Spatial Flux Balance Analysis reveals spatially resolved metabolic heterogeneity in renal cancer

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Background: Understanding spatial metabolism is crucial for unraveling the intricacies of cellular functions in complex biological systems. Despite its significance, spatial metabolomics remains in its infancy. Current pathway enrichment frameworks leveraging spatial gene expression data exhibit limitations, lacking expressivity in flux direction, proliferation rate indication, and exhibiting biases towards pathways with numerous isoforms or subunits.

Methods: In this study, we propose spatial Flux Balance Analysis (SpatialFBA) to harness spatial transcriptomic RNA-sequencing data, thereby identifying spatially resolved metabolic phenotypes. Our method couples constraints on flux boundaries based on differential gene expression with flux sampling.
We applied spatialFBA to a public renal cancer dataset.

Results:
- SpatialFBA successfully recapitulates tissue architecture by clustering feasible flux distributions
- SpatialFBA accurately distinguishes between tumor core and adjacent normal tissue
- Our spatial metabolic analysis unravels the Warburg effect in subpopulations of cancer cells, shedding light on the metabolic reprogramming occurring in specific cellular contexts.

Conclusion: By incorporating real-time spatial transcriptomic RNA-sequencing data, spatialFBA addresses the existing limitations in spatial metabolomics, aligning with the evolving paradigm of digital twin technology. Indeed spatialFBA enhances our ability to create digital representations of cellular environments, obtaining digital replicas that mirror the intricacies of cellular metabolism within tissues, providing a virtual environment where the effects of different perturbations and interventions can be simulated and studied. SpatialFBA may facilitate the identification of spatially specific vulnerabilities in pathological conditions, guiding the development of precision medicine approaches tailored to individualized spatial metabolic profiles.