Differential cell-cell communication networks in anti-PD-1 responsiveness between ER+ and TNBC breast cancer subtypes

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INTRODUCTION

Immune Checkpoint Inhibitor (ICI) therapy is only approved for triple-negative breast cancer (TNBC) with a "hot" tumor microenvironment (TME), presenting high tumor-infiltrating lymphocytes (TILs) and PD-1/PD-L1 expression [1].

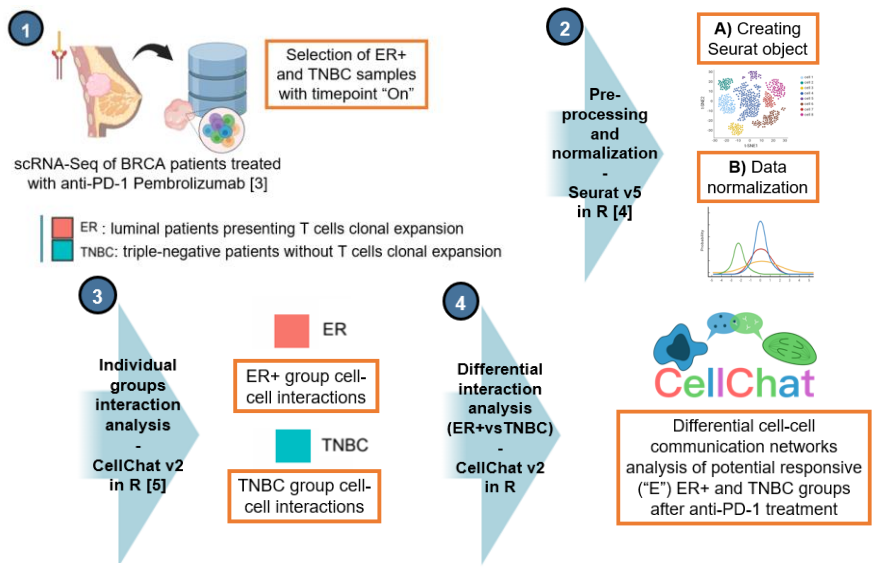
Emerging evidence suggests that breast cancer's luminal (ER+) subtypes, traditionally classified as immune deprived, may exhibit responsiveness to immunotherapy [2].

Positive response to immunotherapy depends not solely on immune infiltration but also on the cellular communication network within the tumor microenvironment (TME) [1].

MAIN GOAL

To investigate this, we analyzed scRNA-seq data from ER+ and TNBC patients treated with anti-PD-1 Pembrolizumab monotherapy, aiming to identify cell signaling pathways that are similar and distinct between subtypes sand are associated with treatment response.

METHODS



RESULTS AND DISCUSSION

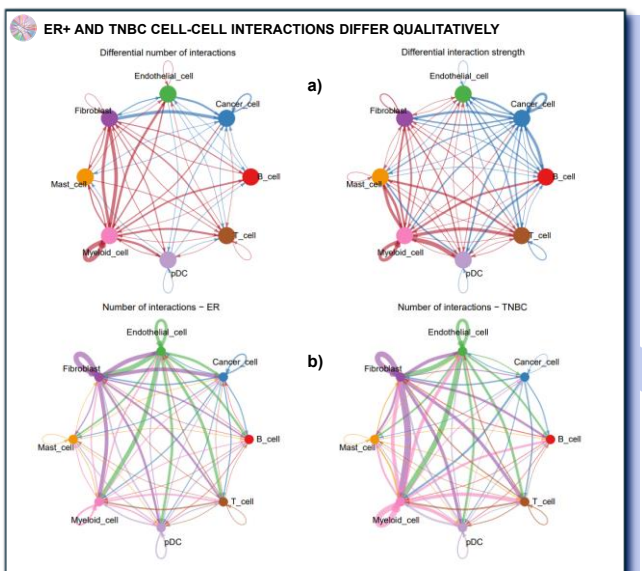


Figure 2. Qualitative differences in cell-cell interactions (ER+ vs TNBC): **a)** differential interactions, in number and strength, red indicates an increase in TNBC, blue indicates increase in ER+; **b)** total number of interactions per group, left representing ER+ group, right representing TNBC group.

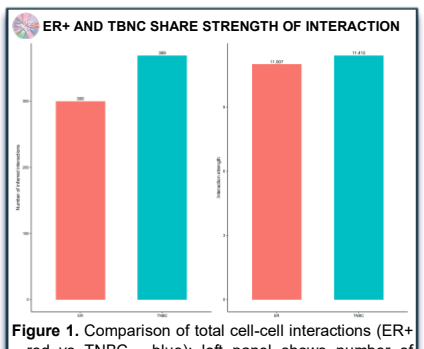
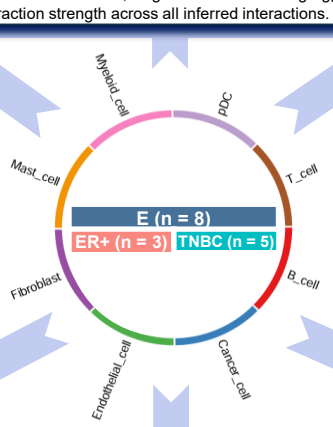


Figure 1. Comparison of total cell-cell interactions (ER+ - red vs TNBC - blue); left panel shows number of inferred interactions, right shows the agreggated interaction strength across all inferred interactions.



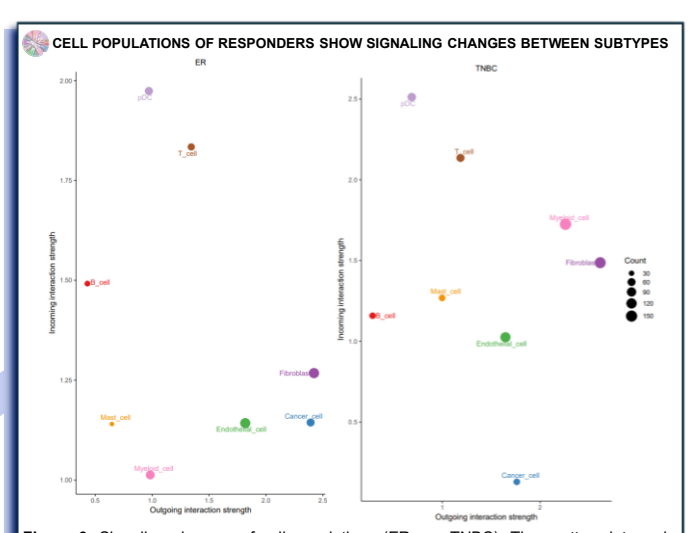


Figure 3. Signaling changes of cell populations (ER+ vs TNBC); The scatter plot x-axis represents the total strength sent from each cell to other populations and y-axis represents the total strength of signals received by each cell from all other cell populations. It allows to understand the cell population's signaling role (sender, receiver, both).

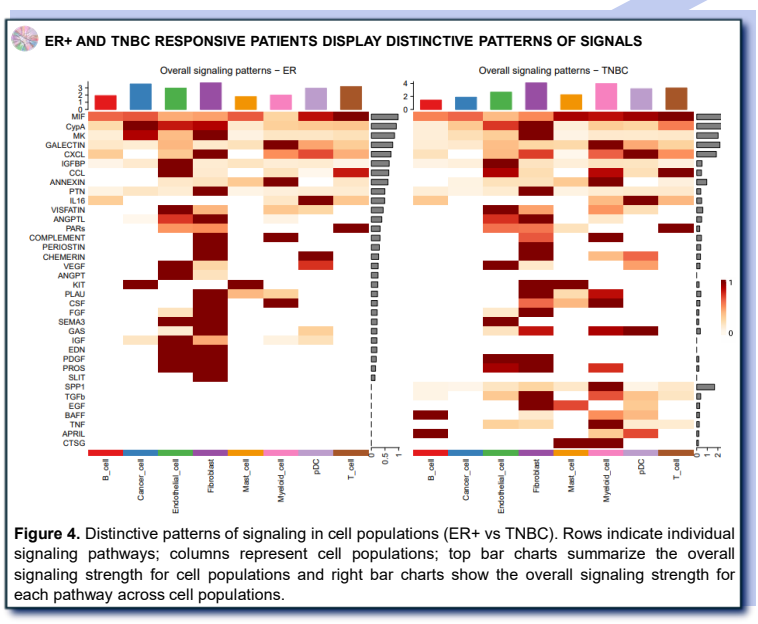


Figure 4. Distinctive patterns of signaling in cell populations (ER+ vs TNBC). Rows indicate individual signaling pathways; columns represent cell populations; top bar charts summarize the overall signaling strength for cell populations and right bar charts show the overall signaling strength for each pathway across cell populations.

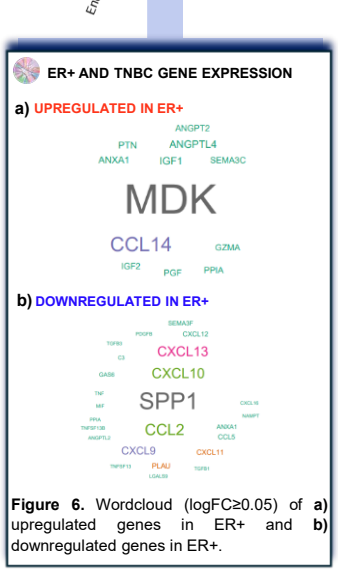


Figure 6. Wordcloud (logFC≥0.05) of **a)** upregulated genes in ER+ and **b)** downregulated genes in ER+.

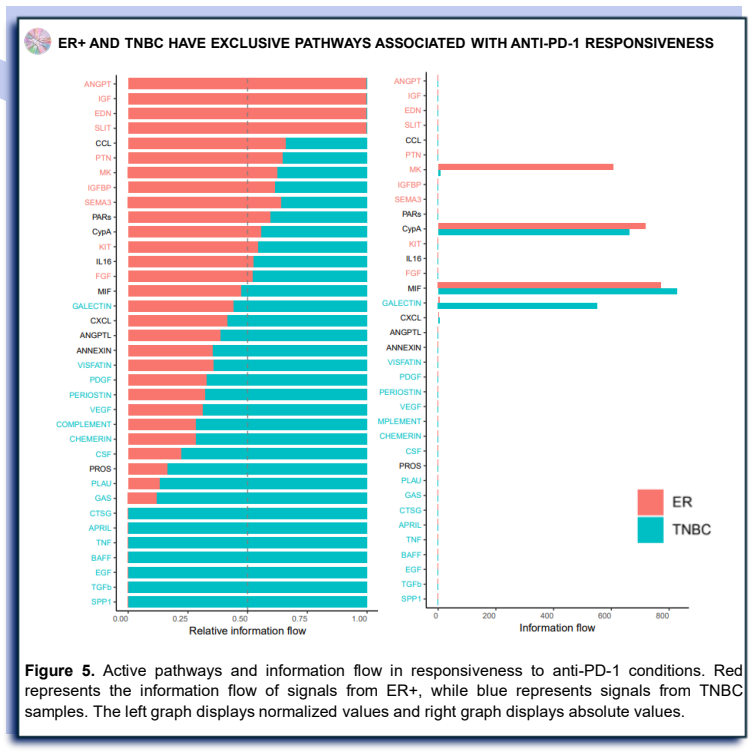


Figure 5. Active pathways and information flow in responsiveness to anti-PD-1 conditions. Red represents the information flow of signals from ER+, while blue represents signals from TNBC samples. The left graph displays normalized values and right graph displays absolute values.

CONCLUSIONS

Our findings demonstrate substantial differences in TME communication networks between responsive ER+ and TNBC patients, suggesting distinct active pathways lead to an immunotherapy-permissive TME in each subtype. Response to anti-PD-1 may depend on specific pathway activation rather than global interaction quantity, offering novel treatment targets for breast cancer subtypes.

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AGRADECIMENTOS