Clinically relevant inflammatory breast cancer patient-derived xenograft–derived *ex vivo* model for evaluation of tumor-specific therapies

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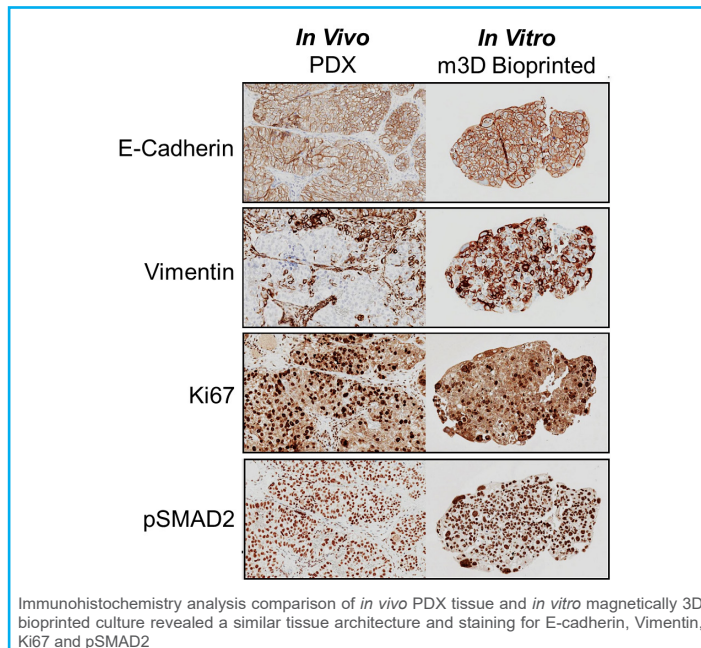
Abstract

Inflammatory breast cancer (IBC) is a rare and aggressive presentation of invasive breast cancer with a 62 % to 68 % 5-year survival rate. It is the most lethal form of breast cancer, and early recognition and treatment is important for patient survival. Like non-inflammatory breast cancer, IBC comprises multiple subtypes, with the triple-negative subtype being overrepresented. Although the current multimodality treatment regime of anthracycline- and taxane-based neoadjuvant therapy, surgery, and radiotherapy has improved the outcome of patients with triple-negative IBC, overall survival continues to be worse than in patients with non-inflammatory locally advanced breast cancer. Translation of new therapies into the clinics to successfully treat IBC has been poor, in part because of the lack of *in vitro* preclinical models that can accurately predict the response of the original tumor to therapy. We report the generation of a preclinical IBC patient-derived xenograft (PDX)-derived *ex vivo* (PDXEx) model and show that it closely replicates the tissue architecture of the original PDX tumor harvested from mice. The gene expression profile of our IBC PDXEx model had a high degree of correlation to that of the original tumor. This suggests that the process of generating the PDXEx model did not significantly alter the molecular signature of the original tumor. We demonstrate a high degree of similarity in drug response profile between a PDX mouse model and our PDXEx model generated from the same original PDX tumor tissue and treated with the same panel of drugs, indicating that our PDXEx model had high predictive value in identifying effective tumor-specific therapies. Finally, we used our PDXEx model as a platform for a robotic-based high-throughput drug screen of a 386-drug anti-cancer compound library. The top candidates identified from this drug screen all demonstrated greater therapeutic efficacy than the standard-of-care drugs used in the clinic to treat triple-negative IBC, doxorubicin and paclitaxel. Our PDXEx model is simple, and we are confident that it can be incorporated into a PDX mouse system for use as a first-pass screening platform. This will permit the identification of effective tumor-specific therapies with high predictive value in a resource-, time-, and cost-efficient manner.

Key features

In this work, magnetic 3D bioprinting provided key experimental advantages, with its a rapid, relatively easy, and reproducible method to bioprint 3D cultures in high throughput. Here are key points:

- Comparison of *in vivo* PDX vs. *in vitro* bioprinted 3D with virtually no difference between 3D *in vitro* and *in vivo*:
    - ☐ Morphology
    - ☐ Protein expression
    - ☐ Coding genes or gene expression
    - ☐ Dose-response
- High-throughput screening (HTS) of 200 compounds NCI library – *in vitro* only because it is too costly to be performed PDX *in vivo* models.
- Dose response comparison *in vitro* 3D vs. *in vivo* PDX comparison with 8 compounds where results were equivalent.
- Validated method for magnetising cells from *in vivo* tissue

Results

Immunohistochemistry analysis comparison of *in vivo* PDX tissue and *in vitro* magnetically 3D bioprinted culture revealed a similar tissue architecture and staining for E-cadherin, Vimentin, Ki67 and pSMAD2

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