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Abstract 5066: Integrating spatial and single cell transcriptomics to identify and characterise biologically driven subgroups in invasive lobular carcinoma **FREE**

Matteo Serra; Andreas Papagiannis; Mattia Rediti; Frederic Lifrange; Nicola Occelli; Laetitia Collet; Delphine Vincent; Ghizlane Rouas; Danai Fimereli; Ligia Craciun; Denis Larsimont; David Venet; Miikka Vikkula; Francois P. Duhoux; Françoise Rothé; Christos Sotiriou



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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 identify and to characterise ILC subgroups based on TME heterogeneity by combining spatial transcriptomics (ST) and single cell RNA-sequencing (scRNA-seq).

Methods: We performed ST (Visium 10x Genomics) on frozen tumor samples from 41 primary hormone receptor positive (HR+), HER2-negative (HER2-) ILCs. Information coming from the morphological annotation of ST slides and the gene expression-based clustering of ST spots was integrated and used as input for a patient level classification (using intNMF algorithm). Subgroups of patients were annotated using morphology, gene set enrichment analysis and ST deconvolution based on scRNA-seq data (CARD software). SCAN-B bulk RNA-seq dataset was used as validation set (HR+, HER2- ILC samples, n = 853).

Results: Four subgroups of patients were identified: proliferative (P, n = 12, enriched in tumor cells and proliferation-related pathways), normal-stroma enriched (NSE, n = 10, enriched in fibroblasts, stroma-related pathways and showing an higher level of colocalization between invasive and in situ carcinoma), metabolic (M, n = 9, enriched in metabolic related-pathways) and metabolic-immune enriched (MIE, n = 10, enriched in adipocytes, metabolic and immune-related pathways). Deconvolution of ST spots with single cell data revealed matching results with morphology (in terms of cell types). We observed an enrichment of myofibroblasts in NSE, an enrichment of cancer epithelial in P and, interestingly, an enrichment of endothelial cells in M subgroup (fdr < 0.25). MIE was characterized by perivascular like-endothelial cells and myeloid cells (monocytes and macrophages, fdr < 0.25). Of note, at the level of the ST slide, myeloid cells in MIE subgroup were more present in the adipose tissue compartment (fdr < 0.25) compared to the rest of the slide. NSE subgroup showed a trend for association with better prognosis. Gene signature-based assignment identified the same four subgroups in SCAN-B: GSEA analysis and comparisons among the four subgroups showed matching results between our dataset and SCAN-B. Of note, in SCAN-B, we observed differences in prognosis among the subgroups, with NSE showing better, M and MIE intermediate and P worse prognosis for overall survival and relapse free interval (p < 0.01).

Conclusions: Four subgroups of ILC based on TME heterogeneity and showing differences in prognosis were identified and validated in external cohort. Of note, two of these groups were related to metabolism, highlighting the value of such process in ILC biology. Importantly, myeloid cells were the predominant immune cell types in ILC, and they showed a specific compartmentalization inside the TME. Further validation is needed.

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