San Antonio Breast Cancer Symposium – December 9-12, 2025

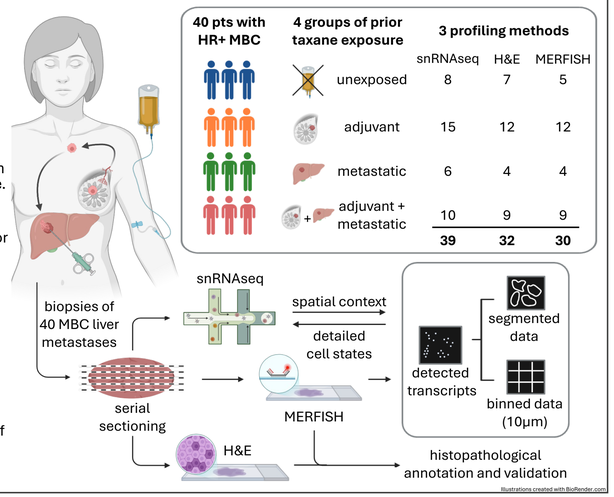
Mapping the imprint of taxane chemotherapy on the metastatic microenvironment in HR+ breast cancer with single cell and spatial profiling

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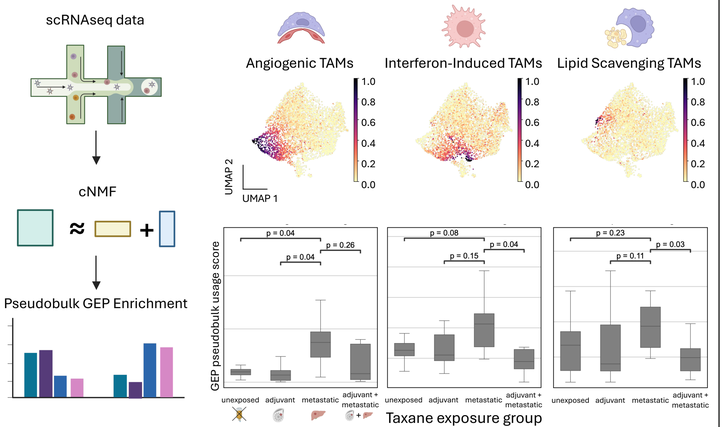
Study design

- The tumor microenvironment (TME) is increasingly recognized as playing a fundamental role in critical elements of breast cancer progression including metastatic dissemination and therapeutic response and resistance.
- Differences between efficacy of checkpoint inhibitors as monotherapies versus in combination with conventional chemotherapies, like taxanes, or antibody drug conjugates promotes the hypothesis that cancer-directed therapies do not only affect tumor cells directly but also shape TME dynamics with potentially pivotal influences on therapeutic response.
- However, the impacts of even common therapies on TME interactions as they occur in patients remain incompletely defined, particularly in hormone receptor positive (HR+) metastatic breast cancer (MBC).
- Here we leveraged advances in single-cell and spatial transcriptomics to profile biopsies of 40 liver metastases from 40 women with HR+ MBC using single-nucleus RNA sequencing (snRNA-seq), Multiplexed Error-Robust Fluorescence In Situ Hybridization (MERFISH) and H&E staining.
- Integration of these data yielded a detailed, spatially resolved atlas of HR+ MBC liver metastases.
- Analyzing the biopsies by prior exposure to taxane-based chemotherapy enabled us to map the imprint of this key therapeutic class with relevance for immunotherapy on the TME of this common and clinically important visceral site of HR+ MBC.



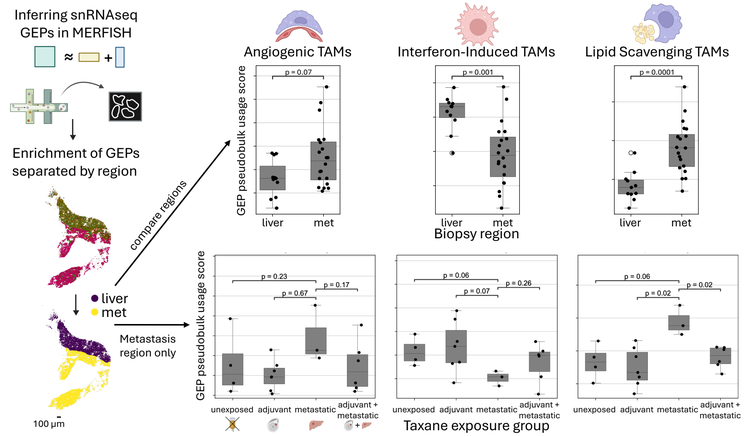
40 pts with HR+ MBC	4 groups of prior taxane exposure	3 profiling methods: snRNAseq	H&E	MERFISH
	unexposed	8	7	5
	adjuvant	15	12	12
	metastatic	6	4	4
	adjuvant + metastatic	10	9	9
		39	32	30

Macrophage states are associated with taxane exposure



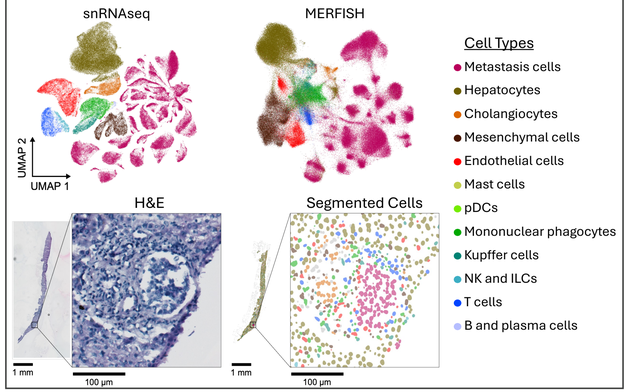
Using cNMF[1], macrophage states were represented by 8 gene expression programs (GEP). Three showed upregulation with taxane exposure limited to the metastatic setting: pro-angiogenic TAMs and lipid-scavenging TAMs, both linked to poor prognosis, as well as interferon-induced inflammatory TAMs.

Region-dependency of macrophage state enrichment

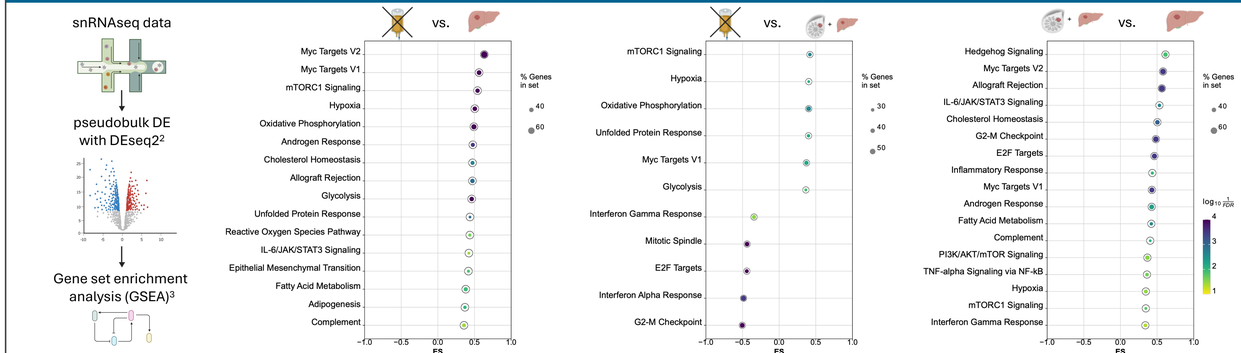


Inferring GEPs in spatial data, pro-angiogenic and lipid-scavenging TAMs were enriched in metastatic regions, while interferon-induced inflammatory TAMs were enriched in the surrounding liver tissue.

Data composition



MYC-associated gene sets are upregulated with taxane exposure in the metastatic setting



DE analysis and GSEA of malignant cells show upregulated gene sets associated with MYC, energy metabolism, and hypoxia in patients exposed to taxanes in only the metastatic setting, even compared to exposure to taxanes in both adjuvant and metastatic settings, which instead is associated with downregulation of gene sets related to proliferation.

Conclusions and Future Directions

- Overall, we identify the relative timing of taxane exposure as compared to the diagnosis of metastatic disease as a determinant of impact on the TME.
- Taxane exposure limited to the metastatic setting was associated with a hypoxic and immune excluded TME with SPP1+ lipid-scavenging and pro-angiogenic macrophages, pericytes, and proliferating endothelial cells; elevated HIF1A activity of non-malignant cells; MYC-driven metabolism in malignant cells; and pronounced exclusion of interferon-induced inflammatory TAMs and T cells.
- Spatial integration identified this phenotype as elevated specifically in metastatic regions compared to the hepatocyte-rich surroundings.
- Together, these data provide a detailed, spatially resolved atlas of liver metastases in HR+ breast cancer, demonstrate the utility of matched single-cell and spatial transcriptomics toward evaluating the impact of cancer-directed therapies on the TME, and identify key features of the taxane-exposed state with potential for future clinical translation.

Acknowledgements

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