Spatial Flux Balance analysis reveals Warburg heterogeneity in renal tumors and lactate-consuming niches in colorectal cancer

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Abstract:
Metabolic heterogeneity plays a central role in cancer progression, therapy resistance, and metastasis. Understanding how spatial constraints shape cancer metabolism requires flux-level resolution, which still lags behind the rapid advances in spatial transcriptomics. To address this gap, we generated high-resolution spatial transcriptomics datasets from paired primary colorectal tumors and liver metastases. We applied a flux sampling–based metabolic modeling framework to enrich these data with estimates of relative metabolic activity, capturing directional information on metabolite consumption and production across spatial locations. We observed that liver metastases retained the metabolic traits of the primary tumor. Strikingly, both primary and metastatic regions exhibited lactate consumption. Notably, this consumption appeared decoupled from oxidative phosphorylation, suggesting a non-canonical metabolic use of lactate, distinct from the classical reverse Warburg effect. To verify that lactate consumption was not an artifact of the model structure or data integration approach, we applied the same strategy to a public spatial transcriptomics dataset of renal cancer, including tumor-normal interface samples. In contrast to colorectal tumors, renal tumors exhibited widespread lactate production, thus excluding a general prediction bias. Although finer spatial gradients were also observed, the overall pattern confirmed a dominant Warburg phenotype and recapitulated well-known cancer hallmarks, such as increased glycolysis and metabolic growth. We then analyzed an independent public dataset of colorectal cancer, which confirmed the presence of lactate-consuming regions, suggesting that this phenotype is not unique to our dataset but may represent a reproducible metabolic feature of colorectal tumors. Spatial transcriptomics, coupled with our spatial Flux Balance Analysis approach, reveals metabolic programs invisible to gene expression alone. This enables hypothesis generation from any sequencing-based spatial dataset, without the need for customization.