A096 · Single-Cell Mapping of Malignant Signaling Networks Guides Drug Combinations

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Single-cell atlases have transformed our understanding of breast-tumor heterogeneity across cells, patients, and clinical subtypes. Building on these advances, rational drug-combination design requires identifying recurrent intracellular signaling pathways and understanding how crosstalk among them may support proliferation, survival, metabolic adaptation, and treatment resistance. We therefore asked which pathways recur across malignant cells of untreated tumors beyond matched-null expectations and which points of convergence could yield mechanistically informed, testable hypotheses for co-targeting. To address this question, we developed a cell-resolved network framework and applied it to 15,753 malignant cells from 14 untreated primary breast tumors. For each cell, expressed genes were mapped onto a protein–protein interaction network using personalized PageRank. The resulting cell-specific subnetwork was partitioned into Leiden communities, and the highest-scoring, expression-weighted community was tested for pathway enrichment. Patient-level pathway recurrence was then compared with matched null distributions that preserved community size and controlled for protein-network degree and gene detection rate. Before null correction, HIF-1, MAPK, PI3K/AKT, and JAK/STAT signaling were frequently enriched. After correction, HIF-1 showed the largest excess over expectation, with a positive observed-minus-null difference in all 14 patients. Rap1, JAK/STAT, sphingolipid, prolactin, Ras, and additional immune, metabolic, and endocrine pathways also exceeded matched-null expectations. In our analysis, HIF-1 emerged as such a convergent pathway. This calls for testing targeting HIF-1 directed pathway in combination with upstream growth-factor or cytokine-associated pathways, including PI3K/AKT/mTOR, Ras/MAPK, and JAK/STAT3.

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Abstract. Single-cell atlases have transformed our understanding of breast-tumor heterogeneity across cells, patients, and clinical subtypes. Building on these advances, rational drug-combination design requires identifying recurrent intracellular signaling pathways and understanding how crosstalk among them may support proliferation, survival, metabolic adaptation, and treatment resistance. We therefore asked which pathways recur across malignant cells of untreated tumors beyond matched-null expectations and which points of convergence could yield mechanistically informed, testable hypotheses for co-targeting. To address this question, we developed a cell-resolved network framework and applied it to 15,753 malignant cells from 14 untreated primary breast tumors. For each cell, expressed genes were mapped onto a protein–protein interaction network using personalized PageRank. The resulting cell-specific subnetwork was partitioned into Leiden communities, and the highest-scoring, expression-weighted community was tested for pathway enrichment. Patient-level pathway recurrence was then compared with matched null distributions that preserved community size and controlled for protein-network degree and gene detection rate. Before null correction, HIF-1, MAPK, PI3K/AKT, and JAK/STAT signaling were frequently enriched. After correction, HIF-1 showed the largest excess over expectation, with a positive observed-minus-null difference in all 14 patients. Rap1, JAK/STAT, sphingolipid, prolactin, Ras, and additional immune, metabolic, and endocrine pathways also exceeded matched-null expectations. In our analysis, HIF-1 emerged as such a convergent pathway. This calls for testing targeting HIF-1 directed pathway in combination with upstream growth-factor or cytokine-associated pathways, including PI3K/AKT/mTOR, Ras/MAPK, and JAK/STAT3.

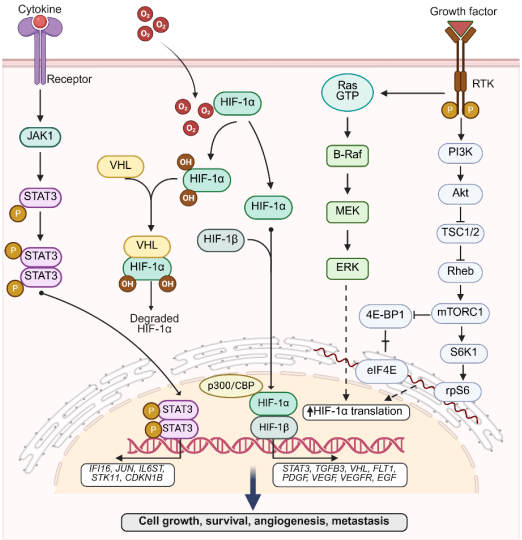

Figure 1. Schematic of upstream PI3K/AKT, Ras/MAPK, and JAK/STAT signaling converging on HIF-1α.