Rapid generation of phenomic and functional profiles of patient-derived 3D cell culture models for identification of treatment vulnerabilities of breast cancer. Early results of the EFRE-PoP project.

Verena I I Kiver[1], Guido Gambara[1,2], Olga Gorea[1], Jens-Uwe Blohmer[1], Philipp Jurmeister[1,2], Carsten Denkert[1], Ulrich Keilholz[1], Caroline M. Schweiger[1,2], Maxine Silvestrov[3], Alessandra Silvestri[3], Christian RA Regenbrecht[3, ✉].

[1]Charité - Universitätsmedizin Berlin, Berlin, Germany; [2]Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany; [3]cpo - cellular phenomics & oncology, Berlin, Germany ✉ christian.regenbrecht@cellphenomics.com

Introduction

Targeted treatment for breast cancer subsets currently relies on the occurrence of estrogen, progesterone and Her2/neu receptors. For triple negative breast cancer (TNBC) there is no identified targeted therapy and treatment relies on chemotherapy. The mutational landscape for breast cancer subsets has been characterized, but drug development has been limited due to the lack of appropriate preclinical models. Development of patient-derived preclinical models has been difficult so far. Our aim is to establish a series of patient-derived 3D (PD3D) cell culture models as a versatile resource for ex vivo drug sensitivity screens as well as secondary establishment of PDX.

Aim and methods

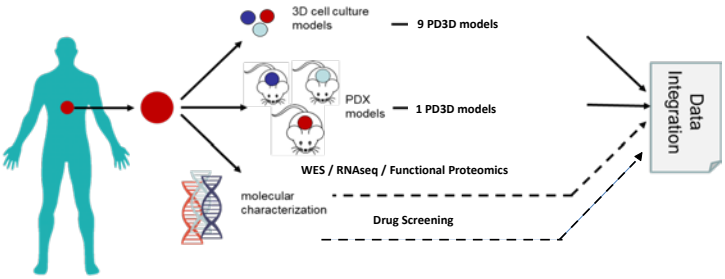
The development of *in vitro* and *in vivo* breast cancer models that resemble the complexity of inter and intra-tumor heterogeneity is crucial to test the efficacy of new targeted treatments aimed to overcome drug resistance driven by tumor evolution. To personalize systemic treatment preclinical testing results and genetic mark-up of tumors have to be combined.

In this study we establish a preclinical platform of scaffold-based breast cancer PD3D models to test chemotherapy response of individual patient–derived samples in comparison to clinical outcomes and linked to molecular genetic markers of the tumor.

Breast Cancer PD3D models

Tumor tissue samples (min. 3mm diameter) from breast cancer patients, both treatment naïve or resistant to received systemic therapy, were collected by a team of gynecologists and pathologists. Ischemia time was minimized. The tissue sample was used establish a cell culture on serum free organoid media in the presence of growth hormones and, in case of hormone receptor positive breast cancer, estradiol supplementation. To address the question whether the genetics features of the model have changed during the process of engraftment and expansion the established models as well as the original tumor samples are currently undergoing molecular genetic profiling. Organoids were than fixed and embedded.
FFPE sections of donor-tissues and derived PD3D models were used for IHC and inspected by a pathologist.
The established standard of care drugs as well as new targeted therapy in clinical trials for breast cancer are currently tested. The drug panel is adapted to the histology of the tumor and the treatment regimen of the individual patient to better compare the results.

Project overview



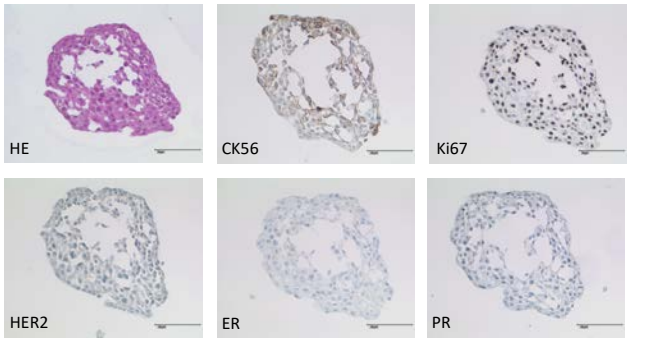
Results

Since May 2017 24 breast cancer samples have been processed. The sample characteristics are summarized in the table.
Breast cancer PD3D organoids had a take rate of 33.3% under our culture conditions. Moreover, hormone receptor positive breast cancer PD3D models were successfully established as PD3D with a take rate of 37.5%.
Adjusted to the growth rate of the PD3D organoids, histopathological testing, molecular genetic testing and drug testing are being conducted in that order. Single results are available but testing is not completed.

Take rates and distribution of breast cancer PD3D models

	Samples	Her2 -, HR- (TNBC)	Her2-, HR+	Her2+, HR -
PD3D N	24	8	15	1
PD3D established	8	3	5	N/A
PD3D eliminated	8	5	2	1
Take rate	33.3%	37.5%	33.3%	0%
PD3D in culture	8	N/A	8	N/A

Breast Cancer PD3D models Immunohistochemistry



Conclusion and outlook

In clinical cancer research there is an urgent need of developing patient-derived cancer models able to resemble inter and intra-tumor heterogeneity to test treatment responses. In this study, PD3D models have been successfully generated from a broad spectrum of breast cancer subtypes with a take rate of 33.3%. The known difficulty of growing hormone receptor positive breast cancer preclinical models was at least in part overcome due to modifications in the culture medium.

Further studies are needed to improve the culture conditions to increase both the take rate and the long term expansion of breast cancer organoids with the final aim of introducing PD3D models as preclinical models as well as predictive tool for treatment selection in clinics.

DKTK German Cancer Consortium
CELLULAR PHENOMICS & ONCOLOGY
EUROPEAN UNION European Regional Development Fund
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN
dkfz. German Cancer Consortium Partner site Berlin