**Background**

Invasive lobular breast carcinoma (ILC) represents 15% of all invasive breast cancers (IBC), but it remains an understudied subtype.

Characterized by late relapse

- Loss of E-cadherin in infiltrating epithelial cells and typical "single-file" pattern of the cells

- Tumor microenvironment (TME) is the set of normal cells, molecules and blood vessels that surround and feed a tumor cell

- Interaction between cancer cells and TME plays a role in defining prognosis in IBC

- TME of ILC is characterized by low presence of TILs, and higher level of TILs are associated to worse disease outcome

**Morphological and co-occurrence analysis**

**Clustering analysis**

**Results**

- Morph. co-occurrence (Fisher’s exact, % of each cluster, per sample)
- ILC classification

**Adipose tissue**

**Adipocytes**

Macrophages, in situ tumor-associated macrophages, defined as the sum of M1 and M2 macrophage gene sets

**Table 1.**

<table>
<thead>
<tr>
<th>H&amp;E slides (Fig. 2a) were annotated using QuPath (Fig. 2b) reaching single cell resolution. The level of co-occurrence (CO) between tumor and each cell type in the TME was computed (for each cell type) as:</th>
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| Where “% mixed spots” is the number of 23 spots containing both tumor and the class of interest and “% tumor spots” is the total number of tumor spots.

**Materials and Methods**

Spatial transcriptomics

- Spatial transcriptomics
- Higher resolution than bulk RNA-seq

**Data**

- Spatial transcriptomics (Fig. 1 - Table 1) was performed on 43 ILC primary frozen tumor samples (9H, HER2) from patients with long term follow up (Table 1.)

**Objectives**

To characterize the spatial transcriptome heterogeneity of ILC including its tumor microenvironment

To interrogate whether spatial transcriptomics may predict the probability of the risk of recurrence in ILC

**Results**

- Higher co-occurrence level of adipose tissue with tumor was associated to worse disease outcome (Fig. 5a).
- Adipocytes-tumor contact area was enriched in metabolic-related (Fig. 5b) pathways. Contact contact area was also enriched in macrophages M2 (Fig. 5c).

**Take-home messages**

- ILC is an understudied subtype, with peculiar biological and clinical features

- Spatial transcriptomics enables the analysis of the tumor microenvironment in relation to its composition and organization

- Heterogeneity, both within individual patients (intra-patient) and between different patients (inter-patient), was observed in both morphology and gene expression

- The presence of this heterogeneity enabled the identification of four distinct ILC subgroups: normal-stroma enriched, proliferative, metabolic, and immune enriched

- Some subtypes showed differences in prognosis also in external datasets

- Adipose-tissue-cancer interactions were associated with worse disease outcome in ILC

- Metabolism seemed to play a key role in ILC biology

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References