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Abstract PO1-15-03: Spatially resolved analysis of tumor microenvironment in invasive lobular carcinoma FREE

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Abstract

Background: Invasive lobular carcinoma (ILC) is the second most common histological breast cancer subtype; however, little is known about its tumor microenvironment (TME). Here, we aimed to study ILC TME using spatial transcriptomics (ST). Methods: We performed ST (Visium 10x Genomics) on frozen tumor samples from 43 primary hormone receptor positive (HR+), HER2-negative (HER2-) ILCs. Of note, 9 samples were coming from patients who experienced disease relapse. Relative hematoxylin/eosin (H&E) slides were morphologically annotated (QuPath software). xCell was used to perform cell type enrichment analysis on sample pseudo-bulks. After cross-samples integration, ST spots were clustered using hierarchical clustering (STutility R package). intNMF algorithm was used to perform clustering at the patient-level by combining: RNA sequencing information (relative percentage of spot-level clusters in each sample), morphology and level of colocalization between cancer cells and the other cell types of the tumor microenvironment. METABRIC (HR+, HER2- ILC samples, n = 122) was used as external validation cohort. Survival analyses (univariable and multivariable adjusting for clinicopathological features) were performed using Cox proportional hazard models. Results: The patient-level classification revealed four groups

showing different biological characteristics. Differences in terms of morphology (annotation) and pathway enrichment analysis based on marker genes (GSEA) were observed between groups. This information allowed us to annotate our groups as: proliferative (P, n = 12, enriched in tumor cells and proliferation-related pathways), normal-stroma enriched (NSE, n = 10, enriched in fibroblasts and carcinoma in situ), metabolic (M, n = 9, enriched in metabolic-related pathways) and metabolic-immune enriched (MIE, n = 10, enriched in adipose tissue, metabolic and immune-related pathways). Interestingly, a significantly higher presence of macrophages M2 was found in MIE group. Using group-specific gene signatures, we were able to reproduce the same 4 groups in the METABRIC. Of note, we observed significant differences in relapse-free survival (RFS) in METABRIC ($p = 0.03$), with NSE presenting better outcome, while P, M and MIE presented worse prognosis. Analysing the area of contact between adipocytes and cancer cells typical of MIE group, we noticed an enrichment in metabolic and M2 macrophages-related pathways. In doing so, we derived a 28 gene signature relative to the tumor-adipocytes contact area. Importantly, our signature was highly expressed in M and MIE groups, and it was not correlated with proliferation-related signatures. Interestingly, the adipocytes-related signature was significantly associated with shorter RFS in ILC patients in METABRIC (univariable: HR 1.4, $p = 0.023$; multivariable: HR 1.6, $p = 0.005$). Since both proliferation and metabolism showed to be key processes in defining prognosis in ILC, we built a prognostic index by integrating our adipocytes-related signature with genomic grade index (GGI, a proliferation-related signature). Our index outperformed other existing prognostic signatures (e.g., Oncotype DX, MammaPrint, EndoPredict, LobSig) in assessing prognosis (RFS) in ILC in METABRIC (univariable: HR 1.7, $p < 0.001$; multivariable: HR 1.7, $p = 0.002$). Conclusions: We identified 4 biologically driven HR+, HER2- ILC groups describing tumor microenvironment heterogeneity. Of note, two of the three groups associated to worse disease outcome were related to metabolism, highlighting the importance of such process in ILC biology and in the future development of new treatment strategies. Moreover, the prognostic power of our index has the potential to refine the assessment of the risk of relapse in ILC. Further validation is warranted.

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