PS2-11-25: Paracrine FGFR activation by stromal signals and its association with immune infiltration in breast cancer

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Abstract

Background: FGFR alterations occur in up to 20% of estrogen receptor–positive (ER+) breast cancers, linked to endocrine resistance, poor prognosis, and relapse risk. They cluster in high-risk subtypes (~25%) with complex rearrangements and immune depletion [1-3]. Here, we used CosMx multiplex RNA imaging to profile FGFR's role in the tumor microenvironment (TME) of primary and metastatic ER+ tumors.

Methods: We built a single-cell spatial transcriptomic meta-cohort of 277 ER+ breast cancer tumors to compare stromal - tumor interactions between high- and typical-risk tumors.

Results: FGF1/FGF7-FGFR1 interactions were enriched in high-risk tumors associated with higher epithelial/lymphocytes fractions. FGFR1 amplification occurred in some FGFR1+ tumors, but in mixed models, the interaction better predicted lymphocyte depletion than amplification, with a shift to regulatory T cells and immune exclusion. The signal appeared in 12 metastases, including matched primaries.

Introduction

FGFR alterations occur in up to 20% of ER+ breast cancers and are linked to endocrine resistance and poor prognosis. These tumors often fall into high-risk integrative subtypes (~25% of ER+ cases) with complex rearrangements and relapse risk [1-3]. Our prior work shows high-risk ER+ subtypes exhibit more immune depletion than typical subtypes including FGFR1-AMP cases (IC6) [3]. Despite clinical rationale, direct FGFR targeting in breast cancer has largely failed. To investigate FGFR's role in the TME and identify vulnerabilities, we used multiplex single-molecule RNA imaging on the Bruker CosMx platform to profile stromal interactions and immune contexture in primary and metastatic ER+ tumors.

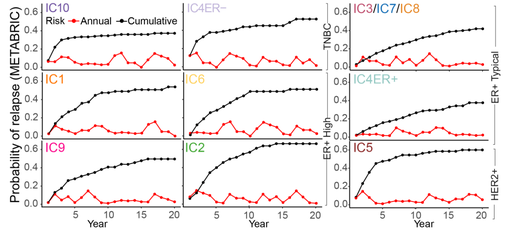


Figure 1. Differential pattern of relapse across the ICs [2-3]. TNBC: triple-negative breast cancer.

Methods and Materials

We constructed a single-cell spatially resolved transcriptomic meta-cohort of ER+ breast cancer, consisting of primary pre-treatment tumors (208 primaries), 69 patients treated per standard of care at Stanford University (28 primaries, 66 metastatic sites), and 4 patients treated on an investigator-sponsored trial of the FGFR inhibitor infigratinib (3 primaries, 6 metastatic sites). We deployed state-of-the-art machine learning algorithms for cell segmentation (CellPose), cell type classification (singleR), and inference of intercellular communication (CellChat).

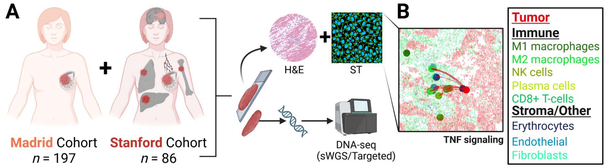


Figure 2. A. Schematic of study design and **B.** Example of cell-cell communication inference [4].

FGF1/7-FGFR1 interaction is enriched in ER+ High-risk

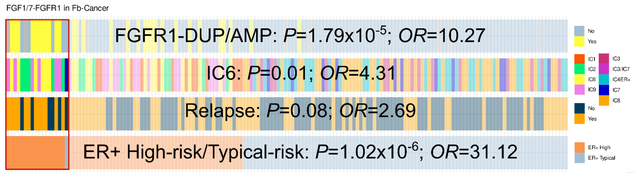


Figure 3. Enrichment of Fibroblasts-Tumor cell interaction *via* FGF1/FGF7-FGFR1 in ER+ High-risk primary tumors.

Fb-Tumor interaction correlates with immune depletion

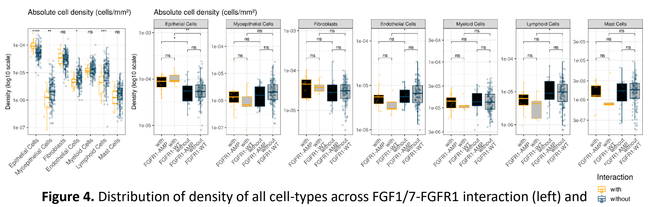


Figure 4. Distribution of density of all cell-types across FGF1/7-FGFR1 interaction (left) and FGFR1 copy number status (right) groups.

Interaction better predicts density differences

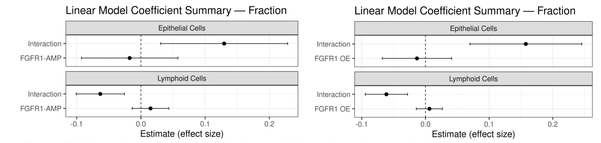


Figure 5. Mixed linear model predicting the Epithelial or Lymphoid Cells fractions.

FGF1/7-FGFR1 tumors are more immunosuppressive

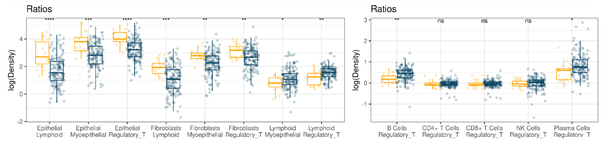


Figure 6. Distribution of density ratios of all cell-types (left) and within lymphoid Population (right) across FGF1/7-FGFR1 interaction groups.

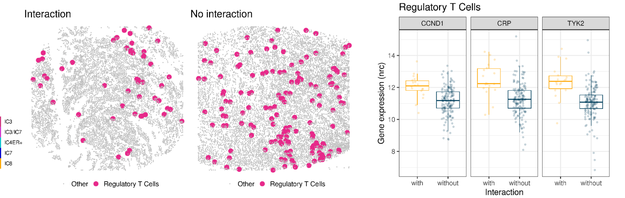


Figure 7. Regulatory T Cells extraction and pseudobulking across FGF1/7-FGFR1 interaction groups (left) and identification of immunosuppressive markers (right).

FGF1/7-FGFR1 tumors are more compartmentalized

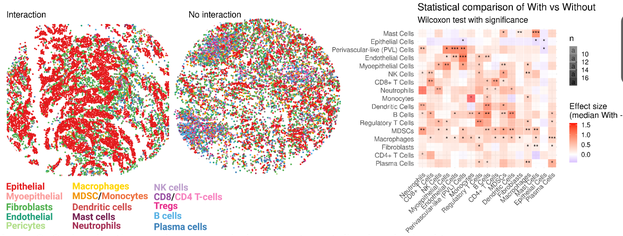


Figure 8. Co-localization analyses revealed compartmentalized and mixed tumors.

FGF1/7-FGFR1 interactions exist in metastatic lesions

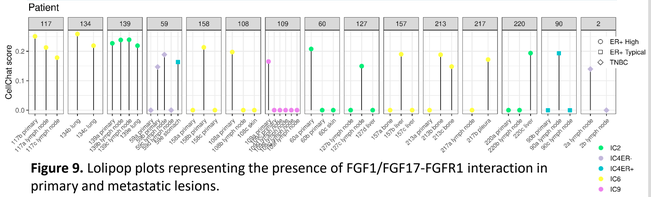


Figure 9. Lolipop plots representing the presence of FGF1/FGF17-FGFR1 interaction in primary and metastatic lesions.

Conclusions & Discussion

We identified a recurrent interaction between tumor-expressed FGFR1 and fibroblast-derived FGF ligands that is enriched in high-risk ER+ breast cancers and associated with an immunosuppressive, immune-excluded microenvironment. Our results indicate that tumor-stromal crosstalk can shape the immune landscape to promote tumor progression and immune evasion. The FGF/FGFR1 interaction represents a potentially targetable axis, with implications for therapeutic strategies that aim to reprogram the tumor microenvironment in high-risk ER+ breast cancer.

Next steps

- Keep exploring the changes in interaction detection in primary/metastatic lesion pairs
- Replicate preliminary findings on additional spatial transcriptomic data
- Orthogonal validation in *in vitro* models with co-culture of fibroblasts and ER+ High-risk cell lines

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Contact

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References

1. Curtis *et al*. *Nature* 2012
2. Rueda *et al*. *Nature* 2019
3. Houlahan, Mangiante *et al*. *Nature* 2025
4. Created by BioRender.com

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