MicroOrganoSphere™: An Automated Platform for Rapid Drug Screening in Patient-Derived Breast Cancer Organoids

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Background

Patient-derived breast cancer organoids are valuable preclinical models to study patient drug responses, demonstrating good correlation with patients' clinical outcomes. However, establishment and expansion of such organoids from patient tumors for drug screening is currently a time-consuming and labor-intensive process. A more rapid and high-throughput method will enable broader utility in diagnostics and drug development.

Methods

An automated, rapid and scalable microfluidic platform was used to process and develop breast cancer MicroOrganoSphere™ (MOS). Drug sensitivities studies on MOS were performed using 10 FDA approved drugs, including Palbociclib, Adriamycin, 5-FU, Gemcitabine, Methotrexate, Everolimus, Paclitaxel, Docetaxel, Ixabepilone, and Vinblastine. The drug response of MOS and bulk organoids were assessed by CellTiter 3D Glo assay after 6 days of drug treatment, while the growth and establishment of MOS was assessed using imaging analysis. The drug sensitivity of breast cancer MOS was analyzed by calculating percent cell viability and normalized growth rate inhibition (GRI) and compared to response in bulk organoids and in vivo xenograft studies.

Results

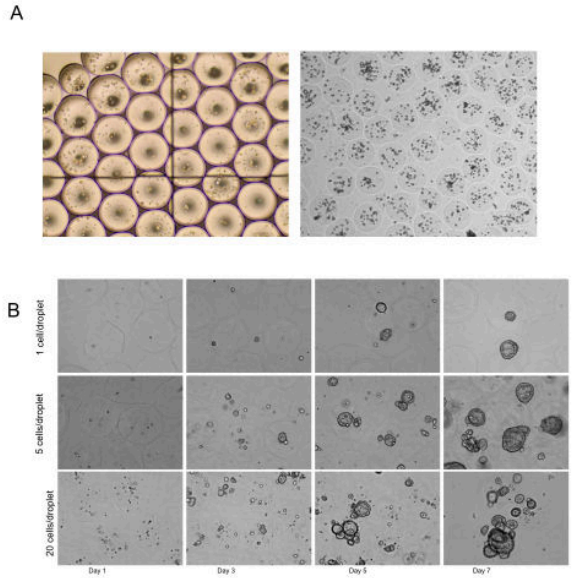

Figure 1. Establishment of MicroOrganoSphere™ techenology. (A) The representative images of undemulsified (upper panel) MOS and demulsified MOS (bottom panel) (B) Representative MOS establishments can be seen after 5 days of culture with different densities (1 to 20 cells/MOS).

Results

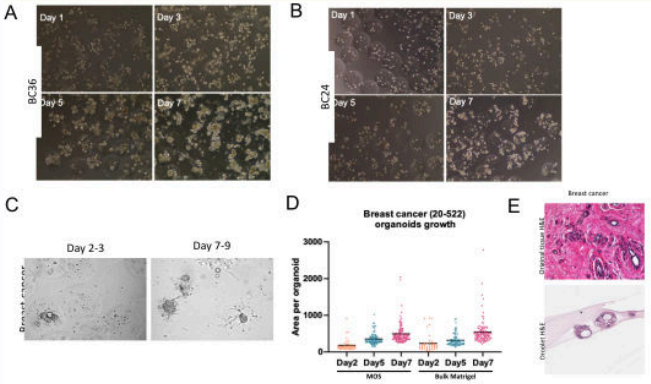

Figure 2. Establishment of breast cancer MOS organoids. (A) Generation of breast cancer MOS from PDX models (PDXO) over 7 days. (B) Establishment of MOS from breast cancer surgical samples was seen as early as 2-3 days with continued growth over 7 days. (B) Growth rate comparing MOS and traditional Matrigel method using the same seeding density. (C) H&E comparing MOS and original patient tumor shows consistent histological features.

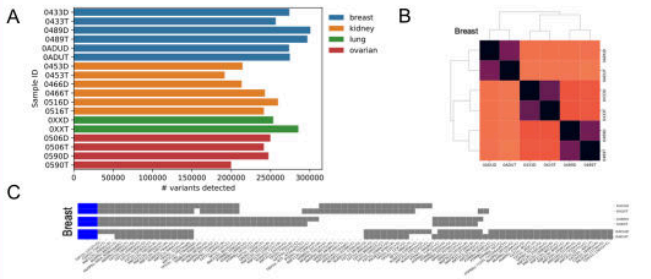

Figure 3. MOS captures genomic features from the parent tissue. (A) Germline mutation analysis showed similar number variants detected between MOS and parent patient tissue. (B) Clustermap of jaccard similarity scores between mutation profiles demonstrated high correlation between MOS and parent patient tissue. (C) The presence (grey) and absence (white) of driver mutations in commonly mutated genes for each cancer type were largely consistent between matched tumor samples and MOS for three patient samples.

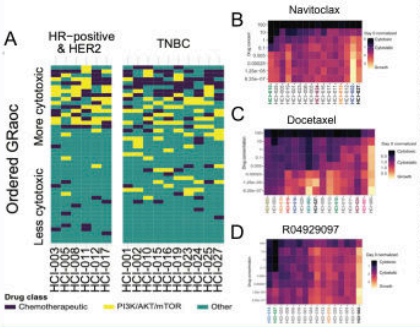

Figure 4. Drug screening using PDXO MOS identifies differential drug sensitivities. PDX-derived MOS treated with a panel of standard of care therapeutics for breast cancer. (A) Heatmap summarizing the differential drug response across PDX-derived MOS lines. Data plotted using growth rate area over the curve (GRaoc) metric. Heatmap of specific response curves to (B) Navitoclax, (C) Docetaxel, and (D) R04929097 across 16 PDX-derived MOS.

Results

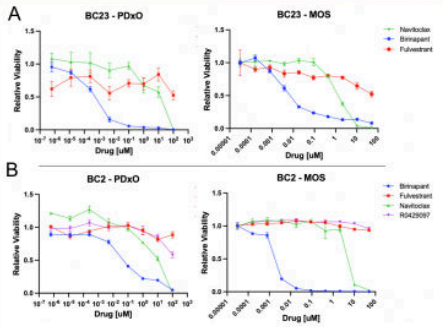

Figure 5. Concordant drug response in PDXO and MOS. PDX-derived bulk organoids (PDxO) and PDX-derived MOS from patient samples (A) BC23 and (B) BC2, responded similarly to Navitoclax, Birinapant, and Fulvestrant. Both BC23 and BC2 appear to be sensitive to Birnapant when tested as bulk organoids and MOS.

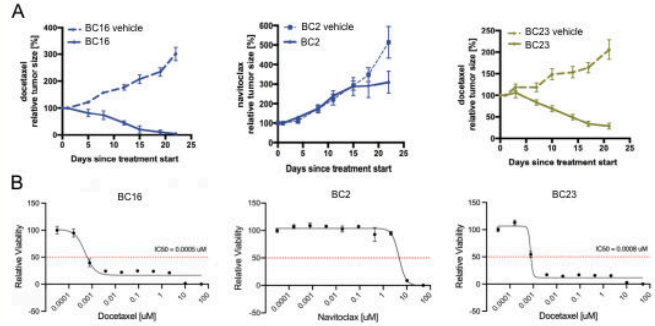

Figure 6. Concordant response in drug treated PDX and PDX-derived MOS. (A) Response of breast cancer PDX lines BC16, BC2, and BC23 treated with docetaxel and navitoclax. (B) Response of breast cancer PDX-derived MOS treated with docetaxel and navitoclax. MOS drug response mimicked the response observed in vivo.

Conclusion

In this study, we show a positive correlation in drug response between MOS, conventional bulk organoids and PDX. Our microfluidic-based, patient-derived MOS assay, provides a rapid, scalable, and cost-effective platform to study drug sensitivity. This technology has the potential to be used for both diagnostics to guide patient treatment and as a screening platform for new breast cancer drug discovery.

Future Directions

- Development of high-throughput drug screening platforms using MOS technology
- Develop diagnostic pipeline for predicting breast cancer patient response

References

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