Comprehensive molecular characterization of patients with metastatic invasive lobular carcinoma (ILC): Using real-world data to describe this unique clinical entity

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INTRODUCTION

ILC is the second most common type of breast cancer and accounts for approximately 10% of all invasive breast cancers. A hallmark of ILC is the lack of E-cadherin (*CDH1*) expression, which is frequently used to discriminate between lesions with borderline ductal and lobular histologies. While the genomic landscape of primary ILCs is well described, less is known about patients (pts) with metastatic ILC (mILC). Better characterization of the genomic and transcriptomic landscape associated with mILC is critical for identifying biomarkers that may provide new insights into ILC tumor biology and ultimately improve long-term outcomes in pts with mILC.

Here, we examined the co-mutational landscape of *CDH1*-mutant disease and investigated transcript-level expression variation between *CDH1*-wildtype (WT) and *CDH1*-mutant cohorts.

METHODS

We retrospectively analyzed de-identified next-generation sequencing (NGS) data from 150 advanced/metastatic pts with ILC and 51 pts with mixed lobular/ductal histology, defined using the histology of the sequenced biopsy. Diagnoses were abstracted from pathology reports submitted at the time of sequencing.

We used the stage documented closest in time to biopsy collection, and samples were excluded if the staging date was unknown or exceeded 180 days after the biopsy date.

Our dataset consisted of samples that were molecularly profiled using the Tempus xT solid tumor assay (DNA-seq of 595-648 genes at 500x coverage, full-transcriptome RNA-seq)[1]. The mutations identified for this study include somatic single-nucleotide variants and insertions/deletions.

[1]Beaubier, N., *et al., Oncotarget* 2019; 10:2384-2396

RESULTS

Table 1. Frequency of co-mutations in *PIK3CA, TBX3, and NCOR1* in *CDH1*-mutant vs. *CDH1*-WT mILC and mixed histology cohorts

Genes	*CDH1* mutant n (%)	*CDH1* WT n (%)	p-value[2]	q-value[3]
mILC	n=98	n=52		
PIK3CA	53 (54%)	6 (12%)	<0.001	<0.001
TBX3	13 (13%)	0 (0%)	0.004	0.13
NCOR1	11 (11%)	0 (0%)	0.009	0.2
Mixed histology	n=12	n=39		
PIK3CA	6 (50%)	12 (31%)	0.3	>0.9
TBX3	0 (0%)	0 (0%)	N/A	N/A
NCOR1	0 (0%)	2 (5.1%)	>0.9	>0.9

[2]Fisher's exact test; Pearson's Chi-squared test
[3]False discovery rate correction for multiple testing

Table 2. Comparison of ER/PR/HER2 status and TMB in *CDH1*-mutant vs. *CDH1*-WT mILC cohorts

Biomarkers	*CDH1* mutant (n=98) n (%)	*CDH1* WT (n=52) n (%)	p-value[4]
HR+/HER2-	92 (94%)	43 (83%)	0.093
HR-/HER2-	3 (3.1%)	5 (9.6%)	
HR+/HER2+	3 (3.1%)	4 (7.7%)	
HR-/HER2+	0 (0%)	0 (0%)	
High TMB[5]	10 (10%)	3 (6.2%)	0.5
Median TMB	3.4	2.1	0.010

[4]Fisher's exact test; Wilcoxon rank sum test
[5]High TMB defined as ≥10 mutations/MB

Somatic landscape of *CDH1*-mutant vs. *CDH1*-WT mILC cohorts

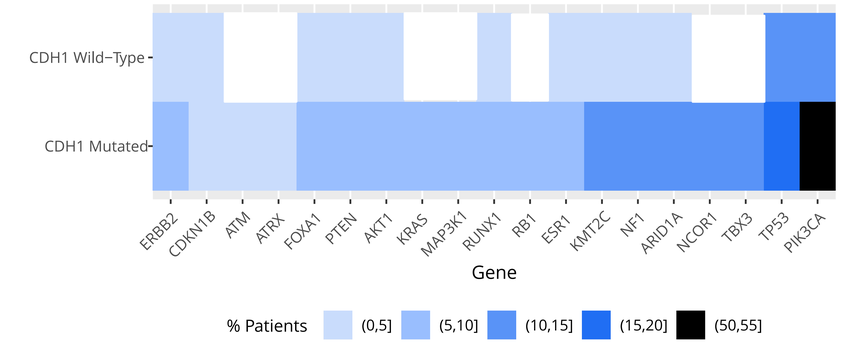

Figure 1. Percentage of patients with any pathogenic/likely pathogenic mutation in the most frequently mutated genes for *CDH1*-mutant and *CDH1*-WT cohorts.

- PIK3CA mutations were enriched in *CDH1*-mutant mILC.

Comparing *CDH1* gene expression between histologies

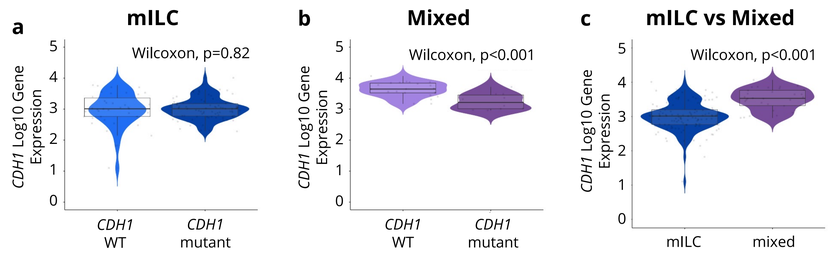

Figure 2. a-b. *CDH1* gene expression in *CDH1*-WT vs. *CDH1*-mutant cohorts for mILC (a) and mixed (b) histologies. p=0.82, Wilcoxon rank sum test (a); p<0.001, Wilcoxon rank sum exact test (b). **c.** *CDH1* gene expression in all patients of mILC and mixed histologies. p <0.001, Wilcoxon rank-sum test.

- *CDH1*-mutant mixed histology pts had lower median log10 *CDH1* expression than WT pts (3.21 vs. 3.65, p <0.001)
- Median log10 *CDH1* expression across all mILC pts was lower than in mixed histology pts (3.01 vs. 3.53, p<0.001).

CONCLUSIONS

Our real-world dataset illustrates that the molecular landscape of *CDH1*-mutant mILC patients is distinct from *CDH1*-WT patients.

mILC differs from mixed histology at a transcriptional level, with lower *CDH1* expression regardless of *CDH1* mutational status.

CDH1 RNA levels in *CDH1*-mutant mixed histology patients more closely resemble those seen in mILC patients, suggesting a use for *CDH1* RNA expression levels in reclassifying mixed histology samples as mILC.

Because *PIK3CA* mutations are more common in *CDH1*-mutant than in *CDH1*-WT disease, therapies targeting *PIK3CA* may be further investigated for their actionability in *CDH1*-mutant mILC cases.

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