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Abstract PS18-01: Spatial Transcriptomics-Derived Classification of Invasive Lobular Carcinoma: Associations with Clinical, Genomic Characteristics, and Prognosis FREE

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Abstract

Background: Invasive lobular carcinoma (ILC) is the second most prevalent histological subtype of breast cancer. This study presents four newly identified ILC subtypes associated with tumor microenvironment (TME) heterogeneity and examines their associations with clinical characteristics and prognosis. Methods: Spatial transcriptomics (ST, Visium 10X) was performed on frozen tumor samples from 43 primary hormone receptor positive (HR+), HER2-negative (HER2-) ILCs. H&E slides were morphologically annotated, and ST spots were clustered by gene expression. By integrating morphology and sequencing data, ILCs were classified based on TME heterogeneity using the intNMF algorithm. Subtypes were annotated using morphology (image analysis), pathway enrichment analysis (GSEA), and cell type composition from single-cell deconvolution (CARD software). Gene signatures for each subtype were derived and used to retrieve the subtypes in METABRIC (ILC cohort, n = 122) and SCAN-B (ILC cohort, n = 853) microarray/bulk RNA-sequencing datasets. Statistical analyses included chi-square and Kruskal-Wallis tests to investigate associations with clinical characteristics and Cox proportional hazard models for univariate and multivariate survival analyses in both METABRIC and SCAN-B. Results: Patient-level classification revealed four ILC subtypes, namely proliferative (P), normal-stroma enriched (NSE), metabolic (M), and metabolic-immune enriched (MIE). In our ST cohort, the P subtype (n = 12) was enriched in tumor cells and proliferation-related pathways; NSE subtype (n = 10) was associated with more fibroblasts, carcinoma in situ, and heightened expression of EMT-related pathways; the M subtype (n = 9) was enriched in endothelial cells, nd heightened AR gene expression; the MIE subtype (n = 10) was dothelial cells, M2 macrophages, and metabolic-related pathways. All four subtypes were identified in METABRIC (NSE = 40, P = 34, MIE = 17, M = 31) and SCAN-B (NSE = 291, P = 226, MIE = 150, M = 186), with GSEA showing consistent differences at the

gene expression level. In METABRIC, the P and MIE subtypes were associated with high and low cellularity, respectively (p = 0.042), and P was also linked to higher tumor grade (p = 0.0187). Notably, the P subtype exhibited more copy number aberrations (CNA) compared to other subtypes (p = 0.0159), but no differences in tumor mutational burden. In SCAN-B, the P and NSE subtypes were associated with larger and smaller tumors, respectively (p < 0.001). The P subtype was also linked to higher tumor grade (p < 0.001), lymph node involvement (p = 0.02), and high Ki67 (p < 0.001). In METABRIC, univariate analysis showed NSE and P subtypes to be associated with good and poor prognosis, respectively, for relapse-free interval (RFI) (HR = 0.56, p = 0.027, FDR = 0.055; HR = 1.8, p = 0.019, FDR = 0.055). Multivariable analysis confirmed NSE's association with good prognosis (HR = 0.47, p = 0.03, FDR = 0.12 for RFI), even when correcting for clinical features. In SCAN-B, univariate analysis revealed an association between NSE and longer RFI (HR = 0.42, p = 0.0018, FDR = 0.0035) and between P and shorter RFI (HR = 2.2, p = 0.0014, FDR = 0.0035). When correcting for clinical characteristics, NSE remained associated with longer RFI (HR = 0.54, p = 0.035, FDR = 0.11), while a trend was observed for P and shorter RFI (HR = 1.6, p = 0.079, FDR = 0.13). Conclusions: Spatial transcriptomics revealed four ILC subtypes describing TME heterogeneity. These subtypes were successfully identified in microarray/bulk-RNA sequencing datasets and associated with different clinical characteristics. Importantly, the subtypes showed differences in disease outcomes, refining prognosis in ILC.

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