A novel approach to prioritize clinically significant cell-cell interactions in human solid cancers

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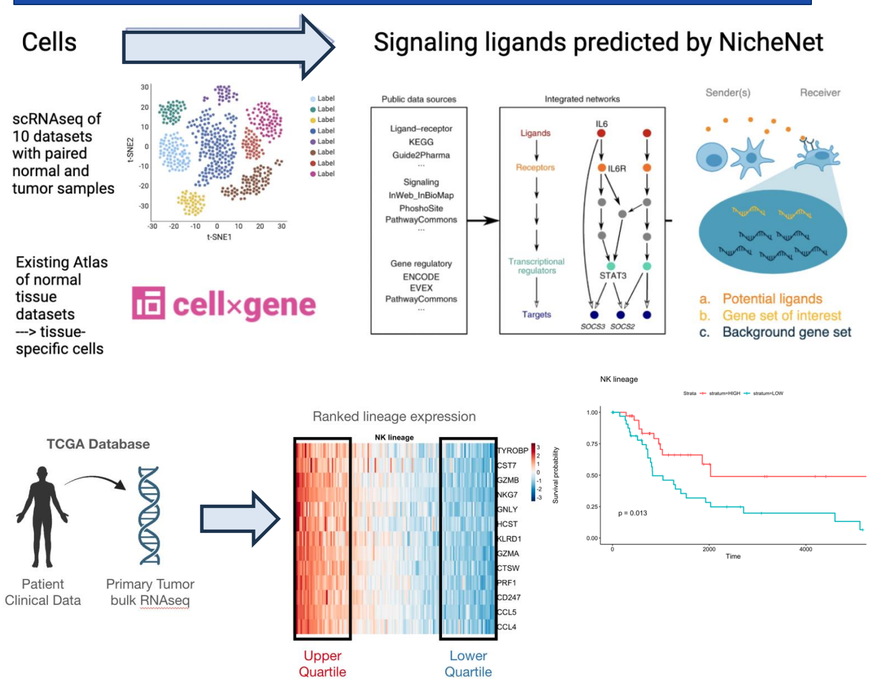
Abstract

Cell-cell interactions, mainly through ligands, induce critical changes in gene expression in the tumor microenvironment. Algorithms including CellPhoneDB and NicheNet are widely used to predict these interactions using single-cell RNA sequencing data. However, their outputs are often difficult to interpret due to the large number of results and their lack of clinical significance. Therefore, a new method is necessary to prioritize clinically relevant cell-cell interaction. In our study, we combined fifteen publicly available single-cell RNA sequencing datasets to identify ligands with high regulatory potential to induce downstream gene expression changes in the tumor microenvironment. Next, we used survival data from The Cancer Genome Atlas (TCGA) to rank patients' expression of cell lineage markers and ligands and determine which predicted cell-cell interactions led to a significant difference in patient outcomes. Our method has the potential to become an individualized tool for discovering and screening novel drug targets and next-generation cancer therapies.

Objectives

- To analyze publicly available single-cell RNA sequencing datasets with patient-matched adjacent normal and tumor tissues.
- To find significant cell-cell interactions that contribute to positive cancer survival outcomes.
- To understand how these communication cell pairs and pathways correlate with each other and together affect survival outcomes.
- To discover potential cancer therapy and drug targets.

Methodology



Results

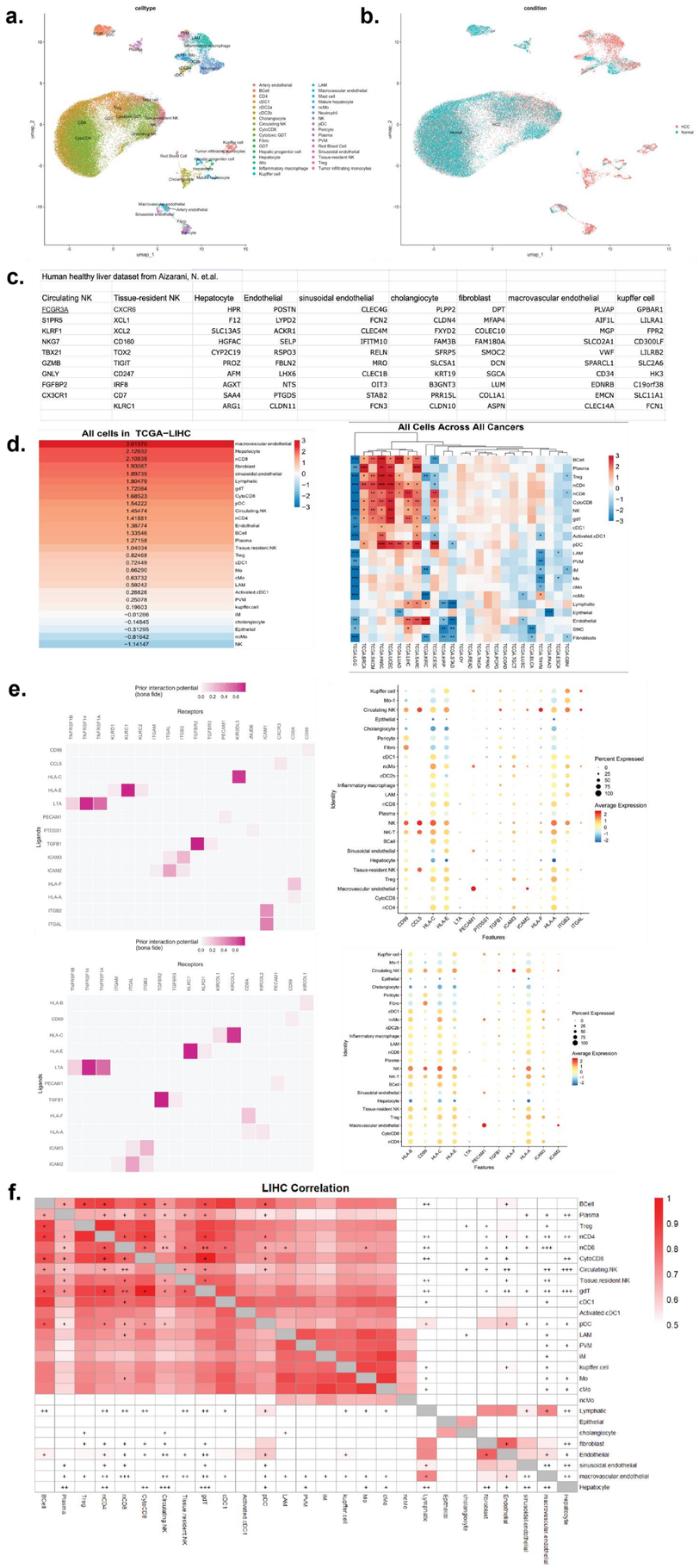
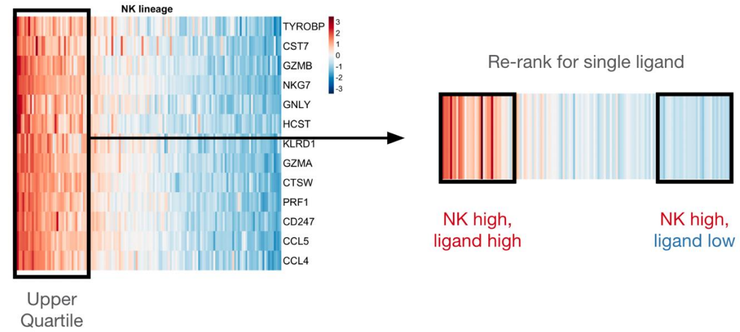


Figure 1. Results for our analysis of human liver cancer. a-b. Harmonized UMAPs of present cell types and tissues; c. A table of lineage markers for tissue-specific cells in normal human liver retrieved from Cell X Gene; d. Single lineage analysis in liver cancer and across human solid cancers; e. NicheNet bonafide ligand prediction and receiver-sender cell pairs prediction on tissue-resident NK cells (up) and circulating NK cells (down); f. Lineage-lineage analysis in liver cancer (color in the boxes indicates correlation and pluses indicate significance).

Conclusion/Future Directions

- Current tissue cell-cell interaction algorithms are difficult to interpret clinically.
- By studying single-cell matched patient data, an algorithm called NicheNet, and TCGA database, we can model the effects of cell-cell interactions on patient survival
- We discovered cell-cell pairs that are potent enough to drive survival or death in patients and form cancer-specific synergy or antagonism relationships with each other.
- Using this information, we can prioritize ligands from cell-cell pairs that modulate patient survival. These ligands can be further used to conduct a drug screen and to build a web tool for others to test hypotheses and prognoses.



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