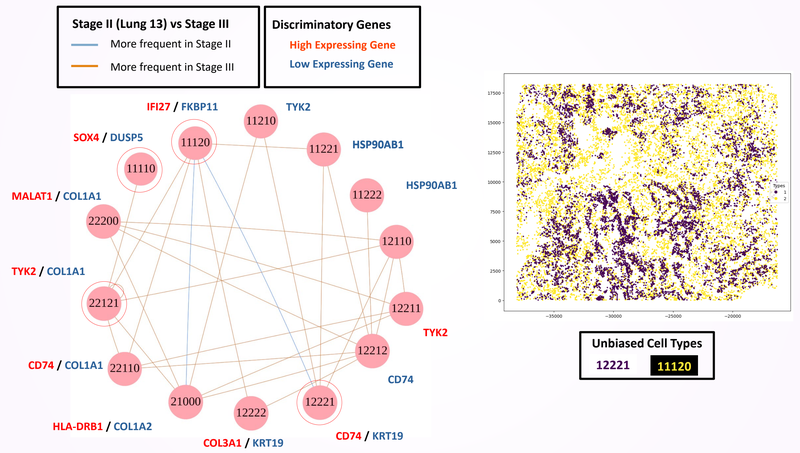
Spatial interaction between 11110:22121 predominantly implicated in lymphoid structures

Spatial interaction between 11120:12221 is mostly immune-rich w/ presence of macrophages

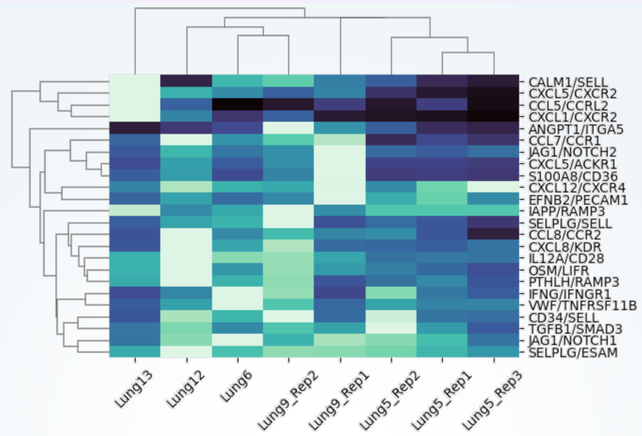
Conclusions

- We demonstrate the generalizability of SpaceIQ Platform by applying it to spatial transcriptomics datasets. The applications to mIF and brightfield pathology datasets has been showcased previously (ESMO 2024, SITC 2024)
- Our recursive unbiased cell typing revealed 16 cell types based on the top 100 most variable cell mean gene expressions.
- Unbiased cell types were characterized by Bayesian probability assignments on known predefined phenotypes and discriminatory genes measured from inverse coefficient variation estimates.
- The inferred microdomains between these unbiased cell types generated the spatial domain network that is associated with cancer stage progression.
- We performed niche mapping and ligand-receptor analysis on selected microdomains to further understand the potential biological and molecular basis underlying its association to cancer progression.

Microdomain Families Emerge from Spatial Domain PMI Network

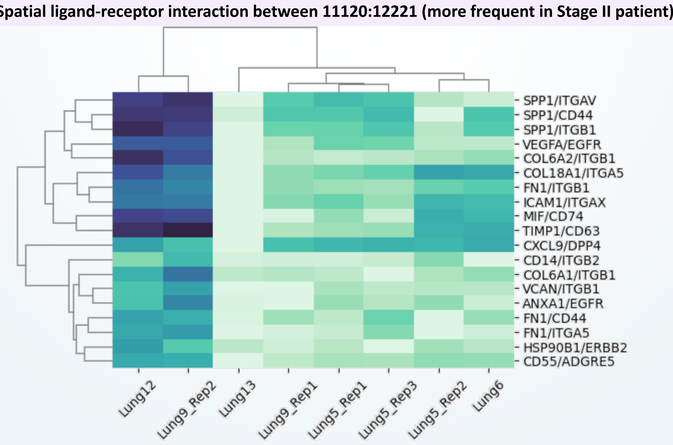


Spatial ligand-receptor interaction between 11110:22121 (more frequent in Stage III patients)



Lung 13 patient (Stage II) is an outgroup in hierarchical clustering

Spatial ligand-receptor interaction between 11120:12221 (more frequent in Stage II patient)



High ligand-receptor interaction despite differential spatial interaction

References [1]Uttam, S, et al Nat. Comm., 2020; [2]Furman SA, Cell. Rep. Met., 2021; [3]Spagnolo D et al, JPI, 2016