Elucidating the Determinants of Chemotherapy Response: A Single-Cell Transcriptomic Characterization of Chemosensitive and Resistant Tumors from Triple-Negative Breast Cancer Patients

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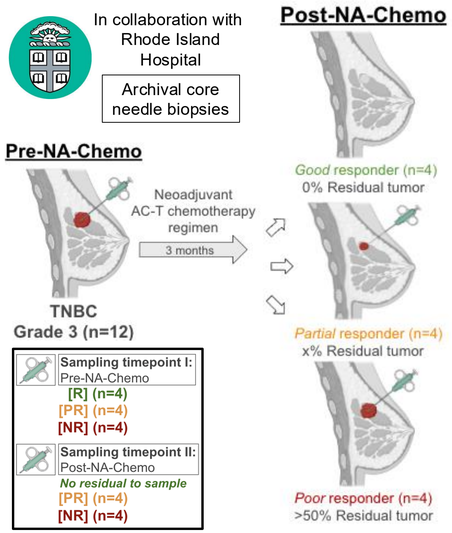
ABSTRACT

Triple-negative breast cancer (TNBC) remains one of the most aggressive breast cancer subtypes, with highly variable response to neoadjuvant chemotherapy and limited predictive biomarkers. In this study, we performed single-cell transcriptomic profiling of core needle biopsy tumor samples from patients classified as chemotherapy-sensitive (CSen) and chemotherapy-resistant (CRes), enabling tumor-intrinsic analysis at unprecedented cellular resolution. This work provides a framework for mechanistically dissecting chemotherapy response heterogeneity in TNBC at the single-cell level and lays the foundation for future precision oncology strategies that stratify patients based on tumor-intrinsic vulnerability rather than histopathologic subtype alone.

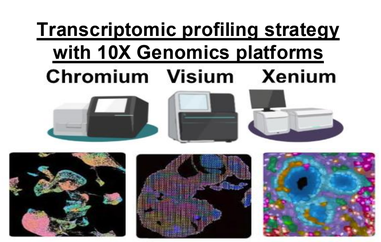
INTRODUCTION

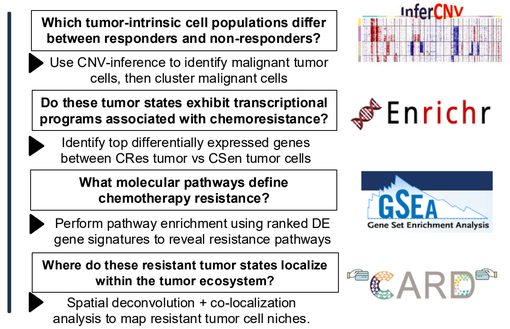
- Breast cancer remains the most commonly diagnosed malignancy in women in the United States. In 2025, breast cancer is projected to account for ~32% of all new cancer diagnoses in women and continues to be the second leading cause of cancer-related death nationally[1].
- Within this broad landscape, triple-negative breast cancer (TNBC) represents a uniquely aggressive and clinically challenging subtype. Although TNBC comprises only 10–15% of all breast cancer diagnoses, it accounts for a disproportionately high share of breast cancer mortality[2].
- Patients with TNBC experience higher recurrence rates, earlier metastatic spread, and significantly fewer targeted systemic therapy options[2].
- Achieving pathological complete response (pCR) after neoadjuvant chemotherapy (NA-Chemo) is one of the strongest biological predictors of long-term survival - yet only ~50% of TNBC patients achieve pCR[3].
- For the remaining half of patients, chemotherapy-resistant tumor cells survive treatment and form minimal residual disease, which frequently seeds early distant relapse and metastatic spread.[4]
- This pilot project focuses on mechanistically dissecting chemotherapy response in TNBC, leveraging high-resolution single-cell data to identify cellular, molecular, and functional features

METHODS



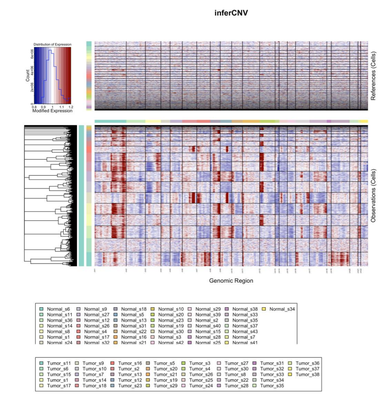
RESULTS

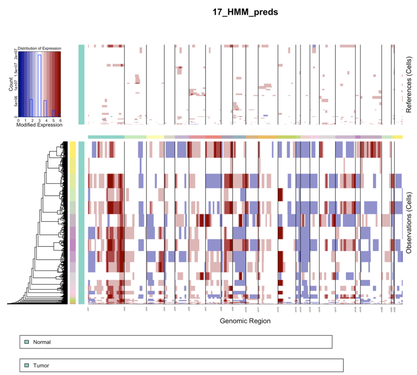




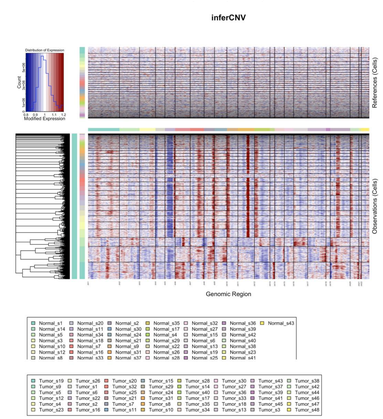
Tumor Cells Display Broad CNV Alterations (InferCNV)

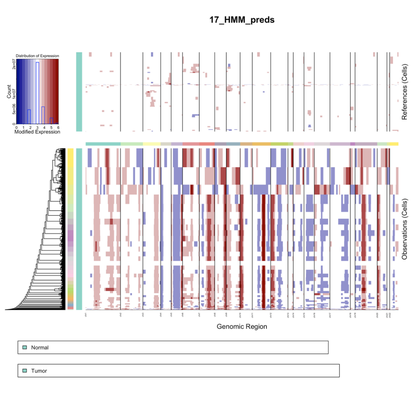
Chemoresistant Patient Tumor Samples (n = 4)





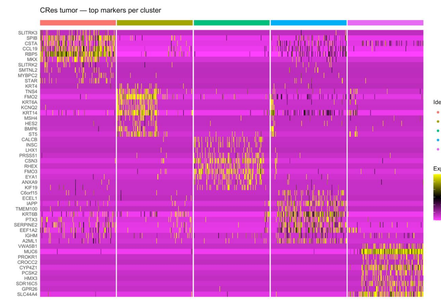
Chemosensitive Patient Tumor Samples (n = 4)



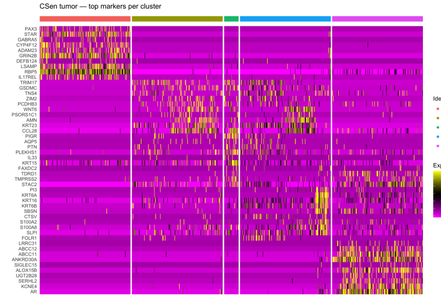


Differential Expression Identifies Chemotherapy Response-Associated Tumor Programs

Chemoresistant Patient Tumor Samples (n = 4)



Chemosensitive Patient Tumor Samples (n = 4)



CONCLUSION

- Single-cell transcriptomic profiling reveals distinct tumor-intrinsic states that differentiate chemoresistant from chemosensitive TNBC.
- CNV inference confirms malignant identity and enables tumor-specific discovery of molecular programs associated with chemotherapy resistance.
- Differential expression and pathway enrichment highlight actionable biological circuits that may underlie treatment resistance in TNBC.
- Spatially mapping resistant tumor states using Xenium panels can define microenvironmental niches, guide biomarker discovery, and translate these signatures toward clinically deployable assays.
- These findings support development of precision oncology strategies to stratify patients based on tumor-intrinsic molecular vulnerability.

Acknowledgements + References

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