Uptregulation of the immune checkpoint protein B7-H3 is associated with an immune suppressive environment in progression from in situ to invasive lobular breast cancer

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Abstract

Invasive lobular breast cancer (ILC) is an understudied subtype of breast cancer with late recurrence, metastasis to serosal surfaces, such as the peritoneum, and dismal long-term outcome. We utilized digital spatial profiling of genes and proteins to interrogate mechanisms controlling the transition from in situ to invasive lobular breast cancer at the molecular level. We discovered that the immune checkpoint protein B7-H3 is upregulated in ILC tumor cells and cells in the tumor microenvironment (TME). B7-H3 may play a role in tumor cell invasion and immune cell evasion. Outside of the basement membrane tumor cells interact with integrins, collagens and other extracellular matrix proteins. B7-H3 is important for tumor cell proliferation and activation of downstream cancer-associated pathways. B7-H3 is also expressed by antigen presenting cells and fibroblasts that play a role in creating an immune-suppressed environment.

Methods

The ILC FFPE tissue sections were stained with four morphology markers: Fluorescent antibody markers for DNA (SYTO13), Pan cytokeratin (Cy3), CD45 (Texas Red) (pseudo-colored yellow). For the RNA assays, a RNAseq probe for NR3C1 (GR) tagged with Cy5. For the protein assays, a Cy5 labeled antibody was used. Selection of regions of interest (ROIs), segmentation for PanCK and statistical analyses were conducted within the GeoMax DSP Analysis Suite Version 2.4.0.421. Spatial deconvolution to obtain cell type abundances was performed using a plug-in tool from nanoString and the tumor/immune cell matrix (https://pubmed.ncbi.nlm.nih.gov/35046414/). Pathway analyses were performed using Gene Set Enrichment Analyses (GSEA)

Conclusions

Model for LCIS to ILC transition

- Baseline: Baseline membrane
- Migration: Migration of B7-H3 allows tumor cells to interact with integrins and collagen and other ECM proteins
- Invasive: T-cell fibroblast

Mapping LCIS cells acquire immune properties of ILC
- Ramp up tumor cell proliferation: B7-H3 has roles in tumor cell proliferation, with activation of downstream ERK, PI3K, STAT pathways
- Evasion of immune surveillance: B7-H3 is also expressed on APCs and inhibits T-cell proliferation and downregulates antigen production

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