Dana-Farber Cancer Institute

Presentation Number: PS3-12-01

T-cell Receptor (TCR) Repertoire Differences Between Stage III Inflammatory Breast Cancer (IBC) and Matched Non-IBC Controls

HARVARD MEDICAL SCHOOL

Abstract Number: 1011

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BACKGROUND

- Inflammatory breast cancer (IBC) is a rare and aggressive subtype of breast cancer characterized by a distinct clinical presentation and poor prognosis.
- Despite multiple studies aimed at understanding the biological drivers of its aggressive behavior, the underlying mechanisms remain elusive.
- Emerging evidence suggests that the host immune system may play a role in the unique clinical course of IBC.
- Prior research has demonstrated that peripheral blood T-cell receptor (TCR) clonotype diversity declines with age, and it is associated with cancer risk and disease progression. **The peripheral blood TCR clonotype repertoire has not been studied in IBC.**

METHODS

- We conducted a matched-cohort study using baseline peripheral blood samples from treatment-naïve patients.
- Stage III cases and controls were matched 1:1 by age such that the ages of each case-control pair were within 5 years of each other. The controls were identified from our institutional annotated datasets (COQD, EMBRACE).
- RNA was extracted from whole blood and subjected to TCR sequencing to characterize the clonotype repertoire.
- TCR clonotype diversity was quantified using established metrics, including Shannon entropy, Richness, and clonality indices.
- We compared the frequencies and uniqueness of CDR3 sequences between IBC and non-IBC patients.
- We also clustered all CDR3 (alpha or beta) sequences from patients using Geometric Isometry-based TCR AligNment Algorithm (GIANA) tool to evaluate CDR3 cluster differences between the two groups.

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ACKNOWLEDGEMENTS / SUPPORT: This study was partially supported by the American Cancer Society and the IBC Network Foundation. We thank Terry Arnold for supporting this research.

RESULTS

- 41 patients with stage III IBC and age-matched 41 patients with stage III non-IBC were included (n = 82).

TABLE 1: PATIENT CHARACTERISTICS

Characteristics	IBC (Cases) n = 41	Non-IBC (Controls) n = 41
Stage	III	III
Age (median, range)	52 (26-87)	53 (26-83)
Subtype		
HR+/HER2-	12 (29%)	25 (61%)
HER2+	18 (44%)	13 (32%)
TNBC	11 (27%)	3 (7%)
Race		
White	37 (90%)	34 (83%)
Black	1 (2%)	1 (2%)
Asian	1 (2%)	3 (7%)
Other/unknown	2 (5%)	3 (7%)

- A trend toward increased TCRα clonotype diversity was observed in non-IBC compared to IBC samples. This was evidenced by higher Shannon entropy and Richness scores in non-IBC samples, reflecting a more diverse T-cell receptor clonotype repertoire. (Figure 1)

FIGURE 1

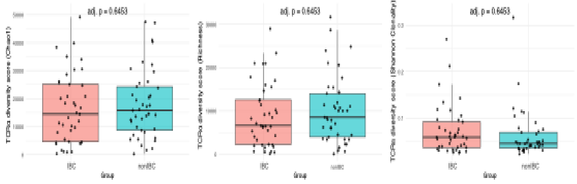


Figure 1. Box plots depicting TCRα diversity metrics (left to right: Chao1, Richness, and Shannon Clonality). Bars show median ± IQR. p values from two-sided Wilcoxon rank-sum tests; multiple testing corrected using Benjamini–Hochberg FDR.

- The distributions of CDR3a clonotype frequencies differ between IBC and non-IBC patients, with rare CDR3a sequences more prevalent in non-IBC (Figure 2).

FIGURE 2

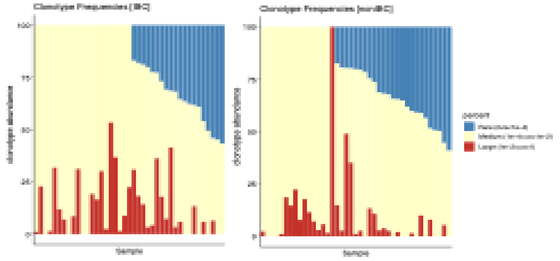


Figure 2. The abundance of CDR3α sequences in individual patients.

- Non-IBC samples also had more unique CDR3 clusters than IBC samples, indicating greater TCR repertoire heterogeneity. (Figure 3)

FIGURE 3

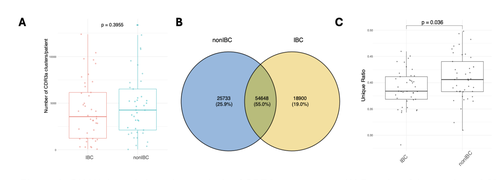
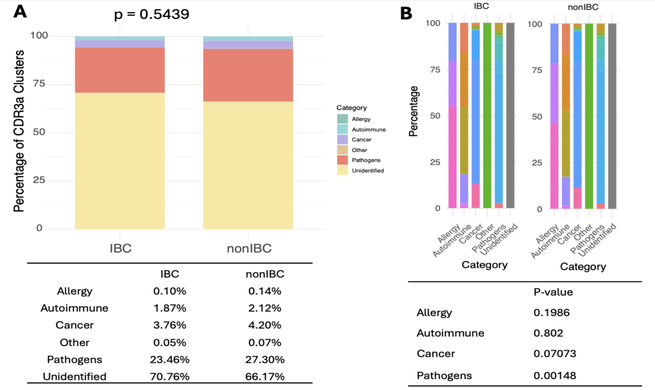


Figure 3. GIANA-based clustering analysis of CDR3α sequences. (A) Bar plot of the number of CDR3α clusters per patient. Bars show median ± IQR. p values from two-sided Wilcoxon rank-sum test. (B) Venn diagram showing the number of unique clusters in nonIBC and IBC patients. (c) Ratio of unique CDR3α sequence in patients. Bars show median ± IQR. p values from two-sided Wilcoxon rank-sum test.

- The distribution of TCRα clones (CDR3α) was analyzed using the McPAS-TCR dataset. Pearson's Chi-squared test demonstrated significant non-random associations, indicating enrichment of specific antigen types within distinct T-cell receptor clusters (Figure 4)



	IBC	nonIBC
Allergy	0.10%	0.14%
Autoimmune	1.87%	2.12%
Cancer	3.76%	4.20%
Other	0.05%	0.07%
Pathogens	23.46%	27.30%
Unidentified	70.76%	66.17%

	P-value
Allergy	0.1986
Autoimmune	0.802
Cancer	0.07073
Pathogens	0.00148

Figure 4. A) Distribution of McPAS-TCR–predicted antigens across CDR3α clusters. p value from Pearson's Chi-squared test. (B) Distribution of McPAS-TCR–predicted antigens across CDR3α sequences. p values from Pearson's Chi-squared test.

- TCR diversity was not significantly associated with survival either group; however, the number of events was low.

CONCLUSIONS

- **In this study, we evaluated pretreatment peripheral blood TCR clonotype diversity in patients with stage III IBC and non-IBC.**
- **Our findings suggest that IBC is associated with a less diverse TCR repertoire, which may contribute to a less effective anti-tumor immune response.**
- **These results warrant further investigation in larger cohorts to determine the clinical relevance and potential therapeutic implications of TCR characteristics in IBC.**