A082 · TissueCircuit disentangles active signaling circuits from cell-type structure

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Inferring cell-cell communication from spatial transcriptomics is confounded by cell-type organization: cells of interacting types cluster together, creating apparent signaling where none occurs. Methods that trace ligand-receptor interactions to downstream targets, such as NicheNet and SpaTalk, do not correct for this, so the co-localization and co-expression of cells that share a type are readily mistaken for genuine communication. We present TissueCircuit, which prunes a prior network of candidate ligand→receptor→downstream circuits to the subset genuinely active in a tissue, explicitly separating true spatial signaling from cell-type structure.

We apply TissueCircuit across three Xenium lung adenocarcinoma sections spanning tumor and matched healthy tissue and two panel designs, benchmark its calibration against permutation and cell-type-shuffled nulls, and validate recovered circuits against prior signaling databases and cross-section reproducibility. TissueCircuit recovers a tumor-specific EGFR circuit, AREG→EGFR→{MYC, KLF5, mTORC1}, absent in matched healthy lung. Cell-type-resolved analysis localizes the circuit to malignant cells, with paracrine input from plasma cells and macrophages, and a ligand-rich but spatially excluded alveolar population serving as an internal negative. A second immune-checkpoint axis, CD80/CD86→CTLA4, is likewise tumor-specific.

By combining prior knowledge with spatial statistics, TissueCircuit turns spatial transcriptomes into testable, tissue-specific signaling circuits, applicable to any receptor or tissue with a prior network. When a matched control is available, it further isolates disease-specific circuits.