

Abstract

Background: Limited understanding exists regarding relapse mechanisms in invasive lobular carcinoma (ILC), which recent studies suggest may involve heterogeneity among subgroups. Greater insight into genomic drivers and immune evasion can facilitate personalized treatment strategies.

Methods: We analyzed a meta-cohort of 401 primary ILC tumors, combining genomic and transcriptomic data, including 254 with whole-genome or exome sequencing. A single-cell spatially resolved transcriptomic cohort of 54 primary ILCs, including metastatic samples, was also established.

Results: ILC tumors exhibited a greater late recurrence rates (55% vs. 37% at 20 years) compared to invasive ductal carcinoma (IDC) at similar genomic architecture. ILC tumors were characterized by lower genomic instability and immune-excluded/stromal-enriched microenvironments. Our findings reveal distinct tumor-intrinsic and extrinsic factors contributing to ILC aggressiveness, warranting further investigation into therapeutic strategies.

Introduction

Previously, we established a genome-driven breast cancer classification scheme across all histological types that defines 11 integrative subgroups (ICs) of disease with distinct copy number aberrations, transcriptional profiles, and clinical outcomes. Specifically, we identified four subgroups of ER+ disease (IC1, IC2, IC6, IC9) with a persistent risk of lethal distant relapse up to two decades after diagnosis, each with focal copy number drivers and two distinct subgroups of triple-negative disease[1,2]. These findings nominate new therapeutic strategies, however, it is unknown how mutational processes and genomic architecture differ between IDC and ILC in this context, nor how their tumor microenvironments (TME) differ.

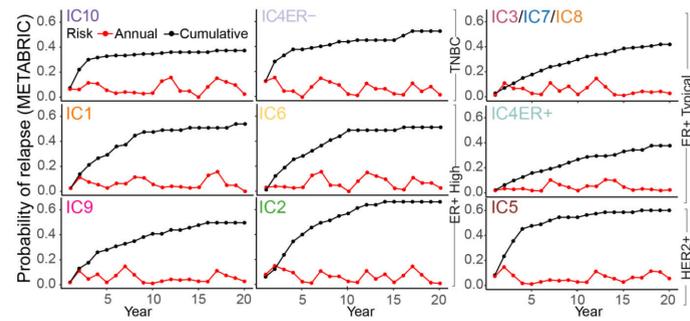


Figure 1. Differential pattern of relapse across the ICs over time. TNBC: triple-negative breast cancer.

Methods and Materials

To interrogate the genomic and immune landscape of ILC, we collected a meta-cohort of 401 primary tumors, including 254 with whole-genome or whole-exome sequencing, 350 with whole-transcriptome sequencing, and 203 with both modalities[3]. This meta-cohort includes the clinically curated METABRIC dataset with 20 years of clinical follow-up. Additionally, we established a single-cell spatially resolved transcriptomic meta-cohort of 54 primary ILCs, including 7 metastatic ILCs with primary and matched metastatic lesion(s).

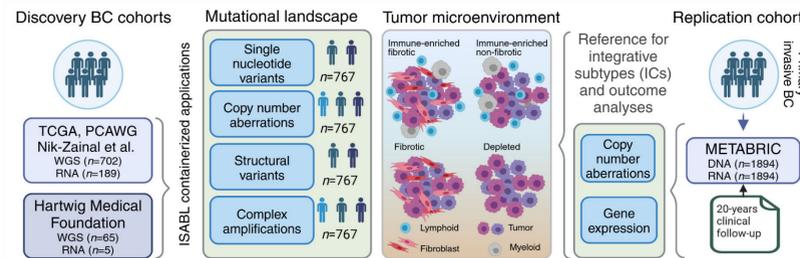


Figure 2. Schematic of the bulk sequencing study design[4].

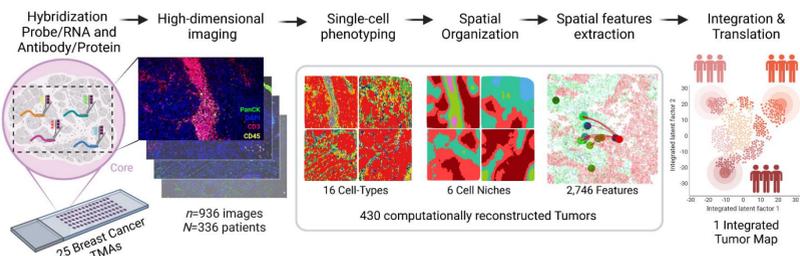


Figure 3. Schematic of the single-cell spatially-resolved transcriptomic pipelines[4].

ILCs exhibit higher risk of relapse

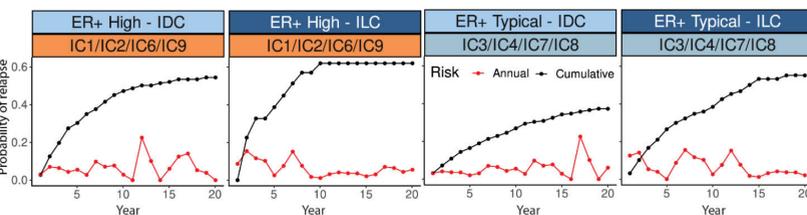


Figure 4. Differential pattern of relapse across ER+ IC subgroups and by histology.

ILCs intrinsic factors correlate with less aggressive tumors

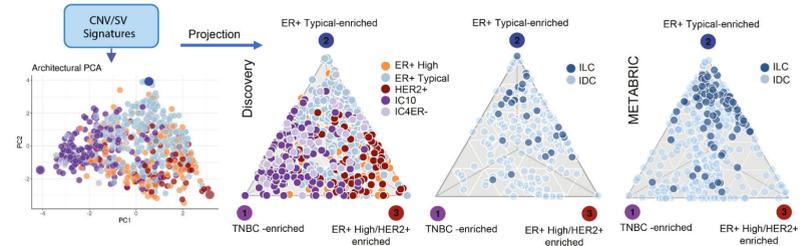


Figure 5. Architectural PCA and its projection in Discovery and METABRIC cohorts.

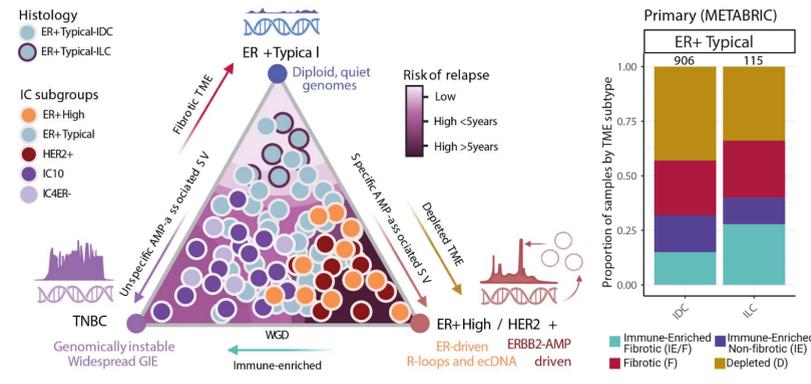


Figure 6. Genomic heterogeneity across breast cancer subgroups[4]. Figure 7. TME subtypes[5].

ILCs demonstrate higher levels of cell-cell interactions

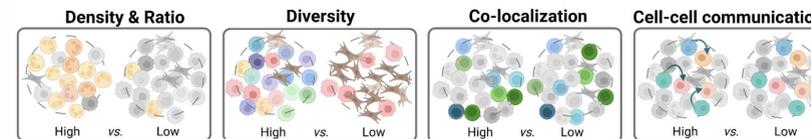


Figure 8. Schematic of the extracted spatial features[4].

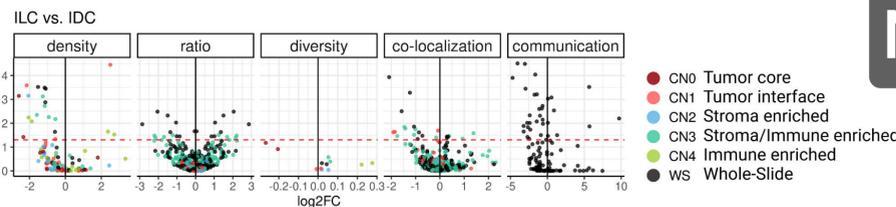


Figure 9. Volcano plots representing the associations between spatial features and histology.

Conclusions & Discussion

Patients with ILC exhibited a higher 5 year recurrence risk (39% vs. 30%) and modestly higher cumulative recurrence risk (62% vs. 54% at 20 years) in the ER+ High-risk group, while this difference was even more striking amongst ER+ Typical-risk tumors, where ILC cases exhibited higher rates of late recurrence than IDC (55% vs. 37% at 20 years). Paradoxically, ILC tumors are enriched for the genomic stable ER+ Typical-risk subgroup that displays quiet genomes compared to other IC subgroups.

Intrinsic factors of ILCs

- Higher % CDH1 mutations
- Lower % TP53 mutations
- Lower fraction genome altered
- Lower ploidy/WGD

Extrinsic factors of ILCs

- Higher fibrotic TME
- Higher density of Fibroblasts
- Higher levels of cell-cell interaction
- Cross-talk with Neutrophils

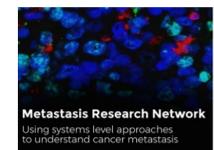
Table 1. Summary of the intrinsic and extrinsic features found in ILC primary tumors.

Spatial transcriptomic profiling suggests an overall higher level of interaction and cell-cell communication between tumor and stromal cells in ILC compared to IDC. Taken together, our data uncover tumor-intrinsic molecular characteristics of ILC and implicate tumor-extrinsic factors in disease aggression.

Next steps

- Keep building TMAs including ILC patients sampled for paired primary and metastatic lesions
- Replicate preliminary findings on additional spatial transcriptomic data
- Orthogonal validation in *in vitro* models for the Receptor/Ligand pairs detected as involved in TME cell-cell interactions in ILC primary tumors

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