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Breast cancer patient-derived whole-tumor cell culture model for efficient drug profiling and treatment response prediction

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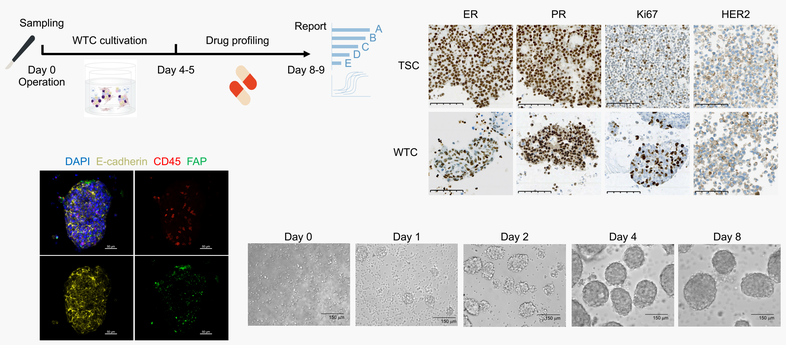
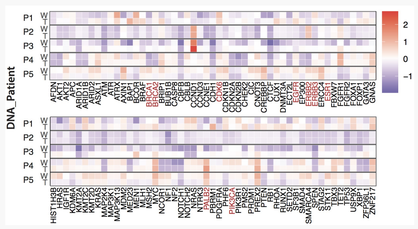
Highlights

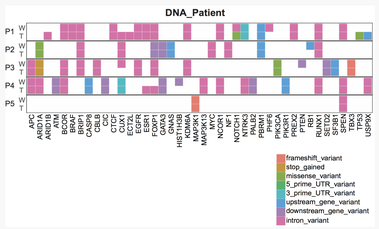
We established a new *ex vivo* model named Whole-Tumor cell Culture (WTC) with a high success rate (±90%) for all types of breast tumors. It represents the original tumor characteristics to a large extent and allows us to accomplish personalized drug testing within 10-days, highlighting its potential for individualized breast cancer therapy. Good predictive value and strong clinical relevance of WTC-based testing were also confirmed in a neoadjuvant validation study. Coupled with genomic and transcriptomic analyses, the WTC model can also help stratify specific patient groups for assignment into appropriate clinical trials and validate potential biomarkers.

Development and characterization of the WTC model

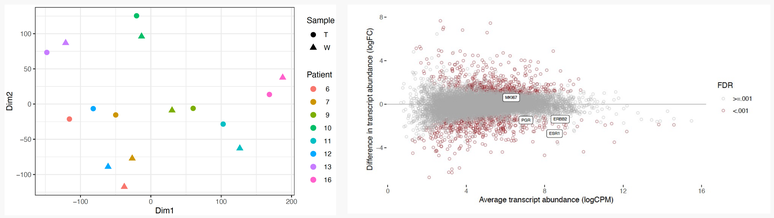


Tumor material is obtained by superficial scrapings procedure from bisected, newly resected breast tumors. The collected tumor scraping cell (TSC) materials were gently processed into single cells. The unselected whole-tumor cell components are then cultured as non-adherent WTC spheres with optimized medium and conditions. This culture model could maintain the expression of essential clinical biomarkers and stable cell compositions to represent the original breast tumors to a large extent.





Both tumor-specific CNA patterns and somatic mutations are retained within the TSC-WTC pairs based on whole-genome sequencing analysis. Examples are shown for the BC driver and actionable genes.



RNA sequencing data reveals the similarity of the TSC-WTC pairs based on global RNA expression patterns, and the transcript abundance of major pathological biomarkers is maintained in the WTC models when compared to the original TSC materials.

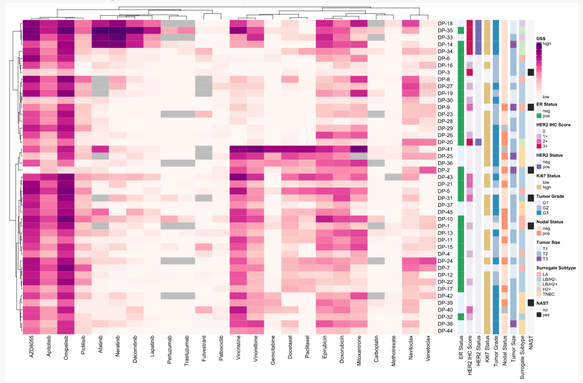
Introduction

Breast cancer (BC) is a complex disease comprising multiple distinct subtypes with specific genomic and pathological characteristics. Although some 30 anti-neoplastic compounds have been approved for clinical use, patient-to-patient variability in drug response is frequently observed. Several patient-derived tumor models have been proposed to serve as therapeutic prediction tools. However, the lack of tumor microenvironment considerations and time-consuming procedures make their clinical utility limited.

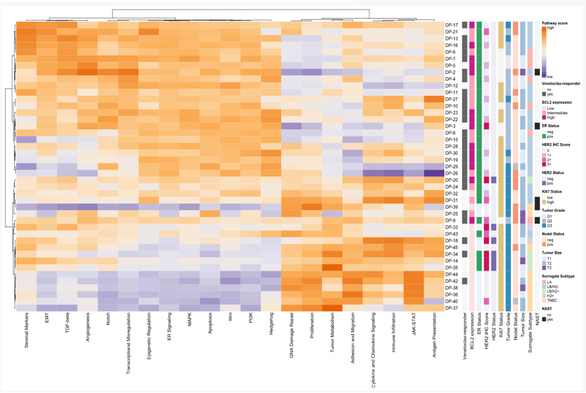
Method

Cells were recovered from newly resected breast tumors as whole-tumor cell cultures (WTCs). Immunohistochemistry, flow cytometry, DNA- and RNA- sequencing were performed to ensure the WTCs recapitulate the biology of original tumors. A broad range of clinically relevant drugs was tested on the WTCs. Cell viability assay, real-time imaging tool, transcriptomic analysis, and panel gene-expression analysis were carried out to investigate the model's predictive value and clinical relevance. A separate validation study was also carried out to compare WTC-based test results and patients' clinical responses in neoadjuvant treatment settings.

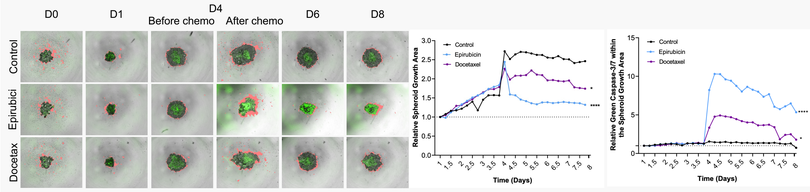
Multi-drug profiling and gene expression analysis indicates the WTC as a promising platform to predict the responses of individual BC patients



Heatmap based on the drug sensitivity score (DSS) of individual patient WTCs. Cells are color-coded by the DSS value (light gray=not available data). Rows correspond to individual patients, and columns represent tested compounds. Samples are annotated with clinical characteristics of the original breast tumors.

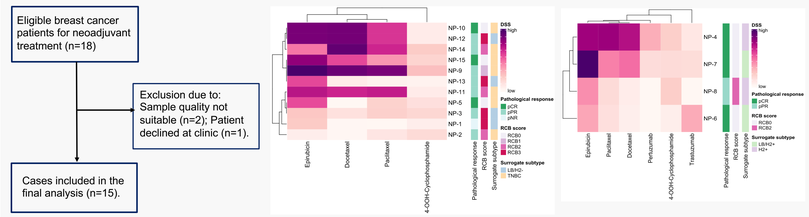


Heatmap based on the signaling pathway scores from the Nanostring BC360 panel. Cells are color-coded by the score values. Rows correspond to individual patients, and columns represent pathways. Samples are annotated with venetoclax responsiveness, BCL2 expression, and the clinical characteristics of the original breast tumors.

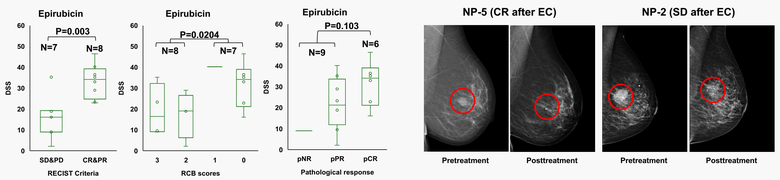


Real-time imaging of WTC over 8 days of culture, with untreated control or added chemotherapeutics at day 4. The red mask demarcates the area with cells surrounding the WTC spheroid, while the light green area indicates Caspase-3/7 levels.

WTC accurately predicts patient response to neoadjuvant treatments



The consistency between WTC-based drug profiling results and BC patients' clinical responses was studied in the neoadjuvant setting. Epirubicin and cyclophosphamide (EC) were first given to all the patients, followed by either docetaxel or paclitaxel. The HER2-positive patients also received trastuzumab and pertuzumab together with the taxane drug.



By evaluation with different criteria, WTC-based drug profiling data were largely in line with the patient clinical responses, particularly for epirubicin and anti-HER2 dual inhibitors. We were able to identify epirubicin as the decisive regimen for patient outcomes in this study and provided distinct DSS reference ranges. Example mammography images are shown for both patients who achieved complete response (CR) and stable disease (SD) after EC treatment.

Significance

There is an urgent demand for discovering more accurate and predictive tools to facilitate precision oncology. Here we report the WTC model could provide us with a platform to efficiently identify drug sensitivity and resistance for individual BC patients. We consider it also a technical breakthrough by considering the stromal components to represent a more unbiased snapshot of the original patient's disease.

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