De novo Metastatic Breast Cancer Primary and Metastatic Tumors Differentially Express Immune-Related Gene Signatures Relative to Recurrent Metastatic Breast Cancer

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Background:

There is insufficient characterization of the molecular alterations that allow tumor cells to metastasize, contributing to inadequate metastasis prevention and treatment. Most of what is known about the biology driving metastatic breast cancer comes from analysis of tumors that have been previously exposed to treatment, capturing both genomic drivers of metastasis and treatment-related alterations. Analysis of untreated primary breast and metastatic tumors from patients with de novo metastatic breast cancer (dnMBC) offers a unique opportunity to detect genomic changes related to metastasis while minimizing confounding variables. Patients with dnMBC have a 10.5 month superior median overall survival from time of metastatic diagnosis compared to those with recurrent metastatic breast cancer (recMBC), as observed in a cohort of 906 patients treated at UNC from 2011-2017. Clinicopathological features and treatment patterns do not entirely explain this difference, thus underlying biologic differences are suspected. Recently differences in expression of immune-related gene signatures between breast primary and metastatic tumors have been described, however whether these occur as a result of the metastatic process or secondary to treatment is unknown.

Hypothesis:

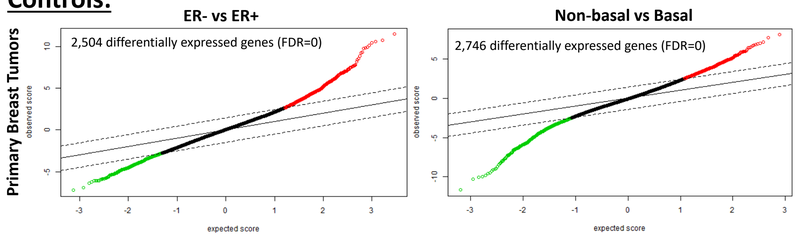
Primary breast and metastatic tumors from patients with dMBC will have higher expression of immune-related gene signatures than tumors from patients with rMBC.

Methods:

- Perform supervised analyses using Significance Analysis of Microarrays on whole transcriptome sequencing results from patients on two previously enrolled studies to assess differences in expression of immune-related gene signatures in primary and metastatic tumors (22,976 genes, 790 gene signatures)
  - **RAP**: Program in which patients agree to allow primary breast and metastatic tumors to be collected and donated to research at time of autopsy
  - **GEICAM**: Genomic analysis performed as part of a trial to determine rate of receptor conversion between primary breast and metastatic tumor biopsies

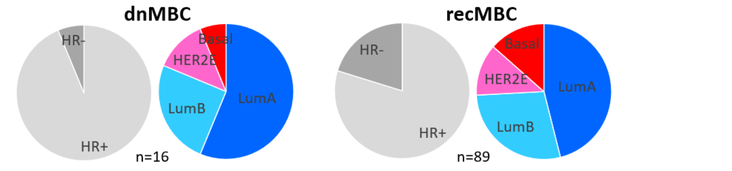
Trial	dnMBC			recMBC		
	Primary Tumors	Metastatic Tumors	Pairs	Primary Tumors	Metastatic Tumors	Pairs
Geicam (206 samples)	14	14	**14**	77	86	**75**
RAP (101 samples)	2	19	**1**	12	58	**9**
Total (430 samples)	16	33	**15**	89	144	**84**

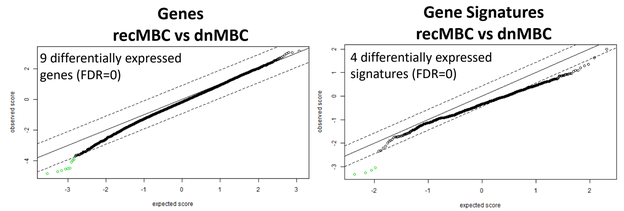
Controls:

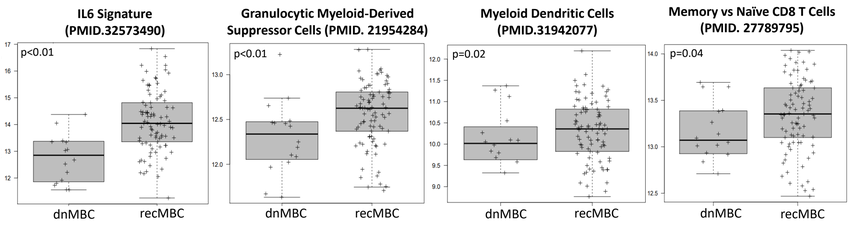


Results:

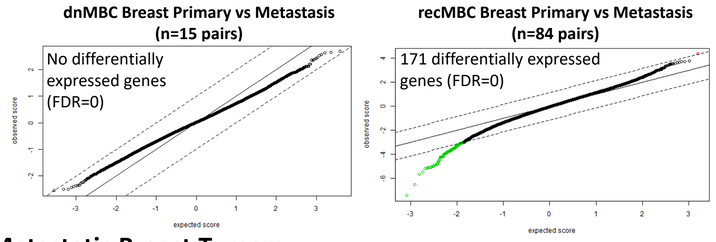
Primary Breast Tumors





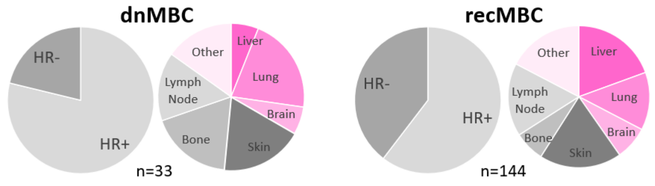


Paired Primary Breast and Metastatic Tumors

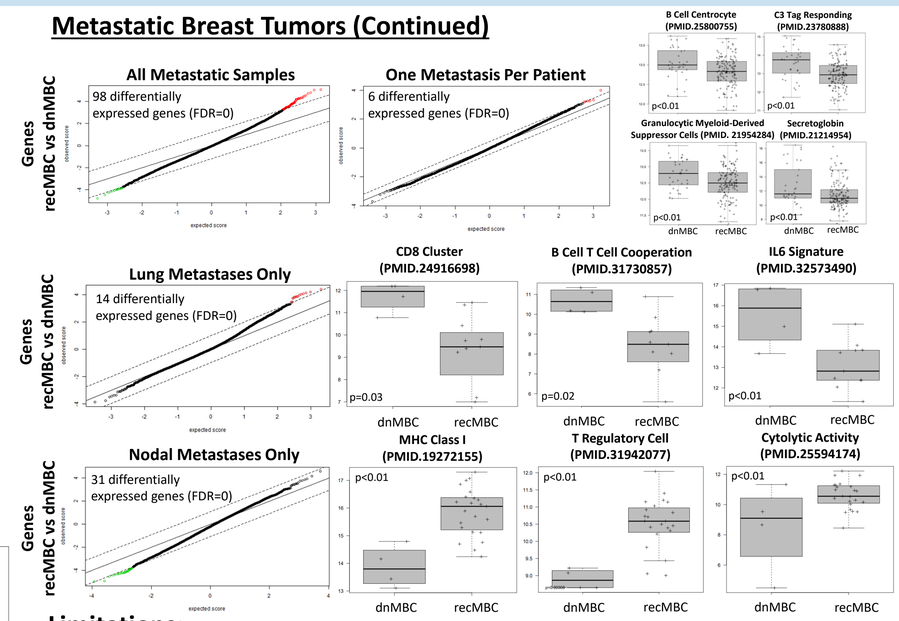


Metastatic Breast Tumors

- 177 metastatic tumors from 118 patients



Metastatic Breast Tumors (Continued)



Limitations:

This study is limited by the small sample size as well as heterogeneous tissue collection methods (fresh frozen versus FFPE). Batch correction has been performed but may not fully account for study differences. Metastases are from heterogeneous sites and normal tissue contamination from each site is possible. While this study was designed to assess untreated tumors, most primary breast and metastatic tumors in the RAP dataset came from patients who had been previously treated and the treatment status of metastatic samples from the GEICAM dataset is unknown.

Future Directions for Research:

In addition to obtaining sequencing data obtained from two additional trials, we have identified 24 patients with dnMBC who have untreated primary breast and metastatic paired samples available for research. We will sequence and analyze these samples along with pairs from 62 patients with recMBC who have been matched by metastatic site and clinical subtype. We will also perform single cell sequencing on dnMBC samples to identify alterations missed by bulk sequencing and analyze DNA mutational data as well.

Conclusion: In a small, exploratory analysis, several differences in expression of immune-related genes and gene signatures were observed between dMBC and rMBC. With a larger sample size and analysis of tumors known to be untreated at time of biopsy, findings can be confirmed, and additional analyses performed.

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