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Patient-derived scaffolds as a 3D model for breast cancer

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
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Hus 2 Hälsovetarbacken, den 10 mars 2023, klockan 13.00
Av Anna Gustafsson

Fakultetsopponent:
Professor Patrick Micke, Uppsala universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. Landberg G, Fitzpatrick P, Isakson P, Jonasson E, Karlsson J, Larsson E, Svanström A, Rafnsdottir S, Persson E, Gustafsson A, Andersson A, Rosendahl J, Petronis S, Ranji P, Gregersson P, Magnusson Y, Håkansson J, Ståhlberg A. Patient-derived scaffolds uncover breast cancer promoting properties of the microenvironment. Biomaterials 2020; 235; 119705

II. Gustafsson A, Garre E, Leiva MC, Salerno S, Ståhlberg A, Landberg G. Patient-derived scaffolds as a drug-testing platform for endocrine therapies in breast cancer. Scientific Reports 2021; 11; 13334

III. Garre E*, Gustafsson A*, Leiva MC, Håkansson J, Ståhlberg A, Kovacs A, Landberg G. Breast cancer patient-derived scaffolds can expose unique individual cancer progressing properties of the cancer microenvironment associated with clinical characteristics. Cancers 2022; 14; 2172. *Authors contributed equally

IV. Leiva MC*, Gustafsson A*, Garre E*, Ståhlberg A, Landberg G. Breast cancer patient-derived scaffolds representing individual cancer microenvironments influence chemotherapy responses in breast cancer cell lines consistent with clinical features. *Authors contributed equally (*Manuscript*)

V. Gustafsson A, Jonasson E, Ståhlberg A, Landberg G. Proteomics of cell-free patient-derived scaffolds from breast cancer identify clinically relevant imprinted proteins and cancer-progressing properties. (*Manuscript*)

SAHLGRENSKA AKADEMIN
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Patient-derived scaffolds as a 3D model for breast cancer

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Abstract

Breast cancer is the most common cancer form in women worldwide. Many patients will have recurrent disease and more efficient targeted therapies are needed. The tumor microenvironment is a heterogenous complex mix of cells and components influencing critical cancer processes including progression, signaling and invasion. In this thesis, we established an *in vivo*-like 3D cell culture platform using decellularized patient-derived scaffolds (PDS) to facilitate cell-cell and cell-microenvironment interactions similar to the situation *in vivo*. The PDS model was extensively evaluated and characterized showing that PDS cultures induced changes in gene and protein expression in cancer cell lines after 21 days of growth. Cancer cell lines growing in PDSs enriched for cells with cancer stem cell properties and decreased cells proliferation compared to monolayer cultures. These findings were corroborated by transcriptomic data from 3 cell lines growing in large PDS cohorts, also showing that genes related to epithelial-to-mesenchymal transition were heavily influenced by properties of individual scaffolds. Innate clinico-pathological characteristics including grade, histological subtype, lymph node metastasis of the cancers, as well as disease-free survival of patients could be identified by gene expression changes in adapting cancer cell lines. The suitability of the PDS model as a drug testing platform was evaluated using well-known endocrine therapies and a CDK4/6 inhibitor which demonstrated that PDS growth induced different cellular phenotypes in response to the drugs compared to 2D cultures, but also presented similarities to other 3D assays. A qPCR-based screen of cancer cell lines growing in PDSs that were treated with chemotherapies identified drug fingerprints that also could be linked to clinical properties of the original tumors, supporting the use of PDSs as a personalized drug testing platform and a prognostic tool *in vitro* that potentially could be utilized as a treatment prediction option for patients. Finally, the proteomic composition of PDSs was delineated using liquid chromatography-mass spectrometry/mass spectrometry identifying subtypes of PDSs based on their relative protein expression which was associated to clinical properties of the PDSs as well as presented important upregulated processes in the PDS model that could be potential therapeutic targets. In conclusion, this thesis elaborated the impact of cancer microenvironments and identified important properties influencing different subtypes of cell-free scaffolds.

Key words: breast cancer, patient-derived scaffolds, cancer microenvironment, 3D model, cancer stem cells, drug testing

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